Combined Anterior Pituitary Necrosis and Bilateral Cortical Necrosis of the Kidneys, Following Concealed Accidental Haemorrhage.*

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WE think that the following case of concealed accidental haemorrhage complicated by both pituitary and renal necrosis, the first to be described in this country, is worth recording. Analysis of the findings suggests various points which may throw some light on the mechanism of production of these complications.

CASE REPORT.

Mrs. E. C., aged 31, 2-para; was admitted to this hospital on August 27th, 1945, complaining of severe constant abdominal pain of 5 hours duration. Her past and family history were not significant. In 1937 she had had a full time normal delivery. In 1941 she had had a 7-months' premature stillbirth, attributed to the cord being round the child's neck.

History of present pregnancy. Last normal menstrual period, January 20th, 1945. Expected date of delivery October 27th, 1945. She booked at her local clinic on June 26th, 1945, and attended again on July 25th. The urine showed no abnormality on these 2 visits, and the blood-pressure readings were 100/70 and 100/60 respectively. The Wassermann and Kahn reactions were negative. Evidently she was not a co-operative patient since she did not take vitamins and iron as advised. Since the latter attendance she had had occasional frontal headaches without visual disturbances. Appetite and sleep were normal, but there had been some oedema of the feet for the 3 days prior to admission.

She was watching cricket on the afternoon of the 26th August, and on returning home felt a desire to micturate, went to the toilet and passed a small quantity of urine. Then it was, at 7.15 p.m., that she began to have severe, constant, abdominal pain. She felt "her tummy turn, tighten, and fill up." She fainted and was admitted to this hospital 5 hours later; having vomited several times, but having had no bleeding or shoulder pain.

On admission the patient was found to be very cold and shocked with marked pallor, oedema of the legs two-thirds of the way up to the knees and also of the lower abdominal wall; no icterus. The pulse was 120, of fair volume; blood-pressure, 150/80. Abdomen: Fundus, size of 34 weeks' gestation (31 weeks by dates), very tense and tender and foetal parts not palpable; foetal heart not heard. Fundi and discs normal. Vaginal inspection revealed very slight bleeding. A diagnosis of concealed accidental haemorrhage was made, and the patient immediately treated for shock on the usual lines of heat, blocks to the foot of the bed, injection of morphia, gr. ¼, and, after blood had been taken for a haemoglobin (5 g. per cent) and blood urea (57 mg. per cent) estimation, she was transfused with 2 pints of Group O4 blood; there being no rhesus negative blood available at the time.

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Progress. While setting up the transfusion the membranes bulged at the perineum; these were artificially ruptured and non-blood-stained liquor escaped. Shortly afterwards a fresh stillborn infant with placenta and membranes were delivered together.

Twenty-six ounces of old and fresh clot and torn placental cotyledons were then expressed, and the patient was given an intramuscular injection of ergometrine 0.5 mg. There was very slight loss afterwards. The placenta was grossly irregular and indented throughout almost half its area, being 9 ounces in weight. Immediately after delivery a catheter specimen of urine, total ½ ounce, revealed 750 mg. albumin per cent.

Thereafter the patient was nursed in a darkened quiet room. She vomited on and off but managed to retain water. During the next night she passed very small quantities of urine on 2 occasions. On the morning of the 28th she was still oedematous, and also, now, were her face and eyelids. There was severe frontal headache, and she was still vomiting. The pulse was 92 per minute, blood-pressure 130/80, blood urea 106 mg. per cent. During the day a further 1 ounce of urine was passed, but as there appeared to be almost complete suppression of urine, she was given 1 litre of isotonic sodium lactate intravenously, in an attempt to bring about diuresis. This was followed by 1 litre of 5 per cent glucose saline at a slow drip.

Next morning, August 29th, only a few drops of urine were obtained by catheter, and there was definite bilateral renal tenderness. For the next 2 days her general condition remained unaltered, although by the graphs (Fig. 1) it will be seen that her output of urine was still negligible, and the blood urea and serum potassium were rising. On the morning of August 31st she complained of indigestion and bilateral renal pain. The tongue was moist and slightly coated, there was no alteration in the oedema, and the fundi and discs were normal. By the evening she was rather drowsy and the respirations somewhat acidotic, and she was not drinking well. She suddenly collapsed and died on the morning of September 1st, the 7th day of her illness.

At no time were measures required for the treatment of symptoms of engorged breasts.

Although the intake of fluid had been satisfactory until the last 18 hours, her total output of urine from the onset of abdominal pain had been approximately 4½ ounces in 5½ days.

The postmortem blood findings were: blood urea, 216 mg. per cent; serum potassium, 32.8 mg. per cent; plasma chlorides, 505 mg. per cent. In addition her blood group was found to be A2 Rh negative, with no anti-Rh agglutinins in her serum. The husband was group O4 Rh positive.

Postmortem Findings.

The postmortem examination was made 3 hours after death. The abdomen contained 150 c.cm. clear fluid, the right pleural space 350 c.cm. and the left space 150 c.cm. clear effusion. The tissues in general were oedematous.

Genito-urinary system. The right kidney weighed 210 g., the left 240 g. Perinephric fat was abundant. The capsules stripped easily revealing a smooth subcapsular surface mottled by alternating small haemorrhagic and intensely pale zones (Fig. 2). The cut surfaces showed a striking widespread anaemic infarction limited to the cortex and columns of Bertini (Fig. 2). There were bands 1 to 7 cm. long, wedges and small irregular areas a few mm. across of pinkish-yellow, firm, coagulative necrosis, bordered by a fine wavy margin of reactive hyperaemia about 1 mm. thick. These hyperaemic borders were both subcapsular and in the cortico-medullary demarcation line. Scattered between the infarcts were a few streaks of surviving cortex. The medulla was congested. All visible branches of the renal arteries and veins were free from thrombus. The renal pelves were normal, the left ureter normal, the right ureter slightly dilated. The bladder was markedly contracted, its mucosa oedematous, the ureteric orifices patent.

The uterus was enlarged and thick walled (3 to 4 cm. in its thickest portion) and showed 2 large crops of subperitoneal petechiae lying round the origin of each Fallopian tube and extending on to the Fallopian tubes and round ligaments. The cut surface showed extension of the petechiae into the superficial myometrium. Many venous sinusoids in the uterine wall were thrombosed. The placental site appeared healthy. There was a small atrophic corpus luteum of pregnancy in the left ovary. Neither ovary was engorged. The right ovarian vein was enormously distended by thrombus (maximum diameter 3 × 2.5 cm.) from its origin up to its entry into the inferior vena cava,

into the lumen of which clot protruded. But there was no main caval thrombosis. The proximal 8 cm. of the left ovarian vein was also thrombosed, but not distended.

was enlarged, unusually pale (rendering the pattern obscure) and showed scattered dilated subcapsular veins. The gallbladder contained about 20 facetted mixed stones, though its mucosa and duct

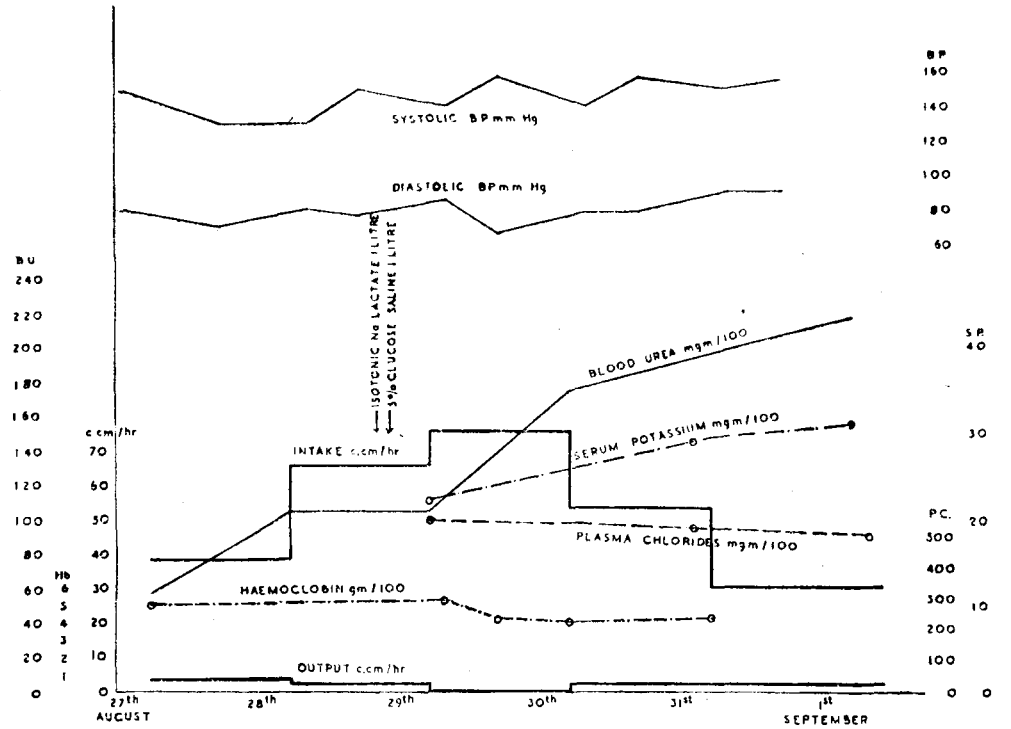

FIG. 1

CHART SHOWING CLINICAL AND BIOCHEMICAL FINDINGS.

Note from above down: 1. Blood pressure readings: note absence of hypotension. 2. Intake maintained and output negligible. 3. Biochemical findings (rising blood urea and serum potassium, and falling plasma chlorides). 4. Haemoglobin readings. Death occurred on the 6th morning.

Cardiovascular system. The valves, chambers and muscles of the heart (280 g.) appeared healthy. The coronary arteries, the aorta and branches were smooth walled, elastic and free from atheroma. There was postmortem clot in the pulmonary artery.

Respiratory system. Apart from a moderate degree of marginal emphysema and partial collapse of their bases, the lungs appeared healthy. The mediastinal lymph-nodes were normal.

Alimentary system. The tongue was moderately furred. The pharynx, oesophagus, stomach and intestines all appeared normal. The liver (1920 g.) appeared healthy. The bile-ducts were patent. The pancreas appeared healthy.

The spleen (300 g.) was enlarged, its pulp firm, the Malpighian bodies prominent. The adrenals appeared normal. The thyroid gland was rich in colloid. The breasts were heavy and tense and when incised gave out spurts of milk. The vertebral bone-marrow was pale. The right femur contained pink marrow in its upper two thirds, but did not show any gross medullary bone resorption. The brain (1280 g.) and its basal vessels were normal. There was a haemorrhagic oedema of the pituitary stalk. The hypothalamus was not engorged. The pituitary gland was fixed whole in

Zenker-formol solution and then bisected. After the chromate had been washed out the cut surface of the gland presented a massive anaemic infarction of the pars anterior bordered by a thin subcapsular haemorrhagic zone. The naked-eye appearance was identical with that of the renal coagulative necrosis (Fig. 2).

Microscopic Findings.

Pituitary. The anterior lobe shows a massive coagulative necrosis which has left only a few surviving cells scattered under the capsule and in the posterosuperior angle beneath and in front of the stalk. The pituitary cells have lost their haematoxyphil nuclear staining. The central sinusoids are empty but those nearer the periphery contain numerous polymorphonuclear leucocytes (many of them vacuolated and showing pyknotic nuclei) (Fig. 3). The sinusoids supplying the surviving cells are engorged. The basement-membranes can still be stained by aniline blue so as to show up the 'skeleton' of the infarcted area. And many of the parenchymatous cells, which stain a uniform pink with haematoxylin and eosin, show ghostly remnants of nuclei and granules when stained by Mallory's or Biggart's method. The pars intermedia and posterior appear normal. The sinusoids of the stalk are intensely engorged and the interstitial tissue at its upper end is flooded with red cells. The arterioles are not thrombosed. But the veins of the stalk, both large and small, contain varying types of thrombus: amorphous hyalinized red-cell masses, organizing fibrin and entangled cells, and conglutinated red cells (Fig. 4). The age of the pars anterior necrosis, judged by the parenchymatous karyolysis, the polymorphonuclear infiltration and the absence of secondary atrophy lies between 3 and 9 days and tallies with the 6 days' survival after delivery.

Kidneys. The cortex and columns of Bertini show a widespread ischaemic coagulative necrosis split up by slender streaks of surviving renal tissue which is also present as a thin layer underneath the capsule (Fig. 5). The medulla is congested but nowhere infarcted. In the depths of the infarcted cortex, karolysis is complete and there is no leucocytic infiltration; the ghosts of glomeruli, tubules and vessels (including dead interlobular arteries distended with hyalinized fibrin thrombus) are readily made out (Fig. 6). The edges of the infarcted areas show a heavy interstitial infiltration with degenerate fatty polymorphonuclears and occasional patches of interstitial haemorrhage. The zone of demarcation between living and dead cortex is surprisingly sharp. It cuts right across the renal structures so as to leave some arterioles and some glomeruli bisected into a living and a dead half. There is not any evidence in the living glomeruli of any previous widespread ischaemic changes nor of any eclamptic oedema of the capillary basement membranes. The living tubules contain cast material and desquamated cells, a few of the living cells are fatty. There are occasional terminal interlobular and afferent arterioles in the living cortex which are distended and occluded by hyalinized material (resembling fused red cells). These vessels are surrounded by a small zone of polymorphonuclears and histiocytes. Elastic stains confirm the extraordinary, almost "paralytic" dilation of some of the interlobular arteries, particularly in the infarcts (Fig. 6). These stand out in all sections. Non-thrombosed interlobular arteries at the edge of the infarcted tissue show commencing acute necrosis of their walls and a surrounding zone of radially grouped pyknotic leucocytes—a typical acute arteritis (Fig. 7). The interlobular and arcuate arteries and veins are free from thrombus or disease, some interlobular arteries show a mild elastosis. The age of the infarcts, judged by the degree of parenchymatous karyolysis and marginal interstitial polymorphonuclear infiltration, tallies well with the clinical history of 6 days anuria. Thus, the renal necrosis judged histologically is likely to be of the same age as the pituitary necrosis.

The picture as a whole suggests the following possible interpretation of the train of events. The infarcted terrain is that supplied by the interlobular arteries. These appear to have been primarily obstructed by stasis leading to thrombosis which has spread both backwards and forwards along these vessels. The grossly diminished or complete loss of blood-flow led to renal functional failure and ischaemic necrosis. How the stasis arose and the significance of the arteritis are discussed later.

Pancreas. The glands and islets are normal. But there is a striking arteritis in all stages of development which involves many of the small and large vessels. The earlier lesions consist of fibrinoid

necrosis of a segment of the adventitial coat. The necrotic collagen is infiltrated with pyknotic nuclei. The next development seen is an extension of the necrosis into the media and a brisk perivascular inflammation. In the advanced stages, the whole of the adventitia and much of the media is swollen and replaced by fibrinoid material and somewhat radially arranged pyknotic nuclei (Fig. 8). The perivascular interstitial tissue is heavily infiltrated with histiocytes and polymorphonuclears some of which extend into the surrounding pancreatic glandular tissue. The lumen of the vessels is free from thrombus. The only thrombosed vessels present are a few small arterioles and venules lying in the neighbourhood of a gravely involved larger vessel.

Liver. There is a widespread fine fatty droplet change affecting all zones of the lobules and, in addition, occasional centrilobular focal necroses (small collections of dead liver cells infiltrated with fresh polymorphonuclears). There is no eclamptic periportal haemorrhagic necrosis.

Uterine wall. Some of the subperitoneal muscle fibres are vacuolated and show glycogenic degeneration of their nuclei. This same layer is rendered prominent by the presence of numerous interstitial haemorrhages. Many uterine veins are distended and filled with aseptic fibrin thrombus showing, as yet, practically no organization. The uterus is lined by fibrin, entangled red cells and masses of pyknotic nuclei derived from decidual cells and polymorphonuclears. There are scattered cystic healthy endometrial glands of the basalis layer.

Right ovarian vein. This is distended by thrombus which consists chiefly of massed red cells (still containing haemoglobin) traversed by strands of fibrin, conglomerated platelets and entangled leucocytes. It all looks of recent formation (less than 5 days). The muscularis has been thinned by distension. The adventitia is oedematous and contains fibrin and free red cells which have spread a little way into the surrounding fatty connective-tissue.

Spleen. There is a moderate increase of polymorphonuclears in the pulp and occasional megakaryocytes in the sinusoids.

Gall bladder. The outer connective-tissue coat shows a mild perivascular inflammatory infiltration with lymphocytes and neutrophil and eosinophil polymorphonuclear leucocytes.

Breast. The acini show a well-marked lactation hyperplasia. Their lumens and lining cells are distended with fat droplets.

Sections of the lung, heart-muscle, hypothalumus, bone-marrow, cervix, adrenal, thyroid and left ovary (which contains a well vascularized corpus luteum of advanced pregnancy) do not show any essential pathological changes.

It is clear from the above clinical history and the naked-eye and microscopic postmortem findings that death was due to renal failure brought on by the massive renal necrosis which had most likely occurred 6 days previously at the time of the concealed accidental haemorrhage. One cannot gauge to what extent the pituitary necrosis, which had occurred at the same time, contributed towards the death.

Discussion.

Sheehan[1] found 11 cases of postpartum necrosis of the anterior pituitary in a consecutive series of 59 postmortem examinations of women dying in the puerperium. Thus, there is about a 1 in 5 chance of its occurrence together with renal cortical necrosis. He also found that in 24 of 28 recorded cases there was a history of haemorrhage at delivery. All these patients were "collapsed." Since haemorrhage and "collapse" are present in almost all cases of renal cortical necrosis, the chances of its coincidence with pituitary necrosis must be even higher than 1 in 5. Sheehan thought the pituitary necrosis resulted from haemorrhage and "collapse" rather than "toxaemia."

Tomlinson[2] described a case of combined pituitary and renal necrosis in a multipara aged 28, who was admitted in the 38th week of her third pregnancy suffering from a urinary tract infection. Following forceps delivery of a stillborn infant and manual removal of the placenta she went into severe shock. She developed anuria and died 6 days later of uraemia. Sheldon and Hertig[3] described 2 cases of renal cortical necrosis in which postmortem examination

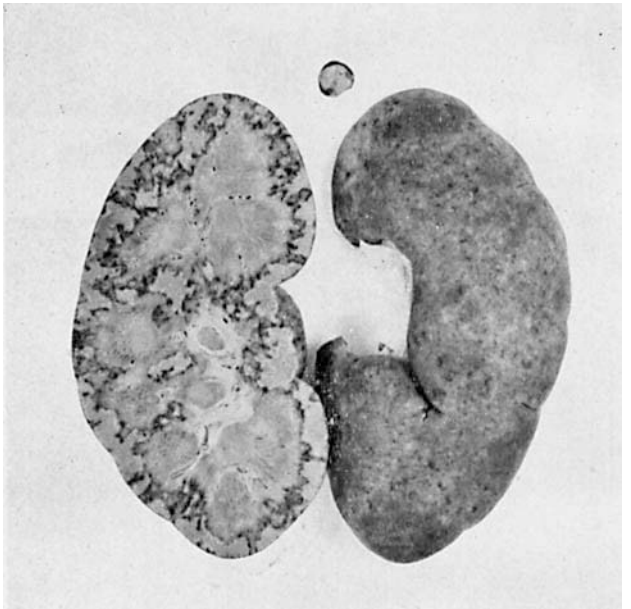

FIG. 2.

Right kidney and pituitary. (Photograph reduced to half natural size.) Widespread pale cortical necrosis bordered by a thin hyperaemic zone, mottled subcapsular surface, ischaemic cut surface of pituitary gland.

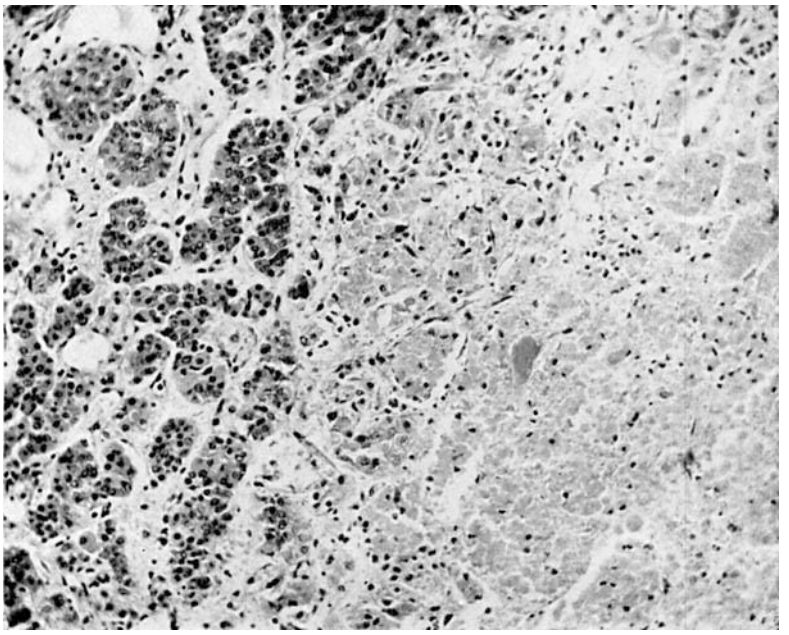

FIG. 3.

Pituitary gland. (Photomicrograph [× 175], Formol-Zenker, Haematoxylin and Eosin.) Border between living cells of the pars anterior to the left and dead to the right.

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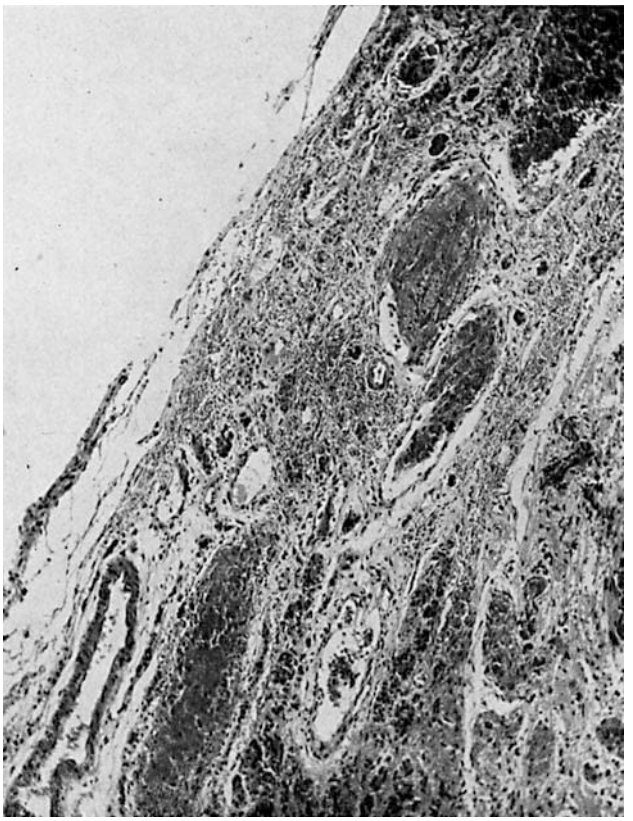

FIG. 4.

Pituitary stalk. (Photomicrograph [× 90], Formol-Zenker, Haematoxylin and Eosin.) Thrombosed veins in the pituitary stalk. The arteries and arterioles are patent.

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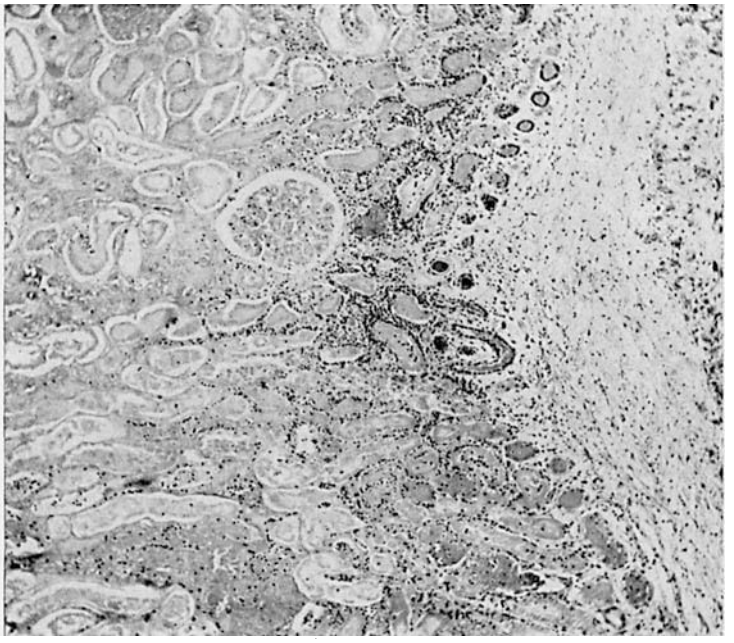

FIG. 5.

Kidney. (Photomicrograph [× 90], Formol-Zenker, Haematoxylin and Eosin.) Oedematous congested renal capsule separated by a thin hyperaemic zone infiltrated with leucocytes from underlying infarcted cortex.

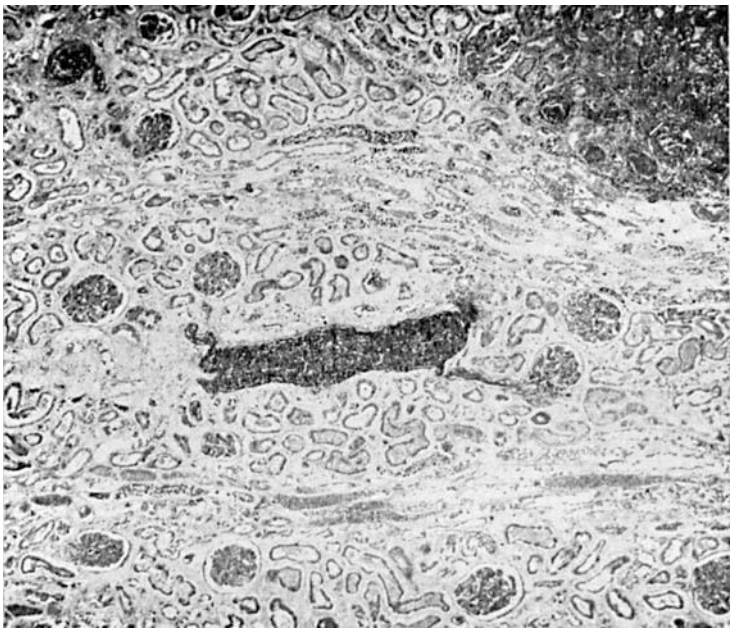

FIG. 6.

Kidney. (Photomicrograph [× 60], Formol-Zenker, Haematoxylin and Eosin.) Distended thrombosed interlobular artery giving off two afferent arterioles which are also thrombosed, in the infarcted cortex.

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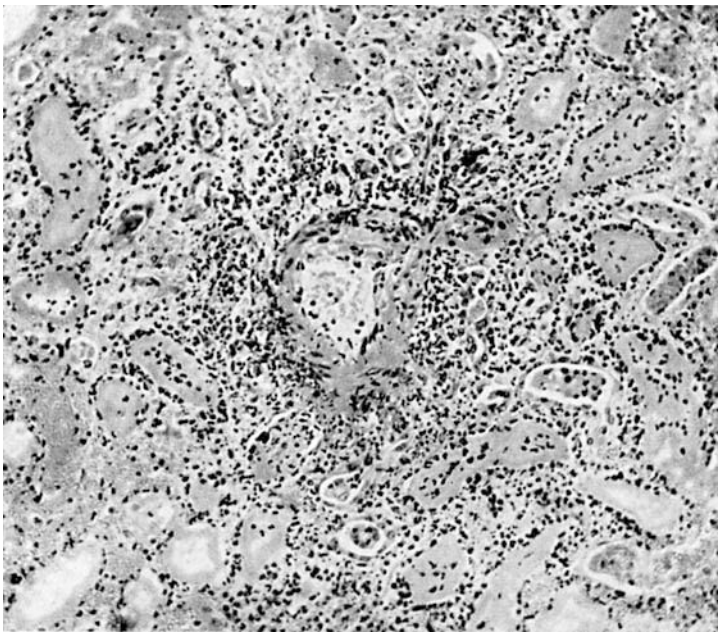

FIG. 7.

Kidney. (Photomicrograph [× 175], Formol-Zenker, Haematoxylin and Eosin.) Acute arteritis of an interlobular artery at the edge of an infarcted area.

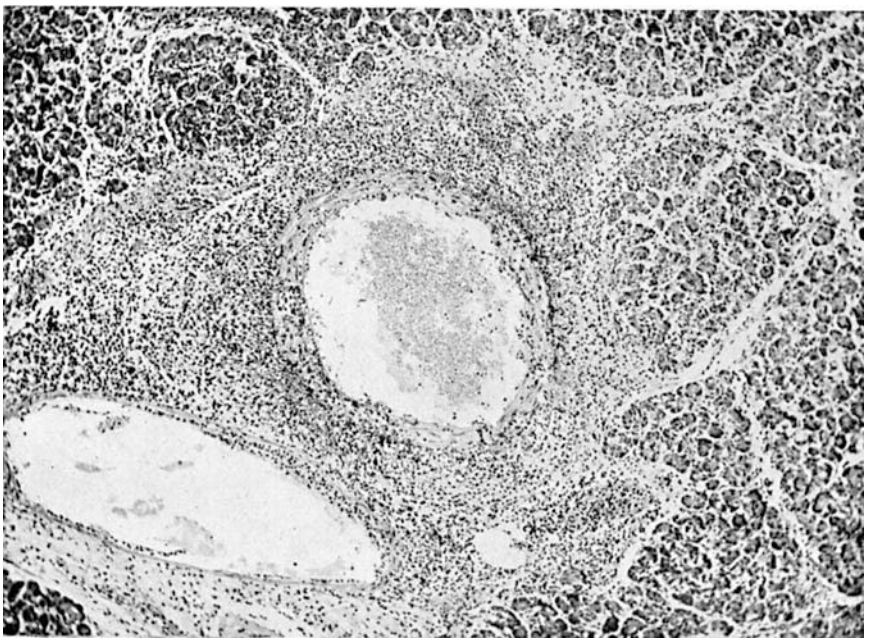

FIG. 8.

Pancreas. (Photomicrograph [× 90], Formol-Zenker, Haematoxylin and Eosin.) Acute necrotizing arteritis with inflammation spreading into the interstitial tissue.

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revealed anterior pituitary necrosis as well. The 1st was a multipara aged 33 who went into labour 7 weeks from term following signs of toxic separation of the placenta. She died 7 days later having passed only 30 c.cm. of urine since delivery. The 2nd was a multipara, aged 40, who went into labour 8 weeks from term following signs of toxic separation of the placenta. She died 11 days later, having passed 53 c.cm. urine since delivery.

Duff and More[4] reviewed the literature up to date on symmetrical cortical renal necrosis. They found a total of 48 authentic cases following pregnancy. Pituitary necrosis was not described in any of these. But, after reading the case histories, one is inclined to believe that in very few, if any, was the pituitary gland examined microscopically. Since 1941, 6 cases of renal necrosis have been described and an associated pituitary necrosis found in 3 of them, as quoted above. It seems reasonable to presume that a careful examination in future cases of renal necrosis will reveal a frequent association with pituitary necrosis, and that our case, and those of Tomlinson, Sheldon and Hertig, are by no means the rarities they at present appear to be.

Each of these 2 conditions has been excellently reviewed[1, 4] already, but various points in our own case are worth further discussion.

Pituitary gland. The haemorrhagic state of the stalk and the presence in it of thrombosed sinusoids were also seen by Sheldon and Hertig. The anatomy of the venous sinusoids of the stalk has been carefully investigated by Wisloki and King.[5] They proved that these are "portal" veins which supply the sinusoids of the pars anterior together with branches of the superior hypophyseal arteries. The sinusoids of the pars anterior drain into the cavernous sinus. Popa and Fielding,[6] who first identified the pituitary "portal" veins, believed, on the contrary, that the direction of flow was towards the hypothalamus. The findings in this case of a necrotic pars anterior and a normal hypothalamus confirm Wislocki's view of the direction of flow, and at the same time imply that the pituitary "portal" veins play a much bigger part than the arteries in the blood supply of the pars anterior, at all events, in late pregnancy.

Accidental hæmorrhage. We could not find a cause for the retroplacental haemorrhage. The histology of the uterus ruled out sepsis. There was not any evidence of eclampsia or essential hypertension or glomerulonephritis in the kidneys. The section of right ovarian vein showed the thrombosis to be of too recent origin to have played any precipitating role.

Renal necrosis. It is possible to suggest a vascular mechanism without resort to toxins. Duff and More[4] concluded in their review that "some unknown factors, given suitable conditions, cause disturbances in the terminal arteries of the renal cortex, the damage done depending on the sensitivity of these vessels to irritation. That in pregnancy these vessels may become hypersensitive. That varying hypersensitivity and intensity of irritation may lead to a series of vascular degenerative changes, including necrosis of the wall and thrombosis. That the same sized arteries of other organs are also hypersensitive; though to a less degree." It seems to us that the unknown factor may be simply the reflex vasoconstriction which follows blood loss and is directed towards accommodating the vessels to the reduced blood volume and maintenance of the mean arterial pressure. The point that there is a definite association of symmetrical renal necrosis with haemorrhage and collapse needs no labouring.

Evidence for a reflex vasoconstriction can be seen that among Duff and More's 48 cases of renal necrosis, in the 21 which followed accidental haemorrhage, the average blood-pressure was 170/109 (the lowest recorded was 118/50).

In their studies on the renal circulation in shock Lauson, Bradley and Cournand[7] found evidence of a considerable degree of renal vasoconstriction in most cases (including the post-haemorrhagic state), and indications that blood is shunted away from the kidneys. (thus confirming the generally held view that the oliguria or anuria of shock results from decreased circulation through the kidneys). We have some clinical evidence in our own case that there was a generalized vasoconstriction following the 26 ounces retroplacental haemorrhage in that the patient was "shocked," pale, anuric and maintained a blood-pressure of 150/80. Granted the hypersensitivity of the terminal renal arteries in pregnancy, renal arteriolar spasm would undoubtedly follow. Whereas relief of the spasm is followed normally by continuation of the circulation at a reasonable renal filtration pressure, in this case there appears to have been a block due to massed red cell thrombus. The possible factors responsible for this might have been intensity of the vasoconstriction, or a paralytic vascular dilatation with stasis following the spasm (Scriver and Oertel[8]) or the increased coagulability of the blood said to occur in the postpartum state. Outside the kidneys, the centrilobular hepatic focal necroses are further evidence of a reduced blood flow as found by Bywaters[9] in his studies of the liver in crushing injuries. It is interesting to note that the degree of anaemia 5 g. per cent haemoglobin, would further aggravate the ischaemic state of the kidneys and other sensitive viscera. In the 9 cases of renal necrosis in the literature in which the haemoglobin level was given, the average figure was 6 g. per cent. This level, after discounting the "physiological" low normal value in late pregnancy and the drop due to haemorrhage, suggests that these patients were anaemic before their catastrophe.

Arteritis. Apart from haemorrhages in the heart, brain and stomach, foci of necrosis round vessels in the pancreas,[4] and in the caecum and adrenals[3] have been described. They have been attributed either to vascular spasm or to the action of some toxic substance. The pancreatic arteritis in our case (as well as the renal) appeared definitely to have commenced in the adventitia. The age of the lesion, judged by the freshness of the polymorphonuclears bordering the necrotic areas, appears on the whole to be definitely less rather than more than 6 days. It is conceivable that it is an ischaemic necrosis resulting from diminished blood flow through the vasa vasorum associated with spasm both of the vasa and the vessel itself. The uraemic state of the patient might account for any "toxic" element in the aetiology of the arteritis. It is relevant to recall that Byrom[10] produced renal cortical necrosis and a necrotizing arteritis of the renal and gastric arteries of rats by repeated subcutaneous injections of vasopressin.

Any factor which causes complete obstruction to the blood flow through the terminal renal arteries will produce a similar ultimate pathological picture of symmetrical renal coagulative necrosis. And since not all cases of such renal necrosis are associated with haemorrhage, or for that matter with pregnancy, there must be more than one mechanism which obstructs the renal circulation. Similarly, arteritis can result from other causes than spasm (for example following sulphonamide hypersensitivity).

But the reflex vasoconstrictive mechanism

described above seems to us to fit in well with the typical findings in cases associated with accidental haemorrhage.

Conclusion.

We suggest that, as in the case of pituitary necrosis, pregnancy renders the patient liable to suffer symmetrical cortical necrosis as a complication of haemorrhage and collapse. Though the latter is a less frequent development than the former, it is not surprising to find the two conditions in common association. The altered circulatory state produces spasm and thrombosis of the renal terminal arterial segments, stasis and thrombosis of the stalk segment of the pituitary "portal" venous system. The resultant anoxia of the tissues supplied by these vessels may be aggravated by the anaemia associated with many of these cases. One may find further evidence of anoxic necrosis in the liver and possibly in the walls of small arteries (in the pancreas and adrenals).

Acknowledgments..

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