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IMMUNOSUPPRESSIVE THERAPY OF ARTHRITIS

Parkland Memorial Hospital

Medical Grand Rounds

May 13, 1971

CORRECTION: The references in the text beginning with No. 29 on page 5 through ref. No. 69 refer to references in the Bibliography <u>one number greater</u>. For example, ref. 30 appears in the Bibliography as ref. 31.

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In spite of optimal management of patients with rheumatoid arthritis (RA), a small fraction remain clinically refractory to therapy. The relentless progression of the disease continues unabated to the point that it threatens vital function or even life. Before that time arrives the physician must weigh the relative risks of the uncontrolled disease against the potential danger of the use of steroids and/or immunosuppressive drugs.

The same may be said of the patient with active systemic lupus erythematosis (SLE), particularly if progressive renal disease is present.

CASE I. [redacted] This 54 WM developed iritis at age 30 and generalized polyarthritis at age 33. Synovial proliferation and joint destruction progressed slowly in spite of aspirin, phenylbutazone, gold and ACTH therapy. At ages 38 and 47, he underwent synovectomies of the left knee and right elbow with improvement in each lasting several years. After surgery at age 47, he was begun on 7.5 mg of prednisone/ day. Seven months later, he developed episcleritis, superficial corneal ulcerations and scleromalacia perforans, and 11 months later, he developed several areas of superficial gangrene of the fingertips and toes compatible with the arteritis of "malignant" rheumatoid arthritis. He had a right cervical sympathectomy, the prednisone was tapered, and he was again given ACTH and topical ophthalmic steroids with some improvement. At that time [redacted] 1965) RA latex fixation test was 3+ positive, Sensitized Sheep Cell Agglutination was positive at 1:224 dilution, and an upper GI series showed a lesser curvature gastric ulcer. The latter healed on antacid therapy.

By one year later ([redacted] 1966), his arthritis was so severe that he could not walk alone, and he again experienced superficial gangrene of several toes. He underwent a lumbar sympathectomy with improvement. He simultaneously developed periorbital edema and pain of the right eye. This proved to be severe episcleritis and inferior serous retinal detachment without retinal breaks in the right eye. The retinal detachment and episcleritis soon spread to the left eye, and was accompanied by crops of numerous subcutaneous nodules over pressure points. He resumed 10 mg/ day of prednisolone without significant improvement.

In [redacted] 1966, after he was legally blind (20/200 bilat.), he was begun on cyclophosphamide (Cytoxan) 100 mg alternating with 50 mg/day, and prednisolone was increased to 60 mg/day. The latter was slowly tapered to 27.5 mg/day over the next 6 weeks and the cyclophosphamide increased to 150 mg/day, then to 200 and later to 250 mg/day. The improvement in arthritis, eye findings and subcutaneous nodules was dramatic over the next 6 weeks. The retinae reattached spontaneously, uveal effusions cleared and the episcleritis and pain improved greatly. Prednisolone dosage was gradually cut to 7.5 mg/day. During the next 4½ years, his subcutaneous nodules completely disappeared, he has been fully ambulatory with only occasional joint pain, and although mild scleritis has persisted, vision has returned to near normal.

FIGURE 1.

IMMUNE ASPECTS OF RHEUMATOID ARTHRITIS

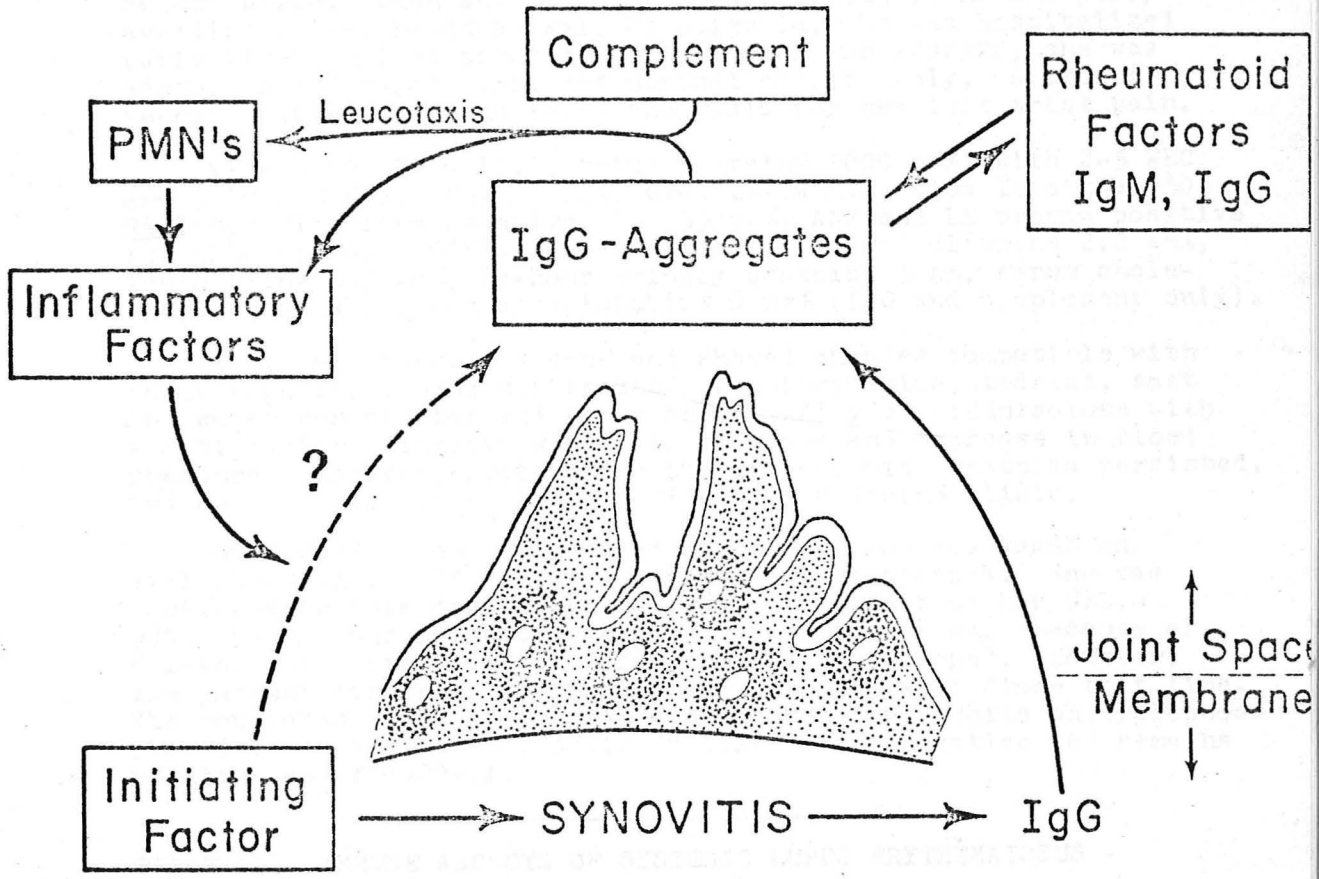

TABLE I. MECHANISMS OF INFLAMMATION IN RHEUMATOID ARTHRITIS

A. Immunological phenomena	
1. Circulating antibody (Ref. 1,2) (Lymphocytes and plasma cells)	γ-Globulin aggregates Complement fixation (Ref. 3,4,5)
2. Delayed hypersensitivity (Ref. 6) (Lymphocytes)	Lymphocytotoxic factors (Ref. 7), Macrophage migration inhibitory factors (Ref. 8)
B. Secondary phenomena	
1. Pannus formation (Macrophages, fibroblasts and granulation tissue)	Lysosomal enzymes (Ref. 9) Collagenase (Ref. 10)
2. Interruption of normal joint metabolism (Ref. 11)	Decreased hyaluronate and cartilage synthesis (Ref. 12)

CASE II. [redacted] This 29 NF was entirely well until [redacted] 1970, when she developed headaches followed 2 weeks later by bilateral ankle edema, arthritis of her left wrist and darkening of her urine. When she also noted periorbital edema and puffy swelling of her hands as well as oliguria, she was hospitalized ([redacted] 1970). Blood pressure on admission was 220/120, she was edematous and x-ray confirmed minimal cardiomegaly. A stenosing tenosynovitis was found to be the basis for her left wrist pain.

WBC= 5900, Hgb= 11.0, urine protein= 1000 mg%, with 2-5 WBC and 5-10 RBC/HPF, BUN= 26 mg%, Creat.=1.9 mg%, ASO= less than 50, RA latex fixation= negative, C3= 55 mg%, ANF and LE preps= positive x2, EKG= normal, protein electrophoresis showed albumin= 2.2 gm%, γ-globulin= 1.0 gm%, 24-hour urinary protein= 5 gm, serum cholesterol= normal, serum cryoglobulin= 6 mg% (IgG and complement only).

A kidney biopsy was done and showed changes compatible with lupus nephritis. She was treated with furosemide, bedrest, salt and water restriction and begun on 60 mg/day of prednisolone with a satisfactory diuresis with loss of edema and decrease in blood pressure. However, proteinuria and microscopic hematuria persisted, and she was discharged to be followed in Medicine Clinic.

On [redacted]-70 when C3 remained at 53 mg%, she was begun on cyclophosphamide 100 mg/day and prednisolone stopped. She was continued on this dose until [redacted]-70, at which time her WBC = 3800 and 24-hour urine proteinhad dropped to 1.8 gm. Because of a laboratory error, the cyclophosphamide was stopped. However, the patient continued to improve and has done well since that time. She now takes 25 mg of Cytoxan every other day. While on cyclophosphamide, her antinuclear antibody test became negative and remains negative as of [redacted]-71.

TABLE II. IMMUNE ASPECTS OF SYSTEMIC LUPUS ERYTHEMATOSUS

1. Diffuse hyperglobulinemia with a variety of autoantibodies against DNA, other cell components, and circulating blood elements (Ref. 13, 14, 15).
2. Immune complexes circulating in the blood and deposited in the walls of blood vessels and along the basement membrane of the renal glomerulus, skin, brain, lung and other tissues (Ref. 16, 17, 18, 19).
3. Lowered serum complement levels (Clq,C3,2,4) which correlates directly with the intensity of disease activity (Ref. 20, 21).
4. Immunoglobulin synthesis by circulating peripheral blood lymphocytes (Ref. 22) several times greater than normal.
5. Decreased circulating antibody response to some antigens (Ref. 23) and increased responses to others (Ref. 24).
6. Improvement following development of Hodgkin's disease(Ref. 25). (Suggesting a major role of delayed hypersensitivity in pathogenesis?)

TABLE III. CHANGES IN THE KIDNEY GLOMERULUS IN SLE
(from Heptinstall, Ref. 26)

Finding	Comment
*1. Localized areas of cellular proliferation usually with some underlying necrosis. Mesangial deposits on electron microscopy.	Early lesion, often reversible with appropriate steroid or immunosuppressive therapy.
*2. Basement membrane thickening-capillary wire loops. Irregular subendothelial deposits on EM.	May be found as an isolated lesion. May be only partially reversible by therapy.
*3. Intracapillary hyaline thrombi.	Fibrin with occasional nuclear material (hematoxylin bodies).
4. Crescent formation by proliferation of cells lining Bowman's capsule.	Infrequent.
5. Glomerular scarring.	Irreversible, end-stage obliteration of glomeruli.

*Very frequent

Steroids and immunosuppressive drugs exert significant anti-inflammatory effects by altering the release, the cellular function, and the rate of cell division of macrophages and polymorphonuclear leukocytes (Ref. 27, 28, 29). Some of this anti-inflammatory action is unrelated to their direct effects on the lymphocyte or lymphoid organs. However, some of the cells responsible for delayed hypersensitivity and the formation of circulating antibody are susceptible to the action of these agents.

FIGURE 2. CELLULAR BASIS OF THE IMMUNE RESPONSE

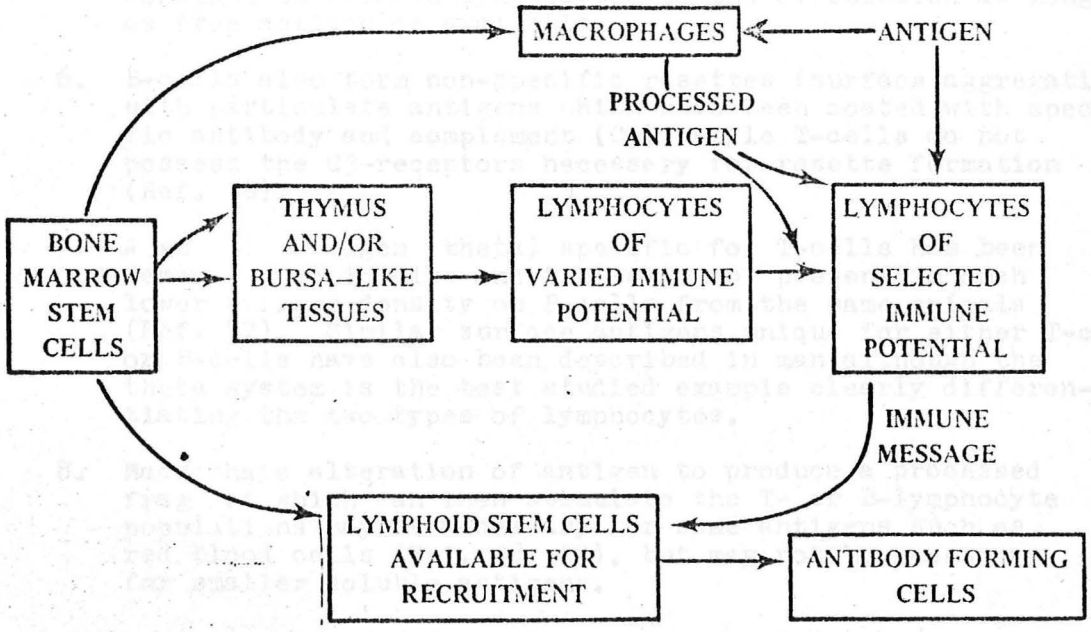

TABLE IV. EVIDENCE FOR THE TWO-CELL SYSTEM OF THE IMMUNE RESPONSE

1. Neonatally thymectomized and irradiated mice may be selectively repopulated with inbred thymus or bone marrow lymphocytes or both. Only those animals receiving both types of lymphocytes are capable of significant antibody formation after antigen stimulation with sheep red blood cells (Ref. 29).

2. Genetically-tagged bone marrow lymphocytes may be shown to contribute the antibody forming plasma cells even though these cells require thymus lymphocytes for recognition of the antigen (Ref. 30).

3. Thymus lymphocytes only carry the ability to cause delayed hypersensitivity and homograft rejection as illustrated by the defect in children with thymic aplasia --DiJorge syndrome-- (Ref. 31).

4. Both cell types carry receptors on their surfaces, probably a portion, or the complete antibody molecule specific for the antigen to which that cell can respond (Ref. 33, 34). However, the thymus population recognizes one portion of a complex antigen molecule -- carrier portion--, and the bone marrow-derived lymphocyte, a completely different portion -- haptenic portion -- (Ref. 35).

5. The sensitized thymus-derived (T-cell) lymphocyte is stimulated to divide by contact with antigen, but the sensitized bone marrow-derived (B-cell) lymphocyte does not divide after antigen exposure (Ref. 35). Presumably the B-cell merely differentiates to a plasma cell at the local site of the antigen. Antigen-induced stimuli to the bone marrow continue to release lymphocytes to the circulation as long as free antigen is available.

6. B-cells also form non-specific rosettes (surface aggregation) with particulate antigens which have been coated with specific antibody and complement (C3), while T-cells do not possess the C3-receptors necessary for rosette formation (Ref. 36).

7. A surface antigen (theta) specific for T-cells has been demonstrated in mice and is lacking or present in much lower surface density on B-cells from the same animals (Ref. 37). Similar surface antigens unique for either T-cells or B-cells have also been described in man although the theta system is the best studied example clearly differentiating the two types of lymphocytes.

8. Macrophage alteration of antigen to produce a processed fragment which can then stimulate the T- or B-lymphocyte populations may be necessary for some antigens such as red blood cells (Ref. 38, 39), but may not be necessary for smaller soluble antigens.

TABLE V. IMMUNOSUPPRESSIVE AGENTS USED IN HUMAN DISEASE
(Modified from Harris & Sinkovics, Ref. 40)

Alkylating agents

Nitrogen mustard (mechlorethamine)
Cyclophosphamide (Ref. 41, 42)
Chlorambucil

Antimetabolites

Purine analogues
6-mercaptopurine (Ref. 43, 44)
Azathioprine
Thioguanine
Cytosine arabinoside
Pyrimidine analogues
5-Fluorouracil
Folic acid analogues
Methotrexate (Amethopterin)(Ref. 45)

Adrenal Steroids

Prednisolone (Ref. 46)

Plant alkaloids

Vincaleukoblastine
Vincristine

Antibiotics

Chloramphenicol
Actinomycin D

Amino acid antagonists

Glutamine
Dauzomycin A
Asparagine
L-Asparaginase (Ref. 47)

Anti-lymphocyte globulin (Ref. 48)

CYCLOPHOSPHAMIDE (CYTOXAN) THERAPY OF RHEUMATOID ARTHRITIS

A thorough, long-term study of the effect of cyclophosphamide treatment of 38 patients with severe, otherwise medically resistant rheumatoid arthritis was carried out by Fosdick et al (Ref. 49). Their excellent results published in 1968 showed 75% of their patients had improved significantly, and encouraged the American Rheumatism Association to sponsor a double-blind trial utilizing a high dose (100-150 mg/day) and a low dose (2 mg/day) groups (Ref. 50). This trial involving 59 patients completely confirmed Fosdick and his coworkers' results. The details of the ARA study are presented below in tabular form.

In addition, other studies of single (Ref. 51) or multiple patients (Ref. 52) have obtained similar impressive results in persons with very severe rheumatoid arthritis. Often an association with depressed immunoglobulin levels was seen in those patients showing the greatest clinical response (Ref. 51, 52).

TABLE VI. ARA-CYTOXAN TRIAL FIFTY-NINE PATIENTS ADMITTED

High Dose (HD): 25 Low Dose (LD): 34
Males 17 Females 42
Age of entry: Median = 51 yrs (25-74 yrs)
Disease duration: Median 7.5 yrs (2-45 yrs)
Rheumatoid Factor: SSCA Positive 95%

TABLE VII. ARA-CYTOXAN TRIAL HD-LD DIFFERENCES IN MEDIAN CHANGE IN MEASURES OF DISEASE ACTIVITY BY 8 WEEK PERIODS

	Period 1	2	3	4
Morning Stiffness (hours)	0.50	0.33	0.25	0.0
Grip Strength (mm Hg)	11.2	4.4	0.6	2.6
No. of Painful Joints	5.0	1.5	1.0	1.0
No. of Swollen Joints	1.0	0.5	2.5	4.5
50 foot walk (secs)	1.0	0.4*	0.1	0.6
ESR - Westergren (-mm/hr)	8.0	3.0*	3.5*	6.0

* Negative difference, ie, LD better than HD group.

TABLE VIII. ARA-CYTOXAN TRIAL BLINDFOLD HAND X-RAY COMPARISON (WEEK 0 VS WEEK 32)

	Total patients	New or Worse Erosions	
		No. of Patients	No. of Lesions
High Dose	18	1	3
Low Dose	24	9	39

TABLE IX. ARA - CYTOXAN TRIAL SIGNIFICANT CHANGE OF TITER IN SSCA

SSCA Titer	No. of Patients High Dose	Low Dose
Unchanged	11	20
Increased	1	4
Decreased	7	3
Total	19	27

TABLE X. ARA-CYTOXAN TRIAL UNTOWARD EVENTS

	High Dose	Low Dose
Total Patients	20	28
Hemorrhagic cystitis	2	0
Dysuria & hematuria	7	0
Herpes zoster	1*	0
Nausea & vomiting 2x or more	9	9
Diarrhea 2x or more	3	4
Major hair loss 2x or more	7	2

*An additional patient was also afflicted with Herpes zoster and withdrew from the study.

TABLE XI. ARA-CYTOXAN TRIAL ELEVEN (OF 59) PATIENTS WITHDRAWN

	High Dose	Low Dose
Gastrointestinal Upset	3*	2
Renal amyloidosis recognized	1	1
Herpes zoster	1	0
Poor response to drug	0	3
Total	5	6

*One also had alopecia and stomatitis.

TABLE XII. GENERAL ARTHRITIS CLINIC EXPERIENCE WITH IMMUNOGLOBULIN CHANGES IN NINE PATIENTS WITH RA TREATED WITH CYTOXAN (Ref. 52)

50% Fall in total joint score occurring at 2 to 6 weeks	8
Decrease in Total γ-Globulin (paper electrophoresis)	6
Decrease in IgG*	7
Decrease in IgM*	5
Decrease in IgA*	1

*Measured by radial diffusion in agar.

Other alkylating agents: thiotepa (Ref. 53) and nitrogen mustard (Ref. 54) given intra-articularly appear to be of limited value. Chlorambucil (Ref. 55) produces clinical improvement similar to cyclophosphamide. Azathioprine and 6-mercaptopurine have usually produced dangerous bone marrow toxicity when used in RA (Ref. 56,57).

IMMUNOSUPPRESSIVE THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Patients with SLE who have progressive renal disease should be treated initially with high doses of prednisolone, possibly on an alternate-day schedule (Ref. 58). However, those who prove refractory to steroid therapy or who develop undue side effects from their treatment whould be considered for supplemental immunosuppressive therapy (Ref. 59).

Unfortunately no properly controlled evaluation of the effect of immunosuppressive drugs has been done in SLE in man, and the confusion about their therapeutic value present in the medical literature is considerable. However, the analogous disease to SLE in the NZB/NZW mouse has identical renal changes to those found in SLE in man, and several excellent controlled studies of these agents have been done in the mouse SLE disease (Ref. 60, 61, 62). These all clearly demonstrate the therapeutic value of cyclophosphamide in arresting advance of the renal disease and reversing certain features of it to normal if the drug is given sufficiently early in the course of the disease. Uncontrolled human studies with cyclophosphamide support this result obtained in the controlled animal experiments (Ref. 63, 64).

Results with azathioprine, 6-mercaptopurine and chlorambucil are less impressive, but these agents are also felt to alter the course of SLE renal disease in some patients (Ref. 65-69), particularly when given along with steroids.

TABLE XIII. MECHANISMS BY WHICH STEROIDS AFFECT INFLAMMATION

1. Block "effector" phase of delayed hypersensitivity (Cohen and Feldman – 1970).
2. Lyse lymphocytes, particularly those of thymic origin (Wira and Munck – 1970).
3. Alter intracellular effects of lysosomal enzymes on lysis of PMN's and macrophages.
4. Alter arteriolar tone – may decrease vasodilation and edema formation indirectly.
5. Probably have little effect on circulating antibody levels except at very high doses.

TABLE XIV. SIDE EFFECTS OF STEROIDS IN MAN

1. Enhance in vivo inactivation of vitamin D (Osteoporosis).
2. Promote gluconeogenesis and block peripheral glucose utilization (Diabetes).
3. Facilitate vasoconstriction (Hypertension).
4. Inhibit growth hormone release (Dwarfism).
5. Decrease killing of phagacytosed bacteria by PMN's (Infection).
6. Increase gastric acid secretion (Peptic ulcer).
7. Lysis of thymus--derived lymphocytes (Lymphocytopenia).

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