BILATERAL CORTICAL NECROSIS OF THE KIDNEYS.*

A Report on Three Cases occurring during Pregnancy.

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Bilateral cortical necrosis is an uncommon but dramatic complication of pregnancy. With its principal clinical feature of extreme anuria and its characteristic gross pathological features it provides a peculiarly precise syndrome.

In 40 of the approximately 50 recorded cases the condition was associated with pregnancy. In the rest the condition was associated with a variety of other diseases. Juhel-Renoy,[1] who was the first to describe the condition, noted it in association with scarlet fever in a girl of 16. Stoeckenius[2] noted it in association with diphtheria; Herzog,[3] with carcinoma of the stomach and peritonitis. Bamforth[4] recorded it in a case of a soldier suffering from dysentery. Fahr[5] also noted it in association with dysentery in two cases.

During the past twenty-seven years 10 cases of acute cortical necrosis have been reported to this Society. Six by Drs Jardine and Kennedy,[6] and four more recently by Drs Davidson and Turner.[7]

We now bring to your notice the records of three more examples of this condition, these presenting some interesting features.

Case I.—Mrs B., aged 26, i-para.—Patient was admitted with a history of not having passed urine for a fortnight. She was five months pregnant. From the second month of her pregnancy she had suffered severely from morning sickness. A fortnight before admission vomiting became much more severe and she retained but little food. From that time till admission she stated that she passed no urine whatsoever. During that time the sickness was still very severe and was accompanied by vague abdominal pain. For the two days prior to admission she had suffered from severe backache, lumbar in situation. The bowels had been constipated, so much so that for four days there had been no motion. On the day of admission she stated that she had been feeling hot and thirsty and had had some

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difficulty in swallowing. She noticed for the first time that her ankles were swollen.

Previous History.—No history of scarlet fever, tonsillitis, or urinary trouble.

Previous Obstetrical History.—First child, aged 5, was full-time and the delivery was spontaneous. No miscarriages.

On Admission.—Patient was a well-nourished, well-developed young woman. Beyond slight pallor of the lips and mucous membranes there was no obvious morbid characteristic. Temp. 97·4°; P.R. 88; Resp. 16. There was slight œdema of both lower extremities, especially marked over the dorsum of the feet. The heart was not enlarged. The sounds were pure. B.P. 110/60. The respiratory system presented no abnormality. Mouth and tongue were dry. Examination of the abdomen showed a uterus of a size consistent with a five-months' pregnancy. There was some vague abdominal tenderness over the uterus. Bimanual examination of the lumbar regions revealed pronounced tenderness over both posterior renal points. The kidneys were not palpable. Vaginal examination: Os one finger; membranes intact.

Nervous System.—No tremor or convulsions. No disturbance of motor or sensory function. Reflexes normal.

Urinary System.—Patient strongly adhered to her story that she had not passed urine for a fortnight and further she had had no desire to do so. Passage of the catheter both before and after admission failed to remove one drop of urine.

History of Further Progress.—On the evening of admission patient received abundant fluid by the mouth and 400 c.c. of glucose saline intravenously. Free action of the skin was promoted by the use of the electric bath. Next morning a further attempt to remove some urine by catheter was made but without success. She felt quite comfortable and there was no material change in her condition. During this day a further intravenous glucose saline was given but still no urine was secreted.

9.8.32.—Professor Johnstone was called in consultation with Dr Matthew and it was decided that immediate termination of the pregnancy offered her the best chances of survival. On the afternoon of this day an abdominal hysterotomy was performed by Professor Johnstone under gas and oxygen anæsthesia. The uterus and the placenta were normal, a special search being made for any signs of retroplacental hæmorrhage. Palpation of the kidneys showed them to be slightly enlarged and tense. Apart from some vomiting patient made an excellent recovery from the immediate effects of the operation.

We do not propose to record her condition from day to day but merely to present a summary. She survived for sixteen days after

operation and during this time a full record of fluid intake, blood pressure, urinary secretion, and many of the biochemical features was made.

Her clinical condition may be summarised as follows:—For the first five days following operation she felt quite comfortable but she was very drowsy and slept a great deal. Indeed, on the 14th she was in frank coma. There was a certain amount of vomiting during this period which diminished in severity. Two days after operation she began to show sporadic twitchings of the face and hands and there was very evident muscular hyper-excitability as evidenced by repeated observations of the supinator reflexes and Chvostek's sign. Œdema also became apparent two days after operation. It was first noticed on the vulva, but within two days it had spread to the face, hands, arms and legs. From the day after operation a small daily quantity of urine was obtained by catheterisation. This never amounted to more than six drachms during this period. The specimens contained a negligible quantity of urea; indeed, the addition of sodium hypobromite to a specimen of the urine obtained on the 10th produced no effervescence at all. Apart from this the urine was crowded with pus cells with a few red blood cells. Bacteriologically there were present *B. coli* and *staphylococci*. No casts were seen.

On the 15th, after being quite unconscious on the previous day, patient was rational and the œdema had subsided to some extent. The twitchings were less evident. However, a new complication was introduced. There began to appear some oozing from the wound. On the 16th there was a moderately severe secondary hæmorrhage, necessitating the operation of secondary suture. No anæsthetic was required and it was remarkable how insensitive the patient was to the introduction of large needles.

For the next four days the picture was one of drowsiness alternating with periods of fretfulness. The œdema was variable. The condition of the wound was now satisfactory. On the 19th patient passed urine herself for the first time during her stay in hospital. This, however, only amounted to some 4 ozs. The evening of this day saw the commencement of the closing phase of the condition. Vomiting became severe and there was continuous retching. She was almost continuously delirious and required sedatives. On the 21st the œdema once more became very pronounced. Twitchings were not now in evidence.

On the 23rd it was evident that broncho-pneumonia was present, and from a condition of continuous uncontrollable delirium patient sank into coma and died on the 25th August, eighteen days after entering hospital. During this period the amount of urine secreted showed an increase and on the day before death an output of 16 ozs. was recorded.

During the whole of this period the skin had been very active, and it was by this route that patient was eliminating the major portion of the large quantities of fluid that were given both orally and rectally. B.P. during this period varied between 140/80 and 110/70. Occasional blood counts showed a progressive secondary anæmia with a moderate leucocytic reaction. No reticulocytosis was present. There was never at any stage any febrile reaction.

Post - mortem Examination — Summary. — Broncho - pneumonia. Peritonitis. Bilateral cortical necrosis of the kidneys.

The body was that of a moderately well-nourished young woman. Post-mortem lividity and rigidity were present. A right paramedial abdominal incision was present and was partly broken down. Between the gaping edges of the wound there was liquefying blood clot. On opening the abdomen a quantity of thick pus was present. This was greatest in amount in the pelvis but was also found around the kidneys and in the subphrenic space.

Stomach and Intestines.—These were healthy apart from a congestion of the overlying peritoneum. There were no intestinal ulcers present. *Liver.*—This was slightly enlarged and pale in colour. It was easily broken up with the fingers. *Spleen.*—This was enlarged but remarkably firm. *Lungs.*—There was some blood-stained fluid in the pleural sacs. On section both lungs presented the signs of a broncho-pneumonia with a good deal of basal congestion. *Heart.*—The pericardial sac contained no excess of fluid. There was slight enlargement of the left ventricle. The heart muscle was pale in colour. *Uterus and Appendages.*—The uterine wound had broken down and there was some degree of infection. The bladder contained a few drops of blood-stained urine. The mucosa was slightly congested, especially in the region of the trigone. The ureters were not thickened. *Kidneys.*—These were slightly larger than normal. The capsule stripped easily. The subjacent surface showed numerous pale yellow areas, some as large as a postage stamp. These areas tended to be recessed. The intervening kidney tissue was slightly congested. On section the cortex showed a number of similar yellow areas, some of which extended down into the pyramids. On section these yellow areas presented a firm surface, there being no tendency to central liquefactive necrosis. The non-necrotic areas varied between a pale cloudy appearance and red congestion. The medulla showed some streaky congestion. The pelves of the kidneys showed a moderate degree of congestion.

Kidney—Microscopic Appearances.—The cortex resolves itself into two well-defined areas. *Area* 1.—In this, the zone of necrosis, the tubular epithelium has undergone complete hyaline necrosis, the epithelial nuclei have ceased to stain, the lumina of the tubules

TABLE.—Data in Case I. (After the 15th vomiting prevented estimation of fluid intake.)

Date.	Blood Urea. Mgrm. per cent.	Blood Creatinine. Mgrm. per cent.	CO_2 Combining Power.	Serum Calcium. Mgrm. per cent.	Plasma Phosphorus. Mgrm. per cent.	Calcium Phosphorus. Ratio.	Plasma Albumen. Mgrm. per cent.	Plasma Globulin. Mgrm. per cent.	A/G Ratio.	Plasma Fibrinogen. Mgrm. per cent.	Blood Cholesterol. Mgrm. per cent.	Blood Pressure. Mm. Hg.	Fluid Intake. Ozs.	Urine Output. Ozs.
7	161	6·5	45	7·4	7·3	1·01	2·31	1·80	1·3/1	·94	120	110/70	...	...
8	...	...	47	...	7·7	...	...	...	...	...	...	120/70	...	...
9	165	6·3	54	...	7·0	...	2·00	1·81	1·1/1	·69	125	110/70	96	...
10	206	6·6	51	6·8	10·5	0·64	1·94	1·63	1.2/1	...	126	110/75	62	0·25
11	235	6·4	46	...	11·7	...	2·19	1·88	1·2/1	·63	133	120/80	86	0·37
12	257	6·7	47	...	10·2	...	2·38	1·94	1·2/1	·63	127	120/80	68	0·5
13	283	7·4	48	...	...	...	...	...	...	...	...	...	72	0·75
14	296	8·0	47	7·4	11·1	0·67	2·63	1·63	...	·38	160	140/80	72	2
15	343	8·8	31	7·3	12·5	0·58	2·43	2·00	1·2/1	·44	167	...	65	3
16	377	9·0	39	7·2	13·3	0·54	1·94	2·43	1/1·3	·44	160	130/80	...	3
17	420	10·0	40	7·2	13·6	0·53	1·16	3·25	1/2·8	·38	130	130/75	...	3
18	439	11·6	32	7·2	14·3	0·50	2·38	1·94	1.2/1	·69	126	...	...	5
19	459	14·0	42	6·9	15·4	0·44	2·63	1·69	1·6/1	·63	145	130/80	...	4
20	...	14·5	41	8·4	15·6	0·54	2·63	1·44	1·8/1	·69	143	125/80	...	9
21	...	...	...	...	...	...	...	...	...	...	...	...	...	12
22	480	13·3	36	9·0	15·6	0·58	3·06	1·44	2·1/1	·75	130	130/80	...	10
23	544	13·3	39	9·3	16·7	0·55	2·56	2·50	1/1	·50	128	...	...	12
24	529	12·0	39	8·2	14·0	0·59	2·38	2·38	1/1	·44	160	130/80	..	16
25	484	11·3	39	7·0	15·2	0·46	2·81	2·31	1·2/1	·69	150	...	...	...

contain granular debris surrounded by annular bands of homogeneous pink material, in which all trace of individual cells has been lost. The glomeruli show some swelling and œdema. There is no evidence of endothelial proliferation of the lining cells of Bowman's capsule. The interstitial tissue is very œdematous and it shows a considerable amount of cellular infiltration, most of these cells being polymorphonuclear leucocytes. The intralobular vessels contain thrombi. Sections stained by the Azan method show a certain amount of fibrin in these thrombi. At the periphery of the necrotic areas tubules and glomeruli show scattered among them irregular aggregations of purple granules. Indeed, some of the glomeruli show up as a homogeneous purple disc. This indicates calcification. To a less extent calcification is to be found in the centres of the necrosed areas. There is no marked congestion of the vessels at the periphery of the necrosed areas.

Area 2.—The surrounding renal tissue presents a confused picture because of the changes due to pyelo-nephritis. The tubular epithelium shows a pronounced cloudy swelling with, in many cases, complete disintegration. The tubules show a pronounced degree of dilatation. The nuclei in most tubules stain well although they are sometimes lying free in the lumen. The glomeruli show some slight congestion, the endothelial nuclei stain well, and Bowman's capsule presents no abnormality. The interstitial tissue is extremely œdematous and in places there are appearances strongly suggestive of fibroblastic proliferation. There is also in some areas an intense round-celled infiltration and here and there frank abscess formation. The vessels do not contain thrombi. There is no evidence of arterio-sclerotic change in the vessel walls. Sections stained by Weigert's method for elastin show no pronounced degree of fragmentation of the internal elastic lamina.

Medulla.—The tubular epithelium shows cloudy swelling. The lumina contain plugs of cellular debris, these being mostly pus cells. The interstitial tissue shows œdema and round-celled infiltration.

Sections stained for fat with sudan III show fat globules in the vessels. The glomeruli stand out prominently in virtue of these globules in the capillaries. There is only very slight fatty degeneration in the renal epithelium.

Liver.—There was present in the hepatic cells an intense cloudy swelling and but little fatty degeneration. These changes are more marked at the periphery of the lobules.

Case II.—Mrs W., aged 30, ii-para. *Admitted.*—29.4.32. *Complaint.*—Bleeding. *Previous Health.*—There is no history obtainable on this point.

Previous Obstetric History.—Has had two children. Last born spontaneously in July 1930.

Bilateral Cortical Necrosis of the Kidneys

History of Present Pregnancy.—L.M.P. September 1931. Up till one day before admission there had been no untoward symptoms. There had been no undue sickness. The bowels had been moving regularly. She had never noticed any swellings of her feet or ankles. There had been no disturbance of vision. On the afternoon before admission she had severe pain in the "small of the back." The pain was continuous and sharp in character. It was totally unlike the pain experienced in the back at the commencement of labour. At about the same time she began to be aware of a headache which rapidly became more severe. It was frontal in its situation. She did not go to bed but rested as much as her household duties would permit. Later in the afternoon, to her surprise, she found that she was bleeding vaginally. The blood loss was fairly copious and in amount was much more than that of an ordinary period. Her doctor was called in and he referred her to the Royal Maternity Hospital, where she arrived at 10.45 P.M. on 29.4.32.

Condition on Admission.—The marked pallor of the face contrasted strongly with the cyanosis of the lips. There was no jaundice. Careful examination failed to elicit the faintest trace of œdema. The heart was not enlarged and the heart sounds were closed. There was some accentuation of the second sound in the aortic area. The blood pressure was 185/135. The pulse was 90. There were no abnormal physical signs in the chest. Examination of the abdomen showed the fundus to be three finger-breadths above the umbilicus. It was hard and tender to the touch.

30.4.32. 1.30 A.M.—As patient was being prepared for a vaginal examination under chloroform, she was seized with a typical eclamptic convulsion. She was anæsthetised with chloroform and a vaginal examination made. The cervix was neither thinned out nor taken up. The os admitted one finger and exploration revealed that the membranes were intact and that no placenta occupied the lower uterine segment. Catheterisation failed to remove any urine from the bladder.

Patient never regained consciousness. During the next seven hours she had over fifteen severe eclamptic convulsions, remaining in deep coma between the fits. The blood pressure gradually fell, being 80/40 some two hours before death. The pulse increased in rate, rising to 180. The temperature fell to 95°. Death occurred at 8.25 A.M. during an eclamptic convulsion. Chloroform had been administered at each fit and three injections of morphine had been given.

Post-mortem Examination—Summary.—Eclampsia gravidarum and early bilateral cortical necrosis of the kidneys. Cerebral hæmorrhage.

The body was that of a well-nourished, normally developed female. Post-mortem rigidity and lividity present: no jaundice. There was

marked œdema of the lower limbs. *Serous Cavities.*—Nothing to note. *Circulatory System.—Heart*—was of average size. There was an average amount of sub-epicardial fat. The chambers were of average size. There was nothing abnormal to note regarding the aortic, pulmonary or tricuspid valves. Blood vessels were healthy. *Respiratory System.*—The mucosa of the larynx and trachea was congested. The pleural surface of both *lungs* was smooth and glistening. All the lobes showed marked congestion. There was no evidence of pneumonic consolidation. *Alimentary System.—Stomach*—of average size. Nothing abnormal to note throughout the alimentary tract. *Liver*—of average size. Extensive subcapsular hæmorrhages were present over the right and left caudate lobes. On section, the liver was of a reddish brown appearance, and what apppeared to be the outlines of the lobules could be seen. These outlines were of a pale, greyish colour. No obvious hæmorrhage was present in the deeper portions of the tissue. *Spleen*—was slightly enlarged. The tissue was moderately firm in consistence and dark red in colour. *Pancreas.*—Nothing abnormal to note. *Suprarenal Glands*—of average size and appearance.

Genito-Urinary System—Kidneys.—Both were rather larger than normal. The capsules stripped, leaving a very red and congested surface. On section, the cortex was broad and well defined from the medulla. The cortex was extremely red, hæmorrhagic, and structureless in appearance. There was a pale, greyish-red, structureless zone immediately at the junction with the medulla. Appearances were typical of bilateral cortical necrosis in its early stages, as the whole of the cortical tissue showed the appearances of early red infarction. The medulla was very congested. There was also congestion of the mucosa of the pelves. In both renal veins blood clot was present. This was not adherent to the wall of the vein, but was firm and somewhat greyish-red in colour, but had the appearance of having been formed some short time before death, as definite post-mortem clot was found in relation to these hard clots.

Microscopic Examination—Liver.—No evidence of actual necrosis of liver cells was present. The portal veins were moderately congested and in the subcapsular region numerous small hæmorrhages were seen. The liver cells in relation to these hæmorrhages showed early degenerative change. In the sections stained for fat there was marked fatty degeneration in the cells of the peripheral zones of the lobules. Although this was well defined the globules were small and appearances were indicative of early fatty change.

Kidney.—There were marked degenerative changes in the subcapsular region. The lining cells of the secreting tubules showed advanced cloudy swelling. The glomeruli were very hæmorrhagic and

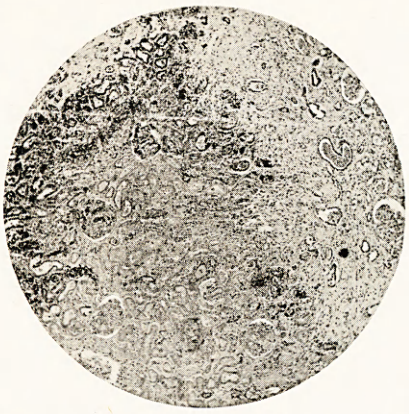

FIG. 1.—Case I. Showing wedge-shaped area of infarction with peripheral calcification. (Low power.)

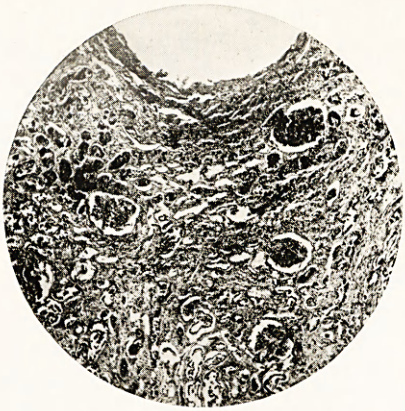

FIG. 2.—Case I. Showing shrinkage of infarcted area with advanced calcification. (Low power.)

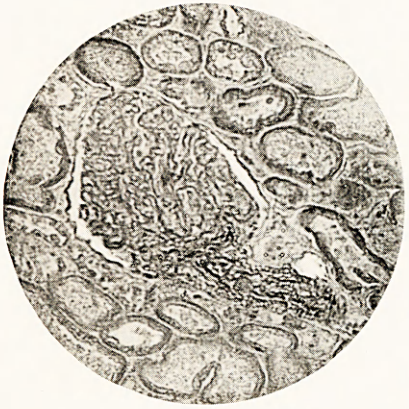

FIG. 3.—Case II. Thrombosis in afferent glomerular vessel. (High power.)

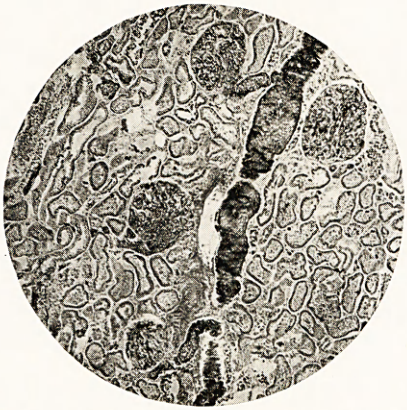

FIG. 4.—Case II. Section stained for fat. Showing intravascular fat globules. (Low power.)

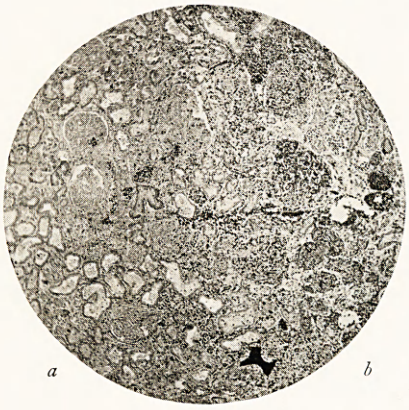

FIG. 5.—Infarcted area (*a*) surrounded by congested zone (*b*). (Case II. Low power.)

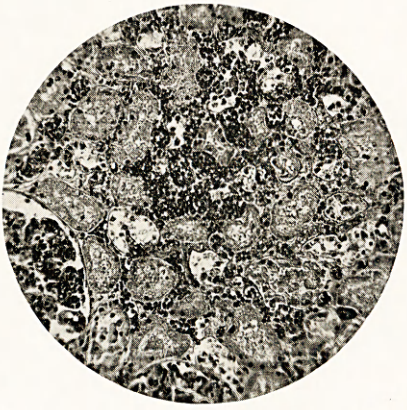

FIG. 6.—Case III. Shows the intense hyperæmia of an early infarct. (Low power.)

congested and there were large areas of hæmorrhage. This congestion and hæmorrhage was well marked throughout the whole of the cortex and probably more towards the periphery. Here and there were small areas where there had been a disappearance of units and replacement by œdematous fibrous tissue. In the other areas, towards the medulla, the lining cells of the secreting tubules showed evidence of complete necrosis. The cytoplasm was swollen and disintegrated and there was a lack of nuclei. What remained of the tubules were filled with coagulated fluid. The glomeruli showed marked congestion and hæmorrhage and there was no abnormal thickening of the capsule. A large number of blood vessels showed fibrous tissue thickening of the intima. Sections stained for fat showed a very profound fatty degeneration occurring in the glomeruli. There was some slight fatty change in the secreting and distal convoluted tubules, but this was not well marked.

Spleen.—Markedly congested and hæmorrhagic. In the Malpighian bodies there were masses of hyaline eosinophile tissue, which had the appearance of hyaline degeneration.

Case III.—Mrs C., aged 29, ii-para. *Admitted.*—26.5.32. *Complaint.*—Swelling of ankles and headaches.

Previous Health.—This had been very good. Has had no serious illnesses. No history of repeated sore throats or of swelling of face at any time.

Previous Obstetric History.—September 1926; full-time child; spontaneous delivery; alive and well. April 1930; full-time; spontaneous delivery.

History of Present Pregnancy.—L.M.P. 18.12.31. Expected date of delivery 25.9.32.

For the first four months of her pregnancy patient felt in good health. She had some slight morning sickness on rising, but never after meals. About four weeks before admission patient noticed that her ankles were becoming swollen, and a few days later she found that the backs of her hands and also her face were becoming puffy. On the day of admission she had found on awakening that she was unable to see clearly and also that there was a great increase in the swelling of her face and ankles. She had a severe pain in the "pit of the stomach." Later in the day she was troubled by an intense headache in the frontal region. Although she did not actually volunteer the information, on being questioned she stated that she had noticed that for the previous fortnight she had not been passing as much water as usual.

Condition on Admission.—(From antenatal clinic where she had reported.) Patient was obviously ill. The face was swollen and of a

marked pallor. The ankles and the lower legs were markedly œdematous. So also were the hands and arms. The mouth was dry and the tongue furred. The breath was fœtid. The bowels had not moved for a day or two. Examination of the abdomen showed a swelling rising up to a point just below the umbilicus. This corresponded roughly to a pregnant uterus at the fifth month of gestation. The uterus was not tender. The fœtal heart was not heard.

The heart was not found to be enlarged but on auscultation there was found to be an accentuation of the second sound in the aortic area. The blood pressure on admission was 158/100. Pulse 76. Patient complained of a slight cough, but there were no physical signs in the lungs. Respirations 20. There is no record of any retinoscopy. No muscular twitchings were present. In the antenatal department patient had been unable to pass any urine, but three ounces were obtained by the catheter. On examination this was found to be loaded with albumin and boiled solid.

Patient was placed at rest in bed and encouraged to drink large quantities of glucose and orange juice. Late on the night of admission she complained bitterly of intense headache, and aspirin and phenacetin were given to help this.

27.5.32.—At about 5 A.M. patient complained of intense abdominal pain of a continuous nature. This pain was situated over the uterus and was quite different to the epigastric pain which had previously troubled her. About one hour after the onset of this pain the membranes ruptured. She was examined vaginally and the os found to be one finger dilated. The presentation was cephalic. She received morphia gr. $\frac{1}{4}$ one hour after the onset of this pain. A catheter was passed during the morning and only one drachm of urine was removed. This boiled solid. Colonic lavage was performed and continued till the result was clear. The pain continued to be severe, and on examination later in the day showed that the fundus of the uterus had risen above the umbilicus and that the uterus was tense and firm and very tender. Concealed accidental hæmorrhage was suspected.

It was decided to carry out an abdominal hysterotomy. At 4.30 this operation was performed by Dr Douglas Miller under stovaine as a spinal anæsthetic. On opening the abdomen the bluish mottling of the uterus denoted that there was some hæmorrhage. The muscle was incised and a five months' fœtus together with a placenta and a large amount of black blood clot was removed. The typical ploughing up of uterine muscle was present. During the operation the blood pressure had dropped to 70/50 and this necessitated the use of ephedrine. From this time the blood pressure never rose again above 120 systolic.

Five hours after the operation a transfusion of one pint of blood was carried out. At this point the patient's condition was as follows, pulse 120, respirations 32, B.P. 110/70.

28.5.32.—Patient's condition was not good. The pulse was very rapid and its rate was 132. The temperature was over 100°. The skin was excreting moderately well. She was vomiting occasionally but drinking plenty. The catheter obtained one drachm of urine. B.P. 118/70.

29.5.32.—Condition the same. About twelve drachms of urine obtained by catheter. Solid with albumin. B.P. 118/75.

30.5.32.—Since admission the exhibition of thyreoid had been carried out. It was decided to try the effect of pilocarpine and accordingly this was given as the nitrate gr. $\frac{1}{12}$. The skin had been acting, but not very well. With the application of the shock cage and the administration of pilocarpine the skin was stimulated to secrete more. No urine was obtainable by the bladder, however. B.P. 120/80. Condition moderate. There were no muscular twitchings and the patient could co-operate in treatment, etc.

31.5.32.—Similar condition. B.P. 120/80. No urine obtained by catheter. Previously the bowels had only been moved by enemata, but on this day there was incontinence with frequent small motions. Patient drinking plenty.

1.6.32.—A secondary suture was required in the wound and this was performed under a local anæsthetic. 500 c.c. of glucose saline given intravenously. One and a half drachms of urine obtained.

2.6.32.—Transferred to Deaconess Hospital under the care of Mr Duncan Morison. The total amount of urine passed during her stay in hospital was therefore 4 oz. 5 drs. during a period of seven days. There is no exact record of the fluid intake during this time but patient drank freely nearly all the time she was in hospital.

2.6.32—(4.30).—A cystoscopic examination was carried out. A few drops of muco-purulent material were present in the bladder. No urine was obtained by the ureteral catheters.

Under gas and oxygen anæsthesia the left kidney was exposed by an incision through the loin. The following interesting observations were made: "The renal capsule appeared pale and semi-translucent, and through it one could see that the kidney substance was of a pale greyish-yellow colour with hæmorrhagic stippling here and there. The contour of the surface did not suggest any unusual elevations other than that suggested by the normal unevenness due to lobulation. The capsule was incised over the convex outer surface of the kidney in its longitudinal axis and was stripped back more easily than normal, all round, down to the hilum. During this process it was observed that the renal capsule was exerting no pressure on the contained kidney

substance and there was no increase in size of the kidney tissue as by engorgement following the stripping of its capsule." Patient was treated by shock cage and magnesium sulphate enemata in order to promote excretion. She died, however, some ten hours after operation.

Post-mortem Report.—Mrs C., aged 27, 4.6.32. Complete cortical necrosis of kidneys. Cloudy swelling of liver and myocardium. Hypostatic congestion and œdema of lungs. The body was that of a well-developed, well-nourished adult female. The superficial tissues were the seat of generalised œdema. Two recently-made surgical incisions were present, one in the middle line below the umbilicus and one in the left lumbar region.

Serous Sacs.—Both pleural sacs, the pericardial sac, and the peritoneal cavity contained considerable quantities of pale yellow serous fluid.

Genito-Urinary System.—The kidneys were of normal shape, but abnormally soft and somewhat increased in size. It was found on section that the entire cortex of each organ had undergone complete necrosis. The cortex was decreased in depth and bright yellow in colour. It was completely structureless. The medulla was deep reddish-brown in colour and at the margin of the boundary zone just subjacent to the cortex the tissue was very congested and hæmorrhagic. The capsule stripped from the non-decapsulated kidney with ease and exposed a smooth yellow surface. The capsule had already been stripped from the other (left) kidney. *Pelves*, *ureters* and *bladder* were healthy.

Uterus was about the size of a cocoanut. A median incision was present in its anterior wall. The uterus was not opened. Its appendages were healthy.

Alimentary System.—*Œsophagus*, *stomach* and *intestines* were healthy. *Liver* was slightly increased in size and abnormally soft. On section it presented a very pale surface. The liver was clearly the seat of advanced fatty change. *Gall bladder* was healthy. *Spleen* was of normal size, shape, and consistence. On section it presented a surface which was only slightly congested. *Pancreas* was abnormally firm and œdematous, but otherwise healthy.

Respiratory System.—*Larynx* and *trachea* were healthy. The *bronchi* and their branches were moderately congested.

Lungs.—Pleural surfaces were smooth, glistening, and transparent. Lungs were of normal size, shape, and consistence. On section they presented moderate degrees of hypostatic congestion. Their tissue was the seat of fairly marked œdema. There was no broncho-pneumonia.

Cardio-Vascular System—Heart.—Pericardial surface was smooth, glistening, and transparent. Subepicardial fat normal in amount and coronary vessels healthy. Heart was of average size, but was tending

to be globular in shape. All its chambers were dilated but the valves were of normal dimensions. The myocardium was pale and soft; it was clearly the seat of advanced cloudy swelling. *Aorta* was healthy.

Microscopical Examination.—On examining a typical N.E. area of necrosis the following changes were observed: *Kidneys.*—Subjacent to the capsule there was a narrow area of intense congestion. Beneath this the epithelium of the convoluted tubules was observed to be swollen, with hazy outlines, the cytoplasm granular, and in most cases the nuclei were quite unstained. In some tubules the epithelium was completely disintegrated and was represented by a mass of granular detritus surrounded by the basement membrane. The *glomeruli* stained poorly and in most instances were swollen. There was no proliferation of the epithelial cells of Bowman's membrane. *Interstitial tissue* was œdematous and there was a moderate amount of round-celled infiltration, these being mostly lymphocytes. There were occasional small hæmorrhages to be observed. Some tubules showed a finely granular lilac colour indicative of calcification. In the centre of the necrotic area the tubular epithelium was almost completely necrosed, it being impossible to distinguish either cells or nuclei. The œdema of the interstitial tissue was very pronounced, widely separating the adjacent tubules. The glomeruli were very congested and in most cases the glomerular tuft completely obliterated the capsular space. Again failure of nuclear staining indicated cellular death. The intralobular vessels had œdematous walls, there being no indication of any cellular proliferation. In each case a thrombus was present. In some instances, in which the afferent glomeruli vessels could be seen taking origin from the intralobular vessels, a continuous thrombus extended into the glomerulus.

At the edge of the necrotic area there was present an intense congestion, the vessels containing thrombi. There was gross hæmorrhage into the tissues. In the non-necrotic areas of the cortex there was advanced cloudy swelling of the tubular epithelium, the nuclei being well-stained and in some cases pyknotic. Again the interstitial tissue was œdematous, round-celled infiltration being prominent especially surrounding the glomeruli. The glomeruli showed but little change. The vessels were slightly congested but there was no thrombosis. In the medulla the tubules again showed cloudy swelling, in some instances proceeding to necrosis. The lumina of the tubules were packed with granular debris. In sections stained for fat the glomeruli were prominent because of the intracapillary fat globules. This could be traced through the afferent vessel to the thrombosed intralobular vessels. Tubular epithelium in all areas showed very little, if any, fatty degeneration.

From a review of the literature and from a consideration of these three cases it is evident that the condition presents a fairly uniform picture. It may be briefly summarised as follows:—

In the majority of cases the disease is associated with pregnancy. It shows no tendency to select the primipara, and most cases are therefore to be found in the 25-35 age-period. It usually supervenes during the fifth, sixth, or seventh months of pregnancy. Previous pregnancies are usually normal. The course of the pregnancy up to the onset of the condition may be quite uneventful but more usually there are disturbances indicative of a degree of toxæmia. These may be hyperemesis, as in the first case, headaches, œdema, dimness of vision, etc. Unfortunately comparatively few of the cases have had any antenatal supervision.

Some of the cases have been associated with eclampsia or some other toxic manifestation, such as concealed accidental hæmorrhage, in which case the onset has been sudden, but in the majority the onset of symptoms is insidious and the patient is more likely to come under notice because of vaginal bleeding or some sign of impending delivery. Constitutional disturbances take the form of headache, backache, anorexia and sometimes vomiting.

The one invariable clinical feature is anuria. This may be absolute or may be an extreme oliguria. It may be of short duration or it may endure for the astounding period of twenty to twenty-five days, as in the first case.

The closing stages are marked clinically by progressive exhaustion and it may be some terminal infection. The classical symptoms of uræmia such as amaurosis, periods of unconsciousness, severe convulsions, etc., are usually absent. The blood pressure is usually normal. Œdema is frequently present although it does not constitute a prominent feature.

Biochemically there is a progressive increase in urea, non-protein-nitrogen and creatinine in the blood. Hyperlipæmia has been recorded. Serum calcium shows a tendency to diminish, inorganic phosphorus increases and the calcium phosphorus ratio approaches unity and may even be inverted. There is a pronounced diminution in the alkali reserve expressed in terms of CO_2 combining power.

Pathological Features. — The kidneys as seen at post-mortem are very little, if at all, enlarged. Microscopically these necrotic areas present a picture of hyaline necrosis similar

to, if not identical with, the appearances found in bland infarction. A fairly constant feature is the presence of thrombosis in the intralobular vessels and in the afferent glomerular vessels. The presence of fat globules in the vessels is an expression of the hyperlipæmia. In a fair proportion of cases arteriosclerotic changes are present.

The liver, unless the condition be present along with eclampsia, merely shows severe cloudy swelling. In some cases focal hepatic necrosis has been described.

In the first case there was no clinical or pathological evidence of preceding renal involvement. The hyperemesis, however, was a probable indication of the presence of a toxæmic element. The onset was characteristically insidious, as it appears that the patient was actually carrying out her household duties while in a state, if not of absolute anuria, at least of extreme oliguria. She was an intelligent woman and was in full possession of her faculties and repeated inquiry elicited the same statement that she had not passed urine for a fortnight. If this statement be correct then in point of duration of anuria this case completely eclipses all others recorded. She passed only a total of 41 ozs. during the seventeen days in hospital. It is exceedingly interesting to note that in one of Clifford White's [8] cases that recovered after decapsulation there were seventeen days of extreme oliguria. One of the cases that Rolleston [9] recorded in 1913 had absolute anuria for eight days. While in hospital the first case had absolute anuria lasting for three days and then during the ensuing four days only 2 ozs. were passed. The first specimen, consisting of only 2 drachms, was remarkable in that it contained practically no urea. Microscopically there were present pus cells, staphylococci and *B. coli*, these latter being probably the result of the catheterisations carried out both before admission and frequently while in hospital. During the last ten days patient passed an increasing amount of urine until on the day before death 16 ozs. were passed and the urea content had risen to over 1 per cent. The only possible explanation of these phenomena is that recovery was occurring to some extent in the kidneys, and in both the biochemical and pathological data there is further evidence of this. The blood urea which on the 23rd reached the very high figure of 544 mgrms. per cent. diminished during the last two days. The blood creatinine which five days before death stood at the extraordinarily high figure of 14·5 mgrms. per cent. thereafter steadily

diminished. The serum calcium was diminished throughout, and the inorganic phosphorus rose steadily to five or six times its normal level. Blood cholesterol was normal and varied within narrow limits. Plasma albumin, globulin, and fibrinogen were observed repeatedly and they underwent certain variations, the significance of which is quite obscure.

Pathologically the extent of the necrosis is not nearly so great as some observers have recorded. It is essentially patchy in distribution, whereas Rolleston[9] has described a case in which almost the whole of the cortex was necrotic, and in Case III. the process has been much more extensive. Microscopically the comparatively small amount of infarcted tissue relative to the rest of the cortex is again noted, and it is upon this that the patient's chances of survival depend. The surviving renal tissue, although it shows a very pronounced degree of degeneration, is probably in no worse a state than the cortex of a kidney recovering from a severe attack of eclampsia. It is a well-established fact that perfect functional recovery from this latter condition may occur.

The necrotic areas show extreme degeneration and in many parts well-established calcification. As far as we know, this latter change has been but rarely described, and although experimentally calcification has been known to occur in the necrotic renal tubules four days after the ingestion of corrosive sublimate,[11] and Kaufmann[12] states that it can occur in three days, the process probably takes considerably longer to supervene in naturally occurring disease. This then affords further evidence of the comparatively long duration of the condition present in this case. The picture, however, is complicated by the presence of the ascending pyelonephritis which has undoubtedly been a late event. The whole case viewed from the clinical, biochemical, and pathological aspects suggests an intense toxæmia of comparatively short duration exercising a selective action on the cortex of the kidneys. During the acute phase of the condition the surrounding cortical areas are so disturbed by the process that they are unable to function. After the toxæmia has ceased—probably after delivery—there is initiated a process of slow recovery in the non-necrotic zones. In the necrotic areas necrosis becomes complete, calcification occurs, and, if the patient survives, fibrosis would follow and the final picture would be a much-scarred kidney, probably, however, in view of its immense reserve, quite capable of performing its

normal excretory functions. Indeed, in Case I. contraction of the necrotic areas has already begun. It may be that if this case had not developed an ascending pyelonephritis recovery might have occurred.

Case III. exemplifies the co-existence of concealed accidental hæmorrhage with cortical necrosis. The total amount of urine

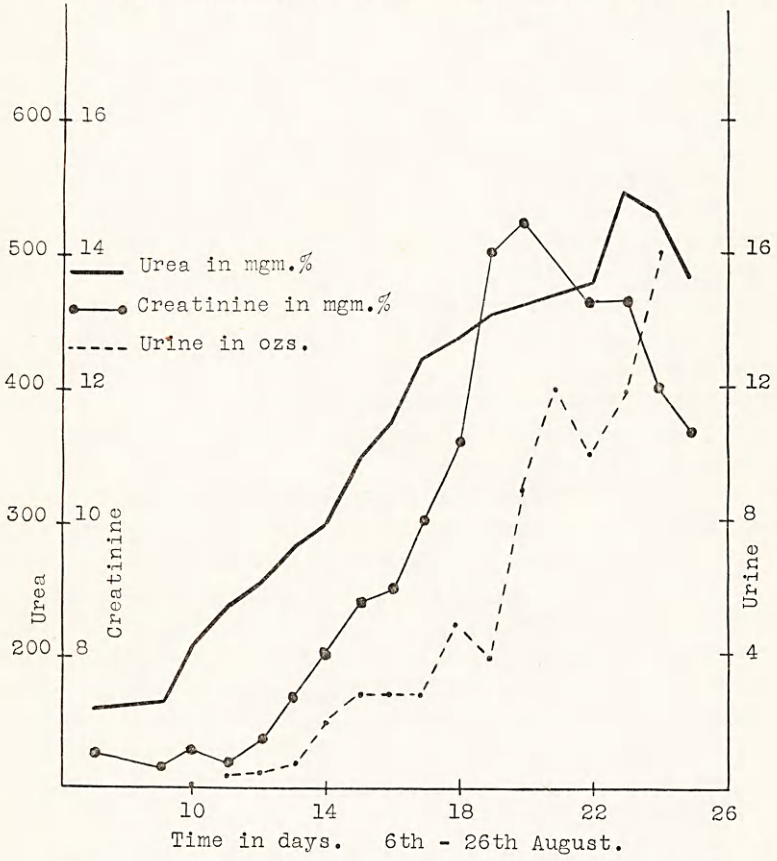

CHART.—Graph of blood urea and creatinine and urinary output in Case I.

passed during her week's stay in hospital was 4 ozs. 5 drachms. The pathological changes are essentially similar to those in Case I. but at an earlier stage. The period of acute toxic destruction has very recently ceased and congestion is still present to a considerable extent. Calcification is just commencing. As already noted, the necrosis is much more extensive than in Case I.

At the operation of decapsulation there was made the most interesting observation that the renal parenchyma showed no tendency to bulge when the capsule was incised. This affords evidence that the stage of congestion was almost over. It is clear that it was too late for this operation to perform any useful function as there was no tension to relieve.

Case II. presents several interesting features. Its claim to be placed in the same category as the others rests entirely on the pathological changes in the kidney as she did not live long enough to display the feature of anuria. The co-existence of renal necrosis with eclampsia is not uncommon and has been noted by Klotz,[14] Herzog,[3] Geipel,[13] Jardine and Kennedy,[6] and others. This indicates fairly conclusively that cortical necrosis has the closest association with the toxæmias of pregnancy. Pathologically the renal congestion is very prominent and the condition may be regarded as characteristic of the red congested stage of an extensive cortical infarction. Another interesting feature of this case is the presence in the ovarian veins of ante-mortem thrombi. This phenomena was noted by Davidson and Turner[7] in a case reported three years ago.

Various hypotheses have been advanced to account for the occurrence of the necrosis in the kidney cortex. In view of the rarity of the condition it must be caused by the operation of some rare mechanism or the chance association of two or more destructive factors.

One of the earliest explanations offered was that of Parkes Weber,[15] who, in 1909, stated it as his opinion that the process was essentially a primary destruction of the renal epithelium and that any thrombosis occurring was secondary. However, after this date it appears to have been the general consensus of opinion that there was a predominant vascular element in the causation and that the areas of necrosis were very similar to, if not identical with, bland infarcts. The three cases just recorded afford ample evidence of the identity with infarction. Case II. shows the early stage of congestion, for even a bland infarct passes through a stage of congestion because of the collateral blood supply, as is shown by the subcapsular congestion of Cases II. and III.

Case III. shows well-established areas of hyaline necrosis at the edges of which calcification is just commencing. Surrounding this infarcted area there is a characteristic congested area.

Case I. shows a still more advanced stage in which the congestion of the boundary zone is almost over, the necrosed area is beginning to shrink, and calcification is well established. If then the condition be in the nature of an infarction it must be due to an interference with the blood supply. What theoretically are the possible causes of such an interference? Embolism is not a likely possibility, in so far as organised emboli are concerned, as post-mortem evidence of a source of such emboli is lacking. An hypothesis, first enunciated by Schüppel,[16] that the condition was due to fat embolism has gained considerable credence. This was based on the presence of numerous fat droplets in the renal arteries and capillaries. However, if such were the case then the occurrence of numerous infarcts in organs other than the kidneys would be a frequent occurrence. Such is not the case. Such observations as have been made on the blood fats indicate a hyperlipæmia and in this fact lies the probable explanation of the presence of these fat globules. Hyperlipæmia has been found to be a constant accompaniment of the renal degeneration occurring in corrosive sublimate poisoning and is probably also a feature of other toxæmias.

The possibility of the obstructive factor being a vaso-spasm has been considered by Professor Jardine in a paper published in 1911,[17] when he recorded a case of cortical necrosis in a woman showing signs suggestive of Raynaud's disease. From his later writings it appears that he abandoned this view. However, there is this to be said for it that vaso-spasm undoubtedly plays a part in eclampsia and in acute nephritis, although it is difficult to conceive spasm being the sole cause of an ischæmia of such duration as to cause an infarction.

Finally, therefore, there remains thrombosis as a possible cause of the infarction. This hypothesis has received much support, notably from Jardine and Kennedy,[6] Rolleston[9] and Torrens.[18] Time does not permit of a discussion of the relative differences between arterial and venous occlusion; suffice it to say that modern pathologists have emphasised the close relationship between those two types of infarction. Two of the three cases recorded show clearly the presence of arterial thrombi.

The actual mechanism of the thrombosis is virtually unknown. It is necessary to fall back on hypothetical toxins manufactured either in the liver or the placenta such as the endotheliolytic component of the eclamptic toxin postulated by Leith Murray.

It seems reasonable to assume that the condition is one of multiple infarctions of varying size occurring in both kidneys due to arterial thrombosis of unknown origin. At the outset both kidneys are enlarged containing numerous intensely congested early infarcts. The intervening renal tissue is compressed by these areas and in addition it must be the site of toxic damage. At this stage there is anuria. Within a few days, if the patient survives, the congestion subsides, pressure is relieved, and the secretion of urine again becomes a possibility. Lastly there remains numerous calcifying areas of necrotic tissue surrounded by cortex making a more or less complete recovery.

Treatment to be rational must obviously follow the pathological picture assumed to be present at any particular period during the illness. Thus, in the early stage, the indication would seem to be to relieve the congestion in the kidney substance and thus to allow the non-necrotic areas the best chance of survival. Possibly the only method of doing this rapidly is bilateral decapsulation of the kidneys. To do any good this operation must be done early in the course of the disease. Although Clifford White[8] and Crook have reported cases proved by biopsy to be genuine cases of cortical necrosis in which a favourable result followed decapsulation late in the disease, it is possible that these cases would have recovered without operation. Mr Morrison found in the case on which he operated that there was no compression on the renal substance several days after the condition was established, and White in the two cases referred to also stated that there was little pressure.

It is a point of nice judgment whether in an early case decapsulation should be attempted. Would it not be better to tide the patient over the first few days of her illness by other means, such as the introduction of large quantities of glucose saline and stimulating the skin by hot air baths, thus endeavouring to stave off the certain uræmia?

As soon as the reappearance of urinary secretion indicates the return of renal function the time has arrived to stimulate the kidney with diuretics. Kellog[19] found that 25 per cent. glucose was an effective diuretic in a case of anuria complicating pregnancy.

Prognosis of this condition must be very gloomy. The first step is the prompt removal of the source of the thrombosing toxin by the termination of the pregnancy. Prognosis will be

also greatly influenced by the actual amount of the kidney destroyed and lastly by the presence or absence of secondary infection.

We are greatly indebted to Dr Edwin Matthew and Professor Johnstone for permission to record Case I. and to Dr Douglas Miller for Cases II. and III. For permission to use the post-mortem material we have to thank Dr James Davidson and Dr Ogilvie. Lastly, we have to thank Dr C. P. Stewart for the biochemical estimations.

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Discussion.

Professor Johnstone said the biochemical observations on the first case were probably unique in their fullness. He related two cases, one of which certainly was symmetrical cortical necrosis, the other probably so. The doubtful case was a remarkable one. The patient, a middle-aged multipara, had been delivered in the Royal Maternity Hospital ten weeks previously after a normal pregnancy. The labour was normal and the puerperium was normal and she returned home at the usual time. Subsequently, her health was perfectly satisfactory until,

about ten days before her admission to hospital, she began to suffer from some vaginal bleeding. For this she was ultimately sent into his Ward at the Royal Infirmary, where on examination she was found to have a small ovarian cyst about the size of an orange, and a somewhat subinvoluted uterus. She was kept under observation for two or three days and her general condition seemed to be quite satisfactory until one morning it was reported that she had passed no urine for twenty-four hours. Catheterisation was ordered, but no urine was found in the bladder. Mr Wade was asked to see the patient in consultation, and he examined her cystoscopically and passed ureteral catheters up to both kidneys, demonstrating that the patient had two kidneys and that there was no calculus in either pelvis. X-ray photographs were negative. The patient, in the meantime, remained entirely free from any symptoms. Before a decision was arrived at in regard to possible decapsulation, it was decided to try a method of treatment which was successful in causing a long and profound diuresis in experimental animals—namely, the intravenous injection of a large quantity of an isotonic solution of sodium sulphate. Two litres of such a solution were rapidly run into the patient's veins with the dramatic result that in the following twenty-four hours—after some five days complete anuria—the patient secreted 270 ounces of urine. In the succeeding days large quantities were secreted, but the quantity gradually dropped and at the end of a week was approximately normal. The condition of the blood chemistry also returned to normal and the patient became and now remains apparently perfectly well. The diagnosis must remain uncertain and even if it was assumed that cortical necrosis was present it is difficult to understand how or why the condition should have arisen as and when it did.

The second case was that of a multipara, aged 42, who was admitted to the Royal Maternity Hospital ten days ago. She was eight months pregnant with her eighth child and her previous history had been one of exceptionally good health. There had been no pathological symptoms during this last pregnancy except a little frequency of micturition during the last few days; no symptoms suggestive of toxæmia. On the 27th of February in the early morning she was seized with cramp-like pains in the abdomen and shortly afterwards there was some loss of blood from the vagina. She was admitted to the Maternity Hospital at 7.45 A.M. in a state of profound shock, dead-white in colour. The abdomen was tender, especially in the region of the left cornu of the pregnant uterus. Placenta prævia was excluded by vaginal examination and the diagnosis of accidental hæmorrhage (mainly "concealed") was made. The blood pressure was 140/120. Only $1\frac{1}{2}$ ounces of urine were obtained by catheterisation and this contained a small quantity of albumin. As soon as possible the

patient received 20 ounces of blood by transfusion and, subsequently, as the uterus was beginning to contract, the membranes ruptured. The patient's pulse improved and she seemed more comfortable. During the afternoon her condition became rather worse, the pulse slowly increasing in rate and the uterus enlarging somewhat in volume. Professor Johnstone decided to perform Cæsarean section and this was done under local infiltration anæsthesia. The uterus presented the typical appearances of concealed accidental hæmorrhage, there being large areas of subperitoneal hæmorrhage, most marked in both cornua posteriorly. The uterus was opened and a macerated fœtus, much dark-black blood clot and an almost completely separated placenta removed. The uterus was then stitched up and the abdomen closed. On the following day the patient's condition was very satisfactory. She expressed herself as being quite comfortable, the pulse and temperature were normal and the fact that she had no desire to pass water called for no special attention. On the second day there was still no passage of urine and forty-eight hours after the operation catheterisation was ordered. Nothing was removed by the catheter except half an ounce of thin pus.

Having in mind the dramatic recovery in the case previously recorded following the injection of an isotonic salt solution, Professor Johnstone consulted Mr Wade and it was decided to transfer the patient to the latter's Ward in the Royal Infirmary. This was done and after X-ray examination, cystoscopy, etc., had excluded calculus anuria, ureteral catheters were left *in situ*. Two litres of sodium sulphate solution were then injected intravenously. During the next forty-eight hours 1½ c.c. of fluid were gathered by the ureteral catheters. These were then withdrawn and on the following day, Sunday, 6th March, there was total anuria. The patient developed marked muscular twitching and sighing respiration and was almost unconscious. On the following day she died and post-mortem examination demonstrated very extensive cortical necrosis in both kidneys. Full report of the post-mortem examination had not been submitted.

Apart from recording these two cases, Professor Johnstone wished only to refer briefly to the subject of the pathology which Dr Kellar had lucidly referred to. It seemed clear from a study of the cases recorded that the condition was due to multiple thrombosis in the interlobular arteries, and inasmuch as one of the few things which they knew about the toxin in eclamptic and pre-eclamptic toxæmia was that it was an endothelial poison, it was tempting to assume that the thrombosis was secondary to damage to the arterial lining. But if so, why was the condition restricted to the kidneys? In quite a considerable number of the recorded cases the condition had been

associated with accidental hæmorrhage, usually concealed, and it was worth consideration whether the loss of blood in these cases might be an additional factor in producing thrombosis by the reduction in the rate of the circulation. It would be interesting to work out the actual proportion of cases in which there was evidence of the two possible causes—toxæmia and slowing of the circulation—at work in combination, as such an observation might throw some light on the etiology. Otherwise they seemed to be thrown back upon a selective action of the toxin which it was difficult to understand. There was, of course, one other possibility, namely, that there was an element of spasm in the arterioles, which favoured thrombosis.

Dr Melville Arnott (in reply) said that with regard to the question of recovery, Clifford White recorded two cases which recovered after decapsulation, and at each operation a small piece of renal tissue had been removed, these showing the typical small areas of infarction. In the cases that recover the total bulk of the infarcted tissue must be small relative to the rest of the cortex. However, clinically, it was quite impossible to estimate the extent of the infarction. It would be interesting to have the opportunity of studying the kidneys of a case which had recovered from bilateral cortical necrosis. If one's conception of the pathological process was correct, then one would expect to find the scars of numerous small bland infarcts. With regard to the possibility of fat embolism one was forced to admit that the explanation of the intravascular fat globules on the basis of a lipæmia rested on only two series of observations. Unfortunately in Case I. of this series the blood fats were not included in the numerous biochemical observations.

There were certain very peculiar variations in the proportions of the plasma proteins, especially the fibrinogen. An unsuccessful attempt was made to correlate these variations with almost every other clinical and biochemical variant in the case. Doubtless, however, somebody before long would be able to indicate their significance.

The President thanked Drs Kellar and Arnott and congratulated them on the way they had investigated the cases and the manner in which they had presented them. It was a model of how a paper of the kind should be handled.