

STREPTOCOCCAL SORE THROAT AND PROTEINURIA

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AFTER an attack of scarlet fever, some patients excrete red cells, casts and protein, but show no other sign of renal disease. Routine examination of the urine brings these cases to light, and the more often this is done, the more frequently are they found (Dittmar, 1897; McCrae, 1913; Lyttle, 1933; Weinstein, 1950). Proteinuria may be the only abnormality (Smith, 1892; Hunter, 1909; Russell, 1925; Snoke, 1937).

After acute pharyngitis and tonsillitis without rash, similar urinary abnormalities may be found (Jones, 1927; de Wesselow, 1935) and in several outbreaks of acute nephritis following epidemics of sore throats, haematuria and proteinuria have been discovered by routine examination of symptomless contacts (Kemp, 1951; Manser and Wilson, 1952; Siegel *et al.*, 1953). In an outbreak of pharyngitis in a military camp, a high incidence of microscopic haematuria, often with a mild proteinuria, was found in the early stages in both streptococcal and non-streptococcal cases, but most commonly in those associated with Type 12, Group A β -haemolytic streptococci. A number of patients also had microscopic haematuria during convalescence; some showed the classical clinical picture of acute diffuse glomerulo-nephritis, others, no clinical abnormalities at all (Stetson *et al.*, 1955).

The significance of these urinary abnormalities is not known, but, if the theory is true that only certain types of Group A streptococci (Types 12, 4, 25 and 49) are nephritogenic (Rammelkamp, 1956) then an association between infections with these types and the subsequent development of urinary abnormalities would be evidence in favour of a relationship between such cases and overt acute nephritis. The meaning of proteinuria alone is particularly difficult to elucidate. It is found in the febrile stage of other infectious illnesses apart from scarlet fever, though rarely exceeding 0.5 G. in

24 hours (Schreiner, 1957), and may even follow the administration of salicylates—commonly given in any infectious illness (Scott, 1963). Moreover, it is known that, among any group of apparently healthy individuals, a number will be found to show proteinuria on routine examination. King and Grombeck (1952) gives an incidence of 3.3 per cent for males in the age group similar to that of recruits for the American Forces. A proportion of such accidentally discovered proteinurics can be shown to have serious renal disease (King, 1956).

All urines probably contain some protein (Rigas and Heller, 1951; Sellers, 1956), though not in amounts detectable by the usual clinical tests. The chances of finding protein by such tests are greater if the urine is concentrated; it is more often found in the mid-morning specimen (Derow, 1942), in adolescence (Stirling, 1887), in girls (Calvin *et al.*, 1926), after exercise (Hellebrandt, 1932; Collis, 1907) and after maintaining certain postures. Bull (1948) was able to demonstrate proteinuria in 77 per cent of healthy sea-cadets in a posture of erect lordosis.

In many such cases the proteinuria is transient, and re-examination of the same group of people may reveal the same proportion with proteinuria, but in different subjects. Thus, merely increasing the number of urines tested will give a higher percentage of proteinurics in any group (*see*, for example, Calvin, 1926; Diehl and McKinlay, 1932). Wolman (1945) showed that 56 per cent of one group of soldiers passed at least one specimen containing protein when eight specimens were tested over five days, and Theobald (1932) found that only 11 out of 22 female students consistently passed urine either free from or containing less than a trace of protein.

Present study

A man of 40 was found by chance to have mild hypertension and the urinary syndrome of acute nephritis after a sore throat. The urine was examined thereafter in all cases of sore throat seen by the author and, over 27 months, five patients with proteinuria were found. They presented problems of diagnosis and management and, to gain more information about such cases, the investigation reported here was undertaken.

Objects:

1. To determine the incidence of proteinuria during and after acute streptococcal pharyngitis.
2. To relate proteinuria and any associated urinary abnormalities to the type of Group A streptococci responsible for the throat infection.
3. To study the effect of treatment on the development of these complications.

Method:

From 30 May 1956 to 31 July 1958, throat swabs were taken from all patients

who complained of a sore throat or who had evidence of inflammation of the throat or tonsils. Those whose throat swab yielded Group A β -haemolytic streptococci were followed up. Patients were asked to send in a specimen of urine every two days for the first eight days and then each week for five weeks. They were seen two or three days later, and again about the eighth day, when a second throat swab was taken. Clinical data and the results of urine tests and swab culture were entered on a special card for each patient.

Two swabs were taken; one was broken off into a bottle of Stuart's transport medium and both were then sent to the laboratory by post, arriving within 24 hours in most cases. Each was sown on to a horse blood agar plate and incubated at 37°C for 24 hours. All β -haemolytic streptococci isolated were grouped and subcultures were preserved for typing in any case with renal complications.

Urines were tested by the author, using the heat and acetic acid method. Any specimen that contained protein was sent in by post to the laboratory for microscopy and culture. Patients with proteinuria were studied more intensively. All were examined and their blood pressure measured. More frequent urine examinations were performed and, in any case with more than transient proteinuria, the output and weight were measured daily and blood was taken for ESR, haemoglobin, white cell count and blood urea.

It was decided that all cases with fever or marked signs or severe symptoms would be treated with either penicillin or sulphadimidine. Patients whose age was an even number received penicillin (oral penicillin V, for five days, except for five cases who received intramuscular penicillin), and those whose age was an odd number were given sulphadimidine for five days. In five episodes (two in the same patient) a candidate for the latter did, in fact, receive penicillin from the start (because of severe symptoms) and in nine instances penicillin was given later on, either because the sore throat had recurred, or because complications had developed.

Results

Over approximately two years, 251 episodes of illness were seen by the author. In four, no swab could be taken and in five cases swabs were not received at the laboratory; three of these patients had no specimen of urine examined and of the other six only one showed a trace of protein—a child of five who was found to have a urinary infection.

In 85 episodes, no Group A β haemolytic streptococci were isolated from the throat swab. In 57 of these episodes no pathogenic bacteria were cultured; in nine cases pneumococci; in two, *Staphylococcus aureus*; in ten, β -haemolytic streptococci, other than Groups A, C or G, and in seven, Group C streptococci were cultured; six of the seven patients harbouring Group C streptococci were males and only one was under 15 years of age.

In 157 episodes a Group A β -haemolytic streptococcus was isolated from the throat swab. Twenty patients appeared more than once in the whole series, but only ten had two episodes of sore throat associated with Group A streptococci. Eighty-eight (56 per cent) were seen within 24 hours of the onset of their illness and 120 (76

per cent) within two days. Males and females were about equally represented. Half the episodes seen were in children under 15, about a quarter being in the age group 5-9 (table I).

One thousand and nine specimens of urine were tested in these 157 episodes and proteinuria was demonstrated at some time in 33 of them (21 per cent). Two patients each had two episodes of proteinuria. In one of these 33 episodes, a faintly positive heat test in a turbid urine was not confirmed by examination of the centrifuged urine, and in four cases urinary infections were discovered to be the cause of proteinuria. The details of the remaining 28 episodes appear in table II.

One patient had acute nephritis when first seen:

Case 1. R.K., aged 5, was seen on 10 February 1958 complaining of headache, occasional vomiting and swelling of the face. Four days previously he had complained of a sore throat. Throat swab gave a moderate growth of Type 1 streptococci. T. 100.8° F, B.P. 110/70. Slight facial oedema. Urine: 2 G. per cent of protein, very numerous white and red cells, granular and cellular casts. Anuria was present for 24 hours and he was then transferred to hospital, where he made a good recovery. One brother had a sore throat and throat culture yielded Group A β -haemolytic streptococci, but his urines remained free of protein.

Two other patients had protein in all, or almost all, specimens tested over several weeks. E.M., a woman of 41 with no previous evidence of renal disease, had a very marked proteinuria (2.5 G./100 ml.) and microscopic haematuria during the acute stage of a sore throat associated with Type 3 streptococci. Proteinuria reappeared following a recurrence of sore throat seven days later and persisted thereafter with occasional red cells and hyaline casts. Pyuria and an *E. Coli* infection were found on the 19th day without symptoms. Urea clearance tests and IVP were normal. Her husband (J.M.) had transient proteinuria following a sore throat at the same time, also associated with Type 3 streptococci.

R.M., a woman of 22, was found to have persistent proteinuria and slight microscopic haematuria after a sore throat associated with Type 1 streptococci. She was found to have a bifid renal pelvis and upper third of the ureter on the right side and the probable diagnosis is chronic pyelonephritis. At one stage she had marked pyuria, an E.S.R. of 50 mm, a blood urea of 50 mg./100 ml., urea clearance of 65 per cent of average values, but at no time any symptoms of renal disease.

If these two patients with persistent proteinuria and the boy with acute nephritis (R.K.) are omitted, there remain 25 episodes in which

TABLE I
EPISODES ASSOCIATED WITH GROUP A STREPTOCOCCI

| Initial treatment | Total | M | F | Duration | | | Age | | | | | | | | | |
|-------------------|-------|----|----|----------|--------|----|-----|----|----|----|----|----|----|----|----|----|
| | | | | 1 day | 2 days | 3+ | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 |
| Penicillin .. | 68 | 31 | 37 | 39 | 16 | 13 | 9 | 6 | 12 | 3 | 5 | 8 | 18 | 4 | 3 | 0 |
| Sulphadimidine .. | 44 | 18 | 26 | 33 | 5 | 6 | 5 | 17 | 2 | 1 | 3 | 5 | 3 | 6 | 2 | 0 |
| Other .. | 45 | 25 | 20 | 15 | 11 | 19 | 4 | 15 | 8 | 2 | 3 | 3 | 6 | 3 | 0 | 1 |
| Total .. | 157 | 74 | 83 | 87 | 32 | 38 | 18 | 38 | 22 | 6 | 11 | 16 | 27 | 13 | 5 | 1 |

TABLE III
EPISODES WITH TRANSIENT PROTEINURIA, BY DAY OF ILLNESS

| | Day | | | | | | | | | | | | | Week | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|------|---------|
| | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | 10th | 11th | 12th | 13th | 14th | 15th | 3rd-6th |
| Episodes tested | 54 | 21 | 69 | 25 | 66 | 39 | 40 | 47 | 52 | 37 | 25 | 19 | 10 | 12 | 140 |
| Urines .. | 54 | 21 | 69 | 25 | 66 | 39 | 40 | 48 | 53 | 37 | 25 | 19 | 10 | 12 | 426 |
| Proteinuria | | | | | | | | | | | | | | | |
| Total .. | 5 | 1 | 4 | 1 | 2 | 0 | 1 | 10 | 5 | 5 | 2 | 4 | 3 | 2 | 5* |
| Per cent .. | 9 | 5 | 6 | 4 | 3 | 0 | 2 | 21 | 10 | 14 | 8 | 21 | 30 | 17 | 4 |
| New cases .. | 5 | 1 | 2 | 1 | 2 | 0 | 1 | 8 | 0 | 2 | 0 | 1 | 0 | 1 | 1† |
| Per cent .. | 9 | 5 | 3 | 4 | 3 | 0 | 2 | 17 | 0 | 5 | 0 | 5 | 0 | 8 | 0.7 |

*Includes G.W. and M.M., both of whom had intervening illnesses, and two episodes in the same patient (P.H.). †G.W.

TABLE II

EPISODES WITH PROTEINURIA (GROUP A STREPTOCOCCI ONLY)

★ = urine test. T = trace or faint trace.

● = protein found (bold figures indicate concentration in mg. per cent).

| Duration of illness | Name | Sex | Age | Tr. | Temperature | | Urine tests | | | | | | | | | | | | | | Total urines | Urines with Prot. | Red cells | Casts | Comments |
|---------------------|----------|-----|-----|-----|-------------|----------------|--------------------|----|---|---|---|---|----|---|---|----|----|----|----|----|--------------|-------------------|-----------|------------|--|
| | | | | | Init. | Onset of Prot. | Day of observation | | | | | | | | | | | | | | | | | | |
| | | | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | | | | | |
| 1 day | JT GD(2) | F | 7 | S | 103.8 | 103.8 | T | T | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 5 | 1 | — | — | Severe sore throat. P/uria again (see below). Few leucocytes seen. Son (GP) also had proteinuria q.v. Sister (MM) also had p/uria. |
| | HG | F | 36 | P | 103.0 | ? | ● | ● | ● | ● | ● | ● | 15 | ● | ● | ● | ● | ● | ● | ● | 7 | 1 | + | — | Sister (MM) also had p/uria. |
| | PM | F | 16 | P | 102.4 | 102.4 | T | ● | ● | ● | ● | ● | 35 | ● | ● | ● | ● | ● | ● | ● | 5 | 2 | — | — | Stopped S/dim on 7th day, recurrence 9th day, few leucocytes in urine + prot. S/dim recommenced. |
| | CM | F | 7 | S | 102.4 | ? | ● | ● | ● | ● | ● | ● | 15 | ● | ● | ● | ● | ● | ● | ● | 10 | 1 | — | — | See case report. |
| | EL | M | 39 | S | 102.0 | 97.0 | ● | ● | ● | ● | ● | ● | T | ● | ● | ● | ● | ● | ● | ● | 8 | 1 | — | hya-line | Sore throat (Grp. A strep.) 4 mths. later: 6 urines normal. |
| | EM | F | 41 | S | 101.4 | 101.4 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 24 | 20 | + | — | Penicillin 10th day, p/uria again later, few leucocytes. |
| | RW | M | 28 | P | 101.2 | 98.4 | ● | ● | ● | ● | ● | ● | T | ● | ● | ● | ● | ● | ● | ● | 6 | 3 | — | — | Congenital cyanotic heart disease. Type 28 (see case report) |
| | ML | F | 12 | P | 101.2 | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 2 | 1 | + | — | Few leucocytes seen. Type 6. Previous p/uria (see case report). |
| | AP PH(1) | F | 30 | P | 101.0 | 101.0 | T | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 34 | 6 | + | — | Father (swab neg.) also had sore throat and proteinuria. |
| | MM | F | 9 | P | 100.0 | 96.0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 6 | 2 | — | — | See case report. |
| | JO PH(2) | M | 39 | S | 97.4 | 99.8 | T | ● | ● | ● | ● | ● | 80 | ● | ● | ● | ● | ● | ● | ● | 6 | 2 | — | — | Recurrence of sore throat on 5th day. |
| | CB | F | 3 | S | 99.6 | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 12 | 4 | — | — | Mother also had p/uria (HG) |
| | RM | F | 22 | P | 98.8 | 98.4 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 15 | 15 | + | — | Type 1 (heavy growth) |
| | RL | F | 13 | A | 97.4 | 98.2 | ● | ● | ● | ● | ● | ● | 30 | ● | ● | ● | ● | ● | ● | ● | 8 | 2 | — | — | Acute nephritis; admitted to hospital. Type 1 strep. |
| | IS | M | 7 | S | ? | 99.0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 8 | 1 | — | — | Type 3. Wife, EM, also had proteinuria. S/dim started on 6th day. |
| 2 | CP | M | 34 | P | 101.2 | 101.2 | T | 20 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 8 | 1 | — | — | See case report. |
| 3 | GD(1) | F | 27 | P | 100.2 | 98.0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 8 | 1 | — | — | Recurrence of sore throat on 5th day. |
| 7 | GP | M | 12 | P | 99.4 | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 4 | 1 | — | Occ. gran. | Mother also had p/uria (HG) |
| 4 | AT | M | 7 | A | 99.2 | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 11 | 3 | — | — | Type 1 (heavy growth) |
| 5 | FH | M | 32 | A | 98.8 | 98.0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 8 | 5 | — | — | Acute nephritis; admitted to hospital. Type 1 strep. |
| 3 | PW | F | 10 | A | 98.4 | 98.6 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 4 | 1 | + | — | Type 3. Wife, EM, also had proteinuria. S/dim started on 6th day. |
| 4 | RK | M | 5 | P | 98.0 | 98.0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 6 | 3 | — | — | See case report. Osteomyelitis after sore throat. |
| 5 | JM | M | 39 | AS | N | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 9 | 2 | — | — | |
| 2 | GW | M | 2 | AP | 97.0 | ? | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | 30 | 9 | — | — | |

a transient proteinuria, not associated with pyuria, was noted. These occurred in 23 patients. One patient (C.M.) was found to have proteinuria on another occasion after a sore throat with a negative culture, but two others had two episodes within the Group A series. One (G.D.) had proteinuria within the first three days on two occasions, associated with a severe sore throat each time, and one other (P.H.) had transient proteinuria, slight on the first occasion, but more marked after the second episode of sore throat when Type 6 streptococci were isolated from both throat and urine. Unfortunately, a vulval swab was not taken so that local parasitism by the organism cannot be excluded:

Case 2. P.H., female, aged 9. 1957: sore throat associated with heavy growth of Group A streptococci. Urines on fourth and eighth days were normal but on the tenth day a trace of protein, a few leucocytes and occasional red cells were noted. The initial treatment was aspirin, but on this day oral penicillin was started. Subsequently seven urines were normal except for a trace of protein on one occasion.

1958: 17 July: moderate sore throat on left side only. T. 99.6° F. Left tonsil was enlarged and injected, with exudate. Both tonsillar glands were enlarged and tender. Swabs: right side—no pathogens; left side—heavy growth Type 6 streptococci. Treatment: sulphadimidine.

The urine was free of protein on third and fourth day and by the third day the sore throat was gone. On the fifth day after she was first seen the throat swab again gave a culture of Type 6 streptococci and the same type was isolated from the urine, which contained 35 mg./100 ml. of protein and a few leucocytes. On the ninth day there was 40 mg. per cent of protein, a few leucocytes and again a growth of Type 6 streptococci; on the tenth day 65 mg./100 ml. of protein in a single specimen. B.P. was 100/65 and she was well. The protein was absent next day but she was put on oral penicillin in view of the persistence of streptococci in the throat. Four urines subsequently contained up to 20 mg. per cent of protein but three later specimens were clear.

One patient with proteinuria had congenital cyanotic heart disease:

Case 3. M.M., female, aged 9. 1957: 10 January: moderate sore throat for one day. T. 100° F. Exudate, injection and swelling of the tonsils, tonsillar glands enlarged, right gland tender. Swab: heavy growth Type 28 streptococci. Treatment: penicillin by injection at first, orally later.

By 12 January her temperature was normal and she was well. The urine was normal. On 14 January (fifth day of her illness) the urine contained 80 mg. per cent of protein and a few epithelial cells. B.P. 116/70. No symptoms or signs. The next two specimens were free of protein but the first urine after she was allowed up contained 35 mg. per cent. Six subsequent specimens, some taken at the beginning and some at the end of the day, were normal but on 20 February she had another sore throat with a positive culture, and, next day, 10 mg. per cent of protein, with a few leucocytes and occasional red cells, were noted in the urine. Her eyes were said to have been puffy for a day. Over the next 20 days protein was found in three out of 12 specimens and a few red cells were noted on one occasion. Blood urea was 23 mg./100 ml. Subsequently ten urines were free of protein. At no time was there oliguria or change in weight.

Comment: a girl aged nine with congenital cyanotic heart disease,

following a sore throat associated with Type 28 streptococci, had transient proteinuria which recurred after a further sore throat associated with Group A streptococci (not typed) six weeks later. Red cells were also found on two occasions and there may have been slight periorbital oedema for one day. Her sister, P.M., aged 16, also had a sore throat, associated with Group A β -haemolytic streptococci, and proteinuria on the first day.

G.W., a boy of 2 appears as the only patient in whom proteinuria was discovered for the first time after the second week. But he was admitted to hospital with osteomyelitis of the calcaneum shortly after his acute pharyngitis and had no urine tests before the sixth week.

If the 25 episodes (in 23 patients) with transient proteinuria are alone considered, the incidence of proteinuria, whether expressed as a percentage of patients tested or as a percentage of urines tested, was highest in the second week after patients were first seen, rising from 10.6 per cent of those tested in the first week, to 12.2 per cent in the second week, and falling thereafter to 2 per cent or less (figure 1). In only five episodes was proteinuria found after the 15th day; two of these patients have had illnesses after their initial sore throat—a second sore throat in one (M.M.), the day before proteinuria recurred, and acute osteomyelitis in the other (G.W.). One patient (P.H.) was responsible for two more of these episodes with proteinuria after the 15th day, and the remaining case was C.B. Her father also had a sore throat, at the same time, with proteinuria on the fifth day, but throat culture was negative.

In table III the findings have been adjusted so as to relate proteinuria to the day of illness. Obviously, therefore, only those seen within 24 hours of the onset of their illness had a urine test on the second day. The percentage with proteinuria was then nine and the figure fell to zero by the seventh day. On the ninth day it rose to 21 per cent and in eight patients (17 per cent) proteinuria was discovered for the first time on that day. Throughout the second

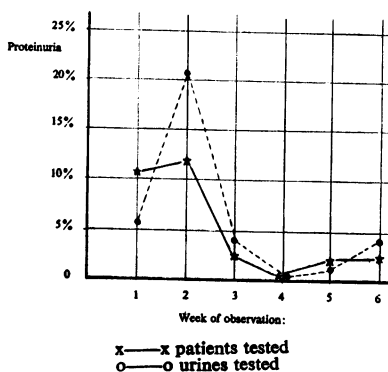


Figure 1
Incidence of transient proteinuria,
by week of observation

week the proportion with proteinuria was generally higher than in the preceding or subsequent weeks. The one patient found to have proteinuria on the 15th day was G.P., who was said to have had a sore throat for seven days when first seen. His mother (H.G.) who had a sore throat at the same time had proteinuria on the ninth day of her illness. The longer the duration of the illness before the patient was seen, the less reliable becomes the timing of the onset of proteinuria. However, if only the 82 episodes seen within 24 hours of the onset of their sore throat are considered, the findings are substantially the same; eight of the episodes tested on the ninth day had proteinuria (27 per cent), seven of them (24 per cent) for the first time.

Figure 2 shows the concentration of protein in the first specimens to show protein in each episode, by day of illness, for all those with transient proteinuria except G.W. All eight urines in the first four days contained 10 mg. per cent or less but of the 16 urines with protein after the fourth day, ten (62 per cent) contained 15 mg. per cent or more, six (37 per cent) containing 30 mg. per cent or more.

Specimens from five of these patients were found to contain small numbers of red cells at some time, four of them between the sixth day and the 14th day only. M.M.'s urine showed a few red cells for the first time the day after her second sore throat. Only one patient was found to have occasional granular cast—on the 14th day (A.T.).

While there was some evidence of a higher incidence of transient proteinuria among females under 20, the increase in proteinuria in the second week and, in particular, on the ninth day, was not due to an excess of that age and sex group among those with a urine test at that time. Whereas five of the eight episodes with proteinuria in the first four days had skin temperatures of 101°F or more at the time of proteinuria, in those cases in which temperature was recorded at the onset of proteinuria in the second week (*see* table II), it was either normal or only slightly raised. In seven cases proteinuria was

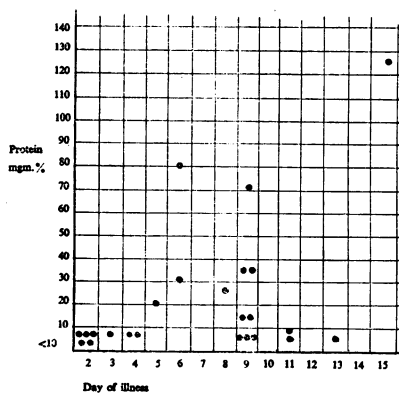


Figure 2
Transient proteinuria: concentration in first specimen to show protein in each case, by day of illness.

noted for the first time in the first specimen tested after the cessation of treatment (penicillin in three cases, sulphadimidine in four), but in the remaining seven cases, three of which received aspirin alone, there was no apparent association between the cessation of treatment and the onset of proteinuria. Seven of the 14 patients with proteinuria in the second week did, however, show some evidence of ill health or sore throat at, or about, the time that proteinuria was noted.

In 115 patients a second throat swab was taken 7–10 days after the first but there was no evidence that persistence of the streptococcus was commoner in those with proteinuria after the first week.

Effect of treatment

The penicillin and sulphadimidine groups were comparable but the group with no specific therapy differed from them in respect of fever, duration of illness and physical signs. Only 58 per cent were seen within the first 48 hours, as against 86 per cent of the penicillin group and 81 per cent of the sulphadimidine group and only six (13 per cent) had a temperature when first seen of over 100°F as against 39 (57 per cent) of the penicillin group and 26 (59 per cent) of the sulphadimidine group.

Proteinuria was demonstrated in 17 of the 68 episodes that received penicillin, as against seven of the 44 treated with sulphadimidine and nine of the 45 with no specific therapy, but this difference is diminished if three patients in the first group and one in the last, all of whom had urinary infections, are eliminated. No such case was seen in the sulphadimidine group.

Apart from this, there did not appear to be any marked difference, whether all the other cases are considered, or only those episodes with transient proteinuria (table IV). A smaller proportion of episodes with proteinuria appear in the group treated with penicillin, after the first week, and the only case after the second week had had a sore throat a few days beforehand.

The streptococcus was typed in seven instances. From J.M. and E.M., husband and wife, the former with transient and the latter with persistent proteinuria, Type 3 streptococci were isolated, and from M.M. (whose sister had transient proteinuria also) Type 28. Type 1 was isolated from four patients; R.K., who had acute nephritis, R.M., who had persistent proteinuria and probable chronic pyelonephritis, F.H., a male of 32 with transient proteinuria, and from a contact of a case of acute nephritis that did not enter the

TABLE IV
EPISODES WITH TRANSIENT PROTEINURIA : EFFECT OF INITIAL THERAPY

| Initial treatment | Total | | | Proteinurics | | | First week | | | | Second week | | | | Subsequently | | | |
|-------------------|-------|--------|----|--------------|-------|----|------------|-----|-------|----|-------------|-----|-------|----|--------------|-----|-------|---|
| | Epis. | Urines | M | F | Total | % | Ep. | Ur. | Prot. | % | Ep. | Ur. | Prot. | % | Ep. | Ur. | Prot. | % |
| | | | | | | | | | | | | | | | | | | |
| Penicillin | 62 | 436 | 3 | 8 | 11 | 18 | 61 | 173 | 7 | 11 | 56 | 84 | 5 | 9 | 57 | 179 | 1* | 2 |
| Sulphad. | 43 | 290 | 2 | 4 | 6 | 14 | 40 | 129 | 3 | 7 | 34 | 48 | 4 | 12 | 40 | 113 | 2 | 5 |
| Other | 44 | 218 | 5 | 3 | 8 | 18 | 30 | 53 | 3 | 10 | 32 | 14 | 5 | 16 | 42 | 119 | 2† | 5 |
| Total | 149 | 944 | 10 | 15 | 25 | 17 | 131 | 355 | 13 | 10 | 122 | 146 | 14 | 11 | 139 | 411 | 5 | 4 |

*M.M. who had a second sore throat. †Includes G.W. who had acute osteomyelitis after sore throat and no urine test before the sixth week.

TABLE V
EPISODES WITH PROTEINURIA AFTER SORE NOT ASSOCIATED WITH GROUP A STREPTOCOCCI
● = urine test, T = Trace or faint trace Bold figures = urine with protein concentration (mg. per cent).

| Duration in days | Negative swab | | | Temperature | | Day of observation | | | | | | | | | | | | | | Weeks | Total urines | Urines with Prot. | Red cells | Treatment | Comments |
|-----------------------|-------------------------------------|--------------|-------------|----------------------|--------------|--------------------|-------------|--------------|-------------|-------------|--------|--------|--------|----|----|--------|--------|----------|-------------|-------------|-----------------|---|-----------|--|----------|
| | Name | Age | Sex | Onset | Prot. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | | | | | | |
| 1 2 | J.R. C.B. | 9 32 | M M | 102.4 101.6 | 97.4 97.0 | ● ● | ● ● | 15 ● | 25 ● | T ● | ● ● | ● ● | ● ● | | | ● ● | ● ● | ● ● | | 3 12 | 2 2 | Occ. — | S. S. | Few pus cells; no follow-up Daughter also had protein- uria after sore throat (Group A) Occasional pus cell. | |
| 1 1 3 | J.T. K.M. D.B. | 9 7 13 | F F F | 99.6 99.0 97.6 | 98.6 97.4 | ● ● T | ● ● ● | 40 T ● | ● ● ● | ● ● ● | | | ● ● | | | | | | 4 4 1 | 1 1 1 | — — — | S. S. Asp. | | | |
| Strept Not 3 | lococcus A, C or J.M. | G: 42 | M | 101.2 | ? | ● | ● | ● | ● | ● | | | | | | | T | T | 7 3 | 3 Occ. | V. Pen. Occ. | Very occasional leucocyte. | | | |
| 3 | D.P. | 11 | F | 97.6 | ? | ● | ● | ● | ● | | | 20 | | 30 | ● | ● | | | 14 4 | — | NH | Few pus cells, frequent epithelial cells. | | | |
| Strept C 2 5 | lococci C and G: I.M. D.B. | 18 25 | M F | 98.6 98.0 | | ● | | 10 ● | 10 ● | T ● | ● ● | ● ● | ● | | | | | 10 11 | 3 2 | Occ. — | A A | | | | |
| Pneumococci 1 | C.M. | 7 | F | 99.2 | ? | 1 | | T | | ● | | | | | | | | | 3 1 | — | S. | Occasional pus cells; also had proteinuria in HS. A. series. | | | |

series. This was a girl of three who presented with frequency and dysuria; throat swab was negative but her father had a sore throat at the same time and a heavy growth of Type 1 streptococci was cultured from his pharynx. Two other cases of acute nephritis occurred among the author's patients during the study. One was sent into hospital by a colleague and the other was seen with an acute tonsillitis by a colleague; two weeks later, routine urine testing showed red cells, hyaline casts and protein and he was found to have slight oedema.

No attempt was made to follow-up in the same way those cases of sore throat who did not give a positive culture of Group A streptococci but some, who were thought clinically to be possible cases of streptococcal infection when first seen, did continue to send in urine specimens. Amongst those with a negative throat culture, the same proportion had proteinuria in the first week as in the Group A series but follow-up was virtually confined to those patients who were discovered to have proteinuria. Two out of eight patients whose throats yielded streptococci other than Groups A, C or G had proteinuria, both in the second and subsequent weeks, and two of the seven yielding Group C streptococci had proteinuria, one in the second and subsequent weeks, but the numbers are too small to permit any conclusions. There did not appear to be any association between the duration of illness and the concentration of protein in the first specimen found to contain protein. Three patients were found to have red cells in the urine (table V).

Discussion

The study here described was designed as a reconnaissance and its limitations must be emphasized. Serological studies were not carried out to confirm that a streptococcal infection had actually occurred in each case. It was not possible to determine the prevalence of different types of streptococci within the community. Standardization of the method of collecting urines was not practicable.

The fact that 21 per cent of the 157 episodes associated with Group A streptococci were found to have proteinuria is not in itself remarkable. A figure of this kind could be produced if sufficient urine specimens from any group were tested under certain conditions. In one of the two cases with persistent proteinuria, present from the start (E.M.), the marked initial proteinuria, its rapid lessening and its recurrence after a further sore throat suggests some effect of the illness itself, but in neither patient can pre-existing proteinuria be excluded. The relationship of the proteinuria to the primary illness

appears most clearly when the 25 (16 per cent) episodes with transient proteinuria are alone considered. Here the striking facts are the rise in the proportion of those with proteinuria in the second week after the sore throat and the marked decline thereafter: and the concomitant increase in the concentration of protein in single random specimens. The particularly sharp rise on the ninth day, so that 21 per cent of the episodes tested on that day had proteinuria—8 (17 per cent) of them for the first time—is in line with the experience of others. In one series (Thomson, 1886) of 180 cases of scarlet fever, 'late albuminuria' was noted most frequently at the beginning of the second and third weeks: "the numbers cluster about the ninth and 15th days and albuminuria here seems greater and longer lasting". Lyttle (1933) found the rise in the excretion of protein, red cells and casts in scarlet fever to occur from the eighth to the 45th day. Rammelkamp (1954) described the rise in red cell excretion as beginning on the seventh day becoming pronounced on the 14th and 21st days. (*See also* Dittmar, 1897, and West, quoted by Smith, 1892).

In half the 14 cases with proteinuria during the second week of observation, proteinuria followed the cessation of treatment; three of these patients, and four others besides, had some evidence of ill health at the time. But five had received no specific therapy before the onset of proteinuria.

The pattern of events in the group, and in individuals within the group, suggests a relationship between the acute pharyngitis, or tonsillitis, and transient proteinuria, but, of course, it is not known whether this is peculiar to Group A streptococcal infections. An association between proteinuria and the generally accepted nephritogenic types of streptococci was not suggested by the few instances in which typing was carried out. Type 3 was found in the throat of one patient with persistent proteinuria (E.M.) and in that of her husband (J.M.), who had transient proteinuria at the same time. Type 6 and Type 28 were isolated from two other cases of transient proteinuria. Type 1 streptococci were isolated from one patient with persistent proteinuria (R.M.), from one case of transient proteinuria (F.H.), from one case of acute nephritis (R.K.) and from the contact of another. Type 1 has been found in association with a family outbreak of acute nephritis (Goldsmith *et al.*, 1958).

It may be noted in passing that in the course of this study routine urine testing led to the discovery of symptomless cases of renal disease. Two of these did not enter the series; a case of urinary

infection in a child and one case of acute nephritis. In addition, four cases of urinary infection were discovered on microscopy of urines with protein, only one of whom had frequency and dysuria, and two cases with persistent proteinuria had symptomless pyuria while under observation.

Summary

Over about two years, in a general practice, 157 episodes of sore throat (in 147 patients), associated with Group A β -haemolytic streptococci were observed and urines examined for protein for up to six weeks.

Proteinuria was demonstrated at some time in 33 episodes (21 per cent). There were 25 episodes (in 23 patients)—16 per cent of the whole—in which proteinuria was transient and not associated with evidence of urinary infection or nephritis. The incidence of transient proteinuria was higher in the second week (12 per cent of those tested), reaching a peak on the ninth day when ten patients (21 per cent of those tested) were found to have proteinuria, eight of them (17 per cent) for the first time, and fell to two per cent or less in subsequent weeks. The chance of finding red cells in the urine also appeared to be higher during the second week and the concentration of protein in single random specimens tended to be greater. A relationship between acute pharyngitis and transient proteinuria, particularly in the second week after the sore throat, is suggested, but it cannot be said whether this is peculiar to streptococcal infections. Proteinuria was found in some patients whose throats did not yield Group A streptococci.

No association between the accepted nephritogenic types of streptococci and proteinuria was demonstrated. Type 1 was isolated from one case of acute nephritis, from the contact of another, from one case of persistent, and one case of transient, proteinuria. Type 3 was isolated from the other case of persistent proteinuria and from her husband who had transient proteinuria. Type 6 and Type 28 were isolated from two other cases of transient proteinuria.

Routine testing of urine in this study led to the discovery of four cases of urinary infection and two cases of persistent proteinuria, one with evidence of impaired renal function.

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In each case there was a low positive titre of neutralizing antibody in the 'acute' specimen of blood taken within 20 hours of the rash appearing, followed by a sharp rise of titre in the 'convalescent' specimen.

Author's summary