efficacious for invasive parenchymal infections.

It was of particular interest to find substantial concentrations of TMP within the internal organs of the patient C.Pi. He was moribund at the time he received his medication, and yet the evidence suggests that excellent absorption and distribution of the antibiotic had occurred. Satisfactory concentrations of TMP and SMX have been reported from children with other illnesses that might be suspected of affecting absorption. Marks *et al* evaluated 25 children with gastroenteritis, all of whom absorbed Septra well.[8] Similarly, Fowle[9] found that in seriously ill children there was generally good absorption of both antimicrobial agents, although greater variability in serum concentrations was encountered in ill or malnourished than in healthy children.

The single adverse reaction encountered during this study was a skin eruption in a single patient. The eruption was similar to those previously reported during Septra or SMX therapy and resolved promptly at withdrawal of therapy.[10,11]

The present report extends the clinical experience with TMP-SMX and offers additional pharmacokinetic data relevant to children. The combination TMP-SMX is easily administered, well tolerated and therapeutically effective in a variety of infections due to susceptible bacteria. There are a number of questions germane to the therapy of children that necessitate continued evaluation of TMP-SMX.

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Immunologic parameters of children with urinary tract infection: effects of trimethoprim-sulfamethoxazole

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Summary: In order to determine whether a deficiency in immunologic response predisposes certain children to recurrent infections of the urinary tract, four groups of children were investigated: a control group; children with extraurinary infections; children with urinary tract infections; and a group of children treated with trimethoprim-sulfamethoxazole (TMP-SMX). In none of the groups were there changes in humoral immunoglobulins, peripheral neutrophil counts, serum complement concentrations or urinary excretion of IgG, IgA or IgM that might predispose to infection. However, children with urinary tract infections were more likely to belong to blood group A (66.6%; expected frequency, 45%) and had a blunted thymidine uptake of their stimulated lymphocytes (RLB) when compared with children with extraurinary infection. As well, their nitroblue tetrazolium reduction (NBT) was significantly lowered and this paralleled their RLB response. We postulated a shared antigenic feature of either their renal-urinary tissue or bacterial antigen with blood group A antigen; this prevents the mounting of an effective immunologic defence.

If TMP-SMX further depresses the lymphocyte response, it may be considered contraindicated in urinary tract infection. In 11 children treated with this drug we found no significant difference between their RLB and NBT responses and those of children with infections of the urinary system treated with other drugs. We conclude that TMP-SMX does not alter the immune responses in children.

Résumé: ***Les paramètres immunologiques chez des enfants souffrant d'infections urinaires: les effets du triméthoprime-sulfaméthoxazole***

En vue d'établir si une insuffisance des réactions immunologiques est susceptible de prédisposer certains enfants à des infections urinaires récidivantes, nous avons

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observé quatre groupes d'enfants: un groupe de témoins; des enfants atteints d'infections extraurinaires; des enfants atteints d'infections des voies urinaires; et un groupe d'enfants traités avec le triméthoprime-sulfaméthoxazole (TMP-SMX). Or, dans aucun des quatre groupes nous n'avons trouvé de modifications ni dans les immunoglobulines humorales, ni dans les numérations des neutrophiles périphériques, ni dans les concentrations du complément sérique, ni dans l'excrétion urinaire d'IgG, d'IgA ou d'IgM, qui auraient pu prédisposer le sujet à l'infection. On a cependant noté que les enfants souffrant d'infections urinaires appartenaient plus souvent au groupe sanguin A (66.6 %; fréquence escomptée, 45 %) et que la fixation en thymidine de leurs lymphocytes stimulés était émoussée (RLB) par comparaison avec les enfants souffrant d'infection extraurinaire. De même, la réduction de nitrobleu de tétrazolium (NBT) était abaissée significativement et cette réduction était parallèle avec la réaction du RLB. Nous formulons l'hypothèse d'une antigénie partagée, soit de leur tissu rénal-urinaire ou d'un antigène bactérien avec un antigène du groupe sanguin A, ce qui empêcherait la formation d'une défense immunologique efficace.

Si le TMP-SMX a pour effet de déprimer davantage la réaction lymphocytaire, il peut être considéré comme contreindiqué dans l'infection de l'arbre urinaire. Chez les 11 enfants traités au TMP-SMX nous n'avons noté aucune différence significative entre leurs réactions RLB et NBT et celles des enfants souffrant d'infections des voies urinaires qui avaient été traités par d'autres médicaments. Nous concluons donc que la TMP-SMX n'altère pas les réactions immunitaires chez l'enfant.

Urinary tract infections are common, recurrent and inclined to become chronic. A multitude of predisposing and causative factors have been proposed to explain their recurrence.[1,2] Recent interest has focused on the host's response to infection of the urinary system.[3-5] In order to explain the high recurrence rates in children (between 40 and 60%)[6] we have hypothesized that one of many causative factors predisposing to either the development or recurrence of urinary tract infection is a dysfunction in the immunologic response of certain children. This may be related to a deficiency in cell-mediated immunity, local or humoral immunoglobulin production or peripheral granulocytic responsiveness.

Gram-negative bacteria, the common pathogens isolated from the urinary tract, sometimes contain cell-wall antigens that crossreact with human isoagglutinins of blood groups A, B or O.[7] We examined the immunologic characteristics of children with urinary tract infections, and also determined the incidence of specific blood groups in these children.

Materials and methods

Hospitalized children ranging in age from 1 to 14 years were subjected to the following tests of immunologic function:

Peripheral granulocytic response

The effectiveness of the granulocytes was assessed by their number and activity. Activity was evaluated in appropriately stimulated cells by their ability to phagocytose and reduce nitroblue tetrazolium, a pale yellow dye, to a blue-black formazan derivative. Failure to do so in the face of infection indicates defective granulocytic function.[8]

Humoral immunoglobulins

The B or bursa lymphocytes are responsible for the production of humoral antibody (IgG, IgA and IgM). As well, local production of antibody, specifically secretory IgA and possibly IgM, takes place in the urinary tract.[5,9,10] B cell function was then assessed by the following tests: (a) humoral immunoglobulins, IgG, IgA, IgM; (b) isoagglutinins, i.e. blood typing; (c) urinary immunoglobulins, IgG, IgA and IgM in concentrated and ultrafiltrated 24-hour specimens (Hyland Laboratory immunodiffusion plates); (d) serum complement levels.

Cell-mediated immunity

1. The T or thymus-dependent lymphocytes are implicated in cell-mediated immunity and take part in such responses as the graft *v.* host reaction and delayed hypersensitivity. When stimulated, lymphocytes revert to a more primitive blastogenic cell inducing DNA synthesis. Stimulation has been shown to result from bacterial infection[11] and can be measured by tritiated thymidine uptake in cultured lymphocytes.[12] Thus the functional integrity of a previously stimulated lymphocyte may be assessed by spontaneous blastogenesis. This reactive lymphocyte blastogenesis (RLB) can be measured and is an index of lymphocyte responsiveness to infection.

2. Delayed hypersensitivity was assessed by intradermal injection of candidin, streptokinase-streptodornase (Varidase), histoplasmin, tuberculin, and mumps and dermatophytin antigens.

We studied four groups of children: healthy controls, children with infections other than of the urinary tract, children with bacteriologically proved urinary tract infection and a group of children with urinary tract infection treated with TMP-SMX.

Study of the last group was pertinent since previous reports have implied that *in vitro* thymidine uptake by human lymphocytes is suppressed by either trimethoprim or sulfamethoxazole and that this depression is augmented by their combination.[13]

Results

No abnormalities were detected in the peripheral leukocyte counts, absolute number of polymorphonuclear neutrophils, serum complement concentration, humoral immunoglobulins IgG, IgA or IgM in the children with urinary tract infection that might predispose them to infections.

The development of isoagglutinins to erythrocyte antigens is related to immunoglobulin production and their absence is associated with immunodeficiency syndromes.[14] As well, certain blood types have been identified as being associated with coliform infections, and an increased incidence of urinary tract infections in blood group A individuals has been implied.[7] The results of our survey of blood typing are presented in Table I. The blood group of 48 children with urinary tract infection was determined. Thirty-two (66.6%) patients were found to belong to blood group A; the expected frequency in the general population is 41%. Group O children accounted for 18.8% of the test group when the expected frequency was 45%. It appears that children of blood group A have an unusual predisposition to infections of the urinary system; this bears out the supposition of Moody, Young and Faber.[7]

To evaluate the local production of antibody the urinary

Table I—Blood grouping of 48 children with urinary tract infection

Blood group	Rh+	Rh-	Total	Percent
A	28	4	32	66.6
B	6	0	6	12.5
AB	1	0	1	2.1
O	7	2	9	18.8
Total	42	6	48	100
	(87.5%)	(12.5%)		

immunoglobulin excretion was determined in 21 controls and 29 children with infections of the urinary tract (Table II). No significant differences were detected in IgG values. However, IgA and IgM values were elevated, confirming the observations of Uehling and Sterhm implying a local production of antibody in response to infection.[5]

The competence of the T-lymphocytes was determined by *in vivo* delayed hypersensitivity testing (Table III). A panel of intradermal skin tests was performed on 36 controls and 42 children with urinary tract infection of comparable age and sex. No significant differences were detected between the control and study groups.

Reactive lymphocyte blastogenesis (RLB) was evaluated in 24 uninfected controls, in 47 children with infections other than of the urinary system and 78 children with infections of the urinary tract (Table IV). A significant difference existed between all three groups but the children with infections of the urinary system had counts that were significantly lower than those with infections in other systems and the control group. We feel this indicates a lesser degree of lymphocyte conversion and thus stimulation.

Nitroblue tetrazolium reduction seemed to be varied, ranging from 2 to 60% NBT-positive cells. However, when NBT reduction was plotted against lymphocyte stimulation (Fig. 1) a regression curve was obtained that was significant ($r = 0.73$, $P = 0.01$). It is apparent that those patients with reduced RLB had correspondingly poor NBT reduction and, conversely, those with normal RLB had a correspondingly higher percentage of NBT reduction.

Eleven patients treated with TMP-SMX underwent the same tests (Table V). Eight belonged to blood group A, two to group O and one to group B. There was no significant difference between these children and the other three groups tested when comparisons were made of delayed hypersensitivity (skin testing), urinary excretion of immunoglobulins (urinary Ig), humoral responsiveness measured by peripheral leukocyte counts, serum complement and serum immunoglobulins. Reactive lymphocyte blastogenesis was not significantly different from that of the children with urinary tract infections, but the NBT reduction was slightly lower. The regression line between NBT and RLB fitted exactly to the regression line in Fig. 1, implying no significant difference in their reaction to infection while on TMP-SMX therapy.

Table II—Urinary immunoglobulin excretion in 21 controls and 29 children with urinary tract infections

	Immunoglobulin excretion					
	mg/dl			mg/24 h		
Group	IgG	IgA	IgM	IgG	IgA	IgM
Control	0.324	0.054	0.046	1.732	0.238	0.169
Infected	0.310	0.065	0.105	1.659	0.304	0.443

Discussion

In the search for the causative factors responsible for the induction and perpetuation of urinary tract infections, a multitude of possible explanations have been proposed. We have postulated a defect in the defence mechanisms of children with such infections but have not found any variations in the expected number of peripheral leukocytes, humoral immunoglobulin production or serum complement levels.

Initially we had postulated an intrinsic defect in local antibody production in the urinary system which could predispose to recurrent infections. This should be recognizable by reduced urinary IgA excretion but we found the levels to be elevated. These studies indicate that urinary secretory globulins are not deficient in recurrent urinary tract infections. We interpret these results as implying a normal host defense mechanism in the urinary tract to the invasion of pathogenic bacteria. T-lymphocyte responsiveness was surveyed, employing delayed skin hypersensitivity to certain intradermally injected antigens. No abnormality was detected, implying that this aspect of T-cell function was intact. B-cell function, as measured by serum complement and immunoglobulin levels, also seems to be intact since no abnormalities in these latter responses were detected. However, host responsiveness was abnormal since the conversion of lymphocytes to the blastogenic form induced by bacterial infection was deficient in children with urinary tract infection and this deficiency correlated with the ability of the peripheral neutrophil to convert nitroblue tetrazolium. Both of these deficiencies had their greatest preponderance in children with blood group A.

The correlation between defective host responsiveness in urinary tract infection and type A children may be explained by

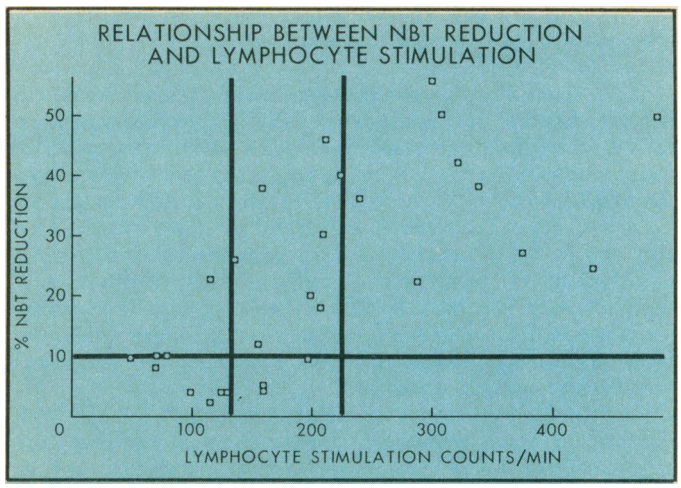

FIG. 1—Relation between nitroblue tetrazolium (NBT) reduction and lymphocyte stimulation in children with urinary tract infections. Horizontal line represents 10% NBT reduction, the division between normal controls and subjects with infections. The first vertical line from the Y axis represents the mean reactive lymphocyte blastogenesis of normal controls, the second vertical line the mean count for children with urinary tract infections (see Table IV).

Table III—Delayed skin hypersensitivity in 36 controls and 42 children with urinary tract infections, matched for age and sex

Group		PPD	Candidin	Mumps	Varidase	Histoplasmin	Dermatophytin
Controls	% Positive	97.1	30.5	58.3	41.6	97.1	97.1
	% Negative	2.9	69.5	41.7	59.4	2.9	2.9
Children with urinary tract infection	% Positive	97.8	36.5	60.9	65.8	100	97.8
	% Negative	2.2	63.1	39.1	34.2	0	2.2

the reduced capacity of the host to respond to certain infections. Drach, Reed and Williams showed that urinary tract pathogenic bacteria contain A, B and O active antigens.[15] Patients responded to B-like bacterial antigen with significant elevations of isoagglutinin B titres but patients did not differ from controls in isoagglutinin A titres and less often detected A-like bacterial antigen than did controls. These workers assumed that there was a deficiency in the recognition of an A-like antigen, implying host tolerance to these bacteria. It would be expected, then, that patients with blood group A might fail to recognize bacteria with A-type antigens and allow those bacteria to invade and replicate without inducing major host defences. In addition, anti-A agglutinating antibodies have not been demonstrated to be antibacterial as have antibodies with blood group B specificity.[3]

The characteristics of the renal medulla, classically the site of origin of renal parenchymal infection, tend to inhibit the invasion by neutrophils and lymphocytes owing to the high osmolality, low pH and high urea content. In addition, it has been claimed that *Escherichia coli* has poor chemotactic activity in both the renal cortex and medulla,[3] which might explain the poor NBT response and poor lymphocyte blastogenesis noted in group A patients.

It has been previously reported that both trimethoprim and sulfamethoxazole independently decrease thymidine uptake of stimulated peripheral lymphocytes *in vitro*. When these drugs are combined the suppression is greatly augmented, a finding that could be clinically relevant.[14] Our studies have not shown a clinically statistically significant difference in the immunologic responses between children with urinary tract infection treated with TMP-SMX and those treated with other antibacterials, as evidenced by an identical regression line when NBT and RLB were compared.

Table IV—Comparison of lymphocyte blastogenesis in normal controls, children with extraurinary infections and children with urinary tract infections

Group	Number tested	Mean count per minute
Uninfected controls	24	128
Patients with nonurinary infections	47	757
Patients with urinary tract infections	78	225

Table V—Comparison of controls, children with extraurinary infection, children with urinary tract infections and children with urinary tract infections treated with TMP-SMX

Test	Control	Non-UTI	UTI	UTI, TMP-SMX
Skin test	N	N	N	N
Urinary Ig	N	-	N	N
Humoral response	N	N	N	N
RLB	133	741	225	199
NBT (%)	<13	42	25	18

Conclusions

Children of blood group A respond to infection in the urinary tract with an altered host responsiveness. This may be due to the inability of the urinary system to induce responses in immune reactive cells sufficient to evoke normal immunoreactivity. Neither the granulocytes nor the lymphocytes in these children appear to have been adequately induced to respond to infections of the urinary tract, as evidenced by the lower RLB and NBT responses. Blood group A children may be particularly susceptible owing to sharing of antigenic patterns between their tissues and bacterial antigens.

We believe that TMP-SMX does not alter the immune mechanisms in children, and the previously noted *in vitro* suppression is not clinically relevant. As noted, children with recurrent urinary tract infection were more likely to belong to blood group A. Blood group A children may be unduly susceptible to bacterial infection because of an antigenic locus shared between renal tissues and the bacterial cell wall. This is manifested by reactive lymphocyte blastogenesis and nitroblue tetrazolium reduction of lesser degree than in children with infections other than of the urinary system.

Although the expected host responsiveness to infection is not induced, the responses of these children to TMP-SMX are normal and intact and this drug does not further suppress their immune responsiveness.

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