PAPERS AND ORIGINALS

Serum and Urinary Fibrin/Fibrinogen Degradation Products in Glomerulonephritis

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Summary

The serum and urine concentrations of fibrin/fibrinogen degradation products (F.D.P.) were estimated in 172 patients with glomerulonephritis. In each case the diagnosis was established on the basis of clinical, renal histological, and ultrastructural findings. Serum F.D.P. concentrations were often raised in all types of glomerulonephritis, though more consistently in active proliferative forms. The urinary concentration provided a reliable and sensitive index of activity, progression, and natural history in proliferative glomerulonephritis. In these forms the urinary F.D.P. content was thought to reflect predominantly lysis of intraglomerular fibrin deposits. In minimal lesion and membranous glomerulonephritis low but abnormal concentrations of urinary F.D.P. were consistently found. It is suggested that in these cases the products are derived from limited proteolysis of fibrinogen filtered through an abnormally permeable basement membrane.

Daily measurement of urinary F.D.P. concentration is of potential value in the differential diagnosis of patients with glomerulonephritis and at the same time provides a sensitive assessment of the activity and natural history of proliferative disease.

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Introduction

There has been considerable recent discussion on the influence of the intraglomerular deposition of fibrin on the natural history of glomerulonephritis and of experimentally induced renal disease (Vassalli, Simon, and Rouiller, 1963; Vassalli and McCluskey, 1965; Wardle and Taylor, 1968; Humair, Potter, and Kwaan, 1969a). In particular, it has been suggested that proliferation of endothelial and mesangial cells with progressive glomerular sclerosis might be a response to the deposition of fibrin within the glomerular capillaries, and it has been claimed that anticoagulant therapy prevents these changes (Vassalli *et al.*, 1963; Kincaid-Smith, Saker, and Fairley, 1968; Humair, Potter, and Kwaan, 1969b; Kincaid-Smith, Laver, and Fairley, 1970; Herdman *et al.*, 1970). Much of the fibrin formed naturally in vivo is removed by fibrinolysis by which an insoluble gel is converted to soluble polypeptide fragments known as fibrin/fibrinogen degradation products (F.D.P.).

The concentration of serum F.D.P. has been found to reflect the activity and severity of renal lesions in which glomerular proliferation is prominent (Steihm and Trygstadt, 1969). However, other non-renal conditions such as deep venous thrombosis and disseminated intravascular coagulation may be associated with a rise in serum F.D.P. (Ruckley *et al.*, 1970; Merskey, Johnson, Kleiner, and Wohl, 1967), and the currently available techniques do not detect abnormalities in the serum when fibrin deposition and lysis are localized and/or minimal as in the case of transplanted kidneys (Colman, Braun, Busch, Dammin, and Merrill, 1969). The urinary concentration of F.D.P. probably reflects more closely the extent of fibrinolysis in the renal tract (Clarkson, Morton, and Cash, 1970) and in the present study a sensitive and quantitative immunoassay has been used to examine both serum and urine values in patients with glomerulonephritis.

Patients and Methods

One hundred and seventy-two patients with glomerulonephritis were studied. The diagnosis was made on the basis of clinical, haematological, and biochemical findings and on the light and electron microscopic appearances of material obtained in each case by needle renal biopsy.

CLASSIFICATION OF GLOMERULONEPHRITIS

Proliferative forms of glomerulonephritis were diagnosed when histological examination showed diffuse or focal proliferation of endothelial and mesangial cells. On electron microscopic examination the presence of material in the glomerulus with the appearance of fibrin or its degradation products (Clarkson, MacDonald, Fuster, Cash, and Robson, 1970) was further evidence of this diagnosis. Among the proliferative category three subgroups—that is, polyarteritis nodosa, membranoproliferative (lobular) glomerulonephritis (Cameron, Glasgow, Ogg, and White, 1970), and acute necrotizing glomerulonephritis—were identified histologically. On clinical grounds further subdivision was possible into acute poststreptococcal glomerulonephritis, glomerulonephritis associated with Henoch-Schönlein purpura, and Goodpasture's syndrome. Positive antinuclear factor and the presence of L.E. cells, together with the typical histological and ultrastructural abnormalities (Muehrcke, Kark, Pirani, and Pollak, 1957; Baldwin, Lowenstein, Rothfield, Gallo, and McCluskey, 1970), distinguished systemic lupus erythematosus (S.L.E.) glomerulonephritis from other proliferative forms. In the presentation of data on serum and urine F.D.P. (see below) most cases have been considered together as unspecified proliferative forms, though S.L.E. and membranoproliferative glomerulonephritis are considered separately.

The diagnosis of membranous (Pollak, Rosen, Pirani, Muehrcke, and Kark, 1968) and minimal lesion glomerulonephritis (MacDonald, Lambie, and Robson, 1959) was based on their histological and ultrastructural appearances.

ELECTRON MICROSCOPIC STUDIES

In 51 patients with proliferative glomerulonephritis in whom the renal biopsy was taken during or within one month of the study (see below) the degree of intraglomerular fibrin deposition as detected by electron microscopy was correlated with maximum recorded urinary F.D.P. concentration as: 0 = no fibrin detected, + = rarefied layer between basement membrane and endothelium containing odd strands of fibrin, ++ = dark deposits between basement membrane and endothelium, +++ = fibrin projecting into capillary lumen and between endothelial cells, ++++ = glomerular capillary thrombosis.

ACTIVITY OF DISEASE

The activity of the disease in each patient was assessed in the light of information available at the time of the urinary study (see below). Cases were considered to be in an active phase if any one or more of the following clinical or pathological features were present: decreasing creatinine clearances, progressive rise in the concentration of serum creatinine, proteinuria in excess of 1 g per 24 hours, red blood cell casts in the urine, focal or diffuse proliferation of endothelial and mesangial cells, and intraglomerular fibrin. The disease was considered inactive or resolving if none of these clinical features were present or if histology showed only foci of glomerular sclerosis with or without capsular adhesions. In 83 patients concurrent clinical and histological data were analysed, in 78 only clinical material was considered because the renal biopsy was performed before one month of the urinary analysis, and in 11 only biopsy and incomplete clinical evidence was assessed.

F.D.P.

Serum and urinary F.D.P. were estimated in all patients by the tanned red cell haemagglutination inhibition immunoassay (Merskey, Kleiner, and Johnson, 1966; Das, 1970). Serum specimens were obtained daily during hospital admissions and periodically at outpatient clinics. In our hands the normal range for serum F.D.P. is 1-20 μg/ml. Whenever possible, consecutive daily urine samples were obtained. Analysis was performed on aliquots of 24-hour collections from inpatients and on early morning specimens posted to the laboratory in the case of outpatients. In 122 patients the period of study was between 7 and 122 consecutive days, the remainder being studied for a minimum of three days. All urine F.D.P. results are expressed in terms of concentration (μg/ml). In hospital, where 24-hour collection was possible, the daily F.D.P. excretion bore a close relation to the F.D.P. concentration in individual patients without serious renal dysfunction. F.D.P. have not been detected in urine from healthy controls in concentrations greater than 0·25 μg/ml.

In addition, urine F.D.P. concentration was measured daily for 7 to 23 days in five patients with uncomplicated polycystic kidney disease and in 15 with acute pyelonephritis or infection of the lower urinary tract during the period of active infection.

Urinary urokinase was measured on standard fibrin plates prepared by the addition of 0·01 ml of thrombin (Parke-Davis) 50 IU/ml in tris buffer pH 7·8 to 10 ml of 10% human fibrinogen (Kabi) in tris buffer pH 7·8. After incubation at 37°C for 20 hours, the area of lysis produced by 0·025 ml of fresh urine diluted 1 in 5 in tris buffer pH 7·8 was compared with that produced by 0·025 ml of urokinase (Leo Laboratories Ltd.) 3 Ploug units/ml in tris buffer pH 7·8.

Twenty-four hour total urinary protein excretion was measured by the biuret method, and protein selectivity by immunodiffusion (Hardwicke and Squire, 1955; MacLean and Robson, 1967).

From five patients with active proliferative glomerulonephritis, two with minimal lesion, and two with membranous glomerulonephritis concentrated urine specimens were analysed by Sephadex G200 column chromatography. Eluates were analysed by the tanned red cell haemagglutination inhibition immunoassay and compared with eluates obtained after chromatography of a solution of 150 mg of human fibrinogen (Kabi) in 7·5 ml of K_2EDTA saline pH 8·5 lysed for 20 minutes at 37°C with 1,000 units of streptokinase in 0·5 ml of phosphate buffer pH 7·5. Lysis was stopped by the addition of 1 mg of soya bean trypsin inhibitor at 20 minutes.

Results

The number of patients in each disease group and the number with active disease during the period of study are shown in Table I. In 83 cases biopsy was performed during or within a period of one month of the study and in these the histological and clinical evaluations of disease activity were in close agreement. Fig. 1 gives the maximum concentrations recorded for serum and urine F.D.P. in each patient. Serum F.D.P. concentrations were commonly raised in active unspecified proliferative glomerulonephritis, S.L.E., and membranoproliferative glomerulonephritis, though no abnormal levels were recorded despite serial testing for 4 to 35 days in 24 of the 71 (34%) whose disease was considered active. However, pronounced variations in daily serum F.D.P. were observed in individual patients with active proliferative disease. A rise in serum F.D.P. was also seen in minimal lesion and membranous glomerulonephritis though less often than in the proliferative form.

Despite massive proteinuria (2-25 g/day) urinary F.D.P. concentration was never greater than 2 μg/ml in patients with minimal lesion or membranous glomerulonephritis. This amount was not increased after the infusion of concentrated human albumin solution on five occasions in two patients with minimal lesion and on four occasions in two patients with membranous glomerulonephritis. By contrast, wide ranges of urinary F.D.P. concentration were found in unspecified proliferative, S.L.E., and membranoproliferative glomerulonephritis. Daily measurements showed pronounced fluctuations

TABLE I—*Numbers of Patients studied and those with "Active" Disease in each Disease Group*

	No. Studied	No. with Active Disease during Study
Proliferative glomerulonephritis* (unspecified) ..	108	53
Systemic lupus glomerulonephritis	23	12
Membranoproliferative glomerulonephritis	12	6
Minimal lesion glomerulonephritis	8	8
Membranous glomerulonephritis	21	21

*Includes poststreptococcal (7), acute necrotizing (7), Henoch-Schönlein purpura (4), polyarteritis nodosa (4), familial nephritis (3), Goodpasture's syndrome (1), partial lipodystrophy (1), and mixed cryoglobulinaemia (1). (The disease was considered "active" in all patients in these categories.)

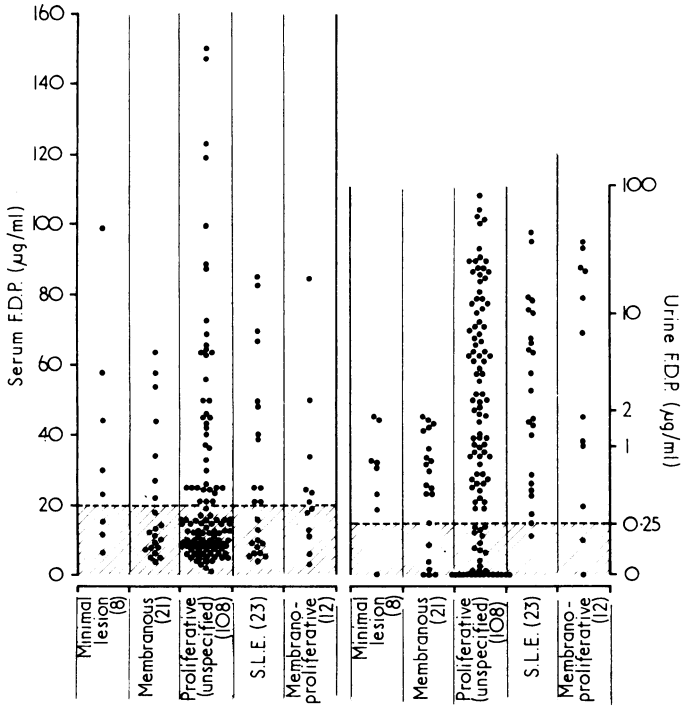

FIG. 1—Maximum serum and urine F.D.P. concentrations in 172 patients with glomerulonephritis. Normal ranges are shaded. Urine F.D.P. plotted on logarithmic scale.

which persisted when the disease remained active and became more pronounced in rapidly progressive cases (Fig. 2). Excretion ceased abruptly when the disease was self-limiting (Fig. 2).

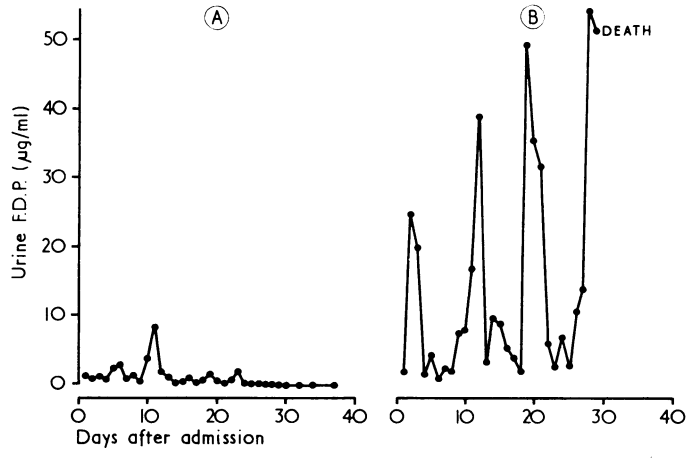

FIG. 2—Daily urine F.D.P. concentrations in two patients with proliferative forms of glomerulonephritis. In poststreptococcal glomerulonephritis (A) abnormal F.D.P. excretion was found during the active phase and ceased thereafter. Acute necrotizing glomerulonephritis (B) was associated with pronounced periodic rises before death.

Apart from four patients all cases excreted F.D.P. in a concentration greater than 2 μg/ml at some stage (Fig. 3). In those in whom the disease was inactive the F.D.P. concentration never exceeded 2 μg/ml. The close relationship between the urinary F.D.P. concentration and the extent of intraglomerular fibrin deposition as judged by electron microscopy in 51 cases is shown in Table II.

No significant abnormality of urine F.D.P. excretion was detected in the patients with polycystic disease, and in those with pyelonephritis or lower urinary tract infection the values never exceeded 0·5 μg/ml.

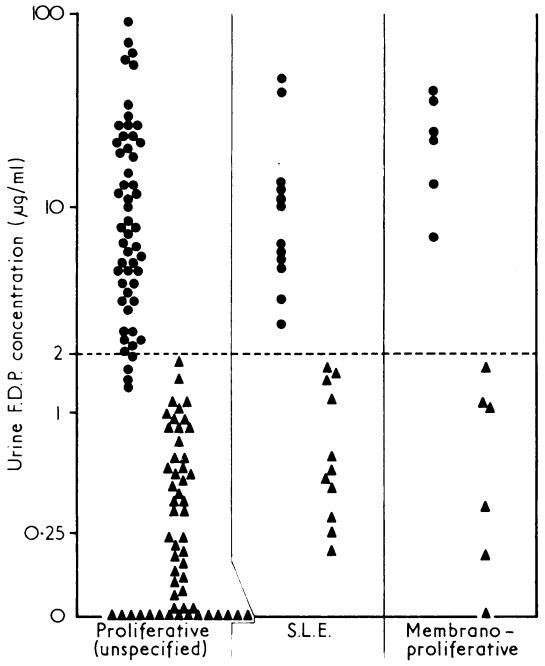

FIG. 3—Maximum urine F.D.P. concentrations recorded in proliferative forms of glomerulonephritis ● = Active disease. ▲ = Inactive disease.

TABLE II—*Relation between Maximum Urine F.D.P. Concentration and the Extent of Intraglomerular Fibrin Deposition in Proliferative Glomerulonephritis*

Glomerular Fibrin Electron Microscopic Grading	Maximum Urine F.D.P. Concentration (μg/ml)					
	<1	1–2	2–5	5–10	10–20	20
0	6	—	1	—	—	—
+	1	7	11	2	2	1
++	—	3	3	3	1	2
+++	—	—	—	1	1	4
++++	—	—	—	—	—	2

0 = No fibrin detected.
\+ = Rarefied layer between basement membrane and endothelium containing odd strands of fibrin.
++ = Dark dense deposits confined between basement membrane and endothelium.
+++ = Fibrin projecting into capillary lumen and between endothelial cells.
++++ = Glomerular capillary thrombosis.

Urokinase and F.D.P. were measured on the same 24-hour urine specimen for between 14 and 29 consecutive days in 13 patients—unspecified proliferative (5), Henoch-Schönlein (2), minimal lesion (2), membranous (2), S.L.E. (1), and membrano-proliferative (1). No significant correlation was found between the values obtained when considered as a single population ($r = 0{\cdot}05$, $P > 0{\cdot}1$), as separate diseases, or in individual patients.

In 143 patients the urine F.D.P. concentration, total protein excretion, and protein selectivity were measured in the same

24-hour specimen. In unspecified proliferative glomerulonephritis, S.L.E., and membranoproliferative glomerulonephritis no relation was found between F.D.P. concentration or 24-hour F.D.P. excretion and the degree of proteinuria (Fig. 4) or its selectivity to plasma proteins ($P > 0{\cdot}1$). This was also true when the groups were analysed individually. In membranous and minimal lesion glomerulonephritis the F.D.P. concentration and excretion were closely related to the degree of proteinuria (Fig. 3) but not to protein selectivity ($P > 0{\cdot}1$ for each disease).

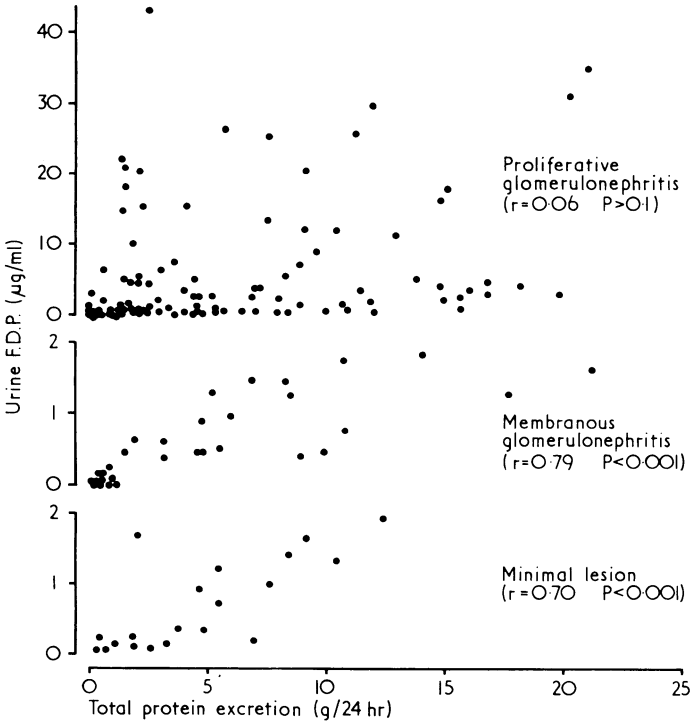

FIG. 4—Relation between total daily protein excretion and urinary F.D.P. concentration in different categories of glomerulonephritis. All proliferative forms are considered together.

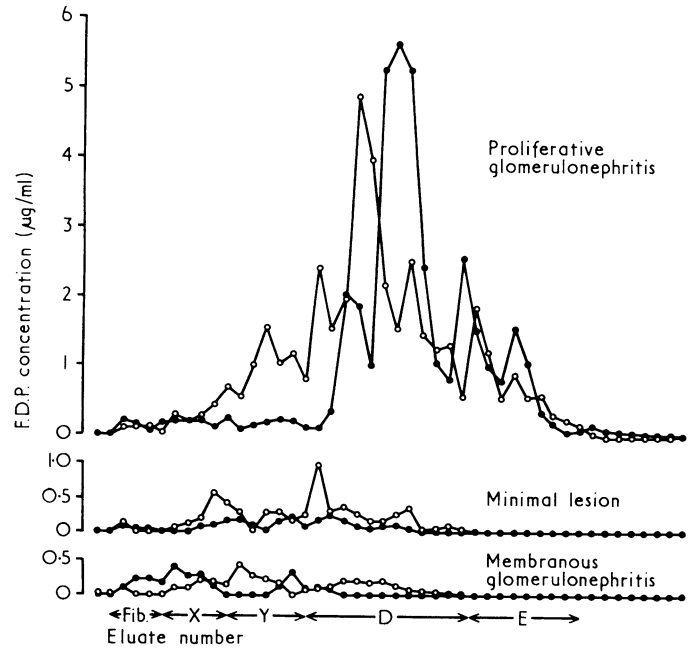

FIG. 5—Results of tanned red cell haemagglutination inhibition immunoassay for fibrinogen and derivatives in eluates obtained from column chromatography of concentrated urine samples. The elution position of fragments from fibrinogenolysis is shown for comparison.

Fibrinogenolysis by the in vitro action of streptokinase on human fibrinogen resulted in the formation of degradation products similar in size to those defined by Marder, Shulman, and Carroll (1969). In minimal lesion and membranous glomerulonephritis small amounts of fibrinogen (M.W. = 300,000), fragments X (M.W. = 240,000), Y (M.W. = 155,000), and D (M.W. = 83,000) were found. In active proliferative glomerulonephritis large amounts of fragments D and E (M.W. = 50,000) were found in addition (Fig. 5).

Discussion

Previous investigations have shown that the serum F.D.P. concentration is correlated with the degree of activity of proliferative glomerulonephritis (Steihm and Trygstadt, 1969), a finding which our data supports. However, raised concentrations are found in non-renal conditions (Merskey *et al.*, 1967; Ruckley *et al.*, 1970), and the serum determination is relatively insensitive in moderate and/or localized renal involvement. On the other hand, the urinary F.D.P. concentration when measured daily seems to provide more information concerning the diagnosis, activity, severity, and prognosis.

Healthy normotensive subjects excrete negligible amounts of F.D.P. (Clarkson, Morton, and Cash, 1970) and this is also the case in the patients with uncomplicated polycystic kidney disease. The relatively low values found in patients with pyelonephritis and lower urinary tract infection is surprising, as all had features associated with inflammation of the urinary tract. However, in view of the abnormal urinary F.D.P. concentrations found in all types of glomerulonephritis, the presence of glomerular damage seems to be necessary, such damage being an inconstant feature of uncomplicated polycystic or infective renal disease.

In minimal lesion and membranous glomerulonephritis, in which there is no histological and ultrastructural evidence of the deposition of glomerular fibrin, urinary F.D.P. excretion did not exceed 2 μg/ml despite heavy proteinuria. Nevertheless, the extent of F.D.P. excretion is closely related to the degree of proteinuria. Moreover, the relatively small quantities of fibrin/fibrinogen derivatives excreted were in the higher molecular weight range (fibrinogen, fragments X, Y, and D). This suggests that in these cases the F.D.P. in the urine arises from fibrinogen, filtered through an abnormally permeable basement membrane, which undergoes partial and incomplete proteolysis in the renal tract.

Urine F.D.P. concentrations often greatly in excess of 2 μg/ml were frequently found in cases of unspecified proliferative glomerulonephritis. In these cases a close relationship exists between the extent of F.D.P. excretion and the extent of intraglomerular fibrin deposition detected by ultrastructural study of renal biopsies. Furthermore, the data indicates that this increased concentration is related to the severity and activity of the disease. Fractionation studies show that a larger proportion of the excreted F.D.P. is of low molecular weight type (fragments D and E). While there are several possible explanations for this finding, the most attractive is that it results from local breakdown of the intraglomerular fibrin. In support of this hypothesis, excretion of F.D.P. in these cases was found to be independent of the degree of proteinuria and its selectivity and also of the urinary proteolytic activity as measured by urokinase excretion. Thus it is possible that F.D.P. in the urine in active and proliferative forms of glomerulonephritis results from two sources: the complete degradation of fibrin formed within the glomerular capillaries (fibrinolysis) giving preferentially D and E products, and limited proteolysis of filtered fibrinogen, as in minimal lesion and membranous glomerulonephritis.

In this study useful clinical information was obtained from the daily estimation of urinary F.D.P. This was especially the case in patients with the nephrotic syndrome in whom the

concentration of F.D.P. was 2 μg/ml or more. In these circumstances the diagnosis of a proliferative glomerulonephritis was almost certain. Daily measurement in unspecified proliferative glomerulonephritis, S.L.E., and membranoproliferative glomerulonephritis also provided information relevant to the activity, natural history, and prognosis. In poststreptococcal glomerulonephritis, for example, after a limited period of activity there was abrupt cessation of F.D.P. excretion at the time of clinical recovery. Where clinical evidence of activity persisted large fluctuations of F.D.P. concentration occurred which increased in magnitude in progressive disease and were similar to the cyclical peaks noticed in renal homograft rejection (Clarkson, Morton, and Cash, 1970). This cyclical pattern may provide a clue to the nature of the inflammatory stimulus and presumably either reflects a fluctuating inflammatory activity or periodic attempts by the fibrinolytic mechanisms to degrade intraglomerular fibrin. Against this latter hypothesis, however, was the absence of parallel changes between excreted urokinase and F.D.P.

Finally, and perhaps most significant of all, in proliferative glomerulonephritis the daily estimation of urine F.D.P. may provide a tool which, at minimal inconvenience to the patient, facilitates the continual review of specific therapy (Vermylen, Dotremont, Gaetano, Donati, and Michielsen, 1970; Clarkson, Cash, MacDonald, Fuster, Lambie, and Robson, 1971).

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Evaluation of Trimethoprim-sulphamethoxazole Compound in Treatment of Salmonella Infections

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Summary

Fifty patients suffering from infections caused by various salmonella species were treated with trimethoprim-sulphamethoxazole compound. Twenty-three had enteric fever and two were biliary carriers of *Salmonella typhi*. The other 25 suffered from infections caused by salmonella species other than *S. typhi* or *S. paratyphi B*. Twenty-one of the patients with enteric fever responded clinically to the drug, one failed treatment, and one died. Two patients suffering from typhoid fever relapsed and three temporarily excreted *S. typhi* in stools following treatment. One of the typhoid carriers was successfully treated. All patients with infections caused by salmonella species other than *S. typhi* or *S. paratyphi B* responded to treatment but 17 continued to excrete the organism in their stools after the course of trimethoprim-sulphamethoxazole compound. Four patients developed rashes during therapy and two became anaemic.

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Introduction

Chloramphenicol has been the drug of choice for the treatment of typhoid fever for over 20 years. However, the rare but serious side effect of aplastic anaemia and the significant incidence of relapse and chronic carrier state following treatment of typhoid with chloramphenicol has led to a search for a safer and more effective agent. The emergence of strains of *S. typhi* resistant to chloramphenicol (Agarwal, 1962) has added a further stimulus to this quest. In vitro most salmonella species are sensitive to ampicillin (Garrod and O'Grady, 1968). However, enteric fever responds less rapidly to ampicillin than to