Rheum.

DRUG-INDUCED LUPUS

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INTRODUCTION

Lupus erythematosus was initially considered to be a chronic but relatively benign disorder of the skin. In 1872, Kaposi first called attention to the systemic nature of this disease. Sir William Osler in 1895 characterized lupus as "a disease of unknown etiology with polymorphic skin lesions - hyperemia, edema, and hemorrhage - arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastrointestinal crises, endocarditis, pericarditis, acute nephritis, and hemorrhage from the mucosal surfaces. Recurrence is a special feature of this disease and attacks may come on month after month or even throughout a long period of years. Variability in the skin lesions is the rule...the attacks may not be characterized by skin manifestations; the visceral symptoms may be present, and to the outward view the patient may have no indications whatever of erythema exudativum...five of the cases had swelling about the pain in the joints..."(1). More than 50 years elapsed before Hargraves and coworkers in 1948 discovered the first immunologic marker of this disorder in the LE cell phenomenon (2).

The LE cell became a powerful tool which facilitated the diagnosis of systemic lupus erythematosus. It was not long after Hargrave's discovery that patients who developed clinical signs suggestive of SLE were studied in the immunology laboratory for the presence of LE cells. In 1953 it became apparent that a significant proportion of individuals treated with the antihypertensive drug hydralazine developed both clinical signs of lupus as well as positive LE preps (3-5). In the thirty years since, over thirty drugs have been linked with the development of lupus-like syndromes. Hydralazine and procainamide (6) are unquestionably responsible for the expression of autoimmune syndromes resembling lupus. Other agents are implicated to produce this syndrome but the associations are less frequent and less well documented.

The specific drugs that are generally accepted as inducers of lupus as shown in Table I are commonly used in a variety of subspecialties including most prominently cardiology, pulmonary, infectious disease, gastroenterology, endocrinology, neurology and psychiatry. It is not surprising therefore that attention has been focused on this problem by clinicians of various disciplines and investigators from a wide assortment of basic sciences. The specialist as well as the primary care physician sooner or later is likely to encounter the clinical problem of drug-induced lupus. This syndrome in addition has tantalized the rheumatologist who views it as a unique opportunity to study the pathogenetic mechanisms underlying such a mysterious and multisystemic disease as spontaneous SLE.

Over the past thirty years the science of immunology has undergone innumerable conceptual advances. In keeping with the growth in immunology our concepts regarding the mechanisms involved in the pathogenesis of both spontaneous and drug-induced lupus have undergone major revisions. The dominant concept for the development of pathologic lesions in both idiopathic SLE as well as in drug-induced lupus continues to implicate an excessive and inappropriate antibody response to antigens present in cellular nuclei such as those detectable by the LE prep. This review will highlight the clinical and laboratory features of drug-induced lupus that distinguish it from idiopathic SLE.

Prevalence of Drug-Induced Lupus

It has been estimated that there are approximately one half million individuals with SLE in the United States and that tens of thousands of these are drug-related cases (7). The incidence of the lupus syndrome varies considerably for each drug. Prospective studies of patients taking procainamide for prolonged periods have revealed that as many as 29% develop a lupus syndrome (8-13). The incidence of hydralazine-induced lupus is considerably lower, ranging between 1 and 3% in recent studies (14-17) using doses less than 200 mg per day and up to 14% with the higher doses used in the 1950's and 1960's (18).

TABLE I
LUPUS-INDUCING DRUGS BY SPECIALTY

Cardiology/Internal Medicine

- Procainamide
- Hydralazine
- Quinidine
- Practalol
- Acebutalol
- Labetalol
- Methyldopa

Endocrinology

- Propylthiouracil
- Methimazole

Pulmonary/Infectious Disease

- Isoniazid
- Nitrofurantoin

Gastroenterology

- Sulfasalazine

Rheumatology

- Penicillamine

Neurology

- Phenytoin
- Ethosuximide
- Trimethadione
- Primidone
- Penicillamine

Psychiatry

- Chlorpromazine
- Lithium Carbonate
- Phenelzine

The incidence of lupus in patients taking all other drugs listed in Table I is relatively rare compared with procainamide and hydralazine. The relative frequency of drug-induced lupus for various agents is summarized in Table II.

TABLE II

FREQUENCY OF DEVELOPING AUTOIMMUNITY DURING PROLONGED DRUG THERAPY*

Drug	% Patients Developing Positive ANA	Lupus
Procainamide	50-83	12-29
Hydralazine		
< 200 mg/day	40	1-3
> 400 mg/day	54	8-14
Isoniazid	20-22	0-1
Chlopromazine	17-30	**
Methyldopa	14-18	**

* > 1 year

**No prospective studies.

It is apparent that the incidence of positive antinuclear antibodies (serologic autoimmunity) greatly exceeds the frequency of autoimmune disease.

Diagnosis of Drug-Induced Lupus

Typically the drug-related cases have a milder disease involving fewer organ systems sparing the kidney and central nervous system. Nevertheless, the majority of drug-related cases fulfill four of the American Rheumatism Association criteria for idiopathic SLE (7). The ARA criteria first proposed in 1971 were revised last year (19) (Table III). While it is debated among rheumatologists whether a diagnosis of idiopathic SLE can be made in a patient who does not meet at least 4 criteria listed here, there certainly is no rule stating that 4 criteria are necessary to diagnose drug-induced lupus in the proper clinical situation. The classic situation is that the patient has no history or serology indicative of lupus prior to taking the drug and that symptoms resolve rapidly over a course of days to weeks after stopping the drug. Criteria for the diagnosis of drug-induced lupus are listed in Table IV. While the literature contains numerous descriptions of patients challenged with the drug to prove the point, this maneuver is not necessary nor is it ethical. If symptoms persist after drug withdrawal, the possibility of idiopathic SLE presents itself to the clinician who must look for other clues.

TABLE III
THE 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*

Criterion		Definition
1. Malar rash		Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash		Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity		Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers		Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis		Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a)	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR*
	b)	Pericarditis—documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a)	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not peformed *OR*
	b)	Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8.Neurologic disorder	a)	Seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR*
	b)	Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a)	Hemolytic anemia—with reticulocytosis *OR*
	b)	Leukopenia—less than 4,000/mm^3 total on 2 or more occasions *OR*
	c)	Lymphopenia—less than 1,500/mm^3 on 2 or more occasions *OR*
	d)	Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a)	Positive LE cell preparation *OR*
	b)	Anti-DNA: antibody to native DNA in abnormal titer *OR*
	c)	Anti-Sm: presence of antibody to Sm nuclear antigen *OR*
	d)	False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody		An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

TABLE IV
DIAGNOSTIC CRITERIA FOR DRUG-INDUCED LUPUS

1. Absence of history suggestive of idiopathic SLE prior to drug ingestion.

2. Development of antinuclear antibodies and at least one clinical feature of lupus during sustained drug therapy.

3. Rapid improvement of clinical features and gradual disappearance of autoantibodies after stopping the drug.

Clinical Spectrum of Drug-Induced Lupus

1. Organ System Involvement

Specific organ involvement in drug-induced lupus contrasts that seen in idiopathic SLE (Table V). The percentages given are derived from two large series representing 676 idiopathic SLE patients (20,21), two series representing 77 patients with procainamide-induced lupus (22,23), and three series representing 106 cases of hydralazine-induced lupus (18,24,25).

TABLE V
CONTRASTING PATTERNS OF TISSUE INVOLVEMENT IN
DRUG-INDUCED LUPUS AND IDIOPATHIC SLE

Site	Proportion Positive (%) Idiopathic	Hydralazine	Procainamide
Kidney	38-46	2-20	0-5
CNS	16-25	0	0-2
Lung/Pleura	---	25-30	---
Pleuritis	45	---	52
Effusion	33	---	33
Infiltrate	8	---	30
Pericardium	31	2	14-18
Joint	92-95	74-95	77-95
Skin	69-72	2-25	5-18

A. Kidney: Renal involvement is uncommon in procainamide-induced lupus. Nevertheless, at least 14 biopsy-proven cases with renal involvement have been reported and recently reviewed by Sheikh et al (26-30). Mouse models for procainamide- induced nephritis have also been reported (31,32). Hydralazine-induced renal abnormalities occur more frequently. Alarcón-Segovia

et al reported that the continued proteinuria, abnormal sediment and renal insufficiency observed in 20% of his patients was clearly related temporally to the ingestion of hydralazine (25).

B. CNS: Nervous system involvement is rare in all forms of drug-induced lupus. One case of polyneuropathy developing in association with procainamide-induced lupus has been reported (33).

C. Lung/Pleura: Several cases of in vivo LE cells in pleural effusions of procainamide treated patients have been reported (34-36). Antinuclear antibodies have been found both within the pleural fluid as well as deposited in pleural tissue in procainamide-induced lupus (37,38). Parenchymal lung involvement in procainamide-induced lupus is considerably more common than in SLE. If extrathoracic features of lupus are absent, the presentation can mimic pulmonary embolus, infection and neoplasm. A search for antinuclear antibodies is therefore justified in patients with pleural and pericardial effusions of unknown etiology in order to avoid unwarranted anticoagulation and antibiotic therapy. Corticosteroids may be necessary in severe serositis, especially pericardial tamponade (see below). The prevalence of pleuropulmonary involvement in procainamide-treated cases in contrast to hydralazine-treated cases may reflect the older age of the patients requiring antiarrhythmics. Urowitz et al reported that elderly people with idiopathic SLE are more prone to develop serositis than younger patients (39) (Table VI).

TABLE VI
EFFECT OF AGE ON ORGAN INVOLVEMENT IN IDIOPATHIC SLE

Age at Dx (Years)	Total No Pts	Manifestations of SLE Skin	Lung
< 30	36	28 (78%)	7 (19%)
≥ 50	9	3 (33%)	5 (56%)

Urowitz, et al, Arth Rheum 10:319-320 (1967)

Persistent pulmonary dysfunction has been reported after pleuritis associated with procainamide-induced lupus (40) but is not as prevalent as with idiopathic SLE (41). Cases of pulmonary hemorrhage (42) and pulmonary hypertension (43) reported in idiopathic SLE have not been reported in drug-induced lupus. In contrast, pulmonary involvement with hydralazine has been rarely reported (44).

D. Pericardium: Pericarditis occurs more commonly with procainamide than with hydralazine (45). Numerous cases of pericardial effusion and tamponade secondary to procainamide (46-49) and one case each associated with either isoniazid (50) or hydralazine (51) treatment have been reported. Such a dramatic presentation may occur in the absence of joint complaints. The diagnosis in these cases was made by finding LE cells in the pericardial fluid. All reported cases have required and responded to brief corticosteroid

therapy in addition to drug withdrawal. Procainamide-induced constrictive pericarditis requiring pericardiectomy has been reported (52).

E. Joint: No substantial difference is seen in the incidence of arthralgia and arthritis in drug-induced lupus and idiopathic SLE (Table V).

F. Skin: Dermatologic findings are relatively infrequent in drug-induced lupus. Dermal-epidermal junction immunofluorescence as measured in the "lupus-band test", was positive in 6% of patients with procainamide-induced lupus and 54% of patients with idiopathic SLE (53).

G. Miscellaneous: Pancreatitis (54) and myositis (55) have been reported in isolated cases of procainamide-induced lupus.

2. Demographic Features

In addition to different patterns of organ involvement, idiopathic SLE and drug related lupus demonstrate contrasting demographic profiles (Table VII). Idiopathic SLE classically affects a young female patient, with a higher incidence in blacks than Caucasians (21,25). In contrast, drug-related lupus affects blacks less frequently (23,56). Perry reported a 3% incidence of hydralazine-induced lupus in blacks in contrast to a 14% incidence in white patients (18). The 8 to 1 female predominance in idiopathic SLE sharply contrasts with the slight male predominance in cardiac patients who develop lupus while taking procainamide (23).

TABLE VII
DEMOGRAPHIC FEATURES IN DRUG-INDUCED LUPUS

Factor	Idiopathic	Hydralazine	Procainamide
Female:Male Prevalence	8:1	1.6:1	0.9:1
Black:White Incidence	2.7:1	0.2:1	0.5:1
Mean Age at Onset (Yrs)	29	50	62

Laboratory Features of Drug-Induced Lupus

1. Antinuclear Antibodies

The hallmark finding for both idiopathic SLE and drug-related lupus is the presence of antinuclear antibodies in the sera of patients. This subject has recently been reviewed with clarity and depth by Tan (57).

The LE Prep: The first antinuclear antibody discovered was the LE factor, an IgG antibody in the sera of patients with systemic lupus that reacts with nuclei from damaged cells. Together with complement, the LE

factor facilitates the phagocytosis of such nuclei by polymorphonuclear leukocytes and monocytes. The classic LE cell is nothing more than a phagocytic cell that has ingested an opsonized nucleus. The antigenic specificity recognized by the LE factor is deoxyribonucleoprotein (58), which is the molecular complex composed of DNA and nuclear proteins. The LE factor recognizes the protein portion of the complex which is composed of histones. To better understand the antigen-antibody reactions that mark both idiopathic SLE and drug-induced lupus, it is necessary to review the structural relationship between histone proteins and DNA.

Deoxyribonucleoprotein: The Relationship Between Histone Proteins and DNA in Nucleosomes

Chromosomal DNA is associated with basic proteins called the histones. The amino terminal portions of the histones have high concentrations of positively charged amino acids, particularly lysine. The positively charged histones and the negatively charged DNA normally interact to form nucleoprotein particles of chromatin in which histones bind noncovalently with DNA as well as with each other. The basic chromatin structure is the deoxyribonucleoprotein particle called the nucleosome (59-62). At the interior of the nucleosome particle is a closely packed octamer of histones comprised of two molecules each of 4 separate species of histone, H2A, H2B, H3, and H4 (Figure 1).

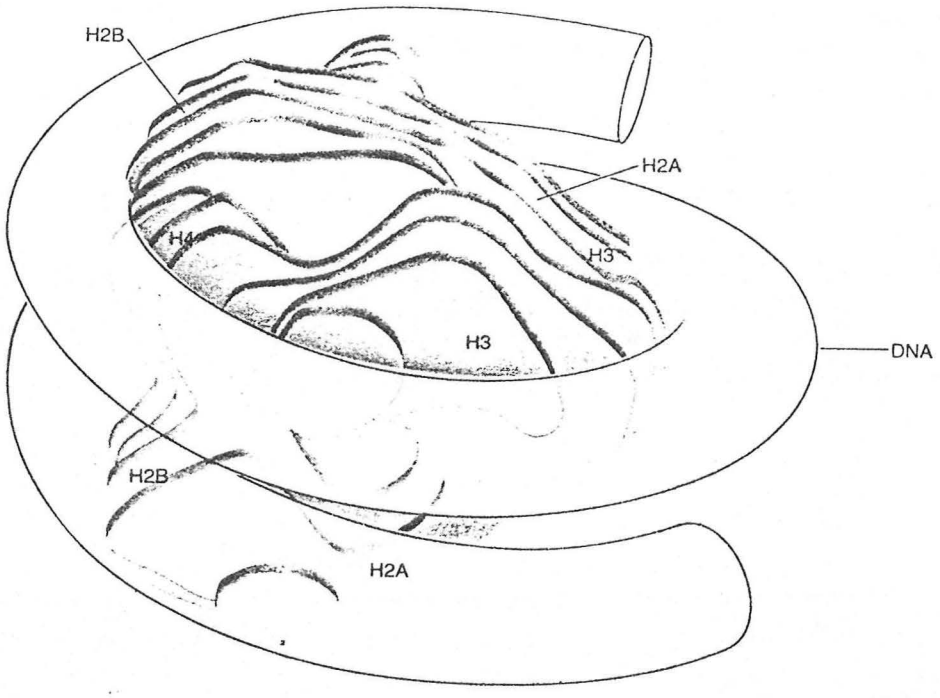


Figure 1: Model of nucleosome core composed of a histone octamer. (from Kornberg and Klug, 1981)

The histone core is surrounded by superhelical turns of DNA. The amino terminal portions of the histones are accessible at the nucleosome surface to degradation by the proteolytic enzyme trypsin while the globular central regions of the molecules are less accessible. These interior core histone molecules are further rendered inaccessible by the condensation of chromatin facilitated by a linker segment. Other histone molecules termed H1 and H5,

together with a variable amount of DNA up to 60 base pairs, link adjacent nucleosomes which themselves are 146 DNA base pairs in length (Figure 2).

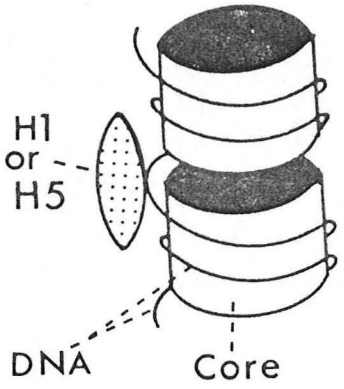


Figure 2: Relationship between nucleosomes and linker segments composed of DNA and H1 or H5 histone proteins. (from Stollar, 1981)

It has been argued that any modification of the primary structure of superhelical DNA might alter the structural relations between DNA and the histone core (61). Such alterations in primary structure of DNA might increase the availability of antigenic groups on certain histones previously hidden by DNA and/or induce a marked conformational change in histone structure. Such alterations might be induced by drug DNA interactions leading to the development of anti-histone antibodies. Of interest, the antinuclear antibodies in drug-induced lupus sera are comprised of anti-histone antibodies primarily.

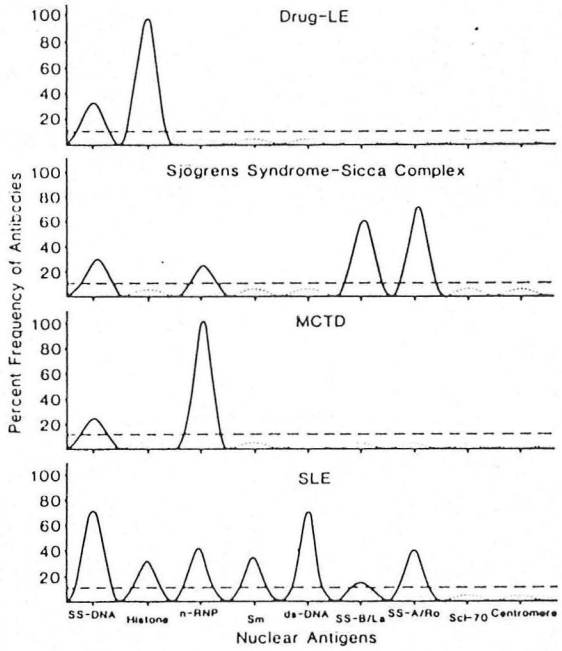


Figure 3: Spectrum of antinuclear antibodies in different rheumatic diseases. (from Tan, 1982)

This tendency of sera from drug-induced lupus patients to show preferential reactivity with histones contrasts the multiplicity of antinuclear antibody specificities seen in idiopathic SLE (Figure 3).

The Fluorescence Antinuclear Antibody Test: The ANA is generally available in most facilities and is the best initial screening test. There is a rough correlation between the immunofluorescence pattern and the specific nuclear antigen recognized (Table VIII). Antinuclear antibodies are measured in the immunology laboratory as shown in Figure 4.

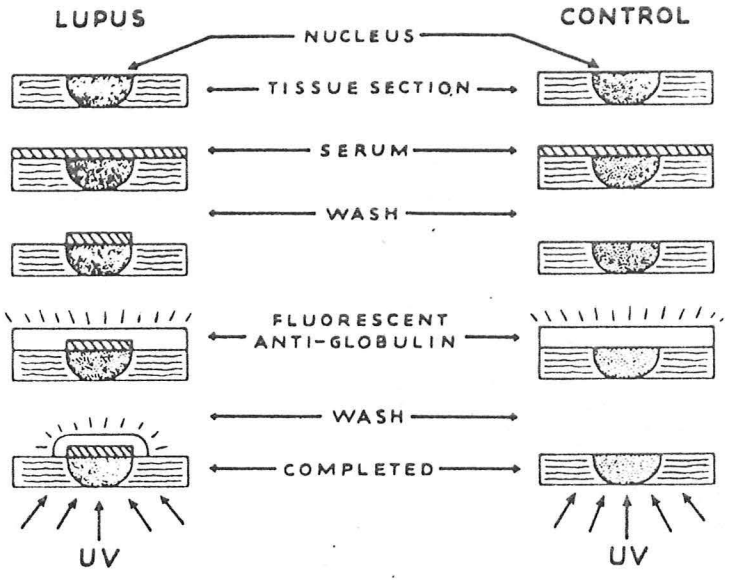


Figure 4: Principle of indirect immunofluorescent tests for antinuclear antibodies.

A tissue section of mouse kidney or liver or a tissue culture cell line is fixed to a slide as a substrate for the antinuclear antibody. The test serum is added to the slide and washed. Only antibodies binding to specific antigens in the cell nuclei will remain on the tissue section. This indirect immunofluorescent technique requires that a second antibody which is tagged with a fluorescein label and specific for human immunoglobulin then be added to the slide. After washing, only the slides containing the initial antinuclear antibody will in addition have bound on their surface the fluoresceinated anti-immunoglobulin reagent. The presence of fluorescence then is observed in the fluorescence microscope.

Specific ANA Patterns: Correlation With Antibody Specificity (Table VIII):

A. The diffuse or homogenous pattern is observed when antibody to deoxyribonucleoprotein antigens, in particular histone proteins, are present in the test serum. The typical ANA pattern observed in drug-induced lupus is diffuse, although a peripheral pattern may be observed occasionally. Tan et al have determined that the predominant antinuclear antibody in drug-induced

TABLE VIII
CORRELATIONS BETWEEN ANA PATTERN AND ANTIBODY SPECIFICITY

ANA Pattern	Antigen Recognized
Diffuse (Homogeneous)	Deoxyribonucleoprotein (including histone protein)
Peripheral (Rim)	Deoxyribonucleoprotein or Native DNA
Speckled	ENA Complex: Nuclear Ribonucleoprotein (nRNP), Sm; SS-A/Ro; SS-B/La
Nucleolar	Nucleolar RNA and RNA-protein complex
Centromere/Kinetochore	Uncertain

lupus is directed to histone proteins. Specific measurement of antihistone antibodies can be performed by methods first developed by Kunkel et al (63) and Stollar (64) and novel techniques by Tan and coworkers (65-70).

B. The peripheral pattern reflects antibody either to deoxyribonucleoprotein or to native DNA. Antibody to the former accounts for their presence in some sera of drug-induced lupus patients. Both diffuse and peripheral patterns can be observed in idiopathic SLE as well.

To distinguish between antibodies to native DNA and to histone proteins, more specific assays can be applied.

Anti-DNA: Antibodies to single-stranded DNA are seen in many rheumatic diseases including drug-induced lupus and are entirely non-specific. Antibodies to native DNA or double-stranded DNA are specific for idiopathic SLE and measured specifically in the Crithidia luciliae assay, Farr assay, and millipore filter assay. These assays are generally available. Published reports indicate that anti-native DNA does not occur in drug-induced lupus (71,72).

Anti-Histone: The techniques to measure histone antibodies are not generally available, in contrast to the anti-DNA test. However, they have proved useful in the specific characterization of antibodies present in drug-induced lupus. The cell line substrate used in the ANA test is treated with 0.1 normal hydrochloric acid to remove some of the nuclear antigens. A classic study by Fritzler and Tan (66) is shown in Figure 5. In drug-induced lupus, all immunofluorescence disappears after such treatment. The fluorescence, however, can be regained after reconstitution of the cells with exogenous histone proteins. In idiopathic SLE, certain sera continue to react with the cells even after the treatment with acid , while other

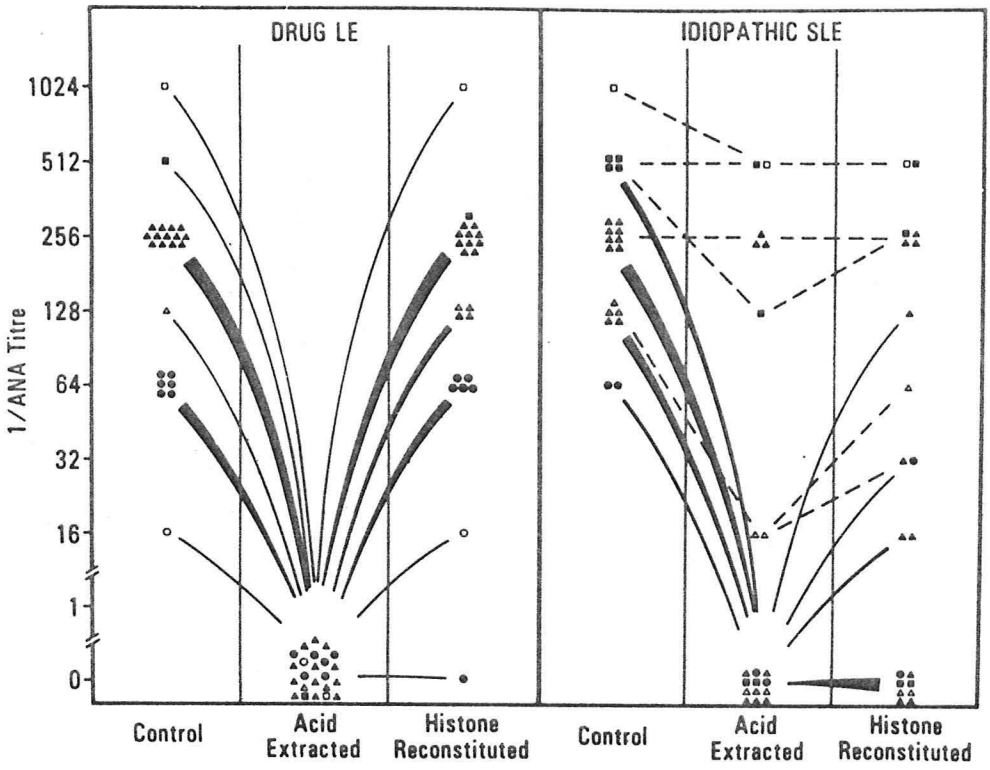


Figure 5: Three-step indirect immunofluorescent technique to measure histone antibodies in drug-induced lupus and idiopathic SLE. (from Fritzler and Tan, 1978)

sera may not regain their ability to generate fluorescence after reconstitution of the cells with histones. In this way, the restricted ANA profile in drug-induced lupus and the polyspecific profile in idiopathic SLE was firmly established.

C. The speckled pattern reflects the presence of antibodies to various saline extractable nuclear antigens. Such a pattern is observed in idiopathic SLE, mixed connective tissue disease (MCTD), and Sjögren's Syndrome, but not drug-induced lupus. If a high titred speckled ANA pattern is observed, a reasonable further diagnostic test would be the ENA which measures specific antibody to extractable nuclear antigens. These include most prominently nuclear ribonucleoprotein (nRNP), Sm antigen originally described in a patient named Smith, and Sjögren's Syndrome associated antigens, SS-A/Ro and SS-B/La. Such ENA antibodies can be detected by either hemagglutination, immunodiffusion or counter immunoelectrophoresis techniques. Since anti-Sm antibody is a specific marker of idiopathic SLE and is present in 35% of cases, it is not seen with drug-induced lupus.

D. The nucleolar pattern detects antibodies to nucleolar RNA and RNA-protein complexes. It is seen primarily with scleroderma and not in drug-induced lupus.

E. The centromere/kinetochore pattern has been described more recently and correlates with the CREST syndrome, which is a more benign form of scleroderma.

2. Serum Complement Levels

The earlier reports of drug-induced lupus emphasized the finding of normal serum complement levels together with the absence of anti-native DNA. This finding was compatible with the view that complement-fixing anti-native DNA antibodies complexed with DNA antigen were involved in the pathogenesis of nephritis in idiopathic SLE, a form of organ involvement that was infrequently observed in drug-induced lupus. While the complement levels generally are normal in drug-induced lupus, this criterion alone is not hard and fast. Documentation of hypocomplementemia has been provided for both procainamide (73-74) and hydralazine-induced (75) syndromes. Circulating immune complexes that tend to fix complement and lead to hypocomplementemia have been reported in 3 of 3 patients studied with hydralazine-induced lupus (76) and in 72% of patients taking procainamide (77).

3. Lymphocytotoxic Antibodies

A variety of other antibodies are seen in patients with idiopathic SLE. These include antibodies to lymphocytes, so-called anti-lymphocyte antibodies or lymphocytotoxic antibodies. Bluestein and coworkers have reported that 65% of their patients with procainamide-induced lupus exhibited lymphocytotoxic antibodies (78) and Hughes et al found a 57% incidence in hydralazine-induced lupus (79) indicating that the spectrum of autoantibodies in drug-induced lupus is not limited to anti-nuclear antibodies.

4. Miscellaneous

False-positive tests for syphillis are present in 10-15% of idiopathic SLE patients (80). Circulating anticoagulants are present in only 0.4 to 2% of patients with idiopathic SLE (80). The antibodies responsible for these two phenomena have been described in hydralazine- and procainamide-induced syndromes but only in isolated case reports (81-84). Cryoglobulins were reported in one patient with procainamide-induced lupus (85).

Lupus-Inducing Drugs: Structural, Metabolic and Genetic Considerations

Prospective studies looking at the incidence of antinuclear antibodies and the development of clinical lupus have been performed only with three drugs: procainamide (8-13), hydralazine (14-17), and isoniazid (86). Procainamide today is the most common drug that leads to the full-blown lupus syndrome. While no controlled prospective studies have been performed with the other implicated drugs, there are convincing case reports of patients that have taken psychotropic medications (87-96), anticonvulsants (97-102), methyldopa (103-105), antiarrhythmics (106-113), anti-hyperthyroid medications (114-117), penicillamine (118-122), sulfasalasine (123-125) and other miscellaneous drugs. Excellent reviews are available discussing the lupus-inducing potential of these drugs (21,126-128). No uniform structure exists to account for the ability of these diverse medications to induce a common autoimmune syndrome, except for hydralazine, procainamide, and isoniazid which exhibit certain structural similarities (Figure 6). These compounds are either aromatic amines or substituted hydrazides. Each is metabolized to a significant degree by the hepatic enzyme N-acetyl transferase. This enzyme catalyzes the transfer of the acetyl group from acetyl-CoA to the amino or hydrazino group of the drug substrate. Striking relationships between the level of

activity of this enzyme and the susceptibility to drug-induced autoimmunity have been observed.

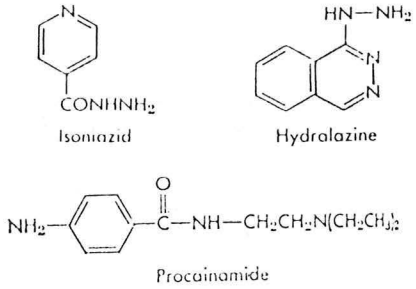


Figure 6: Structural similarity in drugs metabolized by hepatic N-acetyl transferase.

Role of Acetylator Phenotype in Drug-Induced Lupus

The rate of drug acetylation by N-acetyl transferase, or NAT, is a genetically controlled trait. Individuals display either a slow or rapid acetylator phenotype (129-130). The slow acetylator trait is inherited in a Mendelian autosomal recessive fashion. Slow acetylators are homozygous for the recessive allele (rr) and rapid acetylators are either homozygous (RR) or heterozygous (Rr) for a dominant NAT allele (Table IX). The classification of an individual as either a rapid or slow acetylator can be accomplished in vivo by measuring blood levels of acetylator metabolites at a specified period of time after the administration of a test drug such as isoniazid, dapsone, or more commonly, sulfamethazine as is shown in Figure 7.

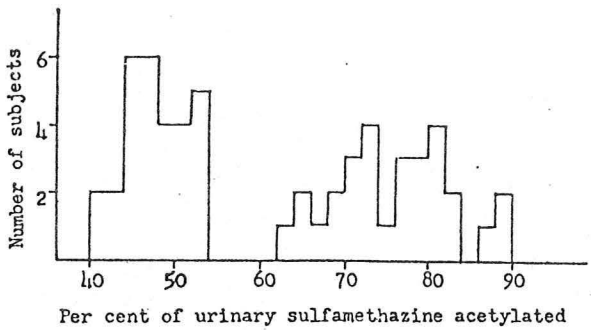


Figure 7: Bimodal distribution of acetylator function in a population. (from Price Evans and White, 1964)

In vitro measurements of hepatic NAT activity can also be determined but these are less clinically useful. The rapid and slow acetylator phenotypes are represented in the United States population approximately to the same degree both in black and Caucasian individuals. The propensity of individuals with the slow acetylator phenotype to develop both antinuclear antibodies and even more strikingly, the lupus syndrome was shown first by Perry and coworkers for hydralazine (56). The two impressive findings from their study of 1970 were first, that only slow acetylators developed the lupus syndrome and second, the development of lupus in slow acetylator phenotype

TABLE IX
AUTOSOMAL RECESSIVE TRANSMISSION OF
SLOW N-ACETYL TRANSFERASE ACTIVITY

Genotype	Acetylator Phenotype
rr	Slow
rR	Fast
RR	Fast

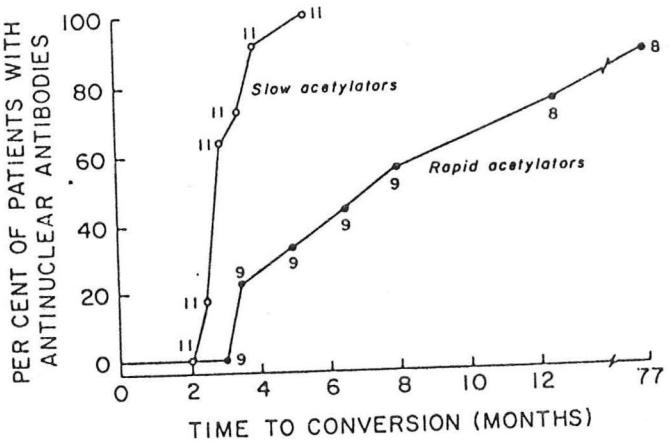
patients was seen only in Caucasians (Table X). Drug-induced lupus occurred most commonly in patients taking greater than 400 mg of hydralazine a day for longer than 6 months. The preponderance of slow acetylators among patients with hydralazine-induced lupus was confirmed by Perry in future studies where he observed that 24 of 25 cases showed the acetylator phenotype (18). Strandberg and coworkers (131) found 29 of 31 patients and Batchelor and coworkers (132) found 25 of 26 patients developing hydralazine-associated lupus were of the slow acetylator phenotype. Occasional patients exhibiting the slow acetylator phenotype when tested by sulfamethazine technique have developed the lupus syndrome while taking hydralazine. Harland (133) described such a patient who exhibited a urinary hydralazine metabolite profile similar to that of a slow acetylator. Subsequently, Schmid and coworkers (134) recommended the measurement of the metabolite, 4-(2-acetylhydrazino)-phthalazin-one (N Ac-HPZ) in urine during chronic hydralazine administration as a more direct index of acetylation capability with respect to the parent drug.

TABLE X
RISK FACTORS FOR HYDRALAZINE-INDUCED LUPUS

Acetylator Phenotype	Race	# Patients	# Positive ANA	# Lupus Syndrome
FAST	Black	15	5	0
	Caucasian	9	4	0
SLOW	Black	15	8	0
	Caucasian	18	14	9

Perry, et al, J Lab Clin Med 73:114-125 (1970)

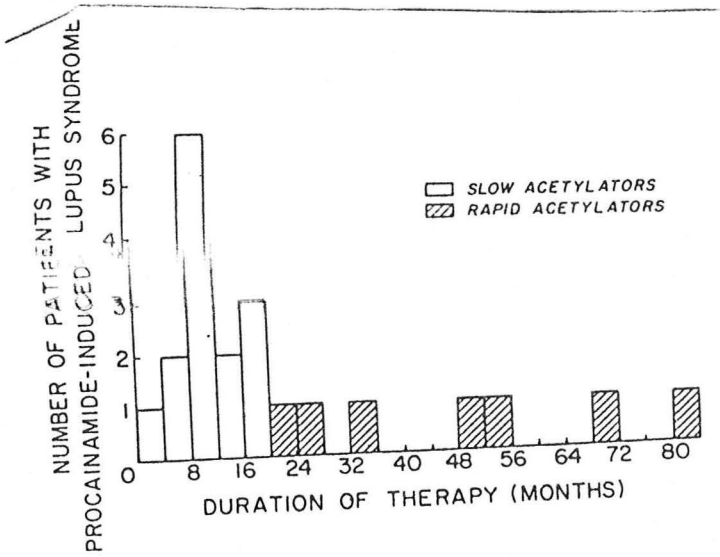
The relationship between acetylator phenotype and the development of toxicity during procainamide treatment has also been studied in detail. A classic prospective study performed by Woosley et al (135) from Vanderbilt demonstrated that slow acetylators more rapidly develop positive tests for antinuclear antibodies reaching a 100% incidence within 6 months, while at 12 months less than 80% of the rapid acetylators demonstrate a positive ANA test (Figure 8).



from Woosley et al (1978)

Figure 8: Effect of acetylator phenotype on rate of developing procainamide-induced antinuclear antibodies. (from Woosley, 1978)

With regard to the development of full-blown lupus, slow acetylators developed the syndrome much more quickly than did the rapid acetylators (Figure 9).



from Woosley et al (1978)

Figure 9: Effect of acetylator phenotype on rate of developing procainamide-induced lupus. (from Woosley, 1978)

This relative difference between slow and fast acetylators markedly contrasts the overall predominance of the slow acetylator phenotype in patients who developed hydralazine-induced lupus. The explanation offered to account for the lesser degree of protection afforded by rapid acetylator phenotypes to patients on procainamide relates to differences in the pharmacokinetics of procainamide and hydralazine. Hydralazine has a first-pass hepatic metabolism of 60-80% and there is almost no renal elimination of the parent drug (136). In contrast, the first-pass hepatic metabolism of procainamide is estimated to be only 15% and 65% of the parent drug is eliminated by renal excretion (136). The incidence of procainamide and hydralazine induced ANA and lupus appears to be a function of the cumulative exposure to the unacetylated drug. Both the amino group of procainamide and the hydrazino group of hydralazine are thus implicated in the development of autoimmunity since these are the sites of the molecule which are acetylated by hepatic N-acetyl transferase. These observations have suggested that drug-induced lupus by both hydralazine and procainamide represents a dose-response function rather than a hypersensitivity or allergic reaction to the drugs themselves.

N-Acetyl Procainamide As An Alternative Antiarrhythmic Agent

The realization that N-acetylated metabolites of both procainamide and hydralazine are not involved with the induction of lupus led to the attempts at using these metabolites as substitute pharmacologic agents. Unfortunately, acetyl hydralazine is not active as a vasodilator nor is acetylated isoniazid active against mycobacteria nor are acetyl-sulfonamides microbiologically active (136). In contrast, the marked antiarrhythmic potency of N-acetyl procainamide (NAPA) (Figure 10) was first discovered in 1974 by Drayer and coworkers (137) from Temple University and Elson and coworkers (138) from Northwestern.

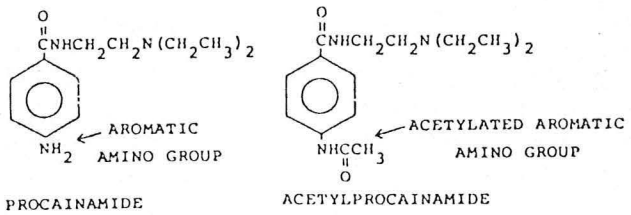


Figure 10: Comparative structures of procainamide and N-acetyl procainamide (NAPA). (from Lahita et al, 1979)

These studies performed mostly in animal models revealed that the antiarrhythmic potency of acetylated procainamide relative to procainamide was 92% with respect to dose and 70% with respect to plasma level. Subsequent clinical studies by these groups as well as the group from Vanderbilt have demonstrated the efficacy of NAPA as an anti-arrythmic agent in man. Stec et al (139) subsequently described the case of a patient with procainamide-induced lupus whose arthralgias and ANA resolved during treatment with NAPA (Table XI). Further work from this group by Lertora et al showed that 4 of 5 patients treated with NAPA for 12 months did not develop antinuclear antibodies (140). Similarly, Lahita et al observed only 1 of 6 patients treated up to 12 months with NAPA to develop a positive ANA in contrast to its development in 8 of 10 procainamide-treated patients (141). These workers in addition

TABLE XI
N-ACETYLPROCAINAMIDE (NAPA) THERAPY AND ANTINUCLEAR ANTIBODY (ANA) TITERS

Weeks of NAPA Therapy	NAPA Dose	Plasma NAPA Level	ANA Titer*
	g/d	*μg/mL*	
0			1:640
2	6.0	28.4	1:160
4	6.0	20.1	1:640
8	6.0	29.3	1:320
12	6.0	27.5	1:640
16	7.5	42.8	1:320
20	7.5	37.4	1:640
24	7.5	37.5	1:320
28	8.0	34.6	1:40
32	8.0	50.4	1:40
36	6.0	55.2	1:80
40	6.0	49.4	1:40
44	6.0	48.0	1:40

* Normal range for ANA titers is 1:40 or less.

Stec, et al, Ann Int Med 90: 799-801, (1979)

documented the lack of development of anti-single stranded DNA in NAPA treated patients in contrast to the development of these antibodies in 50% of procainamide-treated patients (Table XII). A follow-up study by this group in a paper by Kluger et al (142) showed the successful treatment with

TABLE XII
FRACTION OF PATIENTS WITH POSITIVE ANTIBODY TESTS

Duration of Therapy	Antinuclear Antibody		Anti-sDNA Antibody	
	Procainamide Treated	Acetyl-procainamide Treated	Procainamide Treated	Acetyl-procainamide* Treated
10 days–1 mo	6/19 (31%)	0/8 (0%)	4/20 (20%)	0/7 (0%)
1–6 mo	7/10 (70%)	0/8 (0%)†	4/7 (57%)	0/7 (0%)§
6–12 mo	8/10 (80%)	1/6 (17%)‡	5/10 (50%)	0/5 (0%)

Lahita, et al, NEJM 310:1382-1385, (1979)

NAPA of three patients who had formerly developed procainamide-induced lupus and had gone into remission after stopping procainamide. Two other patients were described whose lupus syndrome resolved during treatment with NAPA. Small amounts of unacetylated procainamide on the order of 1 μg/ml were detectable suggesting some low level in vivo deacetylation of the administered NAPA (Table XIII). These levels were not sufficient to reinduce the lupus syndrome, again suggesting the dose-response effect as mentioned previously. Similar results were obtained by Roden and coworkers (143) from Nashville. These clinical observations strongly support the hypothesis that the aromatic amino group on procainamide is important for induction of the lupus syndrome and that acetylation of this amino group blocks the lupus inducing effect.

TABLE XIII
PATIENTS ON ACETYLPROCAINAMIDE (NAPA) THERAPY WITHOUT RECURRENCE OF SYMPTOMS

Patient	Interval Between Procainamide and NAPA Therapy	NAPA Therapy		Average Serum Level	
		Duration	Dose	Procainamide*	NAPA
	mos		*g/d*	*μg/mL*	
016	25	24	6	1.0	18.0
023	3	6	4	†	28.0
031	0.5	6	5.5	0.7	23.0

* Procainamide formed after acetylprocainamide administration represents an in-vivo metabolite formed by deacetylation of acetylprocainamide.
† Procainamide levels were not measured.

Kluger, et al, Ann Int Med 95: 18-23, (1981)

NAPA is not presently marketed for general use. Medco Research, Inc., a research and development firm in Los Angeles now holds the IND (Investigational New Drug) application. A phone conversation with Dr. Manfred Mosk revealed that recent meetings with the FDA have been favorable and that the drug is in the late stages of Phase III trials. Dr. Mosk stated that NAPA has positive inotropic properties that allow it to be considered a Class III antiarrhythmic. The projected lag time to marketing NAPA is estimated at 12-18 months. If a patient with procainamide-induced lupus does not respond to alternative agents for ventricular ectopy such as quinidine and disopyramide (Norpace), NAPA may be applied for under a "compassionate protocol". Of note, quinidine-induced lupus has been reported (106-108) but disopyramide has not been implicated (185). A physician may phone Dr. Mosk and indicate the cardiac history dictating the use of NAPA. After consideration, NAPA might be provided to cases at risk for sudden death. Contact Manfred Mosk, Ph.D. (phone 213/854-1954), 8733 Beverly Blvd., Los Angeles, California 90048.

HLA-D Associations in Drug-Induced Lupus

A dose response relationship, therefore, seems to exist for both procainamide and hydralazine in their unacetylated forms with the development of both antinuclear antibodies and in particular, the development of the lupus syndrome. This fact however, does not entirely explain why certain individuals of the slow acetylator phenotype such as the black population reported by Perry did not develop lupus. Other genetic factors, therefore, have been sought to account for the heterogenous response to the drug with respect to the development of lupus. With regard to hydralazine, Batchelor and coworkers from England have determined that patients with the HLA-DRW4 haplotype have a higher risk of developing lupus during the course of hydralazine treatment (132). They noted in addition that the combination of Caucasian and HLA-DRW4 status in their female patients was a highly significant risk factor for the development of lupus (Table XIV). HLA studies have been reported in abstract form only by a group from Pittsburg with regard to procainamide. The development of procainamide-induced lupus was related to the inheritance of HLA-DR6Y (144). Whether these HLA associations with the development of lupus in drug treated patients involves immune response genes or other mechanisms at present is not understood.

In summary, then, the development of antinuclear antibodies is the first step toward the development of lupus in procainamide and hydralazine treated patients. The rapidity and incidence is determined by the acetylator

phenotype of the individual. The progression from a positive ANA, that is, serologic autoimmunity, to clinical lupus appears to involve other genetic factors that include HLA-DR haplotype, race, and sex.

TABLE XIV
INFLUENCE OF SEX AND PRESENCE OF DR4 ON DEVELOPMENT OF HYDRALAZINE SLE IN 41 SLOW ACETYLATORS

Patients	Females*		Males*	
	DR4 +	DR4 −	DR4 +	DR4 −
Developed hydralazine SLE	13	7	5	0
Did not develop hydralazine SLE	0	5	4	7

*A significantly higher proportion of females (80%) than males (31%) developed hydralazine SLE ($\chi^2=7{\cdot}8, p<0{\cdot}01$).

Batchelor, et al, Lancet i: 1107-1109, (1980)

Role of Acetylator Phenotype in Idiopathic SLE

The importance of acetylator phenotype in the development of drug-induced lupus has led to the hypothesis that the slow acetylator phenotype may predispose to the expression of idiopathic SLE in patients not treated with drugs. Exposure to environmental agents such as hydrazine in the laboratory setting has led to a lupus syndrome in at least one individual with the slow acetylator phenotype (145). Other environmental factors including hydrazine containing synthetic (tartrazine, herbicides, pesticides) and natural compounds (mushrooms, tobacco, and tobacco smoke) may surreptitiously lead to lupus-like illnesses (61,146) (Table XV).

TABLE XV
ENVIRONMENTAL AGENTS THAT POSE A POTENTIAL RISK TO SLOW-ACETYLATOR INDIVIDUALS

Hydrazines	Aromatic Amines
Tobacco	Hair Dyes
Tobacco Smoke	Reduction Products of Azo Food Dyes by Intestinal Bacteria
Mushrooms	
Penicillum oralicum	
Tartrazine	
Herbicides	
Pesticides	

In keeping with the present concept that idiopathic SLE is multifactorial, a number of groups have examined the possibility that such patients are predominantly slow acetylators. While several studies have shown a slight increase in slow acetylator phenotypes among their patients with idiopathic SLE on the order of 60-70% compared with 50-60% in the control groups (146-149), a study by Morris et al of 27 patients with spontaneous SLE found that 43% were slow acetylators and 63% were rapid acetylators (150). Moreover, among four pairs

of first degree relatives, all of whom had idiopathic SLE, 7 of 8 individuals were rapid acetylators. The conclusion from this study was that people who are slow acetylators are at no greater risk of development of idiopathic SLE than are rapid acetylators and that the slow acetylation phenotype is not correlated with familial SLE. This study highlights the growing opinion that drug-induced and idiopathic SLE are distinct clinical diseases involving populations with highly different genetic makeups.

Risk of Exacerbation of Idiopathic SLE by Various Drugs

The probability that the slow acetylator phenotype is not predominantly distributed among patients with idiopathic SLE suggests that such patients are not at increased risk of exacerbating their disease upon taking known offending drugs such as hydralazine and procainamide. This question has been examined by Reza et al who concluded that no exacerbations were seen in seven hydralazine treated patients with idiopathic SLE (151). This study has been criticized, however, by Hess et al (152) who pointed out the fact that the lupus patients were on immunosuppressive therapy which could mask an exacerbation as well as the fact that two of their patients were black and that the overall study was not carried out for more than several months. The approach most rheumatologists would take, however, is that patients with idiopathic SLE who need to be treated with drugs such as procainamide, hydralazine, anticonvulsants and phenothiazines should not be denied these agents. It should be mentioned in this context that several other drugs tend to induce flares of idiopathic SLE in certain patients. These include estrogens, sulfonamides and motrin (ibuprofen). Motrin has been associated with the development of aseptic meningitis in a number of reported cases of idiopathic SLE (153) and is therefore not the non-steroidal anti-inflammatory agent of choice in this disease. Reports of sulfonamide induced exacerbations of SLE or even the precipitation of de novo lupus have appeared since the 1940's (154-156). We have had the opportunity of observing such a reaction in one of our clinic patients to the drug Bactrim. Outpatient administration of this drug for a urinary tract infection precipitated the admission of this patient to Parkland with a presentation resembling toxic shock syndrome. The possibility of such idiosynchratic reactions should be kept in mind by physicians seeing patients with idiopathic SLE on an interm basis with urinary tract infections and musculoskeletal complaints. Regarding estrogens and the birth control pill, idiopathic SLE can be exacerbated by such therapy (21). Prospective studies, however, of normal individuals taking the pill have revealed a low level incidence of ANA on treatment but no documented cases of drug-induced lupus (21). Jungers et al have recently reported that progesterone-containing contraceptives are efficaceous and do not cause flares in patients with idiopathic SLE (157).

Mechanism for Drug-Induced Autoimmunity

A number of possible mechanisms to account for the induction of serologic and clinical autoimmunity by the various drugs discussed so far have been proposed and tested (Table XVI). These include, first, that structural similarities between the drugs and self-antigens may result in immunologic cross reactions particularly at the antibody level. Second, the drug may interact chemically with self molecules to enhance the immunogenecity of such autoantigens as DNA and deoxyribonucleoprotein. Third, the drugs or their metabolites may directly alter the immune system in a pharmacologic

TABLE XVI
HYPOTHETICAL MECHANISMS IN DRUG-INDUCED AUTOIMMUNITY

1. Immunologic cross-reactions between drugs and autoantigens.

2. Enhanced immunogenicity of autoantigens after chemical interactions with drugs.

3. Direct drug effect on immunocompetent cells.

   a. Enhancement of B lymphocyte differentiation
   b. Interference with suppressor cell function.

manner leading to an enhanced positive effect on either B lymphocyte differentiation, macrophage and/or helper T cell function, or to an inhibitory effect on the function of suppressor T cells that normally regulate the reactivity of the immune system to autoantigens.

Antibodies to Lupus-Inducing Drugs: Do Cross-Reactivities With Autoantigens Occur?

In consideration of the first possibility, one must ask whether antibodies directed toward lupus inducing drugs are formed during the course of their administration. With regard to hydralazine, Hahn in 1972 showed that all patients with active hydralazine induced lupus had circulating anti-hydralazine antibodies in their sera (24). This finding has been confirmed more recently by Carpenter and coworkers who found that 16 of 21 patients over a 1 year prospective study developed anti-hydralazine antibodies (14). With regard to procainamide, a study published by Drs. Russell and Ziff in 1968 (158) found a surprisingly high incidence of natural antibodies of the IgM type to procainamide in up to 50% of normal untreated individuals. Even more surprising was the lower incidence of 6% of anti-procainamide antibodies in patients who developed lupus on this drug. If anything, the antibodies to the drug were protective against the development of autoimmunity. Alternatively, these natural antibodies were suppressed during the onset of autoimmunity. A subsequent study from Israel showed that procainamide-induced lupus may occur in the absence of antibodies to the drug (159). Moreover, neither hydralazine in the studies by Hahn et al and Carpenter et al nor procainamide in the latter study by Klajman et al caused inhibition of antinuclear or anti-deoxyribonucleoprotein reactivity of sera from patients with corresponding drug-induced lupus. It is possible that cross-reactivity between nuclear antigens and metabolites of lupus-inducing drugs may exist, however, but such studies have not yet been performed. At this point, it appears unlikely that drug induced autoimmunity results from an immunologic cross reaction between the drugs and self-antigens.

Drug Interactions With Autoantigens

Drug interactions with DNA and deoxyribonucleoprotein were first shown by Dr. Eng Tan. He observed a physiochemical interaction between soluble deoxyribonucleoprotein and hydralazine that resulted in increased viscosity of the reaction mixture (160). Hydralazine added to purified DNA resulted in only a mild increase in viscosity while the drug had no effect on the viscosity of histones by themselves (Figure 11). Tan further studied the

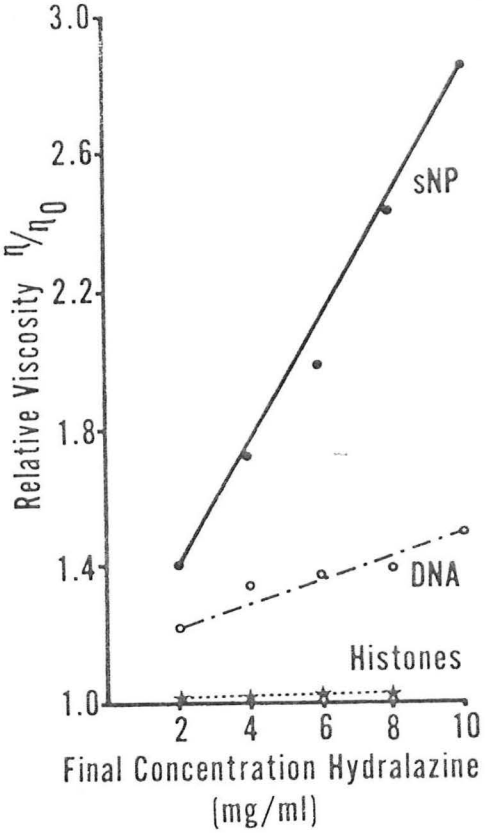


Figure 11: Effect of hydralazine on viscosity of soluble deoxyribonucleoprotein. (from Tan, 1974)

immunochemical characteristics of soluble deoxyribonucleoprotein-hydralazine complexes. He had previously shown that soluble deoxyribonucleoprotein antigen by itself was labile to treatment with either DNAase or trypsin. It was further shown that when the soluble nucleoprotein-hydralazine complex was subjected to the same enzyme treatments, trypsin treated complexes continued to display precipitating activity on immunodiffusion plates but DNAase treated complexes did not (Figure 12).

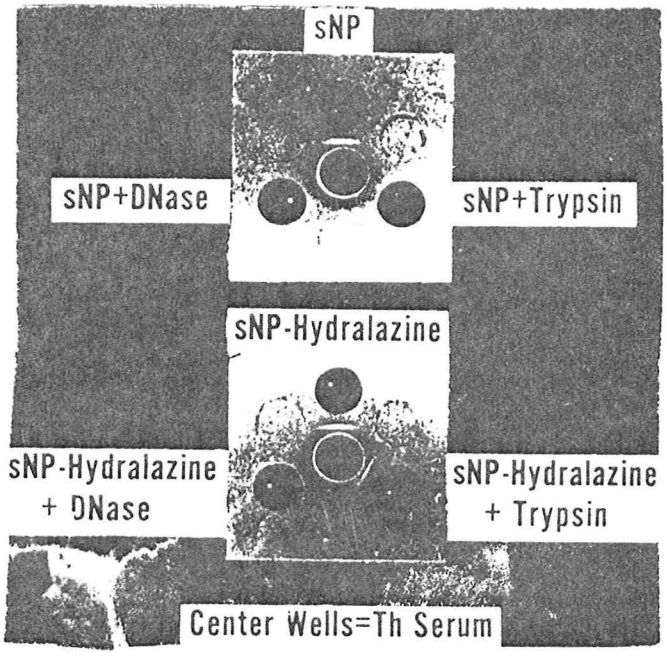


Figure 12: Hydralazine renders soluble deoxyribonucleoprotein resistant to proteolytic degradation. (from Tan, 1974)

Therefore, the complexing of hydralazine with soluble nucleoprotein in some way protected the histone moiety of the soluble nucleoprotein complex from digestion with trypsin. It was therefore postulated from these studies that hydralazine interaction with nucleoprotein in vivo might protect nucleoprotein from breakdown by proteolytic enzymes and thus maintain a potentially immunogenic autoantigen. A demonstration that these interactions occur in vivo, however, has not been forthcoming.

An interesting observation and speculation by Dubroff and Reid was published in 1980 in Science (161). Hydralazine was shown to react with thymidine and deoxycytidine, a reaction that was enhanced by exposure to ultraviolet light. It was proposed that such interactions with pyrimidine bases might alter the structure of helical DNA and expose new histone antigenic sites as proposed above. These workers further postulated that drugs such as hydralazine might modify the DNA and consequently the gene expression in and function of cells of the immune system particularly B and T lymphocytes, thus altering the antibody response. Such interactions were not surprising in view of the prior demonstration in the late 1960's that hydrazines are capable of binding covalently with pyrimidine bases of DNA. As noted previously, hydrazines found in the laboratory have been shown to result in the lupus syndrome in laboratory personnel. Of more general concern, hydrazines found in the environment might interact with pyrimidine bases in vivo leading to the induction of autoimmunity, particularly in genetically predisposed individuals such as those with slow acetylator phenotypes.

With regard to procainamide, Uetrecht and Freeman et al from Vanderbilt showed that procainamide underwent bioactivation that resulted in its ability to interact with bacterial DNA (162) and hepatic proteins in mice (163). This bioactivation was dependent upon mixed-function oxidase activity both in vitro and in vivo. These authors propose that such reactions occur in procainamide treated patients leading to the binding of drug to deoxyribonucleoproteins and the development of antinuclear antibodies. Of note, in their system, N-acetyl procainamide was incapable of binding to hepatic protein, indicating again that the N-acetylation of procainamide must be a protective metabolic pathway. An earlier study in 1974 by Eldredge and coworkers (164) showed that hydralazine altered the intrinsic viscosity and optical rotation of native DNA. Procainamide altered the optical rotation of native DNA, lowered the "melting temperature" of native DNA, and interfered with renaturation of DNA upon heating. These characteristics were not affected by other drugs implicated in the lupus syndrome, i.e. phenytoin, trimethadione, propylthiouracil and methyldopa.

Cross-reactivities Between Anti-Histone Antibodies, Lymphocytotoxic Antibodies and Rheumatoid Factors

It can be discerned from the discussion up to now that the attention of researchers has focused on the induction of antinuclear antibodies and the chemical relationships between nuclear antigens and lupus inducing drugs. It is clear that antibodies to histone proteins and to a lesser degree, single stranded DNA, and transiently to ribonucleoprotein (165), are present in the sera of most drug induced lupus patients. It is not obvious however, as to how such drug nuclear antigen interactions might result in the production of lymphocytotoxic antibodies as discussed earlier. A series of studies both in Norway and this country has detected some surprising cross reactivity

between nuclear antigens and cell surface antigens present on both human lymphocytes and granulocytes (166-169). Of particular interest in the context of a discussion of drug-induced lupus, the nuclear antigens recognized by the anti-lymphocyte antibodies were histone proteins. Additional cross-reactivities with DNA histone have been determined with both polyclonal (170-174) and monoclonal rheumatoid factors (175) as recently described by Agnello and coworkers. Therefore, it is possible that enhanced immunogenecity of histone DNA complexes might induce other types of autoantibodies such as rheumatoid factor and lymphocytotoxic antibody by virtue of cross-reactivity with antigens present on cell surfaces and on the Fc constant region of IgG, the target of rheumatoid factor.

Therapeutic Implications of Cross-Reactivity Between Autoantibodies

Such broad cross-reactivity by an autoantibody has been demonstrated previously by a series of incisive papers from the laboratory of Dr. Robert S. Schwartz in Boston (176). Using monoclonal hybridoma technology, Dr. Schwartz and coworkers have developed monoclonal antibodies directed to DNA both in the MRL/1 mouse model of SLE (177) as well as using peripheral blood lymphocytes from patients with idiopathic SLE (178). Such monoclonal anti-DNA antibodies display cross-reactivity with an assortment of phospholipids including cardiolipin, the substrate for the serologic test for syphillis. Thus, the immunologic basis for the false positive VDRL noted in idiopathic SLE, as well as the circulating anticoagulants that recognize platelet phospholipids, have now been established to be a property of antibodies for

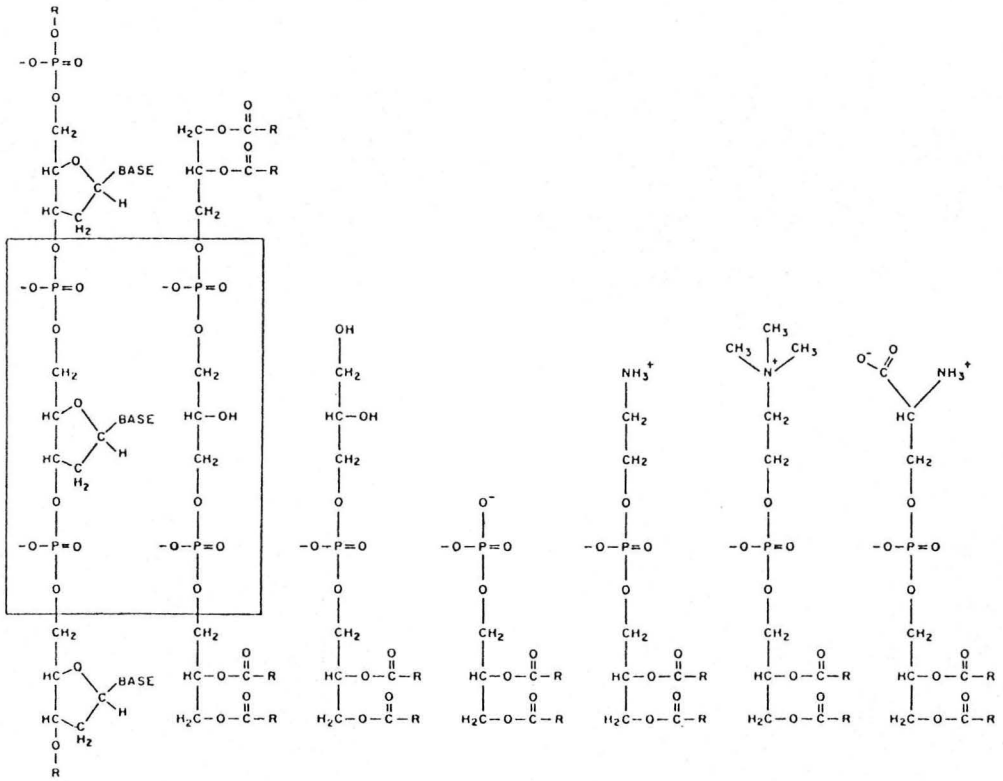


Figure 13: Shared phosphodiester epitope between DNA and phospholipids. (from Lafer et al, 1981)

native DNA. The antigenic determinant or epitope common to all these macromolecules is a phosphodiester linkage also present on the phosphate ribose backbone of DNA (Figure 13).

This development in the field of lupus research has generated much excitement for several reasons. First, it helps explain some of the long observed serologic manifestations of lupus. Second, it offers new hope that a more specific and limited form of immunosuppression might suffice to control the clinical disease without the necessity for broad spectrum immunosuppression to which we are limited at present. Specific immunologic unresponsiveness or tolerance to the phosphodiester epitope either through the use of anti-idiotypic antiserum, tolerogenic forms of this epitope to induce either direct inactivation or blockade of epitope-specific B cells or the induction of suppressor T lymphocytes are all now feasible approaches that would replace our present need to resort to nonspecific immunosuppression. Since the latter results in considerable morbidity and mortality in patients with idiopathic SLE, this new approach may afford a major advance in the treatment of this disorder in years to come. Such an approach, however, requires considerable development and testing in the available murine models of human SLE before clinical trials can be contemplated.

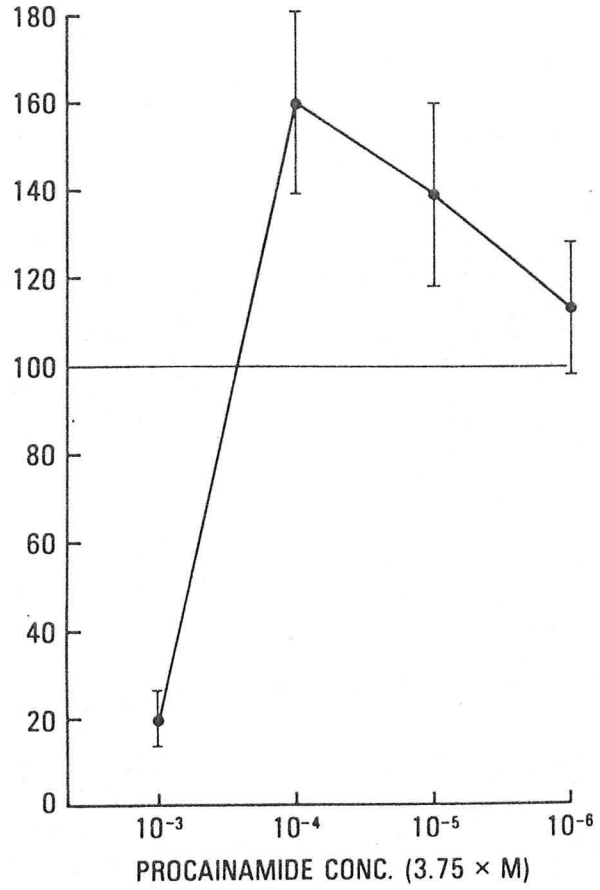


Figure 14: Effect of procainamide on T cell proliferation induced by phytohemagglutinin. (from Bluestein et al, 1981)

Effect of Lupus-Inducing Drugs on Normal Immunoregulatory Mechanisms in Man

The third mechanism invoked to account for drug induced autoimmunity involves a direct pharmacological effect on cells of the immune system resulting in either disorders of immunoregulation by suppressor T cells or direct activation of B lymphocytes, perhaps through the aid of increased helper T lymphocyte function. Parker has argued that β blocker-induced lupus may relate to the presence of β adrenergic receptors on T cells (179). The function of regulatory T cells might be affected preferentially leading to autoimmunity. As an alternative explanation for the broad spectrum of autoantibodies observed in drug-induced lupus, Bluestein and coworkers from San Diego were the first to explore the possible interference by procainamide with cellular immune function (180). They found that procainamide was capable of both augmenting or inhibiting the response of human peripheral blood lymphocytes to phytohemagglutinin in culture in a dose dependent manner (Figure 14). In addition, they demonstrated that lymphocytes from antigen-primed rabbits generated a prolonged antibody response to the antigen when challenged in vitro (78), suggesting the possibility of an alteration in suppressor T cell function. Such an effect was claimed for another drug, methyldopa, implicated in the development of autoimmune hemolytic anemia and several cases of lupus. Kirtland and coworkers (181) found that methyldopa inhibited T lymphocyte suppression of IgG production by peripheral blood mononuclear cells stimulated by pokeweed mitogen. This effect occurred when T cells from normal individuals were incubated with methyldopa and was seen as well in T cells obtained from patients taking the drug. It was noted in addition that an increase in intracellular lymphocyte cyclic AMP was induced by methyldopa. Such increases in cyclic AMP inhibit cell division necessary for the development of suppressor T cells.

Along these lines, three additional studies have examined the possible effects of procainamide on normal immunoregulatory mechanisms. Miller and Salem (182) examined the in vitro response to pokeweed mitogen by peripheral blood lymphocytes from procainamide-treated patients, all of whom had developed positive anti-nuclear antibody tests. The magnitude of the IgG response to pokeweed mitogen was significantly enhanced in cultures containing lymphocytes from procainamide treated patients compared with control cultures. Mixing experiments by these investigators suggested that the basis for this enhancement of the response resided in increased helper T cell function in the procainamide treated patients. In contrast, Tannen and Cunningham-Rungles (183) found that the sera from procainamide-treated patients was capable of inhibiting the mitogenic response by normal peripheral blood lymphocytes to concanavalin A. The identity of this blocking factor was not investigated and quite possibly may be an anti-lymphocyte antibody which could result in such inhibition. The authors did demonstrate, however, that procainamide induces a factor that is capable of modulating subsequent immune function.

Finally, a study performed in our rheumatic disease unit by Ochi and coworkers examined the effect of procainamide on the antibody forming cell response to pokeweed mitogen by normal human peripheral blood mononuclear cells (184). The continuous presence of procainamide enhanced the response in a dose-dependent manner. The basis for this enhancement was shown in cell separation studies to reside in a defect in the generation of suppressor cells by pokeweed mitogen. Thus, procainamide enhanced the response in cultures under conditions which favored suppressor T cell generation. No

effect by the drug was observed when suppressor cells were prevented from developing by the inhibition of T cell proliferation using mitomycin C (Figure 15).

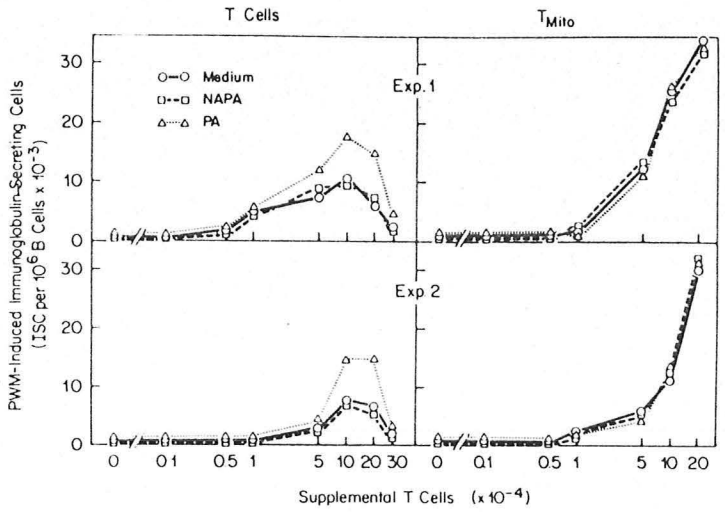


Figure 15: Augmentation of antibody response to pokeweed mitogen by procainamide (PA) but not by N-acetyl procainamide (NAPA) only under conditions favorable for the generation of suppressor T cells. (from Ochi et al, 1983)

This study in addition demonstrated that procainamide inhibited by 50% the generation of classical concanavalin A induced suppressor T cells (Table XVII).

TABLE XVII
EFFECT OF PA OR NAPA ON CON A-INDUCED SUPPRESSION OF ISC GENERATED IN PWM-STIMULATED CULTURES

Additions to cultures used to generate suppressor cells		Suppression of ISC Mean±SEM§
Con A*	Drug†	
		%
0	0	1.5±3.5
	PA	−2.3±4.3
	NAPA	2.5±5.1
+	0	58.1±3.4‖
	PA	27.2±4.3‖
	NAPA	59.4±5.5

While procainamide interfered with the generation of suppressor T cells in both these systems at concentrations obtainable in human serum in treated patients, N-acetyl procainamide had absolutely no effect in either system. This suggested that the unacetylated amino group of procainamide was critical for the immunomodulatory effect observed in culture. In contrast, unacetylated procainamide had no effect on the response of human peripheral blood lymphocytes to another mitogen, staphylococcal protein A under conditions in which suppressor T cells were generated. Therefore, a selective effect by the

drug on certain but not all suppressor T cell circuits was apparent. This finding is consistent with the observation in drug-induced lupus patients that only certain, but not all, types of autoantibodies are formed. Whether altered suppressor T cell function in this study reflects the actual binding of procainamide to the nuclear DNA as proposed earlier by Dubroff and Reid to alter the generation of suppressor cell function, or results from other mechanisms is at present unknown.

To summarize our present understanding of the mechanism by which drugs induce lupus, the hypothesis that drug-induced lupus results from cross-reactivity between the drug and self-antigens has little support. The second and third hypotheses, namely the interaction of drugs with self-macromolecules altering their immunogenecity or alternatively interacting with the cells of the immune system resulting in defects in immunoregulation, both have a growing body of support. These two mechanisms are not mutually exclusive and in fact might both be operative in the pathogenesis of drug-induced autoimmunity.

CONCLUSION

In closing, it is clear that much has been learned over the past 30 years with regard to the mysterious toxicity first noted in hydralazine-treated hypertensive patients. A growing awareness of the potential of various drugs of diverse classes to alter the normal state of immunologic unresponsiveness to self antigens has emerged. The importance of genetic factors, particularly the acetylator phenotype, in addition to certain HLA D locus associations with regard to the development of autoimmunity during the course of treatment with both procainamide and hydralazine is now well established. Research into drug-related lupus has led to drug modifications such as the acetylation of procainamide which now permits the use of this potent antiarryhthmic agent without the development of lupus. Since the discovery of the first anti-nuclear antibody responsible for the LE cell, considerable progress has been made in the further delineation of the diverse spectra of antinuclear antibodies that characterize idiopathic SLE and drug-induced lupus. Surprising cross-reactivities have been discovered between DNA and phospholipids present in various macromolecules, on the one hand, and histone proteins, lymphocyte membranes, and the Fc portion of IgG on the other. These observations help explain the baffling clusters of antibody reactivity seen in particular patients as well as provide potentially new avenues for therapeutic intervention. Interactions between the drugs that induce lupus and self macromolecules have been demonstrated and may account for either increased immunogenecity of autoantigens on the one hand or the alterations in immunoregulatory activities of T lymphocytes. Drug-induced lupus, throughout its history, has been a challenge to the rheumatologist investigator because unlike most other conditions in his field, the etiology of this disorder is known from the start. Although much has been learned, the precise mechanism by which given drugs alter the normal state of immunoregulation remains uncertain. Continued research should provide answers which are likely to extend our understanding of idiopathic SLE as well.

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