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Parkland Memorial Hospital

Medical Grand Rounds

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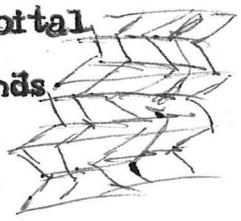

Rheumatic Fever

A wealth of data accumulated in the last 50 years has established the etiologic relationship of the group A streptococcus to rheumatic fever. We accept the fact that all rheumatic fever attacks follow infection with any of the 50-odd types of group A streptococcus but cannot fully explain why only 3% or less of streptococcal infections are followed by rheumatic fever, or why only certain patients have carditis or rheumatic heart disease.

Current Concepts of Etiology and Pathogenesis.

A. Heredity

Concordance of rheumatic fever in homozygous twins is no greater than that observed in tuberculosis or poliomyelitis. Data obtained in a study of 38 pairs of monozygotic and dizygotic twins was consistent with, but did not prove the etiologic role of genetic factors. Less than one fifth of the monozygotic twin pairs were definitely concordant. (See case report 1)

( ) (1) Taranta, A., Torosdag, S., Uchida, I., BULL. RHEUM. DIS. 10:193, 1959.

There is no convincing correlation between rheumatic fever and the ABO blood groups but there does appear to be a higher incidence in rheumatic fever of non-secretors of ABO substances in saliva - 28.9%:22.9%.

(2) Glynn, A.A., Glynn, L. E., Holborow, E.J. Secretion of blood-group substances in rheumatic fever. BRIT. MED. J. 2:266, 1959.

(3) Buckwalter, J. A., Naifeh, G.S., Auer, J.E. Rheumatic fever and the blood groups. BRIT. MED. J. 2:1023, 1962.

B. Epidemiologic.

The attack rates of both primary and secondary rheumatic fever are related to the magnitude of the immune response to streptococcal infection and at least in primary A.R.F. to duration of convalescent throat carriage. These conditions exist in epidemics. Variables in the host that influence the attack rate in secondary R.F. include the presence or absence of R.H.D., duration from last attack and number of previous attacks. (See Tables 1 and 2)

(4) Stollerman, G. H. Factors determining the attack rate of rheumatic fever. J.A.M.A., 177:823, 1961.

(5) Taranta, A. Factors associated with the rheumatic fever attack rate following streptococcal infections. ARTH. AND RHEUM. 4:303, 1961.

It has been suggested (Ref. 55 and 56) that repeated closely spaced infections are conducive to rheumatic fever. Two more recent studies cast doubt on this.

(6) Stetson, C. A. The relation of antibody response to rheumatic fever, in Streptococcal Infections, M. McCarty, Editor, New York, Columbia University Press, 1954.

(7) Taranta, A., Feinstein, A. R., Wood, H. F., Simpson, R. Relationship of rheumatic fever recurrence rate to clinical features in the patients. CIRCULATION, 22:821, 1960.

C. Bacteriologic and Immunologic

The streptococcus and its products have been extensively studied. Immunoelectrophoretic techniques have demonstrated the presence of at least 20 extracellular group A antigens. Normal

and particularly rheumatic fever sera are very rich in precipitating antibodies to non-type-specific extracellular but not to cellular antigens.

(8) Halbert, S. P., Keatinge, S.L. The analysis of streptococcal infections VI. Immunoelectrophoretic observations on extracellular antigens detectable with human antibodies, J.E.M. 113:1013, 1961.

The group A streptococcal wall has 3 layers: - a protein layer on the surface, containing the M protein which determines virulence and type-specificity, a middle group-specific carbohydrate layer and an inner mucopeptide layer which represents the rigid structural component of the wall.

(9) Krause, R. M., McCarty, M. Studies on the chemical structure of the streptococcal cell wall I. J.E.M. 114:127, 1961.

(10) II. J.E.M., 115:49, 1962.

Antibodies to M protein can be detected by the bactericidal test (Ref. 57), and I^{131} labelling technique (Ref. 62) and the antigen localized by means of a fluorescent antibody (Ref. 60). M protein enhances virulence by impeding phagocytosis.

(11) Kaplan, M. H. Localization of streptococcal antigens in tissues. I. J.E.M. 107:341, 1958.

(12) Lancefield, R. C. Current knowledge of type-specific M antigens of group A streptococci. J. IMMUNOL. 89:307, 1962.

Four enzymes which hydrolyze DNA have been identified in association with gr. A. streptococci. These are DNAses A, B, C, & D. DNAse B is produced in largest quantity and the anti-DNAse B titer is a useful test when the ASO titer is borderline or low.

The titer remains elevated for a longer period than the ASO.

(13) Ayoub, E.M., Wannamaker, L. W. Evaluation of the streptococcal desoxyribonuclease B and diphosphopyridine nucleotidase antibody tests in acute rheumatic fever and acute glomerulonephritis. PEDIATRICS. 29:527, 1962.

Some suggestive but unconfirmed studies have shown that the injection into rabbits of a complex of C polysaccharide of gr. A streptococci produces tissue changes probably toxic in nature.

(14) Schwab, J.H., Cromartie, W. J. Studies on a toxic cellular component of group A streptococci. J. BACT. 74:673, 1957. and

(15) FED. PROC. 19:144, 1960.

Cardiac lesions, especially of myofibers, resulting from repeated focal streptococcal infections and resembling the lesions in rheumatic carditis have been described.

(16) Murphy, G. E. Nature of rheumatic heart disease. MEDICINE 39:1960.

This author considers that Aschoff bodies are lesions of cardiac (striated) myo-fibers. Not all pathologists agree.

The concepts of "hypersensitivity" and "auto-immunity" have received increasing attention. Antibodies (both 7 & 19S) to heart tissue have been demonstrated by a number of investigators (See Table 3). We (Ref. 72) have shown a correlation between the presence of carditis and these serum factors (63% incidence in carditis).

More recently, group A streptococci of several strains have

been found to contain an antigenic component in the cell wall which is cross-reactive with antigen in myocardium. It has the properties of a protein, and is associated with M protein although not identical.

(17) Kaplan, M. H., Meyeserian, M. An immunological cross-reaction between group-A streptococcal cells and human heart tissue. LANCET, April 7, 1962.

There has been so far, little success in the production of experimental cardiac lesions by injection of heart tissue. A good review of this aspect is:

(18) Kaplan, M. H. The concept of autoantibodies in rheumatic fever and in the postcomissurotomy state. ANN. N. Y. Ac. Sc. 86:974, 1960.

Current Concepts - Clinical.

A. Diagnostic

More emphasis is now placed upon the diagnosis of antecedent streptococcal infection especially as up to 50% of patients may lack a history of pharyngitis. If the ASO titer is not raised-the performance of at least one of the following tests should show an elevated titer in 90-95% of patients:-antihyaluronidase (AH), antistreptokinase (ASK), anti-DPNase and anti-DNASes. The direct fluorescent antibody technique is a more sensitive and rapid method than culture for detecting organisms in throat smears.

(19) Halperen, S., Donaldson, P., Sulkin, S. E. Identification of streptococci in bacterial mixtures and clinical specimens with

fluorescent antibody. J. BACT. 76:223, 1958.

(20) Warfield, M. A., Page, R. H., Zuelzer, W. W., Stulberg, C. S. Identification of gr. A streptococci in throat smears. AM. J. DIS. CHILD. 101:160, 1961.

New methods of culturing streptococci have been described.

(21) Hollinger, N. F., Rantz, L. In pursuit of the streptococcus, newer techniques for their recovery and identification, and clinical implications. PEDIATRICS. 24:1112, 1959.

If the patient has a proven strept. infection, the next problem is to diagnose A.R.F. The modified Jones Criteria (Tables 4 and 5) demand at least 2 of the 5 major or one major and 2 minor criteria. Remember that in adults over 25, chorea, nodules and erythema marginatum are rare, there are varied causes of arthritis and carditis may be difficult to diagnose.

(22) Pader, E., Elster, S. K. Studies of acute rheumatic fever in the adult. AM. J. MED. 26:424, 1959.

(23) Friedberg, C. K. Rheumatic fever in the adult, criteria and implications. CIRC. 19:161, 1959.

The criteria may not be helpful either in children under 5.

(24) Turner, J. S., Doff, S. D. Rheumatic fever below the age of five. J. FLORIDA MED. ASS. 45:1416, 1959.

It would seem wise to qualify the diagnosis of rheumatic fever with statements such as "with polyarthritis only" "with carditis", "with carditis and CHF" because the prognosis differs according to the presence and severity of heart involvement. (See Table 6)

(25) The evolution of rheumatic heart disease in children. Five year report of a cooperative clinical trial of ACTH, cortisone and aspirin. CIRC. 22:503, 1960.

(26) Feinstein, A. R., Di Massa, R. Prognostic significance of valvular involvement in acute rheumatic fever. N. ENG. J. MED. 260:1001, 1959.

It is now realized that strict criteria must be applied in evaluating carditis. Prolonged PR intervals and grade I and II systolic murmurs no longer spell carditis. In patients with recurrent attacks a consideration of the "true to type" recurrences may be helpful (Ref. 81) (See case report 2).

Two very instructive articles dealing with this aspect are:-

(27) Castle, R. F., Craige, E. Auscultation of the heart in infants and children. SUPP. TO PEDIATRICS 26:511, 1960.

(28) Feinstein, A. R. The stethoscope: a source of diagnostic aid and conceptual errors in rheumatic heart disease. J. CH. DIS. 11:91, 1960.

The high frequency of heart involvement in patients with multiple attacks is open to differing interpretations. Taranta (1962) has suggested that these patients have an increased tendency to recurrences.

B. Other clinical aspects given recent wider recognition include:-

The Rebound Phenomenon-occurs in first 2 months after end of therapy-usually within first 2 weeks.

1) Laboratory Rebound-manifested by abnormalities in acute phase reactants, occurs frequently, sometimes recurs after initial cessation, has no clinical effects and subsides spontaneously.

2) Clinical Rebound-manifested by fever, tachycardia, joint

symptoms, new heart signs: is related to severity of original attack and more likely to occur after therapy with steroids than salicylates (see case report 3).

(29) Elster, S. K., Pader, E. Studies on acute rheumatic fever in the adult: II The rebound phenomenon. ANN. INT. MED. 51: 339, 1959.

(30) Feinstein, A. R., Spagnuolo, M., Gill, F. R. The rebound phenomenon in acute rheumatic fever. I. Incidence and significance. YALE J. BIOL. AND MED. 33:259, 1961.

The latter investigators hypothesised that rebounds represent the appearance of inflammation suppressed during anti-rheumatic therapy. They provided evidence to support the hypothesis by creating rebounds in convalescent patients by giving anti-inflammatory therapy.

(31) Feinstein, A. R., Spagnuolo, M. Experimental reactivation of subsiding rheumatic fever. J.C.I. 40:1891, 1961.

"Chronic" Rheumatic Fever The average duration of activity in R.F. is about 109 $\pm$ 57 days, being longer in those with valvular involvement (124 days) than in those without (89 days). A small number of patients, however, show evidence of activity for very long periods (over 223 days) which is not related to intercurrent streptococcal infections.

(32) Feinstein, A. R., Spagnuolo, M. The duration of activity in acute rheumatic fever. J.A.M.A. 175:1117, 1961.

(33) Taranta, A., Spagnuolo, M., Feinstein, A. R. "Chronic" rheumatic fever. ANN. INT. MED. 56:367, 1962.

C. Therapy

Little new in this area. Still no real evidence that either

steroids, salicylates, or intensive penicillin therapy alter the duration of the rheumatic attack, or reduce the incidence of residual cardiac damage.

No doubt whatever that adequate therapy of strept. infections in the general population and prevention of attacks in rheumatic subjects are the most important therapeutic advances in this disease. Goodrecent reviews are:

(34) McEwen, C. Current status of therapy in rheumatic fever J.A.M.A. 170:1056, 1959.

(35) A comparison of the effect of prednisone and acetylsalicylic acid on the incidence of residual rheumatic heart disease. Report of combined R.F. study group. N. ENG. J. MED. 262:895, 1960.

(36) Stollerman, G. Current evaluation of the diagnosis, treatment and prevention of rheumatic fever. BULL. RHEUM. DIS. 13:293, 1962.

(37) A recent report by Harris, T. N., Friedman, S., Hallidie-Smith, K. A., Coriell, L. L., Fabrizio, D. draws attention to the "Occurrence of penicillin-resistant staphylococci in patients receiving penicillin orally for prophylaxis of recurrences of rheumatic fever". This appeared in A.J. MED. 32:545, 1962.

48% of 125 children harbored coagulase-positive resistant staph. 37% of the strains were bacteriophage group III.

Table 1. RISK OF DEVELOPING RHEUMATIC FEVER AFTER A STREPTOCOCCAL INFECTION ACCORDING TO THE MAGNITUDE OF THE ANTIBODY RESPONSE

In first attacks *:		In recurrent attacks **:	
ASO rise, in units/ml.	Attack rate of RF per strepto-coccal infection	ASO rise, in number of tube-dilutions	Attack rate of RF per strepto-coccal infection
0-120	7/856 (.8%)	2	13/88 (15%)
		3	12/49 (24%)
121-250	19/553(3.6%)	4	6/20 (30%)
		5	5/13 (38%)
> 250	30/545(5.5%)	6+	7/10 (70%)

* Stetson, 1954 (Ref. 6)
** Taranta, Wood, Feinstein, Simpson & Kleinberg, 1960

Table 2. RISK OF DEVELOPING A RECURRENCE OF RHEUMATIC FEVER AFTER A STREPTOCOCCAL INFECTION ACCORDING TO THE ABSENCE, PRESENCE AND SEVERITY OF PRE-EXISTING RHD *

Cardiac Status Before the Streptococcal Infection	Attack Rate of RF per Streptococcal Infection	
no heart disease	18/189	(9%)
heart disease with no or slight cardiomegaly	21/75	(28%)
heart disease with marked cardiomegaly	9/21	(43%)

* Taranta, Feinstein, Wood and Simpson, 1960 (Ref. 7)

Table 3. EVIDENCE FOR HEART ANTIBODIES IN ACUTE RHEUMATIC FEVER

Investigator	Year	Antigen	Procedure	Results
Brockman	1937	Saline Ext. Heart	Complement-Fixation	A.R.F. +
Cavelti	1945	" " "	Agglutination	27/36 A.R.F. +
Osler	1954	Alc. Ext. "	Complement-Fixation	45% of 260 A.R.F. +
Rejholec	1955	Saline Ext. "	Agglutination	6/8 A.R.F. +
Butler	1956	Lyophil. "	A.G. Consump.	8/13 A.R.F. +
Steffan	1958	Lyophil. "	A.G. Consump.	+
Kaplan	1961	Human "	Immunofluor.	10/40 A.R.F. +
Ehrenfeld	1961	Saline Ext. "	Hemagglutination	5/15 A.R.F. +
Hess	1962	Human "	Immuncfluor.	71/171 A.R.F. +
				45/71 A.R.F. $\bar{c}$ carditis+
				19/74 A.R.F. $\bar{s}$ " +

Table 4. Modified Jones Criteria

(From American Heart Association, 1956)

Major	Minor	Other Manifestations
[illegible]	Fever	Weight loss
Polyarthritis	Arthralgia	Easy Fatigability
Chorea	Prolonged P-R interval on electrocardiogram	Malaise
Subcutaneous nodules	Increased erythrocyte sedimentation, presence of C-reactive protein, or leukocytosis	Sweating
Erythema marginatum	Evidence of preceding beta hemolytic streptococcic infection	Pallor or anemia
	Previous history of rheumatic fever or presence of inactive rheumatic heart disease	Tachycardia when sleeping
		Erythema nodosum
		Precordial pain
		Abdominal pain
		Headache and vomiting

Table 5. Major Diagnostic Criteria

1) Carditis

A. Significant apical systolic, apical mid-diastolic or basal diastolic murmur in individual without history previous A.R.F. or evidence pre-existing R.H.D.; or change in character of any of these murmurs under observation.

B. Increasing cardiac size by X-R.

C. Pericarditis manifested by friction rub, pericardial effusion or E.K.G. evidence

D. Congestive failure in absence of other causes in a child or adult under 25.

2) Polyarthritis.

Migratory and manifested by pain and limitation of active motion or by tenderness, heat, redness or swelling of 2 or more jts. Arthralgia alone not a major manifestation.

3) Chorea.

Must be differentiated from habit spasm, athetosis and cerebellar ataxia. Movements must be characteristic, involuntary and of moderate severity.

4) Subcutaneous nodules

Shot-like, hard bodies seen or felt over extensor surface of certain jts., esp. elbows, knees, wrists, in occipital region or over spinous processes thoracic and lumbar vertebrae.

5) Erythema marginatum

Recurrent, pink, characteristic rash of A.R.F., in which the color gradually fades away from sharp scalloped edge, found mainly over the trunk, sometimes on extremities but not on face. It is transient, brought out by heat and migrates from place to place.

Table 6. RESIDUAL CARDIAC EFFECTS IN 447 PATIENTS 7½ YEARS AFTER ACUTE RHEUMATIC FEVER *

STATUS DURING ACUTE ATTACK	NO. OF PATIENTS	CURRENT STATUS				% with RHD
		Dead	RHD	Questionable RHD	No RHD	
Previous RHD						
EH and/or CHF	45	5	36	0	4	91%
Others	32	1	26	0	5	85%
No Previous RHD						
EH and/or CHF	42	3	33	1	5	86%
Diastolic Murmurs	94	0	43	3	48	46%
Systolic Murmurs	54	0	12	2	40	22%
No Significant Murmurs	180	1**	0	2	177	0%
Total	447	10	150	8	279	36%

* Feinstein, Wood, Taranta, Tursky, Spagnuolo and Epstein, 1962.

**Died in auto accident

Case Reports

1) A.R.F. in monozygotic twins

[redacted] ([redacted]) and [redacted] ([redacted]) 13 y.o. [redacted] M. twins.

	Jessie		Lonnie	
	ad [redacted]/60	disch [redacted]/60	ad. [redacted]/60	disch [redacted]/60
Sore throat	10 days P.T.A. followed by ear discharge	-	2 wks. P.T.A.	-
Polyarthritis	4 days P.T.A.	No	5 days P.T.A.	No
Fever	100.8	Normal	101.8	Normal
Pulse rate	108	66	100	70
Heart	gr.I apical > S.M. pulm.	No change	gr.I apical > S.M. pulm.	No change
EKG	normal	-	normal	normal
Hb.	9.7	12.3	10.4	12.5
Wbc.	16,700	8,200	11,200	10,900
ESR	121	20	120	18
CRP	0	-	1+	-
ASO	333	500	333	500

Both boys disappeared to follow-up and prophylaxis, until [redacted]/62 when [redacted]. was re-admitted with a 2 day history of migratory polyarthritis. His twin appeared to be well and was attending school. [redacted] had a low-grade fever, tachycardia, joints, sed-rate 87, CRP 3+, ASO 500 → 625. Exam. heart now revealed a prominent holosystolic apical m. and an early diastolic rumble, confirmed by phonocardiogram. The E.K.G. showed S.T. and T. wave changes. He responded to ASA and was reluctantly discharged [redacted]/62 with a sed-rate of 62. He has again failed to appear in the clinic.

2) "True to Type" Recurrences in A.R.F.

The following three patients from Irvington House, New York illustrate this observation.

1[redacted]

1955, age 8, ARF with polyarthritis
1957 " 10, " " "
1958 " 11, " " " No evidence R.H.D.

2)[redacted]

First seen 1955 age 8 with chorea. History of 2 previous attacks of chorea and evidence R.H.D.
1956-age 9, 4th attack chorea.
1957- " 10, 5th attack chorea. No change in apical mid-diastolic murmur.

3)[redacted]

1954-age 5, polyarthritis and carditis. Had apical diastolic m.
1956-age 7, " " " " "
diastolic m. +A.I
1958-age 9 " " " " "
diastolic m.
1959-age 10, monoarthritis and " " "
diastolic m. +A.I.

3) Rebound Phenomenon

[redacted]. A 26 y.o. [redacted] F. admitted with 10 day history of sore throat and migratory polyarthritis.

	Admission [redacted]-61	Discharge [redacted]-61	Re-admission [redacted]-61	Discharge [redacted]-61
Fever	101.6	normal	100	normal
Pulse rate	100	70	108	72
Polyarthritis	yes	no	yes-2 days	no
Heart	gr.II apical S.M.	no change	no change	no change
EKG	normal	normal	normal	normal
Hb.	10.6	11.1	11.7	11.8
Wbc.	11,100	5,300	8,000	6,200
ESR	90	97	74	76
CRP	2+	1+	3+	1+
ASO	166	333	250	-

ASA Erythromycin

reduced ASA

responded ASA

Historical

(38) Schottmuller, H. MUNCH MED. WSCHR. 50:849, 1903

First description of blood agar technic for differentiating hemolytic from non-hemolytic strept.

(39) Aschoff, L. VERH. DTSCH. PATH. GES. 8:46, 1904.

First description of characteristic pathology of rheumatic fever.

(40) Schick, B. DIE NACHKRANKHEITEN DES SCHARLACH, JB KINDERHEILK. Suppl., p. 65, 1907.

First postulated that delayed manifestations of disease following scarlet fever due to form of allergy to infection.

(41) Lancefield, R. C., The antigenic complex of streptococcus hemolyticus. Demonstration of a type-specific substance in extracts of Str. H.J.E.M. 47:91, 1928.

The antigenic classification of the streptococcus.

Heredity

(42) McKusick, V. A. Genetic factors in diseases of connective tissue, a survey of the present state of knowledge. AMER.J. MED. 26:283, 1959.

(43) Addis, G. J. Blood groups in acute rheumatism. SCOT. MED. J. 4:547, 1959.

(44) Diamond, E.F. Is there a rheumatic constitution? J. PEDIAT. 54:341, 1959.

Epidemiologic

(45) Coburn, A.F., Young, D.C. The Epidemiology of hemolytic streptococcus. Williams and Wilkins, Baltimore 1949.

(46) Rantz, L. A., Maroney, M., Di Caprio, J. M. Anti-streptolysin O response following hemolytic streptococcus infection in early childhood. ARCH. INT. MED. 87:360, 1951.

(47) Rammelkamp, C. H., Denny, F. W., Wannamaker, L. W. Studies on the epidemiology of rheumatic fever in the armed services, in Thomas' Rheumatic Fever: University of Minn. Press, Minneapolis, 1952.

(48) Stollerman, G. H., Lewis, A.J., Schultz, I., Taranta, A. Relationship of immune response to the course of acute, chronic and recurrent rheumatic fever. AM. J. MED. 20:163, 1956.

(49) Saslaw, M. S. Jablon, J. M. Epidemiology of group A beta-hemolytic streptococci as related to acute rheumatic fever in Miami, Fla. Six-year study. CIRCULATION. 21:679, 1960.

(50) Krause, R. M., Rammelkamp, C.H., Denny, F.W., Wannamaker, L.W. Studies of the carrier state following infection with group A streptococci. I Effect of climate.

Relationship not demonstrated.

(51) II. Infectivity of streptococci isolated during acute pharyngitis and during the carrier state.

There was a reversion to a non-M variant in the carrier state which did not cause infection in monkeys.

Both above in J.C.I. 41: p. 568 and 575, 1962.

(52) Nicholas, W.C., Steele, P.C. Occurrence of groupable beta-hemolytic streptococci. Study among school children in Bismarck, N.D., J.A.M.A. 181:197, 1962.

A 1 year study of 260 children in grades 1-6. The gr.A prevalence rate was 16.6% and was 3 times higher in those with tonsils. One case of rheumatic fever occurred - a rate of 0.0037% for the entire city.

(53) Meyer, R.J., Haggerty, R. J. Streptococcal infections in families. Factors altering individual susceptibility. PEDIATRICS. 29:539, 1962.

Evidence from this study suggested closeness of physical contact and stress as important factors.

(54) Potter, E.V., Stollerman, G.H., Siegel, A.C. Recall of type specific antibodies in man by injections of streptococcal cell walls. J. CLIN. INVEST. 41:301, 1962.

(55) Anderson, H. C., Kunkel, H. G., McCarty, M. Quantitative antistreptokinase studies in patients infected with gr. A streptococci. J.C.I. 27:425, 1948.

(56) Rantz, L., Boisvert, P.J., Spink, W.W. The etiology and pathogenesis of rheumatic fever. ARCH. INT. MED. 76:131, 1945.

Bacteriologic and Immunologic

(57) Denny, F.W., Perry, W.D., Wannamaker, L. W. Type-specific streptococcal antibody. J.C.I. 36:1092, 1957.

(58) Emmart, E. W., Turner, W. A. Studies on streptococcal hyaluronidase and antihaluronidase. J. HIST. & CYTOCHEM. 8:273, 1960.

(59) Kushner, I., Kaplan, M. H. Studies on acute phase protein. J.E. MED. 114:961, 1961.

(60) Miller, F. PROC. SOC. EXPER. BIOL. AND MED. 108:539, 1961.

(61) Cole, R. M. Hahn, J. J. Cell wall replication in streptococcus phogenes. SCIENCE. 135:722, 1962.

An ingenious method of locating and following constituents of the strept. cell during growth and division.

(62) Grey, H. M. Studies on the binding between streptococcal M protein and antibody. J.E. MED. 115:671, 1962.

(63) Schwab, J. H. Analysis of the experimental lesion of connective tissue produced by a complex of C polysaccharide from gr. A streptococci. J.E. MED. 116:17, 1962.

Papers by Kaplan, M. H. :-Immunologic studies of heart tissue. I-V.

(64) I Production in rabbits of antibodies reactive with an autologous myocardial antigen following immunization with heterologous heart tissue. J. IMMUNOL. 80:254, 1958.

(65) II Differentiation of a myocardial sarcoplasmic antigen and cardiolipin. J. Immunol. 80:268, 1958.

(66) III Occurence of bound gamma globulin in auricular appendages from rheumatic hearts. Rel. to certain histopathologic features of rheumatic heart disease. J.E.M. 113:1, 1961.

(67) IV Serologic reactions with human heart tissue as revealed by immunofluorescent methods: Isoimmune, Wasserman, and autoimmune reactions. J.E.M. 113:17, 1961.

(68) V Antigens related to heart tissue revealed by cross-reaction of rabbit antisera to heterologous heart. J. IMMUNOL. 88:450, 1962.

Gery, I., Davies, A.M. Organ specificity of the heart.

(69) I Animal immunization with heterologous heart.

(70) II Immunization of rabbits with homologous heart.

J. Immunol. 87:pages 351, 357, 1961.

(71) Ehrenfeld, E.N., Gery, I., Davies, A.M. Specific antibodies in heart-disease. LANCET: May 27, 1961.

(72) Hess, E.V., Fink, C.W., Taranta, A., Ziff, M. Circulating heart antibodies in rheumatic fever: a clinical study. ARTH AND RHEUM. 5:301, 1962.

(73) Crawford, Y.E., McNamara, M. J. The antibody response of rheumatic fever subjects to respiratory viruses. ANN. INT. MED. 56:389, 1962.

Similar response to control subjects.

Clinical

(74) Feinstein, A.R., Wood, H.F., Epstein, J. A., Taranta, A., Simpson, R., Tursky, E. A controlled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children. N. ENG. J. MED. 260:697, 1959.

(75) McMinn,F. J., Bywaters, E.G.L. Differences between the fever of Still's disease and that of rheumatic fever. ANN. RHEUM. DIS. 18:293, 1959.

(76) Bywaters, E.G.L., Thomas, G.T. I Bed-rest, salicylates, and steroid in rheumatic fever.

(77) II Five-year follow-up on patients with rheumatic fever treated by bed rest, steroids, or salicylate. BRIT. MED. J. 1: pages 1628 and 1635, 1961.

(78) Zagala, J.G., Feinstein, A.R. The preceding illness of acute rheumatic fever. J.A.M.A. 179:123, 1962.

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