Evidence is accumulating to substantiate the view that the oxytocic effects of E prostaglandins on uterine myometrium are much more pronounced than those of the F_a prostaglandins. In the induction of labour at term the available evidence suggests that the effective dose range for F_{2a} is about 5 to 10 times that for E₂ (Karim *et al.*, 1969; Embrey, 1970). So far personal experience of the F prostaglandins in early pregnancy extends to only six cases. The dose range was 2–5 µg./min. and the total amount infused varied from 820 to 3,150 µg. Only in one case (receiving the largest dose) was abortion successfully induced, clearly indicating the superiority of prostaglandin E₂ in early pregnancy too. These observations are not at variance with those of Karim and Filshie (1970). They have just reported successful induction of abortion with F_{2a} in 14 out of 15 cases, but they used a very much higher dosage (infusion rate 50 µg./min.; infusion time about 4 to 27 hours) and there were frequent side-effects (diarrhoea and vomiting). No noticeable side-effects could be ascribed to the infusion in any of the cases in this series. The patients were composed and symptom-free. Two vomited, but in each instance only when abortion was well advanced. No significant or constant changes in pulse or blood pressure were recorded in the cases.

It would be unwise, on such limited experience, to make extravagant claims for the use of E prostaglandins in the termination of pregnancy. Nevertheless, the results so far are

encouraging. The technique is simple and merely entails making an intravenous infusion, while it seems to be effective at any gestational age. Present methods of inducing abortion are not entirely satisfactory. Especially in the mid-trimester, the risks of one-stage evacuation (from trauma, haemorrhage, and infection) are great, while the alternatives—for example, irritant pastes, intra-amniotic hypertonic saline, or glucose injections—carry their own dangers. If the efficacy and safety of the prostaglandin E infusion is corroborated in extended trials it may well be a valuable therapeutic procedure in clinical practice.

I wish to thank Professor J. A. Stallworthy for advice and encouragement and gratefully acknowledge gifts of prostaglandins from Dr. J. Pike, of the Upjohn Co., and Dr. D. A. van Dorf, of the Unilever Research Laboratory.

REFERENCES

- Bergström, S., Carlson, L. A., and Weeks, J. R. (1968). *Pharmacological Reviews*, **20**, 1.
 Embrey, M. P. (1969). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **76**, 783.
 Embrey, M. P. (1970). *British Medical Journal*, **2**, 256.
 Embrey, M. P., and Morrison, D. L. (1968). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **75**, 829.
 Karim, S. M. M., Trussell, R. R., Hillier, K., and Patel, R. C. (1969). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **76**, 769.
 Karim, S. M. M., and Filshie, G. M. (1970). *Lancet*, **1**, 157.
 Pickles, V. R. (1969). *Nature*, **224**, 221.

Study of Proteins and Fibrinolysis in Patients with Glomerulonephritis

E. N. WARDLE,* M.A., M.B., M.R.C.P. ; I. S. MENON,† M.B., PH.D. ; S. P. RASTOGI,‡ M.B., M.R.C.P.ED., D.T.M.&H.

British Medical Journal, 1970, **2**, 260–263

Summary: Plasma and urine fibrinolysis were studied in 36 patients with glomerulonephritis and proteinuria. In 40% of these plasma fibrinolytic activator activity was moderately reduced and fibrinolytic inhibitors were increased. Globulins with antiplasmin effect were raised, particularly in the earlier months. Both the serum cholesterol and the plasma fibrinogen were related to the level of serum albumin, and those patients with high fibrinogen levels were also those with poor plasma fibrinolytic activator and those showing a steady deterioration. Urinary fibrinolysis was greatly reduced in most patients and bore no relation to plasma fibrinolysis levels. Hence urokinase is not derived from circulating plasminogen activator.

Introduction

Patients with nephrotic syndrome are apt to develop venous or even pulmonary artery thrombosis (Levin *et al.*, 1967), especially when given steroid therapy. This tendency has been attributed to raised levels of plasma fibrinogen and of inhibitors of fibrinolysis found in the increased α_2 -globulin and β -globulin fractions. Few detailed studies of systemic fibrinolysis have been made and even less attention has been paid to possible immunological inhibition of local fibrinolysis within the kidney. It is, however, known that fibrin is deposited in the kidney in experimental glomerulonephritis (Vassalli and McCluskey, 1964) and that patients with the nephrotic syndrome may show accelerated thromboplastin generation. Kincaid-Smith *et al.* (1968) reported promising results with heparin therapy; this is logical, as immuno-

fluorescent studies may show deposition of fibrin, especially in the proliferative forms of human glomerulonephritis.

We report here the results of a survey of fibrinolysis in a group of 36 patients with glomerulonephritis and proteinuria, designated as "nephrotic."

Methods

Fasting blood samples and early morning urine collections were taken from nephrotic patients. Most were attending for follow-up in the M.R.C. Nephrotic Syndrome Trial. Renal biopsies had shown that five had "minimal change" nephritis, 13 proliferative glomerulonephritis, 11 established end-stage chronic glomerulonephritis, and seven "membranous change," of which two were due to amyloid and five fell into the category of idiopathic membranous glomerulonephritis. Those with minimal change glomerulonephritis had been treated for a mean period of 2.3 years, those with proliferative glomerulonephritis for 2.0 years, and those with membranous glomerulonephritis for 2.4 years; those with established chronic glomerulonephritis had been on supportive regimens for an average of four years, but it is impossible to designate the duration of their illness.

Techniques

Serum proteins and albumin and serum cholesterol were measured in the artificial kidney laboratory by Autoanalyser methods together with the creatinine clearance.

Plasma fibrinogen was estimated by the method of Ratnoff and Menzie (1951).

Euglobulin lysis time was estimated by Von Kaulla's (1963) method slightly modified by Menon *et al.* (1968). It can be expressed in units by multiplying the reciprocal of the lysis time in minutes by 10,000. A logarithmic plot of lysis time against units of activity shows a linear relationship. The normal euglobulin lysis time is 40–110 units.

* Senior Medical Registrar and M.R.C. Clinical Research Fellow.

† Senior Research Registrar.

‡ Senior Research Associate, Renal Unit.

The Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

Fibrinolytic inhibitors of urokinase were estimated according to the method of McNichol *et al.* (1963) expressed as units, with normal values of 40-120.

Urine fibrinolytic activity was assayed on 18 specimens on fibrin plates by comparison of serial dilutions of urine against standard urokinase dilutions. The activity is expressed as Plough units per 100 mg. of creatinine, and normal levels are over 200 units.

Serum levels of globulins α_1 -antitrypsin (M.W. 60,000), α_2 -macroglobulin (M.W. 900,000), and β -lipoprotein 2,000,000) were estimated by radial diffusion in agar plates containing specific antisera (Mancini *et al.*, 1965). For convenience results are expressed as a percentage of normal values obtained from pooled sera.

Urine trypsin inhibitor was estimated by the method of Faarvang (1959) as the inhibitory effect of urine on the digestion of 3% casein by standard concentrations of trypsin. Normal trypsin inhibitor values in urine were up to about 6 units per ml., with a mean of 2.4 units.

Serum fibrin degradation products were estimated on serum specimens collected in aprotinin (Trasyol) and later clotted by thrombin, the Burroughs Wellcome fibrinogen assay kit being used. In normal sera fibrin degradation products are detectable at a level of 5 μ g./ml.

Results and Comments

An overall impression of the range of values among these 36 nephrotic patients for the estimations of albumin, cholesterol, fibrinogen, and the various globulins, together with the fibrinolytic status in terms of plasma activator (euglobulin lysis time), plasma urokinase inhibitors, and urine fibrinolysis is given in Fig. 1. Normal values lie between the ruled lines,

FIG. 1.—Protein and cholesterol estimations.

and it will be seen that, in general, the patients have lower levels of serum albumin and raised levels of serum cholesterol and fibrinogen, and that many have raised values for serum α_2 -macroglobulin and β -lipoprotein. Forty per cent. have a euglobulin lysis time longer than normal, indicating diminished plasma fibrinolysis, and 40% have raised levels of fibrinolytic inhibitors. There was, however, no direct correlation between lower euglobulin lysis time values and the rise in inhibitors, or the level of blood urea, or creatinine; nor could correlations be established between the level of fibrinolytic inhibitors as assayed and the levels of individual globulins selected for assay because of their known antiplasmin

effect. This contrasts with our published values (Wardle and Menon, 1969) for normal patients, in whom a relationship was shown between β -lipoprotein and both the euglobulin lysis time and the inhibitor levels. Strikingly, urine fibrinolysis is much reduced in most of the patients, but did not correspond with the level of plasma activator activity; nor was the reduction of urine fibrinolysis directly proportional to a reduction of creatinine clearance.

The serum α_1 -antitrypsin values are not abnormal. This is an acute-phase reactive protein and in an inflammatory state such as glomerulonephritis raised values might be expected. The molecule, however, is small (M.W. 60,000) and in the presence of proteinuria, as in this group of patients, its loss in the urine is to be expected. For this reason, and to try to explain the poor urine fibrinolysis, urine trypsin inhibitor values were estimated. Normal inhibitor values were up to 6 units per ml. (average 2.4 units) but the nephrotic urines showed appreciable trypsin inhibition, with values ranging from 3.6 to 26.0 and with a mean of 14.1 inhibitor units $\pm$ 7.4. This seems, however, insufficient to account entirely for poor urine fibrinolysis, and a failure of urokinase production by the kidney in nephrosis must be assumed.

To ascertain the role of renal fibrin deposition in the pathogenesis of renal disease (cf. Vassalli and McCluskey, 1965) serum fibrin degradation products were estimated randomly in 30 of these patients with glomerulonephritis. If a value of 40 μ g./ml. is taken as abnormal 5 out of 30 patients had positive fibrin products. Probably serial assays on patients will show that this occurs intermittently in the course of the disease of many patients. The results are summarised in Table I.

TABLE I.—Incidence of Serum Fibrin Products

	Glomerulo-nephritis	Chronic Stage	Acute Nephritis	Malignant Hypertension
Positive at 40 μ G/ml. . .	5/30 (17%)	4/32 (12%)	1/7 (14%)	5/22 (23%)
Positive at 20 μ G/ml. . .	7/30 (23%)	10/32 (31%)	2/7 (28%)	15/22 (68%)

Reference to Fig. 1 shows that two-thirds of the patients have plasma fibrinogen values over 400 mg./100 ml., and Fig. 2 shows a broadly inverse correlation between the serum

FIG. 2.—Relationship of plasma fibrinogen to serum cholesterol and serum albumin.

albumin and the fibrinogen and also a relation between the plasma fibrinogen and the serum cholesterol.

An analysis of the cases grouped according to renal histology (Table II) shows that generally patients with "minimal change" have less disturbance of their fibrinolytic mechanism and retain a normal diastolic blood pressure and near-normal creatinine clearance. The "proliferative" and "membranous" groups have heavy proteinuria and reduced creatinine clearance, and many have raised levels of the three fibrinolytic inhibitor globulins. The mean diastolic blood pressure is raised in those with proliferative glomerulonephritis and in those with established chronic glomerulonephritis. These latter patients have the expected poor crea-

tinine clearance and 73% have poor fibrinolytic activator levels.

When the duration of the illness is considered (Table III) the creatinine clearance is seen to fall with time, while the diastolic blood pressure rises. Proteinuria lessens and accordingly the serum albumin restabilizes. The mean levels of globulins α_2 -macroglobulin, α_1 -antitrypsin, and β -lipoprotein are higher in the earlier phase of the illness, and the euglobulin lysis time is as likely to be prolonged at this stage as in the chronic end-stage glomerulonephritis.

Of the 36 patients the illness had lasted for less than three years in 17. They were subdivided according to four separate criteria of deterioration: a creatinine clearance of below or above 50 ml./min., proteinuria over 4 g./day, a euglobulin lysis time under the normal value of 40 units, or a fibrinogen value over 500 mg./100 ml. For the two subdivisions of each category the relation to the other measurements (Table IV) show that a high fibrinogen level especially is associated with features of bad prognosis. Persistent heavy proteinuria is accompanied by more striking changes in the plasma proteins, cholesterol, and fibrinolytic system. Paradoxically, a low creatinine clearance is accompanied by a better state of the plasma proteins, but probably this is simply because as the glomerular filtration rate lessens proteinuria diminishes.

Discussion

Many patients with glomerulonephritis (and "immunosuppressive" therapy) proceed to long-term dialysis, steroids may have side-effects of their own and benefit mainly those with minimal change histology. The glomerulus may be damaged either by antibodies reacting with the glomerular basement membrane or because of the filtration of antigen-antibody complexes (Dixon, 1968). In immune complex diseases glomerular permeability is increased by the direct action of the complexes themselves, indirectly by local platelet disintegration, releasing vasoactive amines; by the associated fixation of complement; and, finally, from the release of lysozymal hydrolases from accumulating polymorph leucocytes. Fibrin and complexes are removed by phagocytic cells of the mesangium and by the proliferative endothelial response; but once complexes penetrate the basement membrane they localize and destroy the foot processes of the epithelial cells, so worsening proteinuria, and they are no longer accessible to phagocytosis. Fibrin probably plays an accessory part in glomerulonephritis, stimulating the proliferative response (Vassalli *et al.*, 1965) and glomerular scarring as well as crescent formation if fibrin enters Bowman's capsule (Vassalli and McCluskey, 1964; Halpern *et al.*, 1965). Hence local fibrinolysis is therefore important, a suggestion confirmed for acute glomerulonephritis (Goldschmidt and Marosvári, 1968; Humair, 1969; Kwaan *et al.*, 1966; Maggiore *et al.*, 1969).

In the earlier stages of progressive glomerulonephritis some 40% of patients have poor plasminogen activator production and 40% have inhibitors of fibrinolysis. Inhibitors and the plasma fibrinogen appear to be higher in proliferative glo-

TABLE II.—Analysis According to Renal Histology

No. of patients: Duration of treatment	Minimal Lesion	Proliferative	Membranous	Chronic	S*
	5	13	7	11	
	2-3 years	2-0 years	2-4 years	4-5 years	
Cr. clearance	89 ± 11	42 ± 26	57 ± 25	29 ± 24	1%
Diastolic B.P.	74 ± 24	104 ± 22	86 ± 7	104 ± 20	1%
Proteinuria (g.24 hours)	2.2 ± 0.7	5.2 ± 4.2	5.6 ± 1.54	3.8 ± 2.46	
Albumin	2.29 ± 0.66	2.95 ± 0.75	2.64 ± 0.82	3.23 ± 0.78	5%
Cholesterol	336 ± 77	380 ± 218	375 ± 157	254 ± 48	
Fibrinogen	444 ± 169	477 ± 190	438 ± 112	510 ± 185	
E.L.T. units	60 ± 30	44 ± 27	43 ± 18	44 ± 33	
Inhibitors	119 ± 33	161 ± 135	134 ± 95	103 ± 32	
α_1 Antitrypsin	150 ± 54	168 ± 52	196 ± 61	144 ± 46	1%
β -Lipoprotein	133 ± 16	158 ± 82	166 ± 47	106 ± 32	
α_2 -Macroglobulin	218 ± 161	244 ± 162	281 ± 114	143 ± 102	
Percentage Patients in Each Group with Significantly High Values					
E.L.T. < 40 units	40	38	43	73	
Inhibitors > 120 units	40	69	28	36	
Fibrinogen > 500 mg./100 ml.	40	54	28	45	
Cholesterol > 300 mg./100 ml.	60	46	71	27	
α_2 -Macroglobulin > 200%	40	62	86	27	
β -Lipoprotein > 200%	20	46	43	9	
α_1 -Antitrypsin > 200%	40	69	71	45	

*Significance level using Snedecor F test.
E.L.T. = Euglobulin lysis time.

TABLE III.—Analysis According to Duration of Illness

	Less Than One Year	> One Year	> 3 Years	Chronic Undeter- mined
Cr. Clearance*	59 ± 32	57 ± 30	47 ± 36	26 ± 23
Diastolic B.P.†	92 ± 14	92 ± 20	106 ± 18	105 ± 20
E.L.T.	38 ± 16	44 ± 26	60 ± 34	36 ± 33
Inhibitors	124 ± 67	172 ± 161	155 ± 82	103 ± 35
Albumin	2.64 ± 0.51	2.38 ± 0.18	3.14 ± 0.28	3.23 ± 0.24
Proteinuria (g./24 hours)	5.0 ± 4.7	4.4 ± 2.6	4.6 ± 1.9	3.8 ± 2.4
Cholesterol	353 ± 204	467 ± 174	292 ± 118	254 ± 48
Fibrinogen	426 ± 167	480 ± 134	452 ± 144	510 ± 184
% α_2 -Macroglobulin	322 ± 151	206 ± 160	211 ± 105	142 ± 103
% β -Lipoprotein	169 ± 80	155 ± 46	139 ± 38	106 ± 32
% α_1 -Antitrypsin	196 ± 53	155 ± 60	163 ± 66	144 ± 47
No. of Cases	9	8	8	11

*Significant at 1% level for Variance ratio.
†Significant at 5% level using Snedecor F test.
Other values not significant.

TABLE IV.—Analysis of Criteria of Deterioration

	Fibrinogen > 500 mg./100 ml.			E.L.T. < 40 units			G.F.R. < 50 ml./min.			Proteinuria > 4 g./day		
	+	—	S*	+	—	S*	+	—	S*	+	—	S*
Creatinine clearance	43.9	69.6	1.0%	62	57					63	54	
Diastolic pressure	100	86	1.0%	75	93					90	93	
E.L.T.	37.1	47.7	5.0%			1.0%	101	86	5.0%	35.1	47.8	5.0%
Inhibitors	221	84	0.1%	102	118		49.3	28.5		127	107	
Albumin	2.35	2.66	5.0%	2.48	2.57		175	94	0.1%	127	107	
Proteinuria	6.5	3.5	1.0%	4.8	4.7		2.66	2.46		2.34	2.75	1.0%
Cholesterol	545	310	0.1%	433	393		2.4	3.8				
Fibrinogen				523	412	1.0%	325	451	5.0%	502	300	0.1%
α_2 -Macroglobulin	211	305	5.0%	306	246		470	441		526	380	0.1%
β -Lipoprotein	135	181	1.0%	190	147		142	355	0.1%	298	206	5.0%
α_1 -Antitrypsin	188	169		168	181		125	183		179	143	5.0%
							166	183		176	177	
No. of cases	7	10		6	11		6	11		9	8	
Score			9			2			4			6

*Significance level by student's *t* test. Mean values for each group are recorded.

merulonephritis. The contrast with the increase of fibrinolysis seen in the transient state of acute nephritis is notable. Furthermore, by the chronic stage some 70% of patients have poor activator production, but there is no clear relationship to the blood urea or creatinine. How much this can be attributed to a poor contribution to circulating activator by the kidney itself is debatable, but possibly the normal kidney contributes substantially to circulating plasminogen activator (Menon *et al.*, 1968; Nowak *et al.*, 1969). In many types of chronic renal disease urokinase output is diminished (McNichol *et al.*, 1965; Nowak and Zahorska, 1966; Vreeken *et al.*, 1966). It has long been felt that levels of urokinase and circulating plasminogen activator from undamaged endothelial cells do not correspond with one another, and our results confirm this. Though we have not shown how far poor urine fibrinolysis is due to poor urokinase production and how far to inhibitors filtered by the glomerulus, we have found a leak of proteolytic inhibitors, measured by their antitrypsin effect. Moreover, poor urine fibrinolysis, which occurred in all types of glomerulonephritis and was not confined to the chronic stage, could explain a tendency to persistence of casts in the tubules.

We do not wish to imply that the presence of fibrin degradation products are a specific indicator of intravascular coagulation, still less of fibrin deposition in the kidney alone. Nevertheless, raised titres usually indicate local lysis of microthrombi in small blood vessels. The 23% of random cases of glomerulonephritis showing positive fibrin degradation products corresponds to the 20% given by Wardle and Taylor (1968) and to the 22% found by Stiehm and Trygstad (1969) using a precipitin technique. For comparison, in malignant hypertension the figure is 68% and in this condition microangiopathy can often be found (Linton *et al.*, 1969).

The analysis according to duration of disease (Table III) shows that in the earlier years of persistent immunological and inflammatory reaction there are greater changes in the reactive globulins. Fibrinogen levels, however, rise with duration and deterioration. Increased fibrinogen synthesis in nephrosis but a normal catabolic rate has been shown by Takeda and Chen (1967) and a similar situation may occur in uraemia itself. The rise of globulins with a fibrinolytic inhibitor potential— α_2 -macroglobulin and β -lipoprotein—may be a direct consequence of albumin loss and plasma volume depletion. Catabolism of α_2 -macroglobulin is known to be reduced in nephrotics by an amount inversely proportional to the reduction of plasma volume (Kluthe *et al.*, 1967).

Nephrotic patients with hyperlipaemia are, of course, liable to premature atherosclerosis. The serum cholesterol level is correlated with the plasma fibrinogen concentration (Suschke and Foldenauer, 1968) and both values can be related to the level of the serum albumin and hence to the degree of proteinuria. Those patients with high cholesterol and fibrinogen values are those with poor plasma fibrinolysis. β -lipoprotein is known to be a fibrinolytic inhibitor (Wardle and Menon, 1969), while raised triglyceride or cholesterol levels are accompanied by fibrinolytic inhibition (Spöttl *et al.*, 1968; Sweet *et al.*, 1966) and fatty acids may exert some regulatory action on fibrinogen synthesis (Pilgeram and Pickart, 1968). As regards glomerulonephritis a persistently high fibrinogen reflects a gloomy prognosis in terms of morbidity (Table IV). Naturally, deterioration of glomerular filtration rate for which measurement of creatinine clearance is short of ideal (Kim *et al.*, 1969), is the feature that determines death from renal failure or a life on dialysis. Nevertheless the degree of proteinuria or the level of plasma fibrinogen is more closely related to the protein values that we have studied.

This study was originally made with a similar one on fibrinolysis in pregnancy and pre-eclamptic toxæmia (Wardle and Menon, 1969). In pregnancy there is a pronounced physiological reduction of plasminogen activator

release. Thus patients who become pregnant might be expected to show either deterioration of their glomerulonephritis or venous thrombosis, and indeed in occasional patients this is so (Seftel and Schewitz, 1957; Fishberg, 1954). Even so, many nephrotic patients have an uneventful pregnancy (Studd and Blainey, 1969), probably owing to enhanced function of the reticuloendothelial system. This is a known effect of oestrogens (Nicol *et al.*, 1952), but the potential of the reticuloendothelial system for clearing fibrin remains to be investigated (Lee and McCluskey, 1962).

Our thanks are due to Professor D. N. S. Kerr, under whose care these patients are, to Dr. R. Ashcroft for the kidney laboratory estimations, and to Dr. H. A. Dewar for the co-operation of the fibrinolysis unit. We are also obliged to Mr. Alan Martin and Mr. D. A. Piercy for technical assistance. One of us (E.N.W.) is indebted to the Scientific and Research Committee of the Royal Victoria Infirmary, Newcastle upon Tyne, for funds and latterly to the Medical Research Council.

REFERENCES

- Dixon, F. J. (1968). *American Journal of Medicine*, **44**, 493.
 Faarvang, H. J. (1959). *Acta Endocrinologica (København)*, **30**, 285.
 Fishberg, A. M. (1954). *Hypertension and Nephritis*, 5th ed. Philadelphia, Lea and Febiger.
 Goldschmidt, B., and Marosvári, I. (1968). *Klinische Wochenschrift*, **46**, 421.
 Halpern, B., Milliez, P., Lagrue, G., Fray, A., and Morard, J. C. (1965). *Nature*, **205**, 257.
 Humair, L., Potter, E. V., and Kwaan, H. C. (1969). *Journal of Laboratory and Clinical Medicine*, **74**, 60.
 Kim, K. E., Onesti, G., Ramirez, O., Brest, A. N., and Swartz, C. (1969). *British Medical Journal*, **4**, 11.
 Kincaid-Smith, P., Saker, B. M., and Fairley, K. F. (1968). *Lancet*, **2**, 1360.
 Kluthe, R., Hagemann, U., and Kleine, N. (1967). *Vox Sanguinis*, **12**, 308.
 Kwaan, H. C., Humair, L. M., and Potter, E. V. (1966). Third International Congress of Nephrology. Abstracts: free communications, p. 226.
 Lee, L., and McCluskey, R. T. (1962). *Journal of Experimental Medicine*, **116**, 611.
 Levin, S. E., Zamit, R., and Schman, A. (1967). *British Medical Journal*, **1**, 153.
 Linton, A. L. *et al.* (1969). *Lancet*, **1**, 1277.
 McNichol, G. P., Barakat, A. A., and Douglas, A. S. (1965). *Scottish Medical Journal*, **10**, 189.
 McNichol, G. P., Gale, S. B., and Douglas, A. S. (1963). *British Medical Journal*, **1**, 909.
 Maggiore, Q., Jovanovic, B., and Baldini, G. (1969). *Nephron*, **6**, 81.
 Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). *Immunochemistry*, **2**, 235.
 Menon, I. S., Dewar, H. A., and Newell, D. J. (1968). *Lancet*, **1**, 785.
 Nicol, T., Helmy, I. D., and Abou-Zikry, A. (1952). *British Journal of Surgery*, **40**, 166.
 Nowak, A., Kokot, F., Czekata, Z., Dosiak, J., and Kushka, J. (1969). *Thrombosis et Diathesis Haemorrhagica*, **21**, 12.
 Nowak, A., and Zahorska-Markiewicz, B. (1966). *Polish Medical Journal*, **5**, 292.
 Pilgeram, L. O., and Pickart, L. R. (1968). *Journal of Atherosclerosis Research*, **8**, 155.
 Ratnoff, O. D., and Menzie, C. (1951). *Journal of Laboratory and Clinical Medicine*, **37**, 316.
 Seftel, H. C., and Schewitz, L. J. (1957). *Journal of Obstetrics and Gynaecology of the British Empire*, **64**, 862.
 Slöttl, F., Holzknecht, F., and Braunsteiner, H. (1968). *Journal of Atherosclerosis Research*, **8**, 821.
 Stiehm, E. R., and Trygstad, C. W. (1969). *American Journal of Medicine*, **46**, 774.
 Studd, J. W. W., and Blainey, J. D. (1969). *British Medical Journal*, **1**, 276.
 Suschke, J., and Foldenauer, A. (1968). *Deutsches medizinisches Wochenschrift*, **93**, 1705.
 Sweet, B., Rifkind, B. M., and McNichol, G. P. (1966). *Journal of Atherosclerosis Research*, **6**, 359.
 Takeda, Y., and Chen, A. Y. (1967). *Journal of Laboratory and Clinical Medicine*, **70**, 678.
 Vassalli, P., and McCluskey, R. T. (1964). *Annals of the New York Academy of Sciences*, **116**, 1052.
 Vassalli, P., and McCluskey, R. T. (1965). *American Journal of Medicine*, **39**, 179.
 Vassalli, P., McCluskey, R. T., Gallo, G., and Baldwin, D. S. (1965). *Clinical Research*, **13**, 316.
 Von Kaulla, K. N. (1963). In *Chemistry of Fibrinolysis*, p. 79. Springfield, Illinois, Thomas.
 Vreeken, J., Boomgaard, J., and Deggeler, K. (1966). *Acta Medica Scandinavica*, **180**, 153.
 Wardle, E. N., and Menon, I. S. (1969). *British Medical Journal*, **2**, 625.
 Wardle, E. N., and Taylor, G. (1968). *Journal of Clinical Pathology*, **21**, 140.