

Discussion

Patients with Kaposi's sarcoma appear to have normal humoral immunity as measured in this study. Nevertheless, a striking impairment was noted in the delayed hypersensitivity response to dinitrochlorobenzene in those with the malignant form of the disease. Serial testing suggests that the defect in cellular immunity may accompany a malignant change in the clinical manifestation of the disease. Whether the defect is related to the pathogenesis or is the result of this malignant change remains unknown. There is evidence that patients with impaired immunity may be more susceptible to the development of neoplastic disease (Smith, 1968), and Kaposi's sarcoma has been described as arising in a patient with immunosuppression following a homograft (Siegel *et al.*, 1969). On the other hand, some patients with advanced cancer may manifest depressed cellular immunity (Solowey *et al.*, 1965). Further studies will be necessary fully to elucidate the dynamic nature and extent of impairment of cellular immunity in malignant Kaposi's sarcoma and the relationship of immunological status to infectious complications, response to therapy, and the histopathology of the lesions.

The finding of impaired delayed hypersensitivity in advanced Kaposi's sarcoma parallels the observations of the immune disorder in patients with Hodgkin's disease (Aisenberg, 1966; Brown, *et al.*, 1967). Both neoplasms have appeared concurrently in the same patient in much greater than chance association (Reynolds *et al.*, 1965; O'Brien and Brasfield, 1966). The exact pathogenetic and clinical relationships between Kaposi's sarcoma and Hodgkin's disease, however, remain speculative (Lancet, 1967).

We are aware that the distinction between the benign and malignant types of Kaposi's sarcoma is based on clinical grounds alone. In a review of 70 patients seen at Mayo Clinic, Reynolds *et al.* (1965) pointed out the variations in the clinical appearance of the tumour, and attempted to correlate the gross lesion with the histological features. In a large series from Tanzania (Slavin *et al.*, 1969) both the benign and

the relatively fulminant course of Kaposi's sarcoma were emphasized, though pathological correlations could not be made. From the present study there appears to be a valid immunological basis as well as a clinical basis for the division of Kaposi's sarcoma into benign and malignant types.

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Study of Childhood Urinary Tract Infection in General Practice

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Summary: A study of bacteriuria was conducted among 426 of the 436 children under the age of 13 in a general practice in north-west London. Three girls and one boy were found to have asymptomatic bacteriuria, and a further girl with bacteriuria presented with abdominal pain and fever. The calculated incidence of urinary tract infection was 1.4% per annum. Most of the childhood urinary infections in this practice occurred before the age of 5 years, and the incidence of significant bacteriuria in this age group was 4.9% per annum. Five other children (four girls and one boy) in the practice were known to have had proved urinary tract infection. Of the

total of eight children known to have had significant bacteriuria and investigated radiologically, three girls and two boys had radiological abnormalities in the urinary tract.

Pyuria and proteinuria did not prove to be useful in the prediction of asymptomatic bacteriuria. Urinary tract infection with renal tract abnormality was found in this practice to be at least five times as common as diabetes in childhood.

Introduction

Studies of urinary infection in adults in general practice have been reported Fry *et al.*, 1962; Loudon and Greenhalgh, 1962; Gallagher *et al.*, 1965; Mond *et al.*, 1965). Surveys have also been made of the prevalence of bacteriuria in schoolgirls (Kunin *et al.*, 1964; Meadow *et al.*, 1969; Savage *et al.*, 1969)

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and in toddlers in a paediatric private practice (Randolph and Greenfield, 1964). Information on urinary infection occurring in unselected populations of children in domiciliary practice is not available.

The current interest in screening of well populations for non-symptomatic disease is occasioned by the belief that early detection and treatment may prevent subsequent progression. Much of the renal damage resulting from urinary tract infection is thought to have its origin in childhood, when infection is often missed because of the non-specific nature of the symptoms. A study was therefore undertaken of the feasibility and value of the detection of bacteriuria in the childhood population in a single general practice.

Patients Studied

The general practice is situated in a residential area of north-west London. Some 3,200 patients, predominantly a settled population belonging to the professional, managerial, and skilled working classes (Registrar General's social classes I, II, and III), are registered. At the start of the study 436 children under 13 years of age were registered—247 boys and 189 girls. The age and sex distribution of the 242 boys and 184 girls actually surveyed are given in Table I.

TABLE I.—Age and Sex of 184 Girls and 242 Boys at First Screening for Bacteriuria

Age (Years)	No. of Girls	No. of Boys	Age (Years)	No. of Girls	No. of Boys
Less than 1	14	20	7	14	24
1	5	15	8	12	15
2	15	22	9	19	24
3	14	14	10	12	14
4	15	20	11	15	16
5	15	27	12	15	15
6	19	16			

Methods

Organization.—The intention to conduct the study was made known to the patients of the practice by posting explanatory notices in the consulting-rooms, by writing letters to each family, and by discussion with interested parents. As this study concerned only one practice, no attempt was made to enlist the help of educational or public health authorities in publicizing the survey. The letters circulated to the family included an appointment to attend either at the surgery or at an adjacent local authority child welfare clinic. Arrangements for groups of up to 100 to attend at each session were made, about 30 an hour. At the first attendance an appointment was given to each child to return in four to six months, and at the second attendance a third appointment was given. Reminders were sent to every family a week before each appointment. By these means each child was seen three times in the course of eight months. If the specimens were found to be infected or unsatisfactory the child was recalled and further specimens were obtained. During the period of the study 50 children with pyrexias associated with upper respiratory tract infections (45) or exanthemata (5) were screened for bacteriuria on presentation and a week later. A record was also kept of children complaining of dysuria or frequency.

Specimen Collection.—Local cleaning with tap-water followed by drying was performed by the child if old enough, or by his mother, after instruction, or in a few instances by an attendant. Mid-stream urine samples were then collected in sterile glass jars or clean adhesive polyethylene bags and refrigerated at 4° C. immediately. Many toddlers succeeded

when a glass jar was placed in a chamber pot. Delay between cleansing and micturition was minimized so far as possible and was usually under 10 minutes. Bag application was performed by a trained nurse at special sessions.

Examination of Specimens.—Urine samples were examined immediately after removal from the refrigerator by trained medical laboratory technicians, always within an hour of collection. Specimens were cultured by the filter paper strip technique (Leigh and Williams, 1964), and urinary white cell counts were performed on fresh uncentrifuged specimens with a haemocytometer. Paper strip tests were performed to detect glycosuria and proteinuria (Clinistix and Albustix). After 24 hours' incubation the cultures were examined by one of us (R.N.G.) and the results classified as positive, negative, or uncertain. All patients from whom positive or uncertain results were obtained were recalled for re-examination within 48 hours. The criterion of infection was a urinary bacterial count of an organism in pure growth in excess of 10⁵/ml.

Clinical Assessment.—The children found to have significant bacteriuria were seen by one of us (J.M.S.) in a special paediatric clinic for urinary tract infection where clinical and bacteriological assessments were carried out and radiological investigations performed after treatment of the infection, by methods already reported (Smellie *et al.*, 1964).

Results

Screening for bacteriuria was performed on three occasions—in March-April, July, and November-December 1968. Of the 436 children in the practice, 426 (97.6%) attended at the first screening, 420 (96.3%) at the second, and 413 (94.7%) at the third. The negative, uncertain, or probably positive results on the initial culture and a final assessment of the results after repeated culture in the uncertain and probably positive instances are given in Table II. No child gave doubtful or positive results on more than one screening.

TABLE II.—Results of Screening for Bacteriuria in 426 Children on 3 Occasions

Results	Screening					
	First		Second		Third	
	First result	Final assessment	First result	Final assessment	First result	Final assessment
Negative	417	425	415	417	409	413
Uncertain	5	—	2	—	4	—
Positive	4	1	3	3	—	—
Total children screened	426	426	420	420	413	413

Screening for pyuria (urinary white cell count >10/cu. mm. of fresh uncentrifuged urine) was also conducted on three occasions (Table III). Of the four children found to have con-

TABLE III.—Results of Screening for Pyuria in 426 Children on 3 Occasions

Urinary White Cell Count	Screening					
	First		Second		Third	
	Males	Females	Males	Females	Males	Females
>10/cu. mm.	240	180	233	162	233	170
≥10/cu. mm.	2	4	5	20*	1	9
Total	242	184	238	182	234	179

*1 girl was bacteriuric.

firmed asymptomatic urinary infection, one girl showed significant pyuria, while of 41 urines showing significant pyuria only one derived from an infected child. Two children were

found to have significant pyuria on two separate screenings, but without bacteriuria.

Screening for proteinuria with Albustix revealed 36 children (2.9%) with more than trace proteinuria (>100 mg./100 ml.). It rapidly became apparent that there was no correlation between the presence of proteinuria and either pyuria or bacteriuria, even in those with proteinuria in excess of 300 mg./100 ml. (12 children). Glycosuria was found in one child known to be diabetic.

During this study some children were receiving chemotherapy when screened. The numbers at each screening were 8, 8, and 15. Of these, 3, 4, and 8 respectively were receiving long-term treatment for proved urinary tract infection and the remainder for unrelated conditions. The three children treated throughout had presented earlier with symptomatic infections. One had been found to have bilateral vesicoureteric reflux and normal kidneys, and a second showed gross unilateral reflux with a shrunken kidney. In addition, two 6-year-old girls had presented even earlier with symptomatic infections and had not been investigated radiologically. Since they gave sterile urine samples on screening it was not thought appropriate to investigate them during this survey.

Fifty children with upper respiratory tract infections or exanthemata were screened for bacteriuria during the survey and none were found to have positive or uncertain results. One child found to have significant bacteriuria on the second screening had had a sore throat one week previously, and on further questioning was found also to have had slight frequency. During the survey period three children attended complaining of frequency or dysuria. All had repeated urine cultures with negative results.

Between the second and third surveys a 2-year-old girl whose urine had been normal twice on screening presented with abdominal pain and fever. She was found to have significant bacteriuria but not pyuria. Subsequent radiological investigation showed her to have bilateral duplication of the kidneys but no vesicoureteric reflux.

Three girls all aged 4 years and one boy aged 18 months were found on screening to be infected. Their heights and weights fell within the normal range and all were normotensive. Radiological investigations of these four children revealed a left double kidney and ureter in one and unilateral vesicoureteric reflux without renal abnormality in a second.

Discussion

Of the children in this practice, 97% were surveyed on the first occasion and slightly smaller numbers on the subsequent screenings. This very satisfactory response was achieved by considerable effort on the part of the practice team. It was eventually necessary to make more than 40 home visits and nearly 30 home urine collections in the interests of completeness.

Collection of Specimens

The collection of specimens did not prove to be a technical problem either in infants or in older children. Though specimens were collected by the plastic bag method in 34 infants in the first survey and in smaller numbers in the subsequent surveys, the overall frequency of doubtful results was 14 out of 1,259 specimens (1.1%). Very few children were receiving antibacterial treatment and no local antiseptic was used in preparation for specimen collection; we believe that the reason for the very low level of contamination was the immediate refrigeration of the samples on collection and the immediate culture of the specimens on removal from the refrigerator. Furthermore, when bags were used a careful watch was kept so that the specimen was removed as soon as voided.

Symptoms of Childhood Urinary Infection

It is well recognized that urinary tract infection in childhood is often overlooked because the symptoms are not those classically associated with adult infection. The six symptomatic children presented as follows: fever and convulsions in a boy aged 10 days*; fever and abdominal pain in a girl aged 2 years; fever and dysuria in a 4-year-old girl*; fever, dysuria, and loin pain in a girl aged 4 years*; frequency and dysuria in a 6-year-old girl*; and frequency, nocturia, dysuria, and abdominal pain in a 6-year-old girl.* The symptoms in these children were more "typical" with increasing age.

A further reason for missing the diagnosis is the quite erroneous belief in the difficulty of collecting satisfactory urine samples from infants and younger children and the consequent blind use of antibiotics which may later obscure the diagnosis.

Dysuria and frequency are common symptoms of vulvitis in young girls. In the present survey none of the children complaining of dysuria or frequency had infected urine.

Occurrence of Bacteriuria

Over the course of eight months (three screenings) five children were found to have significant bacteriuria. Four of these were asymptomatic and one presented with abdominal pain and fever. Between the first and third screenings four children were found to have "new" urinary infections. This gives a calculated annual incidence of 1.4%. Not all of the children appeared to be equally likely to develop bacteriuria, since all five children found to be bacteriuric were under the age of 5. The calculated incidence of new cases of significant bacteriuria in this age group is 4.9%. Ten children in the practice have now been found to have urinary infections. Their ages at the time of diagnosis were under 1 year (one boy), 1 year (one boy), 2 years (one girl), 4 years (five girls), and 6 years (two girls). Thus 8 out of 10 children known to have had urinary tract infection were already infected before school age. Urinary tract abnormalities were present on radiological examination in five of the eight children where such investigations were undertaken.

These findings suggest that the optimal time for screening children for bacteriuria in the hope of preventing renal disease may be substantially earlier than school entry at 5 years. This is also supported by the results of screening 5-year-old school-girls in Dundee, where 3 of the 20 bacteriuric girls had established chronic pyelonephritis, each with vesicoureteric reflux and a past history of urinary infection (Savage *et al.*, 1969). The earlier the diagnosis of urinary infection is made in children with reflux, the greater the chance of the kidneys being unscarred (Smellie and Normand, 1966).

Contrary to expectation there was little or no relation between upper respiratory tract infection and the finding of bacteriuria. No strong seasonal pattern emerged from the study.

Pyuria, Proteinuria, and Glycosuria

The criterion of significant pyuria in this study was a white cell count on fresh uncentrifuged urine of more than 10/cu. mm. (Table II). Of 41 urine samples showing significant pyuria only one came from a child with bacteriuria. Only one of the five children shown to have bacteriuria during the study was found also to have pyuria. Pyuria was clearly a poor index of the presence of asymptomatic urinary infection or of the need for treatment.

The results of testing for proteinuria were so misleading as an index of the presence of infection as to cause us to abandon the procedure in routine practice.

* Diagnosed during previous studies.

Glycosuria was found in only one child, a known diabetic. It is interesting to note that 10 instances of childhood urinary infection have now been found in this practice and only one diabetic, and that urinary tract infection with structural or functional abnormalities of the renal tract is apparently at least five times as common as diabetes in childhood.

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Pleural Effusion and Fibrosis during Treatment with Methysergide

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Summary: Two patients being treated for migraine with methysergide developed extensive pleural fibrosis, and in addition one of them had bilateral pleural effusions. After treatment was stopped these complications, which are thought to have been due to the drug, cleared in the next few months.

Introduction

Methysergide (Deseril) is effective in the prevention of severe migraine but has many side effects, among which are peculiar fibroses affecting the retroperitoneal tissue, heart valves, coronary arteries, and the myocardium (Ureles and Rob, 1963; Graham, 1964; Sweetnam, 1964; *Lancet*, 1965; Graham *et al.*, 1966). Graham (1967) first suspected a relation between otherwise unexplained pleuropulmonary disease, and similar cases have been reported by Bays (1968) and Lindeneg and Kok-Jensen (1968).

We record below two cases of pleuropulmonary complications which we believe to be due to methysergide and which to the best of our knowledge are the first to be reported from this country.

Case 1

A 50-year-old storeman, who had suffered from migraine for many years and been treated with methysergide 1 mg. t.d.s. for six months, was admitted to hospital because of increasing dyspnoea and abdominal pain. Dullness to percussion and decreased air entry were found at both bases, and chest x-ray examination confirmed the presence of bilateral pleural effusions with evidence of fibrosis.

No asbestos bodies, malignant cells, or tubercle bacilli were found in the sputum. Blood-stained pleural fluid was aspirated from the right pleural space and clear fluid from the left side. Neither specimen contained tubercle bacilli or malignant cells. Pleural biopsy showed dense hyaline fibrous tissue but no evidence of malignancy.

Investigations showed haemoglobin 12.5 g./100 ml., E.S.R. 65 mm. in one hour (Westergren), and total serum proteins 6.6 g./100 ml. (albumin 2.9 g., globulin 3.7 g.). Protein strip showed decreased albumin and alpha-2 globulins. Rose-Waaler and lupus erythematosus latex tests were negative and no L.E. cells were seen. Serum calcium and phosphate were normal.

Intravenous pyelogram gave no evidence of retroperitoneal fibrosis and barium meal examination was normal. Liver and muscle biopsy showed no abnormality.

Methysergide was stopped and since then there has been a gradual lessening of the dyspnoea with pronounced improvement in the chest x-ray appearances and a fall in the E.S.R. to 28 mm. in one hour.

Case 2

A 37-year-old woman schoolteacher was referred for chest x-ray examination because of pain in her left lower chest and back for four months, associated with dyspnoea on effort. In 1956 sarcoidosis was proved on gland and liver biopsy, but there was never any evidence of pulmonary or pleural involvement. She had been treated with steroids for two years, there being no subsequent signs or symptoms of sarcoidosis. For six years she had been treated with methysergide (3-6 mg./day) for severe attacks of migraine.

On examination there was a loud crackling friction rub at the left base and her left lower back was tender. No other abnormalities were found. Haemoglobin (14.5 g./100 ml.) and W.B.C. were normal, and E.S.R. was 33 mm. in one hour (Westergren). Serum aspartate aminotransferase 66 i.u./ml., but serum proteins, electrolytes, and alkaline phosphatase were normal. Latex test was negative and no L.E. cells were seen. Mantoux test was negative at 1:100.

Chest x-ray film showed extensive pleural fibrosis at the left base with high tenting of the left diaphragm. There was no definite evidence of pleural effusion. Intravenous pyelogram was normal.

Methysergide was stopped and her respiratory symptoms rapidly improved. Seven months later she felt well, the friction rub had disappeared, and her E.S.R. was 10 mm. in one hour and her serum aspartate aminotransferase 10 i.u./ml. She had no further attacks of migraine. Within two months of stopping methysergide her chest x-ray picture showed clearing of the lesions at the left base with the exception of obliteration of the left costophrenic angle and some fibrosis in the left interlobar fissure.

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