J. Physiol. (1977), **269**, *pp.* 627–641
With 6 *text-figures*
Printed in Great Britain

NUMBER OF GLOMERULI IN NORMAL AND HYPERTROPHIED KIDNEYS OF MICE AND GUINEA-PIGS*

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(*Received 15 October 1976*)

SUMMARY

1. In mice and guinea-pigs, the number of glomeruli was counted in kidneys during normal growth and in hypertrophy induced by unilateral nephrectomy.

2. In mice, the number of glomeruli increased sharply during the first 2 weeks of life, and more slowly afterwards. Unilateral nephrectomy, when performed during this period of natural increase, induced the formation of supplementary nephrons in the contralateral kidney.

3. In guinea-pigs, the number of glomeruli was almost complete at birth. No evidence of a supplementary increase in the number of nephrons was found in hypertrophied kidneys following unilateral nephrectomy.

4. These results, together with previous data obtained in the rat, suggest that the ability to induce new nephrons after unilateral nephrectomy in different species would depend more on the state of kidney maturity at birth than on differences in the renal mechanisms which lead to hypertrophy.

INTRODUCTION

In mammals, unilateral nephrectomy is followed by compensatory hypertrophy of the contralateral kidney. The extent to which this renal response includes development of new nephrons, as indicated by an increase in the number of glomeruli, has been controversial. In a general review of the literature, Hinman (1926) summarized earlier work indicating agreement on the absence of increase in the number of glomeruli after

* This work has already been partly presented at the XXVIth International Congress of Physiological Sciences (New Delhi, 1974). It was supported by a grant Inserm 75.5.135.5.

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unilateral nephrectomy in adult animals: the rabbit (Mauchle, 1894; Fiori, 1901; Galeotti & Villa Santa, 1902; Zanetti, 1911; Oliver, 1924), the dog (Fiori, 1901; Galeotti & Villa Santa, 1902; Hinman, 1922), the guinea-pig (Fiori, 1901); but with disagreement concerning young animals: an increase in young rabbits (Tizzoni & Pisenti, 1883; Lorenz, 1886; Galeotti & Villa Santa, 1902; Zanetti, 1911), no increase in young rabbits and dogs (Ribberts, 1882) nor in young rats (de Benedetti, 1911). In the same year, Arataki (1926*b*) found no evidence of an increase in the number of nephrons during compensatory renal hypertrophy in either the adult or young rat. This finding was generally accepted until recently (see Nowinski & Goss, 1969).

The problem has been extensively reinvestigated in the rat, where there is now general agreement that compensatory hypertrophy of the remaining kidney occurs after unilateral nephrectomy in both young and adult animals (as shown by Bonvalet, Champion, Wanstok & Berjal, 1972; Imbert, Berjal, Moss, Rouffignac & Bonvalet, 1974; Canter & Goss, 1975; Kaufman, Hardy & Hayslett, 1975; Kunes, Karen, Capek & Jelinek 1976), but that in the adult rat this is not accompanied by a significant increase in the number of nephrons (Bonvalet *et al.* 1972; Imbert *et al.* 1974; Canter & Goss, 1975; Kaufman *et al.* 1975; Kunes *et al.* 1976).

However, some disagreement still exists concerning any increase in the number of glomeruli after nephrectomy in the young rat, where assessment of any change is complicated by the occurrence of a spontaneous increase in the number of glomeruli as a feature of normal renal growth (Bonvalet *et al.* 1972; Canter & Goss, 1975; Kaufman *et al.* 1975; Kunes *et al.* 1976). We found (Bonvalet *et al.* 1972) that unilateral nephrectomy in young rats was followed by an increase in the number of glomeruli in the remaining kidney. This phenomenon was observed only during the first 40–50 days after birth, that is during the period in which the number of glomeruli normally increases (Arataki, 1926*a*; Bonvalet *et al.* 1972). It was not found after this age although an increase in kidney weight was still observed. These results were confirmed by Canter & Goss (1975) and Kunes *et al.* (1976), but challenged by Kaufman *et al.* (1975). They all used glomerular counting techniques. In only one study (Imbert *et al.* 1974), physiological methods (micropuncture and ferrocyanide infusion techniques) were used to determine the number of nephrons in hypertrophic kidneys: the results indicate the development of new functional nephrons after nephrectomy, in the young (but not in the adult) rat.

In species other than the rat, no recent work on the evolution of the number of glomeruli in growing animals and after unilateral nephrectomy has been performed, and the only available data are those quoted earlier.

In view of our results concerning the number of glomeruli during renal hypertrophy in the rat, and of the paucity of recent work on other species, the present study was undertaken to determine whether an increase in the number of glomeruli following unilateral nephrectomy also exists in species other than the rat, and if induction of new nephrons could be related to species differences in the development pattern of the kidney.

METHODS

Experiments were performed on 144 mice belonging to thirteen litters, and fifty guinea-pigs (seventeen litters plus two 2-day old guinea-pigs). From these animals, studies were performed on 273 mouse kidneys and ninety-one guinea-pig kidneys. Each litter was divided into two groups: one group was unilaterally nephrectomized, either on the left or on the right side, at ages ranging from 2 to 65 days; the other group served as control. Animals from the same litter were kept in the same cage, and were fed the same diet. All animals were killed at the age of 90 days. Thus, three categories of kidney were obtained: 'young control' kidneys (removed between the 5th and the 65th day), hypertrophied kidneys removed at the 90th day from the same animals, and kidneys removed at 90 days from adult control animals.

After removal, each kidney was decapsulated and weighed. The number of glomeruli per kidney was determined using the method of Damadian, Shawayri & Bricker (1965): details have been given in a previous publication by Bonvalet *et al.* (1972). The kidneys were macerated in a 50% (vol./vol.) HCl solution at 37° C for 90 min (mice) or 120 min (guinea-pigs). Each kidney was kept in distilled water (100 ml. for mice; 500 ml. for guinea-pigs) at 4° C for 1 day before glomerular counts were performed. For each kidney, two to four 1 ml. aliquot portions were counted, and the variation coefficient of individual counts from the mean was determined: the over-all mean of these variation coefficients was 5·0% ± 0·3 S.E. of mean and 4·3% ± 0·4 for mice and guinea-pigs respectively.

In order to assess whether methodological problems could account for the discrepancies between Kaufman's results (Kaufman *et al.* 1975) and those reported by several groups (Bonvalet *et al.* 1972; Canter & Goss, 1975; Kunes *et al.* 1976) in the young rat, we performed glomerular counts according to Kaufman's technique (Kaufman *et al.* 1975) which involves the counting of ten 50 μl. aliquot portions of a macerated kidney tissue suspension, after previous formaldehyde fixation. Four control kidneys of 90-day-old rats were compared to four hypertrophied kidneys of 90-day-old rats unilaterally nephrectomized at 30 days. We found 27,970 ± 713 S.E. of mean glomeruli in control and 34,340 ± 608 S.E. of mean in hypertrophied kidneys ($P < 0.001$). Thus we confirm by this technique our previous results. However it can be remarked that these figures are lower than those obtained in the rat by our own technique (Bonvalet *et al.* 1972; Canter & Goss, 1975). Consequently, it appears that if different methods may influence absolute values, they should not mask a difference in the number of glomeruli between two series of kidneys. From a more general point of view, it is easily conceivable that maceration methods could underestimate the number of glomeruli (for example, following an overmaceration) but it is difficult to imagine that they could lead to artificially high figures. In addition, high figures in hypertrophied kidneys have also been found using completely different, physiological, methods. It is also difficult to explain discrepancies by simple strain differences since Canter & Goss (1975) and Kaufman *et al.* (1975) who both used Sprague Dawley rats reached different conclusions. We confess that, at the present time, no satisfactory methodological explanation can be advanced. Detailed examination of experimental conditions (difference in the colonies of rats used, feeding and breeding conditions, etc.) would be necessary to elucidate this problem.

RESULTS

Mouse

No weight differences between left and right kidneys were found in control animals, as previously reported by Rosen & Cole (1960). There was no significant difference between the weights of hypertrophic kidneys after left or right side nephrectomy. Thus, left and right kidneys were considered together. The kidney weights of 90-day-old mice are given in Table 1. A great difference was observed between males and females, both

TABLE 1. Weight of control and hypertrophied kidneys of adult male and female mice. The number of kidneys is given in brackets. In the right column, the mean value of the percentage increase in weight of hypertrophied (as compared to control) kidneys in each litter is indicated

Mouse

	Control (90 days)	Hypertrophy (90 days)	% increase
Male	235 ± 4 S.E. of mean (n = 50)	350 ± 7 (n = 42)	49
Female	152 ± 3 (n = 38)	230 ± 5 (n = 29)	51

Kidney weight (mg)

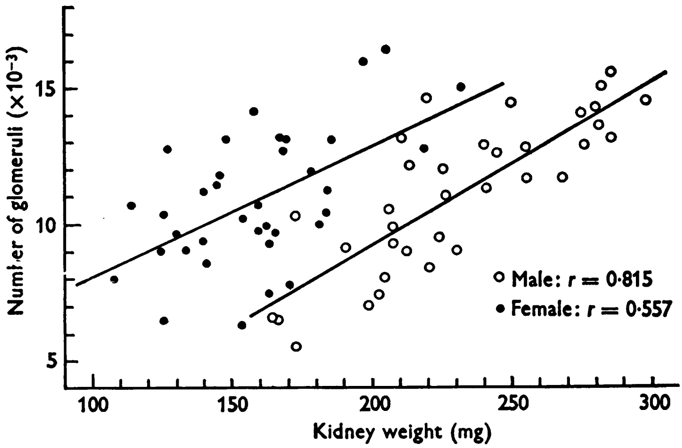

Fig. 1. Number of glomeruli against kidney weight in control 90-day-old mice. Regression lines of positive correlations obtained are given for male and female. The correlations were statistically significant in both cases ($P < 0{\cdot}01$).

in control and in hypertrophied kidneys. However, the percentage increase in kidney weight after contralateral nephrectomy was similar in both sexes.

In contrast, no significant difference in the number of glomeruli was found between males and females. In Fig. 1, the number of glomeruli in

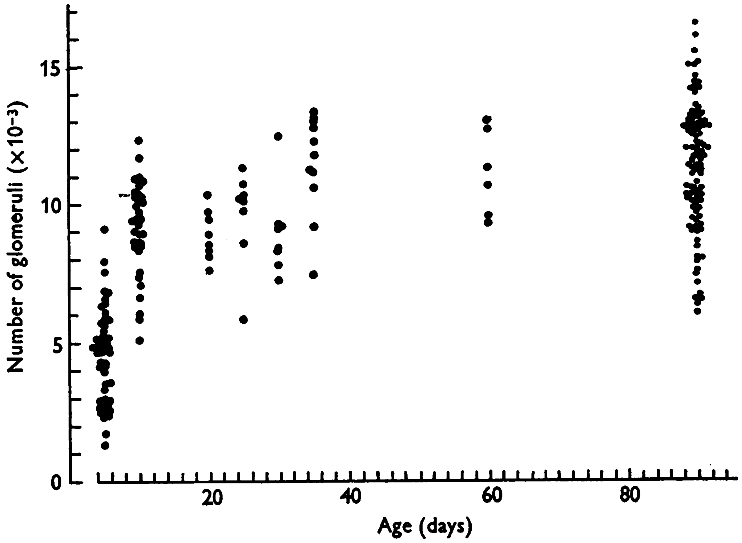

Fig. 2. Number of glomeruli in kidneys of normal growing mice as a function of age.

TABLE 2. Weight of control and hypertrophied kidneys of adult male and female guinea-pigs. The number of kidneys is given in brackets. In the right column, the mean value of the percentage increase in weight of hypertrophied (as compared to control) kidneys in each litter is indicated

	Guinea-pig		
	Control (90 days)	Hypertrophy (90 days)	% increase
Male	2·601 ± 0·056 s.e. of mean (n = 20)	3·617 ± 0·144 (n = 15)	39
Female	2·163 ± 0·069 (n = 12)	3·030 ± 0·154 (n = 10)	40
	Kidney weight (g)		

the kidneys of 90-day-old control animals has been plotted against the kidney weight. It is clear that the number of glomeruli is in the same range for males and females, despite the differences in kidney weight. When males and females are considered separately, a significant correlation between kidney weight and the number of glomeruli is observed within each population ($P < 0{\cdot}01$ in both sexes).

Fig. 2 and Table 2 show the number of glomeruli as a function of age in normal control animals. Males and females were considered together. A sharp increase was observed during the first 10 days after birth, followed by a much slower rise up to the age of 90 days. Mean values are 4369 ± 283 S.E. of mean ($n = 27$) at 5 days, 8165 ± 384 ($n = 43$) at 10 days, and $12{,}083 \pm 1009$ ($n = 88$) at 90 days.

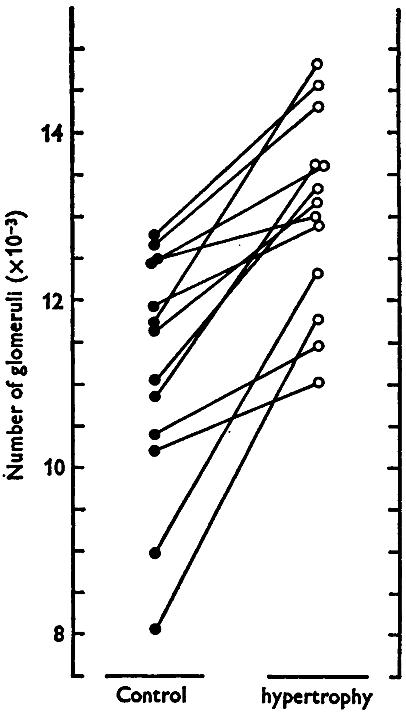

Fig. 3

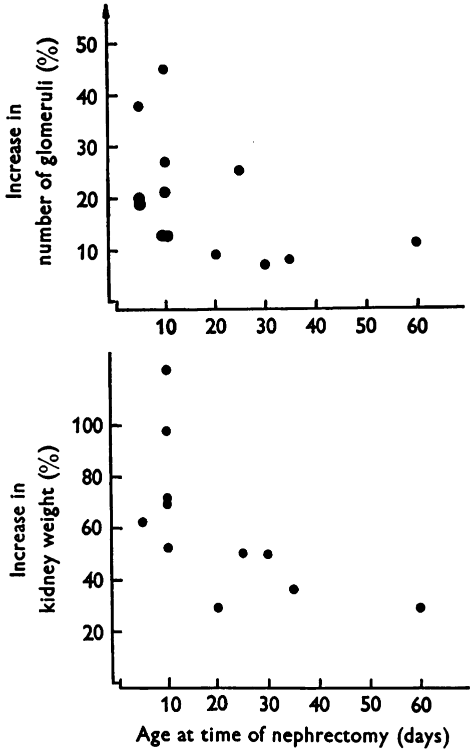

Fig. 4

Fig. 3. Comparison of the number of glomeruli in control and hypertrophied kidneys of mice at 90 days. Each point represents the mean value for one litter. Values of hypertrophied and control kidneys of the same litter are connected by a continued line.

Fig. 4. Percentage increase in number of glomeruli (upper graph) and kidney weight (lower graph) in hypertrophied (as compared to control) kidneys, according to the age of mice at the date of unilateral nephrectomy. Each point represents one litter. For two litters, hypertrophic and control kidneys did not belong to animals of the same sex, so that we could not establish a valuable percentage increase in kidney weight (see text).

Fig. 3 and Table 3 give the mean values of the number of glomeruli in hypertrophied and control kidneys for each litter. In each case, this number is higher for hypertrophied kidneys. The difference between hypertrophied and control kidneys is significant (paired t test) when considering the total population ($t = 7{\cdot}87$, $P < 0{\cdot}001$), or when considering separately nephrectomies performed on the 5th day ($t = 8{\cdot}41$, $P < 0{\cdot}02$), up to the 10th day ($t = 9{\cdot}47$, $P < 0{\cdot}001$) or after the 20th day ($t = 3{\cdot}84$, $P < 0{\cdot}02$).

Fig. 4 shows the percentage increase in kidney weight and number of

TABLE 3. Number of glomeruli in hypertrophied and control mice kidneys. Mean values of the number of glomeruli for each litter in kidneys of young control animals (young control), 90-day-old control animals (adult control) and in hypertrophied kidneys of animals killed at 90 days are shown. The last column gives the percentage increase of the number of glomeruli in hypertrophied (as compared to adult control) kidneys. Numbers in brackets indicate the number of kidneys studied

Litter no.	Age at nephrectomy (days)	Number of glomeruli: Young control	Adult control	Hypertrophy	% Increase Hypertrophy versus adult control
1	5	5,339 (12)	12,200 (9)	14,581 (5)	19
2	5	2,645 (8)	8,925 (6)	12,317 (3)	38
3	5	4,057 (7)	12,567 (6)	15,000 (5)	19
4	10	5,131 (7)	11,613 (8)	13,175 (4)	13
5	10	10,280 (6)	12,675 (7)	14,375 (7)	13
6	10	8,900 (13)	8,070 (10)	11,766 (6)	45
7	10	10,475 (5)	11,062 (2)	13,375 (4)	21
8	10	8,436 (12)	11,675 (8)	14,812 (8)	27
9	20	8,874 (8)	12,466 (6)	13,633 (6)	9
10	25	9,597 (8)	10,842 (6)	13,600 (6)	25
11	30	8,953 (8)	10,206 (8)	11,037 (8)	7
12	35	11,437 (12)	11,937 (8)	12,875 (6)	8
13	60	11,075 (6)	10,350 (4)	11,466 (3)	11

TABLE 4. Number of glomeruli in kidneys of hypertrophied and control guinea-pigs. Mean value of the number of glomeruli for each litter in kidneys of young control animals (young control), 90-day-old control animals (adult control) and in hypertrophied kidneys of animals killed at 90 days is shown. The last column gives the percentage increase of the number of glomeruli in hypertrophied (as compared to adult control) kidneys. Numbers in brackets indicate the number of kidneys studied

Litter no.	Age at nephrectomy (days	Number of glomeruli: Young control	Adult control	Hypertrophy	% Increase Hypertrophy versus adult control
1	5	—	114,875 (2)	128,000 (1)	+11
2	10	101,500 (1)	118,125 (2)	117,250 (1)	− 1
3	10	98,000 (1)	103,500 (2)	105,000 (1)	+ 1
4	15	83,000 (2)	100,200 (2)	98,500 (2)	− 2
5	15	83,500 (1)	104,625 (2)	100,250 (1)	− 4
6	20	66,500 (2)	99,000 (2)	98,000 (2)	− 1
7	20	98,750 (2)	94,750 (2)	115,000 (1)	+21
8	25	88,625 (2)	88,375 (2)	68,140 (1)	−22
9	35	82,000 (2)	72,750 (2)	92,250 (2)	+26
10	35	86,375 (2)	94,750 (2)	115,000 (1)	+21
11	40	64,750 (2)	90,750 (2)	97,750 (2)	− 8
12	40	93,750 (1)	— —	110,750 (2)	—
13	50	114,500 (1)	85,500 (2)	118,500 (1)	+33
14	65	92,166 (3)	115,000 (2)	121,500 (1)	+ 6
15	65	85,500 (3)	92,250 (2)	94,250 (2)	+ 2
16	65	102,916 (3)	109,375 (2)	94,333 (3)	−13
17	80	117,500 (1)	81,000* (2)	61,000* (1)	−25

* Sacrifice at 100 days.

glomeruli of hypertrophied kidneys (as compared to controls) for each litter, as a function of age at which the unilateral nephrectomy was performed. It appears that the increase in the number of glomeruli following nephrectomy is quantitatively important, mainly when nephrectomy was performed during the first days of extramaternal life, and is reduced to about 10 % when nephrectomy was performed after 30 days of age. The data in Table 3 show that the absolute increase in the number of glomeruli is similarly reduced with age. The increase in kidney weight was never less than 30 %. As observed for the number of glomeruli, this increase was more marked in early nephrectomized animals.

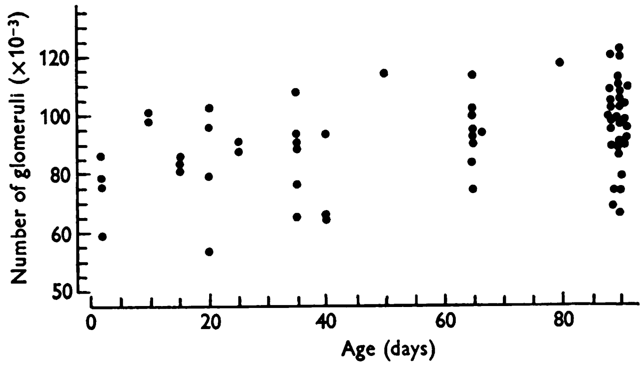

Fig. 5. Number of glomeruli in kidneys of normal growing guinea-pigs, as a function of age.

Guinea-pig

There was no significant difference in weight between right and left kidneys. Kidney weight was lower in females than in males, but the difference was less marked than in mice, as shown in Table 2. Again, the percentage increase in kidney weight after contralateral nephrectomy was similar for both sexes. A positive relationship seems to exist between kidney weight and number of glomeruli for control kidneys of 90-day-old males but the correlation coefficient was of borderline significance ($r = 0{\cdot}3795, 0{\cdot}10 > P > 0{\cdot}05, n = 20$). No significant difference in the number of glomeruli was found between males and females at 90 days (male: 97,150 ± 3801, $n = 20$; female: 100,345 ± 3150, $n = 12$). The number of glomeruli as a function of the age is given in Table 4 and Fig. 5. There was a slight increase from birth to 90 days: mean values of the number of glomeruli from birth up to 20 days (83,038 ± 4110 S.E. of mean) and at 90 days (98,348 ± 2633 S.E. of mean) were significantly different ($P < 0{\cdot}01$). However, the increase is slow and of less quantitative significance than in mice (cf. Fig. 2).

No consistent difference in the number of glomeruli was observed in hypertrophied kidneys when compared to control kidneys at 90 days (Fig. 6 and Table 4). Mean values were 98,348 ± 2633 S.E. of mean ($n = 32$) and 100,736 ± 3021 ($n = 25$) for control and hypertrophied kidneys, respectively. The age at the time of unilateral nephrectomy had no consistent influence on the number of glomeruli in hypertrophied kidneys. Expressed as a percentage of the number of glomeruli in control kidneys for each litter, the change in hypertrophied kidneys was +3·4 % ± 3·7 S.E. of mean when nephrectomy has been performed up to 20 days of age, and +4·6 %

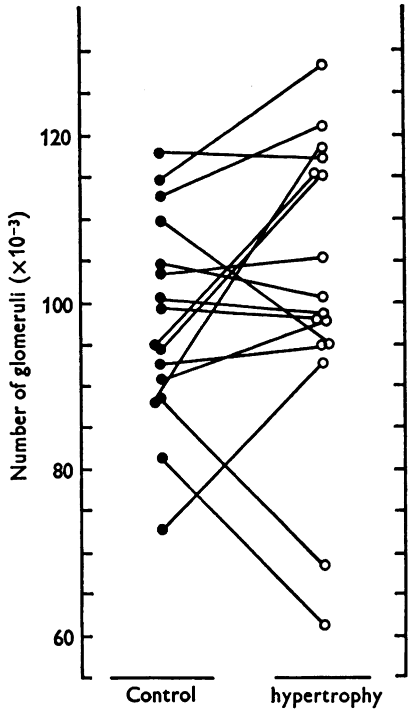

Fig. 6. Comparison of the number of glomeruli in control and hypertrophied kidneys of guinea-pigs. Each point represents the mean value for one litter. Values of hypertrophied and control kidneys of the same litter are connected by a continuous line.

± 6·2 after this age. Neither difference was significant. In contrast with data concerning the number of glomeruli, the sex dependence of kidney weight meant that it was not possible to consider males and females together. In addition, because of the small litters, a statistical analysis of the increase in kidney weight in hypertrophied (as compared with control) kidneys was not possible in most cases.

DISCUSSION

In both the species studied, the kidney was heavier in males than in females. This difference has already been reported in mice (Malt & Lemaitre, 1968). There was, however, no sex difference for the number of glomeruli in either species, which suggests that nephron size is greater in males.

The percentage increase in the weight of hypertrophic kidneys was similar in males and females in both species, which confirms the results already obtained in mice by Malt & Lemaitre (1968). The degree of hypertrophy was more pronounced in mice than in guinea-pigs. The results obtained in mice are comparable to those reported in the literature (Hinman, 1926; Rosen & Cole, 1960; Malt & Lemaitre, 1968; Paulson & Fraley, 1973), and in accordance with several previous observations in various species (MacKay, MacKay & Addis, 1932; Verzar & Hugin, 1957; Dicker & Shirley, 1973; Imbert *et al.* 1974; Canter & Goss, 1975; Kaufman *et al.* 1975). In the guinea-pig, the small number of animals per litter and the absolute necessity of matching sexes rendered impossible a systematic study of the percentage increase in kidney weight as a function of the age at nephrectomy. Fortunately, the absence of sex difference for number of glomeruli allows us to pool together the results obtained in males and females.

During the period of normal kidney growth, the evolution of the number of glomeruli follows a very different pattern in mice and in guinea-pigs. In guinea-pigs, there is a small, slow and uniform increase in the number of glomeruli (Fig. 5). In contrast, in mice there is a sharp increase in the number of glomeruli during the first days of life as the number of glomeruli doubles between 5 and 10 days of age, and then the increase becomes slower but is still more pronounced than in guinea-pigs (Fig. 2). Although all animals were killed at 90 days (when they are adult) we cannot affirm that the number of glomeruli has reached a plateau by this age, and that it does not continue to rise slightly. The figures we found for guinea-pigs are in good accordance with that found by Merlet-Benichou & Rouffignac (1977), but are much higher than the values reported for three animals by Spitzer & Brandis (1974). To our knowledge, no figure for the number of glomeruli in mice has yet been published.

After unilateral nephrectomy in guinea-pigs, no consistent change in number of glomeruli was observed (Fig. 6), whereas a clearcut increase occurred in mice (Fig. 3). For this latter species, the increase in the number of glomeruli of hypertrophic kidneys was more marked in animals nephrectomized during the first 10 days of life. This variation in the magnitude of the response to unilateral nephrectomy resembles that observed for kidney weight (Fig. 4) and it can be seen that the period during which unilateral nephrectomy induces the highest increase in the number of glomeruli of hypertrophic kidneys corresponds to the period of sharp natural increase in the number of glomeruli of control kidneys (Fig. 2). A similar observation has already been reported (Imbert *et al.* 1974; Canter & Goss, 1975) in the rat, where the supplementary nephron production after unilateral nephrectomy also occurs during the period of natural increase in the number of glomeruli, that is until 40–50 days of age. After this age in the rat, the number of glomeruli reached a plateau (Arataki, 1926*a*; Bonvalet *et al.* 1972), and unilateral nephrectomy does not induce the production of new nephrons (Bonvalet *et al.* 1972; Canter & Goss, 1975). Our findings in the mouse are somewhat different since unilateral nephrectomy could induce the production of small numbers of supplementary nephrons after the period of sharp natural increase in the number of glomeruli.

Guinea-pigs are very different from mice, both in the natural evolution of the number of glomeruli and in their response to unilateral nephrectomy: there was only a small, slow (though sustained) increase in the number of glomeruli after birth, and unilateral nephrectomy at any age did not induce new nephron production.

It has already been stated that compensatory renal hypertrophy in young animals differs to a certain extent from that in adults. Increase in kidney weight is more pronounced in young animals (MacKay *et al.* 1932; Verzar & Hugin, 1957; Dicker & Shirley, 1973; Imbert *et al.* 1974; Canter & Goss 1975; Kaufman *et al.* 1975). Two authors (Arataki, 1926*b*; Braun-Menendez, 1946) however did not report this observation. It is interesting to note that Arataki, who found an equal degree of hypertrophy in young and adult animals, could not show an increase in the number of glomeruli in the hypertrophic kidneys of young animals. The RNA/DNA ratio in the remaining kidney after unilateral nephrectomy is lower in young than in adult animals (Brasel, 1972; Dicker & Shirley, 1973). This suggests that the relative contribution of hyperplasia is more important in the compensatory growth of the kidneys of young animals. Antipova (1966) showed that thymidine incorporation following unilateral nephrectomy in young rats was specifically located within nephrogenic areas. Brasel (1972), using D.N.A. polymerase as an index of hyperplasia, showed that there was a much more important increase in early nephrectomized rats as compared to late nephrectomized rats. These different works indicate that there is certainly a difference between the hypertrophy of immature (as compared to mature) kidneys and, although not contributing direct evidence of new nephron production are compatible with our findings.

When one compares the pattern of increase in the number of glomeruli observed in different species, it can be seen that the maturational state of the kidney differs at birth according to the species considered. In guinea-pigs, the number of glomeruli is almost at its maximum at birth, whereas in rats and mice there is still a more or less long period during which the number of glomeruli increases. Such species differences in the maturational state of the kidney at birth, either anatomically or physiologically, have been reported by several authors (Dicker, 1952; Oliver, 1968; Dicker & Shirley, 1971). The rat kidney, in particular, is known to be very immature at birth (Heller, 1947; McCance & Wilkinson, 1947; Dicker, 1952; Falk, 1955; Bogomolova, 1965; Dicker & Shirley, 1971) whereas in the guinea-pig the maturation of the kidney seems to be almost, completed (Dicker & Heller, 1951; Dicker & Shirley, 1971). It is conceivable that, after birth, the presence or absence of ability to produce supplementary nephrons after unilateral nephrectomy would depend more on the maturational state of the kidney at birth than on species differences in renal mechanism leading to hypertrophy. The period after birth, during which nephrogenic zones are present, has been diversely estimated (Baxter & Yoffey, 1948; Muhlenfeld, 1969; Goncharevskaya & Dlouha, 1975). In the mouse, Litvak & Baserga (1964) showed that thymidine incorporation in kidneys is much higher in young animals up to 10 days of age than afterwards. This incorporation is specifically located in nephrogenic zones and corresponds to the formation of new nephrons. Studies in the rat indicate the persistence of nephrogenic areas until approximately the 3rd or 4th week of life (Baxter & Yoffey, 1948; Boss, Dlouha, Kraus & Krecek, 1963). Thus, in species where nephrogenesis is not completed at birth, such as the rat and the mouse, unilateral nephrectomy in young animals would be a stimulus for production of supplementary nephrons from the persistent nephrogenic areas in the remaining kidney.

In conclusion, our results in the mouse and in the guinea-pig indicate that the ability of unilateral nephrectomy to induce supplementary nephrons in the contralateral kidney is present in mice but not in guinea-pigs. This ability is considered to be related to the maturational state of the kidney at birth, which is different in the two species considered.

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