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Healed Experimental Renal Papillary Necrosis and Cortical Scarring in the Rat from 2-Bromoethylamine Hydrobromide

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Summary. Male Sprague-Dawley rats were each given a single subcutaneous injection of an aqueous solution of bromoethylamine hydrobromide (BEA) at dose levels of 80 mg/kg (16 rats), 125 mg/kg (15 rats) and 250 mg/kg (16 rats) or a single subcutaneous injection of water (controls, 15 rats). The dose levels were chosen so as to cause renal papillary injury varying from minor necrotic foci to necrosis and subsequent sloughing of the entire papilla. The animals were killed after 5 months and the kidneys were weighed and examined macroscopically and microscopically for the presence of RPN and cortical scarring. Macroscopically evident RPN occurred in 18 of 43 surviving BEA-treated rats, bilaterally in 16 and unilaterally in 2. Bilateral asymmetry of the extent of sloughing was evident. All kidneys with macroscopic RPN exhibited cortical scarring. Asymmetry of the extent of atrophy and scarring in some animals resulted in a significant unilateral reduction in renal weight and a significant contralateral compensatory hypertrophy. Twenty-three of the 25 BEA-treated rats without macroscopically evident RPN exhibited minor, histologically visible lesions of the renal papillae including necrosis of loops of Henle in the presence of intact collecting ducts. Only 2 of these animals exhibited tiny, unilateral cortical scars, and renal weights did not differ significantly from those of controls. It may therefore be concluded, contrary to certain published proposals: that experimental RPN may be followed by severe renal cortical scarring, reduction in renal size and (in the presence of asymmetrical lesions) compensatory renal hypertrophy, and that necrosis of thin limbs of loops of Henle does not appear to lead to frequent or severe cortical scarring.

Introduction

Human autopsy studies have yielded evidence that renal papillary necrosis (RPN) is the primary lesion of analgesic nephropathy and that cortical scarring occurs

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secondarily, probably as a result of tubular obstruction in or above the necrotic medullary tissue (Sanerkin, 1966; Kincaid-Smith, 1967; Burry, 1968 and 1971). The severely scarred kidneys of advanced analgesic nephropathy are abnormally small. A reduction in renal size has also been observed in some experimental models of renal papillary damage and RPN. Lucke and Hunt (1968) described and illustrated severe cortical scarring and decreased renal size that occurred in rabbits after surgical removal of the papilla had been performed. Davies (1968) observed a similar effect in the same species after producing RPN with ethyleneimine. Murray et al. (1972) studied RPN produced by 2-bromoethylamine hydrobromide (BEA) in rats and noted that the kidneys were often "grossly and uniformly scarred" 3 months later. These three reports would thus appear to substantiate the proposed pathogenesis of cortical scarring in human analgesic nephropathy.

Published reports of other experiments using rats, however, have not recorded similar results. Ham and Tange (1969) and Swales et al. (1973) observed that renal cortical scars that were present 3 months after the production of RPN with ethyleneimine were often small and focal. The latter authors therefore suggested that obstruction caused by RPN might not be the sole mechanism by which cortical scars are formed in human analgesic nephropathy. It is usually stated that, in human analgesic nephropathy, obstruction of the collecting ducts by the RPN leads to cortical scarring (Kincaid-Smith, 1967). Murray et al. (1972) who studied RPN produced by BEA in rats, proposed, however, that obstruction might occur in necrotic loops of Henle.

The experiment to be described was designed to determine whether or not a significant decrease in renal size accompanied renal corticol scarring after RPN was produced by BEA in rats, and whether or not necrosis of loops of Henle alone was followed by severe scarring. The production of necrosis of loops of Henle but not of collecting ducts was achieved by the administration of appropriate dose levels of BEA.

Materials and Methods

Sixty-two female Sprague-Dawley rats weighing 171–268 g (mean, 204 g) were used. They were housed in large cages (up to 16 animals per cage) in a non-air conditioned room and allowed free access at all times to tap water and Purina Chow. The animals were randomly divided into four groups, each containing 15 or 16 rats. BEA was administered at doses of 80 mg/kg body weight (16 rats), 125 mg/kg body weight (15 rats) and 250 mg/kg body weight (16 rats). Fifteen other animals served as controls. Each rat received a single subcutaneous injection of an aqueous solution of the BEA at a dose volume of 1.0 ml/kg body weight. Each of the animals that served as controls received a single subcutaneous injection of water.

After 5 months, the animals were weighed and then killed by cervical Hyperextension. The kidneys were excised and fixed by immersion in neutral, phosphate-buffered 4% formaldehyde. Twenty-four hours later, the perirenal fat and as much hilar fat as possible was stripped from the fixed kidneys, which were then dried with absorbent paper and weighed individually. The presence and extent of any cortical scars were noted. Each kidney was bisected longitudinally and the papilla and pelvis were examined macroscopically and through a stereomicroscope.

The kidneys were processed by routine methods for histological examination. Paraffin sections 4 μm thick were stained with hematoxylin and eosin, and selected sections were stained with Masson's trichrome. Care was taken that longitudinal sections passed through or close to the tips of the papillae.

Results

Death Rates. Four of the 47 BEA-treated rats (one given 80 mg/kg and 3 given 250 mg/kg) died early in the course of the experiment and were excluded from an assessment of the results. No deaths occurred among animals that served as controls.

Macroscopic Appearances of the External Surfaces of the Kidneys. Macroscopically visible cortical scars occurred at all 3 dose levels of BEA but no scars developed in the kidneys of the animals that served as controls. The scars varied considerably in position and extent. They appeared as small, single or multiple pits, as irregular, depressed areas with intervening nodules of preserved cortex, or as extensive, flat-based, depressed areas involving much of the cortex (Fig. 1). Scars sometimes involved one or other renal pole (Fig. 2). When scarring was unilateral or when it was bilateral but unequal in extent, disparity in renal size was sometimes clearly evident (Fig. 1).

Macroscopic Appearances of the Cut Surfaces of the Bisected Kidneys. RPN was easily identified macroscopically because the necrotic portions of the papillae had separated from the viable medulla, leaving an irregular, truncated stump or an excavated, medullary cavity. If the area of RPN was small, a ragged stump remained; if large, a cavity was seen. Detached, yellow to white, hard, calcified, necrotic papillae lay in such cavities in 7 animals (Fig. 3), bilaterally in 3 and unilaterally in 4. In other severely scarred kidneys with deeply excavated medullae, however, such necrotic remnants were not seen.

Eighteen of the 43 BEA-treated animals (4 of 15 given 80 mg/kg, 7 of 15 given 125 mg/kg and 7 of 13 given 250 mg/kg) had macroscopically evident RPN. Of these 18 rats, 2 had unilateral and 16 bilateral lesions. No RPN occurred in animals that served as controls.

Cysts had formed in the scars in several kidneys.

Relationship Between Macroscopic RPN and Cortical Scars. All 18 animals with macroscopic RPN had renal cortical scars, but scars were seen in only 2 of the remaining 25 BEA-treated rats with no macroscopic RPN. These frequencies differ significantly ($\chi^2 = 32$, $P < 0.001$). Every kidney with macroscopic RPN was scarred. The 2 animals with unilateral RPN had ipsilateral scarring only. In the 2 BEA-treated rats with scars but no macroscopic RPN, the scars were unilateral and small.

Relationship Between the Position and Extent of the RPN and the Position and Extent of the Cortical Scars. Macroscopic examination of the cut surfaces of the bisected kidneys revealed that the cortical scars overlay the most deeply excavated parts of the medulla (Figs. 3 and 4). Kidneys with small scars exhibited only small areas of RPN limited to the distal parts of the papillae. Extensive scars occurred only in the presence of extensive medullary excavation.

Microscopic Appearances of Kidneys From Animals With Macroscopic RPN. All kidneys with macroscopic RPN exhibited excavation of the medulla (Fig. 5)

Fig. 1. Extensive, unilateral renal cortical scarring and compensatory hypertrophy of the unscarred contralateral kidney. The scale is in millimeters

Fig. 2. Unilateral scarring involving one renal pole

or truncation of the papilla. In most kidneys, no attached remnants of necrotic tissue remained, and re-epithelialization of the irregular surface was evident. Only infrequently could the openings of the collecting ducts be seen. Dense fibrosis, which varied in position and extent, was present in the remaining medullary tissue. Loops of Henle, vasa recta and collecting ducts enclosed by the fibrosis were variably atrophic. Normal structures were virtually absent from the most densely fibrotic areas (Fig. 6).

Fig. 3. Bisected kidney exhibiting extensive excavation of the medulla. Both the medullary excavation and the overlying scarring are most extensive in the central region of the organ. The detached, calcified, necrotic papilla lies in the medullary and pelvic cavity

Fig. 4. Bisected kidney, the external appearance of which is shown in Figure 2. The medullary excavation is most extensive immediately beneath the scar at the upper pole

When sections had been cut in appropriate planes, the medullary fibrosis could be seen in continuity with cortical scars, whereas normal cortex was drained by collecting ducts which were essentially normal and which were not enclosed by newly formed fibrous tissue. Thus, although serial sections were not cut, the impression was gained that cortical scars were present only where

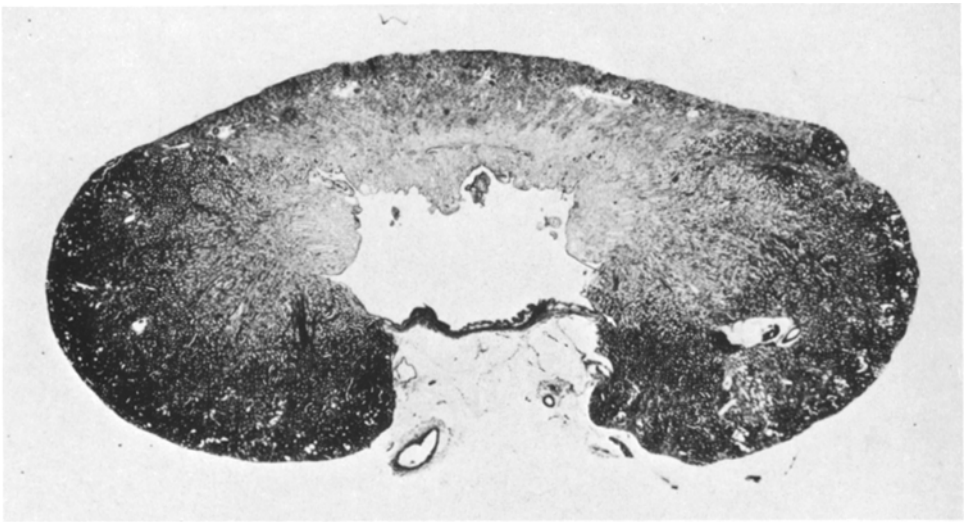

Fig. 5. Low power photomicrograph of a section of the kidney shown in Figure 3. Loss of the papilla, extensive medullary excavation and central ortical scarring are evident. H. & E. X7.5

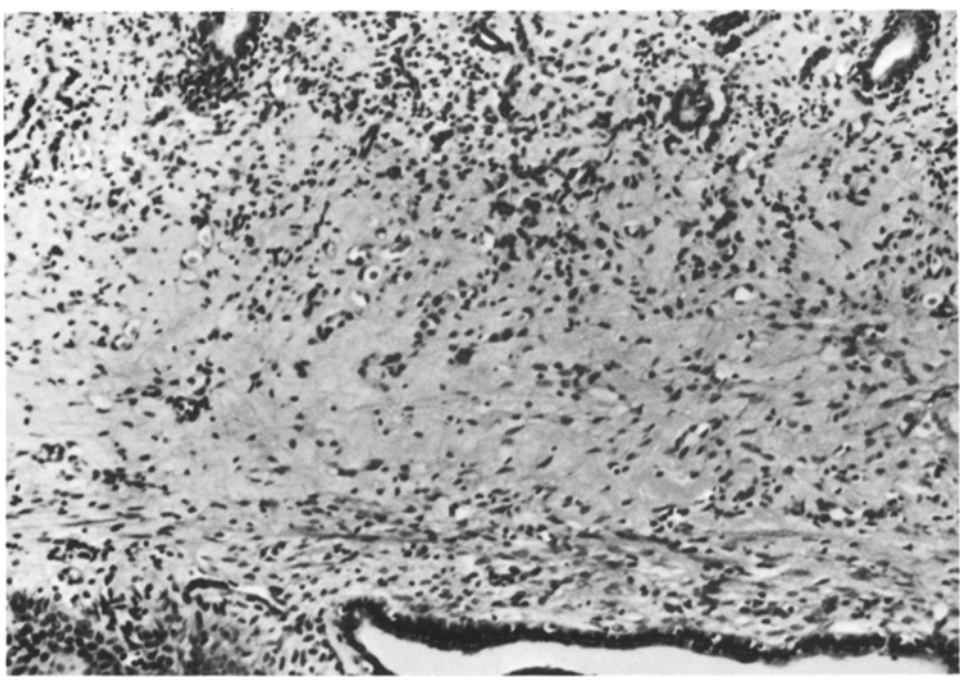

Fig. 6. Dense fibrosis of the outer medulla beneath a cortical scar. The overall appearance of the kidney was similar to that shown in Figure 5. H. & E., X110

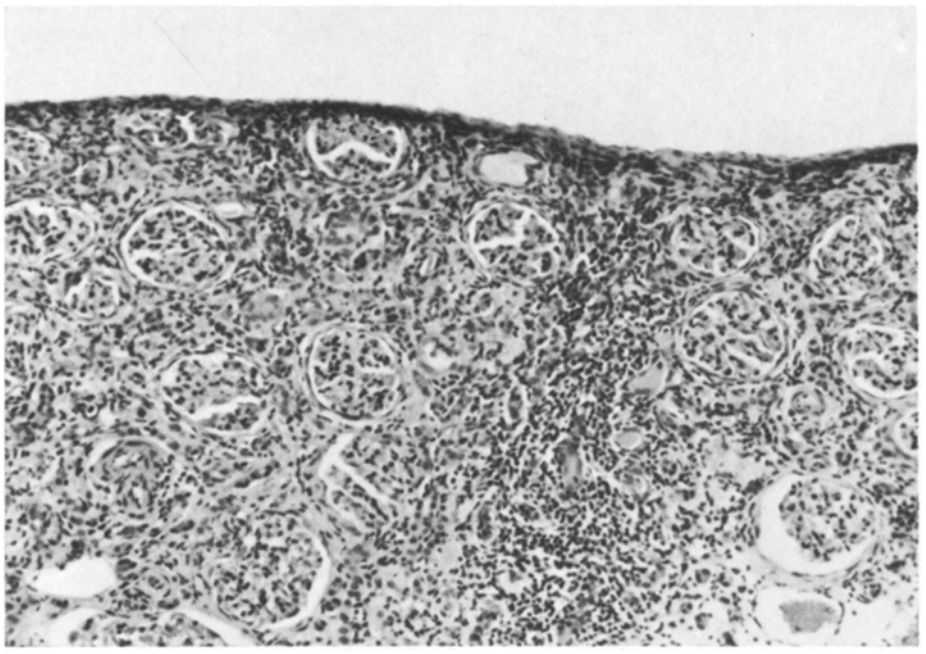

Fig. 7. Portion of a cortical scar. H. & E. X110

the underlying medulla exhibited fibrosis. Furthermore, the most extensively scarred kidneys showed the deepest medullary excavations and the most dense and extensive medullary fibrosis.

Calcification localized in and around basement membranes was observed in several animals in the viable but abnormal medullary tissue above the line of separation of the necrotic papilla.

Cortical scars (Fig. 7) exhibited extreme atrophy of convoluted tubules and cortical collecting ducts. Basement membranes appeared markedly thickened, interstitial fibrosis was present and frequent collections of lymphocytes were seen. Lipochrome pigment was observed in many epithelial cells of atrophic nephrons. Glomeruli were well preserved, but were closely crowded because of the profound atrophy of the intervening parenchyma, and exhibited mild periglomerular fibrosis. Occasional kidneys contained cysts, in both medulla and cortex.

Microscopic Appearances of Kidneys From Animals With no Macroscopic RPN. Twenty-three of the 25 rats with no macroscopic RPN after BEA exhibited subtotal RPN. Collecting ducts persisted, but there was necrosis of interstitial cells, loops of Henle and vasa recta (Fig. 8). In some kidneys the lesion was extensive and diffuse, while in others it was small and was sometimes located centrally in the tip of the papilla whereas surrounding tissue was spared. Interstitial cells were completely lost from involved areas, although loops of Henle and vasa recta were rather better preserved.

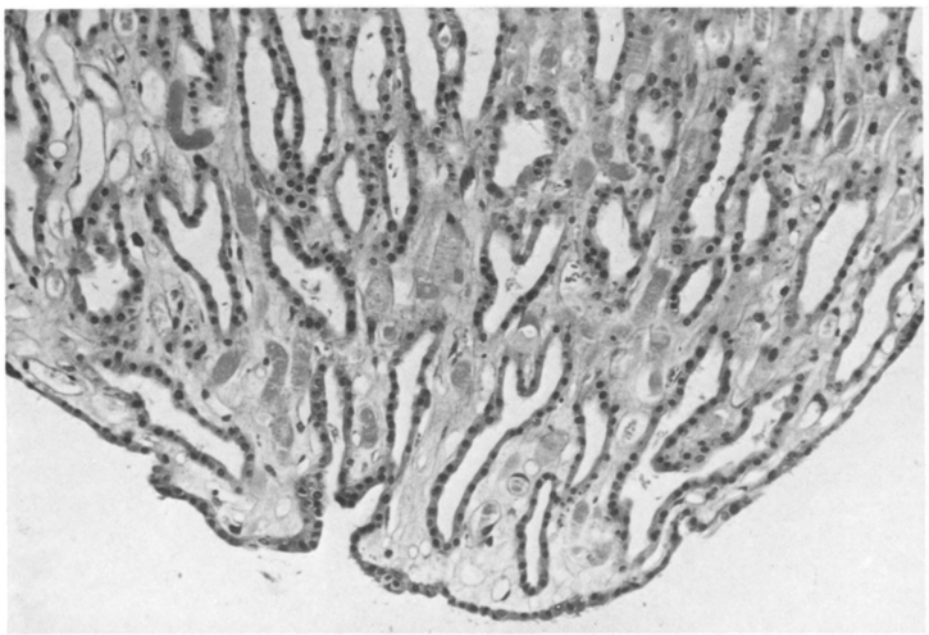

Fig. 8. Photomicrograph of the tip of a renal papilla that appeared macroscopically normal. Subtotal renal papillary necrosis characterized by partial loss of structures other than collecting ducts. H. & E. X150

Only 3 kidneys from 2 rats given BEA were entirely normal in the planes of the longitudinal sections that passed through the tips of the papillae.

Analysis of Body Weights (Table 1). At the beginning of the experiment the means and standard deviations of the body weights of the four groups of animals (controls, those given 80 mg/kg, 125 mg/kg and 250 mg/kg) were, respectively: 198.2 ± 16.8 g, 204.6 ± 15.7 g, 205.8 ± 21.9 g and 207.9 ± 22.5 g. An analysis of variance showed that the body weights of these groups did not differ significantly ($F = 0.701$, $P > 0.2$ for 3, 58 degrees of freedom). At the end of the experiment the means and standard deviations of the body weights of the same four groups were: 242.7 ± 23.1 g, 255.3 ± 22.7 g, 248 ± 22.7 g and 252.1 ± 24.2 g. An analysis of variance again showed that these body weights did not differ significantly ($F = 0.824$, $P > 0.2$ for 3, 54 degrees of freedom).

At the end of the experiment the means and standard deviations of the body weights of the controls, the BEA-treated rats with no macroscopic RPN and the BEA-treated rats that developed macroscopically evident RPN were, respectively: 242.7 ± 23.1 g, 253.0 ± 23.0 g and 250.2 ± 23.1 g. An analysis of variance showed that the body weights of these three groups did not differ significantly ($F = 0.920$, $P > 0.2$ for 2, 55 degrees of freedom).

Thus neither the administration of BEA nor the presence of renal lesions due to BEA had any significant effect on the body weights of the animals.

Table 1. Data concerning body weights of animals in g. BEA no RPN = BEA-treated animals with no macroscopic RPN; BEA RPN = BEA-treated animals that developed macroscopically evident RPN

Group	$\bar{x}$	Σx	Σx^2	n
Zero time				
Controls	198.20	2,973	593,185	15
BEA 80 mg/kg	204.56	3,273	673,255	16
BEA 126 mg/kg	205.80	3,087	642,005	15
BEA 250 mg/kg	207.87	3,326	699,014	16
BEA all doses	206.08	9,686	2,014,274	47
5 months				
Controls	242.66	3,640	890,778	15
BEA 80 mg/kg	255.33	3,830	985,172	15
BEA 125 mg/kg	248.06	3,721	930,287	15
BEA 250 mg/kg	252.07	3,277	833,103	13
BEA all doses	251.81	10,828	2,748,562	43
BEA no RPN	253.00	6,325	1,612,969	25
BEA RPN	250.17	4,503	1,135,593	18

Analysis of Renal Weights. As mentioned above, some extensively scarred kidneys appeared to be abnormally small. Furthermore, when asymmetrical or unilateral scarring occurred, the unscarred or less extensively scarred kidney appeared to be abnormally large in some animals. These observations suggested that unilateral reduction in renal size might be accompanied by contralateral compensatory hypertrophy. A statistical analysis of the renal weights was undertaken to assess the validity of this suggestion.

For the three groups of animals (controls; BEA-treated rats without macroscopic RPN; BEA-treated rats with macroscopic RPN) the following parameters were analysed:

(1) The disparity between the weights of the two kidneys of each animal;
(2) The weights of the smaller kidneys (for each animal, the smaller of the two renal wights);
(3) The weights of the larger kidneys (for each animal, the larger of the two renal weights);
(4) The sum of the weights of the two kidneys of each animal.

Histograms displaying the frequency distributions of these parameters are shown in Figs. 9, 10 and 11.

(1) Disparity Between the Renal Weights. As the histograms in Fig. 9 show clearly that these data are not normally distributed, non-parametric statistical methods were employed:

A. To determine whether or not the three sets of data (from controls; from BEA-treated rats without macroscopic RPN; from BEA-treated rats with macroscopic RPN) were likely to belong to the same population, the Kruskal-Wallis "*H*" test (Kruskal and Wallis, 1952) was used. This test allows the calculation

Table 2. Data concerning body weights in g and absolute renal weights in mg at the end of the experiment A = weight of the larger kidney of each animal; B = weight of the smaller kidney of each animal. BEA no RPN = BEA-treated animals without macroscopic RPN; BEA RPN = BEA-treated animals with macroscopic RPN

Controls			BEA no RPN			BEA RPN		
Body weight	A	B	Body weight	A	B	Body weight	A	B
243	770	730	237	810	780	298	945	940
249	830	710	254	940	770	249	800	770
280	790	690	292	820	735	277	780	605
233	730	660	266	900	740	280	995	680
224	815	740	273	750	710	240	850	585
231	655	655	239	745	710	292	1,210	1,075
272	830	830	268	880	790	273	1,110	285
258	905	800	240	780	715	250	1,060	860
212	740	650	233	845	830	243	1,155	495
207	680	680	241	790	705	240	800	645
222	680	600	233	790	755	238	1,050	580
246	805	695	270	825	825	250	795	750
256	680	650	256	880	870	266	1,160	450
279	930	905	212	630	590	230	685	555
228	835	770	280	760	745	238	740	655
			247	800	690	249	840	525
			230	680	675	214	630	445
			234	815	810	226	1,080	390
			216	740	675			
			246	920	830			
			248	940	900			
			298	1,060	920			
			294	840	790			
			261	690	670			
			257	870	740			

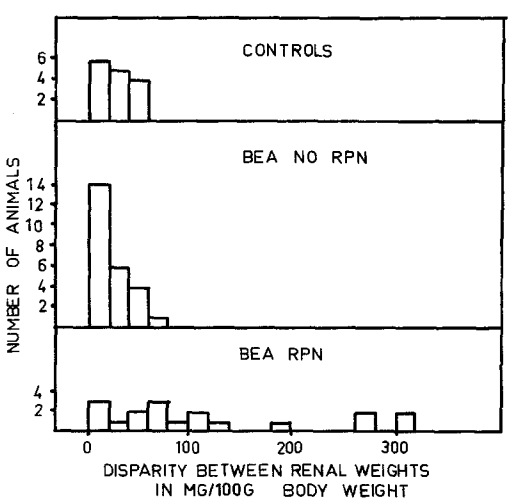

Fig. 9. Histograms showing the distribution of the disparity between left and right renal weights for controls, BEA treated animals without macroscopically evident RPN and BEA treated animals with RPN

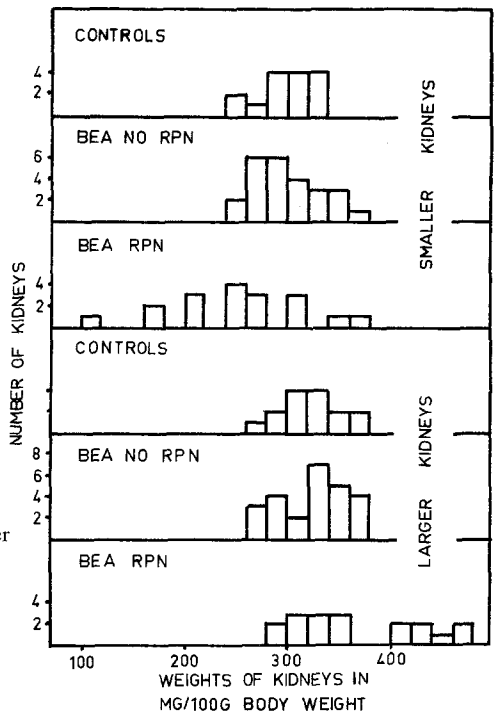

Fig. 10. Histograms showing the distributions of the weights of individual kidneys. The upper three histograms represent, for each animal, the weight of the smaller of the two kidneys; the lower three the weight of the larger of the two kidneys

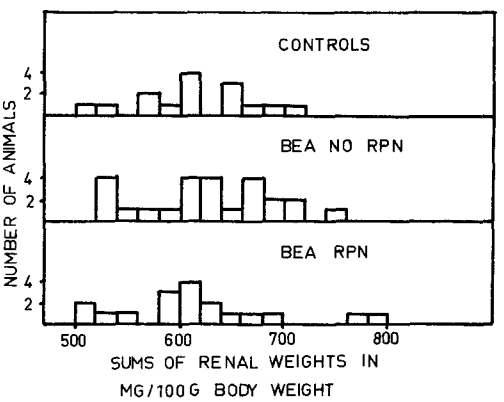

Fig. 11. Histograms showing the distribution of the total renal mass (the sum of the two renal weights) for each animal

of a variable with a distribution approximating that of chi-square with (N-1) degrees of freedom, where N is the number of groups compared.

B. To determine whether or not the data from each of the two groups of rats treated with BEA (those with and those without macroscopic RPN) were likely to belong to the same population as the controls, the Mann-Whitney "U" test (Downie and Heath, 1974) was employed. For the number of animals studied, the U test allows the calculation of a variable which is approximately normally distributed.

Table 3. Results of the analyses of the renal weights

	Groups compared	Test	Significance
Smaller kidneys	CON/BEA no RPN/BEA RPN	ANOVA	$P<0.01$
	CON/BEA no RPN	Modified t	N.S.
	CON/BEA RPN	Modified t	$P<0.01$
Larger kidneys	CON/BEA no RPN/BEA RPN	ANOVA	$P<0.01$
	CON/BEA no RPN	t	N.S.
	CON/BEA RPN	Modified t	$P<0.02$
Combined renal weights	CON/BEA noRPN/BEA RPN	ANOVA	N.S.

ANOVA = one way analysis of variance. N.S. = not significant (i.e.) $P>0.05$. CON = controls; BEA no RPN = BEA-treated animals without macroscopic RPN; BEA RPN = BEA-treated animals with macroscopic RPN

The results of the calculations revealed that the disparity in renal size was highly significantly different among the three groups ($P<0.00005$) and was significantly greater in animals with RPN than in controls ($P<0.002$). The disparity in renal size in the BEA-treated animals without macroscopic RPN did not differ significantly from that in the controls ($P>0.8$).

(2) Weights of the Smaller Kidneys, Weights of the Larger Kidneys and the Combined Renal Weights. Statistical analyses involving relative organ weights (i.e., the ratio organ weight/body weight) require care to avoid erroneous conclusions. The employment of regression analysis or of analysis of covariance have been advocated as possible means of excluding errors of interpretation (Angervall and Carlström, 1963). However, the data for the smaller renal weights, the larger renal weights and the combined renal weights exhibit properties which would appear to abrogate the efficacy and/or the necessity of regression analysis or analysis of covariance. These properties are:

(1) Relatively low correlation coefficients for the relationships between renal weights and body weights.

(2) No significant differences among the body weights of the groups compared.

Therefore, one way analysis of variance was used to compare relative organ weights of the three groups (controls, BEA-treated animals without macroscopic RPN, BEA-treated animals with macroscopic RPN) and a t test or modified t test to compare each of the two BEA-treated groups with the controls. A modified t test was used when the variances of the two groups of data differed significantly (Cochran, 1964, quoted by Snedecor and Cochran, 1967).

The results of these calculations are shown in Table 3, and can be summarized as follows:

(1) The weights of the smaller kidneys differed significantly among the three groups of animals (controls, BEA-treated animals without macroscopic RPN, BEA-treated animals with macroscopic RPN), and were significantly less than those of controls only in rats with macroscopic RPN.

(2) The weights of the larger kidneys differed significantly among the three

groups, and were significantly greater than those of controls only in rats with macroscopic RPN.

(3) The combined renal weights did not differ significantly among the three groups.

It is therefore reasonable to conclude that the production of RPN may be followed by severe scarring and a significant reduction in renal size; that the reduction in renal size observed in this experiment may, in some animals, be unilateral; that unilateral reduction in renal size due to scarring secondary ro RPN may be accompanied by contralateral, compensatory hypertrophy, and that the compensatory hypertrophy is sufficient to maintain the toal renal mass at an approximately normal level.

Discussion

The above findings confirm the experimental observations of others that the production of RPN can be followed by severe cortical scarring (Murray et al., 1972) with reduction in renal size (Davies, 1968). Similar cortical scarring and decreased renal size can occur after the surgical removal of the renal papilla. Furthermore, it was found in the present study that considerable disparity between the weights of the two kidneys occurred and that the disparity appeared to be the result of a significant, unilateral decrease in renal size and of contralateral, compensatory hypertrophy. The hypertrophy appeared to be sufficient to restore the combined renal weight to its normal level. No report which documented renal hypertrophy after experimental RPN was found in the literature. Hypertrophy has been described in human analgesic nephropathy in the columns of Bertin between adjacent scars directly overlying the necrotic papilla (Kincaid-Smith, 1967).

Ham and Tange (1969) and Swales et al. (1973) found some renal cortical scarring but no apparent reduction in renal size 3 months after the production of RPN in rats by the administration of ethyleneimine. If the animals had been maintained for a longer period it is possible that reduction in renal size might have occurred. For example, Lucke and Hunt (1968) found that, after surgical papillectomy in rabbits, the kidneys were slightly contracted after 3 months, severely contracted after 7 months and even more severely contracted after 12 months. The experiment recorded in this paper was planned to take this time factor into account.

Two experiments involving surgical papillectomy in rats did not result in the occurrence of severe cortical scarring. Hardy (1970) found *no* scarring after 90 days. His finding appears to contradict that of Lucke and Hunt (1968), but differences of technique almost certainly explain the apparent contradiction. Lucke and Hunt removed the entire papilla with scissors whereas Hardy, whose objective was to produce minimal renal damage, employed specially modified fine surgical instruments to remove only 20% of the papilla. Hardy found little or no fibrosis of the papillary stump. Xipell and Dawborn (1974) performed unilateral surgical papillectomy in rats with removal of the entire papilla and examined the kidneys at intervals up to 16 weeks later. Eight to 16 weeks after

the surgical procedure, a difference between the weights of the two kidneys from each animal was found. This was due entirely to failure of growth of the kidneys from which the papillae had been removed. These kidneys showed no "gross contraction and scarring" and there was no hypertrophy of the kidneys with intact papillae. In view of the results of the experiment recorded in this paper and the findings of others, quoted above, it would appear that Xipell and Dawborn might not have produced papillary injury which would lead to cortical scarring. Furthermore, if the numbers of animals they studied were approximately equally divided among the groups killed at various times (they do not state this), then there could have been no more than 5 rats examined 16 weeks after removal of the papilla. The previous group was examined after 12 weeks, by which time no apparent reduction in renal size had been noted after the induction of RPN with ethyleneimine by others (Ham and Tange, 1969; Swales et al., 1973). Thus, only 5 animals might have been expected to show evidence of renal scarring and decreased renal size.

The complete absence of renal cortical scarring in controls in the present study suggests that the scarring BEA-treated rats is entirely a consequence of the RPN. The appearances of the scars – diffuse and severe tubular atrophy in the affected areas, thickening of tubular basement membranes, interstitial lymphocytic infiltrations and crowding of undamaged or minimally damaged glomerule – are identical to those that may be seen in human analgesic nephropathy.

Murray et al. (1972) suggested that the cortical scarring that they observed in rats after the production of RPN with BEA was caused by obstruction in the thin limbs of the loops of Henle when these became necrotic. The results of the present study do not support this hypothesis. Twenty-three animals given BEA developed subtotal RPN. Only two of these animals developed minor cortical scars, unilateral in each case. It is conceivable that minor scarring may result from the consequences of necrosis of the loops of Henle, but not the gross scarring associated with a reduction in renal size. A similar association has been described in intermediate papillary necrosis in human analgesic nephropathy: little or no cortical scarring may occur in this lesion, which is the human analogue of subtotal RPN produced in animals in the model of experimental RPN studied in the present investigation.

The impression was gained, both from the macroscopic and the microscopic examination of the kidneys, that cortical scars lay above areas of dense fibrosis and extensive excavation of the medulla in kidneys with RPN, whereas little or no fibrosis and relatively less medullary excavation were seen beneath normal areas of cortex. These observations suggest that obliteration of tubules may be associated with the development of the fibrosis in the medulla. In the most densely fibrotic areas of the medulla beneath cortical scars, no normal loops of Henle or collecting ducts could be seen. Conceivably, obstruction in both of these structures could contribute to the cortical scarring.

Murray et al. (1972) observed that the ventral and dorsal surfaces of the kidneys near the hilum often exhibited no scarring. In the present experiment, the kidneys were bisected in the coronal plane (i.e., the plane perpendicular to that in which Murray et al. bisected their kidneys). However, it was observed

that the poles of the kidneys were often not scarred, and that less excavation and fibrosis occurred in the portions of the medulla draining the poles. It is possible that this distribution of necrosis and the subsequent excavation and fibrosis is the factor that determines the location of the cortical scarring. The validity of this proposal, both for experimental and for human RPN, could be assessed only by further careful morphological study of the animal and the human lesions.

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