operation. We are also grateful to the technicians in the department of virology for their help. Thanks are also due to the Scientific and Research Subcommittee of the United Newcastle upon Tyne Hospitals and the Medical Research Council for financial support.

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Coagulation and Fibrinolytic Systems in Pre-eclampsia and Eclampsia

JOHN BONNAR, G. P. McNICOL, A. S. DOUGLAS

British Medical Journal, 1971, 2, 12–16

Summary

The coagulation and fibrinolytic mechanisms were investigated in a group of patients with severe pre-eclampsia and eclampsia and the findings were compared with those of healthy women in late pregnancy. In patients with pre-eclampsia the following significant differences were found: (1) greater depression of plasma fibrinolytic activity (euglobulin lysis time) than in normal pregnancy, (2) a higher level of inhibitor to urokinase-induced lysis, (3) increased levels of serum fibrin degradation products, and (4) reduced platelet counts.

In patients with eclampsia a progressive increase of the level of serum fibrin degradation products was found over the three days following eclamptic seizures. No such increase occurred after grand mal seizures in late pregnancy. The findings in this study support the view that intravascular clotting is taking place in pre-eclampsia and that this disturbance of the balance between coagulation and fibrinolysis may be localized to certain areas of the vascular compartment, particularly the placental and renal circulations. Fibrin deposition in the maternal vessels supplying the placenta would impair the placental blood flow, which may explain the placental insufficiency which occurs in pre-eclampsia. Likewise fibrin deposition in the renal vasculature will result in glomerular damage and proteinuria. Hypertension may be related to the renal ischaemic changes or a compensatory response to the presence of fibrin deposition in the vascular compartment. This evidence of intravascular fibrin deposition raises the question of the possible therapeutic value of antithrombotic agents to inhibit the clotting process. On a theoretical basis such treatment might be expected to improve blood flow to the placenta and thereby fetal growth.

Nuffield Department of Obstetrics and Gynaecology, Radcliffe Infirmary and Churchill Hospital, Oxford OX3 7LJ

JOHN BONNAR, M.D., M.R.C.O.G., First Assistant

University Department of Medicine, Royal Infirmary, Glasgow C.4

G. P. McNICOL, F.R.C.P., Reader in Medicine

A. S. DOUGLAS, F.R.C.P., Professor of Medicine (Present appointment: Regius Professor of Medicine, University of Aberdeen)

Introduction

The aetiology of pre-eclampsia remains obscure. Jeffcoate (1966) summarized many of the pathological factors known to be associated with pre-eclampsia and affirmed that it was a disease of theories; the possible role of the coagulation and fibrinolytic systems was not included and this aspect has received little attention. In some fatal cases of eclampsia, however, a prominent finding has been widespread fibrin deposition (McKay *et al.*, 1953). Electron microscopical study of tissue obtained by renal biopsy from patients with pre-eclampsia has revealed swelling of the glomerular capillary endothelium and deposition of an amorphous fibrinoid material within the cells and beneath the basement membrane (Pollak and Nettles, 1960; Altchek, 1961). Morris *et al.* (1964) using immunofluorescent techniques showed that the material in the glomeruli was identical to fibrin.

Recently evidence has been accumulating that the fibrinolytic system may be implicated in the mechanisms which influence blood pressure and blood flow (Niewiarowski, 1968). The physiological role of plasminogen activator is most likely to keep the blood vessels free of fibrin deposits, and in situations where the secretion or action of plasminogen activator is impaired fibrin deposition may be more likely to occur. To our knowledge there have been no detailed and serial studies of components of the fibrinolytic enzyme system in a well-defined group of patients with severe pre-eclampsia and eclampsia. The following investigation was undertaken to

throw some light on the role of the coagulation and fibrinolytic mechanisms in this complex disease process.

Patients and Methods

Ten patients with severe pre-eclampsia between 33 and 37 weeks' gestation were studied and two of them developed eclampsia. The diagnosis of pre-eclampsia was based on the following criteria: (1) a blood pressure of 150/100 mm Hg or over, proteinuria of 1 g or over per litre, and clinical oedema; (2) an uncomplicated pregnancy and normal blood pressure up to the 28th week of pregnancy; and (3) normal blood pressure and no proteinuria at the postnatal examination six weeks after delivery. The control series comprised 10 healthy women with pregnancies uncomplicated by any signs of pre-eclampsia. These patients were matched for age and gestation with the group with pre-eclampsia.

One patient with epilepsy was studied before and after epileptic convulsions to compare the findings with those in the two patients who developed eclamptic fits.

Blood was collected with plastic syringes and plasma samples were obtained by mixing nine volumes of whole blood with one volume of 3·8% sodium citrate and centrifuging at 4°C. Serum samples for assay of fibrin/fibrinogen degradation products were obtained by adding the whole blood immediately after venepuncture to tubes containing glass beads and a standard amount of tranexamic acid.

Plasma fibrinogen levels were measured by the method of Ratnoff and Menzie (1965). Plasminogen assays and euglobulin lysis activity were carried out as described by McNicol and Douglas (1964). The urokinase sensitivity test was used as a measure of fibrinolytic inhibitor in the plasma (McNicol *et al.*, 1965). Serum fibrin degradation products were assayed as described by Bonnar *et al.* (1969a). Factor VIII was assayed by the one-stage method of Breckenridge and Ratnoff (1962). The platelet count was performed according to the method of Dacie (1963).

Histological studies were performed on the kidneys of a 24-year-old woman with pre-eclampsia who died suddenly 24 hours after eclamptic seizures which developed immediately after delivery. She had had virtually no antenatal care and was admitted following delivery at home.

Results

In Fig. 1 the levels of fibrinogen, plasminogen, and serum fibrin degradation products in the patients with severe pre-eclampsia are compared with those in the controls. No significant difference was found in the levels of fibrinogen or plasminogen but the levels of serum fibrin degradation products were significantly higher in the patients (8·9 ± 7·4 μg/ml) than in the controls (1·9 ± 1·2 μg/ml).

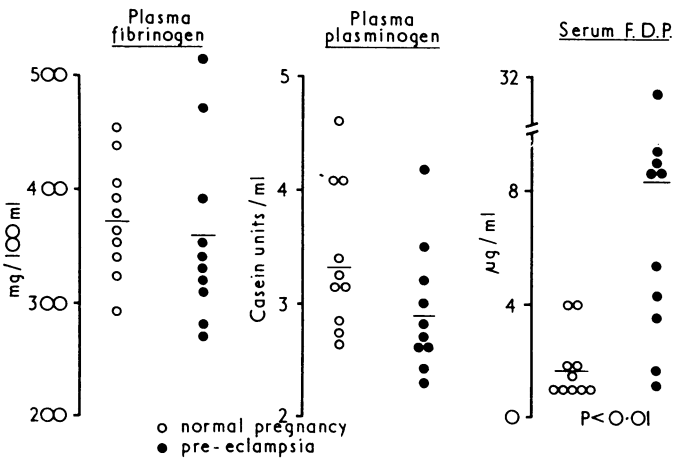

FIG. 1—Levels and mean values of fibrinogen, plasminogen, and serum fibrin degradation products (F.D.P.) in 10 patients with severe pre-eclampsia compared with the findings in 10 healthy patients matched for age and gestation.

Euglobulin lysis activity and the urokinase sensitivity (Fig. 2) were significantly less in the patients, indicating that lower levels of plasminogen activator and higher levels of inhibitor to urokinase-induced lysis were present in the circulating plasma in the patients than in the healthy pregnant women matched for age and gestation.

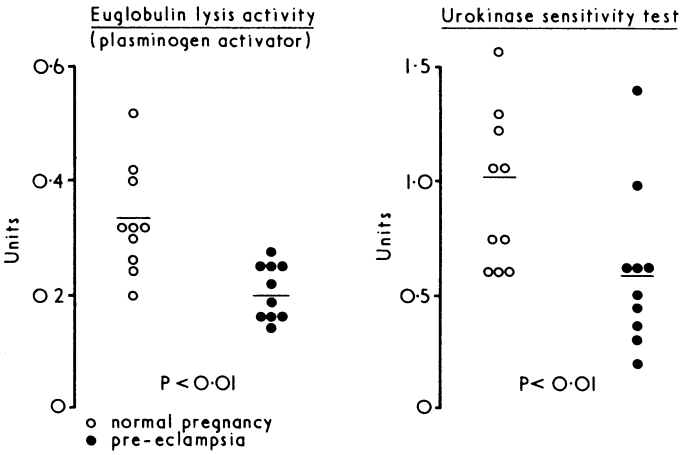

FIG. 2—Euglobulin lysis activity and urokinase sensitivity results with mean values in severe pre-eclampsia compared with the control patients.

In Fig. 3 the levels of factor VIII and the platelet count are compared. No significant difference was found in the levels of factor VIII but the platelet counts were significantly lower in the patients (140 ± 39 × 10^3/mm^3) than in the controls (203 ± 10^3/mm^3).

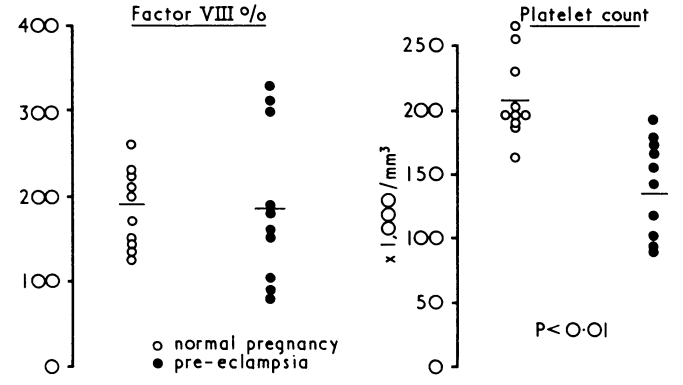

FIG. 3—Levels and mean values of factor VIII and the platelet count in patients with severe pre-eclampsia compared with the control patients.

Serial findings in the two patients who developed eclampsia are shown in Figs. 4 and 5. One of these patients was admitted at 34 weeks' gestation with severe pre-eclampsia and eclamptic seizures developed the day after admission. Surgical induction was not performed as the cervix was assessed as unfavourable and the obstetrician in charge decided on conservative management; five days after the eclamptic seizures fetal death occurred and the patient delivered spontaneously six days later. The euglobulin lysis activity at the lower limit of the normal range until after fetal death is shown in Fig. 4; raised levels of fibrinolytic inhibitor are indicated by the reduced sensitivity to urokinase-induced lysis; the level of serum fibrin degradation products rose from 2·5 to 60 μg/ml over the three days after the eclamptic seizures and during this period the platelet count was depressed. Only minor

changes were found in the levels of fibrinogen, plasminogen, and factor VIII.

Serial results in the patient who developed eclampsia immediately after delivery are shown in Fig. 5. Labour was induced at 37 weeks on account of severe pre-eclampsia. The day before induction of labour the euglobulin lysis activity was greatly reduced and the return to normal fibrinolytic activity did not occur until the third day of the puerperium. We have previously shown that in normal pregnancy fibrinolytic activity returns to normal non-pregnant levels within one hour of delivery (Bonnar *et al.*, 1969b). This delayed return to normal fibrinolytic activity after delivery was found in three of the patients with pre-eclampsia. As shown in Fig. 5 the serum fibrin degradation products level was raised before the onset of labour, and in the three days after the eclamptic seizures it greatly increased and far exceeded the levels found in the first week of the normal puerperium (Bonnar *et al.*, 1969a); the platelet count was depressed until after delivery.

The serial findings in a patient with epilepsy who was admitted at 38 weeks' gestation are shown in Fig. 6. This patient had no signs of pre-eclampsia and she had two grand mal seizures while in hospital. The level of serum fibrin degradation products did not increase after the convulsions, the euglobulin lysis activity remained depressed and reverted to

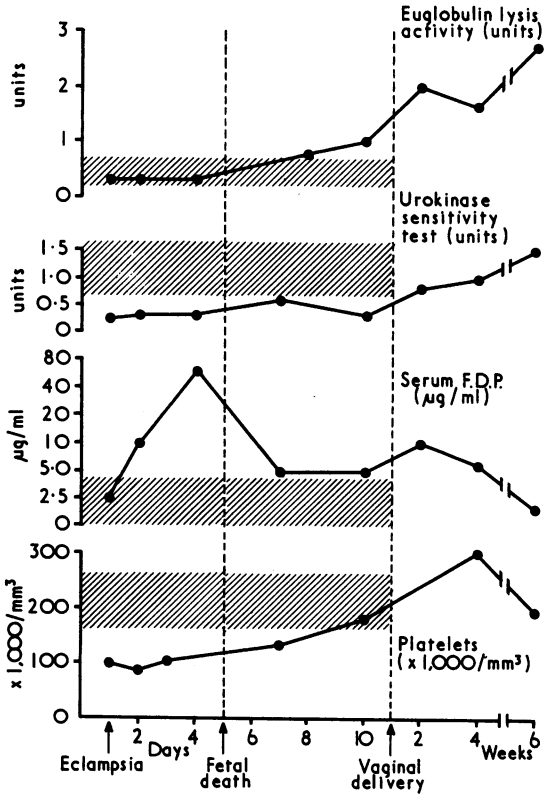

FIG. 4—Serial findings in euglobulin lysis activity, urokinase sensitivity tests, serum fibrin degradation products, and platelet count following antepartum eclampsia and fetal death in utero. The shaded area indicates the range for normal pregnancy before delivery.

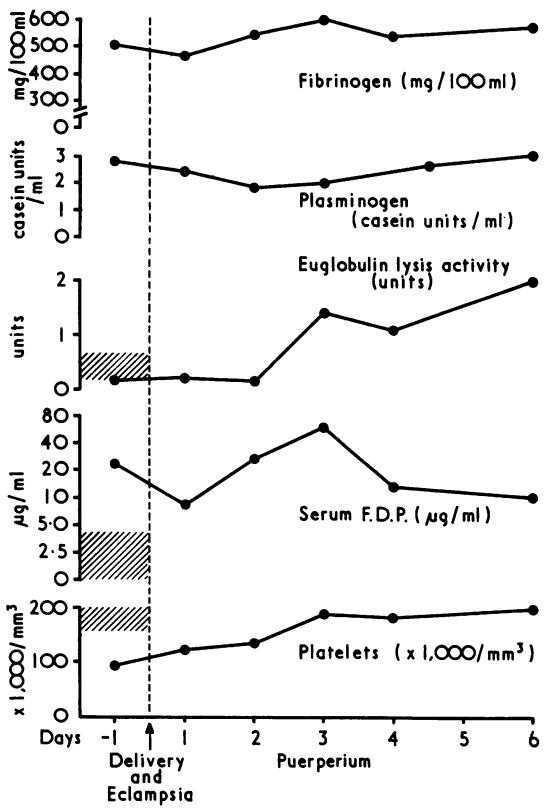

FIG. 5—Serial findings before and after postpartum eclampsia in the plasma fibrinogen, plasminogen, euglobulin lysis activity, serum fibrin degradation products, and platelet count. The shaded area indicates range for normal pregnancy before delivery.

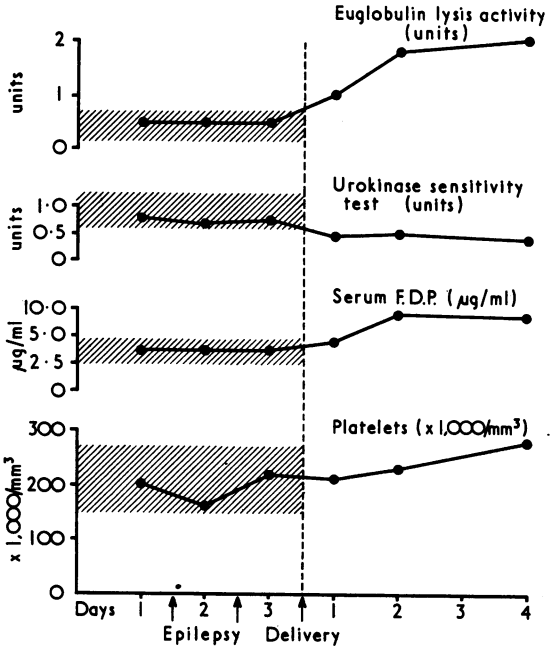

FIG. 6—Serial findings in euglobulin lysis activity, urokinase sensitivity test, serum fibrin degradation products, and platelet count before and after grand mal seizures at term. The shaded area indicates the range for normal pregnancy before delivery.

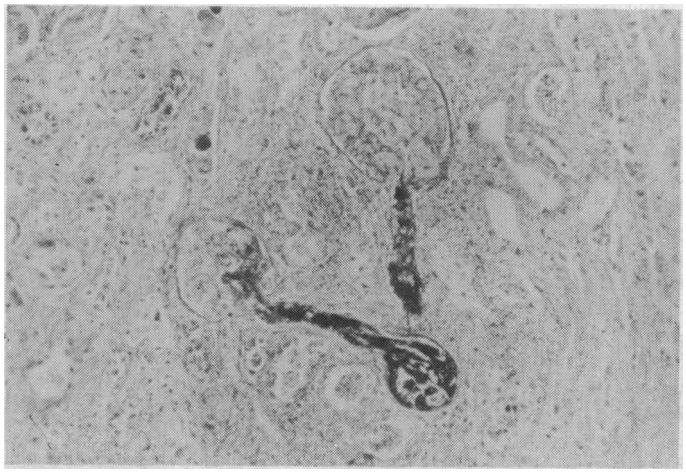

FIG. 7—Histological section of kidney of patient dying after eclampsia showing fibrin thrombi in intralobular artery and extending into afferent arterioles of glomeruli. (Picro-Mallory stain. × 98.)

normal levels after delivery, and the urokinase sensitivity test and platelet count were in the range of the control patients.

The histological section of the kidney of the patient who died 24 hours after eclamptic seizures (Fig. 7) shows that the intralobular arteries and afferent arterioles were occluded by fibrin, which was also present in the glomerular tufts.

Discussion

The findings in this study indicate a difference in certain factors concerned with coagulation and fibrinolysis between patients with severe pre-eclampsia and healthy women in late pregnancy. Recently reported studies on fibrinolysis in pre-eclampsia are difficult to compare with the present series because of different assay methods and the types of patient studied. Nielsen (1969) found no difference in fibrinolytic activity, but the fibrin plate technique which he used does not permit accurate quantitative assessment of fibrinolytic inhibition, and the method may be influenced by differing diffusion rates of activators, enzymes, and inhibitors. Wardle and Menon (1969) found no obvious difference in fibrinolytic activity in women with hypertension near term or mild pre-eclampsia from that in women with normal pregnancies; however, they found higher levels of cryofibrinogen in the hypertensive patients, which were interpreted as indicating a low-grade intravascular coagulation. The patients in the present study had severe pre-eclampsia and would not be readily comparable to those studied by Wardle and Menon. In a recent study in African Negro women Henderson *et al.* (1970) reported significantly higher levels of fibrin degradation products in pre-eclampsia and eclampsia than in normal pregnancy.

The significant differences found in this investigation of severe pre-eclampsia were: (1) greater depression of euglobulin lysis activity than is present in normal pregnancy, (2) a higher level of inhibitor to urokinase-induced lysis, (3) raised levels of serum fibrin degradation products, and (4) reduced platelet counts.

The lowered euglobulin lysis activity reflects reduced levels of circulating plasminogen activator which could result from a reduced production of activator in pre-eclampsia or from the absorption of circulating activator into intravascular fibrin. The increased resistance to urokinase may be a factor in the reduced fibrinolytic activity. In patients with renal disease McNicol *et al.* (1965) found reduced fibrinolytic activity and higher levels of inhibitor to urokinase. The similar changes in severe pre-eclampsia may therefore be related to the renal changes which occur in this condition. The raised levels of circulating fibrin degradation products most probably reflect local fibrinolysis in deposits of intravascular fibrin. A relatively low platelet count in severe pre-eclampsia has been reported (Ward and MacArthur, 1948; Brain *et al.*, 1967); this could also be the result of increased consumption due to intravascular coagulation.

In the two patients with eclampsia the level of serum fibrin degradation products rose steeply over the three days after the eclamptic seizures but no increase was found in the patient who had epileptic fits. Increased plasma fibrinolytic activity has been found in animals after electrically induced convulsions (Fantl and Simon, 1948) and in patients after electric shock therapy (Fletcher *et al.*, 1963). Following the convulsions of eclampsia and epilepsy in late pregnancy plasma fibrinolytic activity remained depressed but high levels of fibrin degradation products appeared in the patients with eclampsia. The explanation could be that in the patients with pre-eclampsia intravascular fibrin was present and the convulsions of eclampsia provoked an increase of local fibrinolysis. Schneider (1947) and Page *et al.* (1951) suggested that eclampsia may be a result of sudden intravascular clotting; such an occurrence would also produce a rise of fibrin degradation products in the circulation. The finding of raised levels of fibrin degradation products may explain why some patients with eclampsia develop bleeding from the gums, skin petechiae, and excessive bleeding from surgical incisions.

McKay (1965) suggested that in pre-eclampsia a low-grade process of intravascular coagulation is present and that the convulsions of eclampsia are the result of a sudden agglutination of platelets and the formation of platelet and fibrin thrombi which obstruct the cerebral microcirculation. Several workers have supported the assumption of intravascular coagulation in pre-eclampsia (Beller, 1964; Hjort and Rapaport, 1965; Vassalli and McCluskey, 1965). The cause of intravascular coagulation is uncertain; McKay *et al.* (1964) suggested that coagulation-activating components may be released from platelets which have been destroyed by adhering to the syncytial trophoblast.

Placental infarcts and intervillous thrombi are a well-known feature of pre-eclampsia, and these changes are probably an important factor in the placental insufficiency which occurs in this syndrome. A disturbance of the balance between coagulation and fibrinolysis in localized areas of the vascular compartment, particularly the placental and renal circulations, could account for many of the features of pre-eclampsia. Fibrin deposition in the maternal vessels supplying the placenta, particularly the spiral arterioles, and consequent impairment of placental blood flow may explain the placental insufficiency which occurs in pre-eclampsia. Similarly, fibrin deposition in the renal vasculature could result in glomerular damage and proteinuria. Hypertension may be the result of renal ischaemic changes or a compensatory response, which is mediated in some unknown way, to the presence of fibrin deposition in the vascular compartment. The extensive fibrin deposition shown in the vessels of the fatal case of eclampsia would account for the development of acute renal failure which may sometimes follow eclampsia.

An important feature of the fibrinolytic inhibition in pregnancy is the abrupt return to normal activity after delivery or intrauterine death. The resolution of the clinical signs of pre-eclampsia after delivery or intrauterine death is well known. The observation that fibrinolytic activity in some of the patients with pre-eclampsia did not return to normal for 24 to 48 hours after delivery also indicates a departure from the pattern of fibrinolytic activity found in normal pregnancy.

The demonstration of fibrin by immunofluorescent studies in the renal glomeruli of patients with pre-eclampsia (Morris *et al.*, 1964) and the present evidence of intravascular fibrin deposition raise the question of the possible therapeutic value of antithrombotic agents to inhibit the clotting process. Such treatment on a theoretical basis might be expected to improve the blood flow to the placenta and thereby the fetal growth. The value of such therapy would require to be evaluated through carefully controlled clinical trials which included placental function studies and monitoring of alterations in the coagulation and fibrinolytic factors induced by therapy.

Whether the changes found in this investigation are related to the pathogenesis of pre-eclampsia or are the effect of the disease process cannot at present be stated. Nevertheless, our findings indicate that intravascular fibrin deposition and disordered fibrinolytic activity appear to be a feature of severe pre-eclampsia. Further study of the coagulation and fibrinolytic systems in pre-eclampsia and of the maternal vasculature supplying the placenta may help to elucidate the pathogenesis of the syndrome and help to provide a rational basis for effective treatment.

We are grateful to Sir Hector MacLennan and Professor E. M. McGirr for their interest in this work; to the Medical Research Council and to F.B.A. Pharmaceuticals Limited for financial assistance; and to Mrs. Christine Pidgeon for her expert laboratory help.

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Serum Gastrin in Chronic Gastritis

M. G. KORMAN, R. G. STRICKLAND, J. HANSKY

British Medical Journal, 1971, **2**, 16-18

Summary

Fasting gastrin levels in serum were measured in 49 patients with different types of chronic gastritis and in matched controls. In 15 patients with established pernicious anaemia the mean (± S.E. of mean) level of gastrin was greatly raised (699 ± 99 pg/ml). In 17 patients with chronic atrophic gastritis, seropositive for parietal cell antibody but with adequate vitamin-B_{12} absorption, the level was also raised (476 ± 74 pg/ml). By contrast, in "simple" atrophic gastritis seronegative for parietal cell antibody the gastrin levels were significantly lower for both diffuse atrophic gastritis (129 ± 31 pg/ml) and multifocal gastritis (14 ± 4 pg/ml). These levels were similar to those in the controls (46 ± 7 pg/ml).

The mechanism of the raised gastrin levels remains uncertain, but neither achlorhydria nor in vivo action of the parietal cell antibody wholly accounted for the hypergastrinaemia.

We conclude that hypergastrinaemia is characteristic of gastritis associated with autoimmune reactions to gastric antigens and pernicious anaemia and that a raised serum gastrin is a useful marker of the type of gastritis that tends to progress to the gastric lesion of pernicious anaemia. The findings suggest that this type of gastritis is an essentially different disease from "simple" atrophic gastritis, and the differences in gastrin levels may be due to sparing of the antral mucosa in the autoimmune type but not in "simple" gastritis.

Introduction

The isolation, purification, and synthesis of human gastrin (Gregory, 1966) led to the development of a radioimmunoassay to measure gastrin levels in blood (McGuigan 1968a). Gastrin levels are raised in the Zollinger-Ellison syndrome (McGuigan and Trudeau, 1968; Hansky and Cain, 1969) and in Addisonian pernicious anaemia (McGuigan and Trudeau, 1970; Yalow and Berson, 1970). Lack of acid inhibition of gastrin release is the suggested explanation of the hypergastrinaemia of pernicious anaemia (Yalow and Berson, 1970). This study examines the relationship of serum gastrin levels to the type of gastritis, the presence or absence of achlorhydria, and the presence or absence of gastric autoantibodies in patients with gastritis.

Monash University Department of Medicine, Prince Henry's Hospital, Melbourne, Australia

M. G. KORMAN, M.R.A.C.P., Research Fellow
J. HANSKY, M.R.A.C.P., Senior Lecturer

Clinical Research Unit, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

R. G. STRICKLAND, M.R.A.C.P., Assistant Physician

Patients and Methods

Forty-nine patients with chronic gastritis and basal achlorhydria and 49 control subjects were studied. The patients were divided into four groups on the basis of gastric mucosal histology, vitamin-B_{12} absorption by Schilling test, and tests for parietal cell antibody (see Table).

Vitamin-B_{12} absorption was estimated by the Schilling test with 1 μg of ^{58}Co vitamin B_{12}, flushing dose of 1 mg of unlabelled vitamin B_{12} two hours later, and a 48-hour collection of urine; an excretion of less than 5% of the administered dose was taken to be diagnostic of pernicious anaemia. When appropriate the test was repeated with 1,000 ng units of hog intrinsic factor (WES 818 Lederle).

Acid secretion was assessed by using the criteria of Kay (1953) following a maximal dose of either ametazole hydrochloride (betazole hydrochloride, Histalog), 1·5 mg/kg body weight, or histamine acid phosphate, 0·04 mg/kg body weight. Results were expressed in total mEq per hour basally and after stimulation. Basal achlorhydria refers to gastric juice with no titratable acidity to pH 7·4. Histamine-fast or Histalog-fast achlorhydria refers to failure to change pH by more than one unit after stimulation and the absence of titratable acidity to pH 7·4. Total achlorhydria refers to the combination of basal and post-stimulation achlorhydria.

Gastric mucosal biopsy specimens were obtained from the body or fundus of each patient by means of Wood's tube (Wood *et al.*, 1949). The average number of biopsy specimens from each patient was five (range 2-17). The specimens were classified, according to te Velde *et al.* (1966), into chronic