PROGRESS IN CLINICAL IMMUNOLOGY

Vol. 4

Edited by

Robert S. Schwartz, M.D.

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Robert S. Schwartz, M.D.

Chief, Hematology–Oncology Division
Department of Medicine
Tufts-New England Medical Center
Boston, Massachusetts

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Preface

Like its predecessors, this fourth volume of *Progress in Clinical Immunology* aims to provide the reader with comprehensive reviews of current topics relevant to the basic understanding and management of immunological disorders. If any justification for these reviews is needed, it should be apparent even to those having only a casual acquaintance with clinical immunology. The rapid expansion of this field has made it difficult, if not impossible, to remain current with the voluminous literature. Indeed, considerable advancements in clinical immunology were already apparent ten years ago, when plans were initiated for the first volume in this series. One reason for this state of affairs is the tremendous progress that has been made in fundamental immunology, in which I include both normal immune responses and experimental immunopathology. This progress has had an important influence on investigations that deal with immune responses of humans, as well as the immunopathology of a variety of clinical disorders, as indicated, for example, by the accelerated application of immunological techniques to the diagnosis and management of many clinical disorders.

Two-way traffic between so-called "basic" and clinical immunology has always existed; the structure of the immunoglobulin molecule was, after all, derived from analyses of human myeloma proteins,* and virtually all of our concepts about immunopathology were initiated by clinical investigations.† Moreover, the first useful animal model of systemic lupus erythematosus, the NZB mouse, was described by clinicians who took the human counterpart of the disease as *their* model when working out the murine disorder.‡ Thus, clinical immunologists have always had an enviably ready access to immediately relevant information from their "basic" colleagues. Perhaps this close working relationship, and a common technical language, account for the rapid forward movement in clinical immunology.

*Edelman GM: Antibody structure and molecular immunology. Science 180:830, 1973.

†Grabar P: The historical background of immunology, in Fudenberg HH, Stites DP, Caldwell JL, Wells JV (eds): Basic and Clinical Immunology. Los Altos, California, Lange Medical Publications, 1978, p 11–22.

‡Howie JB, Helyer BJ: Autoimmune disease in mice. Ann NY Acad Sci 124:167, 1965.

These ideas come to mind when considering the articles in the present volume. For instance, the sophisticated capabilities presently available for *in vitro* evaluation of the immune responses of human lymphocytes were developed largely from precedents in animal systems. Haynes, Katz and Fauci consider this topic in detail, and those who plan to embark on work of this type would do well to consult their extensively documented analysis. Another example of the close ties between experimental and clinical immunology may be found in David Katz's examination of the prospects for the clinical control of IgE synthesis. Katz points out that the "encouraging concordance between mouse and man in terms of what has been previously learned about immunoregulation" renders likely that "a similar concordance will ultimately be true in the case of regulation of IgE antibody synthesis." The importance of Katz's review is that it emphasizes the possibility of the control of allergic diseases by manipulation of *central* immune mechanisms, rather than by inhibition of peripheral manifestations (a conventional approach that all agree is less than satisfactory).

The detection and measurement of circulating immune complexes is another important clinical problem. There are currently at least 25 methods that can detect these complexes, and most of us who do not work directly with them are bewildered, not only by their numbers, but also by their clinical application. Theofilopoulos has comprehensively reviewed this difficult topic and concludes that at present the maximum amount of useful information can be obtained by the simultaneous application of three different techniques: the measurement of Clq, a rheumatoid-factor-based radioimmuno-assay, and the Raji cell assay. The problem of devising acceptable reference standards is particularly difficult, but progress has been made and the outlook for reliable assays that can be applied to the diagnosis and management of a very broad group of diseases is promising.

Another important serological problem concerns lymphocytotoxic antibodies (reviewed by DeHoratius). These antibodies have been associated with viral infections, autoimmune diseases, various malignancies, and even with heroin addiction and schizophrenia. Their pathogenetic significance is obscure. It seems especially important that lymphocytotoxic antibodies constitute a heterogeneous *family* of antibodies which share the ability to cause complement-dependent lysis of human lymphocytes. Some of these antibodies have specificities that recognize subsets of functionally different lymphocytes; others, by contrast, bind to B cells. These antibodies will be a fruitful and interesting topic of clinical research, especially if their *in vivo* immunoregulatory properties can be established.

Systemic lupus erythematosus has been dealt with in two previous volumes of *Progress in Clinical Immunology*.* It is an important and fascinating disorder that presents an apparently endless puzzle to clinicians and investigators. The disease occurs not only spontaneously but it can be induced by numerous drugs; it is this latter phenomenon that Weinstein reviews here. Whether drug-induced lupus *is* lupus can be argued. The hallmark of spontaneous lupus is the presence of antibodies to native DNA; as Weinstein points out, these antibodies are virtually never found in drug-induced lupus. If systemic lupus is a genetic disease—and current evidence supports this

* Andres GA, Spiele H, McCluskie RT: Virus-like structures in systemic lupus erythematosus, in Vol 1 (New York, Grune & Stratton, 1972, p 23); Talal N: Autoimmunity and lymphoid malignancy in New Zealand Black mice, in Vol 2 (New York, Grune & Stratton, 1974, p 101).

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view†—can drug-induced lupus also have a genetic basis? If so, does this mean that up to 10 percent of all of us have "lupogenes" that can be activated by certain chemical compounds? Alternatively, is the mechanism of the disease a conventional cross-reaction of anti-drug antibodies with components of nucleic acids? It seems to me that future research on drug-induced lupus should focus on possible genetic factors.

Finally, the delineation of a group of disorders characterized by autoantibodies to cell surface receptors has been one of the most important advances in immunopathology. These extraordinary antibodies may cause disease either by stimulating the receptor ligand, as in the case of thyrotoxicosis and long-acting thyroid stimulator, or by blocking the receptor, as in the case of myasthenia gravis and the acetylchlone receptor. Harrison and Kahn review a third example, autoantibodies to the receptor for insulin. Of particular interest here is that although these antibodies block insulin binding, they may also mimic the effect of insulin by activation of the receptor. This remarkable finding raises fundamental questions about the action of insulin, which may itself act like an antibody in that its effects entail cross-linking of the insulin receptors. Another interesting aspect raised by Harrison and Kahn is that anti-idiotypic antibodies against anti-insulin antibodies can bind to cell surface receptors for insulin and, when conditions are right, mimic the physiological effect of insulin itself. Although spontaneous autoantibodies to insulin receptors are rare, their study raises issues that are fundamental to both immunology and endocrinology.

Thus, the reviews in the present volume of *Progress in Clinical Immunology* cut across many disciplines, ranging from drug reactions to endocrinology. Some of them deal with questions of immediate clinical applicability, whereas others provide a basis from which future advances can be made and understood.

Robert S. Schwartz, M.D.

†Miller KB, Schwartz RS: Familial abnormalities of suppressor-cell function in systemic lupus erythematosus. New Engl J Med 301:803, 1979.

Contributors

Raphael J. DeHoratius, M.D.
Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

Anthony S. Fauci, M.D.
Clinical Physiology Section, Laboratory of Clinical Investigation, National Institutes of Health, Bethesda, Maryland

Len C. Harrison, M.D.
Diabetes Branch, National Institutes of Health, Bethesda, Maryland

Barton F. Haynes, M.D.
Clinical Physiology Section, Laboratory of Clinical Investigation, National Institutes of Health, Bethesda, Maryland

C. Ronald Kahn, M.D.
Diabetes Branch, National Institutes of Health, Bethesda, Maryland

David H. Katz, M.D.
Chairman, Department of Cellular and Developmental Immunology, Scripps Clinic and Research Foundation, La Jolla, California

Paul Katz, M.D.
Clinical Physiology Section, Laboratory of Clinical Investigation, National Institutes of Health, Bethesda, Maryland

A. N. Theofilopoulos, M.D.
Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California

Arthur Weinstein, M.D.
Division of Rheumatic Diseases, Department of Medicine, University of Connecticut School of Medicine, Farmington, Connecticut

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Arthur Weinstein

1
Drug-induced Systemic Lupus Erythematosus

The first description of a clinical syndrome compatible with systemic lupus erythematosus (SLE) coincident with drug administration appeared in the literature over 30 years ago.[1] Early reports detailed florid cases of multisystem disease associated with sulfonamide and penicillin administration.[2-5] Subsequently, our concept of drug-induced lupus expanded to include a broad spectrum of clinical features ranging from serological changes or mild arthralgia to more severe multisystem disease. Furthermore, numerous drugs which have different chemical structures and widely different metabolic fates were implicated in inducing lupus syndromes.[6] During this conceptual evolution, at least four questions about the role of these drugs in the induction of SLE syndromes have been raised:

1. Do these syndromes represent serum sickness-like reactions which mimic clinical SLE and are "nonspecifically" associated with autoantibody formation?
2. Do these syndromes represent drug-induced acute hypersensitivity reactions which lead to activation or exacerbation of spontaneous SLE?
3. If some of the drugs do cause SLE de novo, are the individuals who develop the syndrome predisposed to do so by recognizable genetic factors—i.e., is there a lupus diathesis?
4. Do some of these drugs induce a lupus syndrome de novo in individuals not otherwise predisposed to develop it? If so, is it related to the peculiar pharmacological properties of the drugs and their metabolic fates?

There is evidence that affirmative answers to each of the previous questions may be valid under certain circumstances and with specific drugs. Most importantly, there is strong evidence that some drugs do cause a lupus syndrome de novo which is based upon the dose and duration of drug thereapy, the metabolic handling of the drug by the individual, and the peculiar pharmacological properties of the drug. In addition, it is possible that there exists in some individuals a genetic predispostion to the development of drug-induced SLE.

HISTORY

In 1945 Hoffman described a patient with a sensitivity reaction to sulfadiazine that resembled clinical SLE.[2] This case report was followed by reports of patients with lupus-like symptoms in association with sulfonamide or penicillin therapy.[2-4] Close scrutiny of these cases reveals that many of the patients had clinical signs of SLE prior to drug administration and these became more severe after drugs were given[1, 2] Furthermore, a number of the patients had severe hypersensitivity reactions to penicillin which did not resemble SLE but were associated with a positive LE cell preparation.[3, 4]

Convincing evidence for a true drug-induced lupus syndrome appeared in the literature in 1953 after the introduction of hydralazine for the treatment of hypertension.[7] Subsequently, a small number of drugs including procainamide,[8] isoniazid,[9] some anticonvulsants,[10] and chlorpromazine[11] were shown to induce a similar syndrome.

A number of reviews and editorials on drug-induced lupus have been published. [6, 12-18]

DRUGS INVOLVED

Prospective studies of the effects of a particular drug on large numbers of patients should yield the most definitive information regarding the capacity of the drug to induce antinuclear antibodies (ANA) or a lupus syndrome. Unfortunately, such studies have rarely been undertaken. Thus evidence for most of the drugs suspected to induce SLE is based on sporadic case reports.

The drugs which have the most pronounced capacity to induce ANA or an SLE syndrome and for which there are convincing prospective studies are hydralazine[7, 19-22] and procainamide,[23-26] and to a lesser extent isoniazid (INH)[27-29] (Table 1-1).

Although anticonvulsants[30, 31] and phenothiazines[11, 32, 33] are implicated in inducing lupus syndromes, no prospective studies of these agents have been performed. In addition, evaluation of published reports on these drugs is complicated by the fact that seizures and psychoses are manifestations of spontaneous SLE and may precede other manifestations of the disease by many years.[34] Penicillamine may well have a propensity for lupus induction, but adequate studies are lacking.[35] The same is true for quini-

Table 1-1
Lupus-inducing Drugs

Definite*	Possible	Unlikely
Hydralazine	Anticonvulsants	Griseofulvin
Procainamide	Chlorpromazine	Phenylbutazone
Isoniazid	Methyldopa	Oral contraceptives
	Penicillamine	Gold salts
	Quinidine	Sulfonamides
	Propylthiouracil	Penicillin
	Practolol	
	Lithium carbonate	
	Nitrofurantoin	

*Controlled prospective studies on large numbers of patients have demonstrated the development of antinuclear antibodies with or without symptoms of SLE in a high percentage of cases.

dine,[36] propylthiouracil,[37] practolol,[38] methylodopa,[39] L-dopa,[40] nitrofurantoin,[41] and lithium carbonate.[42] The evidence for griseofulvin,[43] phenylbutazone,[44] and oral contraceptives[45] is even less conclusive. As previously noted, sulfonamides and penicillin are more likely to cause an exacerbation of preexisting spontanous SLE. The same may be true for gold salts[46] and oral contraceptives.[47]

CLINICAL FEATURES

Many of the patients with drug-induced lupus fulfill the preliminary ARA criteria for the classification of SLE,[48] but not uncommonly the clinical features are milder than in spontaneous SLE and more restricted with regard to systems involved (Table 1-2). Unlike spontaneous SLE, the incidence of drug-induced lupus is not increased in blacks, and there is less female preponderance.[49] The age of occurrence reflects the age of the population at risk to the diseases for which the drugs are used; that is, anticonvulsant-induced lupus has been described most often in childhood, INH- and hydralazine-induced lupus in middle age, and procainamide-induced lupus in middle age and older patients.

Fever and constitutional symptoms are common. With hydralazine, those patients who manifest earlier febrile, serum-sickness-like reactions are at a greater risk for developing drug-induced SLE.

Arthralgias, myalgias, and true polyarthritis are the commonest manifestations and do not differ from those of the spontaneous disease. There is a report of joint fluid examination in a small number of patients.[53] Some patients develop no symptoms except arthritis, but even at this stage the ANA is almost always positive.[51, 52] Malar rashes, oral ulcers, and alopecia are far less common in the drug-induced form than in spontaneous SLE.[51, 52] Discoid lesions have been described in only one case and without histological confirmation.[43]

Pulmonary involvement is very common in procainamide lupus, with both pleuropericarditis and pulmonary infiltrates reported.[51, 54–56] Pericardial effusions and tamponade have been seen with hydralazine,[57] procainamide,[58, 59] and INH[60] and may be the presenting manifestation.

Table 1-2
Clinical Features (percentage positive)

	Spontaneous*	Hydralazine (Ref. 21)	Procainamide (Ref. 51)
Constitutional symptoms	> 80	40	50
Arthralgia arthritis	> 95	74	95
Malar erythema	69	2	5?
Pleuropericarditis	47	10	52
Raynaud's phenomenon	21	0	5
Mouth ulcers	42	0?	0?
Alopecia	72	0?	0?
Discoid lesions	23	0	0
Renal disease	38	20	0
CNS disease	16	0	2

*Culled from 156 SLE patients followed in our clinics.[50]

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Clinical renal involvement is unusual and is more common with hydralazine[21] than with procainamide.[51] In the few reported instances where renal histology was obtained, a mesangial or focal glomerulonephritis was found.[61–65]

Skin rashes of various types occur, most commonly maculopapular eruptions.[21, 51] Less common manifestations include hepatosplenomegaly and lymphadenopathy[21, 25, 51] and acute pancreatitis.[66] Raynaud's phenomenon and central nervous system involvement rarely, if ever, occur.[21, 51] Polyneuropathy has been described in a single case of procainamide-induced SLE.[67]

The onset of symptoms usually occurs many months after the institution of drug therapy,[51, 52] although occasionally symptoms begin much earlier.[68, 69] Often there are prodromal symptoms of arthralgia and arthritis prior to the development of the full-blown multisystem syndrome.[52]

By definition, symptoms would be expected to subside soon after drug withdrawal,[17] and that is the usual course with improvement occurring within days to weeks.[7, 51, 52] Occasionally, symptoms may persist for months to years after stopping the offending medication.[21, 68, 70] Death has been attributed rarely to drug-induced SLE,[61, 62, 71, 72] but the evidence for this is inconclusive. The persistence of symptoms in a few patients suggests that hydralazine and procainamide might at times act as provocative agents in patients with spontaneous SLE, much like sulfonamides.[2, 5, 73]

As opposed to symptoms, serological abnormalities, especially antinuclear antibodies, may persist for months to years after drug therapy is discontinued.[22, 51, 74]

LABORATORY FEATURES

As with spontaneous SLE, there is no laboratory abnormality absolutely diagnostic of the drug-induced illness.[34] The diagnosis can be established with certainty by demonstrating the disappearance of clinical and laboratory signs after drug withdrawal and their reappearance with reinstitution of drug therapy. In practice, however, there are certain laboratory features which drug-induced SLE shares with spontaneous SLE and other features which help to distinguish one from the other.

General (Table 1-3)

An elevated erythrocyte sedimentation rate (ESR) and anemia are not uncommon in the drug-induced disease. Leukopenia and thrombocytopenia occur, although less commonly than in spontaneous SLE.[21, 51, 52, 68] Similarly, hypergammaglobulinemia may be a feature of spontaneous and drug-induced SLE.[52, 68]

Table 1-3
Laboratory Features—General

	Spontaneous SLE	Drug-induced SLE
Elevated ESR	+++	++
Anemia	+++	++
Leukopenia	++	+
Thrombocytopenia	++	+
Hypergammaglobulinemia	++	++

Key: +++, > 50 percent; ++, 10–50 percent; +, < 10 percent.

Serological (Table 1-4)

Coombs' test positivity has been seen in patients with procainamide lupus with complement usually present without IgG on the red cell membranes.[51] The concurrence of Coombs' positivity and antinuclear antibodies can be seen in patients taking methylodopa.[39, 75, 76] Two cases of Coombs' positivity with hydralazine-lupus have been reported.[77, 78] Biological false-positive STS (serologic test for syphilis) may be seen with hydralazine.[21] That antibody has been described in only one patient with procainamide lupus.[78] Rheumatoid factors are common with procainamide[51] but not with hydralazine therapy. Circulating anticoagulants may be seen very rarely,[21, 77, 79, 80] although a recent study suggests that they are commonly present with long-term chlorpromazine treatment.[80a] Recently, a procainamide-lupus patient with a polyclonal cryoglobulin was described.[81] Antilymphocyte antibodies have been found in patients with procainamide-lupus[82] and in epileptic patients taking anticonvulants.[83]

Hypocomplementemia occurs commonly in spontaneous SLE[84] but rarely in hydralazine- or procainamide-lupus.[53, 72, 78, 85] Thus the presence of a low serum complement helps to distinguish spontaneous from drug-induced SLE. Circulating immune complexes, usually present in active SLE,[86] have been described recently in procainamide-lupus.[87] While anti-drug antibodies have been found in patients with the hydralazine syndrome,[77, 88] their significance is unclear.

Antinuclear Antibodies (ANA) (Table 1-5)

Virtually all patients who develop drug-induced SLE have ANA, and the majority have positive LE cell preparations.[51, 52] Furthermore, ANA may be induced in many patients who never develop clinical symptoms or signs.[24, 26, 29]

The antigenic specificity of the antinuclear antibodies varies with the inducing agent.[89] Alarcon-Segovia et al. found that the ANA in INH-treated patients was directed predominately against soluble nucleoprotein,[28] whereas in chlorpromazine-treated patients it was directed against heat-denatured single-stranded DNA.[90] The antibodies were measured by a complement fixation technique. Quismorio et al. also found antibodies to single-stranded DNA by an immunofluorescence spot test in some patients taking chlorpromazine.[33] The antinuclear antibody specificities in patients taking anticonvulsants and procainamide are less restricted and antibodies directed against many nuclear antigens have been found by a variety of techniques.[91–95] Anti-

Table 1-4
Laboratory Features—Serological

	Spontaneous	Hydralazine (Ref. 21)	Procainamide (Ref. 51)	Other
Coombs' test	++	+	++	Methyldopa
False-positive STS	++	++	+	
Rheumatoid factor	++	−	++	
Anticoagulants	+	+	+	Chlorpromazine
Antilymphocyte antibodies	+++	ND	+	Anticonvulsants
Hypocomplementemia	+++	+	+	
Immune complexes	+++	ND	+	

Key: +++, > 50 %; ++, 10–50 percent; +, < 10 percent; −, absent; ND, not described.

Table 1-5
Antinuclear Antibodies (percentage positive)

	Spontaneous SLE	Drug-induced SLE
ANA	>95	>95
LE cells	92	90
Anti RNP	40	20
Anti Sm	20	0
Anti histone	25	90
Anti N-DNA (FARR)	80	0

bodies to ribonucleoprotein (RNP) may precede the appearance of other antinuclear antibodies in procainamide-lupus.[96]

Although antibodies to the Sm antigen and antibodies to native DNA have occasionally been described in drug-induced lupus,[77, 91, 92] these antibodies have not been found in more recent studies[97, 98] which employed more detailed and accurate techniques to detect them. Thus the presence of antibodies to Sm and native DNA is highly specific for spontaneous SLE[99] and is useful in distinguishing spontaneous from drug-induced lupus.

Recently Fritzler and Tan demonstrated that the antinuclear antibodies in patients with drug-induced lupus (mainly procainamide) were directed predominately against histones.[100] The antinuclear antibodies of drug-induced lupus have the ability to fix complement[51, 101] and show a polyclonal immunoglobulin and IgG subclass distribution,[93, 102] a feature of the ANA of spontaneous SLE.

Other

Lymphocyte function has not been extensively studied; however, in one study of lymphocyte responses to mitogens there was no correlation between abnormal lymphocyte function and the development of antinuclear antibody, although abnormalities were found in patients with very active clinical disease.[103] In another experiment, lymphocyte transformation to heat-denatured DNA, but not to native DNA, was demonstrated in hydralazine-lupus.[77]

Analyses of synovial, pericardial, and pleural fluids have been described sporadically. Synovial fluids have been mildly inflammatory with leukocyte counts less than 2000 and with predominately mononuclear cells.[53, 78] Relatively decreased synovial fluid complement (C3) has been demonstrated.[53] These findings are similar to synovial effusions found in idiopathic SLE.[104] LE cells have been demonstrated in both the pericardial fluids[59, 68] and pleural fluids[78, 105, 106] of patients with drug-induced lupus. Pleural fluid hypocomplementemia (CH_{50}) has been described in one instance.[78]

The deposition of immunoglobulins and complement components in the basement membrane of the dermal–epidermal junction of normal skin (lupus band test) is a common feature of idiopathic active SLE.[107] Patients with lupus induced by hydralazine or procainamide may also have a positive lupus band test.[53, 108, 109] The true incidence of a positive lupus band test in drug-induced lupus is unknown, but studies suggest that it is uncommon[108] and that it might become negative with clinical remission[109] as is found in idiopathic SLE.[110]

Pathological studies and biopsy data are sparse, since in most instances the illness is reversible on discontinuation of the drug. Occasionally pathological findings consistent with a focal lupus glomerulonephritis have been found.[21, 61-65] However, other studies have failed to reveal any significant pathology.[68] Glomerular immune complex desposition has been demonstrated rarely.[64, 72] Pleural biopsy specimens have revealed nuclear-associated antibody in the pleural tissue.[111]

ACETYLATOR PHENOTYPE

A genetically controlled polymorphism of the hepatic acetyltransferase enzymes is responsible for different rates of inactivation of drugs such as hydralazine, procainamide, isoniazid, sulfamethazine, and dapsone.[112] The population of the U.S. is evenly divided between slow and rapid acetylators[113]; slow acetylators are homozygous for an autosomal recessive gene, and rapid acetylators are either homozygous or heterozygous for the dominant gene.[112]

Slow acetylators are more prone to develop ANA with hydralazine ingestion. In one study, ANA developed in 60 percent of the slow acetylators who had taken less than 400g hydralazine, whereas none of the rapid acetylators who had taken a similar total dose had detectable ANA.[114] Furthermore, almost all patients who develop clinical symptoms of hydralazine-induced lupus are slow acetylators.[52, 114]

Procainamide-induced lupus is seen in both slow and rapid acetylators. In one study of 12 patients taking procainamide for longer than 3 months, 5 of the 7 patients with ANA were rapid acetylators, whereas 4 of the 5 without ANA were slow acetylators.[115] In contrast, a larger study of 42 patients followed for 5 years showed that of 11 patients with procainamide-lupus 8 were slow acetylators, whereas 10 of 12 patients who did not develop a lupus syndrome were rapid acetylators.[116] Woosley et al., in a prospective study, demonstrated that ANA developed in both slow and rapid acetylators taking procainamide.[117] However, slow acetylators developed ANA more quickly than rapid acetylators, with 64 percent having a positive ANA within 3 months. None of the rapid acetylators had detectable ANA by that time. Consequently, the total procainamide dose ingested at the time of appearance of ANA was much lower for the slow than the rapid acetylators. A retrospective analysis revealed that the clinical procainamide-lupus syndrome also developed after much shorter duration of therapy in the slow acetylators. Thus with both hydralazine and procainamide, the development of ANA and clinical disease occurs more often, more rapidly, and after less drug ingestion in individuals who are slow acetylators than in those who acetylate rapidly. There appear to be no definite effects of acetylator phenotype status on the development of ANA in patients treated with isoniazid.[118, 119]

The acetylator phenotype status of patients with spontaneous SLE is a matter of controversy. Most early studies indicated a predominance of slow acetylators[120-124]; however, Vansant et al. studied 18 patients with spontaneous SLE and found that 44 percent were slow acetylators, a number not statistically different from that in the general population.[125] In that study, there was a higher incidence of hypocomplementemia in the patients with a slow acetylator phenotype. A recent study of 27 patients with spontaneous SLE confirmed that slow acetylators were not at greater risk of the development of SLE.[125a]

CLINICAL STUDIES

Hydralazine

Hydralazine was introduced as an antihypertensive agent in 1952.[126] Subsequently, side effects which appeared after many months of therapy were reported.[7, 19, 127–133] The syndrome of fever, arthritis, skin rashes, pleurisy, leukopenia, and hypergammaglobulinemia resembled SLE clinically, and in some patients LE cells were present. Furthermore, it was recognized that patients taking hydralazine had positive LE cells tests in the absence of clinical symptoms.[134]

The incidence of hydralazine-induced lupus in an unselected hypertensive population has been estimated to be approximately 10 percent.[20, 134] Antinuclear antibodies occur in practically all patients with clinical toxicity.[22, 52] However, a recent prospective study suggests that the clinical illness and the development of ANA may be less common than previously reported.[135]

Factors which particularly influence the development of hydralazine-lupus are the dose of drug—reactions are more common when the daily dose is greater than 400 mg and the total dose ingested is greater than 100 g[52, 70]—and the acetylator phenotype, since slow acetylators are much more susceptible to the development of ANA and clinical manifestations.[52, 114] Another common feature in those patients who eventually develop hydralazine-lupus is initial severe hypertension with good response to hydralazine at the time of the lupus symptoms.[52]

The patients described by Alarcon-Segovia et al. are somewhat unique.[21] Many had a past history or family history suggestive of a connective tissue disorder, and in some patients the symptoms persisted long after the drug was stopped. This observation led the authors to postulate that a latent genetic predispostion to SLE exists as a lupus diathesis and that environmental stimuli such as hydralazine ingestion by these predisposed individuals can evoke clinical symptoms.[136] However, other studies have reported complete reversibility of the syndrome after drug withdrawal.[7, 52] Furthermore, hydralazine, in low doses, has been used in hypertensive patients with known spontaneous systemic lupus erythematosus with no untoward effects.[137]

Procainamide

Numerous early case reports[8, 138–142] of procainamide-induced lupus were followed by studies on larger groups of patients.[23–26, 52, 68, 143, 144] These studies have established that procainamide is the most potent lupus-inducing drug currently in use.[1] Antinuclear antibodies develop in 50–100 percent of the patients taking procainamide for longer than 1 year[24, 26, 116, 143, 144] Antinuclear antibodies may be found as early as 2–3 months after the start of therapy and are usually present within 6 months in those patients who develop them.[26] The incidence of clinical symptoms in patients on long-term procainamide therapy varies from 5 percent to more than 30 percent.[25, 115, 143, 144] Symptoms usually develop after more than 3 months of treatment and often after 1 year of continuous procainamide therapy.[116, 144] Virtually all symptomatic patients have positive ANA tests, and almost all have positive LE cell preparations. The incidence and rapidity of development of positive ANA and clinical symptoms is dependent upon the daily ingested dose and the acetylation rate. Patients who take more than 1.25 g daily[143] and those who are slow acetylators[117] are particularly susceptible to the development of the clinical drug-induced disease.

The clinical features of procainamide-induced lupus that warrant emphasis are the frequent occurrence of pleuropericarditis with or without effusions, and pulmonary infiltrates.[51, 54–56, 58, 59]

The high incidence of ANA and clinical symptoms in patients taking long-term procainamide and the reversibility of the symptoms do not support the hypothesis that there is a latent genetic predisposition to develop procainamide-induced SLE. However, there has been a report of procainamide-induced lupus in siblings.[145] A few reports have suggested that family members of patients with procainamide-induced lupus may have musculoskeletal complaints or serological abnormalities.[146, 147] Other studies have not confirmed this observation,[68] and no studies of large numbers of families have been performed.

Isoniazid (INH)

Sporadic case reports of isoniazid-induced clinical symptoms and serology suggestive of SLE have appeared over the years.[9, 60, 148–151] Three studies of large numbers of patients have demonstrated that antinuclear antibodies occur in 20 percent of patients on long-term isoniazid therapy.[27–29] However, others suggest that the incidence of antinuclear antibody induction might be much lower.[152] The only prospective study showed that ANA in low titers developed within 1 month of therapy in some patients and titers rose with continuing treatment, with 20 percent of patients developing a positive ANA after 1 year.[29] LE cells were not found, and no patient in this study developed the clinical symptoms of drug-induced lupus.

Acetylation phenotype appears to play no role in the development of ANA or symptoms of SLE in patients taking INH.[118, 119]

Anticonvulsants

Many cases of lupus erythematosus following prolonged use of anticonvulsants have been reported. The most frequently implicated drugs are the hydantoins (diphenylhydantoin[64, 153, 154] and mephenytoin[10, 155]), trimethadione,[156] and ethosuximide.[157–160] No case of drug-induced SLE has been reported in a patient receiving phenobarbital alone; however, a single case of SLE in a patient taking primidone, a phenobarbital congener, has been described.[161] Also, a case of pheneturide-induced lupus has been reported.[162]

Studies on large groups of patients, especially children, have revealed suggestive but not conclusive data.[30, 31, 91, 163] An increased incidence of ANA was found in epileptics on chronic anticonvulsant therapy compared to normal controls. However, there appeared to be no differences in incidence of ANA between those epileptics taking anticonvulsants and those taking either no anticonvulsant drugs or phenobarbital alone.[31, 163] A recent study did not reveal a significantly increased incidence of antinuclear antibodies in diphenylhydantoin-treated epileptics compared to healthy controls.[164] The treated patients did have differences in immunoglobulin concentrations and an increased frequency of other autoantibodies compared to the control group. A prospective study of a large group of epileptic children starting on anticonvulsant therapy should help to resolve the issue of whether or not anticonvulsants induce ANA formation. This study has not been performed.

Another problem in interpreting the reports of anticonvulsant-induced SLE is that seizures may be the first manifestation of spontaneous SLE.[34] Thus the anticon-

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