Other fundus abnormalities were optic atrophy of various causes (hydrocephalus and "battering") and choroidal colobomas.

Miscellaneous conditions affecting the ocular adnexae were ptosis (two cases), persistent nasolacrimal duct obstruction, hypertelorism, and Horner's syndrome. There was one boy with persistent hyperplastic primary vitreous previously mentioned in association with microphthalmos.

Discussion

In this group of 171 children the high incidence of ocular abnormalities does indicate that all such developmentally handicapped children should have routine ophthalmic and orthoptic examinations. Some authors have found certain ocular abnormalities in other groups of handicapped children, such as those with cerebral palsy. Breakey (1955) found an incidence of "ocular muscle imbalance" of 48%, Douglas (1961) an incidence of 37% of squint, and Fantl and Perlstein (1961) a higher degree of hypermetropia. Mongols and other mentally handicapped children were found to have an incidence of squint of 25% by Gardiner (1967), and Bankes (1972) noted that most squints in mentally handicapped children had an onset at birth or just afterwards. Venables (1967) also reported a high incidence of squint in "minimally handicapped children" varying from 37% in "clumsy" children to 54% in "problem children." More recently Edwards *et al.* (1972) have shown the value of the ophthalmic examination as part of the evaluation of suspected mentally handicapped children. The evidence they put forward for the routine ophthalmic examination was that the ocular defects of many of these children would have otherwise gone unrecognized and untreated.

Ideally, the routine ophthalmic examination should be carried out in an assessment centre where the whole assessment is geared to the needs of these children, and it is hoped that purpose-built centres will one day be available in all parts of the country.

It has been argued that early detection of ocular defects contributes little to the developmentally handicapped child, but we think that the earlier and better the visual sense functions then the greater the chance the child has of achieving his potential. Particular regard was paid to the visual function of the children by the assessment centre team, and more detailed visual function tests, in relation to other senses, were carried out as part of the Griffiths Mental Development Scale tests. This was in addition to the more formal estimation of vision when this was possible. Reassurance of parents that their child had normal vision and healthy eyes removed a great deal of worry, and sensible discussion and explanation about children with ocular abnormalities went a long way in helping parents to accept a mentally and visually handicapped child. Such advice and reassurance, however, can be given only when the developmentally handicapped child has received full ophthalmic and orthoptic examinations.

This work was possible only with the support and encouragement of the assessment centre team at St. Mary's Hospital (Dr. P. Cox, the late Dr. Alexander, Mr. R. Marsh, Mr. A. Richards, Miss E. L. Rowse, and Miss Woods) and to them go our considerable thanks. Miss R. Offer provided the secretarial help, and we wish to thank her for this.

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PRELIMINARY COMMUNICATIONS

Urinary Excretion of Fibrinogen-related Materials, Complement, and Immunoglobulins in Proliferative Glomerulonephritis and after Renal Transplantation

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Summary

Using a radial immunodiffusion technique we measured the urinary concentration of material related to complement (C3), IgM, and IgG along with fibrin-fibrinogen degradation products and heterophile (sheep) haemagglutinins in 15 patients with proliferative glomerulonephritis and in 10 patients after renal transplantation. There was a significant correlation between all variables measured, and serial studies showed that with the exception of IgG-related materials potentially useful information could be obtained on the detection of rejection and the response to treatment in both conditions. The significance of these observations is discussed.

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Introduction

Histological evidence now suffices to show that in active proliferative glomerulonephritis and during renal homograft rejection fibrinogen-related material, complement (C3), and immunoglobulins may be deposited within the glomerulus (Lachmann *et al.*, 1962; Koffler and Paronetto, 1965; Paronetto and Koffler, 1965; Hadley and Rosenau, 1967; Porter *et al.*, 1968; Herdman *et al.*, 1970; Davison *et al.*, 1973). More recent studies have shown that at least one aspect of these intrarenal events (fibrin deposition) can be monitored in individual patients by the quantification of the urinary fibrin-fibrinogen degradation products (F.D.P.; Clarkson *et al.*, 1970; Clarkson *et al.*, 1971; Davison *et al.*, 1973). Other studies have suggested that the overall intrarenal inflammatory reaction in these conditions can also be followed by

estimating the urinary content of heterophile (sheep) haemagglutinins (SHA) and that when examining responses to treatment, at least in proliferative glomerulonephritis, this latter approach could prove more effective than urinary F.D.P. studies (Hoq *et al.*, 1973).

We describe here a preliminary series of studies in which this work is further extended by comparing the F.D.P. and SHA content with that of C3-, IgM-, and IgG- immunorelated materials in urine from patients with proliferative glomerulonephritis and from those who have undergone renal homotransplantation.

Patients and Methods

One hundred presumed healthy colleagues (50 male and 50 female, aged 18-56 years) were used as controls. Their urine specimens were obtained at random throughout a working day. Fifteen patients with proliferative glomerulonephritis (diagnosed by light and electron microscopy; Clarkson *et al.*, 1971) and 10 who had recently undergone renal homotransplantation (within the previous 100 days) were studied. Urine samples from 24-hour collections were obtained from all inpatients, and outpatients sent early morning specimens to the laboratory through the post. All samples were dialysed against running tap water overnight, concentrated (10-20 times) with polyethylene glycol, centrifuged, and stored at −36°C until assayed. The F.D.P. content was determined by the tanned red cell haemagglutination-inhibition immunoassay, using glutaraldehyde-fixed human red blood cells (Hoq and Das, 1971). The SHA titre was measured using glutaraldehyde-fixed "high reacting" sheep red blood cells and the results expressed as described previously (Hoq *et al.*, 1971, 1973). The urinary content of IgM-, IgG-, C3-, and α_2-macroglobulin-related material was measured by the radial diffusion method of Mancini *et al.* (1965) with commercially available immunoplates. The total urinary protein content was measured by the biuret method (Hiller *et al.*, 1948). All test samples were coded so that no knowledge of their source was available to those carrying out the assays.

Results

Urinary SHA and IgM-, IgG-, and C3- related materials were not detected in the 100 controls nor did the F.D.P. content exceed 0·25 μg/ml. In a selection of urines obtained from patients after renal transplantation and from those with proliferative glomerulonephritis there was a significant correlation between both the F.D.P. and SHA content and the concentrations of IgM-, IgG-, and C3- related materials (see table). Detailed serial studies over at least 10 consecutive days were possible in 10 of the 15 patients with proliferative glomerulonephritis before treatment, and it was evident that not all urine specimens with a high content of IgM-, IgG-, and C3- related materials had high concentrations of F.D.P. or SHA or both. Further investigations on the 10 renal transplant patients studied serially for 10-45 days confirmed previous reports that urine F.D.P. and SHA estimations provided parallel information on the detection of acute

Correlation between F.D.P. and SHA Content and C3-, IgM-, and IgG-immunoreacting Materials in Selection of Urines obtained from Patients after Renal Homotransplantation and from those with Proliferative Glomerulonephritis

Values Compared	No. of Samples Assayed	r	P
F.D.P./C3	96	0·631	<0·001
F.D.P./IgM	52	0·415	<0·01
F.D.P./IgG	96	0·784	<0·001
SHA/C3	96	0·832	<0·001
SHA/IgM	86	0·689	<0·001
SHA/IgG	96	0·770	<0·001

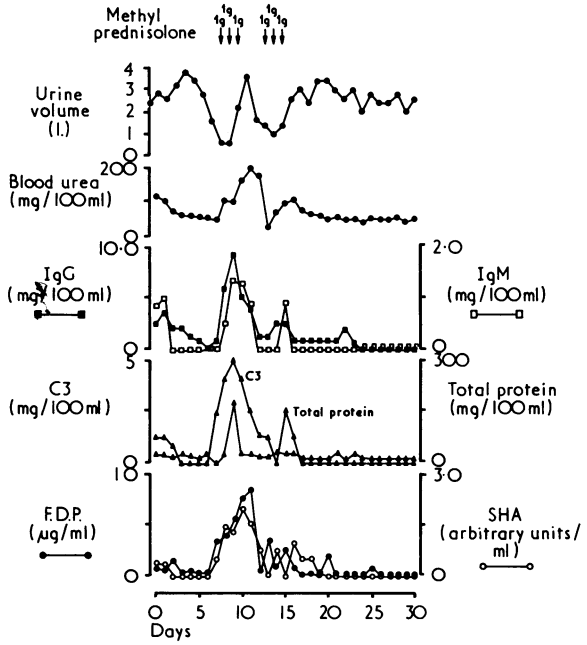

FIG. 1—Blood urea, urine output, F.D.P., SHA, total protein, and IgM-, IgG-, and C3- related material in a patient after renal homotransplantation. Clinical evidence of rejection was apparent on 9th day of study, which subsequently responded satisfactorily to treatment. Throughout the period of study patient was also receiving azathioprine 150 mg/day and prednisone 50 mg/day.

and subacute rejection and the response to treatment. Moreover, similar patterns in the excretion of IgM-, IgG-, and C3- related materials were observed in all patients. An example is shown in fig. 1.

The responses to oral indomethacin were studied in a group of 10 selected patients who were considered to have active proliferative glomerulonephritis as defined previously (Clarkson *et al.*, 1971). The selection of these patients was not random but based upon preliminary serial F.D.P. and SHA studies and on known clinical responses to therapy. In four patients there was a fall in the urine content of F.D.P., SHA, and IgM- and C3- related materials during the period of indomethacin administration. The changes in urine IgG- related material and total protein were consistently less impressive, and there was no fall in the excretion of α_2- macroglobulin-related material. These patients sub-

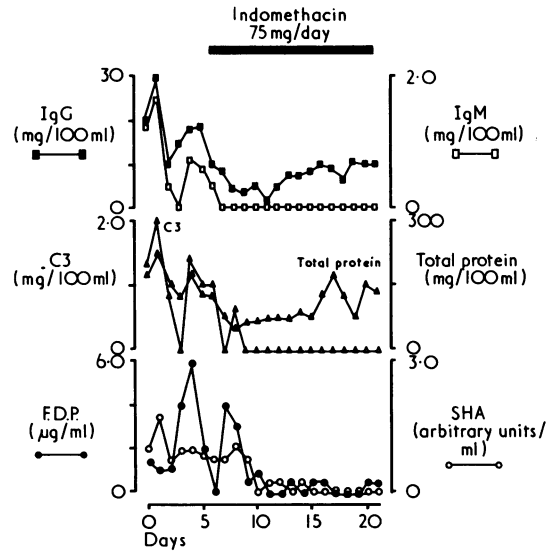

FIG. 2—Urinary excretion of F.D.P., SHA, total protein, and IgM-, IgG-, and C3- related materials in patient with proliferative glomerulonephritis whose renal function stabilized during indomethacin administration.

sequently showed biochemical evidence of improvement or stabilization of renal function. An example of this type of response is shown in fig. 2. In three other patients there was no significant fall in the excretion of F.D.P., SHA, or IgM- and C3- related materials during indomethacin administration (see fig. 3), and in a third group (three patients) though an apparently satisfactory F.D.P. response to indomethacin was recorded the excretion of SHA and IgM-, IgG-, and C3- related materials continued unchanged (see fig. 4). In both these latter groups there was biochemical evidence of continued deterioration in renal function.

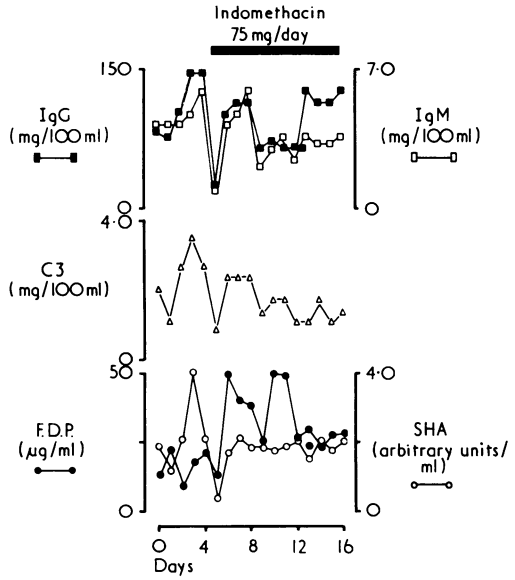

FIG. 3—Urinary excretion of F.D.P., SHA, and IgM-, IgG-, and C3- related materials in patient with proliferative glomerulonephritis whose renal function continued to deteriorate during indomethacin administration.

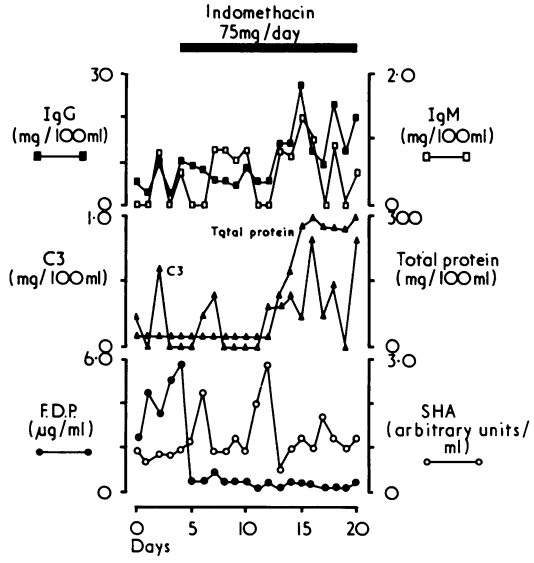

FIG. 4—Urinary excretion of F.D.P., SHA, total protein, and IgM-, IgG- and C3- related materials in patient with proliferative glomerulonephritis whose renal function continued to deteriorate. Note satisfactory F.D.P. response.

Discussion

Previous studies here and in other laboratories have provided data which collectively suggest that increased urinary F.D.P. excretion may be observed in active proliferative glomerulonephritis and during renal homograft rejection (Clarkson *et al.*, 1970; Chirawong *et al.*, 1971; Clarkson *et al.*, 1971; Hume and Pitcher, 1973). The source of this F.D.P. is not yet fully known though there is indirect evidence to suggest that at least in active proliferative glomerulonephritis a significant proportion may originate from lysed intrarenal fibrin (Davison *et al.*, 1973). The cause of this fibrin deposition is also unknown though animal studies would suggest it might be part of a non-inflammatory response to immune injury (Vassalli and McCluskey, 1964; Halpern *et al.*, 1965; Naish *et al.*, 1972). With the exception of histological data based on immunofluorescent studies, however, there are no comparable data in man.

The results of this preliminary study provide strong evidence for concluding that in some forms of proliferative glomerulonephritis and renal homograft rejection the intrarenal fibrin deposition may indeed be an integral feature of an inflammatory reaction to immune damage. The data presented, however, are in no way conclusive for the observations might be explained—at least in homograft rejections—on the basis of enhanced glomerular leakage of plasma proteins subsequent to the known changes in selectivity associated with rejection (Braun and Merrill, 1970). The position with proliferative glomerulonephritis is less uncertain. Previous studies have shown a lack of correlation between F.D.P. excretion and protein selectivity (Clarkson *et al.*, 1971), and in our present study we observed that during indomethacin administration an unchanged excretion of α_2-macroglobulin-related material (the parent molecule has a similar molecular weight to IgM) occurred in those patients who at the same time showed a dramatic fall in the excretion of IgM-related material. Similarly, as the molecular weights of IgG and C3 are close changes in selectivity might be expected to produce parallel changes in response to indomethacin, but this did not occur. Nevertheless, these conclusions must remain no more than tentative until a larger series of patients have been studied and until more information is available on the nature of the immunoglobulin- and complement-related materials in the urine.

The observations obtained from the 10 selected patients with proliferative glomerulonephritis receiving indomethacin may prove to have more immediate practical relevance. By using this technical approach it was possible to show the existence of at least three different types of responders: those whose abnormal excretion of F.D.P., SHA, and IgM- and C3- related materials fell during indomethacin administration; those with no response; and those whose response was confined to a fall in F.D.P. excretion alone. Because of the size of the total group of patients studied in this way it would be inappropriate to comment at the moment on the clinical significance of such subdivisions or indeed to claim that indomethacin is of clinical value in the management of any forms of proliferative glomerulonephritis. Nevertheless, the present evidence suggests that the pattern of responses may be related in some way to clinical outcome, and more detailed long-term investigations are therefore merited. Finally, the data adds support to previous conclusions (Hoq *et al.*, 1973) that at least in some forms of proliferative glomerulonephritis in man the role of intrarenal fibrin deposition may not in the event be such an important factor in the aetiology of progressive renal damage as experimental animal models have suggested (Vassalli and McCluskey, 1964; Halpern *et al.*, 1965; Naish *et al.*, 1972).

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MEDICAL MEMORANDA

Diamorphine-induced Attack of Paroxysmal Hypertension in Phaeochromocytoma

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Phaeochromocytoma is a rare cause of hypertension accounting for less than 0.1% of cases (Sjoerdsma, 1971). We describe a patient with this condition in whom clinical diagnosis was made during an acute myocardial infarction and who developed hypertensive crises and typical attacks in response to diamorphine administration. We believe that diamorphine caused histamine release which stimulated release of catecholamines. We suggest that opiates should not be used in patients with phaeochromocytoma.

Case Report

In 1962 a 42-year-old man was admitted to another hospital with occipital headache, diplopia, and hypomania. His blood pressure (mm Hg) ranged from 160-220 systolic and from 100 to 120 diastolic. A diagnosis of essential hypertension was made and treatment with methoserpidine was started. The patient continued to have headaches intermittently. In September 1970 he had an anterior myocardial infarction; sinus bradycardia and hypertension were noted. After the intravenous administration of diamorphine he developed sinus tachycardia and his blood pressure rose further. He was discharged on practolol with a blood pressure of 150/90 mm Hg. Ten days later the patient was admitted to the surgical unit with faecal impaction and urinary retention. Practolol was withdrawn.

He was seen again on 31 October 1971 30 minutes after the onset of severe chest pain. His heart rate was 36/min and his blood pressure 140/90 mm Hg. The intravenous administration of diamorphine 10 mg and cyclizine 50 mg relieved the chest pain but his blood pressure rose to 200/120 mm Hg and the heart rate to 124/min. He became very agitated, complained of severe throbbing headache, and sweated profusely. The electrocardiograph showed fresh anterior myocardial infarction. He developed frequent "R on T" ventricular ectopic beats which were treated with intravenous lignocaine. He continued to have episodes of chest pain requiring diamorphine administration. After each injection he had a similar reaction, his blood pressure rising as high as 240/160 mm Hg. Ventricular irritability was associated with episodes of ventricular tachycardia resistant to lignocaine. We believed he might have a phaeochromocytoma and pentazocine was substituted as an analgesic. Further progress was uneventful.

Investigations confirmed acute anterior myocardial infarction. Urine and blood analysis for catecholamines showed very high levels. Inferior vena cava sampling and adrenal vein catheterization indicated a right-sided phaeochromocytoma. This was confirmed after operation. Analysis showed that the tumour was predominantly noradrenaline-secreting.

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Comment

Probably the phaeochromocytoma was present in this patient in 1962. Changes in blood pressure and heart rate were attributed at first to an autonomic imbalance after myocardial infarction (Webb *et al.*, 1972). The reaction to diamorphine was so striking and consistent, however, that the diagnosis of phaeochromocytoma had to be considered.

Diamorphine, morphine, and other drugs such as tubocurarine liberate endogenous histamine from tissue stores (Jaffe, 1970) and we believe that this provoked the release of catecholamine from the patient's tumour. Pentazocine does not release histamine (Halpern, 1968) and was used successfully as an analgesic. Histamine in the past has been used as a diagnostic, though dangerous, test for phaeochromocytoma. Hypotensive and antiarrhythmic drugs causing ganglionic and postganglionic blockade sensitize peripheral receptors to circulating catecholamines and, like histamine liberators, are contraindicated in patients with phaeochromocytoma. The patient was fortunate that his hypertension had not been treated with guanethidine or his ventricular irritability with bretylium tosylate.

We would like to thank Dr. E. M. McIlrath for performing inferior vena cava sampling and adrenal vein catheterization, Mr. T. Kennedy who performed the adrenalectomy; and Mrs. J. Crawford for secretarial help.

Requests for reprints to be sent to Dr. J. M. Barber, Ulster Hospital, Dundonald, Belfast

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