Current Practice

DISEASES OF THE SKIN

Management of Pruritus and Urticaria

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The sensation of itching is confined to the skin and the palpebral conjunctiva. Itching is a feature of many skin eruptions, but the clinical diagnosis of pruritus is usually reserved for itching, local or general, which is not accompanied by any physical signs in the skin except those due to scratching or rubbing. Itching is abolished when the epidermis and the subepidermal nerve network is removed, leaving intact the perception of cutaneous pain.¹ While this experimental observation is hardly of therapeutic value, it explains why some patients with intense localized pruritus occasionally "dig out" their itchy skin, preferring the resulting pain to their intolerable pruritus. This phenomenon is by no means confined to patients who are mentally disturbed, but is seen in patients with leukaemia, chronic liver disease, and pruritus vulvae or ani.

In pruritus, whatever its underlying cause, there is a lowering of the threshold for normal itch-provoking physical or chemical local stimuli. The latent period is shortened and the local spread and duration of the effect are increased.^{2,3} There is a wide individual variation in the intensity of pruritus and it may vary in the same individual from day to day even without any treatment. It is essential not to dismiss as psychological disturbance persistent pruritus in the absence of physical signs in the skin. At any age, but in particular in middle life or later, it may be the presenting manifestation of neoplastic disease—especially of the blood or reticulo-endothelial system—liver disease, diabetes mellitus, or renal disease. A recent investigation⁴ of 34 patients who had been provisionally diagnosed as suffering from "general" or "senile" pruritus showed that six had malignant lymphoma, three had other types of neoplastic disease, four had renal insufficiency, two had cirrhosis, at least two had diabetes mellitus, and others suffered from malabsorption and pernicious anaemia. "Psychogenic" pruritus should not be diagnosed just because an underlying organic cause is neither obvious clinically nor demonstrable by routine screening tests. There is as yet no evidence that "central itch" can be produced in man,³ but undoubtedly the threshold of itch perception can be altered by psychological as well as by physical factors such as heat or cold.

Commoner Pruritic Conditions

Parasites

If the history of pruritus is relatively short it is essential to look for parasitic conditions like scabies or pediculosis, whatever the patient's status or background. Sometimes even a small number of parasites may give rise to marked general pruritus with minimal local signs. No other cause of pruritus is as amenable to treatment.

Liver Disease with or without Jaundice

While in jaundice pruritus may precede the onset of skin discoloration, liver disease without bile retention frequently

gives rise to intense pruritus. It is usually generalized but tends to affect particularly palms, soles, and scalp. In jaundice pruritus is relieved at the same time as the biliary obstruction or when the liver cells eventually fail.⁵ A good correlation between pruritus and the level of bile salts in the blood has never been demonstrated, but cholestyramine, a strong basic anion exchange resin, reduces both effectively in a significant number of patients even when corticosteroids have failed to do so.⁶⁻⁸ Sometimes pruritus is relieved by cholestyramine without any change in the level of bile acids. An initial dose of 10–15 g. daily is usually required, but 6 g. appears to be an effective maintenance dose. The drug has an objectionable taste, which is difficult to disguise. Nausea and diarrhoea or constipation are undesirable side-effects, and if given in large doses the drug causes steatorrhoea.⁹ Methyltestosterone,¹⁰ norethandrolone,¹¹ and methandienone (Dianabol) are also often effective in relieving the pruritus in liver disease, but they may aggravate the jaundice and some of these agents further impair liver function.¹²

Pregnancy

General pruritus may complicate pregnancy, particularly during the last trimester. In a recent study¹³ a tenfold to one-hundredfold increase was shown in the level of total serum bile acids in pregnant women with pruritus as well as quantitative changes in the normal ratio of different bile acids. Cholestyramine can be used with advantage and apparent safety in this condition.^{14,15} In the absence of impaired liver functions trimopazine tartrate (Vallergan) may be given with benefit. If these measures fail to alleviate the patient's distress prednisone in the relatively low dose of 5–10 mg. daily may prove effective and may have to be given for a short period only. It is important to exclude an underlying drug sensitivity reaction, especially if the patient is being treated for urinary tract infection with sulphonamides or antibiotics. Vaginal candidiasis should be looked for and treated if it is present. The pruritus of pregnancy nearly always disappears within two or three days of delivery but tends to return with later pregnancies.

Diabetes Mellitus

Pruritus is common in untreated diabetes mellitus but is rarely distressing. Though it is not proportionate to the severity of the diabetes it subsides with adequate control of the underlying condition. These patients frequently have dry skin, which aggravates the pruritus; there is often a good response to treatment with ung. aquosum or glycerin. Women frequently have pruritus vulvae due to candidiasis, but when this is treated the condition improves. Scratch marks become more easily infected than in other pruritic conditions but

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respond well to topical antiseptic applications with a wide antibacterial and antifungal spectrum, such as Conotrane cream (hydrargaphen 0.05%, silicone 20%).

Impaired Renal Function

Pruritus may be intense even quite early in renal failure, when nitrogen retention is still slight; it may subside as uraemia increases. These patients have dry skin, which aggravates their pruritus, and its adequate hydration gives much relief. Apart from the relief of the renal failure oral corticosteroids are often effective in the treatment of this distressing pruritus.

"Senile Pruritus"

Pruritus in the older age groups should never be dismissed as "senile pruritus," suggesting the presence of an irremediable degenerative skin condition. While the horny layer of the epidermis tends to become cracked and less protective with age, thus rendering more vulnerable the underlying epidermis, many patients allegedly suffering from "senile pruritus" have a treatable underlying disorder such as diabetes mellitus, prostatic obstruction with or without uraemia, hepatic disease, or neoplasia. True senile pruritus will be improved by the avoidance of soap, a few drops of a liquid detergent being added in its place to the bath-water, silicone creams to prevent drying out of the horny layer, and, if required, by daily dosages of 0.01 mg. of ethinyloestradiol orally in women or methyltestosterone 5 mg. sublingually in men.

Arteriosclerosis with or without hypertension has been blamed for pruritus in the elderly in the absence of significantly impaired renal function. Tissue anoxia is sometimes given as the cause, as in venous insufficiency, without supporting data. However, pruritus is not a feature of true skin anoxia such as that found in advanced obliterative vascular disease.

Hyperthyroidism

In this condition pruritus is not constant but it may be the presenting feature and may become severe. Aggravating factors are the hyperkinetic skin circulation and the resultant increase in skin temperature, as well as the heightened central irritability. The pruritus promptly responds to treatment of the underlying condition.

Neoplastic Disease

The non-specific skin eruptions which may accompany neoplasia elsewhere in the body have been summarized recently by Sneddon.¹⁶ However, pruritus alone may be the only skin manifestation at a quite early stage of neoplastic disease—especially lymphoblastoma. If initial examination of the blood, bone marrow, and enlarged lymph glands yields only equivocal findings tests should be repeated at intervals of two to three months. The pruritus responds well to treatment of the underlying disease but suppression with oral antihistamines and topical corticosteroids is not adequate in many patients, and oral corticosteroid treatment with 15–40 mg. daily of prednisone may be required.

Anogenital Pruritus

This is a fairly frequent complaint and in most patients is amenable to treatment. In a surprisingly large number of patients, especially those whose motions tend to be rather soft, improved personal hygiene will suffice. Washing rather than the use of soft absorbent paper is required to avoid irritation of the perianal skin by faeces. Perhaps the commonest single

cause of persistent anogenital pruritus is sensitivity to *Candida albicans*, with or without colonization of the perineum and natal cleft. While the majority of adults are asymptomatic carriers of this fungus, its faecal excretion in large quantities, for instance after oral treatment with broad-spectrum antibiotics, may give rise to sensitivity reactions of the natal cleft, perineum, and the vagina in women.¹⁷ This condition responds well to treatment for three weeks with nystatin tabs. 1–2 t.d.s., and local nystatin or hydrargaphen. Women must be treated at the same time with nystatin pessaries, and in denture wearers the hard palate in particular must be examined for candidiasis. If this is present it must be treated or the anogenital pruritus will relapse. Treatment of oral candidiasis is often difficult. In spite of their objectionable taste, nystatin pessaries used as lozenges, six daily for three days, are in my experience a highly effective treatment for this condition, thus preventing rapid recontamination of the bowel with *C. albicans*.

Persistent circumscribed patches of lichenification affecting the anogenital skin may be accompanied by intense and more widespread pruritus. This condition, often described as "neurodermatitis," responds well, if slowly, to topical corticosteroids and sedation with chlordiazepoxide 10 mg. t.d.s., but if it persists proctoscopy and sigmoidoscopy should be carried out in all cases to exclude any related bowel lesion.

General Palliative Measures

Whatever its cause pruritus will be eased by cooling the skin, presumably because it slows down the itch-provoking local process as well as its local perception; sedation is likely to lower central perception and the readiness to respond by scratching. Topical corticosteroids like betamethasone valerate, fluocinolone acetonide, or fluocortolone caproate are highly effective, but their prolonged use may give rise to local and general side-effects. Oral corticosteroids in varying dosage are highly effective in most cases of pruritus, but the side-effects from prolonged administration preclude their use in the majority of patients. Local anaesthetic creams should be avoided because of the risk of contact sensitivity.

Oral antihistamines are widely used with apparent benefit in pruritus. While the role of histamine in the production of itching is established in urticaria and anaphylaxis, its role in the generalized pruritus discussed so far is not established.³ The beneficial effect of these drugs in pruritus may be due mainly to a central mechanism.

Urticaria

The urticarial reaction is the final common path of many and diverse mechanisms. It is erroneous and clinically unhelpful to assume that most urticarias are due to the immediate type of allergic hypersensitivity reaction just because the latter is always urticarial if affecting the skin. While short and very infrequently recurring attacks of urticaria are likely to be due to allergy, with a reasonable chance of identifying the responsible agent, chronic urticaria is much less likely to turn out to be allergic and in many patients even searching investigations fail to identify the cause. There is, however, no evidence to suggest that urticaria is ever due to a purely psychological mechanism, although psychological factors may modify the urticarial reaction and lower its threshold. Other aggravating factors, all amenable to specific treatment, are an increase in skin blood flow due to heating or thyrotoxicosis, premenstrual tension, or menopausal states.

In chronic as well as in acute urticaria a carefully taken history still gives in many cases the most helpful guide to management.

Acute Urticaria

In acute urticaria careful notes should be taken of all items of food or drugs ingested during the twelve-hour period preceding the attack. It is important not to forget foods added at the table, like tomato ketchup or mint sauce. Aspirin may not only give rise to widespread urticaria owing perhaps to an allergic mechanism, it may also aggravate or precipitate chronic urticaria due to other causes by seemingly acting as a chemical mediator¹⁸; patients with urticaria should be warned against all medications containing aspirin. Where in acute urticaria the history suggests that a certain food or drug has caused this reaction its avoidance and accelerated clearance from the alimentary canal should terminate the reaction rapidly without any other measure. With acute as well as with chronic urticaria one should never overlook the possibility of insect bites as sensitizing agent.¹⁹

Severe attacks of acute urticaria associated with sensitivity reactions to drugs, antitetanus serum, or other immune reactions should be treated as serum sickness rather than simple urticaria. Whenever acute urticaria is complicated by malaise, fever, or joint pains the urine should be tested for albumin and blood. If these are present treatment with oral corticosteroids is indicated to prevent any permanent renal damage.

Chronic Urticaria

Patients with chronic urticaria should be investigated in hospital as outpatients or inpatients before being condemned for indefinite periods to treatment with antihistamines—which may considerably interfere with their normal pursuits—or quite unwarranted dietary restrictions. While in many patients with chronic urticaria aetiological factors cannot be demonstrated by conventional methods of investigation,²⁰ precise diagnosis and specific treatment are possible in some.

Factitious Urticaria.—Dermographism, or non-allergic hypersensitivity to trauma, is less marked in sunburnt skin and can be alleviated by regular tanning exposures to ultraviolet irradiation.

Cold Urticaria.—This rare condition can also be alleviated by “hardening” the skin with ultraviolet irradiation. It is important to exclude the presence of cryoglobulinaemia from an underlying systemic disease.

Cholinergic Urticaria.—This condition, which is precipitated by exposure to heat, exercise, or emotional stress, affects usually the younger age groups only. It may respond satisfactorily to a combination of the anticholinergic drug propantheline bromide 15 mg. t.d.s. and meclozine 50 mg. o.n. Ultraviolet irradiation in erythema dosage may also help.

Solar Urticaria.—This condition, occasionally associated with porphyria,²¹ may be controlled by heavy sunscreens applications.

Other Types of Chronic Urticaria.—Patients with other types of chronic urticaria should be investigated for hypersensitivity to pathogenic or saprophytic micro-organisms, to food, and to drugs. Search should be made for dental sepsis and for septic foci in the paranasal sinuses—an older dogma recently restated in a large survey of patients with urticaria²²—though the therapeutic benefit is scanty in urticaria. Intestinal parasites are also a rare cause of chronic urticaria.

Specific Tests

So far as skin testing with foods or drugs is concerned, it has to be realized that urticaria denotes a low degree of allergy, if present, compared with asthma or rhinitis, and that intradermal testing with relatively large amounts of the suspected allergen is required. These tests are not devoid of hazards and should not be done without experience of the required concentrations of

the test solutions and their necessary rate of increase. Skin tests should be done only with substances likely to be relevant in the light of the patient's history, and their clinical relevance should always be established subsequently by therapeutic or dietary measures. In a recent study of 255 patients with chronic urticaria¹⁷ 49 gave large immediate (weal) reactions to *Candida albicans* skin-testing solution. Treatment for three weeks with nystatin tablets (one tablet t.d.s.), nystatin pessaries used as lozenges, six daily for three to four days, and for women nystatin pessaries, one each night for three weeks, produced a clinical cure in 27 out of these 49 patients. Eighteen others, all of whom had weal reactions to baker's or brewer's yeast as well as to *C. albicans*, lost their urticaria only when they also adhered to a yeast-free diet for several months. Several of these patients had developed chronic urticaria after treatment with oral penicillin and had been diagnosed clinically as being allergic to it. They did not react to intradermal testing with penicillin or to penicillin given in therapeutic doses intramuscularly. In two of these patients urticaria could be induced by ingesting 5 ml. of sterile skin-testing solution of *C. albicans*. It seems, therefore, that allergy to *C. albicans* may give rise to chronic urticaria, and should be looked for routinely, as it is amenable to specific treatment.

Unlike acute urticaria, chronic urticaria is much less frequently related to food allergy, but it seems desirable to exclude this possibility. This can be done by allowing the patient to ingest only water and sugar (in any unflavoured form) for 48 hours after gentle purging. If after this period urticaria persists without significant change a dietary cause is very unlikely and a normal diet can be resumed immediately. If the urticaria, however, clears during the sugar-and-water regimen then only two different items of food should be added daily to the diet for easy identification of the factor precipitating the urticaria.

On rare occasions chronic urticaria may be the presenting manifestation of an internal carcinoma and may disappear after removal of the tumour.^{23 24}

Dermatitis herpetiformis may occasionally resemble urticaria clinically, and only diligent search will discover sporadic minute grouped vesicles. This eruption usually responds to dapsone.

Palliative Measures

Oral antihistamines diminish or completely suppress urticaria but the dosage required may be high and the side-effects unacceptable. In my experience meclozine 50 mg. o.n., and if required taken also 25 mg. b.d., or chlorpheniramine maleate (Piriton) 4 mg. t.d.s. is particularly effective in urticaria without being unduly soporific. There is, however, evidence that some urticarial reactions are mediated by kinins rather than by histamine²⁵; this could explain the occasional difficulty in suppressing urticaria even with massive doses of antihistamines.

Sufferers from chronic urticaria in whom a specific disease mechanism or precipitating factor cannot be demonstrated may get some consolation from the knowledge that their disease is practically always benign and that eventually it will disappear as mysteriously as it started.

REFERENCES

- Arthur, R. P., and Shelley, W. B., *Pain and Itch*, 1959. Ciba Foundation Study Group No. 1, London.
- Rothman, S., *Biology of the Skin*, Vol. 1, 1960. Pergamon Press, New York.
- Keele, C. A., and Armstrong, D., *Substances Producing Pain and Itch*, 1964. Arnold, London.
- Rajka, G., *Acta dermatovenereol. (Stockh.)*, 1966, 46, 190.
- Brit. med. J.*, 1962, 1, 307.
- Carey, J. B., jun., and Williams, G., *J. Amer. med. Ass.*, 1961, 176, 432.
- Datta, D. V., and Sherlock, S., *Brit. med. J.*, 1963, 1, 216.
- Oster, Z. H., Rachmilewitz, E. A., Moran, E., and Stein, Y., *Israel J. med. Sci.*, 1965, 1, 599.

- ⁹ Bergen, S. S., Van Itallie, T. B., Tennent, D. M., and Sebrell, W. H., *Proc. Soc. exp. Biol. (N.Y.)*, 1959, **102**, 676.
¹⁰ Ahrens, E. H., jun., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J., and Blondheim, S. H., *Medicine (Baltimore)*, 1950, **29**, 299.
¹¹ Carey, J. B., jun., *J. clin. Invest.*, 1958, **37**, 494.
¹² Alva, J., and Iber, F. L., *Amer. J. med. Sci.*, 1965, **250**, 60.
¹³ Sjövall, K., and Sjövall, J., *Clin. Chim. Acta*, 1966, **13**, 207.
¹⁴ Brown, D. F., Porta, E. A., and Reder, J., *Arch. intern. Med.*, 1963, **111**, 592.
¹⁵ Fast, B. B., and Roulston, T. M., *Amer. J. Obstet. Gynec.*, 1964, **88**, 314.
¹⁶ Sneddon, I. B., *Brit. med. J.*, 1963, **2**, 405.

- ¹⁷ Holti, G., *Symposium on Candida Infections*, 1966. Edinburgh and London.
¹⁸ Warin, R. P., *Brit. J. Derm.*, 1960, **72**, 350.
¹⁹ Bolam, R. M., and Burtt, E. T., *Brit. med. J.*, 1956, **1**, 1130.
²⁰ Calnan, C. D., *ibid.*, 1964, **2**, 649.
²¹ Ive, H., Lloyd, J., and Magnus, I. A., *Brit. J. Derm.*, 1965, **77**, 229.
²² Hellgren, L., and Hersle, K., *Acta Allerg. (Kbh.)*, 1964, **19**, 406.
²³ Davis, H., *Brit. J. Derm.*, 1922, **34**, 12.
²⁴ Urbach, E., *Arch. Derm. Syph. (Chic.)*, 1942, **45**, 697.
²⁵ Winkelmänn, R. K., Vesper, L. J., and Horner, F. A., *Acta Derm. Venereol. (Stockh.)*, 1966, **46**, 279.

TODAY'S DRUGS

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

Gentamicin

This drug is marketed by British Schering Ltd. under the name Genticin.

Chemistry and Antibacterial Activity

Gentamicin was discovered in 1963 as a product of a strain of *Micromonospora purpurea* in the laboratories of the Schering Corporation, Bloomington, N.J. Its chemical structure has not been fully ascertained, but it clearly belongs to the aminoglycoside group of antibiotics. It is a basic substance consisting of two closely related components, gentamycins C₁ and C₂. Gentamicin sulphate is freely soluble in water; the solution has a pH of about 4.5 and is very stable.

Gentamicin has a similar "spectrum" to related antibiotics such as neomycin and kanamycin, but a rather greater activity than these against some species of bacteria. According to the original full description from the manufacturers' laboratory,¹ almost all enterobacteria are sensitive to it, including species of *Aerobacter*, *Escherichia*, *Klebsiella*, *Salmonella*, *Shigella*, *Proteus* (three species fully sensitive, but *P. vulgaris* less so), and *Pseudomonas*. A high degree of activity against *Ps. aeruginosa* is an outstanding property: 25 strains isolated in a London hospital were considerably more sensitive to gentamicin than to either kanamycin or streptomycin.² Among Gram-positive organisms the most sensitive are staphylococci.³ In the same London study² 102 strains sensitive and 57 resistant to neomycin and kanamycin were investigated, and with the exception of two of the resistant strains the two groups were found to be equally sensitive to gentamicin. Streptococci (except *S. faecalis*) and pneumococci are also moderately sensitive, but much less so than to many other antibiotics.

Gentamicin is bactericidal in concentrations little greater than those inhibiting growth. It is influenced by pH in the same way as other aminoglycosides, being much more active on the alkaline than on the acid side of neutrality.^{2,4} Its combined action with other antibiotics has been little studied, but a synergic effect with ampicillin has been demonstrated⁵: this is to be expected from a combination of two bactericidal substances.

Cross-resistance.—Various bacteria can be slowly trained to increased resistance to gentamicin, and they then also become more resistant to neomycin, kanamycin, paromomycin, and even streptomycin.³ Training staphylococci to resistance to neomycin or kanamycin may produce a substantial but not equal increase in resistance to gentamicin.² On the other hand natural and artificially produced resistances do not always behave in the same way, and it is clear that the former may not involve gentamicin. The sensitivity to gentamicin of strains of staphylococci resistant to neomycin and kanamycin has already been referred to: the same properties may exist in *E. coli*.³

Pharmacology

Very little gentamicin is absorbed from the alimentary tract, and the route of administration for a systemic effect is intramuscular injection. Peak concentrations in the blood are reached after half an hour to one hour, and are 2–3 µg./ml. after a dose of about 0.5 mg./kg. body weight.⁶ Larger doses up to 3.2 mg./kg. produce concentrations of 12–16 µg./ml.⁷ The subsequent fall is slow, adequate concentrations persisting for 6–8 hours. Excretion is mainly by the kidney, and it seems from rather divergent observations that at least the greater part of the dose appears in the urine. Protein binding is low, and there is no cumulative effect if renal function is normal.

Clinical Applications

Comparatively few acute and life-endangering infections have been treated with this antibiotic. One report³ records cure of *Ps. aeruginosa* meningitis in an infant, and "improvement" in two bacteraemias and three pneumonias mostly caused by the same organism. In another series of ten pneumonias (*Pseudomonas*, *Proteus*, and *E. coli*) five were cured and five improved.⁸ Cure of a *Pseudomonas* septicaemia was achieved, but the high dosage used caused complete loss of labyrinthine function.⁹ Bacteraemia accompanying *Pseudomonas* infection of burns responded to a combination of local and systemic treatment.¹⁰ The maximum dose usually given to an adult has been 75 mg. at eight-hour intervals: i.e., a total of 225 mg. daily, which is considerably less than that employed with other antibiotics of this group. Many patients have been treated with doses smaller than this: the usual limits mentioned are 1.1–1.8 mg./kg. daily: i.e., about 75–125 mg. for an adult of average weight.

Urinary-tract Infections.—Most clinical experience with gentamicin has been in the treatment of urinary-tract infections, especially when caused by *Pseudomonas* or other Gram-negative species resistant to other drugs. All the general clinical studies reported have been largely concerned with urinary infections.^{3,6,9} It is clear that gentamicin has often been effective when other treatment has failed, but, as always in studies in this field, the ultimate result has been determined by the nature of the predisposing condition. Since from this standpoint case material is so varied, comparisons between different series of results cannot usefully be made. In this series of studies no account seems to have been taken of the fact that gentamicin is more active in an alkaline medium. The difference between that at pH 8.5 and at pH 6.0 has been found to be sixteenfold²: even so this is considerably less than the difference in activity of streptomycin, which for this purpose should always be given after alkalization of the urine if necessary, but the same proceeding might well improve the results obtainable with gentamicin.

Local Application.—The application of a cream or ointment containing 0.1% gentamicin has been successful in the treatment of burns,¹⁰ bedsores,¹¹ impetigo and other pyogenic skin infections,¹² and of nasal carriers of staphylococci.¹³ Oral