this round-the-clock service data can be recorded and analysed and the patient can be given prompt instructions if required. Because of the simplicity of the service, the number of patients reporting regularly may easily increase with the number of available transmitters.

A preliminary survey of the first 200 patients indicated that there was a reasonable chance (88%) of detecting transient disturbances of rhythm because of the long periods during which the patients remained under observation (up to 31 days). The arrhythmia was discovered during routine transmissions and was unrelated to symptoms in only 22 patients (19%), while in all others the detected arrhythmias were accompanied by those complaints for which they were referred. In this respect, the telephone transmitting system was no worse than the Holter technique, which detects arrhythmias even if they are symptomless. Nevertheless, if the complaints are of too short duration or the arrhythmia renders the patient unable to make the necessary telephone call the Holter technique is preferable, provided the dysrhythmia occurs on the day of monitoring.

The immediate analysis and corresponding therapeutic measures that were taken in the six patients in whom multifocal ventricular ectopic beats or short runs of ventricular tachycardia were detected could not have been carried out with the Holter technique since the scanning in this method is always retrospective. In these cases, the telephone monitoring is obviously more efficient and practical.

Another point in favour of the telephone transmission is the convenience of evaluating the effectiveness of antiarrhythmic treatment given. The repeated contact with the medical personnel during the day allows optimal adjustment of drug doses at short intervals without the patient having to attend the out-patient clinic. Safe ambulatory withdrawal of antiarrhythmic treatment can likewise be supervised by the same method.

The results in patients in whom chest pain was considered ischaemic were rather disappointing. A definite electrocardiographic change during pain was discovered in less than a third of the patients, while in the other patients the ST-T changes were not of diagnostic value. In eight of the 32 patients suspected of having angina pectoris the symptoms were accompanied by rhythm disturbances but not by diagnostic ST-T changes. The complaints disappeared on successful treatment of the dysrhythmia.

Another important aspect of this type of patient surveillance is that it helps to exclude the existence of significant cardiac rate or rhythm disturbances in patients suffering from symptoms resembling cardiac arrhythmia. If recordings are normal when symptoms are present unnecessary medication can be prevented and the patient can be reassured. In many such patients symptoms disappeared after they were reassured.

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Bleeding in renal failure: a possible cause

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Summary

Increased concentrations of factor VIII-related antigen (VIII_{RA}), factor VIII-procoagulant activity (VIII_C), and decreased factor VIII-von Willebrand activity (VIII_{VWF}) were found in the plasma of patients with chronic renal failure (CRF). This functional abnormality of the factor VIII protein may partly explain the prolonged bleeding time commonly found in CRF. It was not improved by dialysis, but it was no longer found in patients with normally functioning grafted kidneys after the sixth month after transplantation. VIII_{VWF} levels remained decreased when compared with VIII_{RA} or VIII_C in transplanted patients undergoing acute reversible rejection soon after transplantation. Yet, not only VIII_C and

VIII_{RA} but also VIII_{VWF} were greatly increased in patients with hyperacute irreversible rejection. Possibly a high VIII_{VWF} level in these patients is a thrombogenic factor.

Introduction

Factor VIII-von Willebrand protein in normal plasma is a high-molecular weight glycoprotein measurable by immunological techniques. It consists of factor VIII-related antigen (VIII_{RA}), which is associated with factor VIII-procoagulant activity (VIII_C or antihaemophilic activity) and with von Willebrand factor activity (VIII_{VWF}). VIII_{VWF} is detected in vitro by platelet retention on glass bead columns¹ and measured by the ristocetin-induced platelet aggregation assay.² The relation between factor VIII-von Willebrand protein, platelets, and endothelial cells in the early processes of haemostasis and thrombogenesis is not fully understood. It is known, however, that VIII_{VWF}, which is lacking in patients with von Willebrand's disease, is necessary, in vivo, for the control of skin bleeding time.

In patients with chronic renal failure (CRF) reports of increased VIII_C³ and increased levels of VIII_{RA}⁴ conflict with reports of decreased glass bead platelet retention⁵ and prolonged bleeding time.⁷ In the hope of clarifying this apparent discrepancy we investigated the factor VIII complex components

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in patients with CRF who were either conservatively treated or on haemodialysis and explored the fate of these components in kidney transplant recipients.

Patients and methods

Thirty patients with CRF due to various primary renal diseases who had undergone maintenance haemodialysis for six months to six years were studied immediately before a routine dialysis and, in 10 of them, immediately after dialysis as well. Blood samples from five patients with conservatively treated severe CRF (serum creatinine ranging from 796 to 1149 $\mu\text{mol/l}$ (9–13 mg/100 ml)) were also studied.

Nine patients with renal transplants were also examined at least twice during the first five weeks after transplantation (37 blood samples). All had cadaver kidney transplants matched for two or three HLA antigens. All donor-recipient lymphocytotoxic cross matches were negative. All the patients were given heparin during the first weeks after transplantation and azathioprine and corticosteroids throughout, according to a standard procedure. Four blood samples were obtained from two patients undergoing early irreversible hyperacute rejection. Twenty-two samples were examined from four patients in whom an acute reversible rejection was the only complication during these five weeks of transplantation. During the same period the remaining three patients (11 samples) had acute reversible rejection with either infection or urological complications, or both.

Control samples were taken from 13 patients with normally functioning grafted kidneys six months to five years after transplantation and from six patients whose grafts had been removed after hyperacute rejection and who had been undergoing redialysis for six months to two years.

Twenty-seven normal subjects matched for age and sex were also studied.

Blood was collected in 3.8% citrate solution (nine parts of blood for one part anticoagulant solution). Platelet-poor plasma was obtained after centrifugation at 3000 g for 20 minutes at 12°C and was stored at -30°C.

VIIIIC was tested by a one-stage assay on freshly collected plasma. VIIIRA was measured by unidimensional immunoelectrophoresis according to the method of Laurell⁸ modified as described.⁹ Antiserum was obtained after immunisation of a rabbit with purified human factor VIII according to the method of Marchesi *et al.*¹⁰ The plasma cofactor of ristocetin-induced platelet aggregation (VIIIVWF) was measured by a modification⁹ of the quantitative assay of Weiss *et al.*² The inhibitory effect of the patients' plasma on von Willebrand activity of normal plasma was tested as follows: washed normal platelet suspensions were incubated with an equal volume mixture of normal and patients' plasma, and ristocetin-induced aggregation was compared with the aggregation obtained in the same system using the same normal plasma diluted in buffer.

Statistical analyses were performed with Student's *t* test.

One millilitre of normal plasma was considered to contain 100% of VIIIIC, 100% of VIIIRA, and 100% of VIIIVWF. Therefore the VIIIRA:VIIIVWF ratio was 1.

Results

PATIENTS WITH CHRONIC RENAL FAILURE

VIIIIC, VIIIRA, and VIIIVWF in haemodialysed and conservatively treated patients with CRF are shown in fig 1. VIIIIC was increased in both groups with a wide standard deviation ($178.5 \pm 101.2\%$ and $172.6 \pm 107\%$ respectively). VIIIRA also was increased with a mean value of $152.5 \pm 63\%$ in haemodialysed patients; it was increased (mean $114 \pm 96.2\%$) in some of the five conservatively treated patients. No correlation was found between the degree of increase, on the one hand, and the type of primary nephropathy, the number of dialyses, or the presence or absence of hepatitis B antigenaemia, on the other. VIIIVWF, however, was consistently decreased, with means of $47.3 \pm 31.1\%$ in those undergoing haemodialysis and $48.6 \pm 26\%$ in those treated conservatively. The VIIIRA:VIIIVWF ratios were 3.2 (table 1) and 2.3 respectively.

The results in the 10 patients studied both immediately before and immediately after dialysis are shown in fig 2. Factor VIII clotting assay was inconclusive, as the VIIIIC level was liable to be either decreased or increased after haemodialysis. VIIIRA increased significantly from 119.5% before to 160% after dialysis ($t=3.24$; $P<0.01$). No correlation was found between the differences in VIIIRA

FIG 1—VIIIIC, VIIIRA, and VIIIVWF levels in patients with CRF. Normal values are indicated by box on left. Centre column=patients undergoing haemodialysis. Right-hand column=conservatively treated patients. Horizontal lines indicate mean values.

FIG 2—VIIIIC, VIIIRA, and VIIIVWF before (left) and after (right) dialysis.

and the relative reduction of body weight, the amount of heparin given during dialysis, or the number of dialyses. VIIIVWF, however, remained the same (51%) after dialysis as before (47%) ($P>0.5$).

PATIENTS WITH RENAL TRANSPLANTS

VIIIIC, VIIIRA, and VIIIVWF were $222.5 \pm 125\%$, $295.4 \pm 153.2\%$, and $110 \pm 68.6\%$ respectively and the VIIIRA:VIIIVWF ratio was 2.6 in the nine transplanted patients irrespective of their pathological condition in the first five weeks of transplantation. The results obtained in four of these patients (22 blood samples) in whom an acute reversible rejection was the only unwanted event in this period are shown in fig 3. VIIIIC was $172.26 \pm 94\%$ and did not differ significantly from the value in haemodialysed patients. VIIIRA was increased to $258.6 \pm 83.4\%$ and the difference, compared with that in haemodialysed patients, was significant ($t=5.58$; $P<0.01$). VIIIVWF was slightly higher ($67.4 \pm 25.8\%$) than in the haemodialysis group (47.3% ; $t=2.4$; $P=0.02$) but still significantly decreased when compared with the value in normal subjects ($t=4.5$; $P<0.01$). The VIIIRA:VIIIVWF ratio was 3.8.

In 13 patients with normally functioning grafts at six months to six years after transplantation no differences in VIIIIC, VIIIRA, and VIIIVWF values were found compared with values in normal subjects (see table). The VIIIRA:VIIIVWF ratio was normal. The mean VIIIVWF level was significantly different from its value in haemodialysed patients with CRF ($P<0.01$).

In patients undergoing early hyperacute rejection VIIIIC, VIIIRA, and VIIIVWF levels were very high (see table) and significantly

FIG 3—VIII C, VIIIRA, and VIIIVWF. Comparison between normal values (box on left) and values in patients undergoing acute reversible rejection in early post-transplant period (centre) and mean values ($\pm$ SD) in patients with CRF undergoing haemodialysis (right). VIIIRA:VIIIVWF ratios were: 0.91 in normal subjects, 3.2 in those undergoing haemodialysis, and 3.8 in those with transplants.

Mean VIII C, VIIIRA, VIIIVWF ($\pm$ SD) in normal subjects, patients with CRF undergoing haemodialysis, patients with normally functioning grafted kidneys, and transplanted patients undergoing hyperacute rejection

Subjects	VIII C (%)	VIIIRA (%)	VIIIVWF (%)	VIIIRA: VIIIVWF ratio
Normal subjects ..	98.2 $\pm$ 31.7	94.34 $\pm$ 29.8	102.8 $\pm$ 32.8	0.90
Patients with CRF on haemodialysis ..	178.5 $\pm$ 101.2	152.5 $\pm$ 63.0	47.3 $\pm$ 31.1	3.20
Patients with grafted kidneys ..	179.0 $\pm$ 101.0	136.0 $\pm$ 61.4	103.6 $\pm$ 38.0	1.30
Patients in hyperacute rejection ..	270.0 $\pm$ 96.0	362.5 $\pm$ 171.9	372.5 $\pm$ 211.0	0.97

different from those obtained in the acute rejection group ($P < 0.01$). The VIIIRA:VIIIVWF ratio was normal.

VIII C (228 $\pm$ 160%), VIIIRA (187 $\pm$ 101%), and VIIIVWF (144.1 $\pm$ 70.9%) remained increased in patients who had undergone a hyperacute rejection and were back on maintenance haemodialysis; the results were significantly different from those in the patients with CRF on haemodialysis (for VIIIVWF $t = 5.5$; $P < 0.01$). The VIIIRA:VIIIVWF ratio in these patients was 1.2.

Discussion

Our results confirm the increase in VIII C and VIIIRA already reported in CRF.^{3,4} The striking finding was the association of an increase of these two values with a decrease in VIIIVWF levels. This abnormality is no longer found in patients with normally functioning grafted kidneys after the sixth month after transplantation.

This decrease in VIIIVWF has already been suggested by Hellem *et al*,⁵ Salzman and Neri,⁶ and Castaldi *et al*,¹¹ who showed decreased platelet retention on glass beads in CRF. To the best of our knowledge this has not been reported when

the quantitative method of Weiss,² measuring the plasma activity responsible for ristocetin-induced platelet aggregation, has been used. Thus, if the VIIIRA:VIII C ratio approximates to 1, suggesting a normal association of VIIIRA with the part of the molecule associated with clotting activity in patients with CRF, the VIIIRA:VIIIVWF ratio is considerably increased; this suggests the presence of a partially non-functional protein for the VIIIVWF activity. The increase in VIIIRA:VIIIVWF ratio is not related to any specific type of renal disease. It is found in conservatively treated as well as haemodialysed CRF patients, but it is not yet known at what stage of renal failure it appears. Dialysis did not improve the ratio and the ratio did not differ in short-term or long-term haemodialysed patients; it has been reported that platelet adhesiveness is often unchanged after dialysis and the Ivy bleeding time occasionally shortened.³

We suggest that the low VIIIVWF level partly explains the prolonged bleeding time and the bleeding tendency found in many patients with CRF.^{6,7,11} It seems to be a more plausible explanation than the different thrombocytopathies reported in uraemia by several workers, although these may also be contributory when they are present. Impaired platelet aggregation with adenosine diphosphate^{11,12} and with thrombin^{6,12} is not always found in uraemia, and platelet factor 3 abnormalities in uraemic platelets^{7,13} are more likely to interfere with the coagulation mechanism than with primary haemostasis.

In all the transplanted patients studied during the first five weeks of transplantation, the VIIIRA:VIIIVWF ratio remained increased (2.6), although VIIIRA and VIIIVWF values were higher than in CRF. This suggests, as in CRF, the presence of a non-functional protein in these patients. Moreover, in the transplant recipients in whom an acute reversible rejection had been the only untoward event during that period the VIIIRA:VIIIVWF ratio was even higher (3.8). The difference may be explained by the various degrees of increase of VIII C, VIIIRA, and VIIIVWF in patients with additional infection or septicaemia.¹⁴

Strikingly high levels of VIII C, VIIIRA, and VIIIVWF with a normal VIIIRA:VIIIVWF ratio (0.97) (see table) were obtained in two patients undergoing early irreversible hyperacute rejection. The thrombogenic role of such an excess of functionally normal factor VIII protein may be questioned. Both VIII C and VIIIVWF as well as VIIIRA remained high in patients whose grafts had been removed after hyperacute rejection and who were back on maintenance haemodialysis. The VIIIRA:VIIIVWF ratio was normal. This very different result from that obtained in the haemodialysis group may suggest that in the same patients it could be a predisposing factor to thrombogenesis and hyperacute rejection, and it would be interesting to investigate what would happen in such patients when they are transplanted.

It has recently been shown that endothelial cells synthesise and release a factor VIII containing the same polypeptide subunit present in plasma VIIIRA and having a VIIIVWF biological activity.¹⁵ VIIIRA has been shown by immunofluorescent microscopy to be present in the endothelial cells of glomeruli, peritubular capillaries, arteries, and veins of normal kidneys.¹⁶ Possibly, therefore, the increase in VIIIRA protein in the transplanted patients is a direct reaction to vascular damage occurring in the graft, but no explanation can be provided for the high VIIIRA level found in CRF.

At least three hypotheses can be proposed to explain the decrease in VIIIVWF in CRF patients. The endothelium may release too much of a functionally abnormal factor VIII protein. Alternatively, it may release a normal protein which is either partially degraded in the plasma or partially inhibited by a plasma inhibitor. No evidence of such partial inhibition was found when uraemic plasma was mixed with normal plasma and the mixture tested for VIIIVWF activity. If an inactivator does exist, it is not dialysable, as are inhibitors of platelet function reported in uraemia, such as guanidinosuccinic acid or hydroxyphenolic

acids.^{7 13} Further investigation is necessary to provide an explanation.

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A new look at the neonatal electrocardiogram

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Summary

Among 818 newborn babies whose electrocardiograms (ECGs) were recorded between April 1975 and April 1976 were 57 babies with recordings that fell outside the accepted normal range. Preliminary observations have identified the need to define more clearly the range of normal variation. Twelve babies showed asymptomatic conduction abnormalities, three of which were thought sufficiently serious to need treatment. Two babies died suddenly, one of whom had abnormal conduction on the ECG and histologically demonstrated abnormalities of the conducting system. This continuing prospective study may indicate a link between conducting tissue abnormalities and the sudden infant death syndrome. Ten babies had congenital cardiac anomalies, four of which were first discovered because of an abnormal screening cardiogram. Electrocardiography, a simple and non-invasive procedure, may be a valuable addition to the routine neonatal examination.

Introduction

A project was designed to evaluate the use of a standard electrocardiogram (ECG) as a screening device in the newborn. At

the start of the study there seemed to be at least three reasons why such a study might be valuable.

Firstly, it would enable the normal range of variation in the neonatal ECG to be assessed more accurately. This assessment would be based on statistical analysis and follow-up of many normal and abnormal records. Secondly, it would determine whether a routine neonatal ECG could be useful in the early detection of congenital heart disease. Finally, it would establish prospectively whether there is a relation between conduction abnormalities, especially pre-excitation, and the sudden infant death syndrome (cot deaths).

Although the study is continuing, the results in the first year bore out some of these expectations, and we report them here.

Patients and methods

From April 1975 to April 1976 818 babies who were kept in the local maternity unit for nine days after delivery were screened. The 35% of babies discharged at 48 hours were not included.

Standard ECGs were recorded using the portable Hewlett Packard machine Model 1504A. The usual paediatric plate electrodes were strapped to each limb and disposable Dracard electrodes were used for the chest leads. In addition to the limb leads, V1, V2, V4, and V6 were recorded; more recently VR4 was added.

ECGs were recorded between the 7th and 10th day of life to exclude some of the haemodynamic changes that occur in the first week, during the transition from the fetal to the infant circulatory pattern.

To minimise the mothers' anxiety we told them about the test, explaining that the baby would feel no discomfort and that the procedure was completely safe and designed to supplement the routine clinical examination of the heart. The mother was told the result on the same day, only unequivocal abnormalities being mentioned. All infants with a definite ECG abnormality, together with those with any questionable anomaly or an "innocent murmur," were referred for follow-up, together with an equal number of randomly selected babies with normal ECGs to act as controls. The general practitioner was told of any significant abnormalities. The baby was usually seen for follow-up between 6 and 8 weeks of age, but he was seen earlier if an abnormality needed more careful evaluation. There was a high rate of attendance. Only eight babies failed to return, and all were alive and well at the time of writing.

Preterm babies and those of low birth weight were also included in the series because they have a higher incidence of cot death.^{1 2} The criteria for normality in the ECGs of these infants are slightly different from those for term babies.

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