An Experimental Investigation

INTO THE

ETIOLOGY OF ACCIDENTAL HAEMORRHAGE AND PLACENTAL INFARCTION.*

(Preliminary Communication.)

BY

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(With Special Plate.)

IN spite of much research work within recent years comparatively little has been discovered concerning the causation of accidental haemorrhage. Most writers, including Gordon Ley¹ and Whitridge Williams,² have agreed in ascribing it to toxæmia of pregnancy, while others, led by James Young of Edinburgh, have looked upon the toxæmia as secondary to and consequent upon the haemorrhage. According to Young³ the placenta separated by haemorrhage undergoes necrosis, and during the early stages of the necrosis autolytic products are absorbed into the circulation through the portion of placenta still attached to the uterine wall. These products, acting upon the maternal organs, especially kidneys and liver, set up the changes commonly associated with the toxæmias of pregnancy. The cause of the haemorrhage Young and his followers leave undetermined, but they suggest that it may be ascribed to a primary thrombosis of unknown origin in the veins of the broad ligament or uterus causing engorgement and rupture of the veins of the decidua and uterine wall. It is true that frequently, in cases of concealed haemorrhage, thrombi are found in the ovarian veins; but seeing how free is the anastomosis between the various veins that drain the uterus, it has always seemed to me difficult to believe that this thrombosis, unless it occurred suddenly and involved all the venous drainage of the uterus, could produce haemorrhage even in an organ so vascular as the pregnant uterus. Morse,⁴ for example, found that he could not produce haemorrhage in the uterus of the pregnant rabbit unless he ligatured all the veins—namely, the ovarian, mesometrial, and utero-vaginal—going off from one cornu. If all the veins were ligatured intense utero-placental apoplexy was produced, the uterine wall being ploughed up by the blood. Obviously nothing else can happen in such a vascular organ if all the veins are ligatured, and Morse himself attaches no clinical importance to this experiment. I hope to prove in this paper that the thrombosis is the result of the toxæmia, not its cause. Morse also produced haemorrhage by extreme rotation of the uterus on its long axis. From the latter experiment he argued that torsion of the uterus is a cause of accidental haemorrhage, and especially of utero-placental apoplexy. Whitridge Williams,² in a recent review of the subject, has expressed his scepticism regarding the importance of uterine torsion as a cause, and writes as follows:

"Since the appearance of his [Morse's] paper we have been careful to note the position of the uterus whenever the abdomen is opened, but in none of our patients treated by Caesarean section did the uterus present evidence of being markedly twisted upon its vertical axis. It is true that Polak has reported and pictured an instance in which such torsion had occurred that the Caesarean incision lay in the neighbourhood of the insertion of the left round ligament, but so far as I am aware it is the only evidence that has been adduced in support of Morse's contention."

From my own experience of Caesarean section I can say that I have more than once found a degree of rotation towards the right, almost as marked, without any evidence of haemorrhage. Trauma has also been invoked as a cause. Certainly a definite history of trauma can be obtained in some cases, but the association is probably coincidental.

ORIGIN OF THIS INVESTIGATION.

In September, 1923, while working in collaboration with Dr. W. R. Logan, clinical bacteriologist, Edinburgh Royal Infirmary, on the paths of intranatal infection in the newly born infant, we had injected a healthy rabbit, twenty days pregnant, with an emulsion of *Bacillus pyocyaneus* in saline. Six hours after injection we found the rabbit bleeding profusely from the vagina. On being removed from its cage to the experimental room the bleeding continued, about 3 drachms of blood being lost on the table in a few minutes. Under ether anaesthesia the abdomen was opened and the left pregnant horn exposed. On opening the lowest sac a recently dead foetus was found, and a retroplacental clot entirely or almost entirely separating the placenta (Fig. 1). The foetus with its placenta and adherent clot was removed and preserved. The other sacs (there were four in each horn) contained normal living foetuses and showed no evidence of haemorrhage. The empty sac from which bleeding had occurred was immediately placed in Pick's solution, together with pieces of the mother's liver and kidneys.

Microscopic examination of the sac wall (uterine wall) in relation to which the retroplacental haemorrhage had occurred showed well marked oedema throughout which widely separated the muscle bundles. In the mucosa of the placental site, adjacent to the zone of separation, there was well marked blood extravasation, and at one part the extravasated mass lay in relation to a ruptured maternal capillary, about one-third of the wall of which was more or less completely destroyed. No haemorrhage was observed in the muscular wall of the uterus. The kidney showed acute congestion of the glomerular and intertubular capillaries. The glomeruli were congested, but otherwise healthy. There was acute parenchymatous nephritis, shown by cloudy swelling of the epithelium of the convoluted tubules, so that the latter seemed in many places blocked by the epithelial swelling (Fig. 2). The epithelium of the straight tubules appeared fairly normal. No actual necrosis was observed, and no haemorrhage or thrombosis. There was also present in the kidney a certain amount of old interstitial change. The liver showed round-cell infiltration of the portal tracts and fatty change in the liver cells. The latter, however, is probably a fairly common finding in the normal liver of the rabbit, and we attached no significance to it. There was no thrombosis nor focal necrosis.

Realizing the importance of this result we made numerous attempts to repeat the result in pregnant rabbits, using various organisms and other substances by intravenous injection. In all, 34 experiments were carried out for this purpose subsequent to the success of September, 1923, the materials used being as follows: *B. pyocyaneus* (9 cases); *B. coli* (4); *streptococcus* (1); *B. mesentericus* (1); *B. typhosus* (2); *B. paratyphosus* (2); saline solution (4); *Staphylococcus aureus* (1); pneumococcus (3); histamine (4); ricin (2); toxins obtained by putrefying meat for three weeks and filtering through a Berkefeld filter—injected on three successive days (1). Many of the series died in twenty-four to forty-eight hours after injection, while a few aborted, but in none of the thirty-four did any haemorrhage occur except once, immediately after a histamine injection. Immediately after injection bleeding started, followed by abortion on the operating table. The three other histamine rabbits also aborted, two of them without any haemorrhage, while in the other a slight haemorrhage occurred. As slight haemorrhage at the time of littering is usual in the rabbit we discounted this.

These experiments were concluded in May, 1925, and had ended in almost complete failure to reproduce the first and only success (of September 8th, 1923). There was evidently some factor essential for success that we had so far failed to recognize. Up till this time I had looked on the nephritis not as a predisposing cause of the haemorrhage, but on the nephritis and the haemorrhage as both being due to the same cause—namely, toxæmia—and both as end-results of the toxæmia.

At this stage Dr. Logan withdrew from the investigation as the experimental portion (on the paths of intranatal infection) had been concluded, and the present work seemed to have little or no bacteriological bearing.

* Read at a meeting of the Edinburgh Obstetrical Society, March 10th, 1926.

During the time that the above negative experiments were going on, being interested in the subject of accidental haemorrhage, I had personally been taking very careful notes of all the cases seen in the Royal Maternity Hospital and in private practice, and began to be impressed by the frequency with which I could obtain a history of nephritis or of albuminuria in pregnancies preceding that in which accidental haemorrhage had occurred. But, with one exception, none of these cases had been followed up in the intervals between pregnancies, so it was impossible to say with certainty whether the nephritis accompanying the haemorrhage had preceded or followed the placental separation. In one case, however, the evidence was clear, for I had got the patient back in the interval between pregnancies for examination of kidney function.

The woman was an 11 para; first nine children alive and well; the ninth was born in 1921, the tenth (macerated) in 1922. On July 28th, 1924 (twelfth pregnancy), she was admitted with accidental haemorrhage and albuminuria. The same day she was delivered of a premature stillborn foetus. On leaving hospital her urine contained a trace of albumin; blood pressure normal. On November 10th the urine still contained 1 per cent. of albumin, and on February 15th, 1925, it contained 0.07 per cent.

During her stay in hospital her urea concentration was estimated twice, the highest concentration obtained being 1.8 per cent.; blood urea = 43 mg. per cent., non-protein nitrogen 38 mg. per cent. At the visit on February 15th, 1925, she was again three months pregnant. In May she was admitted with concealed haemorrhage, albuminous urine, and a tense and ligneous uterus. She was treated conservatively by rupture of membranes and pituitary extract, and a 7 months dead foetus was delivered. On discharge from hospital there was still albuminuria.

These cases induced me to believe that nephritis was an important predisposing cause of accidental haemorrhage,

and I decided to make attempts to produce nephritis in animals, and then in those animals in which nephritis had been set up to introduce toxins. If my theory were correct I should then be able to cause accidental haemorrhage.

EXPERIMENTAL NEPHRITIS.

Prior to 1924 we had no even moderately certain method of producing nephritis, either acute or chronic, but in that year were published two important papers² by Shaw Dunn, Haworth, and Jones of Manchester on oxalate nephritis, which showed that it was possible, by injecting oxalates into rabbits, to produce in them the lesions of acute parenchymatous nephritis. In November, 1925, I therefore stocked 34 female rabbits and began attempts to produce kidney lesions according to the method of Shaw Dunn, Haworth, and Jones, with some slight modifications.

Method.

Sodium oxalate was used throughout in 1 per cent. solution. The rabbits were weighed each morning before injection and drawing off blood, and 50 mg. per kilo of body weight, or a dose as nearly as possible approximating this, was injected into the ear vein. This was repeated at varying intervals, depending upon the effect produced. Blood was drawn off also at varying intervals and the blood urea estimated, using a modification of Marshall's urease method and 1 c.cm. of whole blood for each estimation, with frequent controls by standard urea solutions. The blood urea was taken as the clinical index of the onset and duration of the nephritis. The results obtained in three typical cases are shown in Table I.

TABLE I.—Results of Experiments in Three Typical Cases.

Rabbit B 8.				Rabbit B 11.				Rabbit B 30.			
Date.	Weight (Grams).	What Done.	Blood Urea (mg. %).	Date.	Weight (Grams).	What Done.	Blood Urea (mg. %).	Date.	Weight (Grams).	What Done.	Blood Urea (mg. %).
1925.				1925.				1925.			
Nov. 10	1595	Sod. oxalate (1 per cent.) 4 c.cm.		Nov. 10	1800	Sod. oxalate (1 per cent.) 4 c.cm.		Dec. 11	2210	Bled	43
Nov. 13	1510	Sod. oxalate 5 c.cm.		Nov. 13	1850	Sod. oxalate 7 c.cm.		Dec. 17	—	Oxalate (1 per cent.) 5 c.cm.	
Nov. 17	1400	Sod. oxalate 5 c.cm.		Nov. 17	1730	Sod. oxalate 5 c.cm.		Dec. 21	—	Bled	21
Dec. 23	—	Bled	36	Nov. 24	—	Bled	25	Dec. 23	2230	Oxalate 6 c.cm.	
Dec. 29	1750	Sod. oxalate— 10.30 a.m. 8 c.cm. 11.15 a.m. 2 c.cm.		Nov. 25	1775	11 a.m.: Sod. oxalate in 3 doses at half-hour intervals = 50 mg. per kilo		Dec. 24	—	Bled	47
Dec. 30	1800	Bled	86	Nov. 26	—	11 a.m.: Bled	60	Dec. 28	2300	Bled	56
1926.				Nov. 27	—	11 a.m.: Bled	94	Dec. 30	—	Oxalate 11 c.cm.	
Jan. 4	—	Bled	75	Nov. 30	—	12 noon: Bled	86	Dec. 31	2150	Bled	86
Jan. 6	1950	Oxalate— 10.15 a.m. 4 c.cm. 11.0 a.m. 2 c.cm. 11.30 a.m. 3 c.cm.		Dec. 2	—	Bled	85	1926.			
Jan. 7	1730	Bled	58	Dec. 8	—	Bled	47	Jan. 5	1850	Bled	128
Jan. 8	1930	Bled	45	Dec. 23	—	11 a.m.: Bled	33	Jan. 9	2030	1 d Oxalate 10 c.cm.	60
Jan. 12	2050	Oxalate 8 c.cm.		Dec. 29	1700	10.45 a.m.: Sod. oxalate 5 c.cm. 11.20 a.m.: Sod. oxalate 5.5 c.cm.		Jan. 12	1900	Bled	58
Jan. 14	2010	Bled	68	Dec. 30	1700	Bled	64	Jan. 22	2000	Bled	43
Jan. 16	1840	Oxalate 8 c.cm.		1926.				Jan. 26	2360	Oxalate 8 c.cm.	
Jan. 18	2030	Bled	60	Jan. 4	—	Bled	54	Jan. 27	—	Oxalate 8 c.cm. Bled (Partly lost power of legs immediately after injection; recovered in about one hour.)	77
Jan. 20	2250	Oxalate 7 c.cm. Streptococci 2 c.cm.		Jan. 6	1300	10.25 a.m.: Oxalate 5 c.cm. 11.5 a.m.: Oxalate 2 c.cm. 11.35 a.m.: Oxalate 2 c.cm.		Jan. 29	1975	Bled	93
Jan. 22	2225	Bled	43	Jan. 7	1700	Bled	218	Jan. 30	—	Bled	91
Jan. 26	2200	Oxalate 10 c.cm. Bled	56	Jan. 8	1755	Bled	227	Feb. 2	1900	Bled	47
Feb. 26	—	Oxalate (1 per cent.) 10 c.cm. Bled	64	Jan. 14	1730	Bled	25	Feb. 25	20 days pregnant	Oxalate 8 c.cm.	
Feb. 27	—	Bled Oxalate 4 c.cm. B. pyocyaneus 1.5 c.cm.	116	Jan. 16	1725	Bled	34	Feb. 26	—	12.45 p.m.: Oxalate 3 c.cm. B. pyocyaneus 1.5 c.cm.	
Mar. 1	—	Oxalate 9 c.cm. Bled	73	Jan. 18	1735	—				Bled (Kept on dry food for two days prior to injection.)	77
Mar. 3	—	11 a.m.: B. pyocyaneus 1.5 c.cm. Bled Killed at 5 p.m.	56	Jan. 26	1820	Sod. oxalate 8 c.cm.					
				Jan. 27	—	Bled	81				
				Jan. 29	—	Bled	47				

Note.—Rabbit B 8 had full-time young on January 26th; they were dead when found; there was no haemorrhage. On February 26th it was twenty days pregnant again. On March 2nd it had several haemorrhages at 9 a.m. On March 3rd it had profuse haemorrhage at 12.15 p.m.; killed at 5 p.m.

Three of the rabbits were kept in urine cages and twenty-four hour specimens of urine collected, measured, and tested for albumin daily, and the urea concentration estimated.

TABLE II.—Urea Concentration (Rabbit B33).

Date.	Weight (Grams).	What Done.	Blood Urea. mg. %	Urine (24 hrs.). c.cm.	Urine Urea. grams %	Urea Concentration.	Albumin.
1925.							
Jan. 5	2450	Bled	73				—
Jan. 12	—	Bled	58	120	2.3	40	—
Jan. 16	—			20	3.15 + +		—
Jan. 18	—			22	3.15 + +		—
Jan. 20	2400	Bled. Oxalate 1% 10 c.cm.	30	230	2.0	66	—
Jan. 21	2130	Bled	34	130	1.4	41	—
Jan. 22	2130	Oxalate 10 c.cm.		80	1.5		—
Jan. 25	2153	Bled	128	190	2.25	17	—
Jan. 26	2253	Oxalate 5 c.cm.		320	1.8	14	—
Jan. 27	2230	Bled	34	160	1.5	47	—
Feb. 2	2220	Oxalate 10 c.cm.		80	1.9		—
Feb. 4	—	Bled	78	220	1.5	19	Trace.
Feb. 9	2270	Oxalate 9 c.cm.					
Feb. 10	—	Bled	43	72	2.4	54	Trace.
Feb. 15	2200	Bled	73	20	2.2	30	Slight trace.
Feb. 16	—	—		52	3.15 +		"
Feb. 17	—	—		110	2.3		"
Feb. 18	—	—		220	2.15		"
Feb. 18	—	—		400	1.35		"

Note (1) the fall in the urea concentration to 14 on January 25th; (2) the absence of albumin in the urine on that day, when the blood urea reached 128 mg. per cent., and at no time was more than a trace present.

As the ultimate object of the research was the production of accidental haemorrhage, and not the study of nephritis, I merely wanted to be sure that I had produced nephritis, and therefore paid less attention than I otherwise might to the many fascinating physiological and pathological questions involved in the experiments. Two points, however, deserve special notice:

(a) The very rapid rise in the blood urea. After injection with oxalate this not infrequently rose in a few hours to a very high figure (for example in rabbit B11 (see Table I) the blood urea rose in twenty-four hours after injection of 9 c.cm. of oxalate from 54 to 218 mg. per cent.), and would almost as rapidly drop from this high figure to normal.

(b) Even in cases in which the blood urea was at a high figure and in which, therefore, there was an acute nephritis present, albumin might be entirely absent (see rabbit B33 in Table II, in which on January 25th the blood urea was 128 mg. per cent. and yet the urine was albumin-free). This is a point of great clinical importance and will be referred to later.

The work on nephritis was continued throughout November, December, and January, and on February 1st it was stopped and the rabbits mated. At this time I was left with 26 rabbits, 8 having died from various causes connected with the experiments (overdosage, etc.), and in practically all of these 26 I had obtained evidence of the production of nephritis by a rise in the blood urea at some time or other during the course of the work. From histological examination of the kidneys of several of the series I now know that I had produced very well marked early interstitial nephritis as well.

General Account of the Kidney Lesions.

Generally speaking the kidneys appeared enlarged, congested, and oedematous, but in none of my cases so far examined have haemorrhagic lesions been produced. The

capsule stripped easily, even in those that had been killed most recently and which had therefore suffered from nephritis for about three months.

Rabbit B12 may be described as fairly typical of the kidneys so far examined. This animal had been under treatment from November 10th, 1925, till January 26th, 1926, when it died in a convulsion immediately after an injection of oxalate. Its blood urea on January 4th had reached 141 mg. per cent., but at the time of death had fallen to normal, the urea in the heart blood being 30 mg. per cent. The kidneys were congested, but there were no haemorrhages and the capsule stripped easily. Microscopically (Figs. 3 and 4) the glomeruli were swollen and congested, but there was no exudate in the capsular spaces. Cloudy swelling was present in many of the convoluted tubules, but this change was not universal, and was most marked in the first convoluted tubules. Some tubules were dilated and filled with secretion. There was well marked early interstitial change and oedema in the cortex, best marked among the small collecting tubules.

Rabbit B9 had been under treatment from November 10th till January 10th, when it was found dead in its cage. It had previously become much emaciated. Its blood urea had been, at the last estimation, two days before death, 227 mg. per cent., its normal being 26. The convoluted tubules showed marked cloudy swelling and necrosis so that the lumina were almost closed. Some highly refractile fatty granules were present in the cells and some in the lumina of the tubules (Figs. 5 and 6). Some nuclei were pyknotic, others undergoing karyorrhexis or karyolysis. Well marked early interstitial change was present throughout the cortex, and here and there in the newly formed interstitial tissue were deposits of lime salts, probably calcium oxalate. It may be assumed that these originally lay in the tubules that had undergone necrosis, and that they had, as it were, become stranded in the newly formed interstitial tissue.

PRODUCTION OF ACCIDENTAL HAEMORRHAGE.

I decided that on the twentieth day of pregnancy (the duration of pregnancy in the rabbit is thirty days) I would make attempts to produce accidental haemorrhage. Twenty days would correspond to the sixth month in the human subject, a time when accidental haemorrhage frequently occurs.

Rabbit B7 reached the twentieth day on February 23rd, 1926. It had been under treatment from November 10th, 1925, to January 30th, 1926. Its blood urea, however, had never reached a very high figure, the highest being 102 mg. per cent. on January 27th. By January 30th the blood urea had again fallen to normal—namely, 25 mg. per cent.

On February 23rd, at 12 noon, 8 c.cm. of sodium oxalate were administered intravenously. The animal was placed in a cage with clean cotton-wool in the bottom, and was watched constantly. The next day, at 9 a.m., a haemorrhage had occurred. Two parts of the cotton-wool were stained, and the total amount was estimated at about 2 drachms. The rabbit was still pregnant. Blood urea was estimated at 12 noon, and was 79 mg. per cent. At 12 noon 3 c.cm. of oxalate were given plus 1 c.cm. of emulsion of *B. pyocyaneus* in saline. At 1 p.m. two fresh haemorrhages occurred, at 7 p.m. a third, and at 7.30 p.m. it was killed by chloroform. Three foetuses were in the right horn and two in the left. The cornua were removed and placed in fixative. On sectioning the placentas *in situ* after fixation several were found to contain what looked like infarcted areas, but they have not been examined microscopically.

Rabbit B24. This animal had been under treatment by oxalates from November 11th, 1925, till February 2nd, 1926. Its blood urea had risen from a normal level of 25 to 120 mg. per cent. on December 30th. On February 2nd it was still 73.

On February 24th it was twenty days pregnant; 7 c.cm. of oxalate were given at 11 a.m. No haemorrhage occurred all that day. The following day the blood urea = 98 mg. per cent.; 2 c.cm. of oxalate plus 1 c.cm. of *B. pyocyaneus* emulsion were given at 12 noon. No haemorrhage occurred during the day.

The first haemorrhage occurred at 9.45 a.m. on February 26th. The cotton-wool on the floor of the cage was half an inch thick, and was soaked through; the stain measured 3/4 by 1/2 in., and the amount of blood lost was therefore estimated at half a drachm. At 12 noon she aborted two foetuses, which seemed to have been dead for one or two days. She was examined at 12.15 p.m. and found still pregnant. Another large haemorrhage had occurred in the last quarter of an hour, but no further abortion. At 1 p.m. a further large haemorrhage occurred. The animal was killed by chloroform. Just before killing it aborted two more foetuses and one placenta. At *post-mortem* examination the uterus was found to contain three foetuses still.

Rabbit B31 had been under treatment by oxalates from December 11th, 1925, till January 27th, 1926. Blood urea = 107 mg. per cent. on January 4th, but on February 2nd had fallen to normal again (30 mg. per cent.).

No bleeding had occurred before February 26th. At 12.45 p.m. on this day the blood urea estimation = 108 mg. per cent.; 3.5 c.cm. of sodium oxalate were given plus 1.5 c.cm. of *B. pyocyaneus* emulsion. At 2.30 about half a teaspoonful of blood passed. No further haemorrhage occurred, and on examination on March 1st it was found to have aborted without haemorrhage and eaten foetuses.

Rabbit B28 had been under treatment with oxalates from November 24th, 1925, till the end of January, 1926. The blood urea had never reached a high figure, the highest being 81 mg. per cent. on January 21st.

On March 1st the animal was twenty days pregnant. Sodium oxalate 7.5 c.cm. was given intravenously. The next day at 9.30 a.m. it discharged half a drachm of blood. At 11.45 a.m. 1.5 c.cm. of *B. pyocyaneus* emulsion was injected intravenously; the blood urea was now 124 mg. per cent. No further haemorrhage occurred all this day.

At 9 a.m. on March 3rd about 2 drachms of blood had just been passed. The rabbit was still pregnant. At 8 p.m. a fresh bleeding occurred—about 1 drachm. At 12 noon the next day another haemorrhage occurred; there was no abortion, but the foetuses were getting smaller during the last two days and were probably dead. On March 6th a fresh bright red haemorrhage occurred, about half a drachm.

The animal was killed by chloroform on March 8th at 4.30 p.m. The foetuses in the sacs were almost entirely absorbed, only a putty-like material remaining.

PLACENTAL INFARCTION.

Rabbit B30 (see Table I for details of preparatory treatment.)

On February 25th the animal was twenty days pregnant. At 11 a.m. 8 c.cm. of oxalate were injected. No haemorrhage occurred all this day. The next day, at 12.45 p.m., the blood urea = 78 mg. per cent. Sodium oxalate 3 c.cm. plus 1.5 c.cm. of *B. pyocyaneus* emulsion was given intravenously. At 3.30 p.m. it was dull and not eating food, but no haemorrhage had occurred. At 4.45 p.m. a spot of fresh blood passed. At 5.45 p.m. it discharged about half a drachm of blood. There was no further haemorrhage that day.

At 9 a.m. on February 27th the animal aborted one fresh foetus. At 9.35 it discharged more fresh blood, and again at 10.4 a.m.—about half a drachm each time. It was killed by chloroform at 11.30 a.m. One foetus was expelled from the cornu by peristaltic contractions after excision of the uterus, and the foetus in the sac above was partly expelled. The cornua still contained several foetuses. They were fixed immediately in formalin solution. The kidneys seemed to be enlarged, congested, and oedematous.

On March 2nd all the sacs were examined by sectioning with a sharp scalpel, cutting through the foetus transversely and across the placenta and its attachment to the cornu. All the placentas were found to contain numerous thrombi and infarcted areas (three typical ones are shown in Figs. 7, 8, and 9). The foetuses still *in situ* were macerated, but not very markedly so, and had apparently been dead for about two days, the time probably varying somewhat in each individual case. Between the membranes and the uterine wall in one of the sacs there was a haematoma of exactly the size seen in the accompanying figure (Fig. 7). The placental tissue surrounding and between the thrombi was of a firm and liverish consistence, quite different from normal spongy placental tissue. In two cases the uterine wall underneath the placental site was seen to contain blood (Figs. 8 and 9).

Microscopically the infarcted placenta presented all the appearances familiar to us in recent infarcts of the human placenta (Figs. 10 and 11). The villi contained enormously dilated and engorged capillaries. So closely packed were the villi that the intervillous channels seemed to be almost entirely obliterated, and indeed were only visible here and there as slits between the villi. This appeared to be due to the great distension of the foetal capillaries, but was also probably due, as Eden⁶ has shown in the case of the human placenta, to the fact that the thrombus had cut off the supply of maternal blood from the intervillous spaces and thus allowed the villi to fall together. Throughout the fibromuscular wall of the uterus there were several haemorrhages easily evident in most of the sacs to the naked eye. Microscopically these haemorrhages were found to lie amongst the muscle fibres (Figs. 12 and 13), and could in most cases be traced to capillaries the walls of which seemed to have given way. A plasma-like fluid also present amongst the muscle fibres gave the appearance of oedema (Fig. 12).

Rabbit B8—twenty days pregnant (see Table I)—received on February 26th 10 c.cm. of oxalate intravenously; the blood urea at time of injection = 64 mg. per cent. No haemorrhage occurred all day. The next day 4 c.cm. of oxalate plus 1.5 c.cm. of *B. pyocyaneus* emulsion were injected. On March 1st 9 c.cm. of oxalate was given; the blood urea then was 73 mg. per cent. A few drops of blood were found at 9 a.m. on March 2nd. At 9.10 there was a discharge of about $\frac{1}{2}$ c.cm. At 11.20 a.m. 1.5 c.cm. of *B. pyocyaneus* emulsion was injected. The blood urea was 56 mg. per cent. At 12.15 p.m. a further profuse haemorrhage occurred. The animal was killed by chloroform at 5 p.m. The heart blood urea = 116 mg. per cent. Urine obtained from the bladder contained no trace of albumin (Heller's test). The kidneys were large, congested, and oedematous. Each uterine sac contained a mass of material resembling hydatidiform mole, which has not so far been examined microscopically. The urine obtained from the bladder at post-mortem examination contained no trace of albumin (Heller).

At this stage therefore I had attempted to produce accidental haemorrhage in six animals and in all the attempts had been successful. There had been produced external accidental haemorrhage, concealed haemorrhage, including haemorrhage in the uterine wall, and placental infarction. There seemed, therefore, to be no further object in continuing this particular experiment, especially as it was seriously depleting my stock of nephritic animals.

EVIDENCE UPON SPECIAL POINTS.

In the time that has elapsed since the experiments above described I have tried to obtain evidence upon certain matters arising in the course of the work.

1. Is a chronic nephritis necessary as a predisposing cause of the haemorrhage? It seems that it is not, and that an acute nephritis may be sufficient. The first successful experiment in 1923 is proof of this, although there was microscopic evidence of a slight interstitial change in the kidney. Again, in rabbit B35, a fresh non-nephritic animal, no bleeding occurred after injection of oxalates, but it did occur on injection of *B. pyocyaneus* + oxalates, causing a rise of the blood urea to 77 mg. per cent.

2. Is an acute nephritis necessary as a predisposing cause, or is a chronic nephritis sufficient without any acute exacerbation? So far as my experiments have gone an acute exacerbation would seem to be essential. In every case in which bleeding occurred in a chronic nephritis an acute or subacute exacerbation has been superimposed upon the chronic.

3. Organisms of the coliform group seem, so far as my experience goes, to be the most potent in causing haemorrhage. *B. pyocyaneus* and *B. coli* can both cause it, but the latter less than the former.

4. Provided a chronic oxalate nephritis has been previously produced, mere introduction of organisms without oxalate is sufficient to cause the necessary acute exacerbation, and to lead to haemorrhage. In rabbit B11 (see Table I) on March 8th the blood urea was 42 mg. per cent. *B. pyocyaneus* was injected alone, and the blood urea rose to 110 mg. per cent.; bleeding occurred on several occasions and macerated foetuses were aborted at term.

Interpretation of the Experimental Results.

I should like to put before you the thesis that external accidental haemorrhage, concealed haemorrhage, retroplacental haematoma, and placental infarction are an essential unity with a common underlying cause. Each is simply the effect of a toxæmia, the toxin being probably the product of organisms, which first of all produce an acute nephritis, this being predisposed to by an already damaged kidney. One of the functions of the healthy kidney is to excrete toxins of endogenous origin—hence the bacilluria that is found in most healthy pregnant women. If the kidney is severely damaged it can no longer fulfil its functions and the endogenous toxin is locked up in the circulation. It may still further damage the kidney, thus setting up a vicious circle. Acting on the endothelium of the vessels, it destroys it here and there and thus produces thrombosis—for example, in the veins of the broad ligament, or in the muscular wall of the uterus, as described by Whitridge Williams⁷ in 1915, or in the kidney or liver. If it acts on the endothelium of a capillary, the endothelium forming the only coat, the capillary wall may be completely destroyed, giving rise to haemorrhage in the fibro-muscular wall of the uterus. The same occurs in the dilated and engorged capillaries of the decidua, and leads to retroplacental haematoma and to external accidental haemorrhage. The syncytium covering the villi may be looked on as a vascular endothelium, with which indeed it is continuous. Like the endothelium it prevents clotting. If it be damaged here and there by the syncytio-lysin thrombosis occurs in the intervillous space, leading to infarct formation; and, as would be expected, the latter may be associated with external haemorrhage or with retroplacental haematoma (Fig. 14), or with both, as in rabbit B30.

The negative experiments of 1923-4-5 seem to prove that the haemorrhage is not caused directly by the organisms or their toxins, for in most of these experiments the animal died one or two days after the organisms were injected, and yet no haemorrhage had occurred. The toxæmia was therefore exceedingly severe—severe enough to cause death of the animal—and yet produced no haemorrhage. I have lately repeated these experiments with *B. pyocyaneus* with estimations of blood urea. The latter has not increased as a result of the injections and no haemorrhage has occurred. It is probably the kidney acutely damaged by the organisms that fails to excrete endogenous toxins. The latter, accumulating in the circulation, give rise to haemorrhage and

infarction. This opinion is based entirely on these negative experiments and may require modification as a result of further work.

ACCIDENTAL HAEMORRHAGE WITHOUT ALBUMINURIA.

It is said that accidental haemorrhage may occur without nephritis. At present I doubt very much whether this is so, and more evidence is necessary of the absence of nephritis in any given case than is commonly adduced. The mere absence of albumin in the urine is not sufficient evidence of the absence of nephritis, for it is known that acute nephritis may exist without any albuminuria, and examination of the urine in acute oxalate nephritis showed that albumin might be entirely absent even when the blood urea had reached a very high figure. In rabbit B 30 there was no albumin, though the blood urea had reached 128 mg. per cent. In addition to testing the urine for albumin use must in future be made of all the more modern methods of estimating kidney function, more especially the blood pressure, urea concentration test, and blood urea estimation, and where the kidney is available it must be examined histologically as far as possible throughout. Liver function tests, especially the phenol-tetrachlorophthalein excretion test, should also be carried out, for it is possible that a damaged liver may act in the same way as a damaged kidney.

It is also possible that many cases of so-called accidental haemorrhage may be really examples of low implantation of the placenta, and the greatest care must be taken in future to exclude these cases. A case which I treated about a year ago proves that well marked concealed haemorrhage may occur with placenta praevia, and even this possibility must be kept in mind. At least two other similar cases have been recorded—one by Eardley Holland⁸ and the other by Williamson.⁹

In future work an attempt must be made to ascertain the source and nature of the toxins at work, whether chemical or bacterial, and to trace the connexion which undoubtedly exists between accidental haemorrhage and eclampsia. This will involve a carefully co-ordinated and prolonged clinical and experimental study.

SUMMARY.

1. By setting up a chronic oxalate nephritis and then causing an acute exacerbation of the nephritis by introducing oxalates *plus* certain organisms it is possible to produce in pregnant rabbits accidental haemorrhage, both external and concealed, and placental infarction. This method is successful in 100 per cent. of cases.
2. Haemorrhage can be produced, though less easily, by setting up an acute oxalate nephritis and then introducing organisms.
3. A similar result can be obtained, also with less certainty, by producing an acute oxalate nephritis without subsequent introduction of organisms.
4. A similar result can be obtained by setting up a chronic nephritis and afterwards introducing organisms. The latter first set up an acute exacerbation, and haemorrhage occurs later. The result in this case is also less certain than by the first method.
5. In every case in which haemorrhage has so far been caused, an acute or subacute exacerbation of the nephritis, as indicated by a rise in the blood urea, has preceded the haemorrhage.
6. The coliform group of organisms seems to be the most potent in producing the acute nephritis that predisposes to haemorrhage and infarction.
7. An acute oxalate nephritis leads to marked retention of urea, but even when the urea concentration in the blood is at its highest point no albumin may be present in the urine. It is important to bear this in mind before excluding nephritis in accidental haemorrhage.
8. These experiments show that nephritis, acute or chronic, is an important predisposing factor in the production of accidental haemorrhage and placental infarction, and that toxæmia is the exciting cause. It is believed that organisms only act by setting up an acute exacerbation of the nephritis, and that they do not lead directly to

the haemorrhage, the latter being caused by endogenous poisons held up in the circulation by the acutely damaged kidney.

All the work in connexion with this research was carried out in the Research Laboratory of the Royal College of Physicians, Edinburgh, and to the Curator, Superintendent, and Laboratory Committee I am much indebted for the facilities placed at my disposal.

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An Address

ON

THEORY AND PRACTICE IN RELATION TO THE TREATMENT OF CANCER WITH LEAD.*

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(With Special Plate.)

In the investigation of so complex a question as the nature and control of malignant disease it cannot be denied that the conversion of a working hypothesis, with which the investigator must start, into a definite and substantial generalization by the putting together of existing scientific facts and the elucidation of further evidence, is of vastly greater ultimate importance than the initial attempts at control based on the generalization enunciated. By this I mean that, provided a generalization concerning the true nature of malignant neoplasia can be established beyond question, some control of this disease—limited perhaps, as I shall explain later—must assuredly follow, if not at the first attempt, at any rate as the result of subsequent modifications and developments.

It has, therefore, been our chief endeavour to substantiate our hypothesis from every point of view. First let me state what our working hypothesis has been; afterwards I will bring forward evidence as to its correctness—evidence that before long will, we hope, enable us to affirm the generalization beyond criticism.

THEORY.

To us malignant neoplasia appears to be a reversion of the somatic cell to the early embryonic type which forms the trophoblast. We regard the chorionic epithelium as being a normally malignant tissue that comes under somatic control, as we have described in previous communications. It is malignant in that it is dependent on its own efforts to obtain nourishment for itself and, indirectly, for the growing embryo.

We believe that if it be possible for a cell to pass through all the phases of undifferentiation to a differentiated state with increasing specialization, as seen in the human embryo, there should be no difficulty in realizing that a differentiated cell is capable in certain circumstances of retracing the phases back to undifferentiation. This process is known as dedifferentiation, and it has been definitely shown to occur in normal differentiated cells grown *in vitro*.

* This is the full text of the address given by Professor Blair Bell in introducing the discussion on the treatment of cancer by lead at the Medical Society of London on March 22nd. A report of the discussion, including an abstract of Professor Blair Bell's address, was published in our columns on March 27th (p. 568). A report of his reply appeared on page 572.

F. J. BROWNE: ACCIDENTAL HAEMORRHAGE AND PLACENTAL INFARCTION.

FIG. 1.—Experiment of September 18th, 1923. Foetal rabbit with retroplacental haematoma (1), and placenta (2). (Natural size.)

FIG. 2.—Experiment of September 18th, 1923. Kidney section showing acute nephritis. Note the swelling of the epithelium of the tubules and the swollen glomeruli. ($\times 180$.)

FIG. 3.—Kidney of rabbit B12. Shows cloudy swelling in convoluted tubules, swollen and congested glomeruli, and well marked early interstitial change. ($\times 80$.)

FIG. 4.—Same as Fig. 3. ($\times 200$.) The swollen epithelium of the convoluted tubules and the interstitial change are well seen.

FIG. 5.—Kidney of rabbit B9. Shows cloudy swelling of epithelium of convoluted tubes, and swollen and congested glomeruli. Early interstitial change is also present, though less evident than in B12.

FIG. 6.—Same as Fig. 5. ($\times 180$.)

F. J. BROWNE: ACCIDENTAL HAEMORRHAGE AND PLACENTAL INFARCTION.

FIG. 7.—Infarcted rabbit's placenta (B30). The macerated foetal rabbit is shown *in situ*, and with the placenta has been cut transversely. (1) Foetus; (2) haematoma between membranes and uterine wall; (3) uterine wall; (4) infarcted placenta.

FIG. 8.—Another infarcted placenta from rabbit B30. Haemorrhages are seen in the wall of the uterus underneath the placental site. (1) Placenta; (2) thrombi; (3) uterine wall; (4) mesometrium. The macerated foetus has been removed.

FIG. 9.—Another infarcted placenta from rabbit B30. The placental tissue in all these cases, subtending the thrombi, is firm and of liverish consistence.

FIG. 10.—Section of infarcted area from placenta of rabbit B30. The closely packed villi, with dilated, engorged capillaries, are seen. The picture is taken from an area immediately overlying one of the thrombi in Fig. 7. ($\times 75$.)

FIG. 11.—Drawing of infarcted area. Shows villi with dilated and engorged capillaries. At the extreme right is seen the edge of the thrombus which caused the infarction. ($\times 80$.)

FIG. 12.—Haemorrhage and oedema amongst the muscle fibres of the uterine wall (B30). The large cells are decidual cells, which normally are present in large numbers in the uterine muscle of the pregnant rabbit. ($\times 68$.)

FIG. 13.—Haemorrhage in muscle wall of uterus of rabbit B30. The darkly staining areas are extravasated blood, while around are the muscle fibres of the uterus. ($\times 68$.)

FIG. 14.—Human placenta, showing retroplacental haematoma, and placental infarction. The patient from whom this specimen was obtained had also external accidental haemorrhage. This association of infarction and accidental haemorrhage is not infrequent.