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Review

Idiosyncratic Drug Reactions: Possible Role of Reactive Metabolites Generated by Leukocytes

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Idiosyncratic drug reactions represent a poorly understood problem with serious medical implications. Many idiosyncratic drug reactions appear to be hypersensitivity reactions that involve an immune mechanism. The initiating step appears to involve the formation of a chemically reactive metabolite which can act as a hapten. Although the major site of drug metabolism is the liver, we have found that leukocytes, which contain myeloperoxidase and can generate hydrogen peroxide when stimulated, can also generate reactive metabolites. This has obvious implications for such idiosyncratic reactions as agranulocytosis. Furthermore, because of the importance of monocytes in the processing of antigen and the presentation of antigen to T lymphocytes in the initiation of an immunological reaction, formation of reactive metabolites by monocytes may also have implications for other idiosyncratic reactions such as drug-induced lupus and generalized idiosyncratic reactions.

KEY WORDS: idiosyncratic drug reactions; hypersensitivity reactions; drug-induced lupus; agranulocytosis, reactive metabolites; myeloperoxidase; leukocytes, neutrophils; monocytes.

INTRODUCTION

Idiosyncratic drug reactions represent a serious medical problem. By definition, idiosyncratic reactions do not occur in most patients given a drug; however, the large number of patient exposures to medication makes this type of reaction quite common. In addition, their unpredictable nature makes them virtually impossible to prevent and they are frequently life threatening. Idiosyncratic reactions also pose a major problem for the development of new drugs. They are not detected by toxicology testing in animals or in early clinical testing. To illustrate the scope of this problem, one has only to look at the number of drugs that have been recently introduced into the market but subsequently withdrawn because of an unacceptable incidence of serious idiosyncratic drug reactions. Such drugs include practolol, benoxaprofen, ticrynafen, zomepirac, and nomifensine.

The clinical manifestations of idiosyncratic drug reactions vary with the drug and with the patient; however, the type which is the subject of this review is commonly manifested by fever, lymphadenopathy, skin rash, and/or various organ involvement (1,2). The skin rash can vary anywhere from a mild morbilliform rash to a Stevens–Johnson syndrome in which a large portion of the skin is lost. The organs commonly involved are kidneys, liver, lungs, bone marrow or peripheral blood cells, heart, and serosal membranes such as those in joints and pleura. Some drugs are also associated with a drug-induced lupus syndrome in which there is induction of antibodies that bind to cell nuclei. In this syndrome the clinical symptoms appear to be due to the deposition of antigen–antibody complexes.

The mechanism of most idiosyncratic reactions is unknown. With the exception of agents used to treat cancer, most serious adverse drug reactions are not due to direct cytotoxicity. This is presumably because cytotoxic agents would be detected in early toxicity testing and would not be developed any further. Several characteristics of many idiosyncratic reactions suggest the involvement of the immune system:

(1) a requirement for either prior exposure to the drug or a lag period of more than a week between starting the drug and the development of toxicity;
(2) the immediate recurrence of symptoms when a patient who has had an idiosyncratic reaction is reexposed to the offending drug;
(3) the apparent lack of correlation between the dose and the risk of toxicity—this is probably not real but the range of the toxic dose certainly appears to be greater than observed with other types of toxicity;
(4) the presence of eosinophilia; and
(5) the unpredictable nature of the reactions and lack of animal models, which are at least consistent with the known interindividual differences in the immune system.

The mechanism of type I or anaphylactic reactions is reasonably well understood and is not reviewed here. Attempts have been made to demonstrate the "allergic" nature of other idiosyncratic reactions by searching for antibodies that bind to the drug in the serum of patients who have had an idiosyncratic drug reaction. Most of these studies have failed to demonstrate such antibodies (1,3). However, with few exceptions, a molecule must have a molecular weight

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greater than 1000 in order to be antigenic. Very few drugs are this large, and if they are to be antigenic they must be bound to other macromolecules. In these circumstances the drug is known as a hapten. It also appears as if a covalent bond between drug and protein is required for antigenicity, and other types of interactions such as hydrophobic binding are not sufficient (1,3). With the exception of a few drugs such as penicillin, drugs are not sufficiently reactive to form a covalent bond to protein. However, many drugs are metabolized to chemically reactive species which can form a covalent bond to protein. Therefore, the structure of a reactive metabolite bound to protein is likely to be very different from that of the original drug, and antibodies induced would not necessarily bind to the drug. Although the number of studies aimed at detecting antibodies to drug bound to protein is limited, a correlation between the presence of such antibodies and toxicity has been demonstrated. The most compelling example is the finding that patients with serious halothane-induced hepatotoxicity had antibodies to trifluoroacetylated protein and trifluoroacetyl chloride appears to be the reactive metabolite of halothane which acts as a hapten to form this antigen (4). This metabolism of halothane occurs in the liver, and the toxicity is selective for the liver. Recently we have found that many drugs are metabolized to reactive metabolites by leukocytes, and we postulate that this can lead to other types of toxicity such as drug-induced lupus, agranulocytosis, and generalized idiosyncratic reactions (5–9). This review is written with the view that most serious idiosyncratic drug reactions are hypersensitivity reactions (i.e., mediated by the immune system) which are initiated by reactive metabolites formed by the liver, more commonly by leukocytes, and probably by other organs such as the lung. The discussion is limited to hypersensitivity reactions involving the liver (because more is known about some of these reactions) and drug-induced lupus, agranulocytosis, and generalized idiosyncratic reactions (because the idea that these are due to reactive metabolites generated by leukocytes is novel).

IDIOSYNCRATIC HEPATOTOXICITY

Halothane-Induced Hepatic Necrosis

While the incidence of halothane-induced hepatic necrosis was low (about 1 in 10,000), it carried a high mortality rate, and halothane was used extensively. Understanding the mechanism of halothane-induced hepatic necrosis could help in the search for safer anesthetic agents, and an attempt was made to induce hepatic necrosis in animals with halothane to aid in mechanistic studies. The first successful animal model required hypoxia and pretreatment with phenobarbital in addition to halothane in order to induce hepatic necrosis (10). It was found that hypoxia led to reductive metabolism of halothane forming a free radical, and induction with phenobarbital increased this pathway (11). Such a pathway is analogous to the activation of carbon tetrachloride, which is a potent hepatotoxin. Although this mechanism was an attractive hypothesis, the degree of hepatotoxicity in the phenobarbital/hypoxia model was much less than in the clinical syndrome despite the drastic conditions used to increase the toxicity. Thyroxine was also found to increase halothane hepatotoxicity in the rat but the mechanism of toxicity appeared to be different from that in the phenobarbital/hypoxia model (12). It was not clear which mechanism, if either, was similar to clinical halothane hepatotoxicity.

Another clue to the mechanism of human halothane-induced hepatic necrosis was that the risk appeared to be greatly increased by prior exposure to halothane. This result suggested an "allergic" mechanism. Vergani *et al.* (13) found that patients who had developed hepatic necrosis after halothane anesthesia had antibodies which bound to hepatic protein from rabbits treated with halothane (13). Controls which had hepatic necrosis due to some other cause or patients who had been anesthetized with halothane but had not developed hepatic necrosis did not have such antibodies. Neuberger *et al.* (14) and Pohl *et al.* (4) demonstrated that the modification of protein which led to an immunogenic response involved an oxidative pathway leading to trifluoroacetyl chloride which trifluoroacetylated protein. The major trifluoroacetylated hepatic protein was identified as an esterase (15). Thus, the animal model which involved a reductive pathway is probably irrelevant to human halothane-induced hepatic necrosis.

Although it is likely that the antibodies induced to trifluoroacetylated hepatic protein are involved in the pathogenesis of halothane-induced hepatic necrosis, it is not yet clear how these antibodies lead to hepatic necrosis. If antibodies bind to hepatocyte cell membranes they could lead to T cell-mediated hepatocyte destruction.

Ticrynafen Hepatotoxicity

Although ticrynafen (also known as tienilic acid) had been used for several years in Europe, soon after it was introduced on the market in the United States, it became clear that it was associated with a significant incidence of severe hepatotoxicity. Hepatotoxicity was not seen in animal studies. This led to its rapid withdrawal from the market.

The delay between the initiation of ticrynafen therapy and the development of hepatotoxicity and the lack of an animal model suggested that the toxicity might be mediated by the immune system. Beaune *et al.* found that patients with ticrynafen-associated hepatic necrosis had antibodies that bound to a hepatic cytochrome P-450 (16). This P-450 appears to be responsible for oxidation of the thiophene ring of ticrynafen to a reactive metabolite which immediately reacts with the P-450 molecule that formed it; this altered protein is immunogenic and leads to antibody formation. This same cytochrome P-450 also metabolizes mephenytoin and is one of the known common genetically variable P-450s; therefore, patients who lack this isozyme should be protected from ticrynafen hepatotoxicity.

Isoniazid Hepatotoxicity

Isoniazid is another drug associated with a relatively high incidence of severe hepatic necrosis (17). There is an animal model of isoniazid-induced hepatotoxicity (18). The toxicity in the animal appears to be associated with acetylation of the isoniazid followed by hydrolysis to form acetylhydrazine. The acetylhydrazine is further oxidatively metabolized to a reactive metabolite which acetylates macromolecules. The evidence that this pathway is responsible for

toxicity in the animal model consists of the following: (i) acetylhydrazine is hepatotoxic, (ii) acetylisoniazid is much more hepatotoxic than isoniazid, (iii) inhibition of acetylisoniazid hydolysis decreases toxicity, and (iv) isonicotinic acid (the other product of acetylisoniazid hydrolysis) is not hepatotoxic. However, toxicity in the animal model is acute, while hepatotoxicity in humans is usually delayed for more than a month. Although this delay could represent a low level of ongoing damage to the liver, it suggests an idiosyncratic drug reaction involving the immune system. Isoniazid hepatotoxicity is also said to be dose independent, although as with other types of idosyncratic reactions, the risk of toxicity probably increases with the dose. It could be analogous to the animal model of halothane hepatotoxicity, which appears to involve a different mechanism than the human halothane-induced hepatic necrosis. In the case of isoniazid, the human toxicity could be due to an immunological reaction to a reactive metabolite of isoniazid bound to protein. Unlike the animal model, the reactive metabolite responsible for human toxicity could involve isoniazid itself. It has been demonstrated that persons exposed to isoniazid, either by working with the drug or by ingesting it therapeutically, can develop antibodies to isoniazid bound to protein (19). The evidence that human hepatoxicity also involves a metabolite of acetylhydrazine rather than of the parent drug is that the rapid acetylator phenotype is not associated with a large protective effect. Although the effect of acetylator phenotype is controversial and there appears to be only a small protective effect, one would expect a large protective effect if the hepatotoxicity involved direct oxidation of isoniazid to a reactive metabolite. However, acetylhydrazine is also inactivated by the INH acetyltransferase to yield diacetylhydrazine, thereby alleviating toxicity from intermediate acetylated products.

Other Drug-Induced Idiosyncratic Hepatotoxicity

Many other drugs have been associated with idiosyncratic hepatocellular damage; however, little is known about the incidence or mechanisms of these reactions (20). The other hydrazines which are used as antidepressants also cause hepatotoxicity, presumably by a mechanism similar to that of isoniazid (21). Arylamine drugs such as sulfonamides, aminosalicylate, and procainamide can be associated with idiosyncratic hepatocellular damage (20). Phenytoin and other anticonvulsants with a similar heterocyclic ring are associated with generalized idiosyncratic reactions which include hepatic involvement but they are seldom limited to the liver (22). Although the structure is very different, the anticonvulsant carbamazepine is also associated with a generalized idiosyncratic reaction which includes hepatic involvement. In this case the liver involvement is usually characterized by granulomatous hepatitis (23). The sulfur-containing antithyroid drugs are also associated with a significant incidence of hepatotoxicity (20). Valproic acid is associated with severe hepatotoxicity that is similar to Reye's syndrome and is very different from the other idiosyncratic hepatotoxicities (24). Other drugs associated with idiosyncratic hepatocellular damage include phenylbutazone, α-methyldopa, indomethacin, allopurinol, and penicillamine (20).

DRUG-INDUCED LUPUS

Procainamide-Induced Lupus

Procainamide is an antiarrhythmic drug whose chronic use is often limited by the development of an autoimmune syndrome similar to lupus. The incidence of procainamide-induced lupus can be as high as 30% (25). The pathology in lupus appears to involve the formation of antigen–antibody complexes and the activation of complement (26). In idiopathic lupus the major antigen in the antigen–antibody complexes is DNA. Although antinuclear antibodies are also present in procainamide-induced lupus, the pathology is less clear, and most antinuclear antibodies bind to histone protein instead of DNA (27,28). The mechanism by which procainamide can induce the formation of antibodies which bind to histone protein is unknown.

We have demonstrated that procainamide is oxidized by hepatic microsomes to reactive hydroxylamine and nitroso metabolites (29). *N*-Acetylprocainamide does not induce lupus and is not metabolized to a reactive metabolite. Nitrosoprocainamide covalently binds to proteins including histone protein (30). Thus one possibility for the mechanism of procainamide-induced lupus is that procainamide could be metabolized to the reactive nitrosoprocainamide, which could, in turn, react with histone protein. The altered histone protein could induce the production of antibodies which react with histone protein. We have also found that these oxidative metabolites are toxic to lymphocytes in the micromolar range, while procainamide is essentially nontoxic. This result suggests that these metabolites could interfere with control of the immune system (31). However, the hydroxylamine and nitroso metabolites are further transformed in the liver and little, if any, escape the liver (29). Although it is conceivable that the reactive metabolites could result in lupus without escaping the liver, it would make the hypothesis more attractive if the metabolites were formed in cells that have a more direct relationship to the control of the immune system. Initial studies on procainamide metabolism by mononuclear leukocytes (a mixture of lymphocytes and monocytes) were negative. However, when these cells were activated so that hydrogen peroxide (H_2O_2) was generated and myeloperoxidase (MPO) was released, they converted procainamide to the hydroxylamine as shown in Fig. 1 (6). Since a major function of monocytes is to process and present antigen to T-helper cells to initiate an immunological reaction, the production of chemically reactive metabolites in the vicinity of the cell membrane of the monocyte should be optimal for the initiation of an immunological response (8,32).

Other Arylamines Associated with Drug-Induced Lupus

Although procainamide is associated with the highest incidence of drug-induced lupus, many other drugs have been reported to cause lupus. Several of the other drugs that have been associated with drug-induced lupus are also arylamines (8). These include the sulfonamides, aminosalicylic acid, aminoglutethimide, and nomifensine. We have found that sulfadiazine is also oxidized to a hydroxylamine by neutrophils but we have not had a chance to study the other arylamine drugs as yet (33). Practolol and acebutolol are not

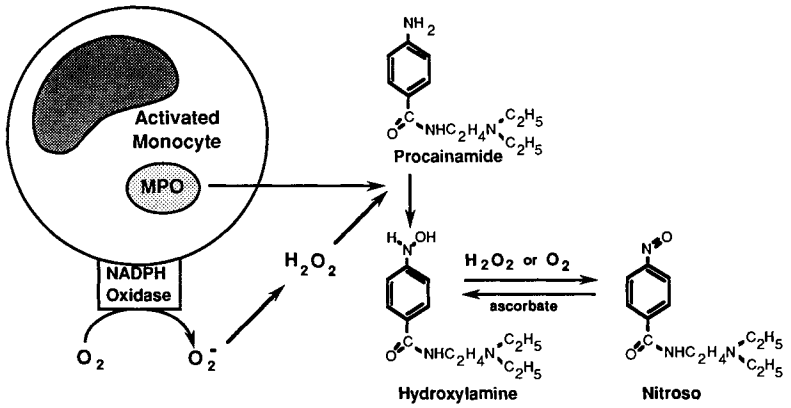

Fig. 1. Oxidation of procainamide by activated monocytes.

arylamines; however, they are extensively hydrolyzed *in vivo* to arylamines and they also have been associated with the drug-induced lupus syndrome (34,35). Among the β-blockers the only two associated with a significant incidence of antinuclear antibodies were practolol and acebutolol, and these are the only two β-blockers that are metabolized to arylamines (36).

Hydrazine Derivatives Associated with Drug-Induced Lupus

Hydralazine is associated with a 10% incidence of lupus (37). We have found that hydralazine is also metabolized by purified MPO/H_2O_2 or activated neutrophils (38). The major product is phthalazinone. Although phthalazinone is not chemically reactive, it has been suggested that its production correlates with toxicity (39). Furthermore, a chemically reactive metabolite, possibly a carbonium ion, is thought to be an intermediate in the production of phthalazinone. Another hydrazine derivative associated with drug-induced lupus is isoniazid. We have also found that it is oxidized by MPO/H_2O_2 to isonicotinic acid, presumably through a reactive intermediate (40).

Other Drugs Associated with the Induction of Lupus

Propylthiouracil is a drug used to treat hyperthyroidism and is also associated with the induction of lupus (41). It is the only drug that has reliably been demonstrated to induce a lupus-like syndrome in an animal model (42). We have demonstrated that propylthiouracil is metabolized by MPO/H_2O_2/Cl^- or activated neutrophils to a reactive sulfonic acid (9). It appears that other reactive metabolites including the sulfenyl chloride, thioester, and sulfinic acid were intermediates in the production of the sulfonic acid, although we were not able to isolate them. This sequence of metabolites is shown in Fig. 2.

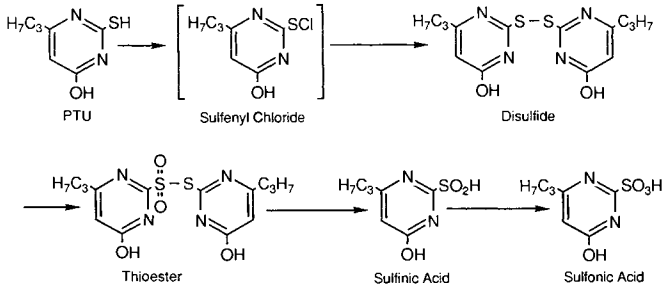

Fig. 2. Oxidation sequence of propylthiouracil (PTU) by activated neutrophils or MPO/H_2O_2/Cl^-.

Phenytoin is an anticonvulsant which has been associated with drug-induced lupus (43). It has been speculated that the toxicity of phenytoin is due to a reactive arene oxide metabolite (44). However, several other anticonvulsants have a very similar spectrum of adverse reactions, including drug-induced lupus, and they do not contain an aromatic ring which could form an arene oxide (8). We investigated phenytoin to determine if it could be metabolized to a reactive species by the combination of MPO/H_2O_2/Cl^-. We found that it was chlorinated to *N,N'*-dichlorophenytoin which is chemically reactive (7). This reaction is shown in Fig. 3. Unlike the other reactive metabolites that we have been able to isolate, *N,N'*-dichlorophenytoin could not be detected after incubation of the parent drug with activated neutrophils. This appears to be due to the reaction of *N,N'*-dichlorophenytoin with the neutrophils. When synthetic *N,N'*-dichlorophenytoin was incubated with neutrophils it disappeared with a half-life of less than a minute. When radiolabeled phenytoin was incubated with neutrophils, covalent binding was detected, and the binding required activation of the cells. Covalent binding to albumin was also detected in the presence of MPO/H_2O_2, and it also required chloride ion. This result supports the hypothesis that the covalent binding is due to the formation of *N,N'*-dichlorophenytoin by activated neutrophils.

Possible Mechanism of Drug-Induced Lupus

We have found that many of the drugs that are associated with the induction of lupus have a nitrogen or sulfur heteroatom which is oxidized to a reactive metabolite by purified MPO/H_2O_2/Cl^- or by neutrophils or monocytes

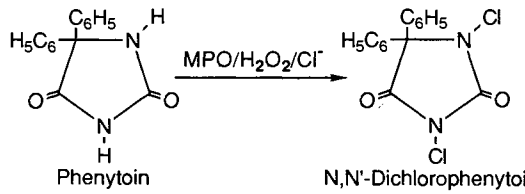

Fig. 3. Chlorination of phenytoin by MPO/H_2O_2/Cl^-.

which contain MPO and can generate hydrogen peroxide (8). As stated before, because of the importance of monocytes in the processing and presentation of antigen to helper T cells in the induction of an immunological reaction, it is tempting to speculate that this is the initial step in the induction of lupus by these drugs. It also provides a possible mechanism by which these drugs could cause other idiosyncratic drug reactions.

DRUG-INDUCED AGRANULOCYTOSIS

Agranulocytosis Associated with Arylamine Drugs

Many of the drugs associated with drug-induced lupus also cause agranulocytosis. The pathology can vary from isolated agranulocytosis to a generalized idiosyncratic reaction which involves blood cells. The decrease in leukocytes can also be due to peripheral destruction or damage to the bone marrow which leads to decreased production of all blood cells (aplastic anemia). Procainamide is associated with a significant incidence of agranulocytosis and the incidence appears to have increased since the introduction of a sustained-release form (45–47). The study with the highest incidence involved patients who were recovering from open-heart surgery (47). This type of major surgery would be expected to activate a large number of neutrophils and this could be one of the risk factors which lead to the high incidence. Antimyeloid-cell antibodies have been found in cases of procainamide-induced agranulocytosis (48). Dapsone is another arylamine associated with a relatively high incidence of agranulocytosis (49–51). We have demonstrated that activated neutrophils metabolize dapsone to a reactive hydroxylamine (5), and Wheetman *et al.* (52) have shown that the hydroxylamine is toxic to bone marrow cells. Sulfonamides are also associated with agranulocytosis, often as part of a generalized reaction also involving other organs (53).

Agranulocytosis Associated with Antithyroid Drugs

The mechanism by which antithyroid drugs inhibit thyroxine synthesis appears to involve the oxidation of the drug by thyroid peroxidase to a reactive metabolite which binds to the peroxidase, leading to inhibition of the enzyme (54). Myeloperoxidase is similar to thyroid peroxidase. The major serious adverse reaction to propylthiouracil and methimazole is agranulocytosis (55). We have found that propylthiouracil is oxidized by activated neutrophils and purified $MPO/H_2O_2/Cl^-$ to several reactive metabolites as described earlier (9). Propylthiouracil-induced agranulocytosis is associated with antineutrophil antibodies (56,57). Together, these data suggest that propylthiouracil-induced agranulocytosis is due to the oxidation of propylthiouracil by activated neutrophils to reactive metabolites followed by reaction of these metabolites to macromolecules on the neutrophil cell membrane. These altered proteins could then induce the formation of antibodies which bind to the haptenized cell membrane, and the antibodies could then lead to the destruction of neutrophils as illustrated in Fig. 4.

Other sulfhydryl-containing drugs such as captopril and penicillamine are also associated with a relatively high incidence of agranulocytosis and are likely to be metabolized to reactive metabolites by activated neutrophils.

Chloramphenicol-Induced Aplastic Anemia

The classic drug associated with aplastic anemia (which includes agranulocytosis) is chloramphenicol. Although it is not an arylamine, it contains a nitro group which is reduced

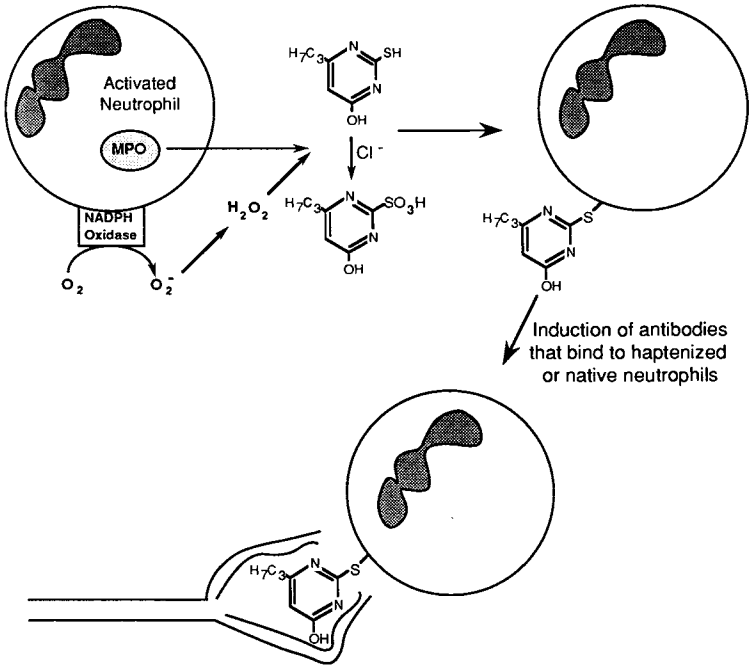

Fig. 4. Proposed sequence leading to propylthiouracil-induced antineutrophil antibodies. The sulfonic acid is shown as the reactive metabolite but there are several intermediate metabolites that are likely to be reactive.

to an arylamine by gastrointestinal bacteria (58). Replacement of this nitro group with a methylsulfone leads to an antibiotic which is not associated with aplastic anemia (59). It has been demonstrated that the aromatic amine of chloramphenicol is oxidized by the liver to the hydroxylamine and nitroso metabolites as shown in Fig. 5 (60). Furthermore, it was demonstrated that the nitroso metabolite but not chloramphenicol was very toxic to bone marrow (61,62). However, it was shown that the nitroso metabolite of chloramphenicol (like that of procainamide) has too short a half-life to get from the liver to the bone marrow (60). Although attempts were made to detect metabolism of the amine by bone marrow, like our early studies with procainamide, the cells were not activated. Yunis (63) has also found that if the benzylic alcohol of chloramphenicol is oxidized to a ketone the product is toxic to bone marrow. The combination of $MPO/H_2O_2/Cl^-$ may also be able to carry out this oxidation.

Unlike propylthiouracil-induced agranulocytosis, which appears to involve peripheral destruction of neutrophils, chloramphenicol-induced aplastic anemia involves destruction of the bone marrow. A toxic metabolite formed by myeloperoxidase-containing cells could lead to bone marrow destruction either through direct toxicity or through an immune-mediated destruction of bone marrow.

Anticonvulsant-Induced Hematological Toxicity

In general, the anticonvulsants are associated with a high incidence of hematological toxicity (64). Trimethadione, mephenytoin, and carbamazepine seem to be responsible for the highest incidence of such toxicity. Trimethadione is commonly associated with neutropenia, with an incidence estimated to be as high as 20%. Pancytopenia and aplastic anemia have also been reported. Mephenytoin is also associated with a high incidence of leukopenia, pancytopenia, and aplastic anemia and this along with generalized idiosyncratic reactions has prevented the common use of these drugs. Carbamazepine is commonly associated with neutropenia (estimates of the incidence are as high as 10%) but this is usually reversible, and aplastic anemia is less common than was feared in early clinical trials. Phenytoin is also associated with neutropenia but agranulocytosis is rare.

Phenylbutazone-Induced Agranulocytosis

Phenylbutazone is associated with a relatively high incidence of agranulocytosis and aplastic anemia (65). Ichihara has demonstrated that the pyrazolidinedione ring of phenylbutazone is chlorinated and oxidized to an alcohol and a hydroperoxide by activated neutrophils (66). Although the authors have evidence that the same species is not the intermediate in all of these metabolites, it appears that a free radical is an intermediate in some of them. Other analgesics with a pyrazolone ring, such as antipyrine and especially aminopyrine, are also associated with agranulocytosis (67,68). Agranulocytosis caused by aminopyrine apparently involves peripheral destruction of neutrophils by antibodies.

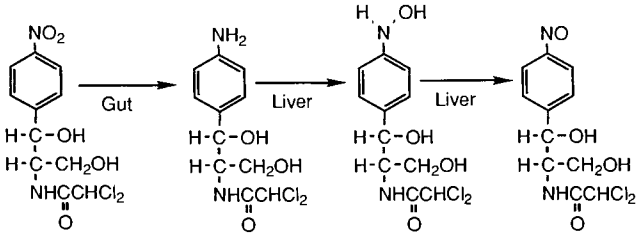

Fig. 5. Reaction sequence leading to the toxic nitroso derivative of chloramphenicol.

Possible Mechanism of Drug-Induced Agranulocytosis

As with drug-induced lupus, it appears as if many of the drugs which are associated with hematologic toxicity are oxidized to chemically reactive metabolites by myeloperoxidase released by activated neutrophils. Some immature cells in the bone marrow also contain myeloperoxidase. In some cases the toxicity appears to involve destruction of the bone marrow and in other cases the toxicity appears to involve peripheral destruction of cells by antibodies (67). It is reasonable to speculate that drug-induced agranulocytosis is due to reactive metabolites generated by activated neutrophils or other cells that contain myeloperoxidase. In some cases it could be due to the drug acting as a hapten to induce the synthesis of antineutrophil antibodies. These antibodies may only recognize neutrophils which have been modified by drug, or analogous to α-methyldopa-induced hemolysis, the induced antibodies may cross-react with normal neutrophils (69). In other cases, the reactive metabolite could cause direct toxicity to bone marrow; however, bone marrow destruction could also involve an immune mechanism.

GENERALIZED IDIOSYNCRATIC DRUG REACTIONS

In many cases idiosyncratic drug reactions are not limited to one organ. Such generalized reactions often resemble serum sickness (1). The most common presentation consists of fever, skin rash, and the involvement of one or more other organs such as the liver, kidneys, lung, bone marrow, lymph nodes, and heart. The rash can vary from a nonspecific maculopapular rash to a life-threatening Stevens–Johnson syndrome. We have also found that hypothyroidism can develop after the idiosyncratic reaction has abated (70). This is intriguing because of the similarity between myeloperoxidase and thyroid peroxidase and we have found that some of the same drugs that are metabolized by myeloperoxidase are also metabolized by thyroid peroxidase (J. Uetrecht, unpublished observation).

Sulfonamide Reactions

The use of sulfonamides, either alone or in combination with trimethoprim, is associated with the highest incidence (~2%) of idiosyncratic reactions among the commonly used drugs (71,72). Many of these reactions are limited to skin rashes, although the skin rash can be quite severe. Another group of patients has a more generalized involvement, with fever and other organ involvement in addition to the skin rash. These two types of reactions appear to be distinct and the presence of fever appears to be the best differentiating feature. We have found that the peripheral blood mononuclear leukocytes from patients who have had a generalized reaction to a sulfonamide are more sensitive than cells from normal controls to the toxic effects of the hydroxylamine of

sulfamethoxazole when tested *in vitro*. In contrast, the equivalent cells from patients whose reaction was limited to the skin were not significantly different from control cells (73,74). These experiments also support the hypothesis that the hydroxylamine or nitroso metabolites are involved in the toxicity.

Phenytoin Reactions

The most common manifestations of idiosyncratic reactions to phenytoin are fever, skin rash, liver involvement, and lymphadenopathy (22,75–76). The lymphadenopathy can be isolated and mimic lymphoma or mononucleosis (77,75). Phenytoin appears to inhibit immune competence and it has even been associated with mycosis fungoides and multiple myeloma (78–82). Similar to the assay for sulfonamide toxicity described above, it has been found that peripheral blood mononuclear leukocytes from patients who have had an idiosyncratic reaction to phenytoin are more sensitive to *in vitro* toxicity; however, in these experiments the parent drug plus hepatic microsomes was used to generate the reactive metabolite instead of using the reactive metabolite directly as in the sulfonamide assay (83). Again it is interesting to speculate that metabolism by leukocytes is responsible for much of the toxicity of phenytoin and related hydantoins because of their prominent effect on leukocytes and the immune system and the fact that we have demonstrated that phenytoin is metabolized to a reactive metabolite by activated leukocytes.

Dapsone Reactions

The most common adverse reaction to dapsone is hemolytic anemia, which appears to be due to redox cycling of the aromatic amine (84). This side effect is not an idiosyncratic reaction and occurs to some degree in virtually all patients. In addition, some patients develop a mononucleosis-like syndrome which has been called the "dapsone syndrome" (85–87). Antidapsone antibodies have been found in circulating immune complexes in patients taking dapsone (88). The presence of these antibodies has yet to be correlated with toxicity.

SUMMARY

Although much more work needs to be done for confirmation, circumstantial evidence suggests that most serious idiosyncratic reactions are hypersensitivity reactions that are initiated by the formation of chemically reactive metabolites. For drugs that form significant amounts of reactive metabolite only in the liver, as appears to be the case for halothane, the toxicity is limited to the liver. We have dem-

Table I. Summary of Toxic Effects of Drugs Known, or Suspected Because of a Functional Group, to Be Metabolized by Myeloperoxidase[a]

Drug	Drug-induced lupus	Agranulocytosis	Generalized idiosyncratic reaction
Arylamine			
Dapsone	±	+	+
Procainamide	+ +	+	+
Sulfonamides	+	+	+ +
Aminoglutethimide	+	+	+
Aminosalicylic acid	+	+	+
Nomiphensine	+	?	+
Chloramphenicol[b]	−	+ +	+
Practolol[b]	+	?	+
Acebutolol[b]	+	?	+
Thionosulfur or thiol			
Propylthiouracil	+	+ +	+
Methimazole	+	+ +	+
Penicillamine	+	+	+
Captopril	+	+	+
Hydantoin and related anticonvulsants			
Phenytoin	+	+	+ +
Mephenytoin	+	+ +	+ +
Trimethadione	+	+ +	+ +
Ethosuximide	+	+	+
Hydrazine derivatives			
Hydralazine	+ +	?	+
Isoniazide	+	+	+
Pyrazolones			
Phenylbutazone	+	+ +	+
Aminopyrine	+	+ +	+
Antipyrine	?	+	+

[a] This is, by necessity, a subjective assessment of the incidence of these adverse reactions largely from *Meyler's Side Effects of Drugs*, Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (see References), and other references listed in this review.

[b] These are not arylamines but are extensively metabolized to arylamines.

onstrated that many other drugs, especially those with arylamine, sulfhydryl, or other easily oxidized functional group, are oxidized by activated leukocytes to reactive metabolites. Because of their reactivity, it is necessary for most reactive metabolites to be formed very close to their site of action. Formation of reactive metabolites by neutrophils could lead to agranulocytosis by direct toxicity to bone marrow cells or could bind to neutrophil cell membrane and induce antibody formation. Because of the importance of monocytes for processing and presenting antigen to T lymphocytes, formation of a reactive metabolite by activated monocytes could lead to drug-induced lupus or more generalized idiosyncratic reactions. The association between drugs with functional groups that can be metabolized by myeloperoxidase and their pattern of toxicity is shown in Table I.

It is interesting to note that many of these drugs also affect thyroid function and that thyroid peroxidase is similar to myeloperoxidase and can metabolize drugs. Finally, since activation of leukocytes is necessary before these cells can metabolize drugs, the presence of an infection or other inflammatory condition which can activate cells may be one of the risk factors for the development of an idiosyncratic drug reaction. It is known that some drugs are associated with a much higher incidence of idiosyncratic reactions in the presence of certain viral infections.

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