EXPERIMENTAL PYELONEPHRITIS. THE EFFECT OF CHRONIC INFECTION ON THE BLOOD PRESSURE IN THE RAT*

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THE frequent association of high blood pressure and chronic pyelonephritis in man may be explained in at least two different ways, first, that the chronic infection produces the rise in pressure, or second, that hypertensive vascular changes so damage the kidney that it becomes more susceptible to infection. We tested the first of these two possibilities experimentally some years ago in the rabbit (Heptinstall and Gorrill, 1955), and found that chronic pyelonephritis could cause a rise of blood pressure when the infection was present in one kidney, the other having been removed surgically. Chronic infection of one kidney caused no rise in pressure when the opposite kidney was present. These findings have a close parallel in the experiments of Pickering and Prinzmetal (1937–8) in which sustained hypertension occurred in the rabbit when one renal artery was compressed and the other kidney removed, but not when one artery was compressed and the other kidney left untouched. Because the rat will develop a sustained rise in blood pressure when one renal artery is constricted in the presence of an intact opposite kidney (Wilson and Byrom, 1941), it was considered that this animal might prove more suitable for experiments on the relationship between chronic renal infection and hypertension. Accordingly in the present experiment a chronic infection was set up in one kidney of the rat, the other kidney being either untouched or removed, and in other rats infection was produced in both kidneys. It was found that a rise in pressure occurred frequently in rats with infection in a sole remaining kidney, less frequently in those with both kidneys infected, and only occasionally in those in which infection was present in one kidney, the other being intact.

METHODS

Forty female Wistar rats (180–200 g.) were divided into 4 equal groups. Acute infection of the kidney was produced by an intravenous injection of 0·5 ml. of a saline suspension of a spundown overnight culture of *Bacterium coli* containing approximately 5×10^8 organisms/ml., coupled with temporary occlusion of the ureter for either 2 or 4 days. The organism was that used in previous experiments and the procedures employed in producing infection are fully described elsewhere (Brumfitt and Heptinstall, 1958). At the end of 6 months the animals were bled for blood urea nitrogen (BUN) determinations and killed by an overdose of ether. BUN estimations were made using the diacetyl monoxime method as described by Rosenthal (1955). Histological sections were prepared from kidney, adrenal, mesenteric arteries, pancreas, small intestine, liver, spleen and heart, and the heart, kidney, and carcass weights obtained. The heart weight/carcass weight ratio which is increased in sustained hypertension was calculated for each animal. Before producing infection a series of blood

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pressures were taken using the method of Friedman and Freed (1949) on the tail under light ether anesthesia. After infection was established, blood pressures were taken twice weekly for 4 weeks and once weekly for the rest of the experiment. The animals were weighed each week and fed on Purina fox chow with unlimited tap water to drink.

Group 1 consisted of rats in which the left kidney was infected, the right not being touched. Group 2 contained rats in which the right kidney was removed at the same time as infection was induced in the left kidney. Group 3 was made up of rats in which infection was produced in both kidneys. Group 4 served as a control and consisted of 2 rats in which the left ureter was obstructed for 4 days, 4 in which both ureters were obstructed for 2 days, and 4 in which the left ureter was obstructed for 2 days coupled with removal of the right kidney. Intravenous injection of 0·5 ml. sterile saline was given at the time of ureteric obstruction.

RESULTS

The salient features of each group are shown in the table.

Group 1 (*one kidney infected, other untouched*)

The animals all gained weight and remained healthy. There was no significant rise in pressure when this group was considered as a whole and no increase in heart weight/carcass weight ratio. In two rats (Nos. 14 and 21) there was a sustained rise in pressure of over 20 mm. Hg, one of these having reached a level of 170 mm. Hg at the 18th week with subsequent fall to a mean of 144 mm. Hg over the last 4 weeks of the experiment. Necrotising arteritis was present in the mesenteric vessels of this animal but no such changes were present in the right non-infected kidney. The two animals just mentioned, together with one showing no rise in pressure (No. 33), had a pyonephrosis on the infected side with only a thin rim of surviving parenchyma which showed chronic inflammatory changes. It was assumed in these three rats that the nylon thread applied temporarily to the ureter had caused a permanent stricture. Four of the remaining animals (Nos. 2, 8, 37 and 40) showed the infected kidneys to be reduced in size with numerous coarse scars. Histologically these scars were almost completely devoid of tubules ; chronic inflammatory cells in the interstitium, normal blood vessels and normal or slightly collapsed glomeruli were invariably present. This remarkable persistence of glomeruli with little evidence of sclerosis and with apparently no tubules was a feature of all groups and is being further investigated. There was sometimes evidence of acute inflammation. The 3 remaining rats (Nos. 6, 11 and 47) had a uniformly shrunken kidney on the left side weighing in one instance as little as 0·12 g. The subcapsular surfaces were smooth and histologically the entire kidney showed changes similar to those seen in the pyelonephritic scars. No normal parenchyma was present. The opposite kidney was hypertrophied in all 10 animals and showed no histological abnormality.

Group 2 (*one kidney infected, other removed*)

Only 5 animals in this group survived the full length of the experiment, the others dying from respiratory infection or from what was presumed to be renal failure. One of these (No. 51) died at $2\frac{1}{2}$ months, another (No. 56) at 4 months, two (Nos. 30 and 83) at 5 months and the fifth (No. 19) at $5\frac{1}{2}$ months. BUN levels were raised in 5 out of 6 animals in which this estimation was made, the two animals with the highest levels (Nos. 19 and 20) having much loss of tissue because of pyonephrosis, but in the other 3 adequate apparently healthy parenchyma

TABLE.—*To Show Pre-operative and Post-operative Blood Pressures (B.P.), Rise in B.P., Highest B.P. Reached, Heart Weight × 1000/Carcass Weight ratio and BUN for Rats in Group* 1, 2, 3 *and* 4.

No. of rat	Pre-operative B.P. (mm. Hg.)	Mean B.P. over last 4 weeks of expt. (mm. Hg.)	Rise in* B.P. mm. Hg.	Highest B.P. reached† mm. Hg.	Heart weight × 1000/ carcass weight	BUN mg./ 100 ml.
Group 1						
2	113	124	11	127	3·84	22·5
6	111	104	−7	123	4·28	23·5
8	109	116	7	140	5·27	..
11	114	113	−1	120	3·70	27
14	116	136	20	144	4·45	23·5
21	115	144	29	170	4·36	43·7
33	117	114	−3	116	3·07	21·3
37	121	123	2	128	3·08	15·5
40	115	125	10	130	2·54	28·5
47	122	118	−4	138	3·52	23
Mean with standard error	115·3±1·21	121·7±3·5	6·4±3·45	133·6±4·7	3·81±0·24	25·30±2·44
Group 2						
17	116	127	11	128	3·51	11·5
18	117	120	3	128	3·62	32
19	117	188	71	215	7·18	83
20	104	172	68	186	7·65	88·9
30	109	152	43	160	6·19	..
44	118	145	27	155	4·09	34
51	117	176	59	194	5·23	..
56	123	198	75	210	7·05	..
62	121	125	4	140	3·80	30·5
83	100	126	26	130	5·66	..
Mean with standard error	114·2±2·23	152·9±8·6	38·7±8·48	164·6±10·2	5·40±0·47	46·65±11·76
Group 3						
10	114	123	9	128	4·21	29·5
23	116	137	21	148	4·34	60·5
28	116	137	21	150	3·87	11·0
41	122	148	26	150	5·89	80·0
50	111	142	31	145	4·07	50·3
80	107	115	8	132	3·20	14·3
84	106	130	24	140	4·15	..
85	104	100	−4	110	3·79	53·5
42	123	120	−3	137	3·70	..
49	94	109	15	110	4·37	..
Mean with standard error	111·3±2·65	126·1±4·7	14·8± 3·61	135±4·6	4·16±0·21	42·73±8·89
Group 4						
5	110	117	7	128	3·28	22·0
7	117	125	8	135	4·44	23·0
9	118	120	2	128	3·84	26·0
12	114	116	2	128	3·54	19·5
25	115	118	3	126	3·63	16·0
35	119	123	4	130	3·12	16·5
61	113	105	−8	124	3·50	29·0
82	118	127	9	140	3·28	23·8
87	105	112	7	122	3·66	25·5
88	111	118	7	124	3·55	23·5
Mean with standard error	114±1·32	118·1±1·9	4·1±1·49	128·5±1·6	3·58±0·12	22·48±1·24

* Difference between pre-operative pressure and mean pressure over last 4 weeks.
† Highest pressure recorded at any time during experiment.

was present. BUN values are not available for the other 4 animals all of which were hypertensive. All died during the night time and no blood samples could be taken. It might be presumed that some of these would have had a raised BUN for 3 of them showed necrotising vascular changes in the kidney, a change often associated with raised BUN. The mean blood pressure for the group was significantly higher than that of the control group ($P < 0{\cdot}001$), the rise being over 25 mm. Hg in 7 animals and over 43 mm. Hg in 6. The mean heart weight/carcass weight ratio for the group was significantly higher than that for the control group ($0{\cdot}005 > P > 0{\cdot}001$). The blood pressure began to rise at 6–8 weeks in 2 rats, at 8–10 weeks in 2, at 10–12 weeks in one and at 16–18 weeks in 2. Very high levels were badly tolerated and death occurred within two weeks once the pressure reached 190 mm. Hg in the 3 animals in which this pressure was reached. In only 2 animals (Nos. 19 and 56) was there loss of weight and this took place in the last week of life. Animals showed weight gain in the presence of very high pressures although not so great as in the control group.

Three rats (Nos. 19, 20 and 83) showed a pyonephrosis with varying amounts of surviving parenchyma. Five (Nos. 17, 18, 30, 44 and 62) showed varying degrees of coarse scarring and two (Nos. 51 and 56) had a diffuse very fine granularity with a few coarser scars. Histologically chronic infective changes were the same as in Group 1, but in those parts of the kidney not scarred by infection in animals with hypertension, the glomeruli had necrosis or eosinophilic material in the tufts, and tubules were dilated and contained lightly eosinophilic coagula. Four of the hypertensive animals showed vascular changes in the kidney consisting of necrotising arteriolitis with an inflammatory cellular component, and intimal proliferative changes in arteries. Necrotising changes with inflammatory cells were present in the mesenteric arteries. There were no arterial changes of any sort in scarred chronic pyelonephritic areas in any animal. There was no relationship between the degree of hypertension and the reduction in size of the kidney nor with the amount of chronic pyelonephritic scarring as judged grossly and microscopically. If the 3 animals with pyonephrosis are excluded, for it was impossible to get an accurate weight of the kidney in these cases, then the mean kidney weight of the remaining 4 hypertensive animals was 1·71 g. compared with 1·49 g. for control animals with only one kidney.

Group 3 (*both kidneys infected*)

All animals remained in good health and none died. Weight gain was not so great as in Groups 1 and 4, and in 3 rats (2 with no rise in blood pressure) there was a slight loss in weight. Three however (Nos. 42, 49 and 84) were inadvertently killed by overdose of ether during the taking of blood pressure at 11, 12 and 18 weeks respectively. It should be added that several animals died during the stage of acute infection and were not included in the experiment. A sustained rise in pressure of some 21 mm. Hg was seen in 5 animals, the rise beginning at 11 weeks in one, 16–17 weeks in three and at 19 weeks in the fifth. As a group there was a significant rise in blood pressure ($0{\cdot}025 > P > 0{\cdot}01$) and in the heart weight/carcass weight ratio ($0{\cdot}05 > P > 0{\cdot}025$) compared with the control group. BUN levels were raised in 5 of the 7 animals in which this estimation was made. The combined weights of the two kidneys in each of these 5 animals was not less than the combined weights of the 2 kidneys from control rats. (Mean of 2·5 g. compared with 2·1 g.)

In 7 rats the kidneys both showed moderate, patchy coarse scarring. Of the other 3, one (No. 23) had a pyonephrosis on one side with a slightly enlarged coarsely scarred kidney on the other ; another (No. 28) showed a minute evenly reduced kidney on one side, the other kidney being enlarged and coarsely scarred ; the remaining rat (No. 85) had finely granular kidneys with intervening coarser scars. Histologically the changes were of chronic infection but in 6 rats there were areas away from the scarred zones where tubules were dilated, containing eosinophilic casts and where glomeruli showed intravascular thrombosis and patchy eosinophilic basement membrane thickening. Two animals with such changes (Nos. 10 and 85) did not have a raised blood pressure. Hypertensive vascular changes were seen in only 1 rat, No. 41, and no intimal arterial thickening was seen in the scarred infective areas of any animal. There was no correlation between the rise of blood pressure and the amount of scarring, nor with reduction of kidney mass, which as described above was actually increased.

Group 4 (*control*)

All animals in this group gained weight and showed no substantial rise in blood pressure. No pathological changes were present.

DISCUSSION

This experiment shows that a significant rise of blood pressure takes place in the group with a chronic infection of one kidney, the other having been removed, and in that with a chronic infection of both kidneys. The way in which this rise comes about however is not clear.

There is no correlation between the amount of infective scarring and the rise in pressure, for some of the greatest rises were in rats with relatively little scarring. Similarly there is no constant relationship between pressure rise and loss of renal substance, a correlation which might have been anticipated from the demonstration by Koletsky and Goodsitt (1960) that removal of three-quarters of the renal tissue in the rat will result in a rise of pressure in 56 per cent of animals over a period of several months. The pressures in these animals were usually 150–170 mm. Hg and were labile, substitution of 1 per cent saline increasing the incidence of hypertension. It was considered that " renal ablation hypertension " was related to disturbances in electrolyte and water metabolism. Three animals in Group 2 (Nos. 19, 20 and 83) with high pressures had an appreciable loss of parenchyma in that all had a pyonephrosis in their only kidney. In no other animals however could it be held that the hypertension was caused by a loss of renal substance as in renoprival hypertension. The persisting renal mass in the other hypertensive animals of Groups 2 and 3 was greater than in the controls, a fact which rules out renoprival hypertension.

In the present experiment a rise in BUN was noted in rats with raised blood pressure, and with the possible exception of Nos. 19, 20 and 83 referred to above, it is more likely that this rise is a consequence of the hypertension rather than an indication of loss of parenchyma which might initiate hypertension.

No relationship was found between the degree of intimal arterial thickening in the infective scars and the rise of pressure, such as occurs in the human (Weiss and Parker, 1939 ; Kincaid-Smith, 1955). In an investigation on this subject in man we found that vascular narrowing in the scars of chronic pyelonephritis was

invariably accompanied by hypertension, and that hypertension in chronic pyelonephritis was usually although not invariably associated with vascular narrowing in the infective scars (Heptinstall and Michaels, unpublished). In the present experiment however the arteries in the chronically infected areas show no intimal thickening, a feature which has been consistently noted in large numbers of rats with chronic infection of the kidney studied over the past few years. Vascular changes of necrotic or proliferative type were found in those rats with raised blood pressure in the non-infected parts of the kidney but were absent from the infective scars. It is considered that these lesions are independent of the infection and are probably the result of hypertension, being identical with those described by Wilson and Byrom (1941) in the non-clipped kidney of rats made hypertensive by the application of silver clip to one renal artery.

The results of this experiment stand in contrast to those of Shapiro, Braude and Siemienski (1959) and Guze (1960). The former failed to obtain any significant rise in pressure in rats with bilateral kidney infection produced by intracardiac injection of either *Bact. coli*, *Proteus morgani*, or *Streptococcus faecalis* var. *zymogenes* combined with massage of the kidneys. A similar experiment by Shapiro and Kobernick (1959) in which kidneys were infected with all three of these organisms followed by removal of one of the kidneys also failed to demonstrate a rise in blood pressure. Guze (1960) was unable to detect a rise in pressure in rats with chronic infection produced by an intravenous injection of *Str. faecalis*. These animals were followed for 12 months and as well as showing no rise in pressure developed no vascular changes. No explanation can be offered for the failure to produce hypertension by these authors when significant rises were found in the present experiment in Groups 2 and 3 which are directly comparable.

On the other hand certain authors have noted a rise in arterial pressure in the rat with chronic renal infection. Spitznagel and Schroeder (1951) produced infection in one kidney by an intravenous injection of *Bact. coli* into rats with one ureter obstructed. Hypertension developed in a significant number of animals but it should be noted that no attempt was made to release the ureteric obstruction and the resultant pathological changes in the kidney were a combination of obstruction and infection. In the present experiment the ureteric obstruction is only temporary to allow infection to take place and free flow of urine can occur once the obstruction is relieved. Vivaldi, Zangwill, Cotran and Kass (1960) produced bilateral renal infection by injecting *Pr. vulgaris* directly into the bladder. Some 55 per cent of animals developing chronic active pyelonephritis showed a rise in pressure above 150 mm. Hg.

While the experiment demonstrated quite clearly that a rise in blood pressure is found in groups 2 and 3 it must be realised that the rat is an animal which develops hypertension as a result of several different procedures on the kidney and that any conclusions may not necessarily be valid for man.

SUMMARY

Chronic pyelonephritis in the rat caused a raised blood pressure when the infection was present in one kidney with the other excised, or less constantly when both kidneys were infected.

Only a very occasional rise in pressure took place when one kidney was infected and the other healthy.

No arterial narrowing was present in the pyelonephritic scars.

There was no relationship between the degree of scarring or reduction in renal mass and the rise in blood pressure.

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