then further degraded to amino-acids by peptidases present in the cells of the mucosa.

In adult coeliac disease it is suggested that the activity of these cellular enzymes is reduced, and this, in addition to a reduction in absorptive area, produces a slowing down in the later stages of proteolysis. The possibility that the changes of absorption observed in the hydrolysis are associated with the rate of absorption of water has been excluded by appropriate control experiments. It was of interest that treatment for several weeks with a gluten-free diet in one of our cases produced a normal type of absorption, as shown by the results of isotope experiments.

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MIGRAINE AS A DEADLY DISEASE

BY

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The vast majority of patients in need of medical attention because of headaches are sufferers from migraine. The occurrence of migraine in the population has been estimated as from 3 to 30%. If only females are considered, and if temporary periods of migraine, say, for one or a few years, are included, 30% is hardly an overstatement, high as it may seem (Ask-Upmark, 1953). If both sexes are considered, and only severe cases embittering life for a number of years are included, 3% may be a more likely approximation (Essen-Möller, 1956).

Possible Causes of Death from Migraine

Although migraine more often than not reduces or abolishes the working capacity of the patient, it is not usually regarded as a fatal disease. Increasing evidence, however, suggests that it is a real danger to life, not least by means of iatrogenic activities. As a matter of fact, death may ensue from migraine under the following conditions.

1. Ophthalmoplegic migraine is more often than not due to an aneurysm of an artery belonging to the circle of Willis. The topography of this aneurysm may involve the oculomotor nerve, so that a distension of the aneurysm will not only produce pain but also an oculomotor palsy with ptosis, etc. The rupture of such an aneurysm may be fatal.

2. Paroxysmal tachycardia of auricular origin is to be looked upon as an equivalent to migraine. Not only is it apt to occur in families with migraine, but there is also the possibility that in one and the same individual some attacks are typical migraine, whereas others are paroxysmal tachycardia. The peculiar phenomenon of urina spastica is characteristic for both types of attacks. It is well known that most attacks of paroxysmal tachycardia are innocent enough, at least if handled properly. There is always, however, the possibility that the heart rate attained may be so rapid as to prevent the auricular contraction from ejecting the blood into the ventricles because of the almost simultaneous contraction of the ventricles. This so-called critical level of the heart rate is about 180. If no adequate assistance is given in such a case the circulation may be blocked just as efficiently as, for instance, by a prolonged Stokes-Adams attack by a solid pulmonary embolism, or by the obstruction of the mitral passage by a pendulating auricular myxoma.

3. There are (rare) instances of migraine which are connected with an outstanding bradycardia during the attacks, say, a heart rate of 20–40. If in such a case ergotamine tartrate is injected intravenously a cardiac standstill may easily be induced. This happened to me once, although by good luck and adrenaline I managed to get the heart going again. As a means of stopping an attack of migraine ergotamine tartrate has decided merits, and it is most efficient if given intravenously. However, if bradycardia is present a word of warning must be issued, at least so far as intravenous administration is concerned. That such an injection in susceptible persons may bring about an attack of status asthmaticus with all its implications is another feature to be remembered.

4. Whereas the fatalities mentioned are rare, there is another complication which, for unknown reasons, has become increasingly common and which obviously is a very real danger. This complication is renal; its anatomical character is interstitial nephritis, and it is by no means uncommon as a cause of death from uraemia. It is apt to

The inaugural meeting of the International Society of Tropical Dermatology was held earlier this year at the Rockefeller Institute in New York. An international congress was suggested for 1962 or 1963.

be encountered in patients with migraine who have taken a large amount of phenacetin or similar compounds over a number of years. These cases are by no means unusual. In our clinic we have had, during the past eight months, at least eight such patients, one of whom died from uraemia, and all the remaining seven (one man and six women) are in a more or less advanced stage of uraemia. The fatal case was that of a male physician, aged 56, who, because of migraine since childhood, had been taking remedies containing mainly phenacetin, so that during the previous 10 years his consumption of this drug could have amounted to 5.4 kg. Among the seven who have so far survived, the common denominator in respect of remedies was phenacetin in all cases; it was also injections of ergotamine tartrate in one woman who had unwisely been taught by some optimistic physician to make these injections herself.

Recent literature has paid considerable attention to the occurrence and pathogenesis of this type of kidney disease (Spühler and Zollinger, 1953; Dahmen, 1958; Jasiński and Wuhrmann, 1958; Sarre *et al.*, 1958; Studer *et al.* (1958); Lindeneg *et al.*, 1959; Moolten and Smith, 1960). It is rather peculiar that the condition has been known to occur only in the 1950s, the first communication on the subject apparently being that of Spühler and Zollinger (1953). On the one hand, it has been maintained that phenacetin is the culprit, that the occurrence of the kidney lesion is closely correlated to the consumption of phenacetin, and that a possible explanation might be the influence of phenacetin on the blood, the kidney lesion presumably being secondary.

On the other hand, it has reasonably been objected that animal experiments have failed to substantiate the claim that the renal lesions are due to phenacetin, that the consumption of phenacetin may be considerable without any impairment of the kidneys, and that lesions of the kidney histologically identical with those presumed to be caused by phenacetin have been encountered in cases where phenacetin has not been taken. The evidence available is therefore conflicting. One is inclined to agree with Heilmeyer, as quoted by Dahmen (1958), that small doses of phenacetin used only occasionally seem to be fairly safe, whereas large doses taken over a number of years may induce a chemical interstitial nephritis, provided that other factors are present. Little is known about these factors, but it is obvious that infections, particularly of the urinary tract, are of importance. This is proved morphologically, since it may be difficult to distinguish between a chronic interstitial nephritis and a chronic pyelonephritis, and there are reasons to believe in a common denominator.

"Phenacetin Kidneys"

Whereas abuse of phenacetin and infections of the urinary tract are exogenous factors, the question may well be asked whether an endogenous disposition might be of importance. Such a constitutional factor may be demonstrated in two ways. On the one hand, since the observations made by Runeberg early in this century, it is well known that malformations of the kidneys conduce to infections, particularly pyelonephritis. A characteristic malformation of the kidneys, described in 1929 (Ask-Upmark, 1929), is closely connected with arterial hypertension, and pyelonephritis may or may not be a responsible link in the sequence of events concerned. In this connexion one may recall certain other malformations and their complication with secondary diseases—for example, bicuspid aortic valves and endocarditis lenta, malformations in the right side of the heart and the cardiac complications of

carcinoidosis, abnormal origin of the great arteries from the aortic arch and the arteritis resulting in "pulseless disease," and cryptorchism and tumours of the retained testis. As regards the "phenacetin kidneys," to the best of my knowledge no evidence to this effect has so far been presented. On the other hand, a familiar occurrence that is at least suggestive of a constitutional factor may be mentioned.

A family under observation in our clinic during recent years is reproduced in the following pedigree, in which heavy contours mark the presence of migraine and striated symbols the presence of renal insufficiency. It will be seen that no fewer than four of the female members either have died from uraemia (two cases) or

The proband of this study was FI 2. Both of her parents died from cancer, and her mother had had severe migraine for many years. Migraine was also recorded in three of her sisters: FI 1, FI 5, and FI 6. The last-mentioned died from pulmonary embolism after delivery when aged 21, whereas the other sisters died from uraemia in our clinic (FI 5 in 1953, FI 1 in 1956). In both these cases the uraemia was caused by a lesion of the kidney in connexion with overuse of phenacetin for several years. FI 2 and her daughter (FII 4) are alive but in a state of chronic uraemia. FIII 4 has repeatedly had severe headache. FII 1 has had a rather severe migraine, which eventually improved. Being aware of the fate of his mother, he has been anxious to avoid phenacetin. His daughter (FIII 1) has been under observation in the department of paediatrics because of an infection of the urinary tract.

are still alive though in a rather advanced stage of uraemia (two cases). In all four instances a heavy consumption of phenacetin was a common denominator. It is at least tempting to assume a constitutional inferiority of the kidneys in such a family, and it seems reasonable to advise members of this family to avoid remedies containing phenacetin except for occasional use. In the future it would be well to remember the possibility of a family factor, whether presented by a more susceptible haemoglobin or by a more susceptible kidney tissue. As to the necrosis of the renal papillae in this connexion, described, for instance, by Lindeneg *et al.* (1959) and also observed by us, one may well remember the peculiar vasomotor behaviour in migraine. The hands and the feet are often cold, and the question may well be asked whether the circulatory conditions of the kidney may present peculiarities to be elicited, for instance, by investigation of the renal blood flow.

Summary

The possible causes of death from migraine are surveyed. If the intracranial aneurysms frequently responsible for symptomatic migraine and occasional cases of paroxysmal tachycardia are excepted, the danger is obviously mainly iatrogenic and lies in the use of ergotamine tartrate, and particularly of phenacetin preparations.

The conflicting evidence about the "phenacetin kidneys" is summarized and attention is called to the

possibility of constitutional factors, as illustrated by a family tree which shows that four members of a family received fatal damage to their kidneys in connexion with medication against migraine.

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PROGNOSIS OF THE ECZEMA-ASTHMA SYNDROME

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The parents of children suffering from infantile eczema are naturally anxious to know the long-term prospects for the child's health. At present there is no definite answer to this question. Numerous investigators have examined various aspects of the prognosis of infantile eczema. Most of these have dealt with groups of children who were referred to hospital. For example, Vowles *et al.* (1955) showed that 55% of such children will still have eczema at the age of 13 years and 50% will have asthma. Purdy (1953) states that a similar percentage will still be affected at the age of 20. Meenan's (1959) investigations of older subjects showed that about 30% of the skin lesions never clear up.

We have had an opportunity of assessing a group of children who were admitted some years ago to the skin department of the Belfast City Hospital suffering from infantile eczema. We were interested in the outlook for these children, through the years, from both the skin and the respiratory viewpoint.

Methods

The records of the skin department for the years 1947-50 were searched, and 43 cases of infantile eczema were found. Similar criteria to those of Purdy (1953) were used in the selection of cases: (1) the diagnosis must have been either infantile eczema or dermatitis (note: during the period the term seborrhoeic was not used in this unit for any child); (2) the face must have been clearly involved; (3) the patient must have been 24 months old or younger when first seen with the disease; (4) the patient must have been 12 months old or younger at the onset of the disease; and (5) there must have been no obvious acquired predisposing factor such as scabies, pediculosis, or antecedent napkin erythema.

Letters were sent to the parents requesting the attendance of these children for interview. If they did not attend and lived within 30 miles (48 km.) of Belfast, they were visited in their homes by one of us. If they lived at a greater distance the parents were provided with a form on which they could indicate the child's present state of health. This was necessary in only two of the 43 cases.

An independent observer who did not know the present state of the children reviewed the case-histories and separated the cases which he considered to indicate a diagnosis of seborrhoeic eczema from those in which a contact factor probably played a part.

Of the 43 cases of infantile eczema, three could not be traced by any means at our disposal, including visits to the last known address, contact with their family doctors, and, finally, the help of the General Health Services Board. Of the remaining 40 patients, one had died of leukaemia and one had emigrated. The cases were further subdivided as in Table I.

TABLE I

		Boys	Girls	Skin Clear in 1959
No. of cases of eczema	43	27	16	
" traced	38*			13
Seborrhoeic eczema	6	3	3	5
Contact dermatitis	3	2	1	3
Infantile eczema	29	19	10	5 (2 of these had asthma)

* Two by letter only, not seen.

In attempting to assess the respiratory complications, 23 children were selected from the above group of 29 with true infantile eczema, and solely on the basis of their living within half an hour's journey of the clinic. These children were requested to attend the clinic with a parent at a time suitable to them. Three refused to come, and therefore 20 were investigated in the following manner.

The parents and children were questioned about the progress of the skin and chest conditions, family history, and other relevant points as set out in the results.

In assessing the respiratory history a four-point system was adopted to indicate the severity of the past symptomatology. Those with no such history were classed as group 0. Mild respiratory symptoms consisting of occasional wheeze or coughs which required treatment as "bronchitis" or asthma less than twice a year on average were group +. More severe symptoms requiring more frequent attention from the family doctor but having no intervening disability for periods of several weeks were group ++. The severely affected individuals with persistent symptoms of wheezing were graded group +++. At the examination of the child special attention was paid to the skin and respiratory systems. The presence and absence of an audible wheeze was noted. All relevant physical characteristics such as standing height and weight were measured.

A Gaensler spirometer with a one-second time-switch was used for the measurement of the ventilatory capacity. Each child was instructed in the technique of performing the test, being seated upright. Five readings were taken of the forced expiratory volume (1 second) and of the forced vital capacity, before and after the use of a spray containing adrenaline and atropine compound B.P.C. from a Wright inhaler for one minute. This was followed by a two-minute interval before repeating the tests. The mean of the last three readings was taken in