

Hypersensitivity to drugs

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Introduction

A drug is a therapeutic agent which is usually of low molecular weight, often less than 1000. From an immunological point of view, it is usually a simple compound which can induce an immune response only when coupled to a larger molecule such as a protein. Landsteiner first demonstrated that this type of simple substance would induce antibody formation if combined irreversibly with other macromolecules. In this situation, the drug acts as a specific determinant group on the larger molecule, i.e. a hapten. In contrast, the freely reversible binding of many drugs to albumin or other plasma proteins is not strong enough to provoke antibody formation.

There are some drugs which are more usually associated with hypersensitivity reactions than others—for example: penicillin, streptomycin, sulphonamides and barbiturates. However, penicillin is not capable of binding covalently with protein, and it is the metabolites of penicillin that determine the antibody response. The same may be true for other drugs. Except in the case of penicillin, the metabolites have not yet been identified, and the absence of proper reagents makes any study of the mechanism of allergy difficult to interpret.

The type of person who is known as atopic tends to develop an allergic response to a wide variety of antigens. These individuals are often subject to hay-fever, asthma and eczema. There is, however, no gross preponderance of atopic subjects among patients suffering from drug allergy, although, in studies of penicillin hypersensitivity, Levine suggests that they are more prone to develop the immediate types of allergy associated with reaginic antibody.

Patients developing allergy to one drug are more likely to develop it to a second which is given at the same time. It has been shown that patients who develop skin-sensitizing antibody—i.e. reaginic antibody—to one substance have a 40% incidence of skin-sensitizing antibody to the second. This compares with an incidence of 5% in a control population (Levine, 1968). This linking has also been shown in anti-tuberculous chemotherapy with PAS and streptomycin (Smith & Zirk, 1961).

Allergy, idiosyncrasy and toxicity

There are several examples of idiosyncrasies which at first sight resemble an allergic response. In patients with favism, a deficiency of glucose-6-phosphate dehydrogenase may predispose to the development of haemolysis when the patient eats broad beans, and haemolysis may also occur after exposure to such drugs as primaquine. What is now known to be the result of an enzyme deficiency might easily be mistaken for an allergy if the mechanism were less well understood. Variation in the metabolism of drugs underlie other toxic effects. The peripheral neuropathy that follows isoniazid therapy occurs in a few patients who are unable to metabolize the drug at the normal rate. Similarly, paralysis after succinyl choline may occur in patients with a pseudocholinesterase deficiency. In the case of succinyl choline, the type of disorder and mode of onset do not suggest allergy. The speed of onset by itself cannot provide a reliable guide however. Although a delayed onset might be expected in allergic disorders, previous exposure can speed up an allergic response very considerably.

It may also be difficult to distinguish a straightforward toxic effect from an allergic one. Aspirin is the commonest drug to cause urticaria and often causes rhinitis and asthma as well, a seemingly obvious allergic triad. Yet there is no evidence at all for an allergic basis and aspirin may yet prove to be more important as an antagonist to bradykinin (Giraldo, Blumenthal & Spink, 1969). There are other instances where it is difficult to distinguish a toxic effect from an allergic one. Thus, jaundice is often a feature of therapy with anabolic steroids (the C_{17} alpha-alkyl-substituted testosterone), but this appears to be a dose-related toxic effect. Similarly, agranulocytosis with cyclophosphamide is a clear example of a toxic effect. With chloramphenicol, which is also a marrow depressant, the question is very open.

With the development of new methods of investigation, a number of drug reactions have come to be better understood. For example, thrombocytopenia, which may be induced by gold treatment, was at one time thought to be toxic in origin. With the development of lymphocyte culture techniques, however, Denman & Denman (1968) have shown evidence of an immunological abnormality, since gold can stimulate the lymphocytes of an affected patient to undergo blast cell transformation. The techniques of investigation which are now available may add considerably to the understanding and clinical management of the individual patient, and the most florid and serious drug reactions are frequently reversible on withdrawal of the offending drug.

Methods of testing

The traditional skin tests still have an important place. When the suspected agent is applied to the unbroken skin, in a patch test, the results should be read in 24–48 hr. Positive reactions developing over 5–6 days may represent primary sensitization induced by the test itself. A positive response provides useful confirmation of the nature of an allergic contact dermatitis. However, these tests are generally useless in other allergic diseases. Prick or scratch tests may be more logical in cases where there is a suspected allergy to a systemically administered drug. High concentrations of the allergen are usually used and a combination with reaginic antibody in the skin may lead to a classical weal reaction. Such tests are hazardous however—for example with anaphylactic penicillin hypersensitivity or in patients with severe asthmatic reactions.

Intradermal tests are both more sensitive and more dangerous. In these skin tests there is the opportunity to observe not only the early flare reaction but also a response due to delayed hypersensitivity at the end of 24–48 hr, as in tuberculin tests. This is

especially true if any immediate weal reaction is blocked by local antihistamines, since in these circumstances the removal of antigen is delayed (Brostoff & Roitt, 1969). These provocative tests, like the provocative inhalation of allergens in patients with bronchial asthma, have the disadvantage that they may not only produce a severe reaction but may also sensitize the patient further.

In the past, the Prausnitz-Küstner reaction was used to detect the presence of allergy of the immediate type to a particular antigen—for example a fish allergy. This reaction is mediated by skin-sensitizing IgE (i.e. reaginic antibodies) and develops within seconds or minutes of exposure to antigen. To elicit the reaction, plasma from an allergic patient is injected subcutaneously into a recipient. If a prick test is then carried out with the appropriate antigen in the same area of skin, a weal and flare reaction develops. This has the advantage that there is no danger of anaphylaxis, but as the plasma recipient is exposed to the dangers of serum hepatitis, the test is now rarely used.

As alternative laboratory tests have developed they have therefore been seized upon in the hope that they may provide better methods for testing for drug sensitivity *in vitro*. The lymphocyte transformation test has been used frequently. Cultured lymphocytes from the peripheral blood of penicillin-sensitive individuals have been shown to transform to lymphoblasts in the presence of penicillin (Halpern, Ky & Amache, 1967). The method has also been said to be capable of detecting sensitivity to tetracycline and ampicillin (Reichenberger & Heitmann, 1969). It is possible that a positive test correlates with circulating antibodies in some instances, but it is more usually accepted as a test for cell-mediated immunity. Its value as an indicator of drug sensitivity is still being assessed.

Yet another test depends on the migration of macrophages. It has been shown that the migration of macrophages out of capillary tubes is inhibited if sensitized lymphocytes are present together with the particular antigen to which the lymphocytes are sensitive. In these circumstances a migration inhibition factor (MIF) is released (David *et al.*, 1964).

The 'lymphokines', of which MIF is an example, are a series of substances which are released by the interaction between sensitized lymphocytes and antigen. Since human macrophages are difficult to obtain, there are considerable problems in applying this technique to clinical situations. Fortunately the lymphokines are not species specific. MIF can be produced by human lymphocytes in culture and its presence can then be detected by tests which make use of guinea-pig macrophages (Thor *et al.*, 1968). It may also be possible to use a direct mixture of human lymphocytes and guinea-pig macrophages (Rajapakse & Glynn, 1970). Another variation on the same theme has been provided by the demonstration that migration of mixed leucocytes from human peripheral blood can be inhibited in the presence of an antigen. This occurs only if the donor of the blood has a delayed hypersensitivity to this antigen (Soborg & Bendixen, 1967).

Sensitization to drugs may involve the production of circulating antibodies as well as sensitized cells. These antibodies can be tested for in various ways. They are sometimes able to agglutinate inert particles which have been coated with antigen, and this is the basis of haemagglutination tests, using antigen-coated red blood cells. Lichtenstein & Osler (1964) have described another test designed to discover reaginic IgE antibody. Sensitized polymorphonuclear leucocytes incubated in the presence of an antigen will release histamine which can be measured. A test can therefore be devised

for the presence of leucocytes which have specific IgE antibody absorbed onto their surface. As it detects only the histamine-releasing (reaginic) antibodies, it is more specific and more useful than other, conventional tests for antibody.

Penicillin allergy

Allergy to penicillin is widespread. Of one series of army recruits who each received a mega-unit of benzathine penicillin, 0.64% required hospitalization (Frank & Stollerman, 1965). In this type of case the mechanism of allergy has been worked out quite well, and it is therefore a good example to consider in detail.

Skin tests, using penicillin G, have been used intradermally with 0.01 units if there is a suspicion of sensitivity present. Larger doses of up to 500 units have been used where there is no likelihood of allergy. Unfortunately, these tests are positive in only 30% of allergic patients and the injection itself may cause sensitization. In the very sensitive subject even these low test doses may induce anaphylaxis.

The metabolites of penicillin which are capable of causing an allergic response have now been partially defined. In most patients the response appears to be directed against a single 'major determinant' (benzylpenicilloyl radical or 'B.P.O.') or against certain 'minor determinants' (benzylpenicilloic acid and penicillenic acid). The various types of allergic response to penicillin may depend on the presence of different antibodies to these determinants and on the route of administration. It is extremely unusual to develop anaphylactic responses to oral therapy.

In some units it is now current practice to use scratch-tests, with major and minor determinants, for any person who requires penicillin and might have an allergy to it (Voss, Redmond & Levine, 1966). The suggestion is that these tests will detect all but the late reactors, in whom skin-sensitizing antibody is not likely to be found. Moreover, benzylpenicilloyl radical, which is used as the major determinant, has the added advantage that it does not sensitize patients itself.

It has been suggested that penicilloylated protein impurities, especially residual proteins extracted from the fermentation medium, may be the cause of much sensitization to penicillin. If this were so, then relatively simple purification procedures might reduce the number of allergic reactions considerably. Unfortunately, these impurities do not appear to play any major role in clinical penicillin allergy (de Weck, Schneider & Gutersohn, 1968). However, in cows, the carboxymethyl-cellulose used to stabilize the penicillin suspension is a potent cause of an allergy which misleadingly appears to be directed against penicillin itself (Wellensiek, 1969).

Some patients also have antibodies against specific side chain determinants of the penicillin molecule, but these are rarely of clinical significance.

The place of eosinophilia in allergic reactions is not yet understood, although it is known that histamine is chemotactic for the eosinophilic leucocyte (see Archer, 1963). Eosinophilia is a common finding in penicillin allergy and Zolov & Levine (1969) demonstrated in a prospective and retrospective survey that it was associated with the presence of reagins.

The clinical syndromes that have so far been attributed to penicillin sensitivity are as follows:

(1) Immediate anaphylactic reactions are found in association with reaginic (skin-sensitizing) antibody. These react with the minor determinants, especially penicillenic acid. Other antibodies—the so-called 'blocking' antibodies—are not usually present in these cases.

(2) Accelerated and late allergic reactions are associated with reagins to the major determinant. IgG blocking antibody is usually present as well. It is probably the presence of this blocking antibody that causes delays in the response.

(3) Recurrent arthralgia and urticaria may develop some 3–21 days after penicillin therapy. This, too, is associated with reagins to the minor determinant—especially benzylpenicilloic acid.

(4) Maculopapular and erythematous reactions are often associated with pruritus. These may develop for the first time after therapy has ceased. Many of these are associated with IgM antibodies.

(5) Haemolytic anaemia occurs most notably in those patients who are receiving penicillin therapy in high doses. In such cases IgG antibodies are found in high titre.

(6) Delayed hypersensitivity to penicillin is probably of little clinical importance. The exception, perhaps, is in contact hypersensitivity.

These reactions are not always purely of one type or another. Once established, they may be modified or prolonged, especially in the case of urticaria or arthralgia, by the presence of penicillin in milk or in aerosol sprays, dermatophytes or air moulds.

Blood disorders

Some of the best-studied drug allergies affect the formed elements in the blood. The first of these to be described (Ackroyd, 1949) was sedormid pupura. Here there is antibody which reacts with human platelets in the presence of sedormid. The reaction is to a drug-platelet complex and the result is agglutination of the platelets. Many other drugs have since been implicated in inducing an allergic thrombocytopenia in the same sort of way. These include chlorothiazide and hydrochlorothiazide (Nordqvist, Cramer & Bjorntop, 1959), digitoxin (Horowitz, Young & Nachman, 1964), quinidine, quinine, novobiocin and others. There are several possible ways of testing for this type of reaction. The simplest is to look for platelet agglutination in the presence of the patient's serum and the drug or to study the inhibition of clot retraction caused in the presence of the drug. Complement fixation and antiglobulin consumption tests can also be used. Though difficult to perform, they are reliable and sensitive.

The mechanism which has been demonstrated in these cases of drug-induced thrombocytopenia also holds true for some types of agranulocytosis. In these cases a serum factor can be demonstrated which will agglutinate white blood cells in the presence of the drug. This has been described with amidopyrine, sulphosalazine (Thirkettle, Gough & Reed, 1963), propylthiouracil (Walzer & Einbinder, 1963) and others.

A drug which is combined with a red cell can also provoke a positive direct Coombs test. This was first described with stibophen but has since been demonstrated with quinidine, PAS, penicillin (Swanson, Channougan & Schwartz, 1966) and cephalosporin. Not all drugs that give rise to a positive Coombs test do so in the same way, and there are three main categories. The first, as described above, involves an antibody which reacts with an antigen bound to the surface of the red cell. In the second type, drug-antibody complexes are formed in the circulation which fix complement and are adsorbed by immunoadherence onto the red cell surface. An example of this type of reaction is provided by quinine, and here the red cell is an 'innocent bystander'. In the third type, a positive direct Coombs test—or frank haemolytic anaemia—may be caused by therapy with methyl dopa or, less frequently, with L-dopa. Here the antibody does not react with the drug nor with any of its known metabolites.

Though provoked by drug therapy, the antibody seems to be directed at the patient's own red cells and is still capable of reacting with those cells in the absence of the drug. This antibody can also react with certain other normal red cells which carry rhesus antigens, usually c and e (Bakemeier & Leddy, 1968). The importance of diagnosis lies in the fact that a withdrawal of treatment is followed by a remission of symptoms, though the positive Coombs test may persist. Mefenamic acid has been reported to induce a similar type of haemolytic anaemia.

Drug-induced systemic lupus

Drug-induced systemic lupus is more variable in its response to the withdrawal of the drug that provoked the syndrome. Arthritis, pleurisy, fever, pericarditis, skin rashes and leukopenia have been increasingly recognized after the use of hydralazine, hydantoins, trimethadione, isoniazid, procaine amide, and, possibly, the oral contraceptives (see Lessof & Russell, 1971). Antinuclear antibody is present and LE cells are often detectable. Up to 12% of all cases of lupus occurring in New York have been attributed to drugs (Lee, Rivers & Siegel, 1966). Hydralazine was one of the first drugs to be implicated but later procaine amide was said to be the drug which is most commonly involved (Siegel, Lee & Peress, 1967).

The mechanism of these drug-induced diseases is unknown but it has been suggested that the subjects affected have a predisposition to develop systemic lupus and that the drug has merely uncovered latent disease. However, it has been reported by Russell & Ziff (1968) that 80% of patients receiving procaine amide develop antinuclear antibody at the end of 2 months. It is difficult to believe that 80% of the population are predisposed to this disease, though spontaneous systemic lupus may indeed be responsible for persistent symptoms in a few cases after therapy has stopped. The lymphocytes of patients with procaine amide-induced lupus are not, however, stimulated to transform by incubation with the drug *in vitro* (Klajman *et al.*, 1970).

Drug jaundice

Jaundice is a feature of several different types of drug allergy but there are many cases where it is arguable whether it is a manifestation of drug toxicity or an allergy. Indeed, in the individual patient it is frequently difficult to decide whether it is due to the drug or to intercurrent or other illness as, for example, when jaundice occurs following imuran therapy in chronic active hepatitis.

Chlorpromazine and other phenothiazines are associated with what is generally agreed to be an allergic jaundice. It can follow administration of even one tablet and usually presents 2 or 3 weeks after starting the drug, even though therapy may have been discontinued. Moreover, it is frequently associated with rashes, fever, eosinophilia and also with an eosinophilic infiltration of the liver. The recurrence of this syndrome shortly after a re-administration of the drug is further evidence of an allergic basis (Sherlock, 1968). Pointers to a drug allergy may be seen with the occasional jaundice following PAS therapy, viz. rash, fever, asthma, eosinophilia and eosinophilic infiltration of the liver, although these are not invariable and are not usually present all at the same time in any one patient. Again, the average time of onset is 2-3 weeks after therapy is begun and the frequency is independent of the dose of drug used (Simpson & Walker, 1960). The same allergic features may be found in the rare sulphonamide jaundice—but in these cases the jaundice is hepatocellular in type rather

than cholestatic (Dujoune & Chan, 1967). Chlordiazepoxide (Librium) seems to be able to give rise to jaundice of either type.

The cholestatic jaundice seen with the C₁₇ alkyl-substituted testosterone is not associated with these features. There is also other evidence to suggest that this is a toxic effect, as with the oral contraceptive agents. The severe hepatocellular disease following therapy with monoamine oxidase inhibitors may also be of toxic origin—but here the reactivation of infectious hepatitis has also been suggested as an aetiological factor. Halothane causes a hepatocellular jaundice, which occurs independently of the dose of halothane used or the type of operation. It is, however, more common after multiple exposures. The disease begins some 1–2 weeks after the anaesthetic and is often associated with fever, rash and eosinophilia. Recently Paronetto & Popper (1970) have demonstrated that the lymphocytes of these patients frequently undergo transformation in the presence of halothane, indicating an immune response to this agent. They noted this reaction in eight out of fifteen persons developing halothane jaundice, and in none of the controls. The difficulty in demonstrating an abnormality of lymphocyte behaviour in every case could possibly be a reflection of the lack of sensitivity of the test employed. This was the first demonstration of abnormal lymphocyte reactivity in an allergic hepatitis and suggests that further work in this field may be of value.

The recognition of allergy in doubtful cases

The difficulty in classifying drug allergies has been emphasized. It is directly related to the lack of knowledge and understanding of their pathogenesis and to the complications which arise when it is not only the host response but also the characteristics of the particular drug which determines the clinical features of the various syndromes. This is most obviously true for the skin rashes and an example is seen in the distinctive rashes which occur with the barbiturates. Some sulphonamides, especially the long acting types, may give rise to the Stevens–Johnson syndrome (Carroll, Bryan & Robinson, 1966) and some to other skin reactions such as erythema nodosum. Other factors which concern the host are important too. For example, ampicillin rashes are much more likely to occur in patients whose response is altered by glandular fever (Levene & Baker, 1968).

Two hundred and eighty-one housewives with contact dermatitis of the hands have recently been studied by Calnan *et al.* (1970). Although most of the cases of allergy concerned substances other than drugs the findings were significant. If the history suggested a specific allergy, tests were carried out with the appropriate substance, but a battery of twenty known sensitizers were also used in identifying allergens which the history alone often failed to detect. An allergic contact dermatitis was finally diagnosed in 42% of cases, an irritant dermatitis in 45% and a combination of both in 13%. In some cases sensitization may occur by means of external contact with the allergen, but ingestion of even small amounts may thereafter perpetuate the dermatitis. The importance of a wide battery of tests in suspect cases is therefore emphasized.

There are many unusual and unexpected types of response which have been shown to be allergic, albeit by circumstantial evidence. An example is the adverse effect which occurs with re-exposure, as in the salivary gland enlargement and fever which are provoked by phenylbutazone or sulphisoxazole (Banks, 1967). Other examples are the pulmonary infiltration and eosinophilia that are caused by nitrofurantoin (Israel

& Diamond, 1962) and the lymphadenopathy, histologically resembling a lymphoma, that follows phenytoin administration (Gams, Neal & Courad, 1968). In almost any complication which arises in a person being treated with drugs, it follows that a drug-induced allergy must be considered and distinguished from idiosyncrasy, toxic side effects or the natural features of the disease for which the drug was first given.

References

- ACKROYD, J. (1949) The cause of thrombocytopenia in Sedormid purpura. *Clinical Science*, **8**, 269.
- ARCHER, R.K. (1963) *The Eosinophil Leucocytes*. Blackwell Scientific Publications, Oxford.
- BAKEMEIER, R.F. & LEDDY, J.P. (1968) Erythrocyte autoantibody associated with methyl dopa therapy: heterogeneity of structure and specificity, *Blood*, **32**, 1.
- BANKS, P. (1967) Hypersensitivity and drug reactions involving the parotid gland. *British Journal of Oral Surgery*, **5**, 60.
- BROSTOFF, J. & ROITT, I.M. (1969) Cell mediated (delayed) hypersensitivity in patients with summer hayfever. *Lancet*, **ii**, 1269.
- CALNAN, C.D., BANDMANN, H.J., CRONIN, E., FREGERT, S., HJORTH, N., MAGNUSSON, B., MALTEN, K., MENEGHINI, C.L., PIRILÄ, V. & WILKINSON, D.S. (1970) Hand dermatitis in the housewife. *British Journal of Dermatology*, **82**, 543.
- CARROLL, O.M., BRYAN, P.A. & ROBINSON, R.J. (1966) Stevens-Johnson syndrome associated with long-acting sulfonamides. *Journal of the American Medical Association*, **195**, 691.
- DAVID, J.R., AL-ASKARI, S., LAWRENCE, H.S. & THOMAS, L. (1964) The specificity of inhibition of cell migration by antigens. *Journal of Immunology*, **93**, 264.
- DENMAN, E.J. & DENMAN, A.M. (1968) Lymphocyte transformation and gold hypersensitivity. *American Journal of Rheumatic Diseases*, **27**, 582.
- DE WECK, A.L., SCHNEIDER, C.H. & GUTERSOHN, J. (1968) The role of penicilloylated protein impurities, penicillin polymers and dimers in penicillin allergy. *International Archives of Allergy*, **33**, 535.
- DUJOURNE, C.A. & CHAN, C.H. (1967) Sulfonamide hepatic injury. *New England Journal of Medicine*, **277**, 785.
- FRANK, P.F. & STOLLERMAN, G.H. (1965) Protection of a military population from rheumatic fever. *Journal of the American Medical Association*, **193**, 775.
- GAMS, R.A., NEAL, J.A. & COURAD, F.G. (1968) Hydantoin induced pseudo-pseudolymphoma. *Annals of Internal Medicine*, **69**, 557.
- GIRALDO, B., BLUMENTHAL, M.N. & SPINK, W.W. (1969) Aspirin intolerance and asthma. *Annals of Internal Medicine*, **71**, 479.
- HALPERN, B., KY, N.T. & AMACHE, N. (1967) Diagnosis of drug allergy in vitro with the lymphocyte transformation test. *Journal of Allergy*, **40**, 168.
- HOROWITZ, H.I., YOUNG, R.C. & NACHMAN, R.L. (1964) Thrombocytopenia due to digitoxin: demonstration of antibody and mechanism of action. *Journal of Clinical Investigation*, **43**, 1236.
- ISRAEL, H.L. & DIAMOND, P. (1962) Recurrent pulmonary infiltration and pleural effusion due to nitrofurantoin sensitivity. *New England Journal of Medicine*, **266**, 1024.
- KLAJMAN, A., CAMIN-BELSKY, N., KIMCHI, A. & BEN EFRAIM, S. (1970) Occurrence, immunoglobulin pattern and specificity of anti-nuclear antibodies in sera of procaine amide treated patients. *Clinical and Experimental Immunology*, **7**, 641.
- LEE, S.L., RIVERS, I. & SIEGEL, M. (1966) Activation of systemic lupus by drugs. *Archives of Internal Medicine*, **117**, 620.
- LESSOF, M.H. & RUSSELL, A.S. (1971) Immunity, autoimmunity and immunosuppression. In: *Progress in Clinical Medicine* (Ed. by R. Daley and H. Miller), 6th edn. Churchill, London.
- LEVENE, G. & BAKER, H. (1968) Ampicillin and infectious mononucleosis. *British Journal of Dermatology*, **80**, 417.
- LEVINE, B.B. (1968) Immunochemical mechanisms of drug allergy. *Textbook of Immunopathology* (Ed. by P. A. Miescher and H. J. Müller-Eberhard), Vol. I, p. 271. Grune & Stratton, New York.
- LICHTENSTEIN, L.M. & OSLER, A.G. (1964) Studies on the mechanisms of hypersensitivity phenomena. IX. Histamine release from human leucocytes by ragweed pollen antigen. *Journal of Experimental Medicine*, **120**, 507.

- NORDQVIST, P., CRAMER, G. & BJORNTOP, P. (1959) Thrombocytopenia during chlorothiazide treatment. *Lancet*, **i**, 271.
- PARONETTO, F. & POPPER, H. (1970) Lymphocyte stimulation induced by halothane in patients with post halothane hepatitis. *New England Journal of Medicine*, **283**, 277.
- RAJAPAKSE, D. & GLYNN, L.E. (1970) Macrophage migration inhibition test using guinea pig macrophages and human lymphocytes. *Nature*, **226**, 857.
- REICHENBERGER, M. & HEITMANN, H.J. (1969) Lymphocyte transformation in patients allergic to ampicillin and tetracycline. *Lancet*, **ii**, 491.
- RUSSELL, A.S. & ZIFF, M. (1968) Natural antibodies to procaine amide. *Clinical and Experimental Immunology*, **3**, 901.
- SHERLOCK, S. (1968) Drugs and the liver. *British Medical Journal*, **i**, 227.
- SIEGEL, M., LEE, S.L. & PERESS, N.S. (1967) The epidemiology of drug-induced systemic lupus erythematosus. *Arthritis and Rheumatism*, **10**, 407.
- SIMPSON, D.G. & WALKER, J.H. (1960) Hypersensitivity to para-amine salicylic acid. *American Journal of Medicine*, **29**, 297.
- SMITH, J.M. & ZIRK, M.H. (1961) Toxic and allergic drug reactions during the treatment of tuberculosis. *Tubercle*, **42**, 287.
- SOBORG, M. & BENDIXEN, G. (1967) Human lymphocyte migration as a parameter of hypersensitivity. *Acta Medica Scandinavica*, **181**, 247.
- SWANSON, M.A., CHANNOUGAN, D. & SCHWARTZ, R.S. (1966) Immunohaemolytic anaemia due to antipenicillin antibodies. *New England Journal of Medicine*, **274**, 178.
- THIRKETTLE, J.L., GOUGH, K.R. & REED, A.F. (1963) Agranulocytosis associated with sulphasalazine (Solazopyrine) therapy. *Lancet*, **i**, 1395.
- THOR, D., JUREZIZ, R., VEACH, S., MILLER, E. & DRAY, S. (1968) Cell migration inhibition factor released by antigen from human peripheral lymphocytes. *Nature*, **219**, 755.
- VOSS, H.E., REDMOND, A.P. & LEVINE, B.B. (1966) Clinical detection of the potential allergic reactor to penicillin by immunologic tests. *Journal of the American Medical Association*, **196**, 679.
- WALZER, R.A. & EINBINDER, J. (1963) Immunoleukopaenia as an aspect of hypersensitivity to propylthouracil. *Journal of the American Medical Association*, **184**, 743.
- WELLENSEK, H.J. (1969) Immunogenicity of synthetic penicillins. *Bayer Symposium*, **1**, 310.
- ZOLOV, D.M. & LEVINE, B.B. (1969) Correlation of blood eosinophilia with antibody class. *International Archives of Allergy*, **35**, 179.

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