Patterns of Antibody Response of Children with Infections of the Urinary Tract

E. NETER^[44], O. R. OBERKIRCHER, M. I. RUBIN, J. M. STEINHART and I. KRZESKA

Departments of Pediatrics and Microbiology, State University of New York at Buffalo, School of Medicine, and Children's Hospital, Buffalo, New York, USA

Extract

An immunologic study was carried out on 140 children with infections of the urinary tract. The diagnosis was based on clinical, roentgenologic, urologic, and bacteriologic findings. Of the patients, 37 (26%) had acute infection and the remainder (103 children, 74%) had chronic or recurrent infection. The hemagglutination test was used to measure the antibody levels against the O antigens of the urinary isolates. The patients were studied for a period of 1-7 years.

An antibody response was documented in all but 10.7% of the subjects. Multiple antibody responses occurred in 55% and single antibody responses in 34.3% of the patients. There was no significant difference in the antibody responses to commonly encountered serogroups of *Escherichia coli* and other bacteria less frequently found in urinary tract infection. In 17 subjects, the antibody titer decreased rapidly within 2-8 weeks, and in 9 subjects reinfection with the microorganisms of identical serogroups led to a recall antibody response. It was shown that in 14 subjects (10%), minimal bacteriuria was accompanied by the production of the corresponding O antibodies, and in an additional 7 subjects (5%), asymptomatic bacteriuria, following or preceding overt infection, led to a specific antibody response.

Continued production of O antibodies over many months was observed following overt infection even in the absence of persisting bacteriuria; in other patients, however, even prolonged bacteriuria resulting from identical serogroups was not associated with the production of the corresponding O antibodies.

It is suggested that determination of the immune response of patients with urinary tract infection may aid in the identification of the etiologic role of urinary isolates, even when present in small numbers; may document infection by two or more antigenically unrelated microorganisms; and may help in the differentiation of relapse and reinfection. Thus, determination of the immune response may be a useful tool in the elucidation of certain aspects of this frequent, but incompletely understood disease.

Speculation

Because infectious agents or their antigens must reach cells of the immune apparatus to elicit an antibody response, documentation of the production of specific antibodies may aid in the differentiation between true infection and urinary contamination, between reinfection and relapse, and in ascertaining the clinical significance of minimal bacteriuria. It may be speculated that since titers of O antibodies decrease substantially a few months after recovery from shigellosis and salmonellosis, persistent elevated antibody titers against O antigens of urinary pathogens are associated with continued antigenic stimulation and may reflect continuation of the pathologic processes.

Introduction

Determination of a specific immune response to an infectious agent has been used as a diagnostic tool for more than half a century. Documentation of an increase in serum antibody is of value in evaluating the etiological role of suspected bacteria, as was done with certain serogroups of *Escherichia coli* as enteropathogens [27]. This approach may provide evidence for the etiologic role when the pathogen is no longer present in the patient. In addition, it provides information to identify onset of infection, elucidates the role of pathogens in suspected mixed infections, and is of aid in epidemiologic studies. Documentation of the immune response also offers opportunities for the study of urinary tract infection. As early as 1898, PFAUNDLER [31] described the development of agglutinins in children with this infection. Only recently has this approach been utilized with modern techniques. The passive hemagglutination test was shown to be a sensitive and specific procedure for the titration of O antibodies against various enteric bacteria [20, 22]. These antibodies are directed against the endotoxic lipopolysaccharides present in the cell walls, also referred to as somatic or O antigens. A comprehensive study of urinary tract infections in children has been in progress in the Department of Pediatrics for more than a decade. As a result of investigations, several patterns of antibody responses have been observed and are the subject of this report.

Materials and Methods

Subjects

One hundred and forty patients (125 females and 15 males) were enrolled in the Pyelonephritis Clinic of the Department of Pediatrics. The clinical, bacteriologic, and immunologic studies were completed and extended for a period of at least 1 year [43]. The subjects ranged in age from 1 month to 16 years. These patients do not represent an unbiased sample of individuals with urinary tract infection; individuals with chronic and recurrent infections are more frequently referred than patients with effectively treated acute infections or subjects with asymptomatic bacteriuria. In addition, follow-up of these patients over many months may have resulted in the recognition of otherwise undetected recurrent infection. Only 37 (26%) subjects had acute infection. A definitive diagnosis of urinary tract infection was based on clinical, roentgenologic, urologic, and bacteriologic findings. Two 'clean catch' samples, followed in case of doubt by a catheterized or suprapubically aspirated urine specimen, were obtained for bacteriologic examination.

Bacteriologic examination of urine was performed

within 2 h after procurement of the specimens and included identification of microorganisms by conventional methods as well as quantitation. For the latter procedure pour plates were prepared with 1 ml of aseptically obtained urine and with 1 ml of urine in a dilution of 1:1,000. This method provided information of a range of $1-10^6$ colonies/ml. Serotyping was performed on all isolates of *E. coli* according to the methods of EDWARDS and EWING [8], with O antisera provided by the National Communicable Disease Center [43]. Blood specimens were obtained monthly during year 1 and if infection continued or recurred sampling was continued. After recovery, blood specimens were obtained three or four times a year. The sera were kept frozen at -20° . Freezing and thawing did not result in a significant loss of antibody activity. Determination of the O antibody response was accomplished by the passive hemagglutination test [23, 26]. Antigens were prepared from all urinary isolates of gram-negative bacteria from each patient. Agar-grown cultures were suspended in phosphate buffer, heated for 1 h at 100° , and centrifuged at $23,500 \times g$. The supernates, containing the O antigens, were kept frozen at -20° . In addition, for control purposes, antigens from five serogroups each of *Salmonella*, *Shigella*, and enteropathogenic *E. coli* were utilized. Twofold serial dilutions of serum (0.2 ml) were mixed with common enterobacterial antigen from *E. coli* O 14 (0.2 ml) to remove antibodies to the latter antigen [16]. The mixtures were incubated at 37° for 30 min. Erythrocytes modified with O antigens of the isolates and of the control antigens (0.2 ml) were then added, and the mixtures were again incubated for 30 min at 37° . The resulting hemagglutination, utilizing human group O erythrocytes, was read grossly after centrifugation at $1,300 \times g$ for 2 min. All tests on a given patient were performed simultaneously, using all serum specimens and all antigens from the individual. Titers are expressed as the reciprocal of the highest dilution yielding visible hemagglutination. The antibody response was considered to be significant if the antibody titer increased or decreased at least fourfold in the absence of a similar change in the titers of antibodies against other isolates from the patients and/or against the control antigens of *Salmonella*, *Shigella*, and enteropathogenic *E. coli*. In the vast majority of patients with *E. coli* infection the specificity of the O antibodies in the serum corresponded to the O serogroups of the isolates.

Results

The study of the antibody response of 140 children with documented urinary tract infection revealed several antibody response patterns: 1) presence or absence of

antibody response; 2) single and multiple antibody responses; 3) antibody responses of short or long duration; 4) recall antibody response; 5) minimal bacteriuria, following or preceding overt disease, with antibody response; and 6) asymptomatic bacteriuria with antibody response.

Since certain serogroups of *E. coli* account for approximately 40–60% of all urinary tract infections due to this microorganism [21], the data on the immune responses of the patients are presented in three categories: 1) *E. coli* serogroups frequently encountered in urinary tract infections (O1, O2, O4, O6, O7, O11, O15, O62, and O75), (UP); 2) *E. coli* serogroups less commonly found in urinary tract infection (NUP); and 3) other gram-negative bacteria including nongroupable *E. coli* as well as the *Enterobacter*, *Klebsiella*, *Pseudomonas*, and *Proteus* (others).

A summary of the pertinent findings on the O antibody response of 140 children with urinary tract infection is presented in table I.

The term 'immune episode' is employed to denote the occurrence of a significant antibody response. The occurrence of two or more independent antibody responses in a single subject, separated by weeks or months, is referred to as 'multiple immune episodes'. Since many patients developed antibodies against two or more antigenically unrelated species or serogroups of microorganisms, the number of immune episodes exceeds that of subjects.

Frequency of the Antibody Response

Study of the antibody response of the 140 patients revealed that a significant increase in the titer of homologous antibodies occurred in 125 (89.3%). This high rate of antibody response probably was related to the fact that the majority of children suffered from chronic or recurrent infection and that antibody responses were measured at frequent intervals with antigens prepared from all urinary isolates. Thus, 77 of 140 patients had 202 immune episodes. In subjects with antibody response, it was noted that commonly encountered serogroups of *E. coli* (UP) accounted for 78 episodes and less commonly found serogroups (NUP) for 70 episodes of all infections due to typable *E. coli*. Antibody response to the most commonly encountered serogroups of *E. coli* are summarized in table II. It can be seen that antibodies were produced by almost all patients (89–100%) against serogroups O1 and O7 belonging to UP and against O8 belonging to NUP. Among 148 episodes associated with typable *E. coli* strains, 78 or 52.7% were related to serogroups belonging to the UP group. This finding is in accord with previously reported bacteriologic observation that UP serogroups account for approximately 40–60% of *E. coli* urinary tract infection [21]. Only 15 patients failed to

reveal a specific antibody response, for a total of 19 episodes; the urinary isolates in the majority (57.9%) belonged to the UP group and only 15.8% to the NUP group. Failure to produce antibodies against the urinary isolates was not due to impairment of the immunologic apparatus, for three of these patients produced both H and O antibodies following immunization with typhoid vaccine.

Single versus Multiple Antibody Responses

Based on bacteriologic and immunologic data, it has been shown that children with chronic and recurrent infection of the urinary tract frequently harbor different microorganisms at different times. It was not unexpected, therefore, that such patients responded to infection with production of antibodies with different specificities. In the present series of 125 patients with significant antibody responses, 48 (34.3%) produced antibodies against a single isolate and 77 (55%) against two or more isolates at different times. No significant difference was noted regarding the frequency of production of antibodies directed against UP and NUP (table IA).

Rapid Decrease of Antibody Titer

In 17 of 125 subjects with 18 episodes (13.6%), the antibody titers decreased within 8 weeks (table IB). There was no significant difference between infections due to UP or NUP. The findings of a representative case are recorded in table III. It may be seen that *E. coli* O66 was isolated in large numbers and the antibody titer against this microorganism was high. A substantial reduction in titer occurred within 2 weeks and a further reduction during the ensuing 2 months. The specificity of this decrease in antibody titer was evident from the fact that a second infection, associated with the presence of *E. coli* O40 in the urine, was followed by an increase in the titer of homologous antibodies.

Duration of Antibody Response

As seen in table IB, 62 out of 125 subjects (49.6%) had an antibody response lasting for less than 1 year and 63 (50.4%) for more than 1 year; 49 patients had antibody responses to two or more organisms, one response lasting less than and the other more than 1 year.

Data on the relation between serogroups of *E. coli* and duration of antibody response are presented in table IV. A longer lasting antibody response occurred more frequently with *E. coli* O8 (NUP) than with *E. coli* O6, O7, and O75 (UP).

Recall Antibody Response

In 9 of 125 subjects (7.2%), a second antibody response to the identical microorganism could be doc-

Table I. Antibody patterns in patients with infections of the urinary tract

Antibody patterns	Number of immune episodes ¹	Number of subjects	%	UP ²		NUP ²		Other micro-organisms	
				No. ³	% ³	No.	%	No.	%
<i>A</i> Antibody response									
Single	48	48/140	34.3	14	29.2	12	25.0	22	45.8
Multiple	202	77/140	55.0	64	31.7	58	28.7	80	39.6
Absent	19	15/140	10.7	11	57.9	3	15.8	5	26.3
<i>B</i> Rapid decrease of antibody titer	18	17/125	13.6	7	38.9	7	38.9	4	22.2
Duration of antibody response									
< 1 yr	97	62/125	49.6	28	28.9	33	34.0	36	37.1
> 1 yr	14	14/125	50.4	4	28.6	1	7.1	9	64.3
Both	139	49/125		46	33.1	36	25.9	57	41.0
<i>C</i> Recall antibody response	9	9/125	7.2	4	44.5	2	22.2	3	33.3
<i>D</i> Bacteriuria < 6 months									
Antibody response < 1 yr	156	47/93	50.5	46	29.5	45	28.8	65	41.7
> 1 yr	63	46/93	49.5	18	28.6	16	25.4	29	46.0
Bacteriuria > 6 months									
Antibody response < 1 yr	8	8/27	29.6	5	62.5	3	37.5	0	0.0
> 1 yr	23	19/27	70.4	9	39.1	6	26.1	8	34.8
<i>E</i> Minimal bacteriuria with antibody response	15	14/140	10.0	2	13.3	8	53.4	5	33.3
<i>F</i> Asymptomatic bacteriuria with antibody response	7	7/140	5.0	3	42.8	2	28.6	2	28.6

¹ Number of antibody responses to different species or serogroups occurring at different times.² UP = serogroups of *E. coli* frequently encountered in urinary tract infection. NUP = serogroups of *E. coli* rarely encountered in urinary tract infection.³ Number and percentage of immune episodes with specific microorganisms.

Table II. Serogroups of *E. coli* and antibody response

Antibody response	<i>E. coli</i> serogroups						Total
	O1	O4	O6	O7	O75	O8	
Positive	18 (90%)	14 (67%)	18 (51%)	16 (89%)	9 (50%)	12 (100%)	87
Negative	2 (10%)	7 (33%)	17 (49%)	2 (11%)	9 (50%)	0 (0%)	37
Total	20	21	35	18	18	12	124

Table III. Rapid decrease of antibody titers

Dates	<i>E. coli</i> O66	Bacterial counts/ml	<i>E. coli</i> O66 Antibody titers (reciprocal)	<i>E. coli</i> O40 Antibody titers (reciprocal)
7-26-67	Positive	> 10 ⁶	1,280	40
8-7-67	Negative		160	40
10-4-67	Negative		40	320

Table IV. Serogroups of *E. coli* and duration of antibody response

Duration of antibody response, yr	<i>E. coli</i> serogroups						Total
	O1	O4	O6	O7	O75	O8	
> 1	8	7	2	3	2	8	30
< 1	10	7	16	13	7	4	57
Total	18	14	18	16	9	12	87

Table V. Recall antibody response

Dates	Urine cultures	Bacterial counts/ml	<i>E. coli</i> O6 Antibody titers (reciprocal)	<i>E. coli</i> O7 Antibody titers (reciprocal)
3-27-65	<i>E. coli</i> O6	> 10 ⁶	< 20	160
3-29-65	—		80	320
5-5-65	Negative		320	80
7-21-65	Negative		20	80
9-20-65	<i>E. coli</i> O7	> 10 ⁶	—	—
10-7-65	Negative		20	2,560

Table VI. Persistent bacteriuria without antibody response

Dates	<i>E. coli</i> O6 urine cultures	<i>E. coli</i> O6 Antibody titers (reciprocal)	<i>E. coli</i> O103 Antibody titers (reciprocal)
12-63	Positive (> 10 ⁶)	< 20	40
12-63 to 6-64	Positive 9 times	< 20	80
6-64 to 11-64	Positive 7 times	< 20	80
12-64	<i>E. coli</i> O103 (> 10 ⁶)	< 20	320
1-65 to 4-68	Positive 48 times	< 20	320-160

umented after a significant fall in the titers of antibodies following the first infection (table IC). The interval was as short as 3–6 months and as long as 2–4 years. Such recall responses were encountered with UP, NUP, and other microorganisms. The bacteriologic and immunologic data of a representative case are summarized in table V and indicate that a significant antibody response occurred to *E. coli* O6 recovered from the urine in March 1965. During the ensuing 5 months this antibody titer decreased substantially, and a recall response to *E. coli* was clearly documented between July and October 1965, at a time when *E. coli* O7 was present in the urine in significant numbers. The specificity of the antibody response was documented by inhibition tests with *E. coli* O6.

Bacteriuria and Antibody Response

The studies of KASS [14] have revealed that a statistical relation exists between the number of bacteria per millimeter of urine from the bladder and the presence of urinary tract infection. In the majority of instances, urine from the bladder of infected subjects contains at least 10^4 , and frequently more than 10^5 , viable bacteria per millimeter. One might expect, therefore, that a relation also exists between the degree and duration of significant bacteriuria and the antibody response. As shown in table ID, no difference was noted in the duration of the antibody response for more or less than 1 year between the group of 219 subjects with bacteriuria lasting less than 6 months and the group of 31 patients with bacteriuria of more than 6 months' duration. Some unexpected patterns, however, have been encountered; namely, persistent bacteriuria without antibody response, persistent elevated antibody titers in the absence of continued bacteriuria, antibody response at time of minimal bacteriuria, and antibody response during asymptomatic bacteriuria.

Persistent bacteriuria without antibody response. The failure to detect an antibody response in the presence of long-lasting bacteriuria with a single serogroup of *E. coli* was an unexpected occurrence. The data from a representative case are summarized in table VI. Antibodies were not detected during 4 years, although *E. coli* O6 was isolated from 64 urine specimens. That the failure of this antibody response was not due to immunologic incompetence was deduced from the observation that the patient produced antibodies against *E. coli* O103 following infection with this microorganism in 1964. Further, no antibodies were detected with antigen prepared from *E. coli* O6 isolated from other patients. Another possibility to be considered was that IgG antibodies of low hemagglutination activity instead of IgM antibodies may have been synthesized by this patient. If this pattern of antibody response was responsible for the absence of detectable hemagglutina-

Table VII. Persistently elevated antibody titers in the absence of persistent bacteriuria with homologous *E. coli*¹

Dates	<i>E. coli</i> O7	Bacterial counts/ml	Antibody titers (reciprocal)
4-65	Positive	> 10^6	5,120
7-65	Negative		1,280
10-65	Negative		640
6-66	Negative		320
8-67	Negative		320

¹ *E. coli* O7 present on 1 occasion and absent in 23 cultures.

Table VIII. Group-specific antibody response at time of minimal or absent bacteriuria

Dates	Cultures		Antibody titers <i>E. coli</i> O73
	Organism	Count/ml	
1-67	Sterile	—	< 20
2-67	Sterile	—	< 20
3-67	Sterile	—	40
4-67	<i>E. coli</i> O73	500	160
5-67	<i>E. coli</i> O73	> 10^6	80

tion, this patient, and others, represents an unusual pattern of urinary tract infection.

Persistent elevated antibody titers in the absence of continued bacteriuria. Persistent antibody production observed in a patient in the absence of continued bacteriuria is illustrated in table VII. It may be seen that the initial bacteriuria in this case was associated with the production of homologous antibodies in high titer. Although *E. coli* O7 was not isolated during the ensuing 2 years, the antibody titer, although reduced, remained at significantly elevated levels.

Antibody response at time of minimal bacteriuria. Minimal bacteriuria (< 10,000 colonies/ml) with a significant antibody response was observed in 14 subjects (10%) with 15 immune episodes (table IE). Since the number of observations was small, it was not certain whether the distribution between UP and NUP was significant.

Antibody response during asymptomatic bacteriuria. Asymptomatic bacteriuria with immune response was noted in 14 subjects. There was no significant difference in the increase of titers of the antibody to UP and NUP (table IF). In all instances the asymptomatic infection either followed or preceded overt disease.

Discussion

The antibody response of 140 children with infection of the urinary tract (26% acute and 74% with chronic or recurrent infection) was determined over a period of 1-7 years. The antibody response to the O antigens of gram-negative bacteria was determined by the passive hemagglutination test on serially obtained specimens of serum. This approach was used rather than comparing antibody titers of these patients with those found in healthy subjects, since 'normal' titers vary significantly with age. The hemagglutination procedure measures preferentially, though not exclusively, IgM antibodies [11]. Since the initial report in 1955 [19], this method has been widely employed, both in this country and abroad [1, 2, 6, 9, 10, 12, 15, 18, 32, 37, 38, 40, 41]. Also, as reported by HOLMGREN and HANSON [17], this test may detect related K antigens. As a result of the present investigations, the following patterns have emerged: 1) single and multiple antibody responses; 2) antibody production for short and long periods of time; 3) recall antibody response; 4) significant bacteriuria with or without antibody response; 5) prolonged bacteriuria without antibody response; 6) minimal bacteriuria following or preceding infection with antibody response; and 7) asymptomatic bacteriuria with antibody response.

A specific O antibody response could be documented in 121 out of 140 patients (89%), representing 250 immunologic episodes. Approximately one-third of all patients had a single antibody response and slightly over one-half had multiple responses. This high frequency was probably related to the fact that the majority of patients had chronic or recurrent infection, that multiple serum specimens were available for study, and that all isolates from urine cultures were used as antigens. Utilizing the conventional bacterial agglutination test, PERCIVAL *et al.* [30] detected an antibody response in 93% of 41 patients with acute pyelonephritis. In the latter study, comparison was made between titers of antibody in patients and those of control subjects.

Previous studies, summarized by NETER [21], have revealed that certain serogroups of *E. coli* occur with greater frequency in urinary tract infection, although this preponderance was not noted in another series [33]. These serogroups are referred to as UP, and the others as NUP. No substantial difference has been noted in the present investigation in the antibody response of patients to UP, to other typable *E. coli* serogroups (NUP), or to other gram-negative bacteria, and the percentages of single and multiple responses were similar (table I).

One of the major problems of chronic or recurrent infection of the urinary tract is the differentiation be-

tween persistence of the same microorganism or the acquisition of new strains. Only with complete identification of the urinary isolates, such as serogrouping and typing, can a reasonable answer be obtained. In adults, TURCK *et al.* [35] found that the same microorganism was recovered from 52 out of 65 recurrences in patients with renal bacteriuria, but in only 11 out of 38 recurrences in 25 subjects with bladder bacteriuria. In 20 children with 102 episodes of urinary tract infection, different organisms or serotypes of *E. coli* were isolated from 70% of the patients, suggesting that reinfection was twice as common as relapse [5]. Study of the antibody response affords an additional opportunity to document the acquisition of new strains. Previously, NETER *et al.* [25] reported on multiple antibody responses. In the present series, multiple antibody responses to antigenically unrelated species of serogroups were almost twice as frequent as single responses (table I).

A recall antibody response should occur in subjects with relapse, provided that the antibody titers against the microorganism had decreased prior to the recurrence. Indeed, in the present series, such a recall antibody response was documented in nine subjects.

For the past decade, quantitation of bacteria present in urine from the bladder, has been employed routinely as an aid to diagnosis. In the majority of patients with definitive urinary tract infection the count of bacteria per millimeter exceeds 10^4 and often 10^5 . This significant bacteriuria is often associated with a specific O antibody response. In some patients, however, the number of bacteria in the urine is much lower. As shown in the present study, a specific immune response to minimal bacteriuria with overt disease could be documented in 10% of the subjects. In addition, 5% of the patients with asymptomatic bacteriuria produced the corresponding O antibodies. It should be emphasized that in these subjects asymptomatic bacteriuria was a phase of chronic or recurrent infection, either following or preceding overt disease. Previously, ANDERSEN *et al.* [3] observed a rise in antibody titers with minimal bacteriuria in three subjects. A similar response was reported [30] in 18% of 86 patients by demonstrating antibody titers above those of normal controls, and in bacteriuric, pregnant women, higher titers of antibodies were observed against their own organisms than in noninfected subjects prior to overt pyelonephritis [10].

It was not surprising that patients with documented urinary tract infection did not develop antibodies against the infecting microorganism. Among 26 subjects with bacteriuria of more than 1 year duration, 13 episodes occurred in the absence of an antibody response. In one patient, *E. coli* O6 was recovered no less than 64 times and yet the corresponding O antibody

titer during this observation period did not exceed 1:20 (table VI). This failure of a specific immune response was not due to immunologic incompetence as some patients responded to an infection with another serogroup of *E. coli* or developed anti-H and O antibodies following typhoid vaccination or a result of lack of available serum specimens at suitable times. Whether this persistent bacteriuria without antibody response is similar to the postulated colonization of the intestinal tract in the absence of antibody production [23] remains to be determined. ANDERSEN *et al.* [3] considered the possibility that failure of the immune response might be related to certain characteristics of the bacterial strains. It is unlikely that this explanation pertains to the present observations, because the *E. coli* strains involved were both typable and typical and belonged to different O groups.

It can be expected that infection of the urinary tract of limited duration is followed by a decrease in antibodies. Indeed, a rapid decrease within 8 weeks was observed in 17 patients and similar observations were previously reported [3, 30, 39]. As shown, antibody titers may remain elevated in subjects whose bacteriuria had terminated for more than 1 year (table VII). Since O antibody titers decreased substantially within a few months following recovery from *Shigella* and *Salmonella* infections [24], it may be expected that persistence of high titers was due to continued stimulation of antibody production by antigen, although not necessarily by viable bacteria. If this was the case, immunologic studies might provide a possible indicator of continued disease, particularly since ANGELL *et al.* [4] reported the existence of active chronic pyelonephritis without evidence of bacterial infection. It is conceivable that antibodies detected by the hemagglutination test used in the present study may have pathogenic significance, for immune hemolytic disease can be elicited by these antibodies in the rabbit [34].

Current information [3, 13, 30, 39] suggests that immune response occurs much more frequently in pyelonephritis than in cystitis. Localized bladder pouch infection of dogs, however, in the proven absence of renal infection, stimulates a marked antibody response [7]. UEHLING *et al.* [36] showed that it was not cystitis *per se* but the kind and degree of disease of the bladder that determined the immune response. Infection associated with a foreign body in the bladder led to a significantly higher antibody response than simple infection, and the introduction even of killed bacteria into the bladder wall also was followed by an antibody response. Thus, future studies in man should be directed toward relating the pathologic processes of cystitis in man to the systemic and local immune response. The classes of immunoglobulins produced, either locally or systemically, as well as their biologic

activities in patients with urinary tract infection, also require further inquiry. Local production of antibodies in the urinary tract has recently been documented [28, 29]. Determination of the serum antibody response is a valuable tool in elucidation of the incompletely understood processes of urinary tract infection in man.

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44. Requests for reprints should be addressed to: ERWIN NETER, M.D., Children's Hospital, 219 Bryant Street, Buffalo, NY 14222 (USA).
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