this type have had adverse effects in large doses or in chronic usage.

Liquid paraffin, once thought harmless, has now earned itself a bad name. It may impair absorption of fat-soluble vitamins, leak from the anus, be aspirated into the lungs to cause lipoid pneumonia, and be absorbed (especially when given in emulsion form) and be deposited in body tissues. These risks are greater in the elderly, and its use should be avoided—at least as a regular habit.

Rectal Evacuation.—Suppositories of glycerine or bisacodyl are sometimes helpful. The latter may cause local discomfort. Enemas should be small-volume solutions: oil for softening and saline for evacuation. Disposable hypertonic saline enemas are convenient, gentle, and reasonably effective. Soap should never be used in enemas.

Manual Removal of Faeces.—This may be required in the initial treatment of faecal impaction: oral laxatives cannot be expected to clear the bowel when the lower end is plugged so effectively with accumulated faeces. Suppositories and enemas may also fail in this situation, although a small-volume enema should be tried as the first step, and this may be repeated daily, its efficacy being judged by repeated digital examinations. With soft faecal impaction bisacodyl suppositories may also be successful: one should be used high up in the rectum and repeated once if there has been no result after two hours.

Large volume washouts with saline may be needed to clear the lower bowel if impaction is high above the rectum.

In the management of faecal incontinence, since most cases are due to spurious diarrhoea associated with faecal impaction, treatment of the latter will deal with the incontinence. For the neurogenic type of faecal incontinence, a regimen of Mist. kaolin et morph., 15 ml every morning, alternating with Senokot 1-2 tablets every night has been advocated by Jarrett and Exton-Smith.[10] In such cases it is essential to exclude the presence of faecal impaction.

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Today's Treatment

Diseases of the Skin

Drug Ill Effects on the Skin

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No systemically administered medication escapes the stigma of causing a rash. Drugs have actions, wanted and unwanted, and the commonest complication of drug treatment is a rash. It may be associated with a systemic disorder (perhaps a third of patients have some sort of kidney dysfunction), but practically always this is minor.

The mechanisms of most drug rashes are mysterious. Allergy has rarely been proved in the individual case. Most of the many diagnostic tests designed so far rely on an immunological system and therefore will not be indicators of other pathological processes. If a simple infallible, rapid, and humane diagnostic test could be devised to implicate the drug, it would transmute the subject of drug eruptions from mythology to science. The drug, so often a scapegoat, might then be absolved when, say, an intercurrent minor virus infection should have been blamed.

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Diagnostic Considerations

The diagnosis is necessarily based on supposition not science. Two main aspects are usually considered: firstly, the timing of the administration of the drug related to the onset of the rash; and secondly the odds. This is a type of league table which balances the drugs that are top suspects (table I) against the form of the eruption. Table II classifies other types of eruption, whose pathogenesis is almost entirely unknown.

The reported frequency of drug rashes depends upon the vigilance of the observers, the prescribing habits of the doctors, the self-medication urges of the patients themselves, and (of increasing importance), the unknowing exposure to drugs, as, for example, quinine in beverages such as Bitter Lemon.

The apparent incidence of rashes may be misleading. Plainly the antibiotics labelled "high risk" are prescribed for more patients than are the hydantoins, which I have listed under "common offenders"—and yet hydantoin may be the more active culprit causing a great diversity of rashes in a higher proportion of patients for whom it is prescribed.

The properties of the drug itself, its impurities, the excipients, and its metabolites will need to be considered. The antigenic determinants may be relevant and may number at least three in sulphonamides and over a dozen in the penicillins.

The type of rash is important diagnostically. An acute erup-

TABLE I—*Causative drugs*

High-risk Drugs	*Common Offenders*
Antibiotics (notably the penicillins and especially Ampicillin)	Hydantoin and derivatives
Sulphonamides (sulphones, sulphonylureas, benzothiadiazines)	Phenylbutazone, indomethacin
Barbiturates	Heavy metals
Phenothiazines	Quinidine
Cytotoxic agents	Phenolphthalein
	Sera (for example, antilymphocyte serum)

TABLE II—*Odd and Rare Skin Reactions from Drugs*

Leukaemoid, lymphoma-like (hydantoins; sulphonamides; and para-amino salicylic acid when used in the treatment of tuberculosis)

Bullous (halogens; narcotics; non-specific pressure damage, and ischaemia due to deep coma and lack of movement); pemphigoid-like eruptions: bullae may be seen in exanthemas; eczematous; light induced eruptions; cutaneous hepatic porphyria

Lichen-planus-like or lichenoid (antimalarials, phenothiazines, heavy metals). Residual hyperpigmentation may cause poikilodermatous signs

Eczematous (inanediones; methyldopa; and gold); as a later stage, 10-20 days, after exanthem; it can progress to exfoliative dermatitis or erythrodermia; systemic ingestion of a drug that has already caused a contact dermatitis. Usually this type of eruption is caused by skin contact with the drug

Light-induced: toxic or allergic mechanisms may be indistinguishable and both may operate
(1) Phototoxic (demethylchlortetracycline, griseofulvin, nalidixic acid).
(2) Photo allergic (sulphonamides; and their derivatives; phenothiazines; some antihistamines)

Haemorrhagic sloughing of skin—deep and widespread lesions at start of anitcoagulant treatment (inanediones, courmarins, never heparin)

tion caused by a drug given systemically will attack primarily the superficial blood vessels of the dermis. Since the epidermis is affected only secondarily owing to the proximity of the angiitis to the basal cell layer of the epidermis the rash will rarely if ever be scaly initially. This contrasts with a contact allergy from a drug touching the skin, when a scaly, vesicular, red, dermatitis results because the epidermis is affected early and its maturation is disordered.

Diagnostic Difficulties

Diagnostic difficulties abound. Four dogmatic statements may be made:

(1) No rash is pathognomonic for a particular drug.

(2) An identical rash may be seen frequently with totally unrelated drugs having no chemical or pharmacological similarity.

(3) Completely different cutaneous disorders may be seen in patients on precisely the same drug. Hydantoin is a notable example.

(4) The same rash seen on a particular patient at a different time apparently may have been provoked by completely unrelated precipitants—a drug, an infection, vaccination, or cancer.

The commonest types of acute eruption presumed to be due to a drug come under the heading of exanthemas. These eruptions are entirely non-specific aetiologically: an identical rash may occur with infections or neoplasms. The former may be caused by bacteria, viruses (vaccinia and herpes simplex are the commonest), rickettsia, mycoplasmata, fungi, and yeasts. Patients with cancer may develop exanthemas 6-12 days after treatment with radiotherapy or with cytotoxic drugs. It is difficult to know whether to blame the drug or the patient or his disease. A second course of the drug to treat metastases may cause a recurrence of the rash within hours. This might be a toxic effect resulting from products of the destroyed cancer cells rather than be of allergic origin. Exanthemas may even be the presenting sign of a cancer. This emphasizes the importance of investigating this variety of eruption and not just dismissing it as "? drug-eruption."

Physical Signs

At the bedside it is convenient to consider adverse drug actions under two headings: predictable; and idiosyncratic or completely unpredictable effects peculiar to the patient—the acute drug rashes.

PREDICTABLE ILL-EFFECTS

Disorders of Pigmentation

There are many types of pigmentary disorders, each with its own special features depending on the drug and the nature and depth of the pigments in the skin. The commonest drugs to cause pigmentation are the tranquillizers: the "purple people" were on large doses of chlorpromazine. Related phenothiazines may cause similar discolorations. Heavy metals cumulatively pigment the skin by various mechanisms. The most commonly implicated metals are silver, gold, bismuth, and arsenic. Important today are the oestrogen-containing hormonal contraceptives, which stimulate melanocytes—particularly the larger melanocytes situated on the forehead and cheeks. The effects of this are not often reversible (chloasma or melasma). Anticonvulsants such as phenytoin, the chemically similar nitrofurantoin, some cytotoxic agents, corticotrophin, cathecholamines, bromides, and antimalarials (mepacrine—yellow; chloroquine—blue or black) are offenders. Paradoxically some of the drugs that cause hyperpigmentation may cause loss of pigment: chloroquine, for example, will pale the hair.

Alopecia

Several drugs will cause hair loss. The mechanism may be quasi-physiological and reversible—as with an oral contraceptive drug (postpartum telogen effluvium effect)—or direct toxic action on the dividing epidermal cells of the hair follicle—as with the cytotoxic group of drugs; thallium and some of the heavy metals; anticoagulants (coumarins and heparin); antithyroid drugs (carbimazole and thiouracil); and hydantoins.

Acne and Acne-like Eruptions

Acne and acne-like eruptions will result from systemic administration of hormones (corticosteroids, corticotrophin, and sex hormones), barbiturates, and antiepileptic drugs, particularly hydantoin. Patients without a genetic tendency to acne will not develop it on taking drugs. The acne-like lesions and granulomas provoked by halogens may be recognized because of the absence of the comedone, the hallmark of true acne.

Itch

Several drug eruptions may cause some degree of pruritus. Indeed, the patient may complain of itch without any obvious eruption, particularly during treatment with drugs causing liver-cell damage or cholestasis, and also with oral contraceptives, opium alkaloids, and similar related substances; and chloroquine. Pruritus ani may be drug-induced from superinfection with candida owing to an ecological imbalance of the gut microorganisms after systemic administration of broad-spectrum antibiotics or oral contraceptives.

ACUTE DRUG RASHES

Acute drug rashes are the untoward idiosyncratic acute vascular reaction patterns that develop in a few patients. The mechanism is always tacitly assumed to be allergic but it is seldom proved to be immunological. The rashes with the penicillins and gold, however, most probably are allergically induced.

UNPREDICTABLE ILL EFFECTS: ACUTE DRUG RASHES

Urticaria

The common variety of urticaria causing large weals the size of

thumb prints is invariably blamed by doctors (and patients) on "allergy." Certainly an allergic reaction will be mediated by the release of certain vasoactive agents, including histamine, from mast cells; and urticaria is the result of increased vasopermeability and vasodilatation. The alkaloids and the morphine group, however, are nonspecific histamine releasers due to their physicochemical nature. Thus any patient with urticaria should not take them and should in addition restrict drinking coffee and tea. Angio (neurotic) oedema maybe regarded as a severe form of common urticaria affecting the upper respiratory tract and face. One of the major signs of serum (drug-induced) sickness is an urticaria but the eruption is part of a general systematized upset with fever, arthralgia, asthma, and protein uria. This well-studied phenomenon is one of the few instances where a drug, often an antibacterial agent, can be presumed to have provoked circulating immune complexes.

The Exanthemas

Usually the exanthemas may be classified on the clinical signs but the morphology of some eruptions may straddle two or more groups. Histopathological examination of the skin, with histochemical or fluorescence microscopy in lupus erythematous, can make the diagnosis more precise. One would expect to see an upper dermal angiitis affecting particularly the venules. The infiltrate may comprise lymphocytes, eosinophils, and in the more severe cases polymorphonuclears. Diagnostic helps to establish "drug eruption" include an eosinophilia and a basophilopenia, low serum complement, and, in addition, antinuclear factors may be present without true lupus erythematosus. A transient proteinuria is common. Challenge with suspected drugs may sometimes be undertaken, particularly in the fixed drug eruption. The eruptions may be listed as follows in order of frequency:

(1) Toxic erythema,
(2) Erythema multiforme,
(3) Miscellaneous.

Toxic erythema is morbilliform or measles-like, usually centrally distributed but possibly universal. The signs may overlap with the urticarias, in which case the rash may be itchy. Sometimes parts of the eruption may resemble erythema multiforme. The commonest cause is the penicillins—notably ampicillin. When the patient has been given ampicillin (often for an undiagnosed sore throat and usually unnecessarily) and happens to have glandular fever, then a rash almost inevitably occurs. The rash from ampicillin may not recur on readministration of the drug so the toxicity and allergenic properties of the drug itself may be questioned and impurities from the manufacturing process (now improved) could be held to have been responsible. Furthermore, the toxic erythema of ampicillin is thought to be specific for ampicillin itself and not to indicate that the patient is sensitive to all penicillins.

Erythema multiforme presents as circular raised red lesions, which are more profuse on the peripheries. The severe form may be bullous. Rarely mucous membranes are affected (called by some Stephens-Johnson disease), when the patient can be severely ill. Sulphonamides are the main offenders.

The miscellaneous group comprises some well-defined clinical signs, each given descriptive names but possibly varying in pathogenesis.

Erythema Nodosum.—Smoothly raised red nodules which may be so tender as to be thought infective, most frequently situated on the shins. The eruption has been assumed, possibly correctly, to be an immunological response. The drug itself could be less at fault than the underlying disease which is often caused by a microorganism. On readministration of the suspect drug the eruption has not been seen to recur.

Fixed Drug Eruption.—Circular, macular, or slightly raised, lesions, may be solitary or numerous. When acute they are red and may be blistered. They resolve leaving an obvious brown pigmentation due to dermal melanin deposition. The lesions recur within an hour or two of re-ingestion of the drug, nearly always in precisely the same areas, but occasionally at sites closely adjacent.

The common offenders in fixed drug eruptions are the barbiturates, phenolphthalein, and antibacterial drugs, but the incidence in a community will depend upon prescribing patterns.

Cutaneous Necrotizing Angiitis (Venulitis).—Histopathological examination shows a venulitis of upper dermal blood vessels. This nonscaly rash may have very many patterns ranging perhaps in the same patient from urticaria to indolent necrotic ulcers. The eruptions have been given names, many of them quasi-descriptive, or implying an (unproved) aetiology or pathogenesis, and all of them confusing. There is ample evidence that eruptions are precipitated by an immunological response since host immunoglobulins and complement may be traced in and around the capillaries and superficial skin venules. In a few cases an antigen, a microorganism, has been identified precisely but the evidence to implicate a drug is frequently solely circumstantial.

Cutaneous Polyarteritis Nodosa.—The cutaneous signs may be very similar to those of necrotizing angiitis, and indeed so also may be the pathogenesis. At the moment most consider it to be a separate disease. Usually it does not affect the internal organs. Perhaps an increase of coagulability of blood due to depression of fibrinolysis (a feature that may be exaggerated by the corticosteroids so often used for its treatment) may cause the arteritis, alternatively it may be secondary to a less obvious venulitis.

Drug-induced Lupus Erythematosus.—Clinically identifiable signs develop often in the light-exposed areas on the face, neck, and dorsa of the hands but the precise influence of ultraviolet in any patient may not be clear. L.E. cells may not be seen in the milder cases, but antinuclear factor will be found, and this latter test is highly sensitive but poorly specific. A characteristic histopathology will be seen. Other indications of systemic lupus erythematosus may be lacking—such as the typical immunohistopathological signs on skin microscopy, low serum complement, light chains in the urine, tubular virus-like inclusions in leucocyte and endothelial cells—so that the pathogenesis may be different. The peculiar pharmacological properties of the drug or an immune response which in its turn precipitates the lupus erythematosus could provoke antinuclear antibody formation so that the nuclear components of cells are altered (hydralazine, isoniazid, anticonvulsants, and procainamide). Alternatively, antibiotics and antibacterial substances, oral contraceptives, antithyroidal drugs, practolol, and other newer medicines may provoke an allergic reaction and start the disease process in the genetically susceptible. The prognosis for drug-induced lupus erythematosus often is far less grave than in true L.E.: complete recovery is common.

Toxic Epidermal Necrolysis ("Scalded Skin Syndrome").—A rare but sometimes lethal complication seen in adults. Part or whole of the depth of the epidermis floats off exposing vast weeping areas so that the patient has to be treated as one severely burned. Identical clinical signs are seen in children when it is vital to investigate for a cutaneous staphylococcal infection.

PURPURA

The traditional clinical division of the purpuras into the thrombocytopenic and vascular damage types is convenient, but even so both varieties may coincide; with cytotoxic agents, for example, it would be difficult to differentiate between them. Allergic mechanisms may be demonstrated in platelet disorders in some patients on quinine, thiazides, para-amino salicylic acid, meprobamate, and carbromal. The participation of the vascular endothelium is suspected but whether the damage to this is due primarily to an immunological or a toxic response is not known. Carbromal gives a characteristic rash which is considered pathognomonic by some but it mimics the "pigmented purpuric" group of eruptions that occur without known cause. Any of the exanthemas may be purpuric, particularly in the dependent areas.

The Future

This article has been written from the point of view of the drug and the rash. Scant attention has been paid to the patient, his genetic make-up—as it might relate to his innate susceptibility to a drug (pharmacogenetics)—his age, whether he is atopic, and his complex chemical environment.

His environment will include chemical additives in foodstuffs, inhalants, the "harmless" excipients and colouring matter in the medicine, and other drugs and their metabolites—a hospital patient may have been committed to a dozen or more of these. Frequently all drugs are stopped when the rash is noticed without regard to which are likely to have given the rash or whether the patient will come to harm with the rash rather than without the benefit of the treatment. Drug interaction is a subject of prime interest. An alteration in the drug activity, as in the anticoagulant action of coumarins when the patient is being treated concurrently with certain other drugs, may often be anticipated. The drug itself may have a variety of pharmacological effects on completely different tissues and enzyme systems simultaneously.

Can a patient, by definition, be considered a normal control test subject? How does his disease influence the action of the drug? An antibiotic may destroy micro-organisms rendering them antigenic—for example, haemophilus, streptococcus, and mycobacteria—or toxic by liberating chemicals and products of their disintegration. Glandular fever (ampicillin), systemic lupus erythematosus, and cutaneous hepatic and mixed porphyria, are known to lead to the development of an eruption when taking some drugs. Acute intermittent porphyria has no skin manifestations but dangerous acute attacks may be drug provoked and erythropoietic protoporphyria causes a photo-induced eruption worsened by hepatotoxic drugs.

Drugs are blamed all too often by doctor and patient for causing rashes. Much new knowledge is required before the diagnosis of "drug-induced rash" can be made honestly and confidently; only then will it be possible to remove the iatrogenous slurr from an innocent efflorescence. There have been many cases of readministration accidentally or electively of a drug presumed to have caused a rash and yet the patient has remained unaffected.

Any Questions?

We publish below a selection of questions and answers of general interest

E.E.G. Follow-up Idiopathic Epilepsy

Is an E.E.G. follow-up necessary in the management of chronic idiopathic epilepsy, and if so, how often should the E.E.G. be done?

If the patient was adequately investigated when his epilepsy first appeared then no further E.E.G. is necessary. But, if at any time over the years there is a sudden deterioration or change in the character of the fits then further investigation, including an E.E.G., is indicated.

Tinted Glasses for T.V. Viewing?

Can tinted glasses play any significant role in the prevention of ocular fatigue caused by television viewing?

Television may cause ocular fatigue because of the long period in which the eyes remain looking at the same point, with very little variation in the direction of gaze. Fatigue may also result from too high a contrast between the light from the screen and dim background illumination. The solution to the latter problem is to raise the general illumination of the surroundings rather than to reduce the luminance of the screen by wearing dark glasses.

Phenytoin and Carbamazepine Combined

An epileptic whose fits had been controlled for the past 20 years by phenytoin sodium developed trigeminal neuralgia. Carbamazepine was substituted for phenytoin with benefit to the neuralgia but the fits returned. Is there any reason why phenytoin and carbamazepine should not be given in combination?

Phenytoin and carbamazepine can be given in combination. Many epileptics are on both drugs. However, as carbamazepine reduces the amount of phenytoin in the circulation by causing a more rapid breakdown of the drug[1] the dose of phenytoin must be increased or else another anticonvulsant tried. There are interactions of this sort between many anticonvulsants. The proof of the pudding is in the eating: varied doses or various anticonvulsants, or both, should be given. Nowadays the larger hospitals can estimate the amount of anticonvulsants in the blood.

[1] Hansen, J. M., Siersbaech-Nielsen, K., and Skovsted, L., *Clinical Pharmacology and Therapeutics*, 1971, **12**, 539.

Notes and Comments

Control of Menopausal Flushes.—Dr. J. R. CLAYDEN (Holmfirth, Yorkshire), and Dr. J. W. BELL (Medical Adviser, Boehringer Ingelheim Limited, Bracknell, Berks) write: With reference to the answer to this question ("Any Questions?" 9 June, p. 608) we should like to draw the attention of your correspondent to recent work concerning the use of clonidine hydrochloride as Dixarit in the treatment of menopausal flushes. This drug in low doses acts to stabilize abnormally reactive blood vessels[1 2] and conferred definite benefit in 9 out of 11 patients with menopausal flushes who were given a similar dose regimen to that used in the prophylaxis of migraine.[3 4]

These preliminary results encouraged the organization of a double-blind trial on a multicentric basis in general practice. Preliminary analysis of the results shows that the drug has a statistically significant effect on the suppression of menopausal flushes. It is intended to publish the full results in the near future. There are obvious advantages in a drug which will adequately control this distressing symptom of the menopause while retaining a simple dosage and avoiding any side effects which may accrue from the prolonged use of hormones in this situation.

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