evidence has been presented which suggests that intraglomerular coagulation may play an important role in the natural history of acute ischaemic renal failure and may be the mechanism by which the septicaemia leads to oliguric renal failure. The presence of urinary fibrin degradation products would appear to support this view. An experimental model which is relevant to the clinical situation is produced by a continuous infusion of endotoxin which results in the deposition of fibrin within the glomerular vessels.

A Study of Antiheparin Activity of Serum and Platelet Factor 4

C. H. J. SEAR AND L. POLLER (*Withington Hospital, Manchester*) The hypothesis that serum antiheparin activity is due to platelet factor 4 (PF4) (Farbyszewski *et al*, 1968; O'Brien *et al*, 1970) has been investigated using biochemical fractionation techniques. Antiheparin activity was measured with a heparin plasma thrombin time system, and clotting times were determined under rigidly standardized conditions with the aid of a photometric clot detection device. Platelet lysates containing PF4 were prepared by freezing and thawing purified human platelets. A comparison of the platelet counts of human whole blood, platelet-rich plasma, and platelet-free plasma with the antiheparin activities of sera derived therefrom suggested that 70-80% of the whole blood serum activity originated in the platelets. Isoelectric precipitation studies at low ionic strength demonstrated a degree of chemical similarity between PF4 and the major serum activity and showed that the precipitation behaviour of PF4 is markedly influenced by its chemical environment. The platelet and serum activities were shown to have similar molecular sizes as judged by gel filtration through Sephadex G-200. These experiments also suggested that both activities reside with low molecular weight species (MW 25000-30000 daltons) that are incorporated into high molecular weight complexes under physiological conditions of pH and ionic strength.

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The Effects of Progestogens on Blood Clotting and Platelet Function

L. POLLER (*Withington Hospital, Manchester*) We have previously shown (Thomson and Poller, 1965; Poller *et al*, 1971a) that oral contraception with combined oestrogen/progestogen preparations results in rises in certain clotting factors and accelerated platelet aggregation and that the progestogen-only preparation, chlormadinone

acetate, a 17 acetoxysteroid, caused no observable changes in clotting factors. Changes in platelet aggregation were only noted after long-term administration (Poller *et al*, 1969, Poller *et al*, 1971b). With the withdrawal from the market of chlormadinone acetate no progestogen has been available.

We have therefore studied the effects of another progestogen, norethisterone, a 19 norsteroid, in two groups of women on clotting parameters and platelet function. The first group had been taking combined preparations previously. The second group had not previously been on oral contraceptives. Raised clotting factors and accelerated platelet aggregation from combined preparations rapidly returned to normal when norethisterone was substituted. No rises of clotting factors have so far been detected in the second group.

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Erythrocyte 2, 3-diphosphoglycerate in Diabetes and Renal Disease

PAULINE M. EMERSON AND J. DARLEY (*Department of Haematology, Radcliffe Infirmary, Oxford*) In patients with well controlled diabetes mellitus, the erythrocyte 2, 3-diphosphoglycerate (DPG) content does not differ significantly from the normal. However, in 15 patients with uncontrolled diabetes, the DPG levels were decreased below the normal range of 4.5 ± 0.5 mM to 2.2 ± 0.4 mM per litre of red cells. The lowered DPG levels counteracted the effect of pH on the oxygen dissociation curve so that the tissue oxygen supply remained unaffected.

The DPG took up to five days to return to normal, and it is suggested that this delay is secondary to a fall in plasma phosphate. Rapid correction of blood pH by intravenous bicarbonate should be avoided, as this leads to a rapid fall in the calculated P_{50} resulting from the persistently low levels of DPG and giving rise to the possibility of tissue anoxia. Preliminary studies on three patients given phosphate supplement during the first five hours of treatment suggest that this regime is not long enough to have a beneficial effect.

In 56 patients with chronic renal failure, blood collected before dialysis gave a significantly raised DPG level of 6.22 ± 1.38 . This did not correlate well with either the plasma phosphate or bicarbonate levels, but correlated fairly well with the haemoglobin concentration. Further studies are being undertaken

in order to calculate the P_{50} in these patients, before the results can be fully evaluated.

Symposium III

Chromosomes and disease

Leukaemia SYLVIA D. LAWLER (*Department of Clinical Research, Royal Marsden Hospital, London*) By using staining methods which produce characteristic banding patterns, it is now possible to identify precisely the individual chromosomes of the normal human set.

The components of structurally altered chromosomes can also be defined. For example, O'Riordan *et al* (1971) have shown that the Philadelphia chromosome, the deleted chromosome that is specifically associated with classical chronic myeloid leukaemia (CML), is a different member of the G group than the extra chromosome present constitutionally in Down's syndrome (Philadelphia chromosome = no. 22 with a deletion involving the long arm. Down's syndrome = trisomy 21).

Reeves *et al* (1972) have shown in four cases that the anomalous F group chromosome found in a variable proportion of cells in about 20% of cases of polycythaemia vera (PV) is a number 20, with a deletion involving the long arm, an observation which confirms the specificity of the anomaly in relation to PV.

The metacentric 'marker' chromosome of C group size, found not infrequently in the blast transformation stage of CML, has now been identified as an iso-chromosome of the long arm of a number 17 (Lobb *et al*, 1972).

The identification of supernumerary or abnormal chromosomes is also proving useful in a follow-up study that is in progress in patients with acute leukaemia first examined in the untreated state. A chromosomal pattern is becoming apparent in acute lymphoblastic leukaemia (ALL). At diagnosis the cases can be divided into three classes according to the karyotypes of the bone marrow cells: (1) predominantly hyperdiploid cells, (2) occasionally hyperdiploid or pseudodiploid and normal cells, (3) not hyperdiploid.

During the course of treatment in ALL the bone marrow does not convert immediately to cytogenetic normality. If serial samples of bone marrow are examined cases frequently are seen to go through a phase of having the occasional hyperdiploid cell before becoming normal. Such hyperdiploid cells usually do not have the same karyotype as the original abnormal population. It remains to be seen whether relapse is associated with the reappearance of a

population of cells that is chromosomally related to those found at diagnosis.

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Cancer of the Cervix A. I. SPRIGGS (*Department of Pathology, Radcliffe Infirmary, Oxford*) As a result of cervical smears, a whole range of conditions is available for study from normal through various presumptive precancerous stages up to fully developed invasive carcinoma of the cervix.

Established carcinoma shows chromosomal abnormalities comparable to those of other carcinomas; there is a stemline with a karyotype differing from the normal in ways which are unique to the particular tumour, with gains and losses of chromosomes and often recognizable markers. Counts near to diploid are the commonest, and counts above 92 are fairly rare. Most of the evidence favours the idea that the whole tumour originates from a single altered cell.

New karyotypically abnormal clones have also been found in microcarcinoma (microinvasive carcinoma).

Carcinoma *in situ* and severe dysplasia present variations which are less easy to describe. All observers have found aneuploidy, but there are conflicting reports about the presence or absence of associated diploid cells. Cultures of epithelium have produced diploid cells only. The commonest regions in chromosome count distributions have been around 46 and around 80. Sometimes the counts are consistent enough to suggest a clone. Similarity in the karyotypes from two separate areas, sometimes with the additional evidence of markers, confirm that clonal proliferation has occurred. In other cases there is a wide spread of counts with no obvious stemline.

The mildest dysplasias have been shown in a few cases to have counts near to 46, but even here abnormal karyotypes have been described. Very few analyses have been made from cells from normal cervixes, and these have been found normal.

Taken together, the picture presented is of a tissue in which aneuploid cell lines compete for supremacy, and in which a dominant clone finally selects itself. At what stage spontaneous regression or rejection of the lesion is still possible remains to be found out.

Antenatal Diagnosis P. E. POLANI (*Paediatric Research Unit, Guy's Hospital, London*) Prenatal diagnosis follows a number of different approaches directed at preventing or detecting fetal abnormality and, when