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Research Article

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Functional and Morphologic Maturation of the Superficial Nephrons

RELATIONSHIP TO TOTAL KIDNEY FUNCTION

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ABSTRACT The functional and morphologic pattern of superficial nephron development was studied in guinea pigs ranging in age between 2 h and 38 days. Concomitent measurements of total kidney function and glomerular counts were also performed.

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INTRODUCTION

Both the ontogeny and phylogeny of the kidney are characterized by a centrifugal pattern of change; the first nephrons to form are those in the juxtamedullary area, and the last, the superficial ones (1–4). Studies of intrarenal distribution of blood flow performed in growing animals have shown a disproportionately high increase with time in the superficial cortical component (5–7). It is not known if the same sequence of events characterizes the increase in glomerular filtration rate which occurs in early life. The problem is of particular significance in view of functional differences shown to exist between superficial and juxtamedullary nephrons (8–10). The first purpose of this study was to answer this question by measuring superficial nephron glomerular filtration rate (SNGFR)[1] and total kidney glomerular filtration rate (TKGFR) and comparing the quantitative relationship between them at various ages.

Another major change that occurs in the developing kidney arises as a consequence of differential rates of glomerular and tubular growth, the anatomical relationship between glomeruli and tubules early in life being in the direction of glomerular preponderance. During maturation, because of more rapid growth of tubules, the ratio gradually assumes that observed in the adult (4). It has been suggested that the early morphologic glomerular preponderance is paralleled by functional glomerular preponderance (11–13). A second purpose of this study, therefore, was to examine the relationship between glomerular filtration and tubular reabsorption during this

[1] *Abbreviations used in this paper:* EFP, effective filtration pressure; GBF, glomerular blood flow; SNGFR, superficial nephron glomerular filtration rate; TKGFR, total kidney glomerular filtration rate; Tm_G, maximal rate of glucose reabsorption.

critical period of development in order to determine if there is in fact a marked deviation from the adult pattern.

These studies were performed in guinea pigs because this animal, like the human, but unlike most of the other mammals, is born with a full complement of functional nephrons.

The results obtained indicate that during postnatal life the kidney continues to develop from the center toward the periphery, the superficial nephrons being the last ones to reach mature levels of glomerular filtration. The increase in TKGFR initially appears to be a consequence of a major increase in the filtration rate of the deep nephrons, whereas after 2–3 wk of age the main contributors to the rise in TKGFR are the superficial nephrons.

The study also shows that proportionality between filtration and reabsorption is maintained throughout development and that in the increase in proximal tubular reabsorption is directly proportional to the increase in proximal tubular length. This would suggest that no appreciable change in intrinsic reabsorptive capacity occurs with age.

METHODS

Studies were performed in 32 guinea pigs, ranging in age between 2 h and 38 days and in weight between 81 and 315 g. In order to ensure accurate determination of the age of the experimental animals, pregnant guinea pigs were obtained and delivery of the offspring took place in our animal quarters.

The preparation of the animals was similar to that described previously (14). Isotonic saline (0.9% NaCl), containing [^{14}C]carboxyl inulin in concentrations calculated to deliver 60 μCi/h in the 1st wk of life, 50 μCi/h during the 2nd wk, and 40 μCi/h thereafter, was infused throughout the experiment at a rate of 0.3–0.8 ml/h according to the weight of the animal. The relatively high rate of administration of isotope during the newborn period was made necessary by the low glomerular filtration rates prevailing at this age. Blood samples were obtained from the arterial catheter, which was also used to record mean arterial pressure.

After a 30 min period of equilibration, timed collections of proximal tubular fluid were obtained. Special care was taken to avoid the use of negative pressure during the collections and to prevent retrograde leak by adequate blocks of mineral oil. The volume of the tubular fluid samples was measured in constant-bore pipettes. Because of the effect of lissamine green on reabsorption (15, 16) and the sensitivity of the newborn animals to the toxic effects of this substance,[2] its use was kept at a minimum. As a consequence, only some of the collections were "late proximal." Transit time was taken as the interval between the diffuse staining of the kidney surface and the appearance of the dye in the tip of the collecting pipette. Simultaneous timed collections of urine and specimens of blood were obtained. At the end of the experiment the renal pedicle of the left kidney was clamped and the kidney removed and weighed on a Mettler H20 T analytical balance (Mettler Instrument Corp., Princeton, N. J.). The organ was then placed in an oven (Thelco model 16, Precision Scientific Co., Chicago, Ill.) at 38°C and left until it achieved constant weight.

The concentration of radioactively labeled inulin was determined in a Packard Tricarb scintillation counter (Packard Instrument Co., Inc., Downers Grove, Ill.). All samples in which the total count was not at least twice background were discarded.

TF/P_{In} and U/P_{In} ratios were used to calculate single nephron and total kidney GFR. Absolute fluid reabsorption by a single tubule was calculated from SNGFR minus V, in which V represents the volume of fluid collected in nanoliters per minute. Work in progress in this laboratory indicates that inulin is a valid marker of glomerular filtration in the newborn guinea pig.

Glomerular number was determined according to the method of Damadian, Shawayri and Bricker (17) as modified by Kaufman and Hayslett.[3] India ink (Gunther Wagner Special Ink) in an amount of 0.5 ml was injected slowly through a catheter inserted into the carotid artery. Each kidney was removed, weighed, divided in small pieces, and placed in a 25% solution of HCl at 50°C. The period required for digestion varied between 60 and 150 min, according to the age of the animal. At the end of this period the preparation was diluted with distilled water to 20 ml and cooled to 4°C to stop digestion. The suspension was then stirred mechanically until the mixture appeared homogeneous, and 10 aliquots of 50 μl each were drawn into volumetric pipettes from various levels of the homogenate. The content of each pipette was deposited on a glass slide and the number of glomeruli was counted in the entire volume of the sample under a dissecting microscope (magnification 40 ×). The number obtained in the aliquots was averaged, and the total number of glomeruli was calculated by multiplying the result by the dilution factor (400).

Microdissection of the proximal tubules was performed according to the method of Dawson (18), as modified by Wahl and Schnermann (19).

The regression curves were calculated to the least square fit by a polynomial (20). The computer program used for this purpose (POLFIT) is part of the library of the Albert Einstein College of Medicine. Data are expressed as mean or as mean plus or minus standard error.

RESULTS

The results of individual measurements of single nephron and total kidney function are listed in Table I. The mean value of SNGFR during the 1st day of life was 0.92 nl/min. The increment in the rate of filtration observed during the subsequent 2 wk was relatively small (0.21 nl/min·day). During the following 15 days the rate of change increased markedly (0.97 nl/min·day), until SNGFR reached a plateau averaging 19.32 nl/min (Fig. 1).

TKGFR increased from 0.19 ml/min per kidney during the first 2 days of life to 1.31 ml/min at 38 days of age (Fig. 2). The average daily change was 0.02 ml/min during the first 15 days of life and 0.03 ml/min for the next 15 days.

[2] Unpublished observations.

[3] Personal communication.

TABLE I

Measurements of Single Nephron and Total Kidney Function

Experiment No.	Age	Body weight	Kidney weight		GFR/kidney*	TF/P_{In}*	SNGFR*	Absolute reabsorption*
			Dry	Wet				
	days	*g*	*g*		*ml/min*			*nl/min*
9	2 h	91	0.102	0.449	0.19	1.80	0.48	0.22
12	1	100	0.098	0.490	0.18	1.42	0.79	0.24
4	2	83	0.141	0.635	0.21	1.93	1.09	0.53
7	2	81	0.086	0.439	0.19	1.52	1.51	0.53
8	4	97	0.146	0.701	0.28	1.66	1.92	0.65
11	4	111	0.133	0.652	0.26	1.70	2.19	0.90
30	5	138	0.157	0.832	0.28	2.18	2.12	1.03
13	6	149	0.145	0.696	0.26	1.37	1.47	0.38
31	7	139			0.29	1.70	2.10	0.80
14	8	146	0.170	0.918	0.33	1.70	1.66	0.68
18	11	121	0.145	0.725	0.38	1.21	2.59	0.48
23	11	175	0.156	0.874	0.35	1.46	2.45	0.72
24	13	135	0.162	0.745	0.38	1.61	3.02	1.04
35	14	154	0.195	0.897		1.58	4.36	1.80
2	15	185	0.219	0.942	0.46	2.17	2.87	1.15
3	16	217	0.224	0.963	0.46	1.72	5.75	2.06
6	16	170	0.216	0.950				
14	17	167	0.194	0.815	0.50			
15	17					1.90	8.42	3.18
22	18	199	0.225	0.968	0.52			
36	18					1.96	3.86	1.90
37	20					1.97	5.88	2.76
29	21	284	0.351	1.404	0.77	2.00	10.70	8.15
16	22	205	0.217	0.651	0.66	2.13	13.15	8.14
33	22	195	0.216	0.842	0.73			
26	22					1.56	13.59	4.44
32	26	230	0.355	1.172	1.04	1.80	18.90	7.62
27	28	301	0.310	1.178	0.95	2.20	20.90	10.74
28	32	286	0.375	1.350	1.10	1.59	18.54	5.67
38	38	315	0.398	1.398	1.21	2.07	20.20	10.34

* Each value represents a mean of two to six individual measurements.

The number of glomeruli was determined in six kidneys from three animals (Table II). The difference between counts of aliquots obtained from the same kidney was no greater than 5%. Variation between left and right kidneys and between kidneys of animals of different ages were small.

The length of 22 convoluted proximal tubules (Table III) was measured in eight animals. Microdissections were not performed in the guinea pigs used for physiological measurements because of the technical difficulties in maintaining the newborn animal in a stable state for longer than 2–3 h and in injecting the latex compound into tubules of small animals that have already been punctured for collection of fluid. The length of the proximal convoluted tubule averaged 1.1 mm during the first day of life and 6.1 mm during the fourth month.

The ratio of dry to wet kidney weight (Fig. 3) averaged 0.20±0.01 during the first 14 days of life and increased steadily thereafter to reach 0.28±0.02 during the fourth week.

DISCUSSION

Morphological studies performed as long as 50 yr ago (1) documented that in most mammals the development of the renal cortex is incomplete at birth. In the rat, for instance, the number of cortical glomeruli doubles during the first week of extrauterine life, and there is an even greater increase in tubular mass. Examination of the surface of the kidney in these animals fails to disclose "open" tubules during at least the first 2 wk of life; as a consequence, micropuncture techniques cannot be employed until this relatively late stage of development (21, 22).

The guinea pig on the other hand, being born with a functional superficial cortex, is particularly suited for

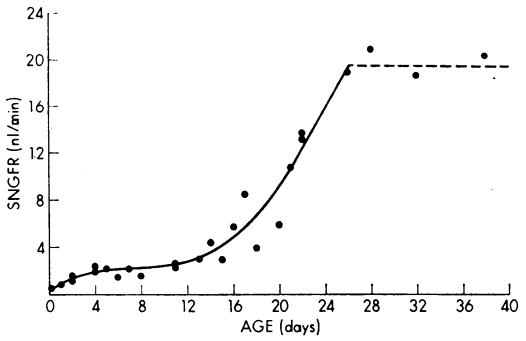

FIGURE 1 Increase in superficial nephron glomerular filtration rate with age. Each point represents the mean of two to six measurements performed in the same animal ($y = 0.297 + 0.725\ x - 0.109\ x^2 + 0.0065\ x^3 - 0.000088\ x^4$, $r = 0.97$).

the investigation of immediate postnatal changes in nephron function.

Changes in filtration rate with age. The results obtained in the present study demonstrate that the ontogenetic and phylogenetic pattern of renal organogenesis persists after birth. The increase in SNGFR during the first 2 wk of extrauterine life was small. At the age of 2–3 wk, a marked rise in the rate of change occurred, which continued up to the age of 4 wk. A similar phenomenon has been observed by us (5, 6) and by others (23, 24) with regard to changes in cortical blood flow. Measurement of pressure for glomerular filtration in developing animals performed in this laboratory (14) suggests that the sudden increase in nephron function is determined mainly by a decrease in resistance at the level of the glomerular membrane and an increase in the surface available for filtration. It is of interest that the rapid increase in SNGFR is paralleled by an increase in the

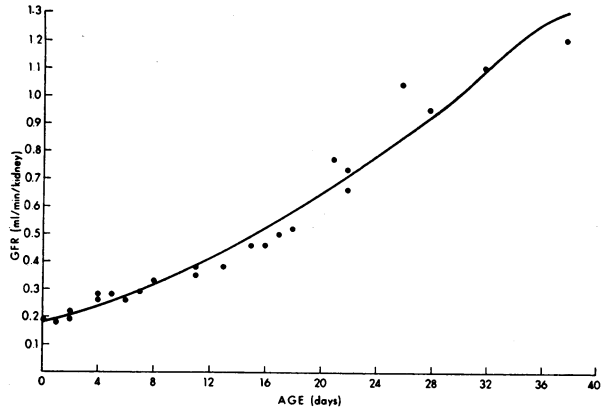

FIGURE 2 Increase in total kidney glomerular filtration rate with age. Each point represents the mean of two to six measurements performed in the same animal ($y = 0.157 + 0.018\ x + 0.00033\ x^2$, $r = 0.98$).

TABLE II

The Number of Glomeruli As Determined in Six Kidneys from Three Animals

Age	Body wt.	Kidney weight		Number of glomeruli	
		Left	Right	Left	Right
days	*g*	*g*			
12	251	1.3	1.3	42.160	40.960
31	278	1.4	1.2	43.040	42.880
49	625	2.4	2.4	41.360	41.520

dry/wet kidney weight ratio (Fig. 3), suggesting a relationship to cell mass.

The values for SNGFR observed by us compare favorably to those reported by Horster and Valtin (21) in puppies. Consideration should be given to the fact that the superficial nephrons of the puppy start to function at about 3 wk of life. One would expect, therefore, a certain lag in time between the two species. The value of 3.22 nl/min found by Horster and Valtin in a 21-day-old dog corresponds to that of a 14-day-old guinea pig. A careful examination of their data suggests that the rate of increase in SNGFR is slower during the first 20 days of observation (up to about 40 days of age) than during the subsequent 20 day period. It would appear, therefore, that the development of the kidney proceeds according to a similar sequence of events, whether or not the animal is born with a functioning superficial cortex. The only other study in which measurements of SNGFR were performed in developing animals is that of Solomon and Čapek (22) in rats. The youngest

TABLE III

Microdissection of Proximal Convoluted Tubules

Age	Length	Age	Length
days	*mm*	*days*	*mm*
1	1.02	18	2.25
	1.00		2.40
	1.12		2.74
3	1.07	24	3.76
	1.13		4.38
			4.49
8	1.25		
	1.52	32	5.38
	1.63		5.88
			6.06
10	1.76		
	1.62	120	6.30
			6.13
			5.81

animals with functional superficial nephrons were 15 days old. The SNGFR at that age was about 1.5 nl/min which would correspond to a 3 to 4-day-old guinea pig. Unfortunately, the large scatter in the data of Solomon and Čapek precludes any further comparison.

Unlike SNGFR, the change in TKGFR with age is smoother over the period of observation covered by the study (Fig. 2). The values observed by us for TKGFR are similar to those found by Potter et al. (25) and by Horster and Lewy (26) in rats.

Since the increase in SNGFR is minimal during the first 2 wk of life, it appears that the increase in TKGFR during early extrauterine life is determined primarily by the increase in the filtration rate of the deeper nephrons. The more superficial units make their major contribution during the third and fourth wk.

This conclusion is supported by an analysis of the rate of increase in superficial nephron and total kidney GFR during these two periods of postnatal development (Table IV). Considering a nephron population of 42,000 per kidney, the estimated average daily rate of increase in single nephron GFR (all nephrons) during the first 15 days is almost 2.5-fold higher than the increase in SNGFR. During the subsequent 15 days, the increase in SNGFR accounts entirely for the observed rate of increase in TKGFR. Using the same set of variables and assuming a 4:1 distribution between cortical and juxtamedullary nephrons, a diagrammatic picture of the superficial and deep nephron function and their respective contributions to total kidney function can be constructed (Table V). It is apparent from these data that a very rapid increase in the rate of filtration must occur in the juxtamedullary nephrons during the first 15 days of life. This increase would be smaller if we postulate that the degree of nephron heterogeneity is higher in the younger animal and that not two but three or more populations of nephrons coexist in the developing kidney. It is likely that until the kidney reaches the relative homogeneity of the adult organ, an infinite gradation in functional capacity exists from the juxtamedullary to the superficial nephrons.

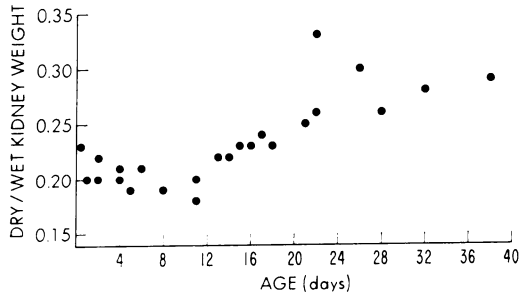

FIGURE 3 Ratio of dry to wet kidney weight from 2 h to 36 days of age.

TABLE IV
Average Daily Increase in Single Nephron GFR (nl/min)

Age	Superficial nephrons	All nephrons*
days		
1–15	0.21	0.48
16–30	0.97	0.71

* 42,000 per kidney.

Proximal tubular function and its relationship to GFR. Morphological imbalance between glomerular and tubular development in early life was demonstrated first in white rats by Arataki (1) and confirmed by Fetterman et al. (4) in studies of the human kidney.

Functional studies performed in young animals and infants appeared to confirm the concept of glomerulotubular imbalance in early life. Tudvad (27) demonstrated that the maximal rate of glucose reabsorption (T_{mG}) is low. Edelmann and associates (28) have shown that the renal threshold for bicarbonate is depressed both in premature and full-term infants. Brodehl and Gellissen (13), utilizing shot-term clearance studies, found significantly higher rates of urinary excretion and lower net and percent tubular reabsorption of certain free amino-acids in infants than in older children. Similarly, it has been shown that the rate of tubular reabsorption of filtered phosphate is low in the infant (29, 30).

Some of these findings, particularly those on glucose reabsorption, have been reexamined recently both in experimental animals and humans. Brodehl, Franken, and Gellisen (31) did not find any difference in T_{mG}/C_{In} ratio between infants and older children. Moreover, in a study performed in puppies Arant, Nash, and Edelmann (32) have found a higher T_{mG}/C_{In} ratio in the newborn than later in life. The discrepancies between these recent and the old studies might be explained by differences in the state of hydration, and therefore, in extracellular fluid volume, or just by a failure to reach Tm in some of the experiments.

The data obtained in the present investigation provide further information regarding reabsorption of fluid in the proximal segment of the nephron, and the relation-

TABLE V
Calculated Values of Deep Nephron GFR at Different Ages (nl/min)

Age	Cortical (80%)	Juxtamedullary (20%)
days		
1	0.9	17.2
15	4.1	43.2
30	19.3	42.1

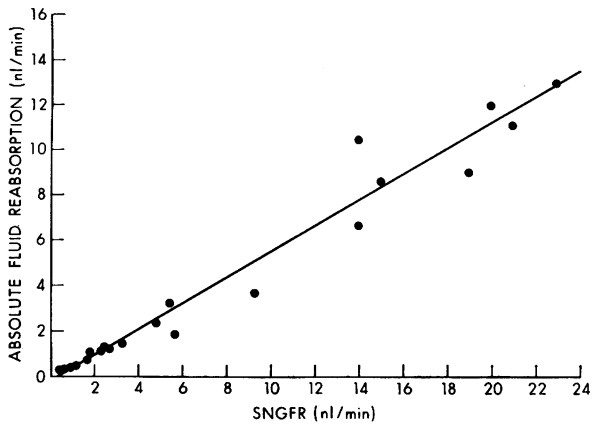

FIGURE 4 Relationship between single nephron filtration rate and absolute reabsorption of fluid at the end of the proximal convoluted tubule ($y = 0.574\,x - 0.225$, $r = 0.98$).

ship between reabsorption and filtration. Fig. 4 depicts the correlation between SNGFR and absolute rate of reabsorption only for those nephrons in which transit time has been measured and found to be above 8 s. This was taken as marker of the puncture site, indicating collection from a late segment of the proximal tubule. The calculated regression line demonstrates a direct relationship between these two variables, with a strong degree of correlation ($r \pm 0.98$). A close relationship is also evident between the increase in proximal tubular length and the increase in SNGFR with age (Fig. 5). It appears, therefore, that as the animal matures, a parallel increase takes place in the capacity of the tubule to reabsorb, on the one hand, and the rate of glomerular filtration, on the other. Further support for this statement is provided by the lack of change in TF/P_{In} as a function of age. With the possible exception of the first 2 or 3 days of extrauterine life, fractional reabsorption at the end of the proximal tubule was found to remain relatively constant (Fig. 6). Similar results were obtained in puppies

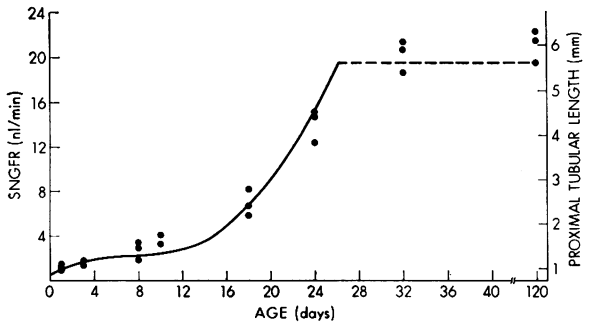

FIGURE 5 Relationship between proximal tubular length (•) and nephron filtration rate (solid and broken line) in superficial nephrons from birth to 4 mo of age.

ranging in age between 20 and 80 days (2). Thus, glomerulotubular balance is present soon after birth and is maintained during the period of postnatal growth and development. This conclusion represents a departure from the long held view (11–13) that both morphological and functional glomerulotubular imbalance with glomerular preponderance are characteristic of the maturing animal and human.

The fact that functional glomerulotubular balance does obtain in the developing animal at a time when morphological imbalance with glomerular preponderance exists suggests either that tubular capacity for reabsorption controls in some way the rate of glomerular filtration, or that glomerular size is a poor indicator of the capacity for filtration. One of the mechanisms underlying the first of these two postulates might be that put forward by Leyssac (33) who assumed that a decrease in tubular reabsorption lowers the effective filtration pressure (EFP) and, therefore, the filtration rate. Although the validity of the experiments which support this theory has been questioned (34, 35), one of the essential features of such a mechanism, namely the ability of the proximal tubular wall to withstand a moderate transmural hydrostatic pressure difference, has been demonstrated recently (36, 37). Moreover, two studies (21, 37) have revealed an even greater hydrostatic pressure gradient across the proximal tubular wall of young animals. It can also be considered that a low proximal tubular reabsorption will result in an increased delivery of filtrate to the macula densa, which, by a feedback mechanism, will result in a decrease in glomerular filtration rate (38–40). It is of interest to note in this regard, that plasma levels of renin were found to be markedly elevated in newborns (41, 42) and that angiotensin was found recently to induce selectively vasoconstruction of the glomerular capillaries of the superficial nephrons (43). Furthermore, indirect and direct methods have documented a high intrarenal vascular resistance in the immediate newborn period and a steep fall thereafter (5, 6, 23, 44). This fall can be experimentally induced by infusion of vasodilators (45).

Evidence that glomerular size need not correlate linearly with the capacity for filtration, at least in the

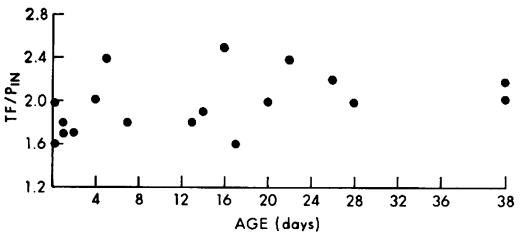

FIGURE 6 Fractional reabsorption of fluid at the end of the proximal convoluted tubule as a function of age.

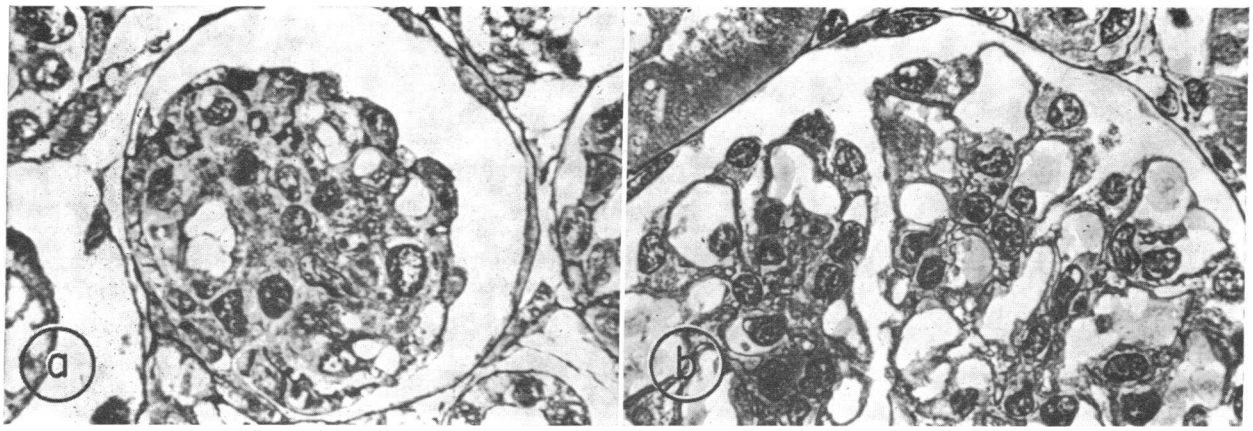

FIGURE 7 Glomeruli of a 1 day (*a*) and 30 days (*b*) animals photographed at the same magnification (562 ×). Notice the difference in the surface area occupied by capillaries.

immature kidney, can be derived from the work of Arturson et al. (46), who demonstrated a significant increase in the permeability of the glomerular capillary membrane with age. Furthermore, surface area available for or used in the process of filtration need not be a function of the glomerular volume, and might vary during development. Measurements of this sort are lacking. However, some insight into this problem can be obtained by comparing the structure of the glomerulus in the newborn with that of an adult animal. Photomicrographs taken under the same magnification (Fig. 7) show that between 1 (*a*) and 30 (*b*) days of life the change consists not only in an increase in diameter, but also in a relative and absolute increase in the area occupied by glomerular capillaries. These morphological changes appear to contribute significantly to the increase in GFR observed in early life. Measurements of pressure gradients for glomerular filtration support this assumption.

SNGFR can be expressed by the equation SNGFR = $Kf(P_{uf})$ where K_f is the product of the effective hydraulic permeability of the glomerular capillary membrane (k) and the surface area for filtration (S) and P_{uf} is the mean pressure for ultrafiltration. Changes in SNGFR may be the consequence of changes in any of these variables, acting independently or in combination (47). In a previous investigation (14) we found that P_{uf} at the afferent arteriolar end of the glomerular capillary increased during the first 15 days of life from 6.4 to 9.1 cm H_2O (i.e., by 50%), whereas the SNGFR was shown in the present study to rise 400% during the same period of time. During the following 15 days P_{uf} increased to 13.9 cm H_2O (another 50%), while SNGFR rose about 500%. Since the permeability of the glomerular membrane increases as a function of age (46) P_{uf} at the foremost end of the glomerular capillary, if anything, will tend to overestimate the mean P_{uf} more in the older than in the younger animals. Or stated in another way, the increase in mean P_{uf} over the period covered by the study most likely was smaller than suggested by our measurements. It should be noted that filtration pressure equilibrium is not implied or required by this statement. Whether or not equilibrium is reached in the newborn animal is not known.

Under equilibrium conditions changes in SNGFR were found to vary directly and proportionately to changes in glomerular blood flow (GBF) (48). This process seemed to be mediated almost exclusively by variations in P_{uf} brought about by a change in the relationship between hydrostatic and oncotic pressures (48, 49). Experiments pereformed by us in puppies (5) have documented a 26-fold increase in GBF of the superficial nephrons and a 4-fold increase in the GBF of the deep nephrons between birth and 6 wk of age. Although the magnitude of these changes might be sufficient to account for the increase in GFR observed during the same period of time, our measurements in guinea pigs (14) indicate that a change in Kf must be postulated to occur during development. The relationship between changes in renal blood flow and GFR during maturation appear, therefore, to be more complex than in the adult animal. The initimate process remains to be defined. The present state of knowledge allows only the conclusion that during postnatal development the increase in TKGFR is the result of both structural and functional changes. Characteristic features of this period are a more advanced state of maturation of the deep nephrons in comparison to the superficial ones, the persistence in the extrauterine life of the centrifugal pattern of change established during the intrauterine development of the kidney and the existence of a functional glomerulotubular balance which probably corresponds to a morphological balance between the capacity of the

glomerulus to filter and the capacity of the tubule to handle the filtrate.

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