

The relation between nongranulomatous uveitis and arthritis

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Arthritis occurred in 20 (30 per cent) of 67 patients with nongranulomatous uveitis, but in only 8 (3 per cent) of 277 patients with other uveal lesions. It was more common in patients with recurrent, acute rather than persistent, chronic nongranulomatous uveitis. The arthritis had distinctive features. It was usually an asymmetrical, non-ankylosing, peripheral polyarthritis involving the lower extremities more frequently than the upper ones. In addition, ankylosing spondylitis was present in almost all male but in no female arthritis patients. Rheumatoid factor could not be demonstrated in the sera of these patients. The data suggest a relation between nongranulomatous uveitis and a distinctive type of arthritis.

The uveal tract consists of iris, ciliary body, and choroid and is the vascular part of the eye. Inflammation in this area (uveitis) is common, usually symptomatic, and produces lesions which in most instances can be visualized readily with the slit lamp microscope and ophthalmoscope. There are a large number of well-established causes of uveitis which have been reviewed elsewhere.^{35, 36}

Determining the cause of a particular case of uveal tract disease is a difficult task which cannot always be resolved in satisfactory fashion. Direct biopsy and culture usually cannot be done. Most agree that the patient should

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be carefully examined to find out whether he has one of the systemic diseases known to cause uveitis. Such a survey generally produces evidence of several diseases known to cause uveal tract lesions. It must also be presumed that he might have other diseases overlooked or undetectable. Some method is needed to demonstrate the presence or absence of a causal relation between the ocular lesions presented by the patient and each one of the etiologic possibilities indicated by the survey.

We have attempted to approach this problem by classifying the ocular lesions found in patients with uveal tract disease into certain categories, some of which might be associated with evidence of one particular disease with sufficient frequency to indicate a relation between the two. We have then examined these patients to determine whether they had evidence of a systemic disease. Close associations have been demonstrated between one particular uveal lesion and histoplasmosis³⁵ and between another and toxoplasmosis.³⁶ The purpose of this communication is to call attention to a relation between still another ocular lesion, nongranulomatous uveitis, and a distinctive type of arthritis.

Since the initial report by Brodie¹ in 1818, there have been many reports of patients with uveitis associated with arthritis.^{1-3, 5-18, 21-34, 37, 39-41, 43} The uveitis generally has had the characteristics of nongranulomatous uveitis. The patient has complained of a painful, red eye with photophobia and blurred vision. Examination has usually revealed in one or both eyes most or all of the signs of acute nongranulomatous iridocyclitis including ciliary congestion, fine keratitic precipitates, aqueous chamber flare and cells, synechiae between iris and lens, and cells in the anterior vitreous. Evidence of involvement of the posterior segment of the eye has been common and has usually consisted of edema of disc and posterior pole. Evidence of discrete nodules or scarring in the iris, choroid, and retina has not been present in most instances and this type of uveitis has, therefore, been termed nongranulomatous uveitis. Ultimately, sub-capsular cataract and degenerative changes in the macula may occur. Obstruction to outflow from the anterior chamber may produce glaucoma. Deposition of calcium in the cornea as band keratopathy occurs commonly in children, but rarely in adults.

The course of nongranulomatous uveitis in adults with arthritis generally has been characterized, at least initially, by acute exacerbations of a few weeks' to a few months' duration followed by complete remissions for a period of months to years in which there is no evidence of active inflammation, but during which such residua as synechiae and cataract may remain evident.^{4, 14, 17, 18, 24, 25, 34} Much more rarely nongranulomatous uveitis in adults with arthritis has run a persistent chronic course from the beginning.^{14, 17, 18} In contrast, nongranulomatous uveitis found in children with arthritis has generally been from the onset a persistent chronic process with complete remissions occurring, if ever, only after a prolonged course.^{2, 9, 11, 29, 37, 40}

The arthritis found in patients with uveitis has been noted to have certain definite characteristics in most instances.^{1-18, 21-34, 37, 39-41, 43} There has usually been asymmetrical, nonankylosing polyarthritis involving peripheral joints, es-

Table 1. *A comparison of data on 67 patients with nongranulomatous uveitis with*

<i>Ocular uveal lesion</i>	<i>No. of patients</i>	<i>Age in years</i>	
		<i>Median</i>	<i>Range</i>
<i>Nongranulomatous uveitis</i>			
1. Acute or recurrent acute	39	41	13-70
2. Chronic in adults	19	39	16-75
3. Chronic in children	9	8	5-21
Total	67	37	5-70
<i>Other lesions</i>			
Clear vitreous:			
1. Disciform detachment of macula, discrete choroidal lesions	81	40	15-74
2. No disciform detachment of macula, discrete choroidal lesions	4	32	16-65
3. Serous disciform detachment of macula, no discrete choroidal lesions	12	35	12-57
4. Hemorrhagic disciform detachment of macula, no discrete choroidal lesions	14	46	13-74
Cloudy vitreous:			
5. Disciform detachment of macula, discrete choroidal lesions	10	46	31-66
6. Disciform detachment of macula, no discrete choroidal lesions	4	46	14-68
7. Focal exudative retinochoroiditis	73	36	11-62
8. Pars planitis	17	28	11-63
Clear or cloudy vitreous:			
9. Anterior granulomatous uveitis	22	38	21-75
10. Miscellaneous	40	42	5-75
Total	277	39	5-75

*No. signifies number positive divided by number observed or tested.

<i>Ocular uveal lesion</i>	<i>Focal infection</i>			
	<i>Respiratory tract</i>		<i>Genitourinary tract</i>	
	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
<i>Nongranulomatous uveitis</i>				
1. Acute or recurrent acute	18/39	46	15/39	38
2. Chronic in adults	9/19	47	4/19	21
3. Chronic in children	5/9	55	0/9	0
Total	32/67	48	19/67	28
<i>Other lesions</i>				
Clear vitreous:				
1. Disciform detachment of macula, discrete choroidal lesions	22/81	35	16/81	20
2. No disciform detachment of macula, discrete choroidal lesions	1/4	25	0/4	0
3. Serous disciform detachment of macula, no discrete choroidal lesions	4/12	33	2/12	17
4. Hemorrhagic disciform detachment of macula, no discrete choroidal lesions	3/14	21	1/14	7
Cloudy vitreous:				
5. Disciform detachment of macula, discrete choroidal lesions	5/10	50	2/10	20
6. Disciform detachment of macula, no discrete choroidal lesions	1/4	25	1/4	25
7. Focal exudative retinochoroiditis	30/73	41	14/73	19
8. Pars planitis	5/17	29	1/17	6
Clear or cloudy vitreous:				
9. Anterior granulomatous uveitis	7/22	32	6/22	27
10. Miscellaneous	10/40	25	6/40	15
Total	88/277	32	49/277	18

those on 277 patients with other ocular uveal lesions

<i>Sex</i>		<i>Arthritis</i>		<i>Spondylitis</i>		<i>Regional enteritis</i>		<i>Focal infection</i>	
								<i>Dental</i>	
<i>Male</i>	<i>Female</i>	<i>No.</i>	<i>%</i>	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
21	18	17/39	44	8/39	21	1/39	26	12/39	31
7	12	1/19	5	0/19	0	1/19	5	5/19	26
1	8	2/9	22	0/1	0	0/1	0	1/9	11
29	38	20/67	30	8/67	12	0/67	0	18/67	27
46	35	1/81	1	0/81	0	0/81	0	16/81	20
3	1	0/4	0	0/4	0	0/4	0	0/4	0
7	5	0/12	0	0/12	0	0/12	0	3/12	25
8	6	2/14	14	0	0	0	0	0/14	0
5	5	0/10	0	0/10	0	0/10	0	0/10	0
3	1	0/4	0	0/4	0	0/4	0	0/4	0
36	37	2/73	3	0/73	0	0/73	0	17/73	23
8	9	0/18	0	0	0	0	0	2/17	12
4	18	1/22	5	0	0	0	0	4/22	18
23	17	2/40	5	0/40	0	0/40	0	10/40	25
143	134	8/27	73	0/277	0	0/277	0	52/277	19

<i>Focal infection</i>		<i>Atopic allergy</i>		<i>Streptococcus skin test score</i>			
				<i>0</i>		<i>1-19</i>	
<i>Total</i>				<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
30/39	77	15/39	38	4/39	10	9/39	23
13/19	68	9/19	47	5/19	26	4/19	21
6/9	67	3/9	33	1/9	11	4/9	44
49/67	73	28/67	42	10/67	15	17/67	25
39/81	48	36/81	44	15/70	21	21/70	3
1/4	25	1/4	25	1/4	25	1/4	25
6/12	50	6/12	50	4/10	40	1/10	10
4/14	29	7	50	3/11	27	1/11	9
7/10	70	7/10	70	1/9	10	1/9	10
1/4	25	1/4	25	0/4	0	2/4	50
40/73	55	20/73	27	13/65	20	8/65	12
6/17	35	6	35	3/17	18	3/17	18
13/22	59	11	50	5/19	26	3/19	16
19/40	48	10/40	25	9/35	26	11/35	31
136/277	49	105/277	38	54/244	22	52/244	21

Table I. *Cont'd*

<i>Ocular uveal lesion</i>	<i>Streptococcus skin test score</i>			
	<i>20-39</i>		<i>40-59</i>	
	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
<i>Nongranulomatous uveitis</i>				
1. Acute or recurrent acute	8/39	20	0/39	0
2. Chronic in adults	2/19	11	1/19	5
3. Chronic in children	1/9	11	0/9	0
Total	11/67	16	1/67	2
<i>Other lesions</i>				
Clear vitreous:				
1. Disciform detachment of macula, discrete choroidal lesions	7/70	10	7/70	10
2. No disciform detachment of macula, discrete choroidal lesions	0/4	0	1/4	25
3. Serous disciform detachment of macula, no discrete choroidal lesions	1/10	10	0/10	0
4. Hemorrhagic disciform detachment of macula, no discrete choroidal lesions	2/11	18	0/11	0
Cloudy vitreous:				
5. Disciform detachment of macula, discrete choroidal lesions	1/9	10	3/9	30
6. Disciform detachment of macula, no discrete choroidal lesions	1/4	25	0/4	0
7. Focal exudative retinochoroiditis	13/65	20	6/65	9
8. Pars planitis	2/17	12	2/17	12
Clear or cloudy vitreous:				
9. Anterior granulomatous uveitis	1/19	5	3/19	16
10. Miscellaneous	3/35	9	2/35	6
Total	31/244	13	24/244	10

pecially those of the lower extremity. Sacroiliac joints and other joints of the spine have been affected commonly, and ankylosis of these joints has been frequent. Subcutaneous nodules and rheumatoid factors have almost never been demonstrated. It has been pointed out that this arthritis has the characteristics of the arthritis of Reiter's syndrome and ankylosing spondylitis rather than those of classical rheumatoid arthritis. No pathogenic organism has been demonstrated consistently in the involved joints. Urethritis and/or prostatitis of unknown cause has been found frequently in male patients with uveitis and arthritis.^{4, 6-8, 10, 14, 25, 26, 27} Ulcerative colitis^{1, 5} and regional enteritis¹ have been found occasionally in patients with iritis and arthritis.

In view of the evidence indicating that nongranulomatous uveitis may be associated with arthritis involving spine and/or peripheral joints, the question arises as to whether this association is due to chance or some relation between the two conditions. Previous reports of a high incidence of anterior uveitis in patients with ankylosing spondylitis,^{3, 8, 14-16, 21, 22, 27, 28, 31, 39} Reiter's syndrome,⁸ and Still's disease,^{29, 30, 37} and of a high incidence of peripheral arthritis and spondylitis in patients with anterior uveitis^{6, 7, 9, 14, 22, 25, 34} suggest that the relation is more than a fortuitous one. We have attempted to answer this question in a consecutive group of patients with uveitis by determining whether those with nongranulomatous uveitis have a higher incidence of arthritis than those with other uveal lesions.

<i>Streptococcus skin test score</i>							
60-79		80-99		100+		> 1. Exact score unknown	
No.*	%	No.*	%	No.*	%	No.*	%
4/39	10	9/39	23	2/39	5	0/39	0
2/19	11	4/19	21	1/19	5	0/19	0
1/9	11	0/9	0	1/9	11	0	0
7/67	10	13/67	19	4/67	6	2/67	3
5/70	7	8/70	11	4/70	6	3/70	4
0/4	0	0/4	0	1/4	25	0/4	0
2/10	20	1/10	10	1/10	10	0/10	0
2/11	18	3/11	27	0/11	0	0/11	0
1/9	10	2/9	20	0/9	0	0/9	0
0/4	0	0/4	0	1/4	25	0/4	0
6/65	9	10/65	15	4/65	6	5/65	8
3/17	18	3/17	18	3/17	18	0/17	0
1/19	5	3/19	16	2/19	11	1/19	5
2/35	6	4/35	11	2/35	6	0/35	0
22/244	9	34/244	12	18/244	7	9/244	4

MATERIALS AND METHODS

Between 1960 and 1963, we have studied 344 consecutive cases of uveal tract disease at The Johns Hopkins Hospital. Each patient was examined by an ophthalmologist and classified in one of the following groups on the basis of the morphology of the ocular lesions (Table I).

Nongranulomatous uveitis⁴¹ (Fig. 1)

Fine keratitic deposits. Anterior chamber cells. Frequent vitreous opacities and diffuse retinal edema. No evidence of pars planitis or discrete lesions of choroid or retina.

The patients with nongranulomatous uveitis were in three subgroups:

1. Acute or recurrent acute nongranulomatous uveitis. This is characterized at least initially by acute exacerbations of a few weeks' to a few months' duration, followed by complete remissions of months' to years' duration during which there is no evidence of active inflammation though such residua as synechiae and cataract may remain evident. Ultimately, the patients may have chronic persistent nongranulomatous uveitis.

2. Chronic persistent nongranulomatous uveitis of adult life which from the beginning has been a chronic process without remission. All cases were of more than 6 months' duration before being classified in this group. The onset was at age 14 years or older.

Table II. *Incidence of arthritis (nonbacterial, peripheral polyarthritis and monoarthritis, and spondylitis) regional enteritis, focal infection, atopic allergy, and delayed skin reaction to streptococcal antigens in patients with and without nongranulomatous uveitis*

	<i>Nongranulomatous uveitis</i>		<i>Other ocular lesions</i>	
	<i>No.*</i>	<i>%</i>	<i>No.*</i>	<i>%</i>
Arthritis	20/67	30	8/277	3
Peripheral	18/67	27	8/277	3
Spondylitis	8/67	12	0/277	0
Regional enteritis	2/67	3	0/277	0
Focal infection	49/67	73	136/277	49
Atopic allergy	28/67	42	105/277	38
Strep. skin test > 1 cm. diameter	57/67	85	190/244	78

*No. signifies number positive divided by number observed or tested.

3. Chronic persistent nongranulomatous uveitis of childhood. This is similar to subgroup 2, but with onset before age 14.

Other lesions

1. Clear vitreous. Disciform detachment of macula or perimacular area with or without subretinal hemorrhage visible at the margins. Small, discrete, nonpigmented or sparsely pigmented choroidal lesions or scars in the peripapillary, mid, or peripheral fundus.³⁵

2. Clear vitreous. No disciform detachment of the macula. Small, discrete nonpigmented or sparsely pigmented choroidal lesions or scars in the peripapillary, mid, or peripheral fundus similar to those in 1.

3. Clear vitreous. Serous disciform detachment of macula or perimacular area without subretinal hemorrhage visible at the margin. No choroidal lesions in remainder of fundus.

4. Clear vitreous. Hemorrhagic disciform detachment of macula. No choroidal lesions in remainder of fundus.

5. Cloudy vitreous. Disciform detachment of macula or perimacular area with or without hemorrhage. Small, discrete, nonpigmented or sparsely pigmented choroidal lesions or scars in the peripapillary, mid, or peripheral fundus.

6. Cloudy vitreous. Disciform detachment of macula or perimacular area with or without hemorrhage. No choroidal lesions in remainder of fundus.

7. Cloudy vitreous. Pars planitis.³⁸ Circumscribed chorioretinitis, or massive exudates in the pars plana. Edema of retina of posterior fundus. Nongranulomatous anterior uveitis (*vide infra*) frequently present.

8. Cloudy vitreous. Focal exudative retinochoroiditis.³⁶ Vitreous opacities are present when the lesion is active, consisting of cellular material visible with slit lamp and/or punctate, filamentous, globular, or veil-like deposits. Active retinochoroidal lesions appear as white or yellow foci which are elevated and have indistinct margins. The overlying retinal markings, particularly blood vessels, are obliterated or distorted. Ultimately, an inactive retinochoroidal

scar develops with absence of normal retinal vascular markings and an accumulation of black pigmentation which is often concentrated at the edges.

9. Clear or cloudy vitreous. Anterior granulomatous uveitis. Mutton fat keratitic deposits. Anterior chamber cells. Iris nodules and synechiae frequently present. No evidence of pars planitis or discrete lesions of choroid or retina.

10. Clear or cloudy vitreous. Miscellaneous. Lesions not described in above categories.

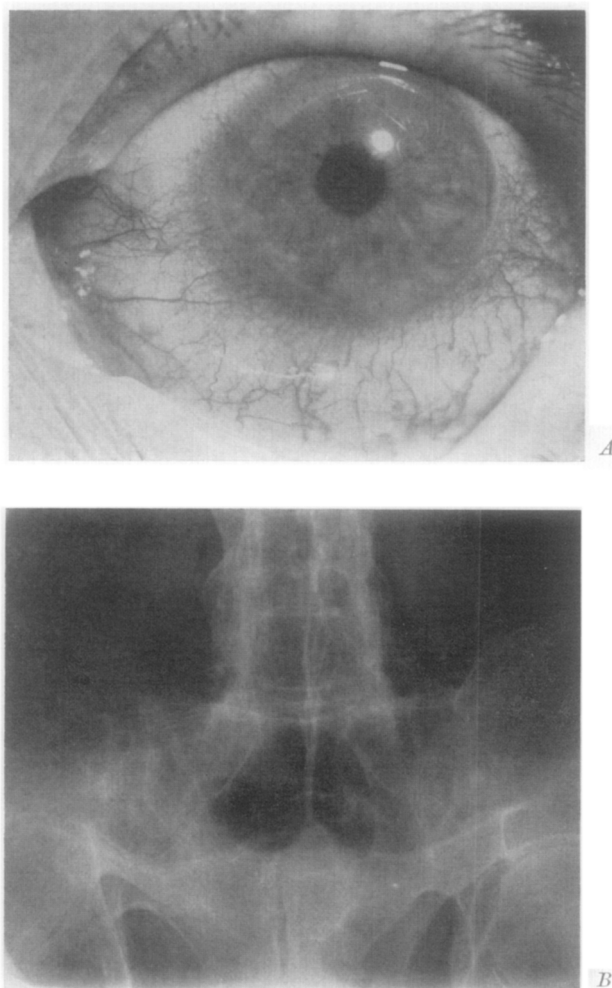


Fig. 1

Examples of various features of nongranulomatous uveitis and the associated arthritis.

Patient 319 (Table III): *A*, Left eye. Recurrent episode of acute nongranulomatous uveitis. There is intense congestion of the ciliary vessels. The patient noted pain in the eye and photophobia. Slit lamp examination revealed many fine keratitic precipitates on the back of the cornea and cells and flare in the anterior chamber aqueous fluid. *B*, X-ray of lumbosacral spine shows typical findings of ankylosing spondylitis, including fusion of both sacroiliac joints, and calcification of spinal ligaments.

Table III. *Characteristics of arthritis in 20 patients with nongranulomatous uveitis*

<i>Patient</i>			<i>Age</i>			<i>Nong. uveitis</i>		<i>Arthriti</i>	
								<i>Peripheral</i>	
<i>No.</i>	<i>Race</i>	<i>Sex</i>	<i>When observed</i>	<i>Nong.* uveitis</i>	<i>Ar-thritis*</i>	<i>Eye involved</i>	<i>Type†</i>	<i>Joints involved</i>	<i>Anky-losis</i>
119	W	M	21	14-21	15-21	OS	A 1	0	0
135	N	M	21	21-21	10-21	OS	A 1	Heel Ankle Hips Elbow	0
239	W	M	35	17-35	17-35	OU	A 1	0	0
96	W	M	47	41-47	40-47	OS	A 1	Toe Shoulder Elbow	0
268	W	M	55	25-55	24-55	OU	A 1	Toes Heel Ankle Thumb	0
168	W	M	56	23-56	23-56	OU	A 1	Knee Finger	0
7	W	M	59	56-59	47-47	OD	A 1	Ankles Knee	0
319	W	M	60	58-60	35-60	OS	A 1	Fingers	0
218	N	M	70	40-70	46-70	OU	A 1	Toes Knees Fingers	+
320	W	F	5	4-5	2-5	OU	A 3	Tarsal Ankles Knees (Fig. 3) Hips Elbows Wrists	0
287	W	F	5	4-5	5-5	OU	A 3	Knee	0
127	W	F	16	16-16	9-16	OS	A 1	Toes	0
298	W	F	31	31-31	23-31	OD	A 1	Toes Heels Knee	0
60	W	F	36	33-36	10-10	OU	A 1	Knees	0
285	W	F	37	37-37	35-37	OS	A 1	Toes Heels Finger	0
82	N	F	38	36-38	7-7	OD	A 1	Hip	0
89	W	F	41	41-41	23-23	OS	A 1	Foot Finger	0
345	W	F	42	31-42	35-42	OU	A 2	Tarsal Ankles Knees Wrists	0
234	W	F	44	34-44	33-44	OU	A 1	Toe Knees Elbows Palms	0
205	N	F	65	55-65	45-65	OD	A 1	Toe Wrists Palm Fingers	0

*Age at onset to age at last exacerbation prior to observation of either nongranulomatous

†Type of nongranulomatous uveitis refers to classification used in Table I and discussed in

‡S.I., L.S., L., D., and C. signify sacroiliac, lumbosacral, lumbar, dorsal, and cervical.

§N.D. signifies not done.

<i>Spine</i>		<i>Subcutaneous nodules</i>	<i>Rose test</i>	<i>Latex test</i>	<i>LE cells</i>	<i>Antistrep-tolysin O titer (Todd units)</i>	<i>Uric acid (mg. %)</i>	<i>Genitourinary tract infection (age*)</i>
<i>Joints involved</i>	<i>X-ray change</i>							
S.I.†	+	0	Neg.		Neg.	125	6.9	0
S.I.	+	0	Neg.		N.D.‡	100	3.7	Gonorrhea (19) Prostatitis (19-21)
S.I., L.S., L.	+	0	N.D.		N.D.	N.D.	N.D.	0
S.I.	+	0	Neg.	Neg.	Neg.	125	3.0	0
S.I.	+	0	N.D.	Neg.	Neg.	12	2.6	Prostatitis (in past) Gonorrhea (19)
I	0	0	Neg.		Neg.	12	4.0	Urethritis (27-52)
L.	+	0	Neg.		N.D.	12	N.D.	Prostatitis (47)
S.I., L.S., L., D. (Fig. 3)	+	0	Neg.	Neg.	Neg.	12	3.2	Prostatitis (19-60)
S.I., L.S., L.	+	0	Neg.		Neg.	12	4.0	Urethral stricture Prostatitis (40-70)
I, C.	N.D.	0	Neg.	Neg.	N.D.	333	N.D.	0
I	N.D.	0	Neg.		Neg.	12	N.D.	0
I	0	0	Neg.		Neg.	166	2.5	0
I	0	0	Neg.		Neg.	N.D.	2.7	Urethritis (27)
I	0	0	Neg.	Neg.	Neg.	12	4.0	0
I	0	0	Neg.		Neg.	N.D.	2.1	Cystitis (34)
I	N.D.	0	N.D.		N.D.	N.D.	N.D.	0
I	0	0	N.D.		N.D.	N.D.	N.D.	0
I	0	0	Neg.	Neg.	Neg.	12	2.5	0
I	0	0	Neg.		N.D.	250	3.7	Pyuria (19) Vaginal ulcers (19-29)
I	0	0	Neg.		Neg.	12	3.9	Vaginal abscess (50)

veitis, arthritis, genitourinary tract infection, or regional enteritis.
Materials and Methods.

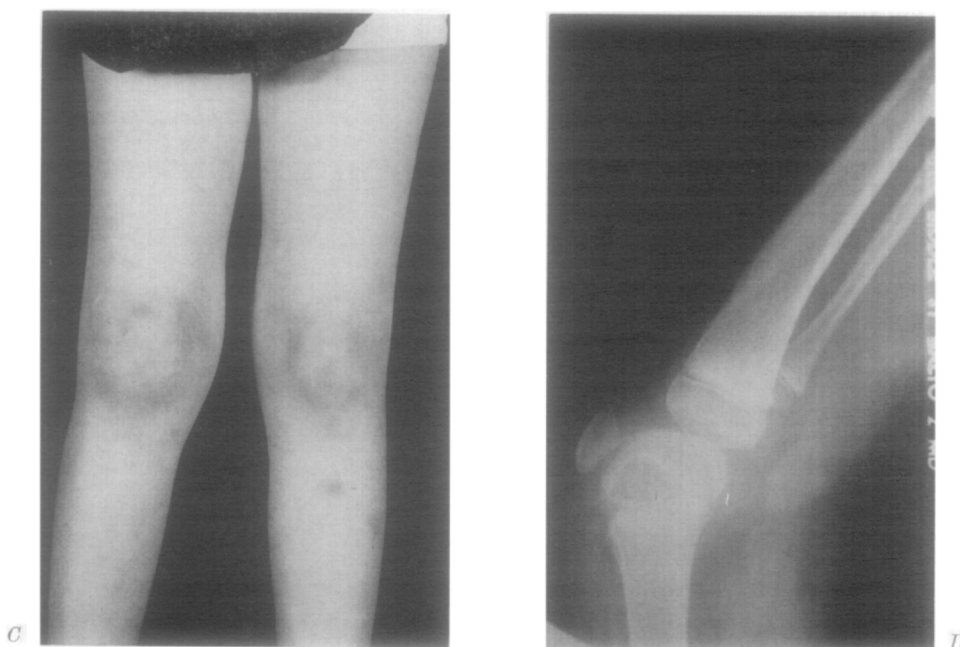


Fig. 1, C and D.

Patient 320 (Table III): *C*, Arthritis right knee. Pain, swelling, heat, and redness were evident and had been present for five months. *D*, X-ray of knee shown above shows soft tissue swelling, but good preservation of joint space, and no ankylosis, sclerosis, erosion or atrophy of apposing bone surfaces.

A medical examination was concerned with finding evidence of arthritis. Complete histories were taken and physical examinations were made. X-rays of representative involved joints were taken and almost all patients with nongranulomatous uveitis had x-rays of the sacroiliac joints. Hematocrit, white blood cell count and differential white blood cell count, and sedimentation rates were measured. Determination of the blood uric acid level and urinalysis were accomplished. Where there was evidence from the above examinations of arthritis, Rose and/or latex tests for rheumatoid factor, LE cell preparation, and determination of antistreptolysin O titer were obtained in most instances (Table III). The patient was considered to have or have had peripheral arthritis if there was a history of or evidence by physical examination of painful, red, hot, swollen peripheral joints which could not be attributed to sprain, contusion, bacterial invasion (as in acute suppurative arthritis), or osteoarthritis. This was classified as monoarthritis if one joint was involved and as polyarthritis if multiple joints were affected. The patient was considered to have spondylitis if there were a history of and physical examination evidence of pain in and limited motion of the spinal joints, plus appropriate roentgenographic evidence of changes in the spine and sacroiliac joints, including erosion, sclerosis, and/or fusion of adjacent joint bone surfaces, and/or calcification of the longitudinal spinous ligaments (Fig. 1).

Table IV. *Characteristics of arthritis in 20 patients with nongranulomatous uveitis*

Male		9/20*
Female		11/20
Nonbacterial peripheral arthritis		18/20
Monarthritis	2/20	
Polyarthritis	16/20	
Upper extremity		12/20
Lower extremity		17/20
Ankylosis		1/20
Spondylitis		8/20 (all male)
Sacroiliitis only	4/20	
Ankylosing spondylitis	4/20	
Rheumatic nodules		0/20
Rose or latex test positive		0/17
ASO titer elevated		0/15
Uric acid elevated		0/14
LE cells		0/13
Prostatitis		7/9
Regional enteritis		1/20

*Numbers indicate number positive divided by number observed or tested.

Table V. *Incidence of arthritis (nonbacterial, peripheral polyarthritis and monarthritis, and spondylitis) in patients with various types of nongranulomatous uveitis*

<i>Nongranulomatous uveitis</i>	<i>Arthritis</i>	
	<i>No.*</i>	<i>%</i>
Acute or recurrent acute	17/39	44
Chronic in adults	1/19	5
Chronic in children	2/9	22
Total	20/67	30

*No. signifies number positive divided by number observed.

In most patients with nongranulomatous uveitis, and in patients with other uveal lesions where foci of infection were suspected from the medical history and physical examination, dental and sinus x-ray examinations were done, and consultations obtained with dentist, otolaryngologist, and urologist or gynecologist.

Because of the reported relation between nongranulomatous uveitis and excessive delayed skin reactions to streptococcal antigens,⁴¹ intradermal skin tests were accomplished with 0.1 c.c. of each of the following antigens from the American Academy of Ophthalmology diagnostic kit⁴²: alpha hemolytic streptococci: 2-10 strains; beta hemolytic streptococci, group A: types L1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 17, 18, 19, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 46, 47, 48; group B: 4 strains; group C: 1 strain; group D: 1 strain; group F: 1 strain;

group G: 1 strain; gamma streptococcus: 1 strain. Skin reactions were read about 48 hours after the application of the test and reported as shown below:

Negative: Diameter of erythema less than 0.5 cm.

1 plus: Diameter of erythema 0.5-1.0 cm.

2 plus: Diameter of erythema 1.1-2.0 cm. Induration present.

3 plus: Diameter of erythema 2.1 cm. or more. Induration present.

4 plus: Necrosis present in addition to the findings described for a 3 plus reaction.

A score system was used in reporting the results. Reactions of 4 plus intensity counted 4, those of 3 plus intensity 3, those of 2 plus intensity 2, and those of 1 plus intensity or negative reactions 0. Those patients with a cumulative score on the streptococcal skin test of 0 correspond to the negative reactors reported by Woods⁴¹ who considered any reaction of less than 2 plus intensity to be a negative reaction for the purposes of this test. Patients with a cumulative score above 0 correspond to the positive reactors reported by Woods, who considered any patient as a positive reactor who had a 2 plus reaction to one or more of these streptococcal antigens.

Other studies done on these patients have been reported elsewhere.^{35, 36}

RESULTS

The results are shown in Table I and summarized in Table II. It is evident that patients with nongranulomatous uveitis have a higher incidence of arthritis (peripheral arthritis and/or spondylitis) than those with other uveal lesions. Arthritis was found in 20 (30 per cent) of 67 patients with nongranulomatous uveitis, but in only 8 (3 per cent) of 277 patients with other lesions. These differences between the groups of patients with and without nongranulomatous uveitis are significant in each instance at the 0.01 level of confidence when analyzed by the chi square test and were observed in all age groups.

The arthritis found in patients with nongranulomatous uveitis tended to have certain characteristics as indicated in Tables III and IV. There was most commonly an asymmetrical polyarthritis involving peripheral joints and usually manifested by local pain, heat, and swelling. The joints of the lower extremity were involved more frequently than those of the upper extremity, and the joints of the foot were often affected. Ankylosis of peripheral joints was uncommon. Roentgenographic changes in involved peripheral joints generally were absent except for soft tissue swelling (Fig. 1).

Spondylitis occurred in 8 out of 9 male patients, but in none of the 12 female patients with arthritis and nongranulomatous uveitis. Four spondylitis patients had sacroiliitis only without demonstrated involvement of other spinal joints. Radiologic evidence of fusion with or without sclerosis or erosion of apposing sacroiliac surfaces was present unilaterally in 1 and bilaterally in 3. Three patients had typical ankylosing spondylitis with roentgenographic changes in sacroiliac joints similar to those in the patients described above plus calcification of longitudinal spinal ligaments and fusion of apophyseal joints in lumbosacral, lumbar, and in one instance dorsal spine (Fig. 1). One patient had roentgenographic evidence of lumbar spondylitis (calcification of

longitudinal ligaments, fusion of apophyseal joints, bony bridges between vertebrae) without x-ray evidence of sacroiliitis. Subcutaneous nodules were not found. Rose and latex tests for rheumatoid factor, LE cell preparations, antistreptolysin O titers, and blood uric acid levels were within normal limits.

Arthritis was found more commonly in patients with certain types of nongranulomatous uveitis (Tables I and V). It occurred in 17 (44 per cent) of 39 patients with the acute or recurrent acute form, in 2 (22 per cent) of 9 children with the chronic form, and in only 1 (5 per cent) of 19 adults with the chronic form. Spondylitis was found only in men with acute or recurrent acute nongranulomatous uveitis.

Urethritis and/or prostatitis had been diagnosed at some time in 6 out of 9 men with arthritis and nongranulomatous uveitis (Table III). Three of these 6 patients with a history of urethroprostatitis had had an episode of purulent urethral discharge diagnosed as gonorrhea and a fourth had a urethral stricture. No concerted attempt had been made in any patient to determine the onset and ending of episodes of urethroprostatitis and it was impossible therefore to obtain data on the temporal relation between episodes of urethroprostatitis, arthritis, and uveitis. At some time during the course of our study, 8 of the 9 men with arthritis and uveitis were examined by a urologist for evidence of genitourinary tract infection. Three patients were found to have ten or more white blood cells in their prostatic fluid and were considered to have active prostatitis. No evidence of active prostatitis was found at the time of the examination in the remaining 5 patients, though 3 of these gave a history of past urethroprostatitis.

Urethritis had been found in the past in only one of the female patients with arthritis and uveitis. Another had had pyuria and vaginal ulcers, a third had had cystitis. At some time during the course of our study, 8 of the 9 adult women had a pelvic examination accomplished by a gynecologist, and a urinalysis also was obtained. There was no evidence at the time of this examination in any of the women examined of urethritis, vaginal ulcers, or infection of the bladder, kidneys, or Fallopian tubes. One woman was found to have monilial vulvovaginitis.

Regional enteritis was found in 2 patients with nongranulomatous uveitis and in none with other ocular lesions (Tables I and II). Each patient had typical clinical and x-ray findings, and the diagnosis was proved by the gross and microscopic character of the lesion found at the time of exploratory operation. One of these patients had arthritis (Table III).

The incidence of focal infection in teeth, respiratory tract, and genitourinary tract was higher in patients with nongranulomatous uveitis than in those with other lesions (Tables I and II). There was no difference between the groups of patients with and without nongranulomatous uveitis with regard to the incidence of atopic allergy (hives, asthma, hay fever, eczema) or delayed skin reaction to tuberculin, toxoplasmin, coccidioidin, blastomycin, brucellergen, or monilia skin test antigens. Delayed skin reactions to streptococcal antigens exceeding 0.1 cm. diameter were of equal frequency and streptococcal antigen skin tests scores were similar in the two groups of patients.

DISCUSSION

Previous reports have pointed out the occurrence of iritis and anterior uveitis in patients with arthritis.^{1-18, 21-34, 37, 39-41, 43} Description of the ocular lesion was complete enough in some of these reports to indicate that the lesion has usually been what is called in this paper acute nongranulomatous uveitis. The data reported in this present paper clearly indicate that arthritis is more common in patients with nongranulomatous uveitis than in patients with other ocular lesions.

The arthritis found in our 9 male patients with nongranulomatous uveitis had distinctive features conforming to a pattern previously described by others.^{4, 6-8, 10, 14, 25, 27} There was usually asymmetrical, nonbacterial, nonankylosing, peripheral polyarthritis, with predilection for joints of the lower extremity, especially those of the feet. Eight of the 9 male patients had symptoms and radiographic evidence of sacroiliitis and/or ankylosing spondylitis.

The arthritis found in our 9 adult women with nongranulomatous uveitis was a peripheral arthritis similar to that found in the men. This type of peripheral arthritis has been described previously in women with nongranulomatous uveitis.^{8, 14, 24, 43} It is of interest that there were no women with spondylitis in our series, and that in other reported series the incidence of spondylitis in women with nongranulomatous uveitis is much lower than in men with the same type of ocular disease. This difference may be connected in some way with the well-established fact that spondylitis is much more common in men than in women.¹⁵

The arthritis found in the 2 young girls with nongranulomatous uveitis did not differ from that found in the adult women in our series, or from that described in the literature on children with nongranulomatous uveitis and juvenile arthritis or Still's disease.^{9, 11, 29, 37}

The arthritis found in these patients with nongranulomatous uveitis usually did not have the characteristics of rheumatoid arthritis, which generally produces symmetrical, frequently ankylosing, peripheral polyarthritis, with predilection for the joints of the upper extremity, especially those of the hands. Rose and latex tests for rheumatoid factor were uniformly negative and subcutaneous nodules were not found. The more distinctive clinical features of lupus erythematosus, rheumatic fever, and gout were absent; LE cell preparations were negative, and antistreptolysin O titers and blood uric acid levels were within normal limits.

Arthritis occurred most frequently in patients with specific types of nongranulomatous uveitis, as previously reported.^{2, 4, 9, 11, 14, 17, 18, 24, 25, 29, 34, 37, 40} Adults with the acute or recurrent acute type, and children with the chronic type had arthritis more frequently than adults with nongranulomatous uveitis which from the beginning had been a chronic process without remission.

In both men and women the arthritis may precede, accompany, or follow the nongranulomatous uveitis. A careful history may be needed to establish the presence of a remote attack of arthritis in a patient with nongranulomatous uveitis or vice versa.

A high incidence of urethritis and prostatitis has been reported in patients with nongranulomatous uveitis and arthritis.^{7, 25, 27} No single organism has been

grown consistently from prostatic fluid, joint, or eye; cultures from these areas have frequently been negative, and it has been the general opinion that if infection is responsible for these cases, its cause, transmission, and pathogenesis are obscure.^{7, 25} The data in this present paper show urethritis and prostatitis may be present or absent in patients with nongranulomatous uveitis and arthritis, but do not indicate the incidence or significance of these findings. More information is needed with reference to the incidence and temporal relations between venereal exposures, genitourinary tract infections, mucocutaneous lesions, and arthritis in patients with and without nongranulomatous uveitis.

As association between arthritis, ulcerative colitis, and regional enteritis has been described^{1, 5}; it is of interest, therefore, that 2 of our female patients with nongranulomatous uveitis had regional enteritis, and one of these had arthritis.

Delayed skin reactions to various streptococcal antigens were equally frequent and of equal intensity in the groups of patients with and without nongranulomatous uveitis. Wood's observation of an increased incidence of strong delayed skin reactions to these antigens in patients with nongranulomatous uveitis⁴¹ was not confirmed.

The incidence of past or present atopic disease (hives, hay fever, asthma, and eczema) was similar in the groups of patients with and without nongranulomatous uveitis. In not a single one of the cases reported here was there definite evidence obtained that uveitis was an allergic reaction to some extrinsic factor. However, it is well established that nongranulomatous uveitis may appear during the course of serum sickness and clear as other manifestations clear.²⁰

It is interesting that the incidences of diagnosed focal infections in teeth, respiratory tract, and genitourinary tract were higher in the group of patients with nongranulomatous uveitis than in those with other lesions. However, the relation of various forms of uveitis to focal infection will have to be determined more accurately by a future study in which all uveitis patients are subjected to equally rigid screening for evidence of focal infection in any given area, where criteria for diagnosing focal infection are established before the beginning of the study and adhered to during the study, and where some method of correcting for the number of years covered by the uveitis is applied.

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