DRUG ALLERGY

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TABLE OF CONTENTS

I. INTRODUCTION

It would be highly satisfactory to trace the origin of the experimental study of allergy back to some investigation supported by, let us say, a generous university's grant or a far-seeing philanthropist's bequest, but the facts are unfor-

tunately otherwise. The support for the first work in allergy came from the gaming tables of Monte Carlo, for it was the Prince of Monaco who took Richet and Portier on an ocean cruise and enabled them, while aboard his yacht, to begin their study of extracts of poisonous jellyfish (74). This work, continued afterwards in the laboratory, resulted in the discovery of anaphylaxis. Others, especially von Pirquet, then extended the work and developed fundamental ideas. Base-born allergy, however, has never quite lived down this bar sinister and has at times suffered snobbish treatment from its legitimate half-brother, immunology. As we consider the waywardness and unforeseeable nature of allergic reactions to drugs and the difficulty in understanding and predicting them through the usual types of toxicological studies in animals, we must admit that the immunologists are at least partly right. The study of allergy has not completely lost the characteristics of its ancestral roulette wheel.

A significant percentage of the undesirable reactions to drugs used in modern medical practice are probably allergic in nature. Certain drug allergies were recognized at the end of the last century or fairly early in this century, and as might be expected, those so recognized were chiefly the very serious, *e.g.*, asthma provoked by acetylsalicylic acid (54) or the bizarre, *e.g.*, fixed skin eruptions caused by antipyrine (23). As extraordinary progress in synthetic chemistry led to the rapid introduction of large numbers of new compounds into medicine, allergic reactions became more frequent and disturbing. Agranulocytosis caused by aminopyrine attracted world-wide attention in and directly after 1931 (168), but it is probably correct to consider the era of practical antibacterial chemotherapy as being simultaneously the era in which the problem of drug allergy reached its present importance (163). The advent of sulfonamides caused a great surge of interest, which was further increased by penicillin and has continued ever since. The total number of reports and editorials devoted to untoward reactions to drugs (excluding intoxications caused by gross overdosage but including some reactions which were probably not allergic in nature) appearing in the Journal of the American Medical Association during the year 1933 was 19. In 1953, 36 appeared.

Although allergic reactions are by definition fundamentally different in their mechanism from the "usual" or "direct" toxic effects of drugs (see below), they can no longer be dismissed as freaks. Indeed, it is expected that any interest in the present review will reside less in the details contained in it than in the fact that, by appearing in this journal, it marks the acceptance of this general subject, which has—quite properly—been studied extensively by experimental and clinical allergists, as a legitimate concern of pharmacologists and toxicologists also. As will be seen, certain factors, *e.g.*, route of administration, which are well known to influence the classical effects of drugs also influence allergic reactions to them. Provided such parallels are not carried to extremes, they offer useful approaches to the study of drug allergy.

II. DEFINITIONS AND CONVENTIONS

It is unfortunately necessary to devote some attention to terminology, even at the risk of provoking sterile disputes, for considerable confusion of terms exists

and hampers communication in this field, especially when the usages of pharmacology and allergy conflict.

Allergy has been defined as "any specifically acquired alteration in the capacity of living tissue to react. This alteration in capacity to react results from exposure to an exciting agent and is manifest upon re-exposure to the same or to an immunologically related agent" (52). If acquired specificity is a part of the definition, then there must be in the allergic organism a locus of chemical or physicochemical alteration which is responsible for the specificity and necessary for the allergic reaction. If such a locus is considered to be the broadest definition of an antibody, then the allergic state always depends upon the presence of an antibody. It cannot yet be proven that the antibody must always be a protein, for in many allergies the antibody has never been isolated, but in all allergic and immune states in which antibody has been successfully isolated and characterized, it has been found to be a protein. The term "antibody" now always refers to the locus at the molecular level.

It is difficult to draw a sharp and universally applicable distinction between immunity and allergy. It is useful to think of allergic reactions as detrimental and immunity as beneficial but this is not a rigid distinction. A diabetic patient who, after previous exposure, reacts specifically to insulin by developing urticaria can clearly be said to be allergic to the drug, but what of the diabetic patient who develops an antibody which simply neutralizes the hypoglycemic action of insulin? Use of the term "anergy" for the latter instance might seem reasonable, but this would only compound the confusion for, although anergy does indeed mean disappearance of the capacity to react, it does not necessarily imply specificity and has in actual use acquired a more limited connotation, *e.g.*, disappearance of skin reactivity to tuberculin as a result of overwhelming tuberculosis. It is probably advisable to use the term "immunity" for all acquired specific alterations in the capacity to react which cause the organism, despite adequate exposure to the antigen, *to remain in the state in which he was prior to exposure.* By this definition the patient with an antibody neutralizing the hypoglycemic effect of insulin is immune to insulin. The development of immunity is thus one way—though of course not the only, and probably not the most common way—in which an organism develops tolerance to a drug.

Because of the established meaning of the term "tolerance" in pharmacology, the popular use of the term "intolerance" for any type of unexpected undesirable reaction to a drug is confusing and not recommended.

It is relatively easy to draw a theoretical line between, on the one hand, allergic and immune reactions to drugs and, on the other, reactions which merely represent an exaggeration or diminution of the usual effects of a given dose. Both asthma and tinnitus following a small dose of acetylsalicylic acid represent hypersensitivity, but the former usually represents allergy and the latter does not. Such exaggeration and diminution of the usual effects of drugs, which represent quantitative rather than qualitative differences and are not acquired through previous exposure to the drug, can be seen in some individuals in any population. It is desirable to have terms for such non-allergic hyper- and hyposensitivity. The terms "hyperergy", "normergy" and "hypergy" form a rational set, but they

have already had some use without the connotation of "non-allergic". "Idiosyncrasy" is a term which has been so promiscuously used for so long that it now has no well-defined meaning and should be abandoned. Rather, it would be desirable to adopt terms which have not already become widely used, perhaps with varying connotations in the minds of different students of this field.

In summary, then, the terminology should enable one to distinguish clearly among the following situations:

A) Abnormal capacity to react to a drug, such that the individual, despite the administration of an adequate dose of the drug, as judged by comparison with normal individuals receiving the drug for the first time, remains in the state in which he was prior to administration of the drug.

1) Where the alteration is acquired, specific, and implies, as previously discussed, the presence of an antibody.

2) Where the alteration is not as in 1).

3) Where it is not known whether the alteration is or is not as in 1).

B) Abnormal capacity to react to a drug, such that the individual, following the administration of an adequate dose of the drug, as judged by comparison with normal individuals receiving the drug for the first time, attains a state different from that in which he was prior to administration of the drug but also different, quantitatively or qualitatively, from that attained by normal individuals after receiving an equivalent dose.

1) Where the alteration is acquired, specific, and implies, as previously discussed, the presence of antibody.

2) Where the alteration is not as in 1).

a) The more usual situation, in which the reaction differs from the normal only quantitatively.

b) The rarer situation, in which the reaction differs from the normal qualitatively yet does not fulfill the criteria of 1), *e.g.*, excitement rather than depression following subcutaneous administration of 15 mg. of morphine sulfate to a human.

3) Where it is not known whether the alteration is or is not as in 1).

The following terms are suggested and will, as far as possible, be used in this review. A1) Immunity, partial or complete. A2) Hyporeactivity or, when complete, unreactivity. A3) Hyposensitivity or, when complete, insensitivity. B1) Allergy. B2)a) Hyperreactivity. B2)b) Metasensitivity. B3) Hypersensitivity. This review, of course, is primarily concerned with B1).

It would be desirable for some such set of terms, not necessarily those suggested here, to be widely adopted and consistently used. If we adopt such terms and keep their meaning *precise* we will have gained an advantage. Introduction of new terms without an increase in precision will only make matters worse and further justify Orwell's attack: "A mass of Latin words falls upon the facts like soft snow, blurring the outlines and covering up all the details " (240). There probably will not be any quarrel with the *principle* of using a normal standard of comparison. It is obvious that certain of the dividing lines implied by the above definitions will be entirely arbitrary, depending upon the range of deviation from the mean that one is willing to accept as normal. It is perhaps not so obvious

that, at least for the definition of allergy, only the reactions of normal individuals exposed for the first time to the drug should be used as a standard of comparison. If the reactions of re-exposed individuals were used, one would at times be faced with an absurd situation, for in some instances the majority or even all of the re-exposed individuals will become sensitized. Sixty-five per cent of a series of 46 children receiving nirvanol regularly for several days became allergic to the drug (201). About three fourths of the population can be made to develop allergy of the skin to poison-ivy (127). Bloch (19) was able experimentally to sensitize all his subjects to primrose.

As the large majority of drugs are relatively simple chemical compounds, the unique theoretical and practical problems of drug allergy are largely those of allergy to simple substances. Allergy to protein drugs is merely one aspect of the wider subject of allergy to proteins. This review, therefore, will be devoted to allergy to simple substances, and many studies involving simple substances which do not happen to be drugs will nevertheless be accepted as relevant.

The determination of ED_{50}, LD_{50} etc. presents peculiar problems when one is dealing with drug allergy. All that will be attempted here is a simple listing of certain considerations which should underlie attempts at solution.

1. A drug fully responsible for an allergic reaction both sensitizes and elicits a reaction. It may therefore have two potencies as an allergen, for its capacity to sensitize may not be the same as its capacity to elicit reactions. A simple experiment with *p*-phenylenediamine and azoaminobenzene suggests this. Under the conditions of the experiment, the former sensitized all of 10 guinea pigs, while the latter sensitized only 2 of 10 others. But 9 of the 10 sensitized to the former also gave positive cross-reactions when tested with the latter (211).

2. This problem becomes more difficult if, as certain work suggests (60), sensitizing and eliciting potencies, though different, are interdependent. The Sensitizing $Dose_{50}$ will then vary with the Eliciting Dose used and the Eliciting $Dose_{50}$, with the Sensitizing Dose used.

3. Clinically the sensitizing potency of a drug is probably more significant than its potency as an elicitor, for a patient's only certain safety lies in not being sensitized in the first place.

4. Most types of allergic reactions to drugs are sufficiently serious to make experimentation in humans, using the reactions as end-points, hazardous. Dermatitis, urticaria and "drug fever" are among the less risky, but even here, clinical experience shows that dermatitis may unexpectedly progress to exfoliation, while urticaria has on rare occasions persisted and caused such prolonged and severe pruritus as to make patients consider suicide.

5. At present, attempts to produce in animals, by sensitizing them to drugs in a manner simulating clinical exposure, many of the types of reactions seen in humans fail in all or most of the individuals used.

6. Precise quantitation of most allergic reactions is at present impossible. Such reactions can be measured on an all-or-none basis (12), but comparison of the potencies of two drugs on such a basis may be misleading. For example, it has been claimed (150) that dermatitis due to sulfonamides seems to be more

severe than that due to penicillin, though the latter may produce dermatitis in a higher proportion of patients receiving it.

7. Whenever it becomes possible to sensitize and challenge successfully a large number of individuals, it will probably be useful to divide them into several different classes, each class receiving a different sensitizing dose, and determine the Eliciting $Dose_{50}$ for each class. A plot of Eliciting $Dose_{50}$ (ED_{50}), as the ordinate, against sensitizing dose may then be made. If such a curve should be found to approach an asymptote or to have a maximum or minimum, the corresponding ED_{50} would be chosen in a manner that was not arbitrary. This ED_{50} itself would not be useful, as it would represent a point where the curve was parallel to the abscissa and small errors in determination of the ED_{50} would produce large errors in the corresponding sensitizing dose. Some standard multiple of this ED_{50} could be chosen, however, in such a way that the slope of the curve at the point corresponding to this multiple was steeper. The sensitizing dose corresponding to the latter ED_{50} could be selected as a Standard Sensitizing Dose. Nickerson (234) has suggested this type of approach, comparing it to the determination of chronaxie. Comparison of the potencies of two drugs could be made in this fashion only if the general shape of the curve were the same for both. Coulson and Stevens (60) have made such a plot of sensitizing dose of ovalbumin versus LD_{50} in guinea pigs. All animals were challenged after the same incubation period, and, therefore, the maximum intensity of allergy attainable with each sensitizing dose was not studied. Under these circumstances the LD_{50} was found to increase along a parabolic curve, with increase in sensitizing dose. The authors did not suggest any method of establishing a Standard Sensitizing Dose, but in the case of a parabolic curve the axis of which is the x-axis, the focus would be the obvious point of reference.

8. The above implies that, if only the techniques of experimental sensitization to drugs can be improved enough, sensitization of a high percentage of individuals will be obtainable. It is entirely possible, however, that with some allergens a certain proportion of individuals will be totally unable to become sensitized under any circumstances. If this proportion is high, the approach suggested above becomes useless.

9. An entirely different approach would be indicated if it should become possible to isolate and quantitate the antibodies responsible for these reactions. The problem would then become one familiar to immunologists. It would not only then be possible to measure sensitizing potency independently of the eliciting dose, but also to study the latter in passively, and hence more uniformly sensitized individuals.

III. MECHANISMS AND CHARACTERISTICS OF ALLERGIC REACTIONS TO DRUGS

A. The hapten theory

One may wish to challenge the validity of the hapten theory but no one can reasonably challenge its central position in the field; discussion of the mechanism of drug allergy will therefore largely revolve about this theory. The most important experiments are those in the series initiated by Landsteiner and

continued by Chase. These experiments are not only thoroughly admirable in their own right but also derive additional credit from the fact that they were begun and pursued before the practical importance of the subject for clinical medicine was generally appreciated. When the rapid increase in the number of allergic reactions to drugs caused an abrupt increase in clinical interest, a considerable body of basic experimental work had already accumulated.

Proteins, certain polysaccharides and lipo-carbohydrate complexes of high molecular weight are generally accepted (376) as complete antigens, i.e., they can by themselves induce the allergic state and elicit allergic reactions. The hapten theory attempts to explain the development of allergy to simple substances of much lower molecular weight by postulating that such simple substances, though not antigenic by themselves, combine with proteins to form antigenic conjugates. The specificity of the conjugate is determined by the hapten, *i.e.*, the simple substance, rather than by the protein.

Although present-day theories of antibody formation are incompatible with the hypothesis that very simple substances of small molecular weight might themselves directly stimulate antibody formation, the theories are to some degree the result of, rather than the cause for rejection of such a hypothesis. But there are facts which make such a hypothesis unlikely. Only large molecules, chiefly protein, have been found to be regularly antigenic when given intravenously to several different species; polypeptides of high molecular weight are antigenic whereas those of low molecular weight are not, although the more rapid renal excretion of the smaller polypeptides may also be a significant factor here (347); type III pneumococcus capsular polysaccharide, free of protein, is not antigenic for rabbits but can be converted into a full antigen by chemical combination with protein, and can in its uncombined state be precipitated by the antibody formed against the combination (116). Although the last observation is probably most easily explained by the hapten theory, it must be admitted that the hapten here is of relatively high molecular weight.

Not only did early workers note the discrepancy between allergic reactions to orthodox protein antigens and those to simple substances, but early experiments also showed that certain simple substances, linked to protein antigen, could determine the specificity of the latter. Such early experiments were the outgrowth of understandable curiosity about the basis for the specificity of proteins themselves. Those who sought a chemical basis were naturally led to study the effect of artificially added chemical groups. Thus, by 1906 Obermayer and Pick (237) were able to sum up a considerable body of work in which they showed that the specificity of iodo- and nitroproteins in precipitation experiments with rabbit antisera were strongly influenced by the iodo- and nitro-groups. They also recognized the importance of diazotization as a method allowing a wide variety of substances to be coupled to proteins for investigations of this type. In 1907 Wolff-Eisner suggested that similar conjugation might occur *in vivo* and account for the antigenicity of simple substances (369). In 1910 passive transfer of allergy to iodoform from humans to guinea pigs via serum was reported (25); such a demonstration of circulating antibody was important because it furnished clear

proof of the allergic nature of the reaction, but, unfortunately, since then passive transfer by serum has failed more often than it has succeeded in drug allergies. In 1911 Cash (39), investigating dermatitis in workmen exposed to East Indian satinwood, experimentally produced allergy of the human skin to a relatively simple substance, chloroxylonine, an alkaloid obtained from the satinwood. Swift (335) in 1912 produced anaphylaxis in guinea pigs, using a mixture of guinea pig serum and neutralized arsphenamine as antigen. For further discussion of these early events the reader is referred to Cormia (58) and Landsteiner (181).

Landsteiner and Lampl (184, 185) diazotized aniline, *p*-aminobenzoic acid, sulfanilic acid, and arsanilic acid to serum and injected these conjugates into rabbits. They obtained immune sera which gave positive precipitation reactions with the sensitizing conjugate. They also coupled acid chlorides to protein and, using these conjugates as antigens, obtained immune sera which gave positive complement fixation reactions with the sensitizing conjugates. Most important for the hapten theory was their observation that such a conjugate could sensitize even when the protein fraction of the conjugate was homologous for the species sensitized. Jacobs (154) also showed this in rabbits with iodinated serum. In later experiments a wide variety of simple chemical substances was diazotized to protein, injected into rabbits, and the specificity of the antisera tested (186). It was possible to obtain antisera which gave positive precipitin tests against the original conjugate and also against a conjugate of the original hapten with an entirely different protein. It was also possible, although more difficult, to obtain antisera which gave positive precipitin reactions against the original conjugate but not against a conjugate of the original protein and an entirely different hapten (188). Such sera therefore contained antibodies directed specifically against the hapten. Moreover, although the unconjugated hapten gave a negative precipitin test against the appropriate antiserum, it was still possible to show by the phenomenon of specific inhibition that the hapten could unite with the antibody in that serum (174, 191). Specific inhibition was demonstrated by adding the conjugate to the antiserum after the unconjugated hapten, or a simple azodye made by coupling the hapten to tyrosine or some other phenol, had first been added. Under these circumstances even the conjugate did not cause precipitation. The inhibition of precipitation was ascribed to prior union between the unconjugated hapten, or the simple azodye containing the hapten, and the antibody. Such union has been more directly demonstrated by dialysis experiments using arsanilic acid as hapten (134).

Furthermore, although certain simple azodyes incorporating the hapten caused, as noted above, only specific inhibition and not precipitation, Landsteiner was able to prepare other simple azodyes, again by coupling anilic acids with phenolic groups (192), which precipitated with antibodies produced against azoproteins containing the appropriate hapten. The antibody-azodye precipitation was inhibited by the simple hapten. Antigen protein is thus not indispensable for the formation of precipitates. Landsteiner and van der Scheer explained the differences in behavior between those azodyes causing precipitation and those not

doing so on the basis of ability to form colloidal solutions. Although extended discussion of this point, which is of great importance for theories of the structure of antigen-antibody precipitates, is beyond the scope of this paper, attention must be called to the work of Pauling, Pressman and their collaborators (248, 249, 250, 251, 262, 263, 264). In a most extensive series of experiments they have obtained evidence that failure of the unconjugated hapten to cause precipitation is due to serological univalence of the hapten, *i.e.*, possession of only one combining site for reaction with antibody, and that the precipitation of antiserum by dihaptenic or polyhaptenic azodyes is a general phenomenon, modified in special cases by such additional factors as steric hindrance. The role of the protein fraction of the antigenic conjugate in precipitation is visualized as dependent on its large size and serological multivalence, *i.e.*, the ability of one protein molecule to unite via haptenic groups with several antibody molecules. Dihaptenic or polyhaptenic compounds are thus able to act in a manner similar to protein-hapten conjugates. In a striking experiment (247) designed to support the lattice theory of antigen-antibody precipitate formation, three types of dihaptenic compounds were compared. In one, both groups were *p*-azophenylarsonic acid;[1] in the second, both were *p*-azobenzoic acid; and in the third, there was one *p*-azophenylarsonic acid and one *p*-azobenzoic acid group. The first compound precipitated antiserum against *p*-azophenylarsonic acid and the second precipitated antiserum against *p*-azobenzoic acid. The third compound gave no precipitate with either antiserum alone, but did give a precipitate when added to a mixture of the two antisera. Pappenheimer (243) has discussed the implications of, and technical objections to these experiments. It is of interest that the third dihaptenic compound gave a positive, though weak response in a bath with the intestine of a guinea pig sensitized by an azoprotein containing only the *p*-azophenylarsonic acid group (32). Precipitation experiments *in vitro* have shown that aggregation of such dihaptenic azocompounds into larger antigen complexes is much greater in the presence of pure antibody than in the presence of serum, the albumin of which presumably decreases such aggregation (243a).

Cross-reactions, *i.e.*, reactions to substances other than the original sensitizing hapten, have been studied by precipitation tests and specific inhibition (174, 191, 195). It has been found that cross-reactions are chemically logical, *i.e.*, they occur most often and most strongly between chemically similar substances, though antisera produced in different individuals against the same antigen may show different patterns of cross-reactions (176). For example, antibody directed against *m*-aminobenzenesulfonic acid gave cross-reactions with *m*-aminobenzenearsenic acid and with *o*-, *m*-, and *p*-aminobenzenesulfonic acid, but not with *p*-aminobenzenearsenic acid (191). Stereo-isomerism is important; cross-reactions between stereo-isomers often fail (189, 190, 191). Specific inhibition experiments are especially well suited to determination of the exact fraction of the conjugate against which the specificity of the antibody is directed. Thus, when the sensi-

[1] The terminology used here is designed simply to contrast the arsonic and benzoic acid groups. Strictly speaking, the haptens in the dihaptenic azodye were p-(p-azobenzeneazo)-benzene-arsonic acid, etc.

tizing conjugate is formed by linking the hapten to the benzene ring of tyrosine in the protein, the specificity of the antibody is apparently not directed strictly against the hapten, but against the hapten-tyrosine part of the conjugate. When Wormall (371) produced antibody in rabbits against iodinated horse serum protein, a type of compound in which the hapten is placed on the benzene ring of tyrosine, inhibition experiments showed that the specificity of the antibody was apparently directed against diiodotyrosine. Jacobs (154) confirmed this. More extensive investigations by Snapper (312) traced the specificity sharply to the 3,5-diiodo-4-oxy-group.

Lest the above seem to have strayed far from the problems of clinical drug allergy, it may be briefly noted that studies of allergy to local anesthetics (121, 173, 326) have produced clinical illustrations of some of the above principles. Cross-reactions follow chemical logic, and individuals differ in their pattern of cross-reactions. Furthermore, human allergies to the cinchona alkaloids have shown the importance of stereo-isomerism (9, 72, 196). The studies of allergy to local anesthetics have raised one incidental point which is, at least from the semantic viewpoint, disturbing. Studies with butyl aminobenzoate (butesin) (172) have shown at least one case in which a cross-reaction to a similar compound, to which the patient had very probably never been exposed, was greater than the reaction to the sensitizing drug, butyl aminobenzoate itself. The experiment would require more data to be convincing but it raises a theoretical question of interest. Given the fact of cross-reactions among several haptens, absolute specificity of the antibody toward any of these haptens appears to be non-existent. Nevertheless, specificity may still be defined as the capacity to react most strongly with the hapten of the sensitizing conjugate. But if the strongest reaction is one of the cross-reactions, how shall we define specificity? Presumably the answer, assuming such experiments are valid, lies in the previously discussed concept that the antibody is directed against—*i.e.*, has maximal reactivity with—a definite group in the sensitizing conjugate formed in *vivo*. This group, like the 3,5-diiodo-4-oxy-group previously discussed, need not be the whole hapten and may consist of part of the hapten with or without part of the protein molecule. If several different haptens are capable, but unequally so, of forming this group, any of them may sensitize, but when a series of the compounds is tested in a sensitized subject, reactivity of the antibody will be maximal against the one most effective in forming the group *in vivo*, regardless of the fact that the most effective one may not have been the sensitizing substance.

Further clinical digression would be out of place at this point, but the above at least serves as a reminder that, despite all the evidence obtained *in vitro* with antisera against haptens, studies demonstrating allergic reactions in living animals were required before the hapten theory could be seriously invoked as an explanation of drug allergy.

Guinea pigs actively sensitized with an arsanilic acid-horse serum conjugate developed anaphylactic shock when later challenged with an arsanilic acid-chicken serum conjugate (175, 187). Klopstock and Selter (175) sensitized guinea pigs with an arsanilic acid-guinea pig serum conjugate and produced anaphylaxis

by later challenging with the same conjugate. A nice parallelism with *in vitro* specific inhibition was established through the finding that those compounds which had *in vitro* caused specific inhibition, *i.e.*, the hapten alone or simple azocompounds made by coupling the hapten with, for example, tyrosine, were capable of desensitizing the animals without themselves causing anaphylaxis. Those azodyes which had caused actual precipitation *in vitro*, *e.g.*, those in which suberanilic or succinanilic acid was the incorporated hapten, did produce anaphylactic shock in appropriately sensitized animals (193) and gave positive reactions in Schultz-Dale isolated tissue preparations (195). Both active and passive sensitization were effected in the systemic anaphylaxis and Schultz-Dale experiments. As would be predicted from the previously mentioned *in vitro* experiments, animals sensitized against *d-p*-aminotartranilic acid-protein conjugates did not cross-react anaphylactically when challenged with a protein conjugate of the levo-isomer. Wedum (359) sensitized guinea pigs and rabbits to various sulfonamides by using protein conjugates and showed, by both *in vivo* and *in vitro* tests, that cross-reactions occurred within this group of compounds.

In experiments with iodoproteins Jacobs (155) produced *in vivo* results consistent with those obtained *in vitro*, *i.e.*, animals actively sensitized by iodoproteins developed anaphylactic shock when challenged with iodoprotein, could be desensitized by prior injection of diiodotyrosine without developing anaphylaxis, and could not be desensitized by prior injection of sodium iodide.

Specific inhibition by the unconjugated hapten has been demonstrated in Schultz-Dale preparations of isolated guinea pig uterus and intestine with antipyrine (231) and a series of phenylarsonic acid derivatives (32), respectively. In the former experiment an antipyrine-protein conjugate was used and gave a positive reaction in the absence but not in the presence of unconjugated hapten, while in the latter protein-free polyhaptenic azocompounds were used instead of hapten-protein conjugates to give positive reactions under analogous conditions.

The parallelism between specific inhibition *in vitro* and desensitization without anaphylaxis has flaws, however. Desensitization by injection of the hapten, arsanilic acid, alone required that relatively large amounts be injected and was not always successful (187). Klopstock and Selter (165), using the same hapten, did not report clearcut desensitization by the hapten alone. The possibility of non-specific desensitization, though not very likely here, must always be considered in experiments involving the intravenous administration of compounds which may be directly toxic to the recipient. But Landsteiner (175) demonstrated the specificity of desensitization by azodyes. Even if the parallelism between specific inhibition and desensitization is accepted, the aforementioned work of Pauling, Pressman and their co-workers, in which precipitation of antiserum by appropriate polyhaptenic azocompounds was found to be the rule, would lead one to expect that such azocompounds would, in proper doses, usually desensitize in the manner that a full antigen can, namely in the course of producing non-fatal anaphylaxis. The influence of the challenging dose on the development of anaphylactic manifestations was shown in the previously mentioned experiments with succinanilic acid azodyes (193), as it has also been shown in anaphy-

laxis in animals sensitized to protein (36, 59, 158, 159). Animals sensitized to protein may be specifically desensitized without signs of anaphylaxis by small doses of the antigen. Similarly, desensitization by those azocompounds which Landsteiner has found to cause no precipitation *in vitro* and no anaphylaxis in sensitized animals might still be related to dosage, and larger doses might have produced overt anaphylaxis. In support of this is the observation by Landsteiner that such azocompounds, in the doses used, did occasionally produce signs suggestive of mild anaphylaxis (187). Against it, however, is the fact that in individuals sensitized to proteins desensitization without an overt reaction can usually be produced only by serial injection of several small doses of antigen. Desensitization without anaphylaxis was produced by a single dose of the arsanilic acid azocompound. However, in the desensitization, by subcutaneous injection of a hapten-protein conjugate, of animals sensitized by intracutaneous injection of picryl chloride (see below) one dose was sufficient, though this dose sometimes gave rise to local edema and reddening of the skin (177).

The aforementioned experiments have been concerned with the immediate type of allergy, the usual characteristics of which are that manifestations occur promptly after an adequate challenging dose has been given, sensitization by the intravenous route is commonly successful, circulating humoral antibodies can in most instances be demonstrated, and desensitization is often feasible. But many, in fact probably most instances of human allergy to drugs are of the delayed or "tuberculin" type, which is usually characterized by delayed response to adequate challenge, pre-eminence of the skin as the route of choice for sensitization, absence of circulating humoral antibodies and failure of most attempts at desensitization. The logical next step in the development of the hapten theory was the investigation of allergies of the delayed type.

Guinea pigs sensitized by repeated intracutaneous injections of unconjugated acyl chlorides developed delayed skin reactions to contact or intracutaneous testing with the unconjugated hapten; gave, on intracutaneous testing with a hapten-protein conjugate, an immediate flare and wheal which was followed by a delayed skin reaction; and developed systemic anaphylaxis when challenged intravenously with the conjugate (182). Tissue from guinea pigs sensitized to unconjugated picryl chloride or 2, 4-dinitrochlorobenzene in the same type of experiment gave immediate positive reactions in Schultz-Dale preparations when tested with the conjugate (177). Circulating humoral antibodies were demonstrated by passive transfer (see below). When guinea pigs were sensitized by intracutaneous injections of the conjugate, they developed only the anaphylactic type of allergy and did not, conversely, develop the delayed type as shown by later skin tests. Animals sensitized by intracutaneous injection of the unconjugated hapten could be desensitized until free of their immediate anaphylactic type of allergy by subcutaneous injection of the conjugate, but this did not abolish the delayed type of allergy.

A further study of the antibody in the serum of guinea pigs sensitized by intradermal injections of various haptens, including picryl chloride and dinitrochlorobenzene, showed that precipitins could be demonstrated with hapten-

protein conjugates and that passive transfer of the antibody to another guinea pig conferred on the recipient the immediate type of allergy, skin reactions or systemic anaphylaxis, depending on the routes used. Heating at 56°C. for 4 hours did not appreciably affect the antibody, in contrast to the effect of such treatment on human reaginic antibody (43).

The results of sensitization of guinea pigs by intracutaneous injections of unconjugated unneutralized arsphenamine seemed to be consistent with the above, for such animals manifested systemic anaphylaxis when challenged intravenously with a mixture of neutralized arsphenamine and guinea pig serum or even with unneutralized arsphenamine alone (183). However, it was later found (58) that when guinea pigs were sensitized by intracutaneous injections of *neutralized* arsphenamine, they did not develop anaphylaxis when challenged intravenously, even if an arsphenamine-protein conjugate was used in the challenge. The skin of these animals developed an urticarial type of allergy as a result of the sensitization with neutralized arsphenamine. When guinea pigs were sensitized by an intradermal injection of arsphenamine-protein conjugate, challenging by intravenous injection of the conjugate led to anaphylaxis.

In apparent contrast to the above, Haxthausen (136) was able to develop a delayed type of allergy in human skin by intracutaneous injection of a mixture of dinitrochlorobenzene and horse serum, but, although there are several reasons to suspect that a conjugate was formed *in vitro*, it is still possible that some unconjugated hapten may have been present and have accounted for the result.

The delayed type of allergy can be fitted into the hapten theory if these experiments are interpreted as showing that injection of a preformed conjugate gives rise only to an allergic state manifested by immediate reactions and not to the delayed type. Conjugates that are formed *in vivo* can according to this interpretation give rise to either. But the rôle of conjugates in the development of the delayed type is by no means proved by these experiments. If we support the theory in one instance on the grounds that known conjugates can be shown to sensitize, we are hard put to support it in the other on the grounds that known conjugates cannot be shown to do so. The above experiments have a very real value, however, in establishing a closer connection between anaphylaxis and delayed allergy of the skin. Landsteiner and Chase (179) succeeded in showing that conjugates can, under proper conditions, sensitize the skin in such a way that delayed allergic reactions may be elicited. A conjugate of picryl chloride and guinea pig red cell stromata was injected intraperitoneally into guinea pigs that had also received intraperitoneal injections of killed tubercle bacilli as an adjuvant. The animals developed both the delayed contact type and the immediate anaphylactic type of allergy, as shown, respectively, by testing the skin with the hapten and injecting a hapten-serum conjugate intravenously. Guinea pigs treated similarly except that they received no adjuvant showed definite anaphylactic but only slight skin sensitization. This experiment incidentally showed also that the skin is not an obligatory route of sensitization for the delayed type of allergy.

In the face of the above experiments, the most cogent objection to the hapten theory is that experiments employing a conjugate preformed *in vitro* do not prove

that such a conjugate is formed *in vivo*. Furthermore, the procedures used to form conjugates *in vivo*, especially diazotization, are too drastic to be expected *in vivo* (119). The latter objection is somewhat weakened by the fact that in the case of aminopyrine gentler treatment *in vitro* succeeded in forming an antigen effective when given by a non-dermal route (287). Aminopyrine, allowed to stand with fresh guinea pig whole blood for thirty minutes, formed a conjugate which would, on intraperitoneal injection, sensitize the animals against later intravenous challenge by the conjugate or by unconjugated aminopyrine. Furthermore, unconjugated aminopyrine, given intraperitoneally, sensitized guinea pigs against later intravenous challenge by the conjugate but not against later intravenous challenge by unconjugated aminopyrine. This finding—that anaphylaxis would occur if unconjugated hapten were used either for sensitizing or for challenging, but not if it were used for both—is puzzling. The authors carried out the indicated controls but the direct toxicity of aminopyrine was probably not sufficiently investigated. The authors were able to show by direct analysis of supernatants and ultrafiltrates, respectively, that aminopyrine mixed with either red cells or serum was firmly bound. Dameshek and Colmes (67) took advantage of this binding of aminopyrine to serum to form a conjugate which produced a positive skin test in patients allergic to aminopyrine (see section IV A). At any rate, it should be kept in mind that the known ability of many drugs to form *in vivo* easily reversible complexes with albumin (119) cannot be accepted as proof that conjugates of the type necessary for sensitization are formed.

The all-important demonstration of the formation of conjugates *in vivo* has been accomplished for a series of substituted 2,4-dinitrobenzenes by Eisen and his associates (83, 84). By chromatographic and spectrographic analysis of hydrolysates of guinea pig skin exposed, during life, to the unconjugated haptens these authors showed *in vivo* combination of the halodinitrobenzenes with the ϵ-NH_2 group of lysine and, in the case of dinitrobenzenes with sulfur-containing substituents, with the sulfur of cysteine or cystine. Reactions of the substituted dinitrobenzenes with keratin *in vitro* also gave results consistent with the above and reactions with γ-globulin *in vitro* gave partly consistent results. But these investigators in their careful exploration have noted certain puzzling facts. For example, those compounds found to be combined *in vivo* with the NH_2 group and not with the —SH group are nevertheless known to combine *in vitro* with the —SH of cysteine. The authors mention but are inclined to disparage the possibility that this inconsistency may be due to failure of the haptens to penetrate deeply enough into the skin to reach layers rich in —SH groups.

Schamberg and Flesh (291) postulated that a thio-β-naphthol which they had found to be a cause of contact dermatitis might displace naturally occurring cysteine in the skin. They tried unsuccessfully to inhibit the reaction by intracutaneous injection of an "excess" of cysteine prior to challenging.

Even after the demonstration of formation of hapten-protein conjugates *in vivo*, direct proof that such conjugates are actually the sensitizing forms would be very difficult to obtain, for the details of sensitization by any antigen are not yet fully known. But very suggestive indirect evidence was obtained through the

finding that, in a series of closely related halo- and nitrobenzenes, the ability of each compound to sensitize guinea pig skin was correlated with the compound's ability to react with aniline *in vitro*. Reactivity with aniline was assumed to be a measure of reactivity with similar chemical groups in protein. This assumption led to the prediction that benzyl and acyl chlorides would be potent sensitizing agents—a prediction verified by subsequent experiments which have already been discussed (182). In a series of 1,2,4-dinitrochlorobenzenes a positive correlation was found between ability to sensitize and ability to cause stimulation of mitosis or, in higher doses, necrosis (28).

The evidence in favor of the hapten theory is impressive, as virtually every strut in its framework is supported by an experiment that appears valid, at least for the simple substances studied in that particular experiment. Some basis for criticism may lie in the fact that the substances chosen for investigation of one supporting point have sometimes been chemically and pharmacologically quite different from those chosen for another. From this point of view, the recent tendency to concentrate investigation on a relatively restricted group of compounds is advantageous. In default of general and incontestable proof for all simple substances, complete proof for even one such substance is probably next best. However, there is perhaps an exception: because of the direct nature of the evidence obtained by experiments such as those of Eisen and his collaborators, it would be very helpful if this type of experiment could be extended to a wide variety of substances and thus support a general statement.

If the present theory is rejected, the other possible choices are the following: (a) the simple substance does not form any larger complex before sensitizing, (b) the simple substance forms a larger complex, but not with protein, before sensitizing, or (c) the reactions to simple substances never involve a true process of sensitization at all. Previous discussion has touched on objections to (a). No good evidence for either (a) or (b) has been produced. Attempts have been made to show that the hapten, without becoming attached to the host's protein, nevertheless modifies it enough to make the latter antigenic for the host (87). The evidence is not convincing. A pre-emptory rejection of (c) seems justified on the basis of the numerous experiments described above. Demonstration of specific antibody by passive transfer, which is the most telling evidence in this respect, will be discussed in Section V A.

Certain extensions of the hapten theory must still be regarded as *sub judice*. Is formation of a hapten-protein conjugate *in vivo* necessary for *eliciting* the allergic reaction in a sensitized individual? The previously described experiments with certain protein-free di- or polyhaptenic compounds suggest that combination with non-antibody protein is not obligatory for eliciting reactions. The very rapid development of anaphylaxis from penicillin, with death sometimes occurring within a few minutes after injection of the drug in occasional patients (96), also suggests that preliminary combination with non-antibody protein may not be important. Klopstock and Selter (165) failed to observe anaphylaxis in sensitized guinea pigs challenged intravenously by appropriate diazonium compounds, although the latter are chemically highly reactive. When such com-

pounds were first allowed to react *in vitro* with protein, however, they formed a conjugate which did elicit anaphylaxis when given intravenously to sensitized animals. But these experiments do not rule out the possibility that some drugs can combine rapidly with protein *in vivo*. The role of easily reversible drug-albumin complexes, which has been discounted in the previous discussion of sensitization, might conceivably be more important in eliciting reactions. The eliciting of delayed skin reactions to substituted dinitrobenzenes seems to require the formation *in vivo* of the same type of hapten-protein conjugate that was found important in sensitization. The skin of guinea pigs sensitized to 2,4-dinitrofluorobenzene was tested by contact with a group of 8 other substituted dinitrofluorobenzenes. Only 4 of the compounds were able to elicit an allergic skin reaction, and there was perfect positive correlation between this ability and the ability to combine with the ϵ-NH_2 group of lysine in the living epidermis (83). The authors state that at least one of the compounds which did not elicit a reaction is known to be bound reversibly to serum albumin. Attempts to convert the non-elicitors into elicitors by incorporating them in di- and trihaptenic compounds were unsuccessful. But a preformed conjugate of an elicitor with lysine, the linkage being at the ϵ-NH_2 group, also failed to elicit a reaction. The last finding, while not fatal to the idea that a conjugate formed *in vivo* may elicit the reaction, certainly raises a doubt.

Though the formation of a conjugate *in vivo* appears to be a necessary condition for sensitization by a simple substance which has not first been conjugated *in vitro*, there is some reason to doubt that it is a sufficient condition. It is true that in many experiments with preformed conjugates, most or all of the animals became sensitized, but such experiments often involved substances deliberately chosen for their high sensitizing potency, coupled to a foreign protein. Landsteiner (176) points out that sometimes only a small percentage of the animals so sensitized have antibodies directed solely or chiefly against the hapten. Eisen regularly found binding of haptens to amino acids in the skin after initial exposure, *i.e.*, before any selection could be made on the basis of presence or absence of sensitization. However, the absence of such selection may lose force in this argument through the fact that the haptens used were potent sensitizing agents and could be expected to sensitize the majority, anyway. Haxthausen (139) injected Co^{60} as $CoCl_2$ into the skin of normal individuals and of patients with contact allergy to cobalt, and measured the rate of disappearance of the radioactivity. No difference was found between the two groups. This question will be further discussed in connection with thrombocytopenia.

B. Types of clinical reactions

In considering any classification one question appears crucial: has the subject advanced to that point where there is enough understanding of true fundamental similarities and differences to enable one to make a classification that will outline such basic similarities and differences? The reviewer doubts that our understanding of the details of the various manifestations of drug allergy has reached the aforementioned point. Until this point is reached, convenience would seem

to be the most reasonable aim of classification and is the basis for the arrangement adopted here. But as classifications based on convenience are makeshifts designed only to last until advances in knowledge permit a better one, it is at once admitted that several other classifications would serve as well for the present.

Lists of certain drugs which are reasonably well established as clinical causes of asthma, angio-edema, urticaria, dermatitis and fever as well as lists of certain drugs which have probably caused depression of bone marrow or blood in man have been tabulated in a previous review (34) and will therefore not be given again here. A good review of the various types of clinical reactions and drugs frequently causing them has been provided by Sherman (301).

1. Reactions which are also seen in allergy to proteins. a) Systemic anaphylaxis, an explosive reaction featuring parageusia, a feeling of compression in the chest, asthmatic dyspnea, acute emphysema, cyanosis, perspiration, urticaria, angio-edema, weakness and dizziness, nausea and vomiting, abdominal pain, fall in blood pressure, unconsciousness, respiratory failure and death, has been clearly seen after penicillin administration (18, 51, 62, 93, 96, 163, 210, 323, 361, 364, 368). Not all of the manifestations listed occur in every instance, and death may occur very quickly, after several hours or not at all. Nevertheless, despite the facts that the reaction may be prolonged and may consist of only three or four manifestations, each of which may be thought of as a reaction in itself, it seems proper to recognize systemic anaphylaxis in clinical drug allergy as an entity, characterized chiefly by its explosive onset, constellation of signs and symptoms and serious nature. The clinical drug reaction resembles human anaphylaxis to foreign proteins. For a summary of the latter see Chase (44). In connection with the common use of the guinea pig uterus in Schultz-Dale preparations, it is also interesting to note that uterine contractions and even abortion are stated to have occurred during human anaphylaxis (300).

Further discussion of anaphylaxis will be found in Section IV A. It is unlikely that penicillin is the only drug causing anaphylaxis in clinical medicine, but its extraordinarily low direct toxicity makes such reactions easier to evaluate. Reports of "anaphylaxis" from many drugs are hard to judge because of the possibility of hyperreactivity to a direct toxic effect, particularly on the heart. Careful observation may reveal concomitant manifestations such as urticaria which suggest anaphylaxis, but such observations cannot always be expected because the physician is so strenuously occupied with emergency treatment of the reaction.

b) Asthma is of particular interest because of the predominant role of paroxysmal bronchial obstruction in systemic anaphylaxis in the guinea pig. This species has been both sensitized and challenged successfully by inhalation of horse dander extract (268). Sensitization of guinea pigs to a simple substance, trinitrophenylmethylnitramine ("tetryl"), by inhalation was carried out by Gell (110), who challenged the animals intravenously with a hapten-protein conjugate. Tissues from guinea pigs sensitized to "tetryl" also gave weak responses in the Schultz-Dale preparation.

A notorious offender is acetylsalicylic acid. A questionnaire survey of "sensitivity" to this drug showed 281 cases out of approximately 88,000 patients seen by practicing allergists (109) (the crude data of the authors have been used, but their corrections have been modified). Death has occurred in asthmatic patients within a few minutes after ingestion of one 300 mg. aspirin tablet (81). The reviewer was impressed by a case history which was described to him and which he had the opportunity of verifying by direct correspondence with the attending physician. A woman, desiring an analgesic and knowing aspirin had in the past precipitated some of her asthmatic attacks, took a proprietary remedy containing aspirin in the mistaken belief that it contained none. The ensuing attack was fatal in about an hour. Psychic factors thus seem to have been at a minimum here.

c) *Allergic conjunctivitis* has been caused by topical administration of such drugs as larocaine (339) and antazoline (antistine) (230), whereas others such as sulfathiazole (108) and neoarsphenamine (115) have caused it on systemic administration. Conjunctivitis is often a prominent feature of the syndrome of erythema multiforme with inflammation of various mucous membranes, sometimes termed the Stevens-Johnson syndrome. Certain cases of this syndrome have apparently been provoked by systemic administration of drugs (40, 297), though not necessarily on an allergic basis. Erythema multiforme without mucosal inflammation has been definitely produced by sulfonamides (7), probably on an allergic basis.

Rhinitis, like conjunctivitis, is, of course, part of the syndrome of allergic coryza, or "hay fever," caused by pollens. When produced by exposure to simple substances, the irritant, *i. e.*, direct toxic effect of the latter, must be considered. Nevertheless, Feinberg and Watrous (97) studied a series of pharmaceutical workers who developed sneezing, rhinorrhea and nasal obstruction when exposed to dust containing chloramine-T or halazone and concluded that allergy to these compounds was responsible, their best evidence being several positive Prausnitz-Küstner reactions. Most of these patients also developed asthma when exposed to the compounds.

It is quite probable that locally applied drugs are more important causes of allergic conjunctivitis than those administered systemically. Theodore (340) states that one can make a reliable clinical differentiation between irritation, *i.e.*, direct toxic reactions and allergy in drug-induced conjunctivitis. Evaluation of this claim is difficult.

d) *Urticaria* is undoubtedly one of the more common types of allergic reaction to drugs, though the ease with which it is recognized may contribute to the frequency with which it is reported.

e) *Angio-edema*, more often termed angioneurotic edema in the past, was studied in a group of 132 patients in Denmark by Bruun (27). In 73 he believed an allergic basis to be "unquestionable" and in 38 of the latter drugs were considered to be the allergens. In 28 of these 38, testing by re-exposure was performed with a positive result. Bruun found aspirin to be the worst offender here, as in 9 of the 28 aspirin was definitely the cause, while in 9 others proprietary medicines

containing aspirin were the cause. The separate ingredients of the latter were not tested. Penicillin is probably much more important as a cause of urticaria and angio-edema in the United States (322).

f) The syndrome of serum sickness, and *g) polyarteritis nodosa and apparently allied reactions,* though clinically distinct, will be considered together.

Rich (270, 271, 273, 274) found fresh lesions of polyarteritis (also termed peri- and panarteritis) nodosa in patients dying during serum sickness and was able to produce polyarteritis nodosa in rabbits by sensitizing them to foreign serum. Other workers (30, 69) confirmed this and also succeeded in preventing the reaction in serum-treated rabbits by suppressing antibody formation with the aid of nitrogen mustard. Germuth (112) injected a solution of crystalline bovine serum albumin into rabbits and produced cardiac, vascular, and renal lesions resembling those of rheumatic fever, polyarteritis nodosa and acute glomerulonephritis, respectively. He also produced "peculiar granulomatous lesions consisting of epithelioid and foreign body cells" in splenic follicles and lymph nodes. Such lesions have been described in polyarteritis. Furthermore, by repeated testing of the animals' sera for antigen or antibody excess, Germuth showed clearly that the lesions began to be seen at about the time that the antigen concentration began to fall sharply, reached their peak around the time that neither antigen nor antibody excess was detectable in the serum, and faded as excess of antibody gradually increased in the serum. The lesions thus coincided in time rather well with the stage of antigen-antibody reaction. Such experiments, as well as clinical studies of the relation between streptococcal infections and rheumatic fever and glomerulonephritis, have drawn attention to the possible role of allergy to proteins in the so-called "collagen diseases", *i. e.*, rheumatic fever, glomerulonephritis, polyarteritis nodosa, lupus erythematosus disseminata, scleroderma, dermatomyositis, rheumatoid arthritis, and possibly others. It is therefore important to review instances in which allergy to drugs has probably been a factor here.

The syndrome of fever, lymphadenopathy, arthralgia, urticaria, and occasionally additional manifestations such as neuritis, first described as an allergic reaction to therapeutic antiserum, and hence still known as the serum sickness syndrome, has been reported after administration of several drugs, including sulfonamides (204), penicillin (123) and iodine (273). Kern and Wimberley (163) even state that it is now the most common allergic reaction to penicillin. It is somewhat surprising that, despite the relative frequency of this apparently allergic syndrome and the wide use of some of the drugs which have caused it, reliable reports of second attacks due to readministration of the offending drug are not easy to find. However, the similarity of the clinical findings to those of true serum sickness, *i.e.*, allergy to heterologous serum protein, and the occurrence in both of a typical incubation period of about a week, make it reasonable to classify this syndrome among drug allergies. Quite possibly the extremely uncomfortable and at times prolonged nature of the reaction impresses both patient and physician to such an extent that later readministration is not likely. One reliable observer who does report experience with patients developing this re-

action to penicillin a second time is Sherman (303). He makes the interesting point that, in contrast to true serum sickness due to protein, there is no shortening of the latent period between re-exposure and onset of reaction in a second attack of the serum sickness syndrome due to penicillin. This suggests that loss of allergy may have occurred before the second exposure (see section IV A). Sherman also notes the absence of demonstrable circulating humoral antibodies in patients showing this reaction to penicillin—again in contrast to the situation in true serum sickness. Rich found fresh lesions of polyarteritis nodosa in one patient who had not received serum but who had received sulfathiazole, and since then the disease has been reported to follow treatment with iodine (272), aspirin (273), dilantin (273), thiouracil (228), methylthiouracil (220) and propylthiouracil (213). Although most of these reports are not conclusive for drug allergy, the above case of polyarteritis nodosa associated with propylthiouracil treatment offers fairly convincing evidence, namely, absence of initial reaction to the drug, sudden appearance of signs and symptoms of the disease on three subsequent readministrations of the drug, improvement with discontinuance of the drug and confirmation of the diagnosis by autopsy. Granulomas and focal necroses have been found in the tissues of patients who had received sulfonamides (133, 198, 217) and may, as suggested above, be part of this general group of reactions.

More recently a syndrome consisting of polyarthritis, fever, polyserositis, pneumonitis, urticaria, other skin lesions, and facial edema and resembling in some respects lupus erythematosus disseminata has been shown to be due to hydralazine (apresoline), probably on an allergic basis (80, 253, 310). The results of the usual test for "lupus erythematosus factor" in the plasma of these patients has been positive in several but not all instances. This test also gave positive results in three patients with somewhat bizarre reactions to penicillin (354), including, in two of the patients, arthralgia. In at least one instance associated with each drug the result of the test has become negative with clinical improvement. The extremely high female/male ratio, characteristic of the usual clinical description of lupus erythematosus disseminata and somewhat difficult to explain if one assumes an allergic basis (163), has not been noted in instances of this reaction to hydralazine.

Despite the great interest of these studies, one should not forget that it is difficult to know how precisely lesions in animals can be equated to lesions in man and also that the classification of the "collagen disease" group into its several present subdivisions may need radical revision in the future. In fact, discussions of lupus erythematosus disseminata, polyarteritis nodosa, etc., often seem like the discussions of general paresis, tabes dorsalis, meningovascular syphilis, etc., that one might expect if the *Treponema pallidum* were still undiscovered.

2. Dermatitis due to drug allergy poses at present a problem in subclassification similar to that previously discussed for the whole subject. A wide variety of clinical types of dermatitis may be produced by the same drug, e.g., arsphenamine (33), in different patients. Contact dermatitis. in which a) direct contact

with the epidermis is the route of exposure for sensitization and eliciting of reactions, b) patch tests represent a valid and reasonably safe diagnostic test and c) a clear analogy with much experimental work in animals exists, may reasonably be separated from the rest. Because of its grave nature and the simultaneous occurrence of lesions in other organs in some patients (see below) exfoliative dermatitis also deserves special consideration. Further distinctions will not be attempted here. An experienced dermatologist (330) states, however, that despite the aforementioned variability of clinical reactions to many drugs, there are certain skin lesions which are definitely characteristic of certain drugs. Even though such correlations are imperfect, they suggest that it is probably not correct to conceive of all these forms of dermatitis as essentially one reaction, for a consideration of other types of allergy will show that it is unusual for one organ in one species to show several striking variations in one allergic reaction, the variations being conditioned by the antigen. Because of the complexity of the skin more detailed knowledge of the histological localization of various drugs will probably be required before the solution of this problem is possible.

Substances that are primarily irritants are often effective antigens and skin sites which are already inflamed are sites of choice for contact sensitization. Sulzberger and Rostenberg (333) showed increased susceptibility to sensitization by local application of simple substances in patients who already had allergic contact dermatitis from other substances, but this experiment might be alternatively interpreted as showing that patients who have shown themselves capable of developing one allergy have a greater than normal capacity to develop others, *i.e.*, the difference might be in the patient as a whole, not in the skin site (see section III C 5). A comparison of the results of exposure to merthiolate in 187 patients with skin diseases and 88 surgical patients showed positive results to subsequent patch tests in 66 of the former and none of the latter (348). But the factor of possible increased number of applications in the patients with skin disease must also be considered here. Although a single controlled study would be more convincing, one is struck by the difference in the results obtained with sulfonamide ointments by Sulzberger (332), who sensitized the skin of 19 per cent of 259 volunteers with artificial burns as site of applications, and those obtained by Gottschalk and Weiss (125), who used sulfonamide ointments on volunteers with no initial skin lesions and found a much lower incidence of sensitization.

Locally applied chemotherapeutic agents, e.g., sulfonamides (50, 61), penicillin (149, 150), streptomycin (309) and bacitracin (222) have attracted much interest as causes of contact dermatitis. In clinical medicine such applications are almost invariably made on sites which are already inflamed. The distinction between hyperreactivity to direct toxic effects and allergy is difficult with many substances in this situation. Holmqvist (147) listed criteria for distinction between hyperreactivity and allergy in dermatitis due to contact with arsenic. He believed the former showed a shorter period between application of the patch test and the stage of maximal intensity of the reaction, sharper localization at the site of patch test, more pustulation and, microscopically, more necrosis and leukocytic exudate (as opposed to spongiosis and vesiculation in allergic reactions). By re-

exposure tests and the use of various compounds and concentrations Holmqvist produced good but not unequivocal evidence for his criteria, but the validity of such criteria in general is by no means universally accepted by dermatologists (283). In fact, Zeligman (375) has questioned the whole body of work in which dinitrochlorobenzene has been used to study contact allergy in guinea pigs on the grounds that he has been able to demonstrate direct toxic effects on the skin when 0.1 to 5 per cent solutions are used, concentrations equal to or even less than those which have often been used by others in such experiments.

The manner in which application of an antigen at one site eventually leads to generalized sensitization of the skin remains unclear. The results of experiments with skin islands show that there is a latent period, sometimes of a few hours after application of the antigen, during which time removal of the island will prevent sensitization. Haxthausen (135) painted dinitrochlorobenzene on human skin, and found that under ordinary circumstances the sensitization would first be demonstrable ten to twenty days after the sensitizing exposure. Freezing of the site of initial dinitrochlorobenzene application by ethyl chloride as late as eight days after the application prevented sensitization. It is tempting to speculate that a hapten-protein conjugate is being formed during this latent period, but it is difficult to see why such a long period is required. We do not know whether the substance eventually distributed to the entire skin is antigen or antibody. It is possible, at any rate, that a certain concentration of antigen remains at the site of original exposure, as the first indication of sensitization at the end of the incubation period is often a "flare-up", *i.e.*, a spontaneous eruption at this site (127). Although the spontaneous reaction usually does not spread beyond the site of the previous sensitizing application, it may occasionally do so (111). One can sometimes show by contact testing that after allergy has developed at the original site, the allergy spreads rapidly and more or less centrifugally until the entire skin is allergic within the next few days. The centrifugal pattern of spread may not be entirely regular (135). Such "flare-ups" might alternatively depend upon this area's being the site of earliest antibody formation. Holmqvist (147), upon patch testing a patient with previous arsenical dermatitis which had been quiescent for twenty months, produced not only a reaction at the site of the test but also a simultaneous, well-localized "flare-up" at a distant site where there had been a patch test twenty months previously and no patch test since then. A similar phenomenon has been observed with streptomycin (63) (see also the discussion of fixed eruptions below). This phenomenon does not directly bear on the possibility that the usual "flare-up" represents the site of earliest appearance of antibody but it does suggest that such a site eventually retains a concentration of antibody higher than that in surrounding areas. A less attractive but possible hypothesis is that the site in question has retained a concentration of antigen greater than that in surrounding areas but still too small to be effective till reinforced by diffusion of antigens from the site of re-exposure.

Techniques using skin islands have been used to trace anatomically the route of spread of sensitization in man (135) and guinea pig (178). Rostenberg (282,

284) and Grolnick (127) have reviewed this work. In man, Haxthausen (137) also performed cross-transplantation of skin in identical twins, one of whom had been sensitized by contact to dinitrochlorobenzene. Subsequent testing revealed that the skin from the sensitized twin lost its allergy upon transplantation to the unsensitized one, while the latter's skin became allergic when transplanted to the former. This result was confirmed in another pair of identical twins. Such experiments suggest that the antibody is not produced locally. Goldsmith (118), on the other hand, points out that his observation of spontaneous centrifugal spread of a "flare-up" reaction in one patient suggests local production of antibody.

In human allergic dermatitis due to drugs, the sensitizing and eliciting doses may be given by any of the usual routes of administration, including the oral, even though attempts to sensitize laboratory animals by the oral route have been regularly unsuccessful. Patients whose skin has been sensitized by direct external contact with a drug may later have a recurrence of dermatitis after receiving the drug orally, and vice versa (56, 330). However, recurrence of contact dermatitis does not always follow systemic administration of the offending drug (150).

The allergic dermatitis produced by some systemically administered drugs, *e.g.*, antipyrine, may be sharply localized to certain small areas of the skin and only these areas may react upon systemic re-exposure. The sites of such fixed eruptions vary from patient to patient. The responsible allergen has usually been a drug, but Cooke (56) describes a case due to tomatoes, and other exceptions to this general rule have been reported (13). Fixed eruptions have been investigated by transplantation experiments without consistent results (13, 301). Attempts to create fixed drug eruptions experimentally have not been entirely convincing (135, 147). The reason for the peculiar localization of these reactions thus remains undiscovered. Hopkins and Lawrence (150) found that patients receiving penicillin intramuscularly sometimes developed a skin reaction localized to areas which had previously been treated directly with penicillin. This type of localization is reminiscent of certain of the "flare-ups" discussed above but presumably the sites of previous penicillin therapy in Hopkins and Lawrence's patients had been infected or in some other way abnormal even before initial exposure to penicillin; otherwise, such local treatment would not have been given.

Some of the drugs which have been reasonably implicated as causes of exfoliative dermatitis have been listed in a previous review (34). Phenylbutazone (butazolidine), which may cause several types of reactions, is a more recent addition to this list (232). Good evidence that at least some instances of drug-induced exfoliative dermatitis are allergic in nature can be found in reports of its occurrence in patients receiving neoarsphenamine (54, 305), quinidine (337), potassium thiocyanate (360) and tincture of iodine (295), the last having been painted on the skin. As previously mentioned, exfoliative dermatitis may be accompanied by serious lesions in other organs (197). There is nothing surprising in the occurrence of such lesions in association with exfoliative dermatitis due to certain notoriously toxic substances, *e.g.*, gold or arsenic compounds, but their

occurrence accompanying exfoliative dermatitis from phenobarbital (214, 367) is more noteworthy.

Sensitization of the skin does not necessarily imply sensitization of mucous membranes (56, 284), even though the two sometimes occur simultaneously.

3. Reactions not characteristic of allergy to proteins. a) Deleterious effects on the blood, either through destruction of circulating elements or depression of the bone marrow, have been observed with many drugs. The effects of benzol, nitrogen mustards, *etc.*, cannot be considered to have an allergic basis, but agranulocytosis due to aminopyrine (67, 259) and thrombocytopenic purpura due to neoarsphenamine (90, 91, 92), quinine (208), quinidine (236), sedormid (215), potassium iodide (71) and phenylbutazone (171) appear to have fulfilled the criteria of allergy.

The serious blood changes apparently produced by allergy to drugs may be classified as agranulocytosis (or in less severe cases, granulocytopenia), thrombocytopenic purpura, and aplastic anemia; the last implies that granulocytes, platelets and red cells are all reduced in number. There can be no doubt that, depending on the drug involved, the granulocytes may virtually disappear while the platelets are unaffected, or vice versa. When both granulocytes and platelets are affected, there is usually concomitant anemia, although on rare occasions this may not hold true (124). Anemia due to drug allergy and unaccompanied by a decrease both in platelets and granulocytes is certainly uncommon, if it occurs at all. In one patient in whom phenylbutazone caused a depression of the white cells without thrombocytopenia, a pre-existing anemia was definitely exacerbated (143). The severe acute hemolytic anemia which sometimes occurred during the first few days of sulfanilamide therapy was probably not allergic in nature but simply represented a hyperreaction, for it occured in a milder degree in most patients receiving the drug and appeared to be independent of previous exposure (340, 357). But reduction in the number of circulating blood cells may depend upon depression of hematopoiesis as well as destruction of the circulating cells, and as Osgood (241) points out, the long life span of red cells as compared with that of platelets and granulocytes makes it more difficult to detect the effects of temporary depression of erythropoiesis than of granulopoiesis or platelet formation.

Antibodies against circulating blood elements, independent of any drug, are known to occur in humans, not only in certain types of hemolytic anemia but also as causes of thrombocytopenia (131, 320) and of aplastic anemia (226). Martensson and Vikbladh (209) demonstrated an antibody against leukocytes in the serum of a leukopenic patient. The patient had received a brief course of streptomycin prior to the discovery of the antibody but the antibody was active in the absence of streptomycin. Similarly antibodies against dog (339) and rat (317) platelets and against guinea pig granulocytes (225) have been produced in rabbits and have caused thrombocytopenia and granulocytopenia, respectively, on re-injection into the donor species. But such relatively straightforward antigen-antibody systems do not closely approach the situation in drug allergies. Somewhat more germane are observations in certain instances of allergy to

foreign proteins in which the granulocytes of rabbits (221, 353) and perhaps of man (152) and the platelets of rhesus monkeys (167) have been found to decrease in number as the result of the reaction between the foreign protein and its antibody; but here also the imitation is obviously incomplete. Attempts to produce agranulocytosis in animals by administration of aminopyrine have had only slight and irregular success (169), and the thrombocytopenia produced in rats by administration of sedormid (17) needs further study before conclusions can be drawn.

In contrast to the unsatisfactory results of animal experiments, clinical studies have furnished a great deal of information. Grandjean (126) showed that the plasma of a patient recovering from quinine-induced thrombocytopenia caused a decrease in the platelet count *in vitro* in the presence of quinine. He commented that the stereo-isomer, quinidine, was apparently not a cause of thrombocytopenic purpura in clinical medicine, but in fact subsequent experience has shown quinidine to be probably a more frequent offender than quinine. In the field of drug allergy, *caveat propheta.* Ackroyd (1, 2, 3, 4, 5) showed that the plasma of certain patients who had recovered from thrombocytopenic purpura due to sedormid (allylisopropyl-acetylcarbamide) contained an antibody which would cause lysis of platelets *in vitro* in the presence of sedormid. The effect on platelets was shown both by a decrease in clot retraction and by lysis of platelets under direct microscopic observation. Lysis required platelets + sedormid + antibody + complement. Complement was fixed in the reaction. It should be carefully noted that platelets from normal individuals were lysed in this system as easily as those from the patients under study. Red and white blood cells were not affected. The plasma of normal subjects could not be substituted for the patients' plasma, even when the patients' platelets were used. In the absence of complement, agglutination of platelets without lysis was produced by sedormid + antibody. Antibodies causing agglutination of red cells in the absence of complement and lysis in its presence are, of course, well known. In the absence of sedormid, antibody + complement had no effect on platelets. Adalin (diethylbromacetylcarbamide) gave cross-reactions with sedormid *in vitro.* Attempts at passive transfer, using the Prausnitz-Küstner technique, were unsuccessful. (Moeschlin (224) also obtained negative results in a more significant passive transfer. When 500 ml. of blood was taken from a patient at the time of acute sedormid-induced thrombocytopenia and transfused into another individual not allergic to the drug, administration of the drug to the latter patient caused no thrombocytopenia.) Antibody could be demonstrated in two patients 6 months and 6 years, respectively, after their last previous exposure to sedormid. The plasma of a third similar patient did not destroy platelets in the presence of sedormid, though clot retraction was still inhibited when sedormid was added to his whole blood, 3 months after last previous exposure. The skin of all three gave a positive result to patch test with sedormid. Ackroyd suggests that in addition to causing thrombocytopenia the antibody may damage capillary endothelium in the presence of sedormid.

Larson (196) studied the blood of a patient who had recovered from thrombo-

cytopenic purpura due to quinidine and showed that here too drug + patient's antibody prevented clot retraction in either the patient's or normal blood. He also was able to demonstrate agglutination of platelets by quinidine + patient's blood *in vitro* but was unsuccessful in producing lysis of platelets. The skin gave a negative reaction to patch test with quinidine. Plitman and Stefanini (258) found that normal platelets transfused into a patient who was suffering from acute quinidine-induced thrombocytopenia but whose plasma quinidine concentration had fallen to a low value had a normal survival time. Bigelow and Desforges (16), studying quinidine thrombocytopenia, obtained essentially the same results as Larson except that they also saw a suggestion of beginning lysis of the agglutinated platelets. They made further observations on the evanescence of the antibody. In one patient it was easily demonstrable *in vitro* 6 days, weakly so 12 days, and not demonstrable 33 days after the patient's last exposure to quinidine. Barkham and Tocantins (9) studied another patient with thrombocytopenia due to quinidine and were able to demonstrate both agglutination and lysis in the quinidine + platelet + plasma system, probably because their *in vitro* experiments were carried out at 25° C. while Larson's preparations were chilled in an ice bath. They confirmed the observations of Bigelow and Desforges that normal platelets washed first with saline were not affected by quinidine + antibody, and also showed that the patient's serum could not be effectively substituted for his plasma in the experiments *in vitro*. Patch tests gave negative results in the patient of Barkham and Tocantins, and the plasma antibody could not be detected by experiments *in vitro* 11 days after last previous clinical exposure to quinidine.

In a single experiment, plasma from a patient recovering from quinidine-induced thrombocytopenia was given intravenously in a dose of 3 ml./kgm. to a rabbit, which was then challenged intravenously with quinidine several times in the subsequent twenty-four hours. No significant change in platelet count occurred (35).

The rapid drop in platelet count observed *in vivo*, sometimes within 15 minutes after oral administration of the offending drug (9), confirms the results of *in vitro* studies in showing that direct attack on circulating platelets occurs. The bone marrow shows no striking megakaryocytic changes during the initial phase (9, 224). It is reasonable to expect antigenic similarities between circulating blood elements and their progenitors in the bone marrow and therefore possible participation of the latter in the reaction, but any effects on megakaryocytes seem to come later (224). An alternative explanation is that the effects on the bone marrow are only secondary to the increased demand and represent stimulation followed, in severe cases, by exhaustion. The rapid onset of bleeding—within 15 minutes after injection of the offending drug in one patient (1)—may reflect not only the sudden drop in platelets but also rapid direct effects on capillary endothelial cells. As an incidental point, the rapid onset of effects following oral administration of these drugs suggests that only a very small dose is necessary for this reaction and this finds confirmation in other observations made by Ackroyd (see section III C 3).

Perhaps the chief importance of these experiments is the demonstration that

anyone's platelets can react with quinidine + antibody. If one assumes that the antigen consists of drug + some protein component of platelets, then it is suggested that an individual who becomes allergic to the drug differs from normal individuals, who do not become allergic after exposure, in the capacity to produce antibody rather than in the capacity to form the necessary antigen. This would be consistent with the known situation in most clinical allergies to protein, where there is no question of individual differences in formation of antigen but only differences in response through production of antibody. But one can argue that it might be more prudent to be less precise about the factor present in the plasma of the patients discussed above, instead of flatly terming it an antibody. Ackroyd's demonstration of complement fixation is strong evidence for the antibody nature of the factor, but the rapid disappearance of the factor from the plasma of some patients is puzzling. Although the assumption that platelets + drug form an antigenic conjugate requires one to accept the occurrence of a surprisingly rapid reaction, rejection of this assumption makes explanation even more difficult (328).

Agranulocytosis due to aminopyrine has been investigated by Moeschlin and Wagner (227) through experiments analogous to those described above for thrombocytopenia. The serum or plasma of a patient who had recovered from aminopyrine-induced agranulocytosis caused no significant change in leukocytes mixed with it *in vitro*, even in the presence of added aminopyrine. Incubation temperatures of both 18°C. and 37°C. were used. However, serum or plasma taken from the patient 3 hours after he had received 300 mg. of aminopyrine by mouth did cause significant agglutination without lysis of the patient's or of a normal individual's leukocytes, when mixed with the leukocytes *in vitro*, even though no further aminopyrine was added *in vitro*. In transfusion experiments, 300 ml. of whole blood was taken from the patient under exactly the same circumstances as above and transfused into a normal recipient. Here again the latter sustained a transient fall in leukocyte count from 5000/mm.^{3} to 888/mm.^{3}. Transfusion of normal blood had no such effect. One week after the recipient had received the former transfusion, he received 600 mg. of aminopyrine without effect on his leukocyte count. A similar set of experiments with a second normal recipient gave confirmatory results. Dausset *et al.* (70) demonstrated *in vitro* agglutinins against normal leukocytes in the serum of two patients during agranulocytosis due to aminopyrine. However, the agglutinins were not effective against the patient's own leukocytes. When the patient's leukocyte count had returned to normal, the agglutinins could no longer be demonstrated, even when aminopyrine was added to the serum *in vitro*. The significance of these agglutinins is uncertain.

The results observed in agranulocytosis thus do not agree closely with those observed in thrombocytopenia except that in both instances most experimental work suggests that the cells of normal individuals usually respond in the same way as those of the patient. It is possible that an antigenic conjugate must be formed before these reactions can occur and that differences in ease of formation of the conjugate account for some of the discrepancies between drugs, but, as

previously discussed, other evidence (67, 287) suggests that aminopyrine forms such a conjugate more readily than most drugs, rather than the reverse. These experiments are not even entirely incompatible with the hypothesis that a directly toxic intermediate product of aminopyrine is formed in certain individuals (28, 63).

Failure of three patients who had repeatedly developed leukopenia from aminopyrine to cross-react to the chemically related phenylbutazone was used as the basis for a prediction that the latter would prove to be "without the tendency to agranulocytosis" shown by the former (352). Subsequent clinical experience (88, 143, 171, 256) has shown that such optimism was unjustified.

Although, as the name implies, granulocytes, especially neutrophils, are the cells most severely affected in this reaction, it is apparent from the very low total leukocyte counts often reported that absolute lymphopenia is also a feature of severe reactions. Rohr (280) deliberately produced attacks in patients allergic to aminopyrine and showed that, whereas the fall in granulocyte count occurs earlier and is more striking than the absolute lymphopenia, the latter is manifest by the time the granulocyte count has sustained its greatest fall. In agranulocytosis as in thrombocytopenia, the rapid disappearance of cells from the blood after clinical exposure to the offending drug confirms the results of *in vitro* experiments in showing that a direct effect on circulating cells is responsible for at least the first phase of the reaction. It is well known that the bone marrow in agranulocytosis may eventually show changes. The same choice of explanations mentioned in the previous discussion of thrombocytopenia confronts us here. (For further discussion, see 224–227, 280.) The very definite malaise which sometimes precedes any changes in the circulating white cells is unexplained. Rarely, more striking manifestations, such as fever, gastrointestinal symptoms, etc., precede the changes in circulating white cells (256). Before leaving the subject of hematological effects, it should be stressed that the above has been written with the definite implication that these reactions are often allergic in nature, although certain puzzling findings are yet to be explained. Some students of this field would probably have chosen to discuss the material on the basis that none of the reactions are allergic, and that the findings "yet to be explained" are those supporting the concept of allergy. The usual, though not invariable, absence of other types of allergic reactions in the patients with hematological reactions to drugs and the intense destruction of the involved tissue are arguments cited by this more skeptical school (328).

b) *"Drug fever", i.e.*, fever that is due to allergy to drugs and that may be unaccompanied by any other obvious manifestations such as skin eruptions, may well have the same basic mechanism as fever associated with other obvious manifestations of drug allergy, as intermediate forms occur. Of the several drugs which have been shown to cause this reaction the sulfonamides (75, 76, 77, 102, 162, 205, 336) have received the most careful attention.

c) *Liver damage* occurring during the administration of drugs often cannot be said to be on an allergic basis (242). But Suggs (329) has described patients with acquired hypersensitivity to cinchophen manifested by liver damage and Hims-

worth (142) has described a similar occurrence with aminothiazole. One cannot be certain that the hypersensitivity in these cases was specific and the liver not thereafter more vulnerable to damage by unrelated drugs (see section IV F). In a patient with a skin eruption and liver damage associated with sulfonamide therapy, specificity was again not shown (104). Keefer (160) also reported the occurrence of liver damage apparently caused by sulfonamides in a patient, but liver damage in animals given sulfonamides has not been shown to be allergic in nature (255). Lichtenstein and Cannemeyer (203) found a syndrome simulating infectious hepatitis or infectious mononucleosis in 81 of 3000 patients receiving *p*-aminosalicylic acid. Although an allergic basis was not proved, many of the patients also showed other manifestations, such as skin eruptions, compatible with an allergic reaction to this drug (see section IV C). Steel (319) has reported a similar case and Thomas (342) has in addition observed recurrence of jaundice on readministration of *p*-aminosalicylic acid. An interesting curiosity, which may, of course, have no relation to liver damage, is the reported development of cutaneous arterial spiders, "spider angiomas", in two patients receiving trihexyphenidyl (148).

4. Unclassified syndromes thought to be due to drug allergy are occasionally reported. All that is mysterious is not allergy and even those unusual reactions which are obvious allergies may be merely variants of one of the above types of reaction. Thus, the syndrome of dyspnea, cyanosis, confusion and fever in a 68 year old man which Harris (132) clearly showed to be due to mercuhydrin allergy may have been simply a variant of "drug fever", with secondary effects in an aged patient. But if syndromes failing to fit established patterns had always been dismissed as mere variants, the very existence of allergy would still be unrecognized.

C. Factors influencing the development of allergy to drugs

For a general discussion of the factors influencing the response to protein and polysaccharide antigens, see Edsall (82). As discussed in section II, accurate determinations of the potency of drugs as antigens, their so-called antigenicity, remains for the most part a problem for future solution. Nevertheless, for rough comparisons between different drugs, routes of administration, doses, etc., simple observations of the incidence of reactions, all factors except the one under study being kept reasonably constant, have often been used. In some of the work discussed below careful distinction between ability to sensitize and ability to elicit reactions has often not been possible, and it should be clearly understood that in such instances the terms, antigenicity and sensitizing capacity, are being used somewhat loosely. In the absence of a convenient term meaning "combined capacity to sensitize and to elicit reactions", it is hoped that the nature of each experiment below will make clear whether the terms used are strictly justified.

1. Chemical nature. Landsteiner recognized early that irritating substances were, on the whole, particularly prone to cause contact allergy. Examples have been given in section III A. But it is nevertheless possible for non-irritating substances to be potent contact allergens, *e.g.*, *p*-phenylenediamine and penicillin.

Reference has already been made to the correlation between reactivity with aniline and sensitizing capacity of one series of compounds. Gell *et al.* (111) compared the ability of 2-phenyl-1,4-ethoxymethylene oxazolone, benzylchloroformate and *p*-nitrobenzoyl chloride to combine with free amino groups of protein with the antigenicity of these substances in rabbits, as measured by development of precipitins. The animals were sensitized by the haptens (sometimes by the intravenous route!) and hapten-protein conjugates were used for the precipitin tests. Factors found to favor antigenicity were a slow rate of reaction with protein and a high conjugation/hydrolysis ratio.

Lepper *et al.* (200) found penicillin in oil and beeswax to cause a significantly higher incidence of allergic reactions than crystalline penicillin in water. There are several possible reasons for the enhancing effect of the oil and beeswax: increased local inflammation, simultaneous antigenicity of the menstruum itself and delayed absorption of the penicillin. All of these factors are known to potentiate antigens under proper circumstances (44, 82). Of 59 cases of penicillin-induced anaphylaxis investigated by the Food and Drug Administration (364) 55 were due to procaine penicillin. Undoubtedly the preponderance of procaine penicillin as offender is at least partly due to its being one of the most commonly used of all types of penicillin. Slowed absorption may again be an important factor and simultaneous antigenicity of both penicillin and procaine is at least a possibility, for patients with dermatitis due to procaine penicillin may be allergic to the procaine (144) or the penicillin. Mayer *et al.* (210) performed skin tests with procaine on two patients who had suffered anaphylaxis from procaine penicillin and got negative results. A large series would be of interest. In the first 9 years of the penicillin era, *i.e.*, through 1949, only 2 anaphylactic deaths due to penicillin were reported. In the 18 months following this, 15 more were reported (163). The period of sharp increase in the number of reports corresponds roughly to the period in which the use of procaine penicillin became widespread. Although most of the deaths have followed intramuscular administration of procaine penicillin, the autopsy findings of acute emphysema (64) support the diagnosis of anaphylaxis rather than simple inadvertent intravasation of the insoluble compound.

Anaphylaxis has been caused by sodium and potassium as well as procaine penicillin (62), by procaine penicillin in oil with aluminum monostearate as well as procaine penicillin in water (51), by penicillin O, benzethacil (N,N′dibenzylethylenediamine-dipenicillin G, bicillin), and penethamate (diethylaminoethyl-penicillin G, neopenil) hydriodide (364). Twenty-six instances of anaphylaxis or anaphylactoid reactions due to penethamate were found by the Food and Drug Administration (364). In contrast to procaine penicillin, widespread use does not explain the high incidence of these reactions to penethamate. As compared with other types of penicillin this drug gives unusually high concentrations in the tissues (156), including the lungs. Penethamate may possibly also possess peculiar direct toxicity causing reactions simulating anaphylaxis (62). Lastly, it must be remembered that the search was particularly directed toward penethamate.

Because sensitization seems to be favored by prolonged absorption of the

antigen, one must consider the possibility that rapidly eliminated drugs may be less likely to sensitize. But such a factor cannot be highly important; otherwise injected aqueous penicillin would not be such an offender. The much higher incidence of allergy to phenobarbital than to thiopental (pentothal) may be mentioned, but allergy to the latter does occur (254) and even if the considerable chemical difference between the two is ignored, the much greater clinical use of phenobarbital is an obvious factor.

2. Route of administration. It is not always possible to separate the influence of this factor from that of the chemical or physical nature of the antigen. All will influence rate of absorption. For soluble bacterial antigens, the subcutaneous route is more effective than the intravenous, while the reverse is true for particulate ones (82). With protein antigens Waksman (353) showed that the route of administration, among other factors, influenced the type of antibody formed. Certain experiments illustrating the importance of route of administration in development of allergy to simple substances have already been described in section III A. The skin was seen to be the best but not the only route for the development of allergic dermatitis. Grolnick (127) has reviewed the work in animals and humans which shows this to hold true for contact dermatitis. Haxthausen's (136) study of the effect of route of administration on the development of dermatitis to dinitrochlorobenzene is interesting, as he explored, at least roughly, various dose ranges in order to detect differences more completely. He showed that both epidermis and dermis could be sensitized by intracutaneous or subcutaneous injections of the hapten or a horse serum-hapten conjugate. Only the conjugate was effective by the intramuscular route (179). The importance of local applications of penicillin in sensitization has been noted in section III B 2 and has also been shown by Templeton (338) and, with special reference to troches, by Kutscher (170).

Although classical anaphylaxis is somewhat difficult to produce in guinea pigs challenged by routes other than the intravenous, fatal human anaphylaxis to penicillin has, as noted above, followed intramuscular (93) as well as intravenous (51) administration. The predominance of the intramuscular over other routes of administration in the clinical use of penicillin is obviously important here. Definite and sometimes severe but non-fatal anaphylaxis from penicillin has also followed oral use (93, 210), inhalation (93), application in an ointment to the eye (37) and instillation into the maxillary sinus (361). Although sensitization to penicillin by the oral route is said to be relatively infrequent (163), one reported case of anaphylaxis from penicillin occurred in a patient who had apparently received only oral penicillin prior to the eliciting dose. The use of routes or preparations permitting slow absorption probably increases the danger of prolonged or recurrent allergic reactions. Kern and Wimberley (163) cite the case of a patient who developed anaphylaxis promptly after intramuscular administration of penicillin, responded to treatment, then relapsed and died.

3. Dosage. The relationship between sensitizing or eliciting dose and response is of theoretical interest, but as regards the eliciting dose it is even more a matter of practical importance. Tests to determine whether a patient is allergic to a

given drug are of two general sorts, those in which material such as serum is taken from the patient and tested for antibody *in vitro* or by passive transfer, and those in which the suspected drug is readministered under controlled conditions to produce a diagnostic and—it is hoped—safe, mild reaction. Demonstration of circulating antibody is at present often unsatisfactory, yet controlled readministration will remain risky as long as the relationship between dose and response remains obscure. Attempts to compromise by restricting the test to the skin may indeed produce a reaction, but its clinical significance is often dubious (see section IV A). It is not surprising, therefore, that instances of unexpectedly severe clinical allergic reactions elicited by low doses of drugs have attracted such sober attention. Brown (24) reports the occurrence of skin eruption at distant sites, local itching and sneezing following the injection of 0.02 units (approximately 0.01 μg.) of penicillin into a patient. Ackroyd (1) provoked thrombocytopenia by administering 1.4 μg. or less of sedormid. A patient who had had allergic conjunctivitis due to streptomycin suffered a prompt recurrence one hour after the intradermal injection of 50 μg. of the drug (63). Falconer *et al.* (91) gave 10 mg. of neoarsphenamine to a patient who three years previously had developed temporary thrombocytopenia from neoarsphenamine. The platelets again fell, to 80,000/mm.^{3}, and the patient developed hemorrhages after the 10 mg. was given. Such instances are impressive. One often feels that no dose small enough to be safe for the allergic patient can be found, and that the only really cautious approach would be to give the drug to the patient in the next bed.

But the minimal eliciting dose is not always of such a low order. Bruun (27) described a patient who could take 500 mg. of aspirin without reaction but developed angio-edema when the dose was doubled. Wurzel and Maycock (373) performed several readministration tests in a patient who had recovered from thrombocytopenia induced by sodium *p*-aminosalicylate. Single oral doses of ¼ gm., ½ gm. and 1 gm. caused slight if any effects, but 4 gm. caused a fall in the platelet count from 318,000/mm.^{3} to 60,000/mm.^{3} in 90 minutes. A dose of 2 gm. three times daily for 5 doses on another occasion caused a drop to 38,000/mm.^{3}. This suggests a graded response to eliciting doses rather than an all-or-none phenomenon. The assumption that such a graded response exists in allergy to proteins is supported by clinical experience with administration of small doses of antiserum or pollen extract in hyposensitization of patients allergic to them (299). But in a large series of anesthetized dogs, actively sensitized by a uniform dose of horse serum, challenging with doses of antigen ranging from 0.21 ml./kg. to 2.0 ml./kg. produced responses showing no correlation with dose. The response was measured semiquantitatively by observations of the degree and duration of fall in blood pressure (79). The simplest interpretation of this result is that the animals were sensitized to a relatively low degree—about one-fourth died when challenged—and that the eliciting doses were all in the range which would evoke the maximum response of which each animal was capable, whereas smaller doses would have been able to elicit less than maximal responses. In a small series of anesthetized guinea pigs, passively sensitized by a large uniform dose of rabbit

anti-ovalbumin serum, challenging with doses of ovalbumin ranging from 1μg./kg. to 100 mg./kg. produced responses showing a positive correlation with dose, though there was much individual variation. The response was quantitated by determining the degree of acute respiratory obstruction through simultaneous measurements of tidal volume and intra-pleural pressure changes (36). A plot of per cent mortality against eliciting dose in a series of guinea pigs actively sensitized to a uniform dose of albumin gave a steep curve (59, 60), although the authors' interpretation of the shape as sigmoid is perhaps questionable. Plotting the mortality against log dose also failed to give a definitely sigmoidal curve. But Becker (12) obtained a straight line when he plotted on probit paper the percentage of patients responding against the log dose given in a series of skin tests to ragweed. In selecting the patients, an attempt had been made to obtain, as far as possible, a group with a uniform degree of allergy to ragweed.

In immunization against proteins antibody can be measured and the relationship between sensitizing dose and response thus determined. Edsall (82) states that once the threshold has been exceeded, increase in antibody response is small in proportion to the increase in dose of antigen, usually lying between the second and third root. With pneumococcus capsular polysaccharide antigens excess even inhibits antibody response (see also section II).

It is unfortunate that more data on allergy to simple substances in relation to this question are not available. Lepper (200) found a significantly higher percentage of allergic reactions in patients receiving at least 500,000 units/day of aqueous penicillin than in those receiving 50,000 units daily. Hopkins and Lawrence (150) studied a series of patients who had been treated with local applications of various concentrations of penicillin to the skin and who were apparently later tested, for the most part, with a single concentration. The percentage of patients found to have been sensitized increased with increasing concentrations. Of course, it is possible that the patients with the most severe initial skin infections had received the highest concentrations in treatment. In his previously cited classical experiment with primrose, Bloch increased the percentage of sensitized subjects by increasing the concentration of locally applied antigen. Von Rechenberg (352) studied the fall in leukocyte count elicited by varying doses of aminopyrine in three patients allergic to the drug. Even if the data from all patients in this interesting experiment are pooled—a procedure open to criticism as neither the doses nor the routes of administration were uniform among patients—they are too few to be at all conclusive, but a plot of per cent decrease in granulocytes against log eliciting dose suggests a relatively steep curve. If any pattern at all is dimly emerging from the sum of the information given above, it is probably this: sensitization to drugs, as to other antigens, increases with increasing doses, but probably not in a linear fashion. In a sensitized individual response seems to increase fairly sharply with increase in eliciting dose when the range of the latter is appropriately chosen.

Individual variation is no new problem in experimental or clinical medicine but in predicting the response to an eliciting dose of a drug allergen, one must deal with the product of two variations and, in clinical medicine, often with

the additional handicap of not even knowing what the sensitizing dose was. The development of techniques permitting estimation of the degree to which a given individual has been sensitized to a drug would make the administration of a "diagnostic" eliciting dose considerably safer but, of course, quite unnecessary. In the present state of knowledge there is no basis for choosing a certain dose range as the range in which a given patient's dose-response curve will increase sharply. Sterling (323) cites the case of a patient who developed anaphylaxis after an eliciting dose of 300,000 units of penicillin. A week later, after recovery, a dose of 30,000 units was tried with equally bad results. Plummer and Wheeler (260) found no difference in the incidence of "drug fever" between a group of patients receiving 6 gm. of sulfadiazine daily and a group receiving 3 gm. daily, though the latter had a much lower incidence of an important non-allergic reaction, renal damage. No difference was found in the incidence of fever and agranulocytosis from thiouracil whether the dose was 100 mg. or 1 gm. daily.

4. Time factors. The number of separate administrations and the interval between them may also be significant. A given quantity of protein generally sensitizes more effectively if administered in divided doses over several days than if given as a single injection (82). But data on the relation of time factors to drug allergy is usually a by-product of clinical studies in which the total quantity of drug was not kept constant and the result may thus simply reflect changes in total dose. The incidence of sensitization to locally applied penicillin was found to be positively correlated with the number of days of treatment (150). Administration of many injections of penicillin, 12 to 54 in one series of 9 patients (323), seems to be an important factor in anaphylactic sensitization to the drug. The above injections were given in several courses with intervals ranging from two weeks to six months between different courses in the same patient. None of the above 9 patients developed anaphylaxis upon receipt of the first injection of any series. This is contrary to the usual laboratory experience with rabbits receiving injections of heterologous protein, in which the first injection after a rest period of several days is the most dangerous of each series. Wofford (368) has been more impressed with the number of clinical instances in which the first injection of penicillin after a rest period elicited anaphylaxis but more data are needed to support this.

There naturally arises the question whether milder manifestations which might serve as a warning occur after any injections prior to the one which provokes anaphylaxis. Only 12 of 84 patients who developed anaphylaxis to penicillin or, in a very few instances, streptomycin gave a history of previous allergic reactions to the drug (364). Sterling (323), however, found that careful questioning usually revealed that patients with a history of anaphylaxis to penicillin had, in fact, noted various symptoms after the one or two injections immediately preceding that which elicited obvious anaphylaxis. They had usually considered these symptoms too unimportant to mention spontaneously. Sterling's findings are reasonable and deserve the careful attention of clinicians. But one should remember that research involving the taking of histories needs controls as much as any other type. Equally careful questioning of a series of patients who had

received numerous penicillin injections without ever developing anaphylaxis would complete the above experiment.

The duration of exposure to a drug given by certain routes, especially by inhalation, will clearly influence the total effective dose received and hence the response. Ratner (268) has shown this in the sensitization of guinea pigs by inhalation.

5. Host factors. Sex, age and the occurrence of other allergies in the individual or his family have been the principal host factors studied. The lack of influence of sex on the development of allergy in general was previously mentioned. This has been found in anaphylactic sensitization of guinea pigs to protein (59) and appears to hold true in general clinical experience with drug allergy. Yet there are instances of sex differences in incidence of drug reactions. The ratio of females to males in the two recent nation-wide studies of aplastic anemia associated with chloramphenicol was 3:1 in the first series (202) and 2:1 in the second (363). This ratio may, of course, merely reflect a sex difference in exposure to the drug, a situation well recognized when agranulocytosis due to aminopyrine was common. The preponderance of females in most series of angioedema (26) is similarly ascribed by Bruun to women's greater use of analgesics, a class of drugs he has found to be a particularly common cause of this reaction (see section III B 1 e).

Age has been found to be of some importance in immunology, young animals being poor antibody producers (82). But Coulson and Stevens (59) claimed that older guinea pigs showed a definite increase in the size of the dose of protein per unit weight needed to sensitize and to elicit anaphylaxis. Schwartz (292) found little correlation between age and development of experimental contact allergy of the skin to dinitrochlorobenzene. The age of patients developing anaphylaxis from penicillin was found to be from 3½ to 67 years (51). Of a series of 28 cases of aplastic anemia associated with the use of chloramphenicol, 17 were in children under 10 years of age (363). This is probably explained, at least in part, by the high relative frequency of exposure to chemotherapy in this age group.

That heredity may strongly influence the response to antigens has been shown by Sand and Sobey (289), among others. They did not, however, find this to be true for every antigen tested. This work was done with complete antigens and it probably would be very difficult to perform a similarly detailed genetic analysis with simple substances, as the authors point out that great attention must be paid to the scale by which results are measured. Nevertheless, Chase (41) has clearly shown that one can breed families of guinea pigs showing significant differences in susceptibility of the skin to sensitization by dinitrochlorobenzene. There was definite though imperfect parallelism between susceptibility to sensitization by this drug and by poison ivy. Grolnick (127), in reviewing the work on contact dermatitis, concluded that the incidence was not usually found to be correlated with family or personal incidence of other allergies. Rocha e Silva (279), on the other hand, concluded from his review of the evidence that there is a positive correlation between development of contact dermatitis and incidence of other past or present allergies in the same patient (see also III B 2). In a per-

tinent study Berkowitz *et al.* (15) found a significantly higher incidence of allergic reactions to drugs in children with other allergies than in those without them. The interpretation is unfortunately clouded to some degree by the fact that the former group of children also had a much higher incidence of side effects, such as vomiting, drowsiness, abdominal discomfort, etc., which did not seem reasonably attributable to allergy. This finding may reflect closer clinical observation of the allergic children, who were apparently more likely than the others to be private patients in this particular study. But other pediatric statistics (51) confirm the higher incidence of allergy to penicillin in individuals with other allergies.

A positive family or past personal history of allergy, especially asthma, was found in a considerable proportion of the patients developing anaphylaxis to penicillin (93, 163, 364). Of 16 fatal cases 4 had a past history of asthma (51). Chase (44) suggests that the relatively high incidence of fatal anaphylaxis in asthmatic patients might be at least partly due to changes wrought by previous asthmatic attacks, *e.g.*, hypertrophy of bronchiolar muscles, which rendered the patient more susceptible to bronchospasm. Bates (10) has also shown that asthmatic patients, even when apparently symptom-free, have abnormal pulmonary function. An observation by Landsteiner, mentioned in section III A, may be recalled here. He noted (176) that when a series of animals received a hapten-protein conjugate, some produced antibody chiefly against the protein while in others the specificity of the antibody was chiefly directed against the hapten. As individuals regularly fail to produce antibodies against their own tissues, one wonders if there may be a positive correlation between individual tendency to produce antibodies against the hapten portion of preformed hapten-foreign protein conjugate and tendency to produce antibody against hapten administered alone. Although this seems a legitimate question, it loses some of its value in the face of the clinical correlation between tendency to develop allergy to drugs and the occurrence of other allergies, for the antigens in the latter are usually heterologous proteins.

IV. FURTHER CONSIDERATION OF ALLERGY TO CERTAIN CHEMOTHERAPEUTIC AGENTS

Although individual consideration of all or even many of the drugs used today is out of the question in this review, it may be profitable at least to choose one group of drugs for more detailed examination. Chemotherapeutic agents have been selected, not only because of the previously discussed high incidence of reactions to them, but also because of their unique theoretical position. Other classes of drugs useful in clinical medicine must affect, at the very least, some one function of the human body. Even if ideal, *i.e.*, with no side effects, any such drug would have the potential toxicity associated with its ability to affect this function. An ideal chemotherapeutic agent, however, would act only on the parasite and affect no function of the host. But such pharmacological inertness by no means implies inability to sensitize the human host, for the type of reactivity with proteins which results in pharmacological effects is not necessarily similar to that permitting sensitization, and pharmacologic inertness simply means failure to

take part in *physiologically significant* drug-protein reactions rather than failure to react with any body protein at all. Allergic reactions would then represent the principal, and, if we except such unrelated matters as superinfection and Jarisch-Herxheimer reactions, the sole undesirable clinical effect of the drug. In practice, many simple substances devoid of appreciable pharmacological effects are important causes of sensitization.

A. Penicillin

Penicillin furnishes an excellent practical illustration. In discouraging contrast to its almost complete lack of direct toxic effects the clinical incidence of allergy to penicillin has been estimated as 6 to 12 per cent (276), although it is probable that some of the earlier reactions were due to impurities in the commercial preparations (311). Penicillin has been well established as a cause of urticaria (288), angio-edema (166), anaphylaxis (see section III B 1 a), and dermatitis, both contact (120) and non-contact (238); it has also been reported (21, 51, 98, 163, 318) to cause almost all the other types of drug allergy, although the evidence has not always been convincing. To the reviewer's knowledge, aplastic anemia and the syndrome simulating lupus erythematosus disseminata have not been reported. The severe local necrosis occasionally seen at the site of penicillin injections should perhaps be classified as an Arthus reaction (163). In this connection an observation by McVay about another drug (216) may be cited. A patient who had 8½ months previously developed anaphylaxis after receiving sulfobromophthalein ("BSP") intravenously in the usual dose of 5 mg./kg. was given an intradermal test injection of 0.1 ml. of a 1:1 mixture of the dye solution with isotonic saline, a total dose of 2.5 mg. of the dye. In addition to an immediate local and systemic reaction after the test dose he developed, over a period of days, swelling of the entire arm with a wide area of necrosis around the injection site. Extravasation of (probably larger) amounts of this dye in clinical practice has been known to lead to local necrosis even in non-allergic patients, and McVay's patient may thus have had merely a hyperreaction, but the occurrence of a previous anaphylactic reaction and an unusually violent and extensive local reaction should be noted. Furthermore, extravasated sulfobromophthalein, as shown by Sievers (308), can produce a fixed sensitization.

The manifestations of anaphylaxis and the effect of certain factors on its incidence in penicillin-treated patients have been discussed in section III B. Skin tests are apparently valuable in predicting anaphylaxis from penicillin in that they seldom give false negative results, although false positive results may occur (93, 163, 210, 323). The Prausnitz-Küstner reaction is also positive in some cases (93, 210). Circulating precipitins have been reported absent (210). Anaphylaxis and contact dermatitis appear to be the only types of allergic reaction to penicillin in which diagnostic skin tests are useful. In the others, even though patients with positive penicillin skin tests are more likely to prove clinically allergic to the drug than those with negative results, the accuracy of the tests is insufficient for clinical use (24, 150, 252). It is probably safe to say that the

unreliability of diagnostic skin tests in most types of allergy to penicillin and their reliability in contact dermatitis can be applied to drugs in general (24, 56, 150, 205, 252, 269, 330). One must be more cautious in generalizing from the results in anaphylaxis due to penicillin, for there is not a great deal of information about anaphylaxis due to other drugs. But the results of skin tests in occasional instances of anaphylaxis due to quinine, thiamine and sulfonamides have been said to confirm those obtained with penicillin (93). The result of the test with sulfobromophthalein in the patient discussed above was, to say the least, not equivocal. It has also been reported (21) that most patients showing positive results to penicillin inhalation tests also gave positive reactions to skin tests. Inhalation tests were carried out by the method of timed vital capacity determination, a method that may be criticised on the grounds that it may be seriously disturbed by fluctuations in the degree of the subject's cooperation. Nevertheless, this does represent at least an attempt to quantitate the allergic response. Any test which permits a greater degree of systemic exposure to penicillin than the skin test becomes more significant—and, it must be stressed, more hazardous—than the skin test. Even the latter is not without risk.

The unreliability of skin tests in most types of drug allergy has deserved and received considerable comment in the literature. When the allergic reaction for which one is testing does not involve the skin at all, an obvious explanation of a negative skin test is a complete lack of antibodies in the skin. But this explanation will hardly serve for instances of dermatitis due to systemic administration of a drug. An attractive possibility, which might hold for both the above situations, is that a reliable skin test could be obtained if only the proper conjugate or metabolite of the hapten were used as test substance. Leftwich (199) gave sulfonamides to normal individuals and then used their serum as skin-testing antigen in patients allergic to these drugs. A combination of aminopyrine and serum has been used in a somewhat analogous manner (67). Although initial successes were reported, others (302) have been unable to confirm them.

Allergy to penicillin is not necessarily persistent. Urticaria and dermatitis may subside while the drug is still being given (166) or fail to recur on readministration (150, 257). Anaphylaxis (361) may similarly fail to recur when the patient is re-exposed to penicillin. It is not safe to rely on such evanescence, however; one patient received a dose of penicillin without reaction and then, after two years, another dose which led to fatal anaphylaxis. Unless unreported exposure occurred during the two years, the most likely interpretation is that the patient was sensitized by the penultimate dose and that the allergic state persisted two years. Urticaria may even recur in waves for a period of one to two months after deliberate administration of penicillin has ceased (341). It is possible that in some such instances unrecognized exposure may be continuing. An interesting example of possible occult exposure to penicillin has been noted by Rosen (281), who claims that penicillin used in treatment of cows' udders may contaminate the milk. Sanchez-Cuenca (288) found the mold Penicillium in both sputum and feces of a patient with a chronic lung abscess who was suffering from urticaria that was due to penicillin and persisted after cessation of penicillin therapy. There is still no proof, however, that the mold is of clinical importance

in sensitizing patients in such a way that they may react to penicillin or *vice versa*. Sensitization by the mold would furnish a neat explanation for the instances in which patients promptly develop reactions on initial administration of penicillin, but this paradox has also been noted with drugs not produced by living organisms. The similarity between dermatitis due to penicillin and that due to fungus infections has impressed dermatologists (331). But Feinberg (94, 96) has reported failure to obtain cross-reactions between penicillin and Penicillium in patients. Studies involving genera other than Penicillium, *e.g.*, Trichophyton, probably confuse rather than clarify this problem. Contact tests of 4 workers who were employed in the commercial production of penicillin and who had developed contact dermatitis showed that one reacted strongly to penicillin and not at all to the mold, one reacted strongly to penicillin and only slightly to the mold, while the others reacted most strongly to intermediate products (107). Cross-reactions between different penicillins are not invariable. Thus, some patients allergic to penicillin G do not react to penicillin O (351), while in others cross-reactions occur (207).

B. Sulfonamides

Sulfonamides have been well established as causes of angio-edema (206), asthma (267), dermatitis, both contact (50, 125) and non-contact (122, 296, 336, 343) and "drug fever" (29, 205, 245, 336). Occurrence of the serum sickness syndrome from sulfonamides is well recognized (204) and their apparently causative role in some instances of polyarteritis nodosa has been discussed in section III B 1 g. Sulfonamides have also been reported as causes of anaphylaxis (93), conjunctivitis (256), agranulocytosis (65, 100, 161, 229, 275), thrombocytopenia (117, 153, 218) and aplastic anemia (219). Para-aminobenzoic acid in doses abolishing the therapeutic effectiveness of sulfathiazole did not cause a cross-reaction, but also failed to prevent dermatitis and fever from simultaneous administration of sulfathiazole in a patient allergic to the latter (325). Compared with other sulfonamides, sulfathiazole caused a particularly high incidence of allergic reactions, especially fever (76, 77, 336). Though cross-reactions among sulfonamides can occur, this is by no means invariable (75).

Sulfisoxazole (gantrisin) has recently attracted attention because of the unusually low incidence of renal damage associated with its use. But it remains to be seen whether the incidence of allergic reactions will be low. Agranulocytosis (212) and thrombocytopenia (109a) following its administration have been reported. Two unusual patients with hyperglobulinemia, plasmacytosis and, at autopsy, no multiple myeloma or granulomas were described by Robertson (277), who noted that both had received sulfonamides, among other drugs; but the interpretation of these changes as allergic in nature is still open to question.

C. Drugs used primarily in the treatment of tuberculosis

Drugs used primarily in the treatment of tuberculosis are responsible for numerous allergic reactions which, especially in the earlier period when only one or two effective drugs were available, have given rise to serious problems in treatment. Streptomycin was found (309) by patch tests to have caused a 7.7 per cent

incidence of contact sensitization in a series of nurses handling it. This drug has also been well established as a cause of non-contact dermatitis (145), urticaria (145), asthma (145) and "drug fever" (17). Although many instances of dermatitis due to streptomycin are mild, severe exfoliative dermatitis may occur (315). Exfoliative dermatitis developing during treatment with streptomycin and *p*-aminosalicylic acid may be accompanied by evidence of severe visceral damage, *e.g.*, anuria (49), another example of the relation between such lesions and exfoliative dermatitis mentioned in section III B 2. Eosinophilia, sometimes marked, very commonly occurs in patients receiving streptomycin, but is not necessarily accompanied by other, more definite evidence of allergy (315). Although the fact that most patients receiving streptomycin are tuberculous makes evaluation of blood changes difficult, the drug has been implicated (370), on reasonable grounds, in cases of aplastic anemia.

Cross-reactions between streptomycin and dihydrostreptomycin do not always occur (141, 145). Dihydrostreptomycin is itself capable of sensitizing (145).

Para-aminosalicylic acid has been well established as a cause of "drug fever" (266) and dermatitis (319). It has also been reported to cause angio-edema (356), urticaria (356), conjunctivitis with other evidences of coryza (356), liver damage (203, 319, 347), thrombocytopenia (373) and agranulocytosis (164).

Isonicotinic acid hydrazide has been reported to cause "drug fever", dermatitis, asthma, thrombocytopenia and agranulocytosis (53). A report of its causing urticaria seems well-founded, but the claim that passive transfer of the Prausnitz-Küstner type was successful in this instance is not entirely convincing (22). The thiosemicarbazone, amithiozone, has been shown to produce several types of toxic effects, which are not necessarily allergic in nature, but it should be noted that agranulocytosis (261) is among these effects.

D. Chloramphenicol

The question of the relation between this drug and aplastic anemia has become a *cause célèbre*. Careful surveys (202, 363) have led to this conclusion: "It should be emphasized that it cannot be stated categorically that chloramphenicol, or many of the other drugs discussed in this report, actually caused the blood dyscrasia which developed following their use. Nevertheless, the evidence that chloramphenicol acts in this manner in certain susceptible individuals is recognized even though scientific proof is lacking. It is equally certain that blood dyscrasias occur infrequently when chloramphenicol is administered." Although the survey which produced this conclusion deserves high praise for its organization and completeness and the reports are in many ways very useful, the ambiguity of the word "recognized" in the above conclusion is regrettable and perhaps even a little disingenuous. The surveys appear to the reviewer to have produced evidence of a significant correlation between the use of chloramphenicol and the development of aplastic anemia, and therefore, all other things being equal, patients receiving this drug run a greater risk than those who do not. To the eminently practical question, "How much greater risk?", a clear answer does not seem to be available. As the survey indicates, most patients receiving chloramphenicol do not develop aplastic anemia and this disorder can, of course, be

seen in the absence of any exposure to chloramphenicol. The possibility that the aforementioned correlation depends on some as yet unappreciated factor of statistical bias, rather than a cause-effect relationship, must be admitted, but it seems remote.

One aspect of this question that is not at all clear is the role, if any, of allergy. Aplastic anemia due to chloramphenicol may represent a hyperreaction rather than an allergy. The drug's nitrobenzene group has attracted attention, for aromatic nitro- and amino-compounds have long had a sinister reputation for deleterious effects on blood and blood production. Compounds of this series or their metabolites have been shown to exert direct toxic effects upon circulating blood cells and bone marrow (316). Yet when entire series of patients treated with chloramphenicol have had careful blood studies from the beginning of treatment, the findings do not appear to have shown a trend toward depression of blood and bone marrow (14, 78). Patients developing aplastic anemia from chloramphenicol therefore seem to be statistically in a different population and not merely at the extreme of a normal distribution. This suggests allergy but does not prove it; for example, a discrete unusual metabolic defect might cause such patients to convert chloramphenicol into directly toxic metabolites of a type not produced in normal individuals taking the drug. But such a defect would hardly be expected to *develop during treatment.*

E. Tetracycline derivatives and other antibacterial chemotherapeutic agents

Thus far, none of these has challenged the position of penicillin as the worst offender among chemotherapeutic agents responsible for allergic reactions, but it is a cardinal principle in this field that in our present state of knowledge (see V D) a new drug must have extensive clinical trial before one can make a reasonable estimate of its capacity to produce allergic reactions. The extraordinarily heavy use of chemotherapeutic agents makes evaluation possible sooner than in the case of less commonly used drugs. But it is probable that in every instance many months or even years must elapse before adequate evaluation is possible for there is an additional time factor involved. This is the gradual dissemination through the literature of information that a new drug has been found to cause certain reactions, with subsequent increased activity on the part of other physicians in searching for and finding more examples. Dermatological experience has thus far produced the impression (233) that bacitracin, neomycin, gramicidin and polymyxin, applied locally to the skin, are not as serious causes of sensitization as penicillin and streptomycin. Allergic reactions have been reported from chlortetracycline (101, 114, 244), oxytetracycline (101, 157, 244), tetracycline (265, 362) and carbomycin (99). Cross-reactions are stated (286) to have occurred between chlortetracycline and oxytetracycline in a fixed eruption.

F. Quinacrine

Quinacrine (mepacrine, atabrine), administered over long periods of time, has been well established as the cause of chronic lichenoid dermatitis, "atypical lichen planus." Other reactions during quinacrine administration, *e.g.*, aplastic

anemia (246), have also been reported, but the skin lesions have been the object of particular interest. Bazemore (11) readministered quinacrine to 51 patients who had subsiding chronic lichenoid dermatitis from previous quinacrine administration. Five developed an acute dermatitis which was in itself unlike their lichenoid dermatitis and was not associated with simultaneous exacerbation of their healing lichenoid lesions. The other patients continued to receive 200 mg. of quinacrine hydrochloride daily for two to three months. Nine of these patients developed new lichenoid lesions, with exacerbation of their old lesions, but the earliest this occurred was 23 days after readministration had begun. These observations, which argue against an allergic basis for the lichenoid dermatitis, are at variance with those of Clarke (16), who reported prompt exacerbation of this type of dermatitis when quinacrine was readministered to a patient whose lesions were in a "static" state and perhaps also with those of Wechsler (358) which, however, involved another drug. Wechsler found that readministration of quinidine caused prompt recurrence of an eruption, stated to be similar to lichen planus, that had first appeared in the patient after 3 months of quinidine administration and had disappeared when the drug was withheld. An intermediate result was obtained by Shatin (298) who studied a small group of patients developing an apparently similar type of dermatitis during treatment with *p*-aminosalicylic acid. The three patients who developed the reaction during the first course of treatment did so 4, 6½ and 14 months, respectively, after the start of treatment. Patients who tolerated the first course without reaction and developed dermatitis only after a rest period and readministration did so 6 weeks after readministration had begun.

Schamberg and Shelley (290) have made interesting observations that may be pertinent here. They have found permanent histological changes, *e.g.*, loss of sweat ducts, in dermatitis due to quinacrine. Such permanent anatomical changes may conceivably predispose the skin to further damage from the drug and result in a more rapid appearance of new lesions from a second course of treatment than from the first. Even if this admittedly speculative explanation eventually proves incorrect, the underlying principle deserves re-emphasis. Reactions that develop only after a long period of drug administration during a first course of treatment, become quiescent during a rest period and then reappear promptly after the start of a second course may reasonably be considered to be associated with some type of change which persisted through the rest period. If circumstances such as the length of the rest period make simple cumulation of the drug an unlikely explanation—a matter which, incidentally, cannot be lightly dismissed when the drug is quinacrine—then the possibility of an allergic basis may be seriously considered. But the persistent change need not always reflect an antibody and definite decision can often be made only if it is feasible to test for the hallmark of antibodies—specificity.

V. FURTHER BASIC CONSIDERATIONS UNDERLYING CLINICAL PROBLEMS OF DRUG ALLERGY

In this review no attempt has been made to arrange the material for maximal clinical usefulness. Whether successful or not, the attempt has been to stress those

aspects of laboratory and clinical reports that seem to bear on fundamental questions and so give a better idea of our strategic than of our tactical position. But as the material in previous sections has been restricted to that bearing on the relatively few questions considered therein, certain work dealing with important questions that underlie practical problems of prevention, diagnosis and treatment have been included in a scattered fashion or omitted entirely. The present section is intended to atone, at least in part, for these omissions.

A. The demonstration of antibody

A regularly successful technique for the demonstration of the responsible antibodies in cells or fluids removed from patients allergic to drugs is clearly needed. The difficulties have been many. The "atopic" types of clinical allergy such as urticaria might seem to be a promising group to study, for, when the antigen is a protein, skin-sensitizing antibodies (reagins) are often shown by the Prausnitz-Küstner technique. But even here the test usually fails if one is dealing with allergy to a drug (355) (see, however, section III B 1 c). The limitations of the circulating humoral antibody found by Chase (43) in guinea pigs sensitized against simple substances have been described in section III A. A most important advance has been the use of leukocytes instead of serum. Landsteiner and Chase (180) transferred the delayed type of cutaneous allergy to picryl chloride in guinea pigs, using peritoneal exudate. Haxthausen (138) produced suggestive though not conclusive evidence that lymphocytes are more important than granulocytes as carriers here. He also transferred the delayed type of skin allergy to dinitrochlorobenzene in guinea pigs by injecting pooled white cells from the blood of donors intraperitoneally into the recipients. Oliveria-Lima (239) succeeded in transferring epidermal allergy to neoarsphenamine in guinea pigs, using cells of peritoneal exudate as carrier. In humans with contact dermatitis from simple substances, an attempt was made to transfer the allergy by excising lymph nodes and injecting a suspension of the ground nodes into the skin of normal individuals. The results were inconclusive (140). Chase (45) has reviewed his own and other work in this field. Using simple chemical substances or tuberculin as antigen and guinea pigs almost exclusively as donors and recipients, various investigators have succeeded in passive transfer with cells obtained as described above or from lymph nodes, thymus or spleen. The cells have been administered intracutaneously, intraperitoneally or intravenously. The route of challenge has been cutaneous, subcutaneous or intraperitoneal. In the latter instance systemic as well as skin reactions have been obtained. Specificity has been demonstrated. Furthermore, when large numbers of cells have been transferred by any of the aforementioned routes, circulating humoral antibodies giving rise to the immediate, anaphylactic type of reaction have also been demonstrated in the recipient. The success of passive transfers has been shown not to depend upon any particular method of sensitization of the donors but does depend upon careful treatment of the carrier cells. Thermal damage to these cells results in failure of transfer. Allergy develops in the recipient too quickly after cellular transfer for the effect to be ascribed simply to transfer of antigen in the cells with subsequent active sensitization of the recipient. Chase, noting the repeated

failure to demonstrate potent antibody in extracts of such cells, has suggested the possibility that by means of cells one may be transferring the mechanism for antibody formation rather than already formed antibody. An alternative explanation, of course, is that the correct technique for extracting antibody from the cells has not yet been discovered. Extracts of skin of patients with contact dermatitis have failed to yield antibody (66). The nature and site of formation of antibodies responsible for drug allergies must therefore await future clarification and a very complex situation may eventually be revealed. Even the plasma γ-globulins have been shown to be synthesized by extra-hepatic tissues (223).

As the skin can be passively sensitized by cells injected intravenously or intraperitoneally, the route by which antibody eventually reaches the skin is naturally of interest. Attempts have been made to show migration of tagged lymphocytes into the skin (130) but this phase of the problem, including the relative importance of the various types of cells, is still unsolved.

B. Duration of allergy to drugs. Desensitization

It is obviously easier to obtain information about the duration of allergic reactions to drugs than about the duration of the allergic state. The latter may persist for many years (278) but such is not invariably the case, as has been shown for nirvanol (201, 304), phenylbutazone (171) and penicillin (see section IV A). Studies with sulfonamides (162) have shown that fever may recur on readministration at a time when the skin and conjunctiva no longer show their former allergy. In one of the few extensive studies of this question Nielsen and Bang (235) retested 103 patients who, 2 to 19 (mean 13½) years previously, had given positive reactions to patch tests. Twenty-two allergens, chiefly simple substances, were involved and, as each patient was tested with several substances, there had been 185 positive reactions at the time of initial testing. At the time of retesting, 15 reactions were stronger than the original, 44 were the same, 18 had diminished and 111 had become negative. The authors do not concur with those who believe that old age leads to a non-specific weakening of skin reactivity but did find a marked positive correlation between exposure to the offending allergens in the interim between the two tests and retention of the allergic state. Furthermore, a few experiments in this group of patients suggested that the second patch test did not of itself cause significant re-sensitization of those who had lost their allergy, though it is well known that patch tests may on occasion sensitize. This study thus has important and encouraging implications for the clinician. But allergic reactions to drugs sometimes disappear even during continued administration of the responsible drug (see section IV A).

A most important but difficult distinction is that between spontaneous loss of allergy, occurring coincidentally with continued exposure to the drug, and loss of allergy *as a result of* this continued exposure, *i.e.*, genuine hypo- or desensitization. Many attempts at such deliberate desensitization in drug allergies have been reported as successful, but one usually wonders whether the allergy might not have disappeared equally soon without the "desensitizing" doses of the drug. This is not simply sour skepticism and withholding of due credit; there are valid

reasons for questioning many claims. In the first place, desensitization has seldom been successful in experimental allergies of the delayed type. Secondly, the duration of the allergic state is, as noted above, sometimes relatively brief. Lastly, many reports describe the following sequence of events: an allergic reaction occurs during a first course of treatment, the drug is withheld, a relatively long rest period without any exposure elapses and, finally, a course of "desensitizing" exposures is begun without any reactions and also without any demonstration that the patient was still allergic at the end of the rest period, before the "desensitization." Reports of effective desensitization are much more convincing when it is shown, by deliberate or accidental production of a reaction at the outset of desensitization, that the patient is still allergic at that time and when it also seems clear that a hypothetical plot of response per unit dose against time would show a line parallel to the time axis for a relatively long time prior to the start of desensitization and a sharp drop to zero during a relatively brief course of desensitization. Such a plot is, of course, a practical impossibility at the moment but there are convincing reports of desensitization of patients with dermatitis (6) and probably mild anaphylaxis (73) from penicillin as well as dermatitis and conjunctivitis from streptomycin (48, 63). Florey (106) has discussed in some detail desensitization in penicillin allergy.

It would be interesting to know if patients in whom apparently effective deliberate desensitization has been carried out remain permanently desensitized. There is probably no known reliable technique for *deliberate permanent* desensitization of individuals allergic to proteins (44) and one might paradoxically have a higher incidence of eventual return of drug allergy in those desensitized as a direct result of administration of the drug than in those who spontaneously lose their allergy.

Reports have been criticised above on the grounds that failure to show recurrence of the allergic reaction just before desensitization was attempted mars their scientific value. This should not be confused with criticism of the clinical management of the patients concerned. Certainly from the latter, more important standpoint, the fewer reactions the better.

Efforts to prevent sensitization from taking place by preliminary administration of the potential allergen in small doses or by less effective routes have had conflicting results (42, 128, 366). The experiments differed from each other in important details and it does not seem possible to draw general conclusions from them at present.

The occasional disappearance of an allergic reaction during continued exposure to the responsible drug does not change the fact that prompt withdrawal of the drug is usually the safest practice. Therefore early recognition of reactions, especially the more dangerous types, is an important aim. Attempts to avert agranulocytosis by repeated leukocyte counts seemed logical, as it has been shown that otherwise asymptomatic patients with leukocyte counts below 4000/mm.^{3} during thiouracil treatment were more likely to develop eventual agranulocytosis than comparable patients with normal counts (349). If we reject the rather unlikely possibility that agranulocytosis is always an all-or-none reaction which

cannot be influenced by stopping administration of the drug once the leukocyte count has begun to fall, then we must accept the theoretical value of repeated counts. Young (374), however, was unable to find evidence in the literature that any feasible schedule of leukocyte counts actually decreased the incidence of agranulocytosis from sulfonamides. Furthermore, there are disheartening examples of the fact that agranulocytosis is indeed sometimes uninfluenced by stopping administration of the drug at an early stage (88). In fact, this has even been observed when prodromal symptoms led to discontinuance of the drug before the circulating white blood cells had shown any abnormality at all (256). Phenylbutazone was the offending drug in these instances.

C. Influence of other drugs

1. Adrenocorticotropic and adrenal cortical hormones of the "glucocorticoid" type have various effects on allergy, ranging from failure to prevent either sensitization or the eliciting of reactions, as in anaphylaxis (89), to apparent suppression of antibody formation, as in some instances of hemolytic anemia (68) and the Arthus reaction (89), or suppression of the response of sensitized animals to challenge, as has been shown for cardiovascular and renal lesions of rabbits (113). The last-mentioned type of effect is probably the one most frequently responsible for beneficial action of these hormones in clinical allergies (57). In clinical medicine, where the use of these potent hormones without any obvious indication is not advisable, they cannot be clairvoyantly given before allergic reactions have occurred, and most reports deal only with effects in patients already sensitized, although one interesting and somewhat disturbing exception is described below. These hormones have been reported to be valuable in the treatment of numerous allergic reactions to drugs, including asthma due to aspirin (33), angio-edema (33, 306), urticaria (33, 306), the serum sickness syndrome (33, 306) and conjunctivitis (306) due to penicillin, angio-edema (33) and exfoliative dermatitis (33) due to iodine, exfoliative dermatitis due to sulfathiazole (365), dermatitis due to systemic administration of sulfadiazine (33), contact dermatitis and keratitis due to atropine (33), and "drug fever" due to *p*-aminosalicylic acid (306) and hydroxyphenylcinchoninic acid (33). Benefit has even been reported in penicillin-induced anaphylaxis (306), although more rapidly effective treatment should be given first in this emergency. Favorable results have been reported in instances of agranulocytosis from combined sulfonamides (31), sulfisoxazole (212) and thiosemicarbazone therapy (350) as well as in thrombocytopenic purpura from a gold compound (350), but Steinberg *et al.* (321) found that ACTH failed to save a patient who developed agranulocytosis while taking phenylbutazone. Even prophylaxis may fail, for another patient who received phenylbutazone and 75 mg. of cortisone per day simultaneously for about six weeks nevertheless developed agranulocytosis plus an increase in severity of previously existent anemia. One must, of course, distinguish between the above type of situation and the equally disastrous but fundamentally unrelated instances in which ACTH or cortisone seems to have allowed an overwhelming infection to set in, with bone marrow depression secondary to the latter (313).

Two experiments that bear only indirectly on this problem are nevertheless of interest. In one, cortisone given to rats simultaneously with rabbit antiserum against rat platelets gave no protection against the effect of the antiserum (317). In the other (221) three groups of rabbits were studied. The first group received cortisone, those in the second were adrenalectomized and maintained on desoxycorticosterone, and the third group consisted of controls. All groups were then actively sensitized to horse serum, cortisone and desoxycorticosterone administration being continued in the first and second groups, respectively. When rabbits from all three groups were challenged intravenously with antigen and the magnitude of the subsequent acute drop in number of circulating granulocytes was compared among the groups, no significant differences were found.

In the previously mentioned instance of beneficial effect of ACTH on contact dermatitis due to atropine, a weakening of the reaction to patch test was observed at the same time. But in controlled experiments reactions to patch tests in series of patients sensitized to various substances have been found not to be influenced to any significant degree by cortisone given orally (334) or topically (293).

But it would certainly be wrong to conclude that the good results obtained from these hormones in allergic reactions to drugs were fortuitous. On the contrary, the real value of ACTH and cortisone in many such reactions has been proved by the instances of relapse when treatment with these hormones was stopped or the dose decreased too soon (306, 350), with subsequent improvement when proper doses were begun again. Although leukocytosis is known to occur in patients recovering from agranulocytosis, the extreme temporary leukocytosis, reaching 142,500/mm.^{3} (75 per cent neutrophils), that was observed in a patient receiving ACTH therapy for sulfisoxazole-induced agranulocytosis suggests that ACTH may owe part of its action to stimulation of bone marrow in this disorder. The leukocyte count returned to normal after ACTH administration was stopped (212). As in other clinical uses of these hormones, the occurrence of side effects restricts the usable dose range and one cannot easily explore the effect of larger doses in those reactions that resist treatment with usual doses.

ACTH may itself cause reactions which are apparently allergic, *e.g.*, urticaria, angio-edema, skin eruptions or anaphylaxis. Shulman and his associates (306) collected statistics on several hundred patients with various disorders, not all drug allergies, treated with ACTH in several clinics. The results suggested an incidence of about 2 per cent for reactions to ACTH. Cortisone may be helpful in the treatment of reactions to ACTH, according to this group of investigators.

Houghton (151) found ACTH useful in suppressing allergic reactions to streptomycin and *p*-aminosalicylic acid when it was necessary to continue treatment with the latter two drugs in patients who had become sensitized to them. Furthermore, in contrast to the relapses discussed above, 6 of 8 patients with definite acquired hypersensitivity to *p*-aminosalicylic acid or streptomycin were found to have lost their hypersensitivity when ACTH was finally withdrawn after having been given for 6 to 8 weeks. Comments previously made regarding distinction between desensitization and spontaneous loss of allergy with time apply here also, but in any case ACTH is obviously useful in abruptly suppressing

the reactions and keeping them suppressed while the allergic state is gradually lost.

The non-specific nature of these hormonal effects must, of course, never be forgotten. For example, the well-demonstrated effectiveness of ACTH in the treatment of dermatitis due to compounds of gold or arsenic (314) does not help one decide whether these reactions are allergic in nature.

2. Antihistaminic drugs. The effects of ACTH and cortisone cannot be ascribed to antihistaminic action, as they do not appear to exert such action (89, 95) but, as Pillsbury (257) has shown, certain types of allergic reactions, *e.g.*, urticaria, can be suppressed by antihistaminic drugs. Their clinical usefulness has been discussed in a previous review (34). Allergic reactions to antihistaminic drugs themselves are by no means uncommon (8, 85, 86, 327). One might question whether a drug will remain as effective therapeutically when it is given in the face of an allergic reaction, even if the latter is suppressed. This question is especially pertinent when antihistaminic drugs are used for suppression, as there is then no reason at all to doubt that the antigen-antibody reaction still takes place in the usual way. Clinical results in patients receiving such suppressive therapy as well as in the numerous patients who have continued to receive various drugs despite unsuppressed reactions due to them strongly suggest that the pharmacologic effectiveness of drugs is not hampered by allergic reactions to them. This question has also been studied by experiments with drug effects on skin (285). Though open to criticism on technical grounds, these experiments are of interest in that they gave results consistent with the above conclusion. Investigations of possible correlation between pharmacologically and serologically active parts of molecules have not produced clear results (176).

But the comments in section V B concerning the general advisability of withholding drugs from patients allergic to them apply here also. The fact that one may be able to suppress allergic reactions to a drug still does not justify the risk of its continuance unless the drug is indispensable. The occurrence of drug allergy is one good reason why, even in diseases against which a very satisfactory drug exists, it is desirable to have an equally effective "spare" drug, especially if the two are not chemically alike.

D. The development of new drugs

There has been a call for practical measures to insure the earliest possible general recognition and publication of frequent or dangerous reactions to new drugs (20). Such palliative measures deserve support, as it is inexcusable to neglect all temporary improvements in the sole expectation of the radical cure which may or may not ever materialize. Another suggested approach has been the use of tests such as the administration of "pyrogens", which might detect early damage to bone marrow by putting it under stimulus (328). This faces theoretical and practical difficulties. But, clearly, a more desirable end is the development of new drugs that can in advance be safely predicted to cause few or no allergic reactions in patients. Animal tests might seem to be the most likely basis for such predictions, in view of the proven usefulness of such tests in

general toxicology, but we still await a generally useful test for the antigenic potency of drugs. Evaluation of capacity to sensitize the skin and mucosae by contact has received the most attention. Topical application to the conjunctivae of rabbits and intradermal injection into guinea pigs have been the methods chiefly used (346). An intermediate approach has been the use of human volunteers for experimental contact sensitization. This has been used to evaluate dyes under consideration for use in clothing (105) and can, of course, be used for drugs, but, because of failure to imitate clinical conditions closely enough, the test is not always reliable (146, 307, 346). Although one can conceive of all grades of allergy, the differences between sensitized and unsensitized individuals is in practice often sharp. A drug with even a relatively low incidence of serious allergic reactions is dangerous in clinical medicine. These two facts combine in making it difficult to perform adequate animal tests without using an unwieldly number of animals. But an even greater problem is the previously mentioned inability to reproduce reliably certain allergic reactions to drugs, *e.g.*, agranulocytosis, in any laboratory animals. Attempts have, of course, been made to overcome these difficulties (38, 299). For example, by analogy with sensitization of the skin, it was hoped that preliminary direct injury to bone marrow might render this tissue more vulnerable to sensitization. Techniques using adjuvants have been borrowed from immunology. Preformed conjugates of drugs with bone marrow, and other chemical derivatives of drugs, *e.g.*, reduction products, have also been used in attempted sensitization. These efforts have thus far been unsuccessful (328).

It should be possible to evaluate the reliability of future tests based on techniques of successful animal sensitization—if such techniques are developed—by submitting to the test drugs already known from clinical use to cause a high incidence of allergic reactions and comparing the results with those obtained when drugs well known to cause a low clinical incidence of allergic reactions are similarly tested. Even the techniques for sensitization of the skin of animals, which have yielded so much useful information about the mechanism of drug allergy, may fail when used to predict clinical results. Thus, acetylglycarsenobenzene (solusalvarsan) was introduced into medicine with great encouragement from animal tests suggesting a lesser tendency to cause reactions than other arsenical drugs then in use. The disappointing inaccuracy of this prediction was shown by the high incidence of clinical reactions (129, 324).

Retreating once more to the principle of early recognition of danger after the introduction of a new drug into clinical medicine, one can see that practical techniques for the isolation and identification of antibody would be an advance of tremendous importance.

VI. APOLOGIA

Although examples of reactions to various drugs have been given above, it should be stressed that no claim of completeness can be made here. Readers searching for previous reports of a particular drug reaction should consult, among others, Sherman (301), Beerman (13), Fischer (103), Wright (372) and Cooke (56).

Discussion in the foregoing sections has ranged from the drawing of simple corollaries to unabashed speculation. Although it has seldom been possible to attribute the various hypotheses to individual investigators, for one writer has usually added to the thoughts of another, the reviewer has little more right to claim authorship of the hypotheses than of the data reported here. Interpretations from numerous writers have been intentionally included here in addition to their results, for it seems foolish to assume that experienced workers' data alone are worth noting and that their ideas are of no interest to anyone. Nevertheless, it is hoped that in such instances the text has made clear where the proven stops and the unproven begins. In any case, the readers of review journals are not likely to be of the type that has not learned to make such a distinction. In the end, the dullest fact in the world takes precedence over the glossiest hypothesis.

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