Drug Eruptions

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ILACA BAĞLI DERİ DÖKÜNTÜLERİ

Bazı hastalıkların kendiliğinden iyi olabileceğini düşünerek ilaç sU-.l-tae başlamakta ac<-!*- c!mı--mt>- iz. İlaçların yaptığı pek çok deri döküntüsü tipi olup, bunlardan en sık görüleni rash'dir ilaca bağlı döküntüden şüphelenildiğinde, döküntüden önce hastanın aldığı ilaçlar dikkatle soruşturulma . .< FİÜ- :"•;!• ı oluşan allerjmin benzeri, diğer bir ilaçla da oluşabilir (Cross-allergenicity}. Kaşıntılı deri lezyonlarında yaygın olarak kullanılan antihistaminik ve lokal anestezik içeren preparatlar, kontakt dermatite neden vegin • ıı kullanılmamalıdır. İlaç döküntülerinin rne . i .:!an* kısaca; ailerjik, toxic ve ışığa bassa- olarak sınıflandırılabilir.

Allerjîk dö . ütülerde; daha önceden hassasiyete neden olan bir ilaç alma hikayesi ve ilacın k>-.il mdi ile bulgularda süratle koybolma söz konusudur.

!"Kanthematic i•'•ilintilerden, yaygıneritematözmaçulo-papüler. erupsiyon.(Resim—1) kastedilmektedir. Ampiçilli: ; upsiyonlan genellikle exanthematic olup tedavinin 5—14. günlerinde başlar.

' ' : ' :>-.!rial -ü-.!'!!!*' rin başta gelen nedenleri arasında salisilatlar gelmektedir. Aspirin, başka bir : - deıile oluşan urticariayı artırabilir.

:•-: 'tema ¡w ••. değişik hastalarda değişik görünümler verirse de genellikle ortası mor renkte ¡ •' •: kırmızı makülo-papüler deri lezyonlandır..

Eritema nodosuma yol açan ilaçlar arasında penicillin, : a : idler, salisilatlar ve barbitüratiarsayılabilir.

Üaç döküntüleri her atakta hep aynı sahada görülebilir.

Bazı ilaçlar **SLE**'a benzer bir tabloya neden olabilirler. I5vın arın başında procainamide, hy<i . ,-¡¡1, phenytoin ve primidone gelmektedir.

Bunların dışında phemphigus benleri, toxic, acneiform, lichenoid ve purpurik döküntülere neden olan ilaçlar da vardır. Uzun süreyle chlorpromazbo alanlarda, Güneş'e maruz kalaıı sahalarda >> .mentasyon olu şabilir. Beta-bloker ı practolol) alan hastaların bazılarında psoriasiform döküntüler oluştuğu bildirilmiştir

We should never forget than some diseases resolve spontaneously and that drugs should therefore be reserved for those patients who require them. Furthermore, the greater the number of drugs a patient receives at any one time the greater is the likelihood of a drug reaction — especially in the elderly patient.

The most frequent complication of drug therapy is a rash. There are many types of drug eruption and a particular drug may be cabaple of producing more than one type of eruption. Most drugs have, at some time or another, been reported as the cause of an exanthematic or urticarial eruption. Nevertheless many cutaneous reactions that are produced by drugs can have other causes also. A drug eruption may be preceded by pruritus and accompanied by fever. Nowadays, penicillins — particularly amptiictiin (Amfipen, Penbritin, Pentrexyl, Vidopen) and amoxycillin (Amoxil) — and co-trimoxazole (Bactrim, Septrin) are frequent causes of drug eruptions but it must be noted that they are extensively prescribed.

When a drug eruption is suspected, it is essentia! to enquire into the medications taken before the eruption appeared. This should include asking about proprietary preparations bought by the patient, sometimes on the advice of a pharmacist, friend or relative. Hypersensitivity to streptomycin is sometimes associated with allergy to the related antibiotics neomycin, kanamycin, and gentamicin. Cross-allergenicity exists among all penicillin derivatives as they all possess the penicillin nucleus, 6-amino-penicillanic-acid. There is also cross-reactivity between

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penicillins and cephalosporin derivatives, and about 10 % of patients allergic to penicillin are also allergic to the cephalosporins (Mawer, 1977). No penicillins should be given to patients who have a clear history of hypersensitivity either to benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V) or to those who respond with urticaria or anaphylaxis to any penicillin since these Type I reactions are associated with hypersensitivity to the penicillin nucleus or to its breakdown products.

Topical preparations containing antihistamines and/or local anaesthetics are extremely popular for the control of 'itch' and can often be purchased without a prescription. However, neither antihistamines nor local anaesthetics (excluding lignocaine) should be applied to the skin because of the real danger of their causing a contact dermatitis. People whose epidermis does become sensitized in this way may develop a widespread eruption if at some future date they receive these or related drugs systemically. For instance, a patient sensitized to diphenhydramine hydrochloride by its topical application (Caladryl lotion) may experience a severe eczema if he takes the oral diphenhydramine-containing hypnotic Mandrax of one of the many diphenhydramine-containing cough preparations. Derivatives of para aminobenzoic acid such as containing hypnotic Mandrax of one of the many diphenhydramine-containing cough preparations. Derivatives of para aminobenzoic acid such as benzocaine and amethocaine are strong sensitizers yet they are present in commonly prescribed antipruritic ointments, throat lozenges and throat sprays. The sensitized individual may respond to an injection of the related local anaesthetic procaine with allergic swelling at the site or even urticaria and may also show cross-reactions with hair dye (paraphenylenediamine) and sulphonamides.

Mechanisms

For convenience, the causative mechanisms of drug eruptions may be classified as allergic, toxic, and light-sensitivity.

Allergic

Evidence of drug allergy may be suggested by a history of a previous sensitizing dose, the appearance of a reaction to a small dose, and the rapid disappearance of symptoms and signs on discontinuing therapy.

Unfortunately in practice the situation is not so straightforward. Thus a previous sensitizing dose may not be necessary if the drug is a foreign protein or if large molecular weight impurities are present, and with long-acting drugs, such as some penicillin preparations, a single administration may be sufficient to provide both sensitizing and challenging doses.

There are many types of allergic eruption.

Exanthematic. — The term exanthematic indicates widespread erythematous maculo-papular eruption (fig. 1) which may be morbilliform. Ampieillin eruptions are usually exanthematic and appear 5 to 14 days after starting treatment. If patients treated for infectious mononucleosis are excluded, ampieillin rashes occur in from 3 to 8 % of those receiving the antibiotic (British Medical Journal, 1975). Almost all patients with infectious mononucleosis given ampieillin early in the course of their infection develop a distinct irritant coppercoloured purpuric maculo-papular eruption over the trunk and then the limbs (fig. 2) 7 to 10 days after starting antibiotic therapy the same eruption may occur, but much less commonly, with other penicillins.

Maculo-papular erythematous eruptions in patients on co-trimoxazole therapy are usually due to the sulphamethoxazole component but the trimethoprim can also be responsible for rashes of this nature.

Exanthematic eruptions can occur with maprotiline hydrochloride (Ludiomil), a tetracyclic antidepressant with structural similarities to the tricyclic antidepressants (for example, imipramine hydrochloride).

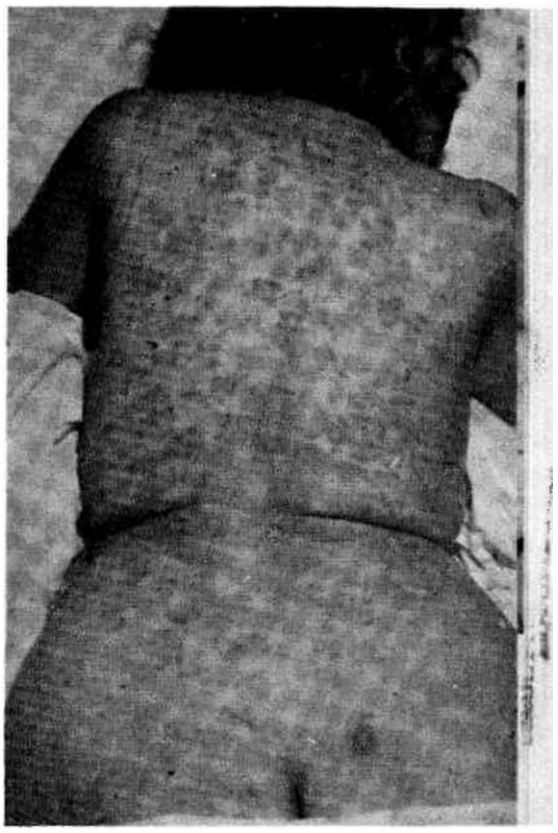


FIG. 1. — Exanthematic eruption due to sulphamethoxazole (in Septrin)

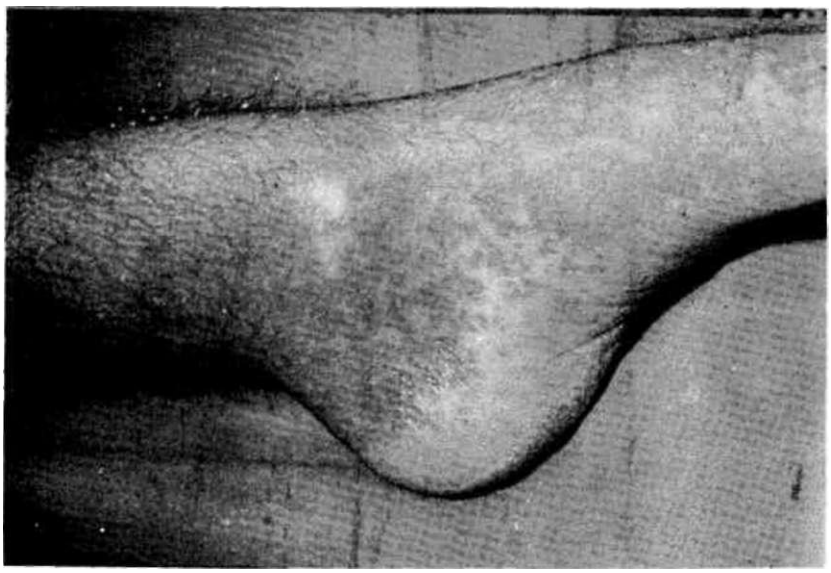
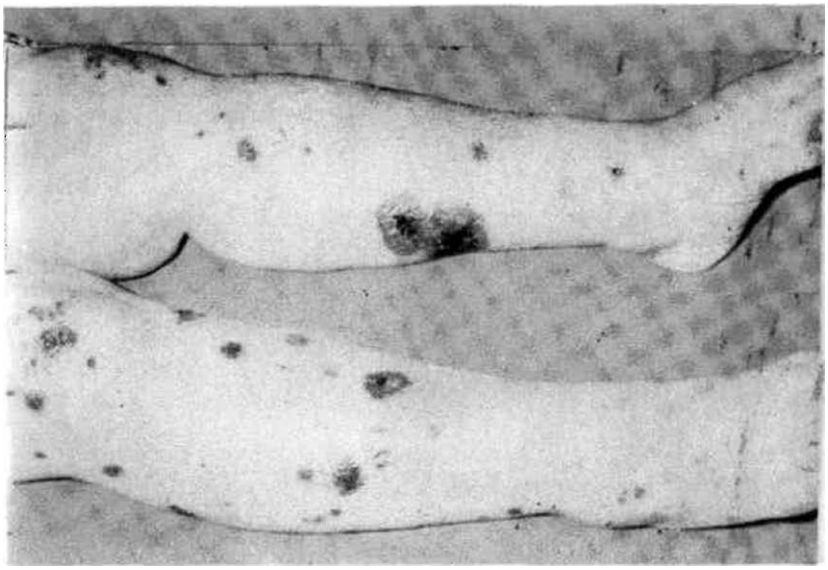


FIG. 2. — Purpuric ampicillin rash in a patient with infectious mononucleosis



FÍG. 3. — Purpura due to frusemide

Urticarial. — Ordinary urticaria is characterized by the appearance of irritant transient pink weals. If it becomes widespread and involves the mucosae, treatment should be started promptly.

An urticaria due to penicillin may present as long as four weeks after the last dose of penicillin, and persistence of a penicillin urticaria may be due to the occasional presence of minute amounts of penicillin in dairy products or to the production of penicillanic acid by fungi in the skin.

A patient who develops urticaria with one barbiturate should avoid other barbiturates. Salicylates are a common cause of urticaria and aspirin can exacerbate an urticaria of some other origin.

Recurrent urticaria due to food or drugs may sometimes by induced by preservatives or azo dyes in these commodities (Michaelsson and Juhlin, 1973).

Purpuric. — Meprobamate purpura is non-thrombocytopenic and follows in the train of irritation, malaise, fever, and flexural erythema — it may well be a toxic rather than an allergic purpura. Meprobamate (Equanil, Milonorm, Miltown) is chemically related to carbromal: the hypnotic Carbrital contains carbromal. Purpura caused by thiazide diuretics (and the structurally similar drug frusemide |LasixJ) may either be thrombocytopenic or non-thrombocytpenic; when the legs are already oedematous, as is

often the case, blisters and necrotic ulcers may compicate the purpura (fig. 3). Billings and his colleagues (1974) described three patients with vasculitis due to alclofenac (Prinalgin).

Erythema multiforme. — Clinically, the skin lesions in different patients may differ and the mucosae may be involved. Red round maculo-papular skin lesions with a purplish centre, which is often vesicular, are common (erythema iris — fig. 4). However, larger maculo-papular lesions, which may become bullous, another from of presentation (fig. 5).

The most severe form of bullous erythema multiforme (Stevens-Johnson syndrome) has been reported with sulphonamides, barbiturates, chlorpropamide (Diabinese, Melitase) and suspected with diflusinal (dolobid) (Hunter et at., 1978), but it is uncertain whether the mechanism is allergic or toxic.

Fryiff ma nodosum. — This presents as tender discrete nodules, few or many, commonly over the shins but sometimes more extensively, Penicillin, sulphonamides, salicylates and barburates are cause.

Fixed. - In a fixed drug eruption the same limited areas are involved in each attack. Lesions are circular, erythematous, and either maculer or slightly raised with blister formation. They may be single or multiple, and they resolve often leaving brown melanin pigmentation. The lesions will recur within a few hours of exposure to the drug. Phenolpthalein is the common offender and may be contained in laxatives, icing sugar, sweets, wine and toothpaste.

Systemic lupus erythematosus (SLE). — This may be precipitated by the administration of drugs or certain drugs may produce an SLE-like picture. The drug-induced syndrome accounts for about 2 % of all cases of SLE.

Laboratory tests that are positive include the presence of antinuclear antibodies, leucopenia, LE cells and an elevated sedimentation rate in some cases antinuclear antibodies appear in the absence of any clinical manifestations. Frequent clinical manifestations include polyarthritis, fever, pericardial and pleural effusions and lymphadenopathy. Drug-induced SLE seldom results in renal or cerebral disease and has a lower incidence of cutaneous manifestations than the spontaneous form; males are affected as often as females and the condition is usually reversible when the drug is discontinued. Except for anticonvulsant-activated lupus, drug induced forms usually occur in older individuals rather than in the young women who are typically affected by SLE. The most frequent drug incriminated at present is procainamide (Pronestyl) but other wellknown drug inducers include hydralazine (Apresoline), phenytoin (Epanutin) and primidone (Mysoline).

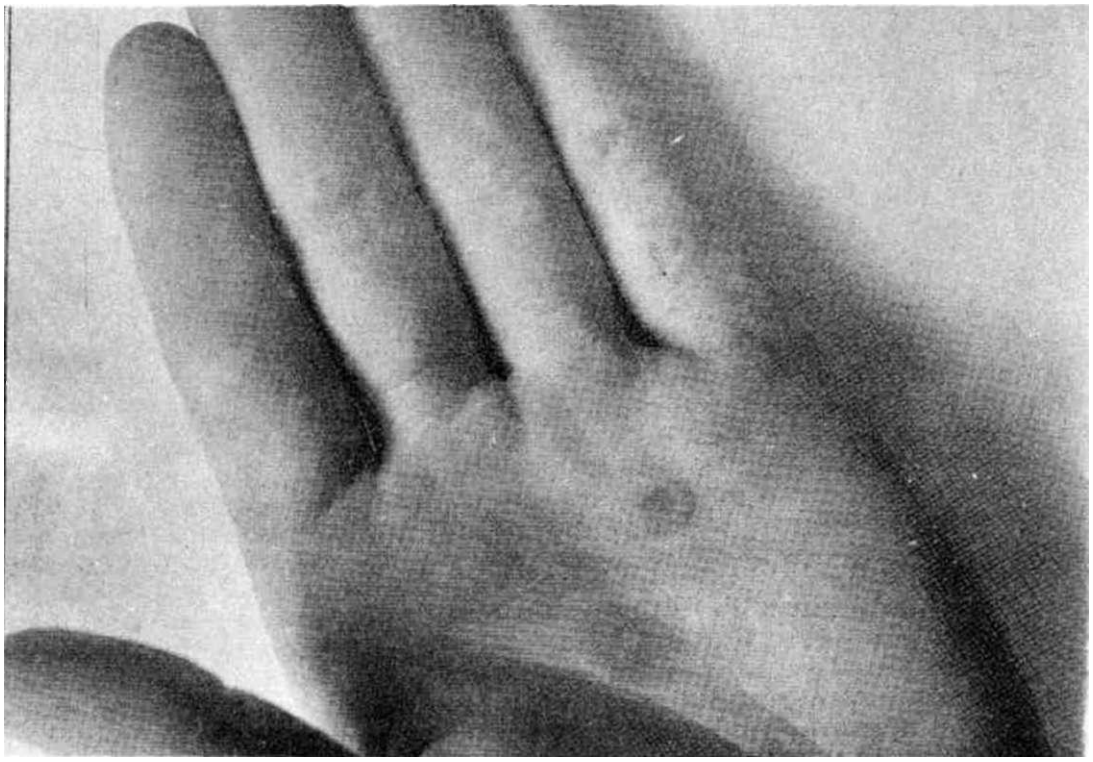


FIG. 4. — Target of lesions of erythema multiforme iris on the palm

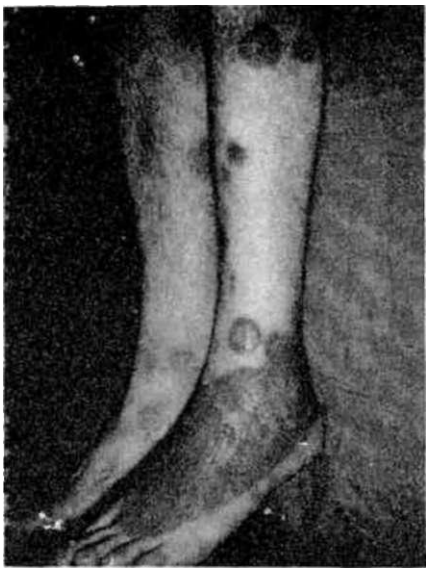


FIG. 5. — Large erythematous plaques, some with obvious blister formation, of severe erythema multiforme due to sulphamethoxazole

Eczematous. — Both ethionamide (Trescatly) and methyldopa (Aldomet, Dopamet, Medomet) eczemas are seborrehoeic in type, the former mainly involving the forehead, the latter being more widespread.

Thiazide diuretics (which are sulphonamide derivaties) may also produce eczematous eruptions if given to patients sensitized by topical use of sulphonamides.

Pemphigus. — This severe epidermal blistering eruption can be induced by penicillamine (Cuprimine, Depamine, Distamine), rifampicin (Rifadin, Rimactane), phenylbutazone (Flexazone, Butacote, Butazolidin, Butazone), and levamisole.

Toxic

Toxic reactions to drugs depend on the dosage of the drug and correlate with the known pharmacological properties of the causative agent. However, in some persons, including the elderly, such reactions may occur with therapeutic doses. Dosage of anticoagulants, and of cytotoxic drugs with their well-konwn effects on either the bone marrow or circulating blood cells, must be calculated with special care.

Acneiform. — Androgenic and anabolic steroids, corticotrophin, corticosteroids (fig. 6), iodides and bromides are causes. Phenytoin an phenobarbitone may aggravate pre-existing acne.

Lichenoid. — A lichen planus-like eruption can occur with chloroquine (Avloclor, Nivaquine, Resochin), gold and methyldopa. Lichenoid eruptions have also been described with beta-blocking agents including practolol (Eraldin), propranolol (Inderal), oxprenolol (Trasicor) and more recently labetalol (Tradate) (Gange and Wilson Jones, 197S Brandford et al., 1978).

Purpuric. Apart from anticoagulant overdosage, combination of certain drugs with warfarin (Marevan) can result in purpura (by drug interaction). Such drugs include salicylates, phenylbutazone, **Clofibrate** (Atromid-S) and naproxen (Naprosyn) which displace warfarin from serum albumin. Oral antibiotics **which** disturb the endogenous production of vitamin K **by** intestinal bacteria, can produce purpura in patients on warfarin therapy.

A severe haemorrhage may be the result of discontinuing barbiturates, dichloralphenazone (Welldorm), Mandrax (methaqualone and diphenhydramine), glutethimide (Doriden) or griseofulvin (Fulcin, Grisovin) whilst remaining on oral anticoagulants. This is because the former drugs stimulate the microsomal enzymes and thus accelerate the degradition of the anticoagulant the drug interaction takes place during metabolism in the liver.

Any drug that causes aplastic anaemia can be implicated in thrombocytopenia but some direct marrow toxins — for example, antimitotic agents, gold, sulphonamides — can have a selective effect on the platelets producing thrombocytopenia and purpura. Phenylbutazone and oxyphenbutazone (Tandacote, Tanderil), indomethacin (Imbrilon, Indocid), phenytoin sodium, methoin (Mesontoin), troxidone (Tridione), carbamazepine (Tegretol), chlorpromazine (Largactil) and other phenothiazines, chloroquine are well-recognized causes **of** aplastic anaemia.

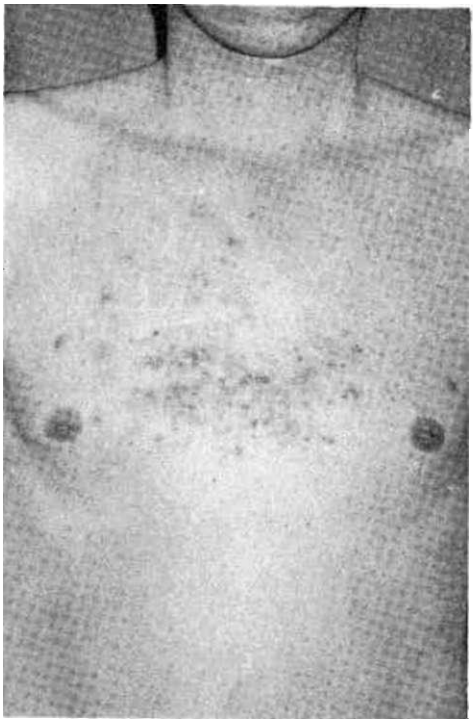


FIG. **6.** — Steroid acne in a man of 31. He developed acne localized to the chest whilst receiving oral prednisolone

Pigmentation, — Slate-grey pigmentation of ligh-exposed areas occurs with prolonged high dosage of chlorpromazine and later the skin may assume a marked purple tint. Hydantoinates produce facial pigmentation (melanin) in about 10 % of those receiving the agents Hyperpigmentation is common with long-term therapy with corticotrophin or its synthetic analogues (Synacthen depot, Cortrosyn depot).

Exfoliative dermatitis. — It is important to remember that many drug eruptions may evolve into an exfoliative dermatitis if severe enough or if the drug is continued after the original eruption has begun.

Mercury is little used therapeutically now but some topical applications containing it are unfortunately still prescribed and thus the danger of mercury absorption and poisoning still exits.

Corticosteroid-induced. — The easily traumatized skin heals slowly in those on systemic (fig. 7) or topical corticosteroid therapy. Topical corticosteroids, particularly the more potent ones, can give rise to striae, which are usually irreversible, and skin atrophy, which is often reversible. Both epidermal and dermal atrophy with increased skin fragility, telangiectasia, poikilodermatous change, purpura of senile type, and loss of subcutaneous tissue can occur. Even smal quantities of a potent steroid (a potent steroid is a steroid preparation stronger than hydrocortisone cream BPC or hydrocortisone ointment BP) applied to the face for prolonged periods can produce marked atrophy of the skin.

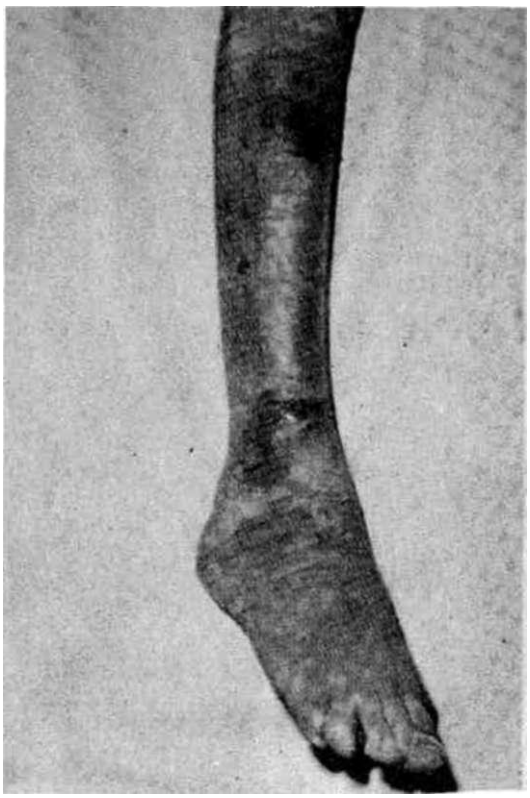


FIG. 7. — Boomerang-type steroid ulceration produced by trauma in a patient on systemic corticosteroids. Steroid purpura is also present.

Hirsuties is also occasionally seen at the site of prolonged steroid application and infection is a not uncommon side effect in view of the fact that steroid inhibit the normal inflammatory response. Suppression of the pituitary-adrenal axis (which may have secondary effects on the skin) following percutaneous absorption of potent and usually fluorinated steroids is well recognized, it is usually temporary but using more than 30g/week of a potent steroid in an adult (or less in a child) for prolonged periods is inadvisable.

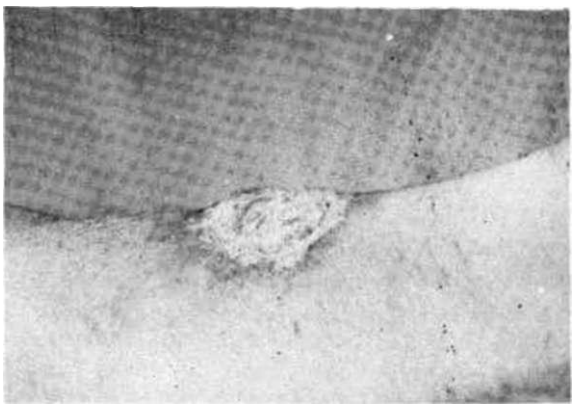


FIG. 8. — Bowen's disease (intraepidermal carcinoma) overlying the Achilles tendon regien

Oncogenic. — Many older patients received trivalent arsenic medication years ago in tonics, for psoriasis, epilepsy or acne. Warty keratoses, Bowen's disease (fig. 8) and even internal carcinoma may occur years later as a complication of this therapy.

Psoriasiform. — A psoriasiform-like eruption (fig. 9) in patients receiving the beta-blocking agent practolol was reported by Felix and his colleagues (1974). Other eruptions were seen with the drug and adverse reactions could also affect the eyes, oral and nasal mucous membranes, ears and peritoneum. Psoriasiform eruptions with other beta-blockers — for instance, oxprenolol (Holt and Waddington, 1975 Levene and Gange, 1978) and propanolol (Jensen et al., 1976) — have also been reported.

Alopecia. — Scalp hair fall is a wellknown and usually reversible side effect of certain drugs including anticoagulants, cytotoxics, carbimazole (Neo-Mercazole), levodopa (Berkdopa, Brocadopa, Larodopa, Levopa), sodium valproate (Epilim); it may laso follow the use of oestrogen-containing oral contraceptives.

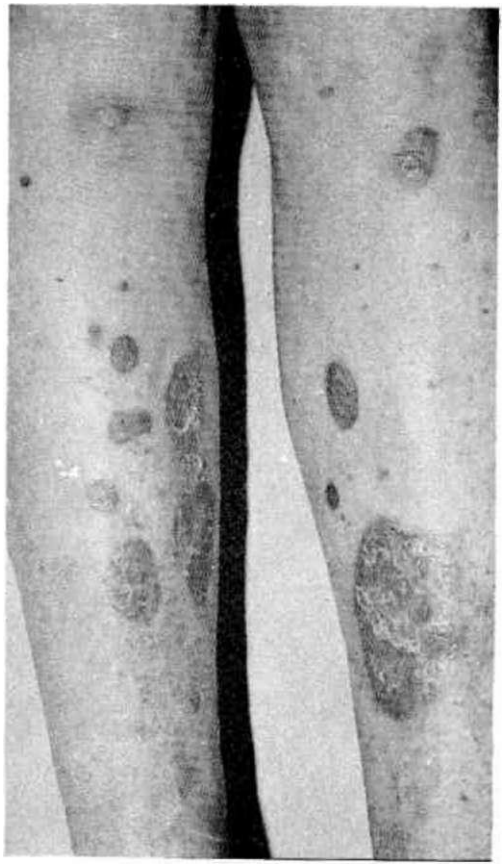


FIG. 9. — Practolol psoriasis

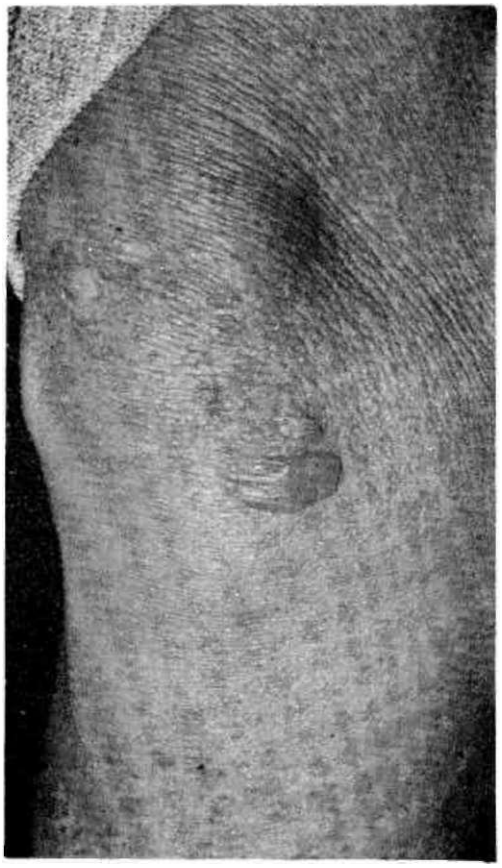


FIG. 10. — Blistering phototoxic reaction due to nalidixic acid

Light sensitivity

On exposure of the skin to light, some drugs give rise to a phototoxic reaction with urticaria, erythema, oedema or blister formation (fig. 10) whilst other can produce a photo-allergic response manifested as an eczematous or lichenoid eruption.

Drugs with phototoxic potential include chlorpromazine, nalidixic acid (Negram) and tetracyclines. Demethylchlortetracycline (Ledermycin) seems to be the tetracycline that most frequently produces this reaction.

Drugs with proto-allergic potential include chlordiazepoxide (Librium), chlorpromazine,. protriptyline (Concordin), diphenhydramine, promethazine (Phenergan), griseofulvin, sulphonamides and their derivatives such as thiazides and chlorpropamide.

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