# MCV/Q

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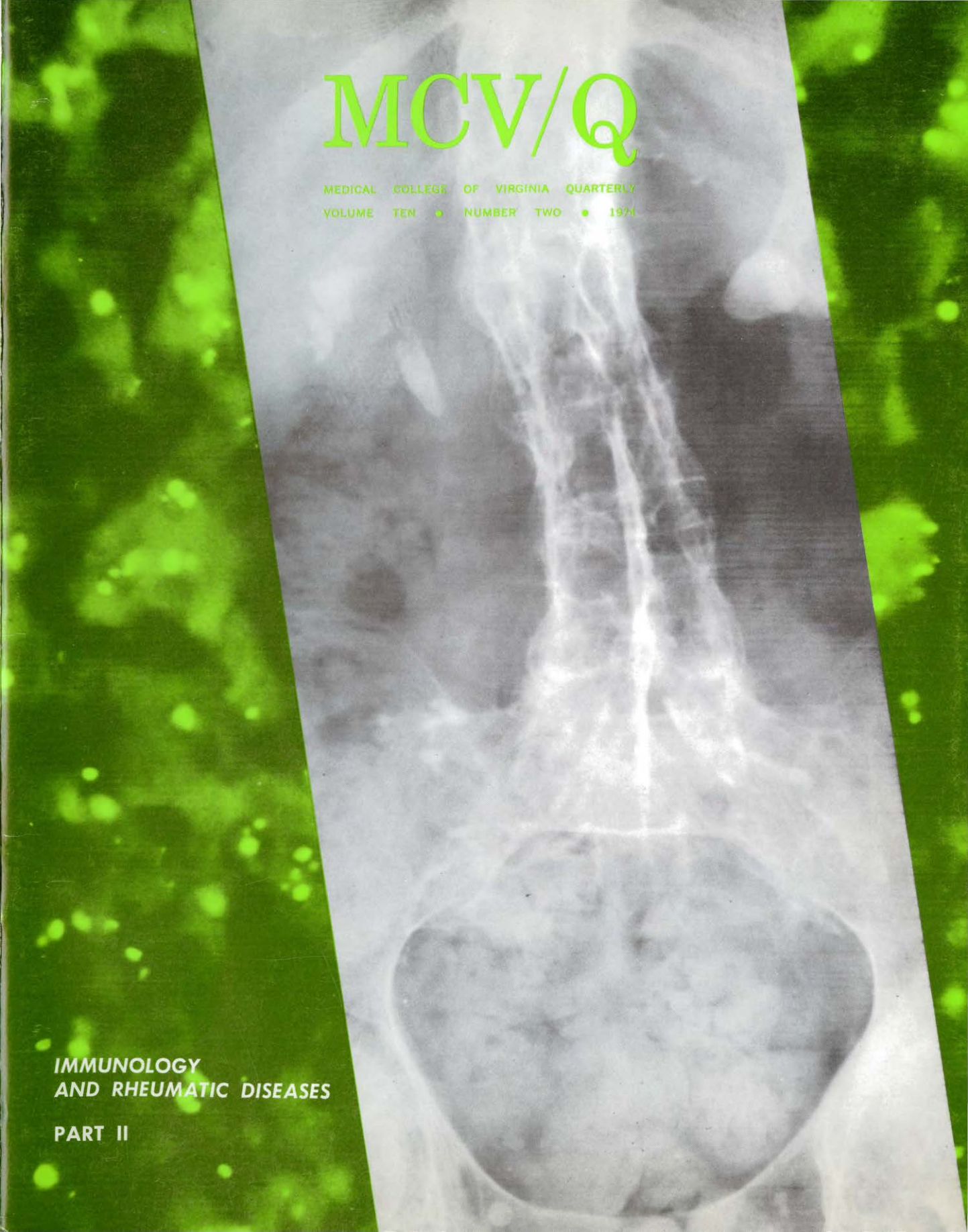


## *IMMUNOLOGY AND RHEUMATIC DISEASES*

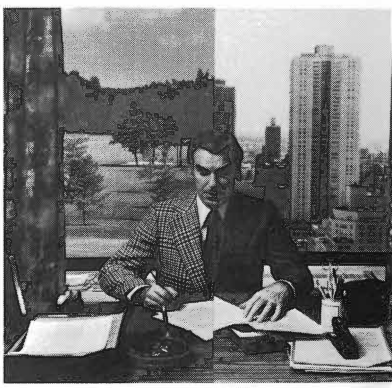
**PART II**

# The management of anxiety:

# Counseling and pharmacotherapy

**Changing the patient's perspective**

In the management of anxiety, the negative feelings the patient has about himself and his behavior may often be altered in a positive manner by discussion, counseling and reassurance. Changing the patient's perspective is often the first significant step toward helping him to learn more appropriate, less anxious ways of living. The physician recognizes that the patient has certain positive qualities and he utilizes this "healthy core" to effect constructive change in outlook and life-style. When excessive anxiety is reduced through such a psychotherapeutic approach, there is no need for adjunctive psychotropic medication.

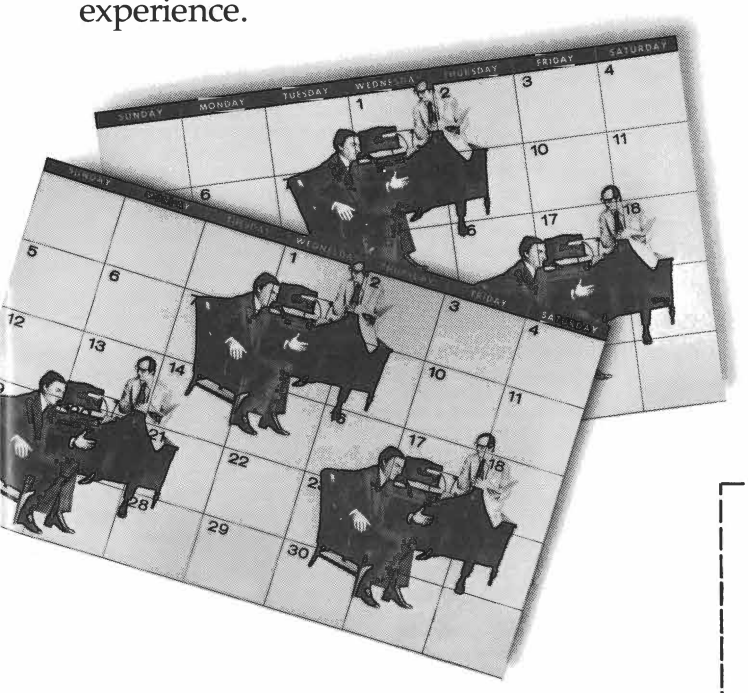


**The patient and his milieu**

The physician may also take steps to identify and mobilize constructive factors in the patient's over-all environment—a motherly neighbor, a dependable friend, a community club—that could furnish favorable experiences and thereby help reduce his anxiety. A change in environment to remove undesirable influences or modifications in the patient's work, personal associations and recreational activities may be indicated.

### Short-term psychotherapy

A great deal may be accomplished for the anxious patient in regular therapeutic sessions lasting as little as 10 to 15 minutes. These may be scheduled for one to four times monthly over a specified period, depending on the level of the patient's anxiety and the problems involved. Many interested physicians have gained increasing skill in this area through postgraduate training and experience.




### The adjunctive role of pharmacotherapy

When counseling and other nonpharmacologic measures do not prove sufficiently effective, pharmacotherapy can provide a valuable adjunct to other measures. An effective antianxiety agent can help foster the necessary rapport and communication between physician and patient. The drug chosen should have a wide margin of safety and be relatively free of undesirable side effects. It should be compatible with other agents required in the patient's total medical regimen. When the patient's anxiety has been reduced to manageable levels, pharmacotherapy should be terminated.

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**Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

**Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido —all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

**Usual Daily Dosage:** Individualize for maximum beneficial effects. *Oral—Adults*: Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients*: 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)

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Regretfully, but with an eye to survival, we must ask all others who wish to continue to receive the *MCV/Q* to subscribe at the prices quoted on the contents page. We hope that you regard this publication as well worth the modest cost. To assure that you do not miss succeeding issues, please take a minute to complete the order form provided herein and mail it as soon as possible.

# MCV/Q

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*A Scientific Publication of the School of Medicine*
*Health Sciences Division of Virginia Commonwealth University*

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CONTENTS

*Immunology and the Rheumatic Diseases*

Sponsored by the School of Medicine, Department of Continuing Education, and the Division of Connective Tissue Diseases, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University and by the Virginia Chapter of the Arthritis Foundation

ROBERT IRBY, M.D., *Guest Editor*




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# Introduction

This issue of the *MCV/Q* is a continuation of the first issue of this year, which was devoted to the subject of Immunology and the Rheumatic Diseases. Many of the papers presented at the 45th Annual McGuire Lecture Series were published in the first issue and this will complete those papers which were submitted for publication. In addition to subjects in the fields of juvenile rheumatoid arthritis, ankylosing spondylitis, and infectious arthritis, papers covering immune complex reactions in SLE as well as delayed hypersensitivity are included. Because of recent advances in the study of histocompatibility antigens (W-27) in patients with connective tissue diseases, this subject is also discussed in this issue.

**ROBERT IRBY, M.D.**
*Professor of Medicine*
*Department of Medicine*
*Medical College of Virginia*
*Virginia Commonwealth University*

# Viruses and the Connective Tissue Diseases*

MORRIS ZIFF, M.D., Ph.D.

*Rheumatic Diseases Unit, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas*

A number of observations in the last few years have attracted attention to the possibility of viral infection in systemic lupus erythematosus (SLE). One of these is the occurrence of interwoven tubular structures, usually in the endothelial cells of the kidney but also in the lymphocytes and in fibroblasts when SLE skin fibroblasts are cultured. These tubular structures have resembled viruses (they were thought by their discoverers to be myxo- or paramyxoviruses), but it has been argued (1) that they are not viruses because of their size and appearance and because they have been produced in tissue cultures from subjects who do not have SLE; they occur in many other conditions which are not related to SLE. These tubular structures do not occur, however, in rheumatoid arthritis (RA). The conclusion, at this point, would seem to be that they are not viruses. Nevertheless, from their randomness and their odd appearance, it seems likely that we may be seeing the effects of a virus, perhaps a very common virus, on the endoplasmic reticulum of the cell.

There has been a group of papers in which the point has been made (2, 3, 4) that the titers of a number of viral antibodies (usually myxo- and paramyxoviruses) are somewhat elevated in patients with SLE. It has been argued that this simply represents the overall hyper-γ-globulinemia of SLE, although we have not noted the relationship with γ-globulin levels. It should be pointed out that there has been no outstanding elevation of any particular viral antibody titer. The antibody titer to measles, an RNA virus, has been consistently elevated to a significant degree. This may mean that antibody to this virus cross-reacts well with an unidentified RNA virus which is actually involved.

* Presented by Dr. Ziff at the 45th Annual McGuire Lecture Series, November 9, 1973, at the Medical College of Virginia, Richmond.

**Cellular Immunity in SLE.** Hahn and coworkers (5) have reviewed the evidence for reduced delayed hypersensitivity in SLE. About half of investigators have noted decreased skin test reactions in this disease. Patients with SLE also tend to develop lymphomas somewhat more commonly than expected. Presumably these patients do not have adequate immunologic surveillance for rejection of lymphomas on the basis of diminished cellular immunity.

Regarding cellular immunity, it is known that thymus-derived lymphocytes undergo blastic transformation and produce lymphokines. When the T cell has been stimulated, it can also subserve the antigen to stimulate B lymphocytes (bone marrow-derived) to produce antibody.

With regard to the possible role of a virus in SLE and the fact that depressed cellular immunity seems to be present, it is fairly well accepted that virus infections, in general, decrease delayed hypersensitivity as measured by skin tests and by the response of the circulating T cells of the infected patient to mitogens like PHA and concanavalin. Also, if one adds a virus like rubella to lymphocyte cultures, the capacity of the T cells in that culture to undergo a response to mitogenic agents is diminished.

As is well known, the New Zealand Black (NZB) mouse, particularly its $F_1$ hybrid, is an excellent model for SLE. The NZB $F_1$ hybrid mouse has also been shown to have decreased cellular immunity (6). It has a decreased capacity to induce graft-versus-host disease in a recipient mouse strain. There is also a decreased responsiveness to mitogenic agents and a high incidence of lymphomas.

For unexplained reasons, T cells in man form rosettes with sheep red blood cells. These rosettes represent a measure of the T cells circulating in the blood. Wybran and Fudenberg (7), using this

method, found that patients with viral infections have reduced numbers of circulating T lymphocytes. In our laboratory, Drs. Hurd and Giuliano have observed decreased numbers of spontaneous rosette-forming cells in patients with SLE suggesting decreased cellular immunity. This could be a result of coating with an immunosuppressive globulin or a true deficiency of T cells.

**Autoantibody Formation.** It should be pointed out that in SLE, we are concerned not as much with T cell function as with the results of B cell activity since these cells produce autoantibodies such as anti-DNA, both double- and single-stranded, antinuclear antibody, anti-RNA, both double- and single-stranded, as well as other types of autoantibodies. Are such autoantibodies found in virus infections? Two conditions stand out—one, infectious mononucleosis, an EB virus infection, and the other, cytomegalovirus infection. In these conditions, we see antinuclear antibody, rheumatoid factor, mixed cryoglobulins, Coombs autoantibodies, and so forth.

The NZB mice are infected with murine leukemia viruses. This strain, unlike other strains, does not develop tolerance to the murine leukemia viruses and eventually develops antibodies to these viruses. These form immune complexes which circulate in the blood and in time the mice develop proteinuria. The immune complexes eventually deposit in the basement membrane of the kidney. If NZB $F_1$ hybrids are injected with nonleukemogenic viruses such as LCM, which is an RNA virus, or with polyoma, which is a DNA virus, antinuclear antibody is enhanced, the glomerulonephritis is aggravated and the mortality rate goes up (8). These viruses, it appears, exert an adjuvant effect in stimulating autoantibody formation. Nucleic acids are known to have adjuvant effects. Weight for weight, the RNA of the tubercle bacillus is as effective an adjuvant as the tubercle bacillus itself (9). Powell and Steinberg (10) have examined the adjuvant effects in the NZB-NZW mouse of poly I–poly C, a synthetic double-stranded RNA, and have found an increase in antibody, not only to double-stranded RNA, but also an increase to DNA. Cone and Johnson (11) have shown that poly A–poly U increased the antibody response against sheep red blood cells. One may speculate from these kinds of results that the viral nucleic acids may also have an adjuvant effect on both antibody and autoantibody formation.

It appears likely that if a virus were to be the cause of SLE, it would be so by affecting T lymphocyte function. In our laboratory (12), we have demonstrated that T cells produce a relatively low molecular weight factor, which has a stimulatory effect on antibody formation by B cells. Fialkow, Gilchrist and Allison (13) have shown that T cell stimulation can lead to autoantibody formation. $F_1$ hybrid mice injected with parental cells undergo a graft-versus-host reaction in which the donor T cells proliferate. These mice develop antinuclear antibody after each injection of T cells, presumably because of the elaboration of a helper factor by the proliferating T cells.

There is also evidence that a suppressor population of T cells exists which presumably inhibits autoantibody formation. The first evidence for suppressor T cells came from our laboratory (14) in a study of the effect of antilymphocyte globulin on the immune response of rabbits. When rats were treated with this agent, the antibody response to keyhole limpet hemocyanin was increased instead of reduced. This result has been interpreted by others (15) to indicate that there is a type of T cell whose function is to suppress the antibody response. Subsequently, Baker and co-workers (16) showed that there was an increased response to pneumococcal polysaccharide in mice upon treatment with antithymocyte serum.

Recently, Steinberg and co-workers (17) showed that neonatal thymectomy of NZB mice accelerated the formation of anti-DNA antibodies and that this change could be reversed by grafting these mice with one-week old thymuses, but not with ten-week old thymuses. Suppressor T cells presumably are lost in the NZB $F_1$ hybrid at an early age. This seems to be the cause of the aggravated form of the disease observed in thymectomized animals.

It is well established that autoantibodies develop in the aged (18). Phytohemagglutinin responsiveness, which is a measure of T cell function, also decreases. These changes may reflect a loss of suppressor T cells with age in man. When Teague and Friou (19) administered syngenic thymocytes from young mice to older mice who were producing antinuclear antibodies, these antibodies disappeared, suggesting that suppressor T cell function had been restored. The explanation for these phenomena, most clearly enunciated by Allison (20), is that we are dealing with a particular type of tolerance in the normal state which does not permit autoantibodies to form.

This tolerance resides in the T cell, as originally suggested by Weigle (21). The B cells which produce antoantibody are not tolerant and when they are stimulated by helper substance from helper T cells or freed from the suppressive action of suppressor T cells, they become free to synthesize autoantibody in the presence of autoantigen. In speculating about the role of a virus in autoimmune phenomena, one might suppose that an infected individual would have T cells sensitized to the causative virus, whatever virus that might be. This virus could then stimulate these sensitized T cells to produce a helper substance. As a result, potentially responsive (nontolerant) B cells would gain the capacity to produce autoantibodies. Thus, viruses might act as adjuvants for autoantibody formation by stimulating sensitized T cells to produce helper substances, which could then stimulate B cells to produce autoantibody in the presence of autoantigen. They could also interfere in some unexplained manner with the suppressor effect of suppressor T cells by producing a broad interference with T cell function since, as mentioned, T cell levels are, in fact, low in the virus diseases (7).

Another interesting line of evidence which should be mentioned comes from the studies of Lewis and co-workers (22) who have injected filtered suspensions of spleens of dogs with SLE to CA $F_1$ mice. These mice have, as a result, developed antinuclear antibodies. This finding suggests the presence of a filterable agent, probably a virus, in the affected donor dogs, having the capacity to produce antinuclear antibodies.

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# The "Three R's" of Delayed Hypersensitivity*

DAVID HORWITZ, M.D.

*Associate Professor, Rheumatology Division, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville*

Delayed hypersensitivity is one of several immune responses initiated by thymus-derived (T) lymphocytes. Other functions of T cells are listed in Table 1 and summarized in reference 1. The mononuclear infiltrate of delayed hypersensitivity is a collaborative phenomenon between T lymphocytes and monocytes. This collaboration can be separated into components which I have chosen to call the "three R's" of delayed hypersensitivity. In this discussion I will define these "three R's" and examine the usefulness of this concept in clinical medicine.

Hematoxylin and eosin sections of skin biopsied 48 hours after intradermal injections of antigen characteristically show mononuclear cells around blood vessels and in connective tissue. As early as 1951, however, Gell and Hinde (2) reported that the monocyte was the principal participant in the skin site. In 1963, McCluskey (3), using radioisotopic techniques, found that 90% of the mononuclear cells in the reaction site were blood-borne and originated from cells that had divided 48 hours previously. Subsequently, cell transfer studies have provided conclusive evidence that the rapidly dividing cells originated in the bone marrow and were precursors of the blood monocyte. The evidence is as follows: 1) Injection of immune lymphocytes into nonimmune, irradiated recipients failed to transfer positive skin reactions (4); 2) Injection of bone marrow cells from nonimmune donors to sensitized, irradiated animals resulted in positive responses (5); 3) Local injection of nonimmune macrophages into the skin of irradiated, sensitized recipients elicited positive responses in these areas (6).

These studies indicated that two populations of cells are required to elicit delayed hypersensitivity. The first are radioresistant, which were later defined as long-lived, T lymphocytes. The second population are cells of the monocyte/macrophage system and are derived from radiosensitive precursors in the bone marrow.

From this information we can develop a concept of delayed hypersensitivity consisting of three components (Table 2). First, sensitized T lymphocytes, perhaps with some help from macrophages, *recognize* intradermally injected antigen. Secondly, antigenic contact triggers a *response* in sensitized lymphocytes. Within a few hours these cells release soluble mediators (7) called lymphokines into the environment and later, activated small lymphocytes transform into blasts and proliferate. Thirdly, through the amplifying effects of lymphokines, such as migration inhibitory factor (MIF) and monocyte chemotactic factor (MCF), other leukocytes, predominantly monocytes, accumulate at the skin test site and comprise the *reaction* of delayed hypersensitivity. This mononuclear infiltrate is similar to that of any other chronic inflammatory reaction. The triggering event, however, is an immunologically specific response of T lymphocytes.

Techniques are available to evaluate each of the "three R's." The number of circulating T cells available for antigen *recognition* can be quantitated by several methods. The most widely used method at this time is a rosette technique. When sheep erythrocytes are incubated with human lymphocytes at 4°C, the erythrocytes form rosettes around T cells (8). Secondly, heterologous anti-T lymphocyte serum has been developed (9) and may be used to quantitate T cells either by immunofluorescence or cytotoxicity.

The second component, *response* to antigen, can be evaluated by measuring the lymphocyte proliferative response to antigen. In these studies lymphocytes are cultured with test antigen for five-

* Presented by Dr. Horwitz at the 45th Annual McGuire Lecture Series, November 8, 1973, at the Medical College of Virginia, Richmond.

TABLE 1

THYMUS-DERIVED LYMPHOCYTE FUNCTIONS

1. Delayed hypersensitivity
2. Activation of macrophages to resist infection
3. Rejection of allografts and tumors
4. Regulation of antibody production by B cells

to-seven days and proliferation is assayed by measuring incorporation of a radiolabeled DNA precursor.

Alternatively, one can measure lymphokine production from antigenically stimulated lymphocytes. Migration inhibitory factor has received the most attention (7). Various techniques to measure MIF have been developed which are based on the inhibition of leukocyte migration by the culture supernatants of stimulated lymphocytes. The method of Rocklin and David (10) correlates well with delayed hypersensitivity. These workers use guinea pig peritoneal macrophages as effector cells. Other workers have substituted human "buffy coat" leukocytes for guinea pig macrophages (11). Results obtained with these cells as the indicator cells, however, did not always correlate with cutaneous skin reactivity to antigen (12).

I prefer to measure MCF rather than MIF, because both *response* and *reaction* can be evaluated. With this technique we can detect mediator production from a given patient's lymphocytes and also evaluate the capacity of that subject's monocytes to respond to his own mediator. With a method to measure leukocyte chemotaxis, we can evaluate both lymphocyte and monocyte function.

To perform this technique a chamber is divided into an upper and lower compartment by Nuclepore® membrane. Monocytes are placed in the upper chamber and the chemotactic stimulants in the lower chamber. The specific migration of cells from the upper to the lower surface of the membrane filter is quantitated (13).

These in vitro methods can be used to define the component that is defective in patients with impaired delayed hypersensitivity. Lymphocytes from children with a congenitally absent thymus gland (the DiGeorge syndrome and Nezelof syndrome) fail to form rosettes with sheep erythrocytes or to proliferate in response to mitogens. These children, then, do not have sufficient T lymphocytes capable of antigenic *recognition.*

Impaired cell-mediated immunity in chronic mucocutaneous candidiasis may be due to several defects, either in a *response* or *reaction.* Patients with this disease usually have adequate numbers of circulating lymphocytes but may have selective defects in lymphocyte or monocyte function. In some subjects, blast transformation is intact but MIF is absent (14). In others, mediator production is intact, but these patients' lymphocytes fail to proliferate in response to antigen (15). Finally, Snyderman (16) reported a patient with chronic mucocutaneous candidiasis whose monocytes responded poorly to a chemotactic stimulus. Although it is tempting to speculate that the defects detected with in vitro

TABLE 2

DELAYED HYPERSENSITIVITY
A COLLABORATIVE PARTICIPATION OF LYMPHOCYTES AND MACROPHAGES
IN AN IMMUNOLOGICALLY SPECIFIC INFLAMMATORY REACTION

| Component | Assay System |
|---|---|
| 1. The *recognition* by small (thymus-derived) lymphocytes of material which is antigenic to the host. | Quantitation of T lymphocytes by:<br>1. Spontaneous rosettes without sheep erythrocytes.<br>2. Immunofluorescence or cytotoxicity using heterologous antihuman thymocyte serum. |
| 2. A *response* of sensitized lymphocytes as detected by the release of soluble factors (lymphokines) and later by cell division. | Generation of lymphokines<br>1. Migration inhibitory factor (MIF)<br>2. Macrophage chemotactic factor (MCF)<br>Blast transformation and proliferation |
| 3. A mononuclear inflammatory *reaction,* consisting predominantly of "activated" macrophages, which leads to the attack, destruction, and sequestration of autologous or foreign materials. | Monocyte response to MCF<br>"Skin-window" assay |

techniques accurately reflect an in vivo disturbance, the data must be interpreted with appropriate caution at this time.

Delayed hypersensitivity may be impaired in conditions without a demonstrable defect in cellular function. Serum factors inhibit lymphocyte function in certain diseases and several examples are listed in Table 3. The role of these serum inhibitors has not been defined. Moreover, primary disorders of lymphocyte function have not been differentiated from secondary effects caused by serum factor in many diseases with impaired cellular immunity. Recent studies from this laboratory suggest that anergy in such diverse diseases as systemic lupus erythematosus (SLE) and primary intracranial tumors (17) is caused by serum inhibitors rather than defective cells. Fractionation of inhibitory serum in patients with each of these diseases revealed an IgG factor that broadly suppresses reactivity of allogeneic as well as autologous lymphocytes. This inhibitory IgG factor has been named lymphocyte regulatory immunoglobulin (LRG) and increased LRG in SLE may, in part, explain decreased delayed hypersensitivity. Patients with SLE and other diseases also have a lymphocytotoxic antibody that may depress cell function.

In summary, I have attempted to develop a working model of delayed hypersensitivity that may be useful in understanding areas puzzling to the nonimmunologist. The reader is urged to ask the following questions in order to evaluate scientific papers dealing with defective cellular immunity in various diseases. First, did the patients studied have adequate numbers of circulating lymphocytes and monocytes? Secondly, did the methods used evaluate a single component of delayed hypersensitivity or were several components analyzed? Finally, did the authors distinguish a primary cellular defect from secondary humoral effects? Separation of delayed hypersensitivity into "three R's" may be helpful in organizing and understanding present information.

TABLE 3

DISEASES WITH SERUM INHIBITORS OF LYMPHOCYTE FUNCTION

1. Hematologic and solid tumors
2. Systemic lupus erythematosus
3. Tuberculosis
4. Multiple sclerosis
5. Hepatitis
6. Lepromatous leprosy
7. Ataxia telangiectasia
8. Multiparous women
9. Multiple transfusions

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# Immune Complex Reactions in Systemic Lupus Erythematosus* **

JOHN STAIGE DAVIS, IV, M.D.

*Professor of Internal Medicine, Chief of the Division of Rheumatology, University of Virginia School of Medicine, Charlottesville*

We should first try to define systemic lupus erythematosus (SLE). Table 1 lists criteria proposed by a committee of the American Rheumatism Association (1). If four of these 14 major criteria are positive, then there should be about 98% specificity for SLE. There are clearly many facets to this disorder. Let us consider mechanisms that might account for a multisystem disease such as this.

A good model is that of experimental serum sickness. Though Germuth (2) provided much of the renewed impetus to study serum sickness in the '50's, it is Dixon (3) who has fully explored the variables of immune complexes and disease.

When a rabbit is given a single intravenous injection of bovine serum albumin (BSA) labelled with $^{131}I$, one notes disappearance of the BSA in serum over a period of about 13 days. First there is a rapid fall, then an equilibrium develops, and then suddenly there is total disappearance of the injected BSA. Coincident with the rapid disappearance of BSA, one can measure antigen-antibody complexes. Finally, free antibody to BSA is detected. During the period when these immune complexes are found, the rabbits develop heart disease, arthritis, nephritis, and other manifestations. It is a self-limited disease, however, and when free antibody is found the disease clears up. Hemolytic complement (C) has been measured also; with the appearance of immune complexes, the C level falls, later returning to normal. This then is the model of experimental serum sickness in the rabbit; what about immune complexes in man?

We are postulating that many manifestations of SLE probably result from deposition of circulating immune complexes. Numerous data are now available which would support this concept. What can we now do to find these complexes and characterize them? If we can show what is in these complexes, we should know something more about pathogenesis.

Table 2 lists some of the methods that are available today. These methods are mostly limited to research laboratories. I have listed these methods as either analytical or preparative. Cryoprecipitation is both analytical and preparative; furthermore, cryoprecipitates are easily measured since all one needs is a refrigerator and a centrifuge. Recent studies by McIntosh et al. (4) suggest that cryoprecipitates correlate well with immune complex formation in rabbits; evidence in man is not as convincing since it is difficult to recover a specific pathogenetic antigen in SLE cryoprecipitates.

C1q precipitation was first described by Agnello et al. (5); here one utilizes purified C1q to precipitate with serum factors in double diffusion systems. Rheumatoid factor (RF) can be used in the same way. Efforts in our lab are now being directed toward an analysis of the characteristics of C1q reactive factors. It is of interest that C1q and RF seem to detect different substances in serum. Passive agglutination of RF-coated cells is another method which detects complexes, as is complement fixation (which is a way of interpreting "anticomplementary serum"). Recent work in England has shown complement fixation and C1q precipitins not only in

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TABLE 1

PRELIMINARY CRITERIA FOR CLASSIFICATION OF SLE

1. Facial Erythema (Butterfly Rash)
2. Discoid Lupus
3. Raynaud's Phenomenon
4. Alopecia
5. Photosensitivity
6. Oral or Nasopharyngeal Ulceration
7. Arthritis without Deformity. [One or more peripheral joints involved with any of the following in the absence of deformity: a) Pain on motion, b) Tenderness, c) Effusion or periarticular soft tissue swelling.]
8. LE Cells
9. Chronic False-Positive STS
10. Profuse Proteinuria
11. Cellular Casts
12. One or both of the following: a) Pleuritis, b) Pericarditis
13. One or both of the following: a) Psychosis, b) Convulsions
14. One or more of the following: a) Hemolytic anemia, b) Leukopenia c) Thrombocytopenia

SLE serum but in sera from patients with dermatitis herpetiformis, ulcerative colitis, regional enteritis, and coeliac disease (6, 7). Lymphocyte inhibition is another technique recently reported: B cells, which kill sensitized tumor cells, are inhibited by serum containing aggregates or immune complexes (8). Platelets can also be agglutinated by complexes.

Cryoprecipitation is, at the same time, a preparative method. Likewise C1q can be linked to Sepharose® columns through cyanogen bromide to facilitate removal of C1q precipitins from serum for analysis (9). Hopefully, the immune complexes and/or aggregates will stick and everything else will wash through; then the bound material can be eluted off with salt and the residue analyzed. Serum can also be run directly through agarose columns with exclusion of large molecular weight materials. In summary, the main point here is that many methods are being developed to find and characterize aggregates and complexes; the simplest method is probably cryoprecipitation.

TABLE 2

DETECTION OF CIRCULATING IMMUNE COMPLEXES AND/OR AGGREGATES

| Analytical | Preparative |
|---|---|
| Cryoprecipitation | Cryoprecipitation |
| C1q detection in agarose gel | C1q precipitation |
| RF detection in agarose gel or reverse hemagglutination | Adsorption to columns of insoluble C1q |
| Complement fixation | Isolation by column chromatography |
| Lymphocyte inhibition | |
| Platelet agglutination | |

Figure 1 shows various factors which we measured longitudinally in one SLE patient several years ago. The relationship between serum cryoglobulins and C levels is particularly noteworthy (our normal range for serum hemolytic complement is 34-48 CH5O units/ml) and one can clearly see the reciprocal relationship between C and cryoglobulin during the time span. This negative correlation is not always seen but usually is.

Figure 2 shows findings in another patient. Here the C level is first found in the normal range at a time when no cryoglobulins are seen. As the cryoglobulins appear, C levels begin to fall. It should also be noted that the antinuclear factor (ANF) remained fairly constant during this time period, though no titers were done. It has been our experience that when we use a 1:4 dilution of serum for the ANF test, little change in ANF can be noted between acute exacerbations and remissions of SLE. With prolonged remission, however, the staining may become less intense, though the ANF rarely disappears entirely in SLE patients. RF titers (usually low titers, when found) also tend to remain quite constant in SLE patients, though RF was not found in either of the patients shown in these figures.

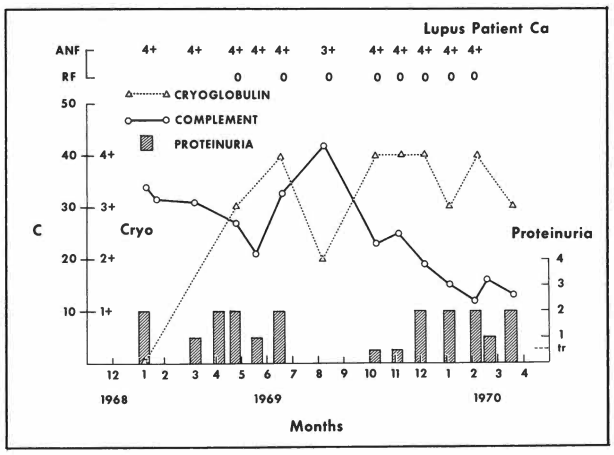


Fig. 1—Laboratory findings in a patient with SLE over a 16-month period. The reciprocal relationship between C and cryoglobulins is noteworthy. Antinuclear factor and proteinuria are relatively stable during this time.

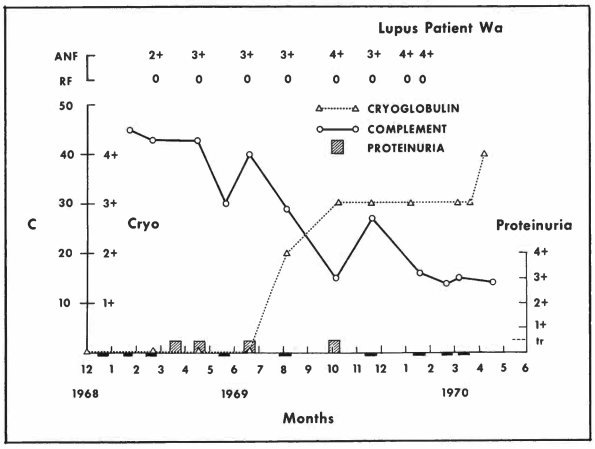


Fig. 2—Laboratory findings in another patient with SLE. Very little proteinuria is noted even when the C level is low and large amounts of cryoglobulin are found.

C1q precipitins have been found primarily in SLE patients with low serum C levels according to one report (10). In a group of 30 SLE patients with low C levels, 23 were positive for C1q precipitins; of those SLE patients who had normal C levels, none were positive for C1q precipitins. A few patients with miscellaneous diseases were positive (6/150).

Table 3 shows our results: Of 908 total sera tested for C1q precipitins, 19% were positive. (These sera came from patients who had a variety of diseases and were mainly suspected of having a connective tissue disease or vasculitis.) Of the lupus *sera,* 15% were positive and of the lupus *patients,* 43% were positive on at least one occasion. Sera from patients with other diseases were positive 27% of the time, the 28% positivity of nonlupus *patients* reflecting the fact that many of these patients were only studied by this technique on one occasion. Of particular note is the finding of C1q precipitins in other diseases besides SLE—a finding supported by other investigators (6, 7, 10).

TABLE 3

C1q PRECIPITATION

| | Total | # Positive | % Positive |
|---|---|---|---|
| Total Sera | 908 | 174 | 19 |
| Lupus Sera | 601 | 90 | 15 |
| Lupus patients | 95 | 41 | 43 |
| Other Sera | 307 | 84 | 27 |
| Other patients | 216 | 61 | 28 |

TABLE 4

C1q PRECIPITINS VS. CRYOGLOBULINS

| | # Positive | % Positive |
|---|---|---|
| Total Sera (106) | 16 | 15 |
| Lupus Sera (74) | 11 | 15 |
| Other Sera (32) | 5 | 16 |
| Cryoglobulins (106) | 0 | 0 |
| Cryo. Supernatants (106) | 24 | 23 |
| Lupus (74) | 18 | 24 |
| Other Sera (32) | 6 | 19 |

Results of the C1q precipitin test as it relates to sera with cryoglobulins are shown in Table 4. One notes that of the 160 sera tested here, 16 were positive for C1q precipitins; and of these 16 sera, 11 were SLE sera and 5 were other disease sera. Only some of these sera had cryoglobulins, but we treated them all as if they did—that is, they were all centrifuged after 48 hours in the cold and the supernatant transferred to another tube for testing against C1q. The cryoprecipitates, whether visible or not, were resolubilized at a ten-fold concentration and also retested against C1q. No cryoprecipitates showed a precipitin line, suggesting that 1) there was not enough material, 2) the material did not react with C1q, or 3) that the cryoprecipitate was already saturated with bound C1q. Of more importance, however, was the finding that of the 106 supernatants, 24 (instead of 16) were now positive. All of the 16 sera which were positive originally remained positive when the supernatant was checked and eight sera which were originally thought to be negative were now positive after removal of any cryoprecipitates. These studies have suggested to us that cryoglobulins have properties, at least in part, distinctive from C1q precipitins. Possibly the cooling and centrifugation of certain sera lead to aggregation of small complexes that do *not* spin down as cryoglobulins, but *do* subsequently react with C1q, even at room temperature!

For several years, we have been interested in how RF might modify IgG aggregates or immune complexes in human disease (11, 12). We have wondered whether RF might affect the deposition or metabolism of complexes by changing their size or their physicochemical properties in some other way. Small, soluble complexes might be made insoluble by RF; this might serve a protective function or a pathogenetic function depending on the circum-

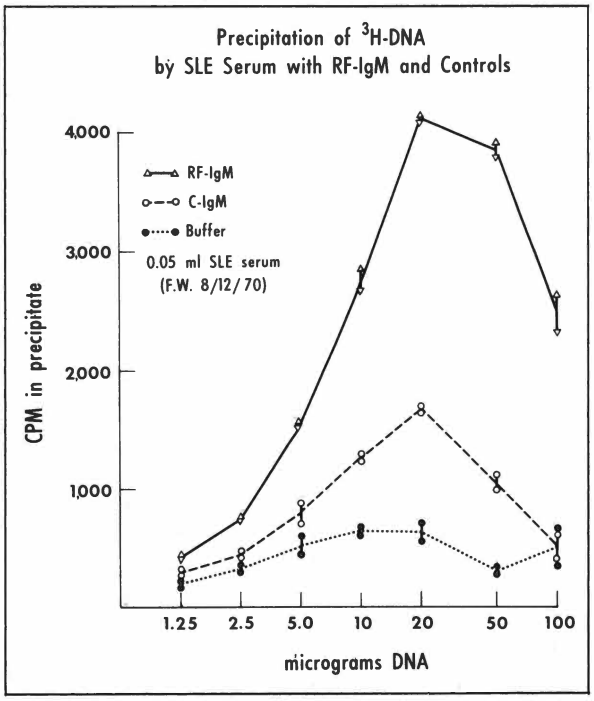


Fig. 3—Effect of IgM rheumatoid factor on DNA-anti-DNA complexes. Constant amounts of IgM [either control (C) or containing rheumatoid factor (RF)] are added to constant amounts of anti-DNA (SLE) serum and increasing amounts of DNA. Much more radioactive DNA is found in the precipitate when RF is added than in appropriate control systems.

stances (13). Figure 3 shows that RF has the capability of precipitating partially soluble DNA–anti-DNA complexes formed in vitro when one adds increasing amounts of labelled DNA to an SLE serum. It can be seen that much more precipitate is formed (based on counts of radioactive DNA in the precipitate) in the presence of RF than when the complexes are formed in the presence of control-IgM or buffer alone. We interpret these findings to mean that RF can interact with and precipitate DNA–anti-DNA complexes, thus converting these partially soluble complexes into insoluble complexes. As mentioned above, such a function for RF in vivo could be either protective or damaging.

Figure 4 shows effects of RF on cryoprecipitates. It would appear that RF has the potential for either increasing or decreasing cryoprecipitation, probably depending on characteristics of the cryoprecipitate. Conceivably one might be dealing with a system analagous to an antigen-antibody complex which would precipitate at equivalence but would resolubilize in both antigen and antibody excess.

Table 5 shows the sort of data being accumulated currently on patients seen at the University of Virginia Lupus Clinic. In the serum of this patient before treatment, a C1q precipitin was found, along with 3+ cryoglobulins, strong anti-DNA activity, a low C level, and strong ANF staining. After institution of steroid treatment, the C1q precipitin disappeared, but then we found material in the serum reacting with RF! (This often-seen reciprocal relation is of great interest to us, but we don't understand it.) Cryoglobulins disappeared (as did the anti-DNA antibodies) and at the same time the serum C level returned to normal. Since starting treatment, the patient has done well, and we have continued to be on the lookout for the reappearance of those factors associated with disease activity as we slowly lower the steroid dose.

Table 6 is an analysis of serum material bound to C1q on a cyanogen bromide Sepharose® column.

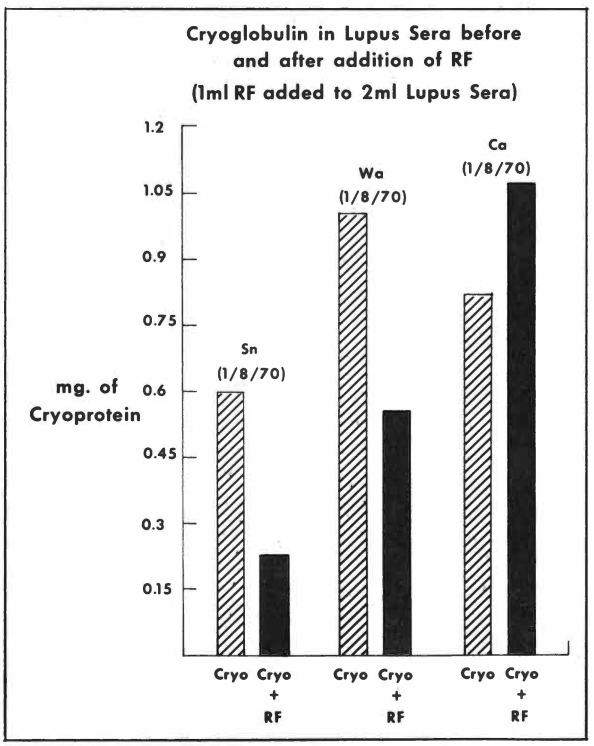


Fig. 4—Effect of IgM rheumatoid factor on three SLE sera containing cryoglobulins. After addition of RF to fresh sera Sn and Wa, less cryoglobulin was detected after 48 hours at 4°C; when RF was added to serum Ca, however, more cryoprotein was detected.

TABLE 5

S. P. (SLE)

| | Complexes | | | | | |
|---|---|---|---|---|---|---|
| | C1q | RF | Cryo | Anti-DNA | ANF | CH50 |
| 4/6/72 | + | − | 3+ | 3+ | 4+ | 10 |
| Treatment Started | | | | | | |
| 4/11/72 | − | + | ND* | 3+ | ND | 13 |
| 4/13/72 | − | + | ND | 2–3+ | ND | ND |
| 4/17/72 | − | − | ND | 2–3+ | ND | ND |
| 4/21/72 | − | − | 1–2+ | 2+ | 1–2+ | ND |
| 5/2/72 | − | − | 2+ | − | ND | 40 |
| 6/13/72 | − | − | − | − | 3+ | 53 |
| 7/25/72 | − | − | − | − | 3–4+ | 48 |
| 11/21/72 | − | − | − | − | 3–4+ | 45 |

* ND = Not Done

One notes the presence in the two eluates of IgG and IgM but no anti-DNA or DNA. Currently, we are analyzing these eluates by a variety of techniques including animal immunizations (to elicit antibodies to any infectious agents which might be there). Characteristics of C1q precipitins are also being compared with characteristics of cryoglobulins. It should be noted at this point that normal serum also contains significant amounts of material which bind to the C1q adsorbent.

In summary, we can draw very few firm conclusions about immune complexes in patients with SLE. SLE patients during episodes of disease activity often show both cryoglobulins and C1q precipitins in their sera, but in our experience, the sera may show only one of the factors and occasionally neither one is found. When cryoglobulins are removed from sera, C1q precipitins not only remain in the supernatant but occasionally may be found in the supernatant for the first time. This finding suggests that cryoglobulins and C1q precipitins are at least in part distinct. RF may interact with DNA–anti-DNA complexes and cryoprecipitates at least in vitro. Studies are in progress to further characterize the material found in these complexes. Hopefully, a particular antigen or a particular characteristic of SLE complexes will be found which will lead to a better understanding of the primary cause and intermediate mechanisms involved in the serious disease known as SLE.

TABLE 6

ANALYSIS OF ELUATES BOUND TO INSOLUBLE C1Q

| | E.F. (SLE)* | J.D. (N)** |
|---|---|---|
| IgG (mg) | 3.12 | 0.73 |
| IgM (mg) | 0.49 | 0.31 |
| IgA (mg) | 0 | 0 |
| C1q | + | Trace |
| DNA | − | − |
| Anti-DNA | − | − |
| RF | 1:8 | 1:8 |
| Pptns. vs C1q | + | + |

* SLE = Lupus serum eluate
** N = Normal serum eluate

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# Ankylosing Spondylitis*

JOHN BAUM, M.D.

*Professor of Medicine, Pediatrics, and Preventive Medicine and Community Health, University of Rochester School of Medicine, Rochester, New York*

Within the last few years, the study of ankylosing spondylitis has produced some of the more remarkable new developments in the field of the rheumatic diseases. In modern days the disease has been described in Germany by Strümpell and in France by Marie. As a result, in Germany it is known as Strümpell's disease and in France as Marie's disease. Physicians in the United States and England, to be fair, call it Marie-Strümpell disease. It should be emphasized at this point that ankylosing spondylitis is not a variant of rheumatoid arthritis as it had been considered for a number of years. The term rheumatoid spondylitis is still occasionally used but should be completely abandoned.

The initial diagnosis of ankylosing spondylitis is often a difficult one to make. The best criteria we have are quite simple. They are 1) limitation of motion of the lumbar spine; 2) pain in the low back; and 3) limitation of chest expansion. As you can see, no laboratory tests except the x-ray film are used and in the early stages, x-ray film examination may not be helpful.

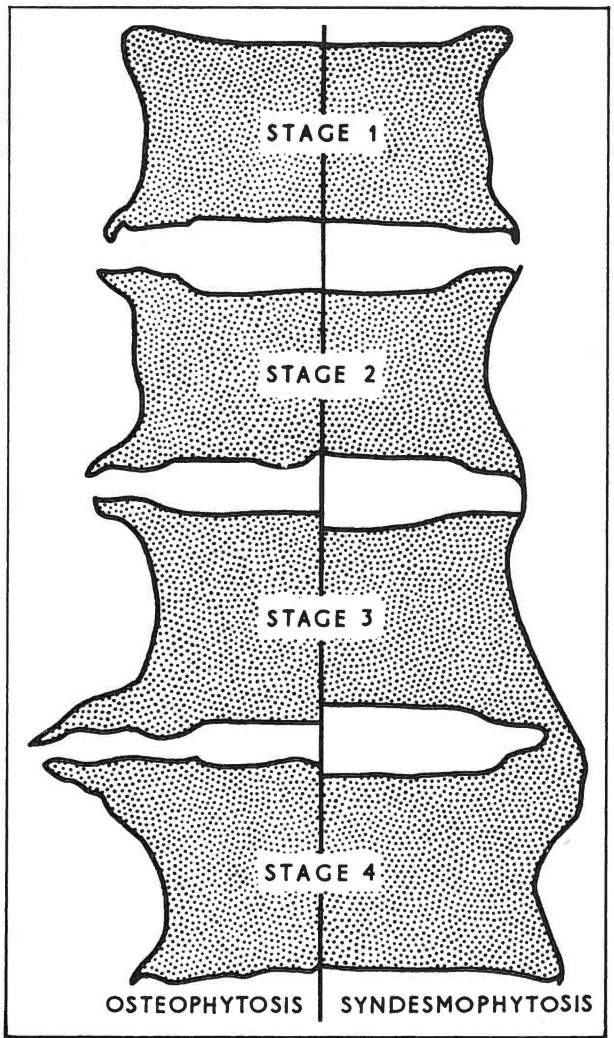
Examination of the lumbar spine in some studies shows that limitation of extension may actually be a better way of separating normal from abnormal spines (1), although limitation of flexion (flattening of the lumbar curve) is usually what we look for in the back examination. Moll and Wright (2) have shown that lateral spinal flexion is the best way to distinguish between spondylitis and lumbar disc disease. Spondylitis will also cause limitation in this direction.

The erythrocyte sedimentation rate can be normal in patients with ankylosing spondylitis. Even patients with rather marked degrees of pain can have normal sedimentation rates while patients who may just show changes in the sacroiliac, hips, or back without pain can have a significantly elevated sedimentation rate. Of course, rheumatoid factor is not found in these patients and can be of diagnostic help only by its absence.

The patient with ankylosing spondylitis is usually a young white male who gives a fairly typical story. Back pain usually wakes him up in the small hours of the morning. It is rare that he will complain of being unable to go to sleep because of pain. He will usually awake because of discomfort in the lower back and get out of bed. He may get relief (and go back to sleep) lying on the floor or sitting up in a hard back chair or sitting on the floor with his back against the wall. The pain frequently, as with sciatica, goes down the back of the legs. Alternation of the radiating pain from one side to the other is a typical feature which helps to distinguish the symptoms from those produced by a lumbar disc protrusion.

Examination of the x-ray films may initially show erosions in the sacroiliac joints and finally fusion, and of course, the "bamboo" spine of late disease is well known. The development of the changes in the spine can be shown diagrammatically so one can differentiate the syndesmophyte of ankylosing spondylitis from the osteophyte of degenerative joint disease (Fig. 1). This is taken from a recent article of Riley, Ansell, and Bywaters (3). On the left in the figure is seen the progression of osteophytosis and on the right, the progression of syndesmophytosis. The osteophyte is associated with disc narrowing. The bony plate is marginal and most importantly is horizontal as seen in stages three and four. It is built up at the base with subperiosteal bone. The base appears to lie against protruded disc substance. In ankylosing spondylitis, there is no

* Presented by Dr. Baum at the 45th Annual McGuire Lecture Series, November 9, 1973, at the Medical College of Virginia, Richmond.



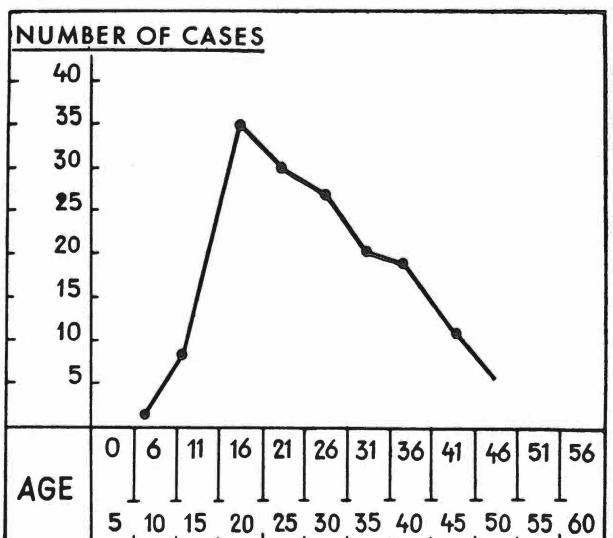

Reprinted by permission from *Ann Rheum Dis* (3).
Fig 1.

disc narrowing or protrusion. A vertical plate is built up in the outer layer of the annulus fibrosis. These syndesmophytes will ultimately bridge in stage IV of the disease.

Ankylosing spondylitis is a disease of young males, seen in Figure 2 where the peak in a large series is found to occur in the late teens and early 20's (4, pg. 10). There is, however, a group of ankylosing spondylitics who start at an earlier age. Barbara Ansell and Eric Bywaters in Taplow, England followed up 139 patients with juvenile rheumatoid arthritis (JRA), 55 males and 84 females, for at least 15 years into adult life. What was striking about the 55 males was that 9% of them, as they went on to adulthood, developed typical ankylosing spondylitis.

Joint involvement in ankylosing spondylitis is, of course, different from that seen in patients with rheumatoid arthritis. Forestier (4) showed (Table 1) the high frequency of hip involvement in this disease when compared to patients with rheumatoid arthritis. In the rheumatoid, there is much more peripheral joint involvement.

There are a number of complications which are more specific and more frequent in ankylosing spondylitis than in many of the other forms of arthritis. Most of the complications that have been noted are listed in Table 2. Iritis is said to occur in up to 20% of patients. Aortic insufficiency is usually seen quite late in the disease. Heart block is rarely seen but also probably represents the same type of inflammatory action in the myocardium as is seen in the aorta. Amyloidosis, again, is not seen frequently but is a recognized cause of death in ankylosing spondylitis—certainly more so than with rheumatoid arthritis. Atlantoaxial subluxation is a constant threat to these people with spine fusion and can sometimes be fatal after only moderate degrees of trauma. Cauda equina involvement is rarely seen but, again, is a well-recognized problem. Pulmonary fibrosis of the upper lobe is of interest because this fibrosis, which may be typical of spondylitics, has been mistaken for tumor, tuberculosis, and the like.




From Forestier, J. et al., (4). Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.
Fig. 2.

TABLE 1

PERIPHERAL JOINT INVOLVEMENT AT ONSET*

| Joint | Ankylosing Spondylitis (200 patients) % | Rheumatoid Arthritis (100 patients) % |
|---|---|---|
| Hips | 42 | 10 |
| Knees | 29 | 62 |
| Ankles | 7 | 58 |
| Feet | 12 | 28 |
| Shoulders | 30 | 64 |
| Elbows | 3 | 46 |
| Wrists | 5 | 82 |
| Hands | 7 | 94 |
| Temperomandibular | 6 | 8 |
| Sternoclavicular | 11 | 7 |

* After Forestier (4)

It probably accounts for some of the earlier statements made about the higher frequency of tuberculosis in these patients. It is remarkable how good pulmonary function is in these men with limited chest expansion. A recent study indicates that impairment of lung function is minimal in most of the patients with this disease (5).

The variants of ankylosing spondylitis are shown in Table 3. All of these conditions can show sacroiliitis and indeed in some cases, go on to more extensive spinal involvement quite similar to those seen in ankylosing spondylitis. I will mention some of these again later because of an interesting relationship.

For many years, it has been felt that there were strong genetic features connected with ankylosing spondylitis. Several years ago, when I was still in Dallas, Morris Ziff and I, seeing our patients at the Veterans Administration Hospital, were struck by the relative rarity of ankylosing spondylitis among our black patients. (One of the earliest clinicians to note this rarity was Elam Toone in 1949.) He found, in a group of patients that he was studying in the McGuire Veterans Administration Hospital in Richmond, 26 white and only three black patients with ankylosing spondylitis (6). Table 4 shows what we found in Dallas at the Veterans Hospital when we looked at the frequency of ankylosing spondylitis in relation to a number of other disease admissions rates and the male population of Dallas (7). As you can see, although the admission rate to the Veterans Hospital clearly reflected the racial distribution of the population, there was a marked discrepancy in the relative ratio of patients

TABLE 2

COMPLICATIONS OF ANKYLOSING SPONDYLITIS

Iritis
Aortic Insufficiency (Aortitis)
Heart Block (Myocarditis)
Amyloidosis
Atlantoaxial Subluxation
Cauda Equina Involvement
Upper Lobe Fibrosis

with ankylosing spondylitis. We were not satisfied with this view, thinking perhaps we might have an unusual situation. When data were pooled from a number of VA hospitals, we found a fourfold difference in the frequency of ankylosing spondylitis between whites and blacks. A search of the African literature showed that there are virtually no patients with ankylosing spondylitis in Africa among the black native population. A review of genetic studies in the United States indicated that the black population of the United States has a 20-25% admixture of white genes. This admixture of white genes would very nicely account for the fact that ankylosing spondylitis was only found in about 20-25% of the expected frequency, if it had the same distribution in the blacks as it did in whites.

This information was subsequently utilized by Schlosstein, Terasaki, Bluestone, and Pearson (8) at the Wadsworth VA Hospital in Los Angeles. The transplantation antigen known as W-27 was found in 8% of a caucasian population but was found in 88% of a group of patients with ankylosing spondylitis. It was also interesting to note that W-27 is not found in Black Africans and is present in an approximate frequency of 4% in Black Americans. To further support the relationship of this antigen to ankylosing spondylitis, W-27 was found in eight of ten Black Americans with ankylosing spondylitis.

Another and perhaps more striking correlary of

TABLE 3

VARIANTS OF ANKYLOSING SPONDYLITIS

Psoriatic Arthritis
Ulcerative Colitis
Crohn's Disease
Whipple's Disease
Behcet's Disease
Reiter's Disease

TABLE 4

RACIAL DISTRIBUTION OF ADMISSIONS AND OF ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS, AND REITER'S SYNDROME AT DALLAS VETERANS ADMINISTRATION HOSPITAL

| | Number White | Number Black | % White | % Black | White-Black Ratio |
|---|---|---|---|---|---|
| Males—Dallas, Texas (1960 census) | 263,354 | 61,911 | 81 | 19 | 4.2 |
| Male Admissions (10 months, 1966) | 5,182 | 1,227 | 81 | 19 | 4.2 |
| Ankylosing Spondylitis (1959–1966) | 41 | 3 | 93 | 7 | 13.7 |
| Rheumatoid Arthritis (1959–1966) | 90 | 16 | 85 | 15 | 5.6 |
| Reiter's Syndrome (1959–1966) | 7 | 4 | | | 1.8 |

this data was recently presented by Rodney Bluestone of this group at the XIIIth International Congress of Rheumatology in Kyoto, Japan (9). In Table 5 are seen their most recent data. As you can see, W-27 is found in 14 of 156 patients with psoriasis alone. This is just about the frequency found in the normal population; however, in those patients with psoriasis who develop spondylitis it has been found in four of six individuals. In patients with colitis who developed spondylitis, this high frequency was again found. Perhaps even more remarkable are 15 out of 16 juvenile rheumatoid arthritics with W-27 who had spondylitis. Chronic Reiter's syndrome had the W-27 antigen in every case. Perhaps more astonishing were the studies they subsequently did looking at patients with acute Reiter's syndrome. Even those who do not have spondylitis showed W-27 in a remarkably high frequency.

We now seem to have a new tool for the diagnosis of some forms of arthritis. For example, in male children who develop what appears to be juvenile rheumatoid arthritis, looking for W-27 might give us a strong clue as to the future course of their disease. A similar use could be in suspected Reiter's syndrome. This has certainly opened the door to a most fascinating series of studies and conjectures about the relationship of the W-27 antigen and spondylitis.

In the treatment of ankylosing spondylitis, radiation therapy was at an early date, found to be effective for relief of pain; it's use was given up because of a reported high frequency of blood dyscrasias following its application. There are still some authors who feel that its limited use in patients who are having pain in spite of other therapy is of distinct benefit and of low risk (10). Indomethacin and phenylbutazone are the most frequently used drugs in the treatment of this disease. An observation was made recently that a patient with severe ankylosing spondylitis who did not respond to the above mentioned drugs responded quite well to penicillamine therapy (11). Steroids are of little use in this group of patients. Teaching the patients exercises in an attempt to increase diaphragmatic breathing is of benefit and exercises may sometimes help to maintain the spine in better position.

It is worth noting that what we have learned about this disease in recent years has provided us with better methods of establishing the diagnosis and prognosis of ankylosing spondylitis.

TABLE 5

| | Frequency of W-27 |
|---|---|
| Psoriasis with Spondylitis | 4/6 |
| Psoriasis Alone | 14/156 |
| Colitis with Spondylitis | 4/6 |
| JRA with Spondylitis | 15/16 |
| Chronic Reiter's with Spondylitis | 8/8 |
| Acute and Chronic Reiter's | 22/23 |

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# Histocompatibility Antigens and Spondylitis* **

ROBERT IRBY, M.D.

*Professor of Medicine, Division of Connective Tissue Diseases, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

WILLIAM EDWARDS, M.D.

*Fellow in Rheumatology, Division of Connective Tissue Diseases, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

JAMES PIERCE, M.D.

*Professor of Surgery and Microbiology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

RODERICK MACDONALD, M.D.

*Chairman of the Department of Ophthalmology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

**Dr. Irby:** For some time the influence of heredity in ankylosing spondylitis has been fairly well established, but the exact mechanism has not been understood. Although there has been some evidence of familial clustering in peripheral rheumatoid arthritis, studies by Jacox and others in Rochester, New York have indicated 25 of 28 siblings of monozygotic twins to be discordant for rheumatoid arthritis.

The subject of this discussion is HL-A antigens and spondylitis. Since many people do not understand the language of the geneticists, Dr. James Pierce will tell us what we need to know about HL-A antigens. Questions that often arise include: 1) What are HL-A antigens? 2) What is meant by HL-A 27? 3) How does one go about identifying antigenic determinants in tissue typing?

Later we will try to document how some of this material applies to many of the rheumatic diseases in which spondylitis is often a feature. In conclusion, Dr. Macdonald of the Ophthalmology Department will comment on various aspects of anterior and posterior uveitis, how the diagnosis is made, and what the treatment is of each. Uveitis is often a complication of ankylosing spondylitis and

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Reiter's disease. A representative case involving uveitis, arthritis, and the presence of HL-A 27 will be reviewed.

**Dr. Edwards:** J. C. is a 30-year-old black male who was first seen in the Emergency Room of the Medical College of Virginia Hospitals on September 3, 1973. At that time, he complained of pain in his back and left wrist. He stated that approximately six days earlier, while doing manual labor, he had experienced pain and swelling in his neck. The pain migrated to his left hip, then between the scapulae, and finally into the left wrist. Two weeks prior to these complaints, he described a two day illness characterized by diarrhea from which he recovered with no therapy. Past medical history was significant in that he had been treated five years earlier by his local physician for a urethral discharge. There is no family history of arthritis.

Physical examination at the onset of his illness revealed a T 100.4°F, P 104 per minute, and BP 120/74. There was pain in the area of the cervical spine when his head was deviated to the right or left. In addition there was tenderness to percussion over the midthoracic vertebrae, and a painful, warm, swollen, erythematous left wrist. Also noted was a small papular lesion on his left heel. An arthrocentesis of the wrist was unsuccessful. Laboratory studies included a hemoglobin 16 gm%, WBC's 12,600 (78% polys, 13% lymphocytes, 9% monocytes), erythrocyte sedimentation rate (ESR) 15 mm per hour (Wintrobe), and a urinalysis with a few WBC's and RBC's but no protein, sugar, or acetone. Repeat ESR's have been 30–40 mm per hour. The following tests were either negative or normal: rheumatoid pattern, antinuclear antibody, lupus erythematosus cell preparations, antistreptolysin-O titer, and urine and blood cultures. An intermediate strength PPD was negative at 72 hours. Roentgenographic studies of his chest, cervical spine, thoracic spine, and pelvis were normal. X-rays of the left wrist showed soft tissue swelling only. Scrapings for the papular lesion on his foot grew *Trichophyton mentagrophytes*. HL-A 27 was found to be present using the lymphocyte microcytotoxicity test.

Because of the concern that the patient was suffering from an infectious arthritis, he was treated with antibiotics. There was no response to this therapy and by mid-September he had, in addition to the left wrist, developed painful swelling of his right ankle and pain to palpation in his right wrist. Anti-inflammatory drugs, including salicylates, Butazolidin®, and gold, did not help. Colchicine was likewise ineffective.

On October 8 he presented with an inflamed and swollen right eye. Photophobia was present. An ophthalmological consult found a visual acuity of 20/100 with a raised intraocular pressure in the right eye. The left eye was normal. The etiology for this nongranulomatous anterior uveitis was unknown but felt to be related to the arthritis. Later a posterior uveitis was also noted. Complete resolution of the uveitis occurred over the ensuing six weeks, while the patient was treated with alternate day corticosteroids in a progressively decreasing dose. The arthritis also improved.

Subsequently the patient has complained of left heel pain, yet no objective signs to document the development of bony spurs have occurred. There is no evidence of active synovitis although he does have some limitation of motion of his right ankle and left wrist. He denies any further back pain and is no longer on any medications.

**Dr. Irby:** We are not at all sure of the exact nature of this gentleman's illness. When the patient was first seen on arthritis rounds, the lesions of his feet were suggestive of keratoderma blennorrhagica. It was felt that we were dealing with a case of ankylosing spondylitis, possibly Reiter's spondylitis, or seronegative rheumatoid arthritis. The latter diagnosis was entertained because of the lack of characteristic x-ray findings in the sacroiliac joints or syndesmophytes on the margins of the lumbar spines. After *Trichophyton mentagrophytes* were cultured from the patient's foot, the only things we had to go on were the clinical picture of arthritis of an asymmetrical nature, past history of urethritis, and uveitis. Dr. Pierce's laboratory determined HL-A 27 to be present, so this gives us an opportunity to present recent data on the new trend in "spondylitisology," that of antigenic determinants by tissue typing for the histocompatibility antigens.

**Dr. Pierce:** In my discussion of histocompatible antigens, I want to review several things, such as the rapidly changing development of this field, the lymphocytotoxicity test—which provides a basis for detecting these antigens, some comments on the genetics of inheritance of this system of antigens, the nomenclature, a source of constant confusion, and finally, the association of disease states with HL-A antigens.

The field of histocompatibility typing began in 1954, when Dausset, in Paris, discovered that anti-

bodies were present in the sera of patients who had received multiple transfusions, which were directed against leukocytes but not erythrocytes. In 1958 Payne and Rolfe at Stanford University found that women who had had multiple pregnancies had similar antileukocyte antibodies. It was in this same year that the first leukocyte antigen was discovered using antisera, prepared from these patients, which had reacted in common with leukocytes of certain other patients. This particular antigen was HL-A 2 which is the most frequent HL-A antigen found in Caucasians, being present in over 50% of a random population. A significant advance was made in 1964, when Terasaki devised a microtest for detecting these antigens. The advantage of the microtest over the macrotest is that one thousand rather than ten tests can be performed on one milliliter of serum. A series of international workshops were held in the late 1960's. In Torino in 1967, it was first reported that the HL-A antigens were inherited in a Mendelian dominant fashion from parent to child. The discovery that there are two HL-A loci relatively close together on an autosomal chromosome was made in 1970 at the Los Angeles workshop.

The lymphocyte microcytotoxicity test detects surface antigens of lymphocytes. These antigens react with specific antibody to form a sensitized lymphocyte which then reacts with rabbit complement. This results in the formation of holes in the cell membrane of those lymphocytes with attached antibody, allowing a dye to pass into the lymphocytes that have been killed. Thus the dark cells seen via the inverted phase microscope are dead cells containing dye. In a typical positive well, all the cells will be dead. The antisera used for these reactions are derived from multiparous women.

How are these antigens controlled genetically? The genes for HL-A antigens are located on an autosomal chromosome, with each child receiving one chromosome from his mother and one chromosome from his father. Two loci controlling a different series of antigens are located on each chromosome. Therefore, there are two-to-four antigenic possibilities for each offspring. An individual with only two HL-A antigens is rare, but this could occur if he received an identical pair from his mother and father. More common but still unusual and occurring in 10% of the population is the presence of only three HL-A antigens; the majority of people have four HL-A antigens. One should distinguish between the incidence of the antigens on a given chromosome, or gene frequency, and phenotypic frequency which is the incidence actually observed in people. The gene frequency of a given antigen is approximately one half the phenotype frequency. Because they are inherited in a Mendelian dominant fashion, there are four types of offspring with respect to HL-A antigens that a pair of parents may have (Fig. 1). Therefore, 25% of siblings will be HL-A identical. Also every child will share one haplotype, which is one pair of antigens controlled by the two genes on one chromosome with each parent. Therefore, a child will share two of the antigens of his father and he will usually have two additional antigens from his mother which are different from those of his father. There is also the chance, which is less than 1:4, that a sibling will share no HL-A antigens with another sibling.

What about the nomenclature of these antigens? HL-A designates antigens recognized by the World Health Organization Committee, which set up criteria for their identification. To be recognized, there must be two monospecific antisera which define the HL-A antigen and which do not overlap with other recognizable HL-A antigens. Tentative recognition is given to an antigen, when one monospecific serum identifies it and many labs recognize it. This is termed the W-classification system and what was orginally designated W-27 is now designated HL-A 27. HL-A antigens have frequently been discovered in a number of labs simultaneously, which has led to confusion because they are given local designations. For example, HL-A 5 has been designated by local groups as AO 45, BT 25, 4C, TO 5, DA 5, and TE 11. Obviously, it is easier to speak of HL-A 5, so order is gradually coming into the field.

Where do we stand in discovering these antigens? In the first segregate series controlled by one genetic locus, the gene frequency of those ten W and HL-A antigens already discovered adds up to 0.978. If all antigens have been discovered, the gene frequencies should add up to 1.00. On the second segregate series, 15 W and HL-A antigens have been discovered, but their gene frequency adds up to only 0.897, so approximately 10% of this group of HL-A antigens remain undiscovered. There is a difference in the racial distribution of these antigens. For example, HL-A 2 is found in 50% of Caucasians while HL-A 9 is found in over 70% of Orientals. One can see that a difference of gene frequency of these HL-A antigens would provide a basis for difference of disease incidence in different racial groups which

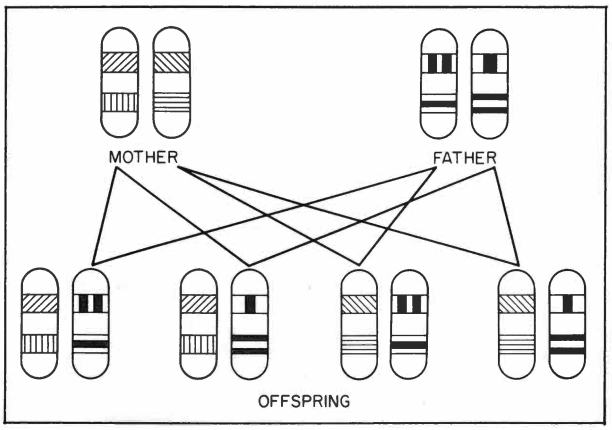


Fig. 1—This illustration depicts a pair of autosomal chromosomes from each parent with the two HL-A loci on each chromosome and the pattern of inheritance of the HL-A antigens; 25% of the siblings will be HL-A identical.

is relevant to our patient today. The association of HL-A 27 with ankylosing spondylitis and with Reiter's syndrome is striking.

Caution should be introduced, however, about the association of an HL-A antigen and a disease state. For example, some investigators have found a significant association of HL-A 5 with Hodgkin's disease while others have found no significant association at all. This is not very surprising, because if 21 antigens are studied for association with a disease, the chances are that one antigen will be significantly associated with the disease by chance if the level of significance is $P = 0.05$. Therefore, a correction factor is introduced. The level of significance is divided by the number of antigens studied in the search for an association. In the case of 21 antigens, the P value would have to be less than 0.0024 to have a significant association.

Two other points should be made about this system of antigens—one is that HL-A antigens are found on the surface of all somatic or nucleated cells, so they are accessible to involvement with diseases; secondly, this is the most polymorphic genetic system found so far in man, so it lends itself to individualization. Even though the incidence of a disease may be very small, there is a real possibility that it will be found associated with a given HL-A antigen.

**Dr. Irby:** Although the possible association of HL-A antigens with disease susceptibility has been investigated for many years, it has been only within the past two years that three convincing examples have come to light (Table 1). In psoriasis, there is an increased disease incidence in first degree relatives and in adult celiac disease, the incidence in relatives is six times normal. Patients with rheumatic diseases have provided many interesting and significant correlations with HL-A antigens (Table 2). Earlier studies and subsequent HL-A antigen investigators have demonstrated a striking relationship between HL-A 27 and ankylosing spondylitis and between HL-A 27 and Reiter's syndrome (Tables 3, 4).

**Dr. Macdonald:** Some years ago the principle way of classifying uveitis was on the basis of granulomatous uveitis, in which the primary inflammatory cell was the epitheloid cell. In the anterior segment of the eye, the exudation was that of a heavy proteinaceous material with many synechiae, compared to the nongranulomatous variety, in which the cell type was nonepitheloid with generally a much less severe reaction. In the granulomatous types of uveitis, or in iridocyclitis, the actual offending agent was considered to be present. For some years, this classification was expounded by Dr. Woods at Johns Hopkins University. At present, uveitis is generally classified according to where it is found in the eye, that is, anterior uveitis (involving mainly the iris), both segments (involving the iris, ciliary body, and choroid), and those involving only the choroid. It is of particular interest that the leading cause of anterior segment disease is unknown; in both segments, the third most common cause is unknown; and in the posterior or choroidal variety, many are unknown. Much work remains in order to properly determine the basic etiologies of uveitis. In the anterior segment variety, ankylosing spondylitis appears to be the third most common cause in this series.

In the literature, a system for studying the problem of sympathetic ophthalmia was propounded by Elschnig in 1910. He proposed that melanins in the uveal pigment of the eye where indeed the exciting factors. The studies were carried out by complement fixation tests. This has subsequently raised the question of the role of melanin in the eye. A further interesting question of the relationship of pigmentation in the skin to the Vogt-Kayanagi-Harada syndrome of vitiligo, poliosis, and dysacousis has been raised.

As we progress through clinical and research experiences, our concepts necessarily change. In 1941 Dr. Woods at Johns Hopkins reported a study of 343 cases of uveitis of which 80% were caused

TABLE 1

HL-A ASSOCIATED WITH DISEASE*

| | | | |
|---|---|---|---|
| Celiac Disease | HL-A1 | $2\frac{1}{2}$–3 × Normal | Stokes, 1972 |
| | HL-A8 | 3 × Normal | Falchuk, 1972 |
| Ch. Active Hepatitis | HL-A1 | | |
| | HL-A8 | 3 × Normal | Mackay, 1972 |
| Psoriasis | HL-A17 | | Russell, 1972 |
| | HL-A13 | 3 × Normal | White, 1973 |
| Ankylosing Spondylitis | HL-A27 | 10 × Normal | Schlosstein, 1973<br>Brewerton, 1973 |

Also some correlation lymphoma, multiple myeloma, SLE, and lymphoblastic leukemia with various phenotypes HL-A.

* The association of certain HL-A antigens with disease states has proven to be more than a chance correlation.

by tuberculosis. In 1960 Dr. Woods reported another series including 134 cases of uveitis. In this study, only 20% of the cases were caused by tuberculosis, whereas 36% were caused by toxoplasmosis, 13% by histoplasmosis and 22% were of unknown etiology. Dr. Kaiser reported a study involving 110 patients with uveitis, and 38% of these were caused by histoplasmosis which was the largest single group. Much of this is, of course, attributable to the fact that Louisville lies in the Ohio Valley which is endemic for *Histoplasma capsulatum*. In our series of over 400 cases of uveitis, 60% have been posterior (choroid), 18% anterior, 12% midsegment, and 10% involving all segments of the eye. Approximately 58% of the cases of anterior uveitis had an unknown etiology. There are probably two reasons for this. First, there are many types of diseases which will produce a purely anterior uveitis. Secondly, ophthalmologists are divided into two groups—one group does everything diagnostically; the second group treats them all with steroids and a large majority get well anyway. Therefore, many patients with the anterior uveitis appear to have no known cause. In our group with anterior uveitis, there were four cases of ulcerative colitis with spondylitis (6%) and six cases of Reiter's disease or other

TABLE 2

HL-A 27 IN RHEUMATIC DISEASE PATIENTS*

| Condition | Presence of HL-A 27 | Percentage | Source |
|---|---|---|---|
| Normal | 119/1456 | 8% | Russell, 1972<br>Brewerton, 1973<br>Schlosstein, 1973<br>White, 1972 |
| Rheumatoid arthritis | 10/119 | 8% | Schlosstein, 1973 |
| Gout | 6/66 | 9% | Schlosstein, 1973 |
| Ankylosing spondylitis | 35/40 | 88% | Schlosstein, 1973 |
| | 72/75 | 96% | Brewerton, 1973 |
| Reiter's syndrome | 25/33 | 76% | Brewerton, 1973 |
| Acute anterior uveitis | 26/50 | 52% | Brewerton, 1973 |
| Psoriasis | 9/156 | 6% | White, 1972 |
| | 6/44 | 14% | Russell, 1972 |
| Psoriasis/spondylitis | 10/14 | 71% | Metzger, 1974 |

* A compilation of rheumatic diseases and HL-A 27 shows its strong association with ankylosing spondylitis, Reiter's syndrome, and psoriatic spondylitis.

TABLE 3

RACIAL ASPECTS OF ANKYLOSING SPONDYLITIS*

1. Random study McGuire VA H: 26 white, 3 black.—Toone 1949
2. Combined VA H study, 301 pts. 10% black.—Baum 1971
3. HL-A 27 absent in Black Africans.—Dausset
4. HL-A 27 only 4% in Black Americans.
5. HL-A 27 present in 8 of 10 Black American spondylitics.

* The above figures demonstrate the relationship of HL-A 27 and ankylosing spondylitis on Black Americans.

rheumatic diseases (8%). Therefore, 14% of our cases of anterior uveitis had some rheumatological problem. Ninety-six percent of the cases in our series with midsegment disease had no apparent diagnosis after workup. Two percent were diagnosed as spondylitis. Perhaps, a reason for the small number of diagnoses is that ankylosing spondylitis and sacroiliitis have, in the past, been overlooked.

**Dr. Irby:** So what can we conclude from this discussion?

1. There is an 88–95% incidence of HL-A 27 antigen in patients with ankylosing spondylitis and a 76% incidence in patients with Reiter's disease against an 8% incidence in a controlled Caucasian population.

2. First degree relatives of spondylitics have 20–30 times the risk of developing spondylitis and 50% of these will have HL-A 27.

3. The HL-A 27 antigen may be a useful tool in diagnosis or prognosis, particularly in early rheumatic disease patients including those with juvenile rheumatoid arthritis.

4. There is a possibility that HL-A 27 may predispose a patient to develop Reiter's disease or ankylosing spondylitis; however, much work needs to be done in this regard to implicate HL-A 27 as an etiological factor.

TABLE 4

HEREDITARY ASPECTS OF ANKYLOSING SPONDYLITIS*

1. 30× more prevalent among relatives of spondylitic patients than controls.—Stecher
2. 22.6× more prevalent in relatives of spondylitics than controls.—De Blecourt
3. W-27 found in 31/60 1° relatives.—Brewerton
4. No blood group association.

* The hereditary aspects of ankylosing spondylitis are clinically apparent as well as genetically significant.

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# Juvenile Rheumatoid Arthritis: Early Diagnosis, Management, and Prognosis* **

JOHN J. CALABRO, M.D., F.A.C.P.

*Chief of Medicine & Director of Rheumatology, Worcester City Hospital; Consultant in Pediatric Rheumatology, New England Medical Center, Boston, Massachusetts; Professor of Medicine, University of Massachusetts Medical School, Worcester*

Rheumatoid arthritis (RA) is the major chronic rheumatic disorder of childhood. It affects as many as 250,000 American children and is slightly more common in girls than in boys.

Juvenile rheumatoid arthritis (JRA) is arbitrarily defined as RA beginning before the age of 16. It rarely begins before six months of age, and most cases appear between the ages of one and three with a second peak at 8-12 years of age.

Despite the inclination to link RA and JRA as identical diseases, one occurring in adults, the other in children, there are a number of striking differences between the two (1–5). In a comparative survey (Table 1), high fever and rheumatoid rash occurred far more frequently in children than in adults with RA. Another important difference is that chronic iridocyclitis developed in 8% of patients with JRA. Such ocular involvement is rare in adults with RA, if it occurs at all. Of all children with JRA, the most susceptible group are those with the mildest form of disease—those whose initial onset is monarticular and those whose course of disease is oligoarticular (pauciarticular); about one in five will develop this potentially serious eye inflammation. A monarticular onset, primarily of a knee, was found more often in JRA than in adult RA. This is difficult to explain, as is the relative infrequency among children of subcutaneous nodules. Fewer children (8%) had rheumatoid nodules than adults (20%). They occurred, however, in the same areas in both groups. Nodules are seen frequently at the elbow or may be found in any area of pressure or friction, such as the knuckles or at the back of the heels. Rheumatoid factor in the serum, as observed by either a positive sheep cell agglutination or latex fixation test, is present in only 10–25% of JRA patients, whereas in adults, it is found in 50-85%. Failure to appreciate the relative infrequency of rheumatoid factor in JRA constitutes one of the major pitfalls in early diagnosis.

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## EARLY DIAGNOSIS

Clearly, it is precisely these major differences that have created much of the difficulty in the early diagnosis of JRA. The problem would be simpler by the recognition of three distinct modes of onset. These are *acute febrile* (*systemic*), *polyarticular,* and *monarticular*. The frequency, severity, and character of initial systemic and articular manifestations help to differentiate each.

An acute febrile or systemic onset is marked by systemic manifestations, including high fever, rash, generalized lymphadenopathy, splenomegaly, and heart involvement. Joint manifestations are variable; occasionally only arthralgia is present. In polyarticular onset, defined as the involvement of more than four joints, the arthritis predominates and is frequently generalized and symmetric, similar to RA in adults. Systemic manifestations are less prominent than in an acute febrile onset and fever is low grade. In a monarticular onset, arthritis is confined to a single joint, usually a knee; except for iridocyclitis, systemic manifestations are either absent or minimal.

TABLE 1

MAJOR DIFFERENCES BETWEEN 100 CHILDREN AND 100 ADULTS WITH RHEUMATOID ARTHRITIS

CONSECUTIVE REFERRALS TO AN ARTHRITIS CLINIC

| Disease Feature | Frequency (%) Children | Adults |
|---|---|---|
| High Fever | 20 | 3 |
| Rheumatoid Rash | 36 | 2 |
| Chronic Iridocyclitis | 8 | 0 |
| Monarticular Onset | 32 | 6 |
| Subcutaneous Nodules | 8 | 20 |
| Rheumatoid Factor* | 23 | 76 |

* By the latex fixation test, titer of 1:160 or greater.

**Acute Febrile Onset.** About 20% of all JRA patients present with an acute febrile or systemic onset. Recognition is easy when obvious arthritis is present in addition to several typical systemic manifestations of the disease (Fig. 1). Sometimes, however, only arthralgia is present and then the differential diagnosis can be difficult. In those without arthritis, the child's appearance may provide the first diagnostic clue. These children are irritable, listless, anorectic, and losing weight. They often wish to be left alone and assume a position of generalized flexion. Of the many systemic manifestations, fever and rash have the greatest diagnostic value. Both may be associated with generalized lymphadenopathy (particularly axillary and epitrochlear nodes), splenomegaly, hepatomegaly, pericarditis, myocarditis, pneumonitis, and a striking neutrophilic leukocytosis.

*Fever.* First, it should be remembered that high fever may precede detectable signs of obvious arthritis by weeks, months, or rarely, by years (6). Rectal temperatures must be taken every four hours around the clock in order to disclose the characteristic quotidian or double quotidian febrile pattern (Fig. 2). Typically, there are one or two daily temperature peaks above 102°F, occasionally even to hyperpyrexic levels (fever to 105°F) (6). Diurnal ranges are wide, often as much as 8°F or 9°F, so that both hyperpyrexia and normal or subnormal temperatures occur within the same day. The fever usually, but not always, responds to aspirin provided large quantities, up to as much as 130 mg/kg (1 gr/lb) daily, are given. If the critical daily quantity of aspirin is then reduced, even by as little as 150 mg, the fever recurs promptly (6, 7). Eventually the fever pattern may become relapsing or even periodic (6), at which time other typical features of JRA become manifest, thereby facilitating a correct diagnosis.

*Rash.* The rheumatoid rash develops in up to 90% of children with an acute febrile onset (8) (Fig. 1). It consists of macular or slightly maculopapular lesions, usually discrete but sometimes confluent, that are found on the trunk and extremities and occasionally about the neck and face. Rarely is the eruption pruritic.

While it may be persistent, more frequently the rash tends to be fleeting or evanescent, with migratory macules appearing briefly in the late afternoon

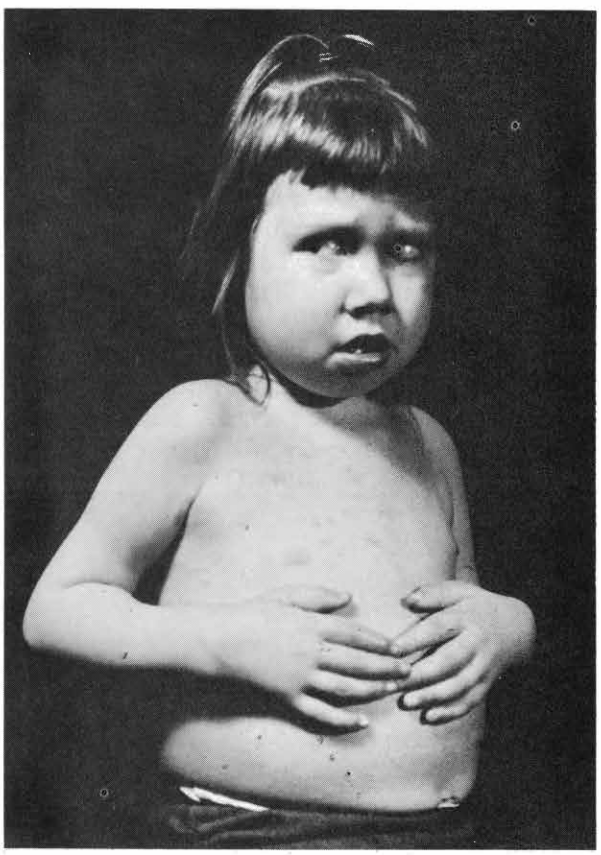

Fig. 1—The five-year-old girl above with acute febrile onset refuses to rotate her head because of cervical pain. Note typical anxious appearance, axillary prominence resulting from lymphadenopathy, symmetrical swelling of hand and wrist joints, and macular rash on the chest. (Reprinted by permission from *Med Clin N Amer* 25:567, 1968.)

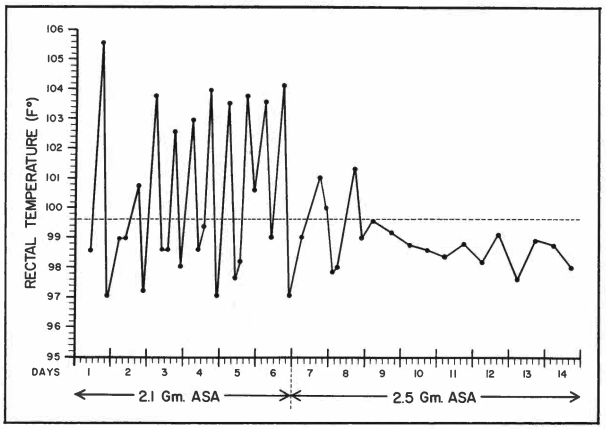


Fig. 2—The characteristic fever pattern of acute febrile onset, as shown above in a six-year-old boy, bears considerable diagnostic importance. High fever with its single and double daily peaks is suppressed only when the daily aspirin dosage is pushed to 110 mg/kg; patient's weight is 22.7 kg. (Reprinted by permission from *N Engl J Med* 276:11, 1967.)

or early evening, often in conjunction with fever spikes. The rash is most florid in areas where the skin has been rubbed or subjected to mild trauma, such as the light pressure of clothing. This manifestation is known as the Köbner phenomenon; it may be useful, diagnostically, when parents report rash that is not present at the time the child is being examined. The typical rash may be elicited by making scratch marks on the extremities or along the lower abdomen. Within several minutes, linear chains of isolated macules will appear that often persist for a day or two (Fig. 3).

Clearly, in these patients, it is the invariable combination of fever, rash, arthralgia, and other systemic features that leads one to an early diagnosis of acute febrile JRA. Otherwise, these patients are considered to have "fever of unknown origin." They will be hospitalized repeatedly, undergo exhaustive diagnostic workups, and receive needless courses of various antibiotics and even exploratory laparotomy. Differential diagnosis includes eliminating infection as well as other causes of high fever accompanied by rash and joint pain.

One of the most important disorders to rule out is systemic lupus erythematosus (SLE), which is unusual in a child younger than five years of age. Occasionally, the early skin lesions of SLE may resemble the rheumatoid rash, particularly when localized in the arms and trunk. Eventually, the rash of SLE takes on its typical *butterfly* distribution over the face and the diagnosis becomes apparent. Also, in SLE, the rash is not evanescent, is not timed to fever spikes, and does not produce an isomorphic response. Further, SLE may be confirmed by the presence of oral lesions, renal abnormalities, and LE cells. Finally, the absence of antinuclear antibodies virtually excludes a diagnosis of SLE.

Connective tissue disorders other than SLE must also be excluded. The rashes of Henoch-Schönlein (anaphylactoid) purpura, polyarteritis, and hypersensitivity angiitis are usually purpuric or ecchymotic. Also, each of these disorders is commonly associated with hypertension and renal manifestations which do not occur in JRA. In the child with arthritis and purpura, one must also suspect acute leukemia. Signs that suggest leukemia are severe anemia, leukopenia, and destructive lesions on x-rays of joints, each of which is distinctly unusual in the initial months of JRA (9).

**Polyarticular Onset.** This mode of onset, with arthritis of more than four joints, occurs in about half of all JRA patients. Most children appear ill and fail to grow. Rash, lymphadenopathy, and splenomegaly occur less frequently than in acute febrile onset, and the fever is low grade—peaking at 101-102°F once or twice daily. Polyarticular JRA is recognized easily when the pattern of joint involvement is generalized and symmetric and involves the hands (Fig. 4); however, when the arthritis is confined to large joints, is asymmetric, or is migratory, it may be confused with other

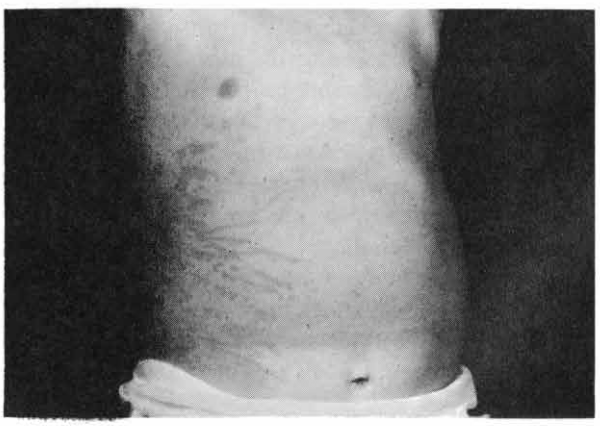

Fig. 3—Physician has evoked linear macules (Köbner phenomenon) by lightly scratching the patient's abdomen. (Reprinted by permission from *J Pediat* 72:611, 1968.)

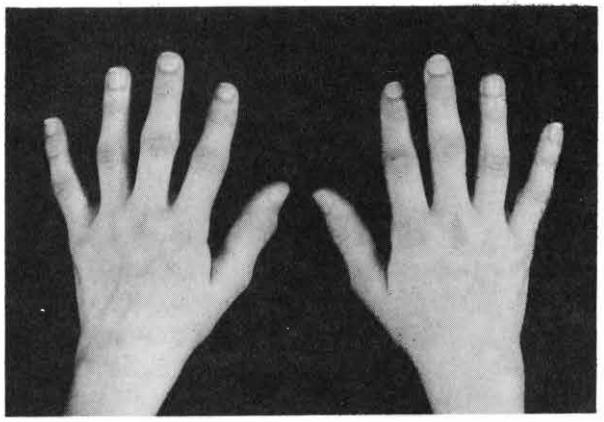

Fig. 4—Hands of a ten-year-old girl with polyarticular onset disclosing symmetrical swelling of proximal interphalangeal, metacarpophalangeal, and wrist joints. (Reprinted by permission from *Med Clin N Amer* 52:567, 1968.)

rheumatic disorders, particularly rheumatic fever (RF).

The individual macules of RF usually appear as open rings with distinct outer edges; there are only a few discrete macular rings with pale centers (Fig. 5). Typically, the erythema marginatum of RF extends centrifugally while the proximal skin returns to normal. It rarely lasts for more than a week or two, unlike the rash of JRA which persists for months.

Differential diagnosis is aided by close observation of the fever pattern; quotidian or double quotidian fevers suggest JRA, while remittent or sustained fevers point to RF. Several other features help to rule out RF. The most important include onset under four years of age, cervical involvement, a poor mucin clot on synovial fluid analysis, generalized lymphadenopathy, hepatosplenomegaly in the absence of cardiac failure, and arthritis lasting for more than 12 weeks.

Arthritis develops in 3% of all children who are vaccinated against rubella and involves primarily the knees or wrists. Developing within two-to-eight weeks after vaccination, the arthritis is self-limited, persisting for a few days to several weeks. The most important laboratory clue is a rising hemagglutination-inhibition antibody titer.

Another misdiagnosis is childhood dermatomyositis, primarily because the arthritis is so similar to that of JRA. Initially, loss of muscle strength is minimal and serum muscle enzyme levels may be normal while only arthritis predominates. Clues to an early diagnosis of dermatomyositis include a violaceous periorbital edema (heliotrope facies) and the presence of atrophic and scaly erythema of the skin over extensor surfaces of joints, particularly the knees, elbows, and hands.

**Monarticular Onset.** While the knee is the most common site of a monarticular onset (Fig. 6), the presentation may sometimes occur in other joints such as the ankle, elbow, wrist, or even a finger joint (10). Swelling, stiffness, and pain are usually minimal except when the hip is involved. Occasionally, painful tendinitis or bursitis, particularly of the heel, may be a presenting symptom. Symptoms or attention to the problem may be precipitated by trauma, a deceptive characteristic and a major pitfall in diagnosis of this mode of onset.

It is ironic that the mildest form of JRA, a monarticular onset, which comprises a third of all JRA patients, carries with it the serious threat of blindness from iridocyclitis (11). What makes this ocular manifestation particularly treacherous is that it is so often asymptomatic in its evolution, smoldering quietly for weeks or months until failing vision alone compels attention. It may be the initial manifestation of JRA or it may occur at any time in the course of the disease, even after the arthritis has remitted. If undetected and untreated, it may lead to blindness, primarily from band keratopathy and cataracts. While iridocylitis may occur in all children with JRA, those with monarticular onset are by far the most susceptible.

Except for the iridocyclitis, one cannot rely

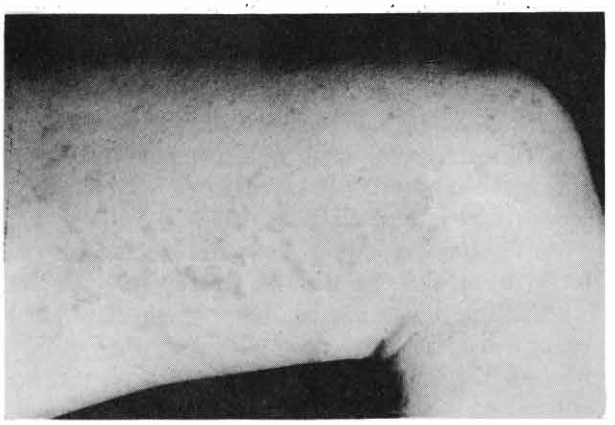

Fig. 5—In rheumatic fever, most macules appear as open rings with distinct outer borders and are larger than those observed in JRA. (Reprinted by permission from *J Pediat* 72:611, 1968.)

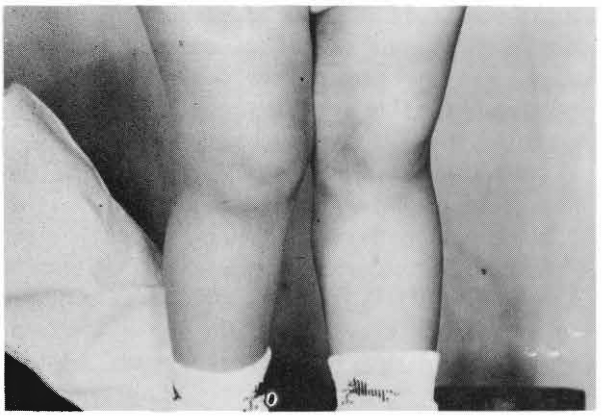

Fig. 6—Monarticular onset in a three-year-old girl with painless swelling of the right knee.

on systemic manifestations in this mode of onset. Lymphadenopathy and splenomegaly occur infrequently, while low-grade quotidian fever and rash are only occasionally present. Routine laboratory studies, such as the CBC and ESR, are frequently normal.

When one joint is involved, the single best test—if the disease is to be differentiated from acute infectious arthritis, which may rapidly destroy the joint—involves arthrocentesis and evaluating the synovial fluid. The first clues are provided by study of the gross appearance of the fluid. In JRA, the fluid will be clear-to-opalescent, in traumatic arthritis it may be clear-to-blood-tinged, while in infectious arthritis it will be cloudy or turbid. Examination of a drop of the fresh, uncentrifuged fluid under an ordinary microscope may reveal bacteria in infectious arthritis.

Next in order is inspection of the mucin clot. A few drops of synovial fluid are added to a small beaker containing about 10 ml of 5% acetic acid. If the sample is too small to allow this, the acetic acid can be drawn into the syringe, and even a slight amount of synovial fluid coating the syringe will suffice for the test. After allowing a minute for the clot to form, the container is shaken. A good clot forms a firm, ropy mass that does not fragment when shaken. A poor clot quickly flakes and shreds, clouding the solution. If the etiology of the arthritis is traumatic, the clot will be good; if rheumatoid, it will be good or poor; and if infectious, it will be poor.

The clinical laboratory is required for further synovianalysis. In traumatic involvement, the white cell count will be below 5,000, with fewer than 50% neutrophils; in JRA it will be between 15,000 and 25,000 and the neutrophils will range from 50-90%; in infectious arthritis, white cells will soar to counts of 50,000-100,000 and more than 90% will be neutrophils. Of particular interest are the paired determinations of serum and synovial fluid glucose levels; only in traumatic arthritis will these be about the same or show a disparity of less than 10 mg%. In JRA the difference will generally fall between 10-25 mg%, while in arthritis of infectious origin, it will usually be over 50 mg%

A negative tuberculin skin test usually rules out active tuberculous arthritis. If it is still necessary to pursue this possibility, synovial biopsy will generally show caseating granulomas and giant cells, while in JRA one will see nonspecific synovitis with hypertrophy, increased vascularity, and round-cell infiltration.

**Laboratory and X-Ray Aids.** Low-grade anemia and an elevated ESR are frequent, except in patients with a monarticular onset in whom values for hemoglobin, hematocrit, and the ESR are often normal. In acute febrile onset, there is a neutrophilic leukocytosis, usually between 20,000 and 30,000 cells, but sometimes as high as 50,000 cells/mm$^3$. A less striking leukocytosis occurs in a polyarticular onset, while white cell counts are often normal in a monarticular onset. Leukopenia rarely occurs in JRA; its presence should lead one to suspect leukemia or SLE.

The latex fixation test is positive in only 10-25% of children with JRA. Elevated titers are found primarily among children whose disease begins at 12-16 years of age. Antinuclear antibodies (ANA) are present in 10-30% of patients with JRA. Titers, however, are much lower than those found in children with SLE. Miller (12) has shown that the incidence of ANA is highest in girls and in patients under six years of age. ANA also seems to correlate with the presence of iridocyclitis (2). As for serum immunoglobulins, persistently elevated levels of IgG, IgA, and IgM are generally associated with an increased incidence of hip involvement and a poorer functional status. Serum electrophoresis may reveal low albumin and elevated $\beta$- and $\gamma$-globulins. It also serves to detect underlying hypogammaglobulinemia.

Antistreptolysin-O (ASO) titers, prolonged and moderately elevated, occur in about 30% of patients with JRA. The titers appear to be nonspecific and are also found in childhood tuberculosis, nephrosis,

and hepatitis (5). They can be inhibited by adding albumin to the test procedure, in contrast to specific ASO titers, which indicate recent infection with Group A β-hemolytic streptococcus. Intramuscular monthly injections of benzathine penicillin over a period of 12 months failed to lower titers of ASO in six of our patients with JRA, seemingly confirming the nonspecific nature of these titers (5).

Early x-ray findings are also nonspecific and include soft tissue swelling, early closure of epiphyses, and periosteal proliferation (5). Osseous erosions are only late findings, and their early presence should lead one to suspect leukemia or other forms of malignancy (9).

## COURSE OF DISEASE

The subsequent course of disease is largely determined by the mode of onset (1) (Table 2). Three patterns of disease course may evolve: polycyclic acute febrile, polyarthritis, and oligoarthritis (also known as pauciarticular arthritis).

Ten of our 20 patients with an acute febrile onset have had recurrent flare-ups of systemic features, primarily high fever and rash, and little or no arthritis—a disease course designated as *polycyclic acute febrile*. The number of acute febrile attacks has varied from one to as many as ten in a single year. None of these ten patients has ever developed chronic arthritis. The other ten patients developed *polyarthritis* or the simultaneous arthritis of more than four joints. This occurred either at the onset of disease or only after months-to-years of recurrent acute febrile attacks. One girl had periodic fever that recurred regularly every three months for as long as nine years (from age 3-12) before she developed polyarthritis (6).

Of the 32 patients with a monarticular onset, 22 became *oligoarthritic*, with chronic, often recurrent, arthritis of only one-to-four joints; the ten remaining children developed polyarthritis.

Children with a polyarticular onset remained polyarthritic. Altogether then, 68 patients (48 with a polyarticular onset, ten with an acute febrile onset, and ten with a monarticular onset) eventually developed polyarthritis (Table 2). The course of polyarthritis took two forms, one characterized by exacerbations and remissions (58 patients), the other by an unremitting and progressively downhill course (13 patients)—resulting in marked joint deformities and an enhanced susceptibility to secondary amyloidosis. Amyloidosis should be suspected when there is progressive hepatosplenomegaly or when proteinuria develops that is unrelated to gold therapy.

## MANAGEMENT

The aim of treatment is to provide a setting that will give the young patient a reasonably normal childhood. Management must include an active home program and regular follow-up care, because therapy may have to be changed at any time during the long course of the disease (13).

From the outset, the physician must recognize that he can only initiate and supervise therapy. The actual treatment will be given in the home, and the results will depend on establishing a working relationship with the parents. Therefore, the physician must educate and motivate the parents. He must teach them all about their child's disease—what they must do, and what they may expect. This is clearly the best way to reassure the parents and to allay their anxieties.

TABLE 2

THE ONSET, COURSE, AND OUTCOME OF 100 PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS OBSERVED FOR 15 YEARS*

| | | | | Outcome (%) After 15 Years | | |
|---|---|---|---|---|---|---|
| Modes of Onset | % | Course of Disease | % | Still Active | Classes III-IV | Iridocyclitis |
| Acute Febrile | 20 | Polycyclic AcFeb | 10 | 1 | 0 | 0 |
| Polyarticular | 48 | Polyarthritis | 68 | 28† | 13† | 2 |
| Monarticular | 32 | Oligoarthritis | 22 | 7 | 0 | 6‡ |

* During these 15 years, 88 of our 100 children were maintained only on aspirin. Only four children have received oral steroids for more than one year, two because of protracted iridocyclitis; eight are currently on gold therapy.

† Including three deaths, one from postsurgical sepsis, one from secondary amyloidosis, and one of suicide.

‡ Two children are blind in one eye.

**Drug Therapy.** *Salicylates.* While physical therapy is the most important part of home care, it can only be made possible by the use of antirheumatic drugs that reduce joint inflammation and increase mobility. Whatever the mode of onset, aspirin, in individualized doses, is the drug of choice. Active disease can be suppressed in most children by four-to-six daily doses, totaling 90-130 mg/kg (2/3-1 gr/lb) daily. Acute febrile disease requires the more frequent and higher doses.

Early signs of chronic salicylate intoxication can easily be overlooked. Parents must be instructed to watch for lethargy and episodic hyperpnea, changes that are especially important in a child who is too young to complain of tinnitus. When these symptoms occur, aspirin should be stopped for 24 hours, and then reinstituted at slightly lower doses.

*Adrenocorticosteroids.* These drugs are administered in heart failure due to myocarditis as well as in pericarditis, vasculitis, and protracted iridocyclitis. For short periods, they may also be given in acute febrile disease or to patients who either do not tolerate or who fail to respond to aspirin. Intra-articular injections of steroid may also prove beneficial, especially when one or two joints are so seriously inflamed that exercise and other rehabilitative efforts are being compromised.

*Chrysotherapy.* Children with polyarthritis who respond poorly to aspirin should be given a trial of gold therapy; however, only physicians experienced in its use and potentially serious side effects should prescribe and administer gold. Gold salts are injected intramuscularly at weekly intervals in a dose of 0.5-1 mg/kg. Complications are more frequent during the early months of therapy and in children less than six years old. Renal and hematopoietic side effects are potentially fatal, and it is, therefore, necessary to monitor the patients with weekly blood and urine tests. These tests must be evaluated before each injection.

*Other Drugs.* The antimalarial drugs are not recommended for routine use in children. Chloroquine is especially dangerous; the accidental ingestion of as little as one gram (four tablets) may cause rapid cardiorespiratory arrest. Serious toxic effects to phenylbutazone and oxyphenbutazone include hepatitis, thrombocytopenia, and agranulocytosis, which seem to occur more frequently in children than adults. For this reason, these drugs are currently contraindicated in children 14 years of age or under. So, too, is indomethacin. The place of immunosuppressive or cytotoxic agents has not yet been evaluated in JRA.

**Eye Care.** Susceptibility to iridocyclitis is enhanced in all patients with JRA. The recognition and therapy of iridocyclitis should be entrusted to an ophthalmologist. In those with minimal arthritis, the most susceptible group, slit-lamp examinations are required every three months, even if the arthritis is in remission. Patients who have had previous iridocyclitis should be examined on a monthly basis. All other JRA patients should be examined regularly by slit lamp at six-month intervals. Ophthalmologic screening should be routine until patients reach adulthood, at which time attacks tend to become acute and routine screening for silent iridocyclitis is no longer necessary.

**Supportive Care.** Appropriate rest, splinting, and exercise are fundamental to the prevention and correction of deformity. An increase in the hours of sleep at night and a nap during the day facilitate the resolution of synovial inflammation. Complete bed rest must be avoided, however, since this may cause undue flexion contractures and muscle atrophy.

Bivalved splints, made of plaster of paris or of plastic, are used to rest inflamed joints or to correct deformities. Traction, sandbags, or other means of keeping joints in proper alignment may be used in place of resting splints. For sustained deformities—a flexion contracture of a knee, for example—serial splinting may be useful. New bivalved splints are applied every one-to-two weeks as the range of motion improves. Splints may be removed daily to permit prescribed exercises and then replaced.

A physiatrist or physical therapist must teach the patient or parents a program of regular daily exercises that can be performed in the home. Daily activities, in addition to formal exercise, should be those that maintain strength and move joints primarily through motions of extension. Games and sports can help to achieve these goals, but those which involve sharp impact to the joints, such as basketball or football, must be avoided. Swimming is an excellent sport, since it promotes mainly extension-type movement and has the added advantage of the positive buoyancy of water. Keeping the child in school also assures that mental activities are maintained. Provisions must be made, however, to allow the patient more freedom than other children.

**Surgery.** Established deformities can be successfully corrected by a variety of procedures, even in

the presence of active disease. Early synovectomy, or the removal of granulation tissue early enough to prevent erosion of cartilage and bone, however, is an area of current controversy. The correct timing of the procedure and the proper selection of patients are the issues at the moment. Generally, children six years or younger are poor surgical risks because of their inability to cooperate fully with important postoperative measures.

## PROGNOSIS

Generally, the prognosis for children is quite favorable (1, 2). Of our 100 patients now observed prospectively for 15 years, 64 are in remission (Table 2)—they are not taking any drugs and have no evidence of active articular or systemic disease. All 64 patients are in functional classes I and II and therefore capable of all ordinary activity.

Active disease was present in 36 patients, including the three who died. Of the 36, 28 have had a course of polyarthritis. Only one of ten patients with a polycyclic acute febrile course and seven of 22 with oligoarthritis continue to be active, affirming the benign nature of these two patterns of disease course.

Only 13 patients are in the unfavorable American Rheumatism Association functional classes III and IV and are capable of little or no activity. Each has had a course of unremitting polyarthritis and ten have had progressive hip involvement. Three of these patients died, one of staphylococcal bacteremia following knee synovectomy, one from secondary amyloidosis, and the third of suicide. Permanent stunting of growth occurred in seven of these 13 patients, six of whom also had pronounced micrognathia and progressive cervical involvement.

One of our most striking observations is that chronic iridocyclitis appeared and recurred primarily in patients with the least amount of joint involvement (Table 2). Of the eight patients with iridocyclitis, six had oligoarthritis, two of whom lost vision in one eye. Iridocyclitis subsequently recurred in three of these six children and in two when their arthritis had been in remission for as long as four years.

## CONCLUSIONS

Varying degrees of systemic and articular involvement characterize the three modes of onset observed in JRA. Systemic features, notably high fever and rash, characterize an acute febrile onset which may be observed weeks, months, and even years before objective arthritis develops. In polyarticular onset, the arthritis predominates and is frequently generalized and symmetric, similar to adult RA. Monarticular onset, with arthritis confined to a single joint, is the mildest form; it poses, nevertheless, the major threat of potential blindness from chronic iridocyclitis.

Treating the patient with JRA is a long-range collaborative effort, the success of which will largely depend on early diagnosis along with home care and parental cooperation. For all modes of onset, and subsequently during active arthritis, aspirin continues to be the drug of choice. Management must include regular follow-up and comprehensive care to prevent joint deformity and blindness due to asymptomatic iridocyclitis. The prognosis is generally favorable, as gleaned from our 15-year prospective study of 100 patients, and this allows us to discard old fears that JRA is inevitably unremitting and largely intractable to treatment.

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# A Review of Some Aspects of L-Forms and Gonococci* **

CHARLES L. COOKE, M.D., BERNARD GERMAIN, M.D., BONNIE BALDUCCI, M.S., HARRY P. DALTON, Ph.D.

*From the Division of Connective Tissue Diseases, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

Systemic manifestations of gonococcal disease, such as arthritis, are often sterile on the usual culture methods used to grow gonococci. Allergic mechanisms have been invoked to explain this but with little evidence to support the concept (1–3). With the report by Holmes et al. (4), that L-forms of gonococci were isolated from joint fluid of a patient with gonococcal arthritis, we decided to investigate the possible role of L-forms in gonococcal disease.

**Biology of L-Forms of Bacteria.** Kleineberger in 1935 (5) first described L-form formation in *Streptobacillus moniliformis* organisms. L-forms of organisms are also known as protoplasts, variants, or spheroplasts. In protoplast formation, organisms lose their normal rigid cell walls and are able to survive, reproduce, and revert to the normal cell wall possessing parent forms. These features distinguish L-forms of bacteria from mycoplasmas, which never have rigid cell walls. Media, made hypertonic with sucrose, sodium chloride, or other things, are necessary to grow L-forms without lysing the cells and destroying them. Lacking cell walls, L-forms do not show up on the usual Gram's stain.

Numerous species of bacteria, including *E. coli*, staphylococci, enterococci, and certain fungi are capable of L-form formation (6). This phenomenon can be induced by the presence in hypertonic media of certain amino acids, some antibiotics, lysosomal enzymes, or the combination of complement and antibodies.

The question of pathogenicity of L-forms is far from answered. Work by Gutman et al. (7) clearly demonstrated that protoplast formation is a mechanism whereby organisms can persist in the urinary tract despite antibiotic therapy. Antibiotic therapy with ampicillin caused *Proteus mirabilis* organisms in their patient to revert to L-forms which are quite resistant to ampicillin. With cessation of therapy, the organism can revert to the parent form possessing a cell wall—thus assuring persistence of the infection.

Seven L-form media, the formulae of which have previously been published (8), were simultaneously inoculated with a recently isolated strain of *Neisseria gonorrheae*. In order to increase L-form colony recovery, one of the four cell wall antibiotics (ampicillin, benzathine penicillin, methicillin, or potassium penicillin G) was incorporated into the seven media. This comparison was repeated with 21 strains of gonorrheae and with each of the four antibiotics to give a total of 588 comparisons. There was a total of 187 cultures which demonstrate the presence of L-form cultures; however, three media accounted for 62% of the positive cultures. These three high recovery media were used, without antibiotics, in conjunction with chocolate and Thayer-Martin media, in two clinical studies designed to isolate L-forms or coccal forms of gonorrheae.

In the initial clinical study we cultured on high recovery media material from the urethral exudate of twelve patients with acute urethritis. None of these grew L-forms. In the second clinical study we

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cultured joint fluid from 17 patients with acute arthritis. Twelve of these had clinical features suggestive of gonococcal arthritis; again, no L-forms were grown. Five patients with either gout or osteoarthritis grew no organisms. Thus we were unable to demonstrate a role for L-forms in the pathogenesis of gonococcal disease.

That L-forms are present in some patients and stages of infection cannot be denied on the basis of Holmes' work; neither can it be denied on the basis of the work of Orcinnikov and Delektorskij (9) who have demonstrated, by use of electron microscopy, the presence of wall-less gonococcal cells in prostatic secretions. The possibility also exists, however, that gonococcal L-forms are transitory—that is, they are injured cells on the way to death and do not significantly enter into the pathogenic process. This possibility is reinforced by the present study and also by that of Orcinnikov and Delektorskij, because they were able to demonstrate gonococcal L-forms using electron microscopy; but in no case were they able to grow the organism.

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# Summary of Papers Presented at the 45th Annual McGuire Lecture Series* **

ROBERT IRBY, M.D., PROGRAM CHAIRMAN

*Professor of Medicine, Division of Connective Tissue Diseases, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond*

It is the purpose of this presentation to quickly review some of the important points of the papers which were presented at the 45th Annual McGuire Lecture Series on the subject of immunology and rheumatic diseases. The first paper was presented by Dr. Mullinax who gave a background on the historical aspects of immunology, beginning with Jenner and cowpox immunology and immunity to attenuated smallpox demonstrated in milk maids, continuing through the contributions of Pasteur, von Pirquet (on serum sickness), Bence Jones, and Hargraves (with the LE cell in 1948), down to modern immunology with antibody structure by Dr. Porter in 1960. Dr. Mullinax also briefly alluded to light chains and heavy chains, suggesting that there were two domains in light chains and four domains in heavy chains. (This subject was later presented in more detail by Dr. Franklin.) He then turned to the B cells and T cells, indicating that B cells were producers of humoral or circulating antibodies whereas the T cells dealt more with cellular immunity and delayed hypersensitivity. He also introduced the five types of immunoglobulins known at this time.

Dr. Horwitz described the "three R's" of delayed hypersensitivity. The three R's included recognition, response, and reaction, all of which contributed to the afferent as well as the efferent limb of the inflammatory reaction. He demonstrated scanning electron microscopic pictures of B lymphocytes showing rough contour in contrast to the T lymphocytes which had a smooth contour. He then mentioned how these reactions were studied through skin windows and demonstrated the rosette technique with lymphocytes and sheep red cells. The disorders of recognition were due to absence of T lymphocytes. The diseases associated with serum inhibition of the lymphocyte function included various hematologic disorders and solid tumors, SLE, TB, multiple sclerosis, hepatitis, and leprosy. He also stated that as far as the immunosuppressant effects of drugs on delayed hypersensitivity are concerned, cyclophosphamide had the greatest effect on the B lymphocytes whereas 6-MP had the greatest effect on the T lymphocytes.

Dr. Moncure talked about laboratory studies in the diagnosis of rheumatic diseases, covering the third component of complement and ANA titers. He described the various immunofluorescent patterns which we see in SLE—peripheral, homogenous, and nucleolar. About one-half of the patients with nucleolar patterns are found to have systemic sclerosis. He stated that perhaps the ANA test was more sensitive and less specific than the LE test. Patients with juvenile rheumatoid arthritis were not likely to develop positive rheumatoid factor tests.

Dr. Davis discussed immune complex reactions of systemic lupus erythematosus. He demonstrated very well the work of Dixon in the original study with iodinated bovine serum albumin and anti-BSA antibody formation, with incorporation of complement and deposition of complexes in the skin, joints, and heart in complex disease. He also mentioned the fact that rheumatoid factor added to the system would further precipitate the DNA–anti-DNA in the system, possibly indicating the role of rheumatoid factor in rheumatoid arthritis.

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Dr. Rothfield's subject was the diagnosis and treatment of lupus nephritis. She mentioned the various types of kidney lesions—focal, diffuse, and membranous—in SLE nephritis and demonstrated beautifully the immunofluorescent pattern in the various types. She pointed out that in order to study the uptake in the immunofluorescent pattern in patients who have membranous glomerulonephritis, an H & E section present with the immunofluorescent sample is needed. She also stated that CNS lupus may have complexes deposited in the cord. Elaborating further, Dr. Rothfield indicated that focal glomerulonephritis patients do not die of renal insufficiency and that hematuria correlated closely with activity in SLE. Patients with the diffuse lesions are nearly all dead within three years even with prednisone and they have the worst prognosis. All membranous glomerulonephritis patients have nephrotic syndrome and in children, particularly, SLE presents a poor prognosis. Dr. Rothfield's general measures for treatment included rest, avoiding sun light and immunizations, proper handling of infections, and avoiding pregnancy. The treatment for focal nephritis is steroids. Patients with membranous nephritis do not do well on steroids or immunosuppressive drugs such as Cytoxan® since this is not an inflammatory lesion and, therefore, would not necessarily respond readily to them. Diffuse SLE nephritis, of course, is the indication for the use of combined steroid and immunosuppressive therapy. The question is still uncertain as to whether or not this really will prolong the life of patients with systemic lupus.

Next, Dr. Ziff delivered the first McGuire Lecture entitled, "The Rheumatoid Synovium." He pointed out that in the rheumatoid synovium there is a proliferation of the lining layer as well as an infiltration of the deep layer. The two types of cells which are present are phagocytic and synthetic cells, the synthetic cells being the fluid producers. He also mentioned the presence of the IgG rheumatoid factor complexes which are present in the deep layer. The formation of inclusion bodies with release of lysosomal enzymes is thought to be one of the methods of inflammatory reaction. The second half of the cycle is the activation of complement complexes which cause chemotaxis. The A and B cells are the cells in the lining layer, whereas the deep layer contains deposits of IgG and IgM and deposits of C3 and C4. This IgG site was indicated as the site at which rheumatoid factor is formed.

Dr. Owen spoke about synovial fluid. He demonstrated the value of examining a regular wet-prep and how one can use compensated polarized microscopy to differentiate between calcium pyrophosphate crystals and gouty crystals. He stated that rheumatoid arthritis (RA) cells are not diagnostic of rheumatoid disease but can be quite helpful in diagnosis if present in the synovial fluid. He also discussed the benefit of determining synovial fluid complement since when elevated, it is an aid in differentiating Reiter's syndrome from some of the other nonspecific cases of inflammatory synovitis.

Dr. O'Brien followed with a discussion of some of the newer nonsteroidal anti-inflammatory drugs used in the treatment of rheumatoid arthritis. He began by covering the use of aspirin, gold, and antimalarials. He pointed out that the problem in drug evaluation is that in early studies, particularly with indomethacin, investigators were not geared up for control studies. We now feel that indomethacin for treatment of rheumatoid arthritis is not as good as it was at first thought to be. It may be superior to placebo; perhaps, it is equal to small doses of phenylbutazone. Dr. O'Brien maintained that a patient should not be placed on a drug study unless he was not doing well. He mentioned newer preparations under investigation, some of which have been discontinued because of fatal hepatitis. Some promise was shown for the proprionic acid derivatives, one of which was fenoprofen calcium which is less toxic than aspirin. In a dose of 400 mg per day, it is about as effective as 15 aspirin tablets daily without the side effects of aspirin. We have been using this drug on an experimental basis here for over a year now and find that it is very effective in the management of some cases of rheumatoid arthritis. He mentioned some of the other indole derivatives, all of which have somewhat the same effect as Indocin®.

On the second day of the symposium, Dr. Buckley spoke on the immunodeficiency diseases. She discussed agammaglobulinemia associated with arthritis and reported four patients who had hypogammaglobulinemia. The B cells in these cases are not able to produce IgG. She also discussed selective IgA deficiency. Some of these patients have ataxia telangiectasia and chronic, recurring infections, atopic disease, autoimmune disease, and diarrhea. The lymph node biopsies from these patients may show two different types of findings. The B cell deficits will show absence of the cortical

follicles in the lymph node, whereas the T cell deficits may show some derangement in the medulla of the lymph node. She demonstrated some of the ways of marking B and T cells by using the rosette method which Dr. Ziff discussed later. The two types of agammaglobulinemia were contrasted—the Bruton type and the other type in which the plasma cells did not secrete IgA. Patients with B cell deficits can live to adulthood but severe T cell deficit patients die within two years. This is the "Swiss" type of agammaglobulinemia. Bone marrow transplantation from a histocompatible sibling may be a life-saver and about half of those done have been successful. For treatment of B cell deficiency, she indicated that the simple use of γ-globulin is not sufficient, that all five classes of immunoglobulin need to be replaced by plasma infusions in lieu of injection of γ-globulin. Dr. Buckley encouraged the use of the "buddy system," siblings or friends who live in the same home who are HAA negative.

Dr. Calabro talked about juvenile rheumatoid arthritis, early diagnosis, management, and prognosis. He indicated that juvenile rheumatoid arthritis usually came on before the 16th year of life and pointed out the differences in the features of juvenile rheumatoid arthritis and adult rheumatoid arthritis. The major difference is that adults have rheumatoid factor present and juveniles, as a rule, do not. Also, subcutaneous nodules are more common in adults than in children and the fever, rash, and iritis are usually not present in adult rheumatoid arthritis but are present in juveniles. Dr. Calabro described three modes of onset: the acute febrile or Still's type, the polyarticular, where four or more joints are involved, and the monarticular, where only one joint is involved. Patients of the third group are more likely to develop chronic iridocyclitis and they get into real difficulty as time goes on. The fever is a "double" type of fever whereby the temperature at sometime during the day may go down to below normal. The fever usually responds very promptly to aspirin in large doses. The Köbner phenomenon, similar to an urticarial type of reaction, is one in which the rash can be brought out with a simple stroke on the skin. Although quite helpful, this is not specific for the rash of juvenile rheumatoid arthritis in that other types of rashes may behave similarly. The laboratory aids here are the presence of anemia, elevated ESR and lymphocytosis. These children frequently have positive ANA titer, may have positive ASO titer, and the x-ray will frequently show periostitis. In Dr. Calabro's 15-year follow-up, many of the monarticular patients went on to develop polyarticular states and the same was true for patients with the oligoarticular type. Treatment consisted of aspirin, gold salts, and steroids, with steroids particularly advisable in the acute febrile Still's patient where there was pericardial or eye involvement.

Dr. Baum discussed ankylosing spondylitis which he said was not a variant of rheumatoid arthritis. He stated criteria for diagnosis of ankylosing spondylitis and demonstrated certain feaures in the examination of a patient with ankylosing spondylitis. A very interesting x-ray finding, the syndesmophyte, was discussed—vertical syndesmophytes in spondylitis versus horizontal osteophytes in osteoarthritis. The various associated complications—aortitis, iritis, heart block, amyloidosis, subluxation, and pulmonary fibrosis—were discussed. The variants of ankylosing spondylitis—psoriatic, chronic ulcerative colitis, Whipple's, and Reiter's spondylitis—were discussed. The work that has been done, particularly by Dr. Schlosstein and Dr. Terasaki at Los Angeles on the transplant antigen W-27 locus, was summarized. Eighty-eight percent of patients with ankylosing spondylitis demonstrated this antigen as opposed to an 8% incidence in a random population. This certainly points to some genetic aspect in ankylosing spondylitis. It may also have something to do with the prognostic significance, particularly in children, if a patient possesses a W-27 antigen locus.

Dr. Franklin, "Mr. Immunoglobulin," talked about the G, A, M, D, and E myelomas and described the structure of the immunoglobulin molecule with the Fab fraction or the antigen binding site and the constant fraction (Fc) of the immunoglobulin. He listed the various H-chains and L-chains of IgG, A, M, D, and E and talked about the J-chain. By the time a diagnosis of multiple myeloma is made, the chances are that the patient has had the disease some 15 years prior to the time that bone lesions appear. The bone pain is usually the factor which brings the patient to the doctor. The other disorders, macroglobulinemia, H-chain disease, and the benign monoclonal gammopathy were discussed. Benign monoclonal gammopathy is present in about 3% of patients over 60 years of age. There are about 35 cases of γH-chain, about 50 cases of αH-chain, and only 7 cases of μH-chain disease reported. These are very rare, but they have certain characteristics of γH-chain myeloma and may simulate lymphoma.

Palatal and uvula swelling are two things which sometimes aid in making the diagnosis. Rarely do these patients have bone lesions and recurrent infection is usually the reason for seeking medical attention. These patients have a characteristic electrophoretic pattern. Patients with αH-chain disease usually have malignant lymphoma of the intestine and malabsorption. The αH-chain is produced in the plasma cells lining the intestine and may or may not be malignant. Of seven elderly patients with μ-chain disease, all had chronic lymphocytic leukemia. Lymphadenopathy is usually absent and these patients have hepatosplenomegaly and a high incidence of Bence Jones protein and κ-light chains in the urine. The finding that is very helpful in diagnosis of μ-chain is the presence of a large vacuolated plasma cell which can be found in the bone marrow. The bad effects caused by these proteins are the hyperviscosity syndrome, cryoglobulinemia and Bence Jones protein, the latter of which damages the kidney. They have bleeding and clotting disorders, infections, hemolytic anemias, and amyloidosis. Dr. Glenner and his group at NIH now have indicated that light chain fragments are present in amyloidosis.

Dr. Waller discussed the serum agglutinators and indicated that rheumatoid factors were IgM, whereas the serum agglutinators were antiglobulin antibodies or IgG which are a normal constituent of serum. These are closely associated with suppurative infection, particularly gram-positive organisms. The hidden sites on the Fab fragment are responsible for the formation of the serum agglutinators after papain or pepsin digestion. There are about 14.9% positive serum agglutinators in a hospital population as opposed to 0.5% in our arthritis clinic. Large abscesses usually have positive tests; subacute bacterial endocarditis may have positive tests for serum agglutinators.

Dr. Ziff presented the second McGuire Lecture on "Viruses and the Connective Tissue Diseases." Again he stated that T cell lymphoblasts in the presence of antigen can convert B cells into plasma cells to produce serum antibody and that virus infections would diminish T cell formation. Dr. Ziff discussed further the concept of T cell helper and T cell suppressor substances in which he indicated that viruses might be an enhancing mechanism to stimulate the B cells to produce autoantibody.

Dr. Bisno spoke on the subject of acute rheumatic fever and glomerulonephritis with streptococcal antigen. He did mention the fact that ASO is frequently elevated in throat infections and not necessarily elevated in pyoderma. The sequelae of the throat infections are more likely to produce acute rheumatic fever than acute glomerulonephritis, whereas the sequelae of the skin infections are more likely to produce acute glomerulonephritis. Dr. Bisno briefly discussed the streptozon test, on which he and his associates are now working, which may be very helpful in the diagnosis of streptococcal infection and sequelae.

Dr. Blaylock's lecture included a discussion of urticaria, hives, eczematous dermatitis and rheumatoid lesions. IgE is the immunoglobulin which is present in patients with urticaria, hay fever, asthma, and penicillin allergy. He noted that pemphigus vulgaris has 7S γG which is usually laid down between the cells and around the keratinocytes. Gamma G globulins will vary in pemphigus vulgaris, whereas in bullous pemphigus the serum globulins usually stay the same. IgG is usually deposited on the basement membrane similar to that in SLE. Dermatitis herpetiformis produces IgA on the basement membrane.

Dr. Cooke discussed methods of early diagnosis of gonococcal arthritis and the absolute necessity of instituting prompt treatment.

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*In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.*

*Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

*Usage in Pregnancy.* Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

*Acute CNS Manifestations.* Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

*Usage in Children.* Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

*Ambulatory Patients.* Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

**Precautions:** *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

*Impaired Renal or Hepatic Function.* Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

*Myocardial Infarction.* As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

*Biliary Surgery.* Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

*Patients Receiving Narcotics.* Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

*CNS Effect.* Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

**Adverse Reactions:** Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under **WARNINGS**); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, toxic epidermal necrolysis.

**Dosage and Administration:** *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.

*Children Under 12 Years of Age.* Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

*Duration of Therapy.* Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

**Overdosage:** *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition. *Treatment.* Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

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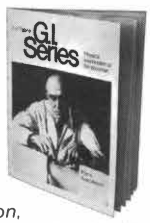
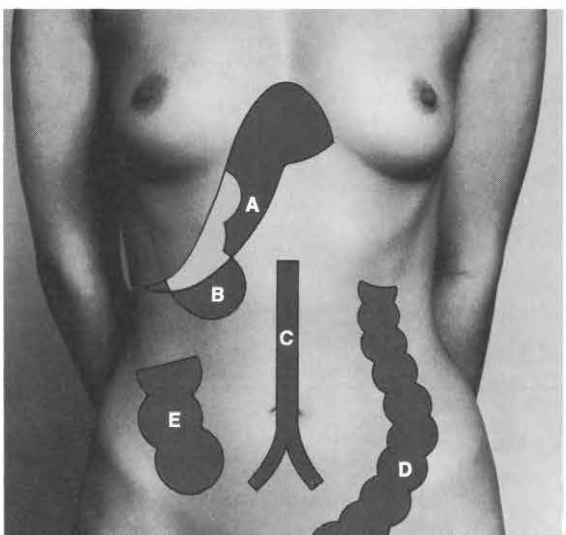



The A. H. Robins G.I. Series consists of six booklets, designed to provide a quick, yet comprehensive review of basic procedures and practices in G.I. medicine—with particular emphasis on the physical examination as performed in the office or at bedside. If you have teaching responsibilities, limited quantities are available: Part 1—*Inspection*, Part 2—*Palpation*, Part 3—*Percussion*, Part 4—*Auscultation*, Part 5—*Abdominal Pain* and Part 6—*Differential Diagnosis of Abdominal Disorders*. Write to: The Medical Department, A. H. Robins Company, 1407 Cummings Drive, Richmond, Virginia 23220.

***Normally palpable organs:*** the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B); the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.



**A service to medical education from A. H. Robins:**

Excerpted from Volume 2 of the **G.I. Series** on physical examination of the abdomen: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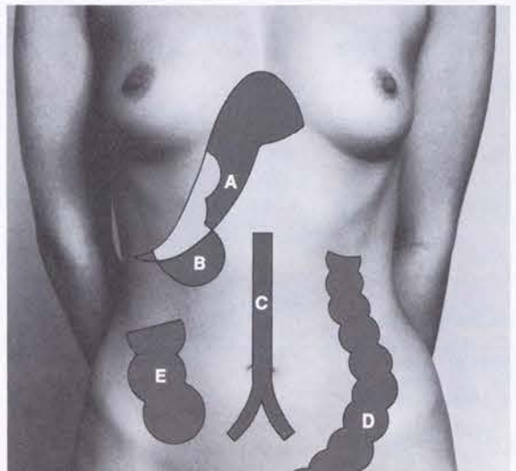


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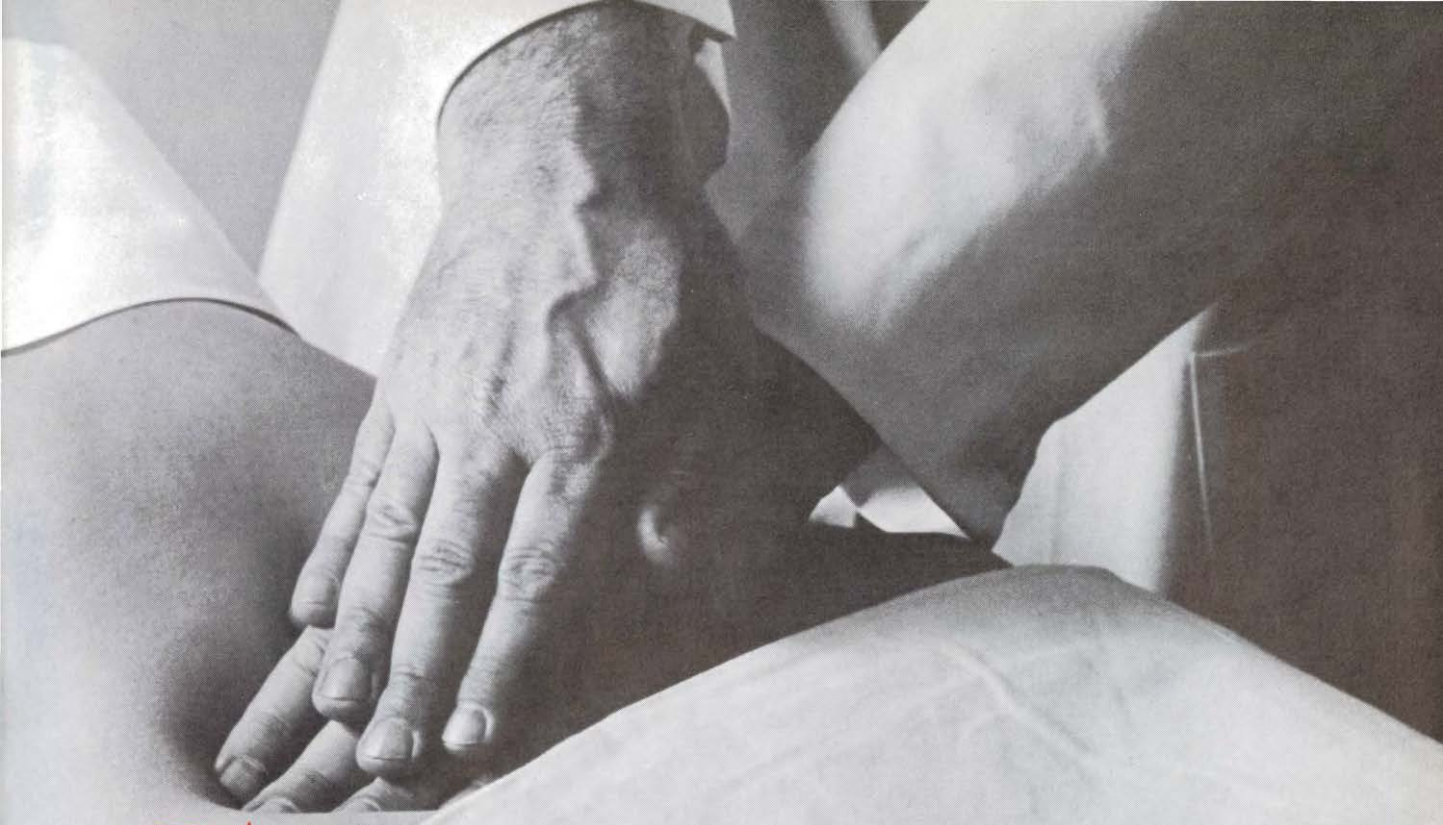

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**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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