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The sizes of renal glomeruli in fetuses and infants

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INTRODUCTION

Although many studies have been performed on the sizes of human renal glomeruli, we have found no combined study of the pre- and perinatal growth of glomeruli. Most studies have taken note of the fact that the nephrons of the infant are not a uniform population. Fetterman, Shuplock, Philipp & Gregg (1965), using maceration methods, divided the kidney cortex into three zones: superficial, mid-cortical and juxtamedullary. They studied the kidneys from 23 children, from term to 18 years of age, who had died of trauma or short illness. They found a great difference in the sizes of glomeruli between the three zones at term which rapidly decreased with age so that all were equal in size at 16 months. Darmady, Offer & Woodhouse (1973), also using maceration, gave average values of the sizes of glomeruli from a series of 9 children from term to 6 years. They stated that glomeruli increased in size from term to 4 months of age, then decreased to 1 year, then increased to 1½ years and remained stable to 5 years. Zolnai & Palkovits (1965) measured glomerular growth using tissue sections and measuring glomerular diameters. They divided the cortex into two zones, inner and outer. They examined five kidneys from children aged between 2 days and 1 year and two cases from 1 to 10 years, and came to the conclusion that the inner zone growth was 'more intensive' than the outer. Other workers have only measured glomeruli from small numbers of infant kidneys. Thus Dunnill & Halley (1973) measured seven below the age of 16 years; Elias & Hennig (1967) one 6 months old and one 7 years old child; McLachlan, Guthrie, Anderson & Fulker (1977) included one 29 weeks fetus and one 13 months old child and van Damme & Koudstaal (1976) measured sizes of glomeruli in one 1½ years old child.

Many different methods have been used to derive glomerular sizes and all the methods have difficulties. Maceration techniques were said, by Elias & Hennig (1967), to produce swelling which resulted in larger measurements given in the papers using this method than in those using tissue sections. Within studies which used paraffin tissue sections, the results could not always be directly compared due to different fixation and processing methods, different glomerular populations measured and different methods of measuring the glomeruli. Abrams, Lipkin & Hennigar (1963) and Hanberg Sorensen (1972) showed that if hilar sections of glomeruli were measured, then the variation of glomerular size within each kidney was considerably reduced. The use of the hilar section ensured that an equatorial cut of the glomerulus was measured and reduced the ratio of the size of the object measured to the section thickness.

Reviewing methods for estimating glomerular areas in tissue sections, Kawano *et al.* (1971) and Hanberg Sorensen (1972) concluded that the camera lucida drawing method of finding glomerular area was more reproducible than either the point

Table 1. *Results of pre-term measurements*

Age in weeks gestation	No. in group	Mean crown–rump length (cm)	Mean juxta-arcuate areas μm²	S.D.	Mean mid-cortical areas μm²	S.D.	Mean superficial areas μm²	S.D.
12	2	7·6	9736·5	1549·3	7031	1525·9	4891	1565
14	3	15·5	8831·3	962·5	5888·7	585	4472·7	564
16	3	18·7	9862	968	5911·7	374	4478	485
18	4	21	7612	292	5040	122·6	4259	579·2
20	6	21	7611	813·8	5169·8	193	4416	649
22	2	25	6961	214·4	4528	676·7	4086	276·7
26	5	24	6920	1127	4851	980	4567·4	249
28	6	25·8	7537	1059	4578·8	745·7	4492·7	856·4
30	9	27·2	7095	984	4768	750	4714·6	590
32	5	28·4	6564·6	435·6	4200·4	497	4118·8	947·3
34	6	30	6951	1176	4889·7	764	4383·3	497
36	3	31·3	7040	2075·6	4471	1148·7	4334	1027
38	4	35	6808	737	5025	142·9	4765	980
40	11	35	7349·8	1042	6970	644	4648	658

Table 2. *Results of post-term measurements*

Age	No. in group	Mean crown–rump length (cm)	Mean juxta-arcuate areas μm²	S.D.	Mean mid-cortical areas μm²	S.D.	Mean superficial areas μm²	S.D.
2 weeks	4	37	7457	2377	4722	1322	4763	862
2 months	6	41	9313·5	1228·9	5930	1104	5573	660
3 months	8	43	9406	1239	6694	775	6529·7	872·6
6 months	8	46	9395·6	1934·8	6962	965·6	6272	987
9 months	5	48·5	9628	1013	7748	561	7696	364·3
12 months	5	50·5	12750	1419·7	9108	2205	8896	1639
2 years	4	55	12650	1595	11623	1749·9	10846·5	5320
3 years	4	57	14221	1342	12077	2400	11716	1532
5 years	4	63	12588·8	1904	12087·7	1662	12754	1190

counting method or two diameter measurements and, if the size of the glomerulus was taken as the area bounded by the Bowman's capsule, it was also the fastest method.

It was decided to base measurements on hilar sections of glomeruli and to measure capsular size. This study covers infants from 12 weeks gestation to 5 years of age.

MATERIALS AND METHODS

The material examined came from the post mortem files of Sheffield Children's Hospital. The tissue was fixed in buffered formalin, embedded in paraffin wax and cut at 6 μm. Each section used contained the full width of a lobe from the tip of the papilla to the edge of the cortex, and was taken from the middle part of the kidney.

There are sections from 7000 children on the files. A random series of sections was first surveyed for suitability of the block, which ensured that the section was an ideal cut from papillary tip to edge of cortex and excluded any kidney showing pathological lesions. When this was completed, the necropsy reports were scrutinised and any specimens from children with histories of congenital heart lesions, maternal pyelonephritis or pre-eclamptic toxaemia, hypernatraemic dehydration or chromosomal abnormality were excluded. The sizes and weights of the children were then examined and cases were excluded if the crown–heel lengths were outside 2 S.D. of the mean (Documenta Geigy, 1962; Gairdner & Pearson, 1971; Usher & McLean, 1969) or if the body and kidney weights were not within 2 S.D. of the mean (Emery & Mithlal, 1960).

Babies dying within 2 days of birth were included in the pre-term survey together with stillbirths. The case selection was carried out before the quantitative study and the kidneys were measured from 117 children, the observer not knowing the age of the child at the time of examination. The number of cases in each age group is shown in Tables 1 and 2.

Only glomeruli where a hilum was visible were measured. The Quantimet 720 image analysing computer and image editor were used to measure the glomeruli. The magnification used was one picture point $-0{\cdot}054\ \mu m^2$.

In order to avoid boundary zone errors, the cortex was divided into five zones, only three of which were measured. These three were juxta-arcuate (1), mid-cortical (3) and superficial (5) zones. The two intermediary zones (2 and 4) were not measured.

In each section examined, a starting point was chosen at an arcuate artery. The juxta-arcuate zone was then examined. A glomerulus was counted as being in the juxta-arcuate zone if it had a hilum and was close to the arcuate vessel. Starting from the marker vessel and working progressively across the section, each glomerulus in the juxta-arcuate region was examined and if the above criteria were fulfilled, the glomerulus was measured.

When the juxta-arcuate zone was completed, the starting point was again found. The cortical depth was measured by counting its depth in microscopic fields using glomeruli as markers. The centre of the cortex was found and any glomerulus in this field with a hilum was measured. This was repeated across the cortex.

When the mid-cortical zone had been sampled, the starter point was again found. The outer edge of the cortex directly above the starter point was examined and any glomerulus with a hilum, closest to the edge of the cortex, was measured. Some of these were immature but all structures were counted if they had a vascularised tuft and a definite capsule and hilum.

A reproducibility study was first performed on 5 kidneys of differing maturities. Increasing numbers of glomeruli were measured, and the number plotted against mean glomerular area (Fig. 1). The mean values became constant at about 10 glomeruli per zone. The juxta-arcuate glomeruli showed the greatest variability in size; 10 glomeruli were, therefore, measured in each zone, making 30 glomerular measurements per slide.

RESULTS

In the measurements on pre-term children (Fig. 2), variation in the juxta-arcuate zone was larger than that in the mid-cortical or superficial zones. The juxta-arcuate and mid-cortical glomeruli showed an initial decrease in size from 12 to 20 weeks gestation. After this initial decrease, however, the juxta-arcuate, mid-cortical and superficial glomeruli remained at the same size up to birth. The superficial glomeruli remained the same size from 12 to 40 weeks gestation.

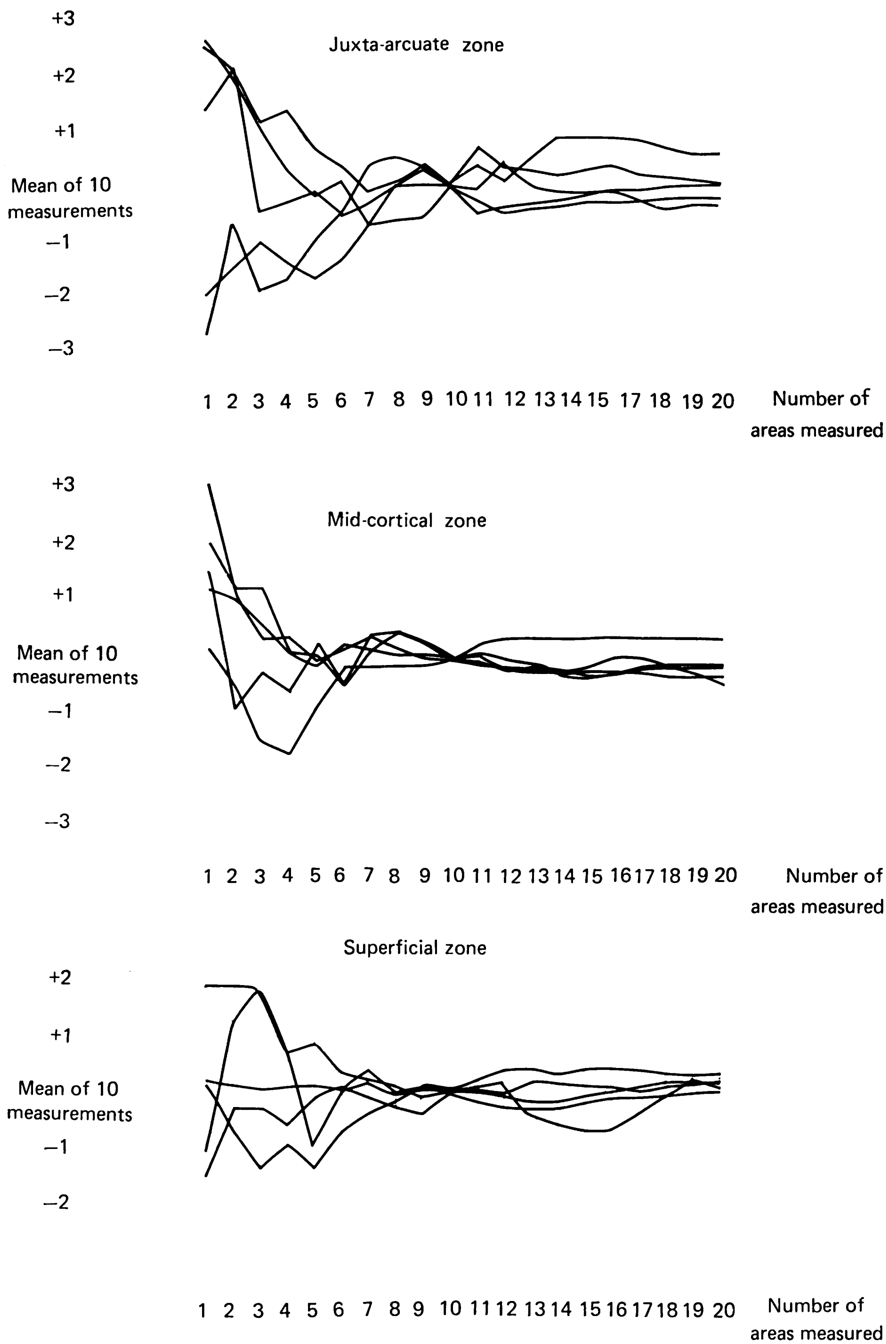

Fig. 1. Reproducibility graphs. The means of the measurements are plotted against the number of glomeruli measured. The mean values at ten measurements are superimposed and become steady at ten glomeruli. The juxta-arcuate zone glomeruli show the most variation and the mid-cortical the least.

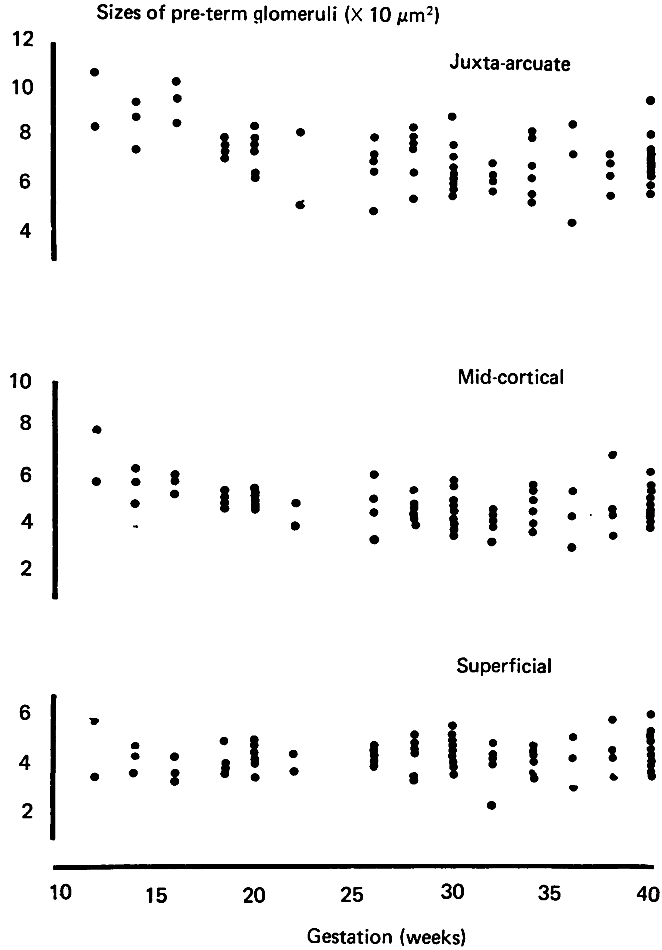

Fig. 2. Measurements from pre-term children. The juxta-arcuate and the mid-cortical zone glomeruli show an initial decrease in size until 20 weeks gestation. This is not observed in the superficial zone glomeruli.

The results of the pre- and post-term measurements are given in Tables 1 and 2 and the mean lines shown in Fig. 3.

The glomeruli in the juxta-arcuate zone showed an immediate increase in glomerular area after birth and then continued to grow steadily until 2 years, when the rate of growth slowed considerably. The mid-cortical zone glomeruli also began to enlarge at a similar rate after birth, the rate levelling off when the glomeruli were the same size as those of the juxta-arcuate zone, i.e. at about 2 years. The glomeruli in the superficial zone had a growth curve similar to that of the mid-cortical glomeruli. By the age of 3 years, the difference in size of the juxta-arcuate glomeruli and the rest had disappeared.

DISCUSSION

The sizes of glomeruli recorded in this study compare well with previous studies on the same age group (see Table 3). Our results agree closely with those published by McLachlan *et al.* (1977) who measured 100 random glomeruli per case using

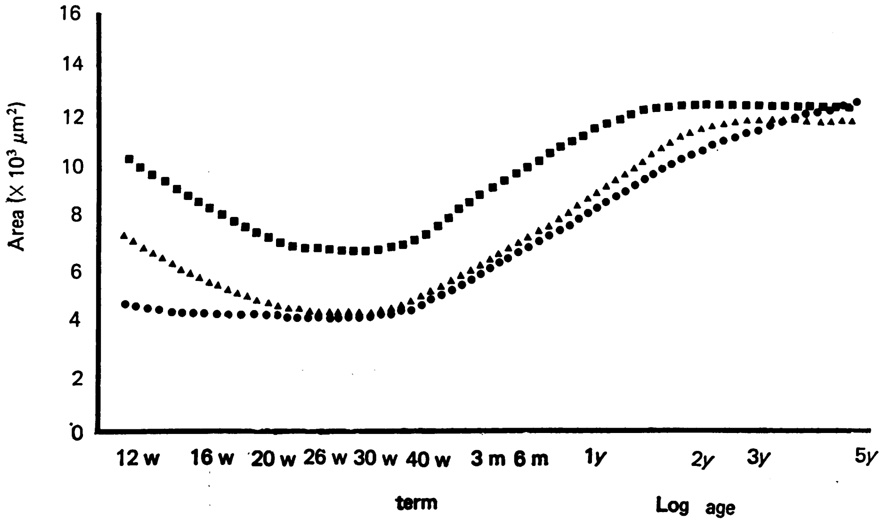

Fig. 3. Mean lines of the areas of glomeruli in all three zones during the total age range measured. There is an immediate increase in size of all glomeruli at birth. By 2 years of age, all glomeruli are approximately the same size. ■, juxta-arcuate; ▲, mid-cortical; ●, superficial.

Table 3. *Comparison of results*

Author	Age group	No. in group	Juxta-arcuate areas µm²	Juxta-arcuate areas S.D.	Mid-cortical areas µm²	Mid-cortical areas S.D.	Superficial areas µm²	Superficial areas S.D.
McLachlan, Guthrie, Anderson & Fuller (1977)	29 weeks gest.	1			Mean 4000			
This study	28 weeks gest.	6	7537	1059	4587	746	4493	856
McLachlan *et al.*	13 months	1			Mean 8900			
This study	12 months	5	12750	1419·7	9108	2205	8896	1639
van Damme & Koudstaal (1976)	1½ years	1	8050	2770	—	—	6151	3010
Hanberg Sorensen & Ledet (1972)	47 years	1	18583	—	—	—	12304	—
This study	5 years	4	12589	1904	12088	1662	12754	1190

the Quantimet 720. Smaller sizes were recorded by van Damme & Koudstaal (1976) who used point counting to find areas of glomeruli and then calculated the radii of the glomeruli, treating them as spheres. These radii were then re-converted into areas, again treating the glomeruli as spheres. The differences in the methods are enough to explain the differences in results. Hanberg Sorensen & Ledet (1972), who measured 10 hilar sections in 2 zones of the cortex by the camera lucida drawing method, obtained results which compare well with our oldest group.

Our results confirm that the size of the glomeruli becomes constant within the first 2 to 3 years after birth. Fetterman *et al.* (1965), using maceration techniques on 23 kidneys from term to 18 years of age, found that all glomeruli were the same size from 16 months onwards. Roosen-Runge (1949), who measured glomerular diameters using an eyepiece micrometer, found that all glomeruli were the same size at 14 months old but retarded children still had glomeruli of different sizes at 10 years of age. Zolnai & Palkovits (1965) measured random diameters of glomeruli with an eyepiece micrometer from 7 children between term and 10 years. They found that the juxta-arcuate glomeruli were always larger than those in the outer cortex but that the size difference was greatest in the postnatal period. Hanberg Sorensen & Ledet (1972), in their 47 years old specimen, also found that the juxta-arcuate glomeruli were larger than the superficial. Thus our results are in accord with Fetterman *et al.* and Roosen-Runge, and not with Zolnai & Palkovits, and Hanberg Sorensen & Ledet.

Our finding of the levelling out of glomerular sizes may be due to the relative slowing of the juxta-arcuate zone growth before the outer zones (see Fig. 3), thus allowing the mid-cortical and superficial zones to attain the same size as the juxta-arcuate. However, it has been suggested by Kampmeier (1926), Friedman, Grayzel & Lederer (1948) and Emery & Macdonald (1960) that glomeruli in the deeper layers of the cortex in young children may scar and involute naturally, not as part of a pathological process. Thus the larger juxta-arcuate glomeruli may disappear in the older children, helping to equilibrate the sizes throughout the cortex.

The study of the pre-term infants shows an unexpected feature of a decrease in size of the juxta-arcuate and mid-cortical glomeruli between 12 and 20 weeks gestation which is not found in the superficial glomeruli. This does not seem to have been observed previously. The superficial glomeruli in the younger fetuses become the mid-cortical glomeruli later in development; these glomeruli appear to enlarge as the cortex grows beyond them.

In the uterus, the kidneys are producing urine, and in the very young kidney there are few glomeruli. It seems reasonable for the size of the glomeruli to be related to functional demand. The majority of nephrons are formed before 32 to 36 weeks gestation described as the end of Period 3 of kidney development by Osathanondh & Potter (1963). At the end of this period, the last nephron forms the termination of the collecting tubule, which means that further terminal growth, branching of the tubule, or induction of new nephrons is impossible. Thus, during kidney development, as more nephrons are formed, the load is more widely shared and the demand on each single glomerulus is less. Arant (1978) found that, in infants born before 34 weeks gestation, the glomerular filtration rate was constant, and low. It increased rapidly after 34 weeks gestational age, which may correspond to the increase in glomerular size.

The postnatal glomerular growth spurt may also be explained by the functional demand. This hypothesis is being tested at present by a study of glomerular size in children who have survived for varying times after premature birth.

SUMMARY

An attempt was made to obtain normal values of the sizes of glomeruli in the fetus and child.

The kidneys of 117 children from 12 weeks gestation to 5 years of age were measured and the difference in size between the juxta-arcuate, mid-cortical and superficial glomeruli was examined.

Juxta-arcuate and mid-cortical glomeruli showed an initial decrease in size from 12 to 20 weeks gestation. This was not seen in the most superficial glomeruli. After the initial decrease, the juxta-arcuate and superficial glomeruli remained at the same size until birth. The superficial glomeruli remained the same size from 12 weeks gestation to term.

There was an immediate increase in size after birth in all three groups which slowed down after 2 years, when all three groups became the same size.

The changes in size of the juxta-arcuate and mid-cortical glomeruli may be explained by functional demand.

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REFERENCES

ABRAMS, R. L., LIPKIN, L. E. & HENNIGAR, G. R. (1963). A quantitative estimation of variation among human renal glomeruli. *Laboratory Investigation* **12**, 69–76.

ARANT, B. S. (1978). Developmental patterns of renal functional maturation compared in the human neonate. *Journal of Pediatrics* **92**, 705–712.

DAMME, B. VAN & KOUDSTAAL, J. (1976). Measuring glomerular diameters in tissue sections. *Virchows Archiv A: Pathological Anatomy and Histology* **369**, 283–291.

DARMADY, E. M., OFFER, J. & WOODHOUSE, M. A. (1973). The parameters of the ageing kidney. *Journal of Pathology* **109**, 195–207.

DOCUMENTA GEIGY. *Scientific Tables*, 6th ed, p. 608. Macclesfield: Geigy Pharmaceutical Co. Ltd.

DUNNILL, M. S. & HALLEY, W. (1973). Some observations on the quantitative anatomy of the kidney. *Journal of Pathology* **110**, 113–121.

ELIAS, H. & HENNIG, A. (1967). Stereology of the human renal glomerulus. *Quantitative Methods in Morphology*, pp. 130–166. Berlin, Heidelberg, New York: Springer.

EMERY, J. L. & MACDONALD, M. S. (1960). Involuting and scarred glomeruli in the kidneys of infants. *American Journal of Pathology* **36**, 713–723.

EMERY, J. L. & MITHLAL, A. (1960). The weights of kidneys in late intrauterine life and childhood. *Journal of Clinical Pathology* **13**, 490–493.

FETTERMAN, G. H., SHUPLOCK, N. A., PHILIPP, B. S. & GREGG, H. S. (1965). The growth and maturation of human glomeruli and proximal convolutions from term to adulthood. *Pediatrics* **35**, 601–619.

FRIEDMAN, H. H., GRAYZEL, D. M. & LEDERER, M. (1948). Kidney lesions in stillborn and newborn infants. 'Congenital glomerulosclerosis'. *American Journal of Pathology* **18**, 699–706.

GAIRDNER, D. & PEARSON, J. (1971). A growth chart for premature and other infants. *Archives of Disease in Childhood* **46**, 783–787.

HANBERG SORENSEN, F. (1972). Quantitative studies of the renal corpuscles. I. Intraglomerular, interglomerular and interfocal variation in the normal kidney. *Acta pathologica et microbiologica scandinavica* **80**, 115–124.

HANBERG SORENSEN, F. & LEDET, T. (1972). Quantitative studies of the renal corpuscles. II. A methodological study. *Acta pathologica et microbiologica scandinavica* **80**, 721–728.

KAMPMEIER, O. F. (1926). The metanephros or so-called permanent kidney in part provisional and vestigial. *Anatomical Record* **33**, 115–120.

KAWANO, K., MCCOY, J., WENZL, J., PORCH, J., HOWARD, C., GODDARD, H. & KIMMELSTEIL, P. (1971). Quantitation of glomerular structure. *Laboratory Investigation* **25**, 343–348.

MCLACHLAN, M. S. F., GUTHRIE, J. C., ANDERSON, C. K. & FULKER, M. J. (1977). Vascular and glomerular changes in the ageing kidney. *Journal of Pathology* **121**, 65–78.

OSATHANONDH, V. & POTTER, E. L. (1963). Development of human kidney as shown by microdissection. III. Formation and inter-relationship of collecting tubules and nephrons. *Archives of Pathology and Laboratory Medicine* **76**, 290–302.

ROOSEN-RUNGE, E. C. (1949). Retardation of post-natal development of the kidney in persons with early cerebral lesions. *American Journal of Disesases of Children* **77**, 185–200.

USHER, R. & MCLEAN, F. (1969). Intrauterine growth of liveborn Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. *Journal of Pediatrics* **74**, 901–910.

ZOLNAI, B. & PALKOVITS, M. (1965). Glomerulometrics. III. *Acta Biologica Academiae scientiarum hungaricae* **15**, 490–423.