Current Practice

DISEASES OF THE SKIN

Ichthyosis

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The word ichthyosis (Greek *ikthus*, fish) describes patients who in the untreated state have visible cutaneous scales which can be removed. The term xeroderma (Greek *xeros*, dry; *derma*, skin) is reserved for patients with a dry skin, generally without visible scales. During the winter months some patients with xeroderma are so much worse that they resemble those with mild ichthyosis, but in practice it is usually not difficult to distinguish the two entities.

In the great majority of cases ichthyosis is inherited. In most patients the disorder is apparent in the first year of life and in all by the age of 5. Ichthyosis which develops for the first time in adult life often has a sinister significance, and may be the presenting sign of Hodgkin's disease; but the condition has developed as a toxic effect of drugs, such as triparanol and butyrophene. However, this event is sufficiently uncommon to suggest that further investigation of the metabolic pathways involved might be useful.

On theoretical grounds it is possible to suggest two different mechanisms whereby visible scales appear on the skin surface. There may be an increased rate of keratinization, usually caused by accelerated epithelial cell proliferation, or a disturbance in the elimination of scales—desquamation is retarded—and ichthyosis may then be regarded as an abnormality of keratin separation. Despite much research it cannot be said with certainty which of these is the more significant abnormality in ichthyosis. The probable explanation is that despite the apparent similarity in morphology of the different groups a different mechanism may be involved in each.

Although the sweat glands are probably reduced in number in the autosomal dominant variety of ichthyosis vulgaris, absence of sweat glands per se does not give rise to ichthyosis. Patients with anhidrotic ectodermal dysplasia have a smooth, shiny integument.

The nomenclature of the various types of ichthyosis has always been confused, so that various diagnoses have been made for the same condition in different age groups by practitioners in various specialties and in different countries. To add to the confusion new names are still being invented for conditions that have been described for as long as medical records have existed.

Classification

The most satisfactory initial classification for genetically determined disorders is one based on the mode of inheritance. Should the mode of inheritance of disorders be dissimilar, then they must have different causes; genetic counselling will not be the same, and the prognosis and response to treatment will probably differ as well. There are essentially two types of ichthyosis vulgaris, one autosomal dominant and the other sex-

linked (more precisely, X-linked), whereas the two types of ichthyosiform erythrodermia, the bullous and non-bullous, show respectively an autosomal dominant and autosomal recessive mode of inheritance. The latter is sometimes named ichthyosis congenita because it is often present at birth.

Types of Ichthyosis

Ichthyosis Vulgaris

This is the common type of ichthyosis, and is inherited as an autosomal dominant. It is seldom noticed before the age of 3 months, and many patients are only mildly affected throughout their lives, with minimal lesions on their arms and legs. In addition, many patients improve so much as they grow older that no clinical effects may be evident in the summer, and their children would therefore seem to have normal parents. However, repeated clinical examination, as well as a careful history, will usually reveal that this is not so, and that one of the parents had some manifestations of the gene, however slight.

In addition to the ichthyosis, characterized by fine white branny scales, it is often possible to see hard elevations round the hair follicles (keratosis pilaris), as well as increased palmar and plantar markings. The central part of the face, rather than the sides, may be affected, but the skin of the flexures and neck is generally normal. When the trunk is involved the ichthyosis is less marked on the abdomen than on the back, and there is often localized shiny hyperkeratosis at the elbows, knees, and ankles. Many of these patients have one or more of the manifestations of atopy (asthma, eczema, and hay fever syndrome), and chapping of the hands and heels is a common complaint. The histology may show some hyperkeratosis, with a diminished or absent granular layer, and it is probable that there is some reduction in the number of sweat and sebaceous glands.

Sex-linked Ichthyosis

Sex-linked ichthyosis is probably best considered under this diagnostic heading, with the term ichthyosis vulgaris reserved solely for patients with the far more common autosomal variety. Biochemically it is probably more closely related to ichthyosiform erythrodermia than to ichthyosis vulgaris. This form of ichthyosis is transmitted by clinically unaffected females, and manifests itself only in males. It follows that the parents and children of males with sex-linked ichthyosis will have a normal skin, but their daughters will be obligatory heterozygotes able to transmit the condition to their sons. A son can never inherit the condition from his father.

The onset is in the first three months of life, often in the first week, and the children are said to have "peeled all over"

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shortly after birth. They are nearly always severely affected, because the whole skin surface is involved, and one or two of the flexures may be affected in as many as 30% of the patients. There is some change in the distribution with age. Children characteristically have thick scales in the scalp, with the ichthyosis of the side of the face and neck giving a "dirty" appearance. In adults it is the abdomen rather than the back, the legs, and possibly the popliteal fossae which are the most severely affected. The scales may be similar to those seen in ichthyosiform erythrodermia, and tend to be shed more profusely ("moulting") in the spring and autumn. The palms and soles are normal. The histological appearances are essentially the same as those seen in the non-bullous ichthyosiform erythrodermia, though the changes are not so marked. Several patients have been described in which sex-linked ichthyosis is associated with mental deficiency, hypogonadism, and other abnormalities, but these must be very rare.

It has now been established beyond doubt that the gene for sex-linked ichthyosis and that for the Xg blood group are within measurable distance of each other on the X chromosome.

Bullous Ichthyosiform Erythrodermia

As with ichthyosis vulgaris, and in common with many other conditions inherited as autosomal dominant traits, the clinical picture is very variable in this group of patients, and they generally improve when they reach adult life. Mildly affected people may simply show hyperkeratosis localized to the flexures and periumbilical region, whereas those who are severely affected show gross hyperkeratosis covering the entire body, giving rise to the descriptive term porcupine man, or ichthyosis hystrix (Greek *hystrix*, porcupine) gravior. In this group bullae may be quite inconspicuous, so that it may be difficult to obtain a history that they have occurred. In other patients bullae dominate the clinical picture for many years, and prevention of secondary infection is a very important part of the management. Should extensive blistering develop at birth, systemic cortisone therapy may be life-saving. Although the bullae may still occur they are seldom troublesome after the age of 20.

When the hyperkeratosis affects the face it is the lower rather than the upper part which is more involved. As a rule all flexures are affected and they may present a moist appearance. Small, shotty scales are shed in large quantities, but the palms and soles are usually normal. The erythrodermia is best seen in adults if scales are removed, but in the newborn it may be so striking that the infant looks as if he has been boiled alive. The histological changes include hyperkeratosis and vacuolation in the upper epidermis, which are diagnostic of the malady.

Ichthyosiform Erythrodermia

Ichthyosiform erythrodermia is inherited as an autosomal recessive, and children with this condition are born to parents who are usually unaffected but who are often related. The baby may be premature, with a low birth weight. The dry skin is seen within the first day or days of life, and the appearance of the infant may be such that a diagnosis of collodion baby¹ is made before the onset of the more characteristic generalized hyperkeratosis, uniformly distributed over the trunk and limbs, makes the true diagnosis evident. The process is particularly evident in the flexures, which have a dry appearance.

¹ Much confusion has been caused by attempting to limit this diagnosis to a particular entity. Although it is permissible to use the term to describe the appearance of certain babies in the neonatal period, it must be remembered that it may be seen in any one of five different conditions—namely, sex-linked ichthyosis, bullous and non-bullous ichthyosiform erythrodermia, the Sjögren-Larsson syndrome, and lamellar ichthyosis.

The face is usually involved, and as the upper part is more severely affected than the lower ectropion may develop as the patient grows older. This is due to excessive dryness of the skin, and it can be prevented by the application of an emollient to the lower eyelids. These patients shed large, dark scales, and the palms of their hands and soles of their feet are generally abnormal, with increased palmar markings or thickening with desquamation or gross hyperkeratosis. It is quite exceptional for the condition to improve as the patients grow older; many seem to become worse, if this is possible. An underlying background of erythrodermia is seen in babies, but this is much less obvious in older patients, and may become visible only when scales are removed. Histological section shows increased thickness of all the layers of the epidermis.

It is very probable that the condition known as "harlequin foetus" represents the most severe degree of this condition; the gross thickening of the skin encases the infant in a rigid cuirass, which makes respiration impossible, and the infant is stillborn or dies soon after birth.

There are at least three other conditions in which ichthyosis is a feature, and in which it is transmitted as an autosomal recessive trait; all are extremely rare. In the first, well described by Sjögren and Larsson, ichthyosiform erythrodermia is associated with spastic diplegia and severe mental retardation. Patients such as these with multisystem abnormalities are important, because they may provide the clue to the underlying biochemical abnormality. However, in spite of extensive investigation the error in metabolism is still unknown in this syndrome.

On the other hand, with the second condition—heredopathia atactica polyneuritiformis, originally described by Refsum—success was achieved when it was shown to be due to an inborn error of lipid metabolism, leading to storage of 3,7,11,15-tetramethylhexadecanoic acid. Patients with this condition are of normal intelligence, but have progressive nerve deafness, retinitis pigmentosa, and polyneuritis. The ichthyosis is often inconspicuous but is present sufficiently often to suggest that it is a true manifestation of the syndrome.

The third condition may be a variant of ichthyosiform erythrodermia, but the clinical appearance and course differ so much from that seen in the latter condition that it is probably a separate entity. The patient may be severely affected at birth (collodion baby), and later develop large loose scales, but finally the skin clears completely. This has been given the name lamellar (Latin *lamina*, thin leaf) ichthyosis.

Treatment

The effect of prolonged warm weather on ichthyosis vulgaris is dramatic, and many patients choose to live in the tropics because the disorder is then no longer apparent. The heat of an English summer is seldom sufficient to produce more than a partial alleviation. By contrast both types of ichthyosiform erythrodermia have no seasonal variation, and the patients often say that they feel tired and exhausted in the summer. Ultra-violet light therapy is of no value for any of these patients.

There have been no recent advances in the treatment of these disorders, and it is difficult not to feel helpless when faced with sex-linked ichthyosis or one of the varieties of ichthyosiform erythrodermia. Cortisone may be life-saving during the neonatal period in patients with severe bullous ichthyosiform erythrodermia, but with this exception there are no agents which can be given by mouth or injection for long periods of time which are therapeutically effective. Large doses of vitamin A may produce temporary alleviation, but the amount necessary to control the lesions cannot be given continuously because of the danger of serious toxic effects.

Since the great majority of patients with ichthyosis will always have it, treatment should be simple, cheap, and cosmetically acceptable. In addition, patients should be able to carry

out the treatment without too much disturbance of their routine. It is important to emphasize to all that treatment must be continued indefinitely, but not necessarily daily, and when this is done the cosmetic result may be very good indeed. Some female patients take care of themselves so well that it may be impossible to see that they are affected, and since the most common form is ichthyosis vulgaris a good prognosis can usually be given.

Observation of a large number of patients in their homes reveals how few continue with the ointments that have been prescribed for them in the hospitals or by their general practitioners. This suggests either that the ointments are unsatisfactory or it may reflect failure on the part of the physician concerned to instruct the patients in their use. Almost invariably when treating themselves patients use white soft paraffin or one of the commercial preparations such as Nivea or Astral, or occasionally ung. aquosum *B.P.*, which they buy in large quantities. The classical combination is glycerin, soft paraffin, and lanolin—for example, glycerin 10 ml., soft paraffin 10 g., and lanolin to 30 g. Boots sell a product with a complicated formula but an easy name, E 45, with a vanishing cream base, which renders it suitable for the face as well as helping to prevent chapping of the hands.

The keratin of the horny layer is hydrophilic, but the water is soon lost in most environments by evaporation. Although the only way to treat a dry-skinned patient is by the application of grease, the most important function of the grease is to prevent evaporation of water, and it is little use if the skin is dry. Treatment is satisfactory only if the skin has been moistened first.

The following regimen may be found to be helpful. Two ounces of ung. emulsificans *B.P.* is creamed in a jug of hot water, and this is poured into the bath two or three times a week in the evening. After a brief bath, and while the skin is still moist, the patient applies the ointment which has been found to be most satisfactory, and sleeps in a different set of pyjamas to that which he usually wears, or in a plastic suit. It must be emphasized to the patient that the three essential features are moistening of the skin, using large quantities of ointment, and continuing treatment.

A few other observations may be helpful. Detergents and other degreasing agents should not be used. Gloves are essential in the winter, particularly if there is a tendency for the hands to crack or chap. Physical exercise is generally helpful, but a hot dry atmosphere (central heating) can make the skin worse, and water vapour should be added to the air of the house.

TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Mefenamic Acid

This drug is marketed by Parke, Davis and Company under the name of Ponstan.

Chemistry and Pharmacology

Mefenamic acid is *N*-(2,3-xylyl)-anthranilic acid. It has analgesic, anti-inflammatory, and antipyretic actions, which have been demonstrated in both animals¹ and in man.

One laboratory test of anti-inflammatory activity commonly employed is the potency of a drug in delaying the onset of skin erythema in guinea-pigs after exposure to ultraviolet irradiation. Mefenamic acid shares with phenylbutazone the ability to delay this response and also to inhibit the rise in temperature induced in rats by injection of a pyrogen.

One of the naturally occurring metabolites of tryptophan is 3-hydroxyanthranilic acid, a compound related to mefenamic acid. It has been suggested that a derangement of tryptophan metabolism exists in rheumatoid arthritis, and abnormally high excretion rates of its metabolites have been recorded in the collagen diseases. While these observations are, at best, pointers for further research, they may possibly indicate a link between a biochemical lesion associated with these diseases and the anti-inflammatory activity of mefenamic acid.

Tests carried out in animals do not reveal any specific toxic effects which might cause anxiety when the drug is used in human subjects. Large intravenous doses (50 mg./kg.) of mefenamic acid produced a flaccid depression or convulsions or both in a group of rats, but prolonged oral administration caused no demonstrable changes in the same species.

Indications

Mefenamic acid was first described in 1962, and has been slow to gain acceptance as an alternative to the more commonly

prescribed preparations. This may be due at least in part to the scarcity of good clinical trials; but this is in turn related to the difficulties inherent in an objective assessment of pain relief or anti-inflammatory activity.

Reports of the clinical use of mefenamic acid are of varying worth, ranging from isolated case reports to double-blind controlled comparisons with both placebo and standard analgesic preparations. In an attempt to make the pain-stimulus precisely reproducible Williams *et al.*² investigated normal subjects, using a sphygmomanometer cuff inflated to 200 mm. Hg pressure to abolish blood flow into the right arm. Ischaemic pain was then induced by rapid and repeated finger movement, and the time that elapsed before pain forced the subject to stop was accepted as an index of his pain threshold. These experiments served to demonstrate a significant effect of mefenamic acid on pain threshold.

A trial performed in Britain³ was conducted as a double-blind procedure in 15 patients with osteoarthritis of one or both hips. Mefenamic acid 500 mg. three times a day for 14 days was compared with phenylbutazone 100 mg. three times a day for a similar period. The authors concluded that the analgesic potency of these drugs was roughly the same at the given doses. The activity of mefenamic acid has also been confirmed in a trial from general practice.⁴

A recent hospital trial was carried out in 68 female out-patients suffering from rheumatoid arthritis.⁵ In this study mefenamic acid was compared with aspirin and phenylbutazone, though the patients were allowed free access to paracetamol throughout the trial. Although a double-blind technique was employed, doses were adjusted in response to patients' needs. The authors concluded that 1.7 g. mefenamic acid was roughly equivalent to 0.33 g. phenylbutazone or 2.4 g. aspirin in analgesic effect.

Side-effects

Side-effects that have been described include dyspepsia, constipation (which may be only a temporary effect), diarrhoea, and skin rashes; the last two constitute indications for withdrawal of the drug. One patient was withdrawn from a clinical