MIGRAINE AS A SEQUEL TO INFECTION BY L. ICTEROHAEMORRHAGIAE

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Of recent years migraine has been attributed to a bewildering assortment of causes, ranging from heredity (Friedman and Wilson, 1947), through allergy (Crowe, 1946), and personality (Alvarez, 1947), to the comprehensive list drawn up by von Storch (1947). The estimate of Scott (1941) that "much has been written and little has been established as to the aetiology of migraine" seems largely true to-day.

The following observations, which were made in the course of a follow-up study of former cases of Weil's disease in the South Wales coalfield (Atkins *et al.*, to be published), seem worthy of record even at the risk of further complicating the subject.

Method of Study

During 1953 all earlier cases of serologically proved Weil's disease which were known not to have been immediately fatal were traced. Fifty-eight such cases were known to have occurred in the area of the coalfield, but five of the patients were found to have left the area and three had died by 1953. Fifty cases therefore remained for study, and in all but one the specific agglutination reaction remained positive at a titre of 1 in 100 or more in 1953. Each man was questioned about his health both before and after his attack of Weil's disease and clinically examined; in addition to general questions designed to elicit anything thought worth mention by the patient, the questionary included specific questions about various symptoms, one of which was headache.

Although estimates are available of the prevalence of migraine among the general population of the United States, it was thought worth while to make use of a control group of South Wales miners known to be serologically negative for *L. icterohaemorrhagiae*. These were also questioned about their experience of headache, and it is hoped that variation in the interpretation of answers, as well as in the definition of migraine, was avoided by the observer's use of similarly phrased questions for both groups.

The definition of migraine which has been adopted is based on that of von Storch, quoted by Marshall (1949). This requires that, to qualify as migrainous, headaches should be recurrent, though not necessarily hemicranial; and they should be accompanied by at least one of the following features: associated visual symptoms—classically scintillating scotomata; temporary gastro-intestinal symptoms—usually nausea or vomiting; or hereditary migraine diathesis, occasionally with an epileptic history. Since the follow-up study had not been designed to investigate the aetiology of migraine, information on the last alternative criterion of von Storch is not available. The diagnosis therefore rests here on a history of recurrent headache with either scotomata or gastro-intestinal disturbance, or both; it can perhaps be said that these criteria are thus more strict than those of von Storch. It may be that opportunity will later occur to study the hereditary factor.

Prevalence of Migraine

Among the 50 men in the control series, 6 (12%) described headaches satisfying the above criteria. This represents a prevalence greater than was to be expected from estimates in America (Scott, 1941; Friedman and Wilson, 1947), where about 7% of the population are said to be affected—the more so as females are said to be two or three times as often affected as males, and the control series here comprised males only. This point may be borne in mind when considering the prevalence observed in the former cases of Weil's disease.

Among the latter there were 24 men who suffered from migraine by the same criteria—a prevalence of 48%, or nearly half the cases. This difference of prevalence in former cases of Weil's disease and the controls is highly significant ($\chi^2 = 15.4$, n = 1, $P<0.001$). It is clear that had comparison been made with American estimates of prevalence among the general population, instead of with the control series, the prevalence among former cases of Weil's disease would have seemed even more striking.

The prevalence of migraine among former cases of Weil's disease of different ages at the time of their infection is shown in Table I. As the period elapsing since infection might also have influenced the prevalence of migraine, these cases are also broken down into their quinquennia of infection.

TABLE I.—*Age at Infection with L. icterohaemorrhagiae, and Date of Infection by Quinquennia, of Men in South Wales Surviving Attack. (Numbers Subject to Migraine in Parentheses)*

Ages	1935–9	1940–4	1945–9	1950–	Total
11–20	—	—	3 (2)	1 (1)	4 (3)
21–30	5 (3)	5 (3)	3 (1)	1 (1)	14 (8)
31–40	5 (1)	2 (1)	5 (3)	1	13 (5)
41–50	3 (1)	6 (3)	3 (1)	1	13 (5)
51–60	—	2 (2)	4 (1)	—	6 (3)
Total ..	13 (5)	15 (9)	18 (8)	4 (2)	50 (24)

It will be seen that migraine occurs fairly evenly among these different categories, there being no tendency for a rising prevalence with age. This fact is of importance in establishing the validity of the control series; for this was unavoidably deficient in men above the age of 50, and contained a disproportionate number of middle-aged men (Table II). It seems likely that this lack of correspondence in age composition of the two series has not overestimated the difference in prevalence of migraine between them.

TABLE II.—*Ages, in 1953, of Former Cases of Weil's Disease and of Controls. (Numbers Subject to Migraine Shown in Parentheses)*

Age	Former Cases	Controls
11–20	1 (1)	0 (0)
21–30	4 (3)	6 (1)
31–40	10 (5)	17 (1)
41–50	12 (5)	22 (3)
51–60	13 (6)	5 (1)
61–70	10 (4)	0 (0)
Total	50 (24)	50 (6)

As might be expected, both the frequency and the severity of attacks were described in most of the former cases of Weil's disease as diminishing with the passage of years, the course of the disorder being similar to that generally seen in ordinary migraine sufferers. On the other hand, as mentioned above, it originated in those of 45 and over nearly as frequently as in those infected at an earlier age.

Among the 24 cases in the Weil's disease group there were 4 individuals whose migraine preceded their infection. The influence of this infection upon established migraine varied, but only one man described aggravation. Subtracting these cases, it will be seen that migraine appeared in 20 cases (40% of those infected) as a sequel to this specific infection, and during convalescence in most cases.

Lest suggestion between one case and another might have led to distortion of histories, upon which alone the diagnosis of migraine must be made, care was taken to keep the men separate at the time of interview. Moreover, since Weil's disease had occurred mainly in relatively closed communities, it was possible to analyse results for each of these geographical groups separately. The results of such analysis show

similar prevalence of migraine in each of the four main widely separated areas of the coalfield where cases have occurred.

Allied Vasomotor Disturbances

In view of modern concepts of migraine as a localized cerebral vasomotor disturbance allied to Ménière's disease (Atkinson, 1943) it may be of interest to record the following observations.

Among the 50 men there were eight who described giddy attacks dating from their infection, but none had associated tinnitus or gross deafness for conversational speech. Only one of these had a diastolic blood pressure of over 100 mm. Hg (mean of three readings at rest). All but two of them were migraine sufferers, though the precise chronological relationship between headaches and giddiness was not investigated. Vertigo was thus associated with headache in a quarter of the cases of migraine.

No cases of epilepsy or its equivalents were found among the 50 cases, nor was a family history of such forthcoming in any of them.

In six cases there was complaint of numbness, tingling, and clumsiness of the fingers and hands, often on waking, and usually more severe in cold weather, since the specific infection; but facilities for proper investigation of these phenomena were lacking. A further patient complained of frequent attacks of "cramp" in the legs and hands since his infection.

Significant hypertension, as judged by a mean resting diastolic pressure of over 100 mm. Hg (there were no cases with signs of failure), was found in 6 of the 24 migraine sufferers. Of these, four were over 50 years of age and the youngest was aged 39 at the time of examination. Among the 26 free from migraine only two had significant hypertension. In addition, before this follow-up study was begun, one former patient had died of a stroke at the age of 65, another of cardiac failure following hypertension aged 52, but it is not known whether either of these men suffered from migraine during life.

Discussion

Such a prevalence of hypertension in men of these ages might be found perhaps in 50 men drawn from the general population. However, this finding of hypertension in a quarter of the cases of migraine may be in accord with the views of Gardner *et al.* (1940) that migraine sufferers may become hypertensive in middle life.

The finding of so large a number of cases of migraine among this series, small as it was, does seem to indicate a probable causal relationship between infection with *L. icterohaemorrhagiae* and migraine. There exist other areas of Britain where this infection is not uncommon, and which offer opportunity for confirmation of this point.

It seems that, if such a causal relationship is established, existing views of the aetiology of migraine may need some modification. Such specific infection is not mentioned in the comprehensive list of causes drawn up by von Storch (1947), nor in the secondary "trigger mechanisms" listed by Friedman and Wilson (1947). Moreover, the latter's insistence upon a primary inherited susceptibility to migraine would appear untenable in the face of such a prevalence as the 48% reported above, even though family histories have been neglected in this study.

It seems possible that migraine may result from the meningitis which is so often a feature of infection with *L. icterohaemorrhagiae*. This would account for the occurrence of vasomotor disturbances in other regions, if those were also established as a significant sequel to the infection. It may be that follow-up investigation of other types of meningeal infection would throw light on this possibility.

The onset of migraine regardless of age in this series underlines the possibility of this diagnosis being correct even in those presenting symptoms late in life. In areas where infection with *L. icterohaemorrhagiae* occurs it would certainly seem wise to test the appropriate agglutination reactions before submitting the patient to such procedures as cerebral arteriography.

Summary

The health of 50 men who had formerly been infected with *L. icterohaemorrhagiae* has been studied.

The prevalence among them of cases of hypertension, and of symptoms suggesting various types of vasomotor disturbance, is recorded. Of these former cases of Weil's disease 48% suffered from migraine. In a control group the prevalence of this disorder was 12%. The difference is of high statistical significance.

The literature on the aetiology of migraine is briefly reviewed and discussed in the light of these findings.

Thanks are due to the miners who so readily co-operated in this study; and to Dr. J. C. Broom, of the Wellcome Research Laboratories, and Dr. R. W. S. Harvey, of the Public Health Laboratories, Cardiff, for performing agglutination reactions in these cases and, with Dr. C. R. E. Freezer, of Church Village Hospital, for help in planning the follow-up of them.

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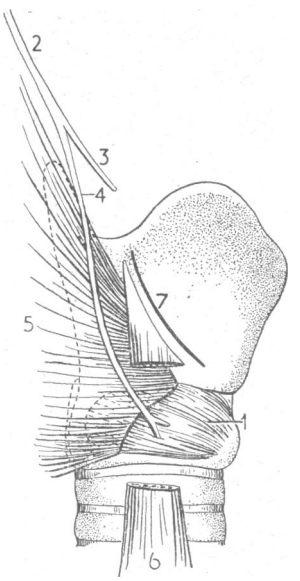
Medical Memoranda

Thyroid Enlargement and the Crico-thyroid Muscle

The importance of the crico-thyroid muscle has not been stressed in any textbook dealing with diseases of the thyroid gland and the operations carried out for the cure of these diseases. The muscle takes origin from the anterior part of the cricoid cartilage and runs upwards and backwards in two parts—an oblique part inserted into the lower border of the thyroid cartilage in front of the oblique line, and the horizontal part inserted into the inferior cornu and the lower border behind the oblique line. The nerve supply is the external branch of the superior laryngeal nerve, which comes from the vagus. The nerve runs *superficial* to the inferior constrictor of the pharynx but deep to the sterno-thyroid muscle; both these muscles are attached to the oblique line on the thyroid cartilage. The diagram makes these details clear.



1, Crico-thyroid muscle. 2, Superior laryngeal nerve. 3, Internal laryngeal nerve. 4, External laryngeal nerve. 5, Inferior constrictor muscle. 6, Sterno-thyroid muscle. 7, Oblique line.

The function of the crico-thyroid muscle is to tense the vocal cords. Damage to the muscle or its nerve will produce a voice which is incapable of varying its pitch. It can be described as a monotone voice at about F, middle register.

The patients complain that they are unable to sing or alter the pitch of the voice; also, the voice gets tired easily. It is not