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The Malformations of the Urinary System in Autosomal Disorders

G. I. Kravtzova, G. I. Lazjuk and I. W. Lurie

Laboratory of Teratology and Medical Genetics, and Department of Pathological Anatomy, Medical Institute, Minsk, USSR

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Summary. Data from the world literature about the pathology of the urinary system in autosomal chromosomal disorders are analyzed and compared with our own morphological investigations of this system in 63 cases of chromosomal disorders (Patau's, Edwards', Down's, Orbeli's, Wolf-Hirschhorn's syndromes, partial trisomy B and inversion of chromosome 2). The urinary system is most frequently involved in "cat-eye", triploidy, Orbeli's, Patau's and Edwards' syndromes. All known malformations of the urinary system are observed in children with chromosomal diseases, except infantile polycystic kidney and medullary "sponge" kidney. The authors recognize specific and nonspecific abnormalities of the urinary system. Nonspecific abnormalities, as simple renal dysgenesis, may be observed in all chromosomal disorders. Specific abnormalities are found only in certain chromosomal diseases. These malformations are an excess of embryonal lobulation of the kidney with the increase of its weight and cystic changes (Patau's syndrome), crossed renal ectopy with fusion and horseshoe kidney (Edwards' syndrome), unilateral renal agenesis (Orbeli's syndrome), hypospadia (Wolf-Hirschhorn's syndrome). A possible pathogenesis of malformations of the urinary system in chromosomal disorders is discussed.

Key words: Chromosomal abnormalities — Kidney, ureter, urethra malformations.

Since 1959, when the chromosomal ethiology of Down's syndrome was established, more than 20 syndromes due to autosomal aberrations have been described in the literature (Lazjuk, 1974). These syndromes show multiple congenital malformations of various systems, including the urinary system. Some autosomal disorders involve this system as a rule, and frequency of malformations of the kidneys in some syndromes is about 60–70%. Sometimes the renal abnormalities determine the clinical behavior or lead to death. At the same time data about morphology of the urinary system in chromosomal disorders are scanty (Egli and Stalder, 1973) and there are no detailed descriptions of histology of kidneys.

Therefore we consider it advisable to summarize our morphological investigations of the urinary system in chromosomal disorders and the data found in literature. From 1967 to 1974 we examined, post mortem, 63 children with autosomal disorders (Patau's syndrome—24 cases, Down's syndrome—28, Edward's syndrome—7, Wolf-Hirschhorn's, Orbeli's syndromes, partial trisomy B and inversion of the chromosome 2—each 1). Eponyms of these syndromes are presented in Table 1. 487 fetuses, stillborns and children without congential malformations dying under one year old were used as controls.

The main types of renal abnormalities were renal agenesis, dysplasia and hypoplasia, anomalies of form or position of kidney and hydronephrosis. The main malformations of the urinary system for the syndromes with carefully studied morphology are presented in Table 2.

Table 1. Eponyms of chromosomal disorders

Eponym of syndrome	Karyotype	Rational title
Down's	47, XX(XY), 21+	Trisomy for the chromosome 21
Edward's	47, XX(XY), 18+	Trisomy for the chromosome 18
Patau's	47, XX(XY), 13+	Trisomy for the chromosome 13
"Cat cry"	46, XX(XY), 5p−	Loss of the short arm of chromosome 5
Wolf's-Hirschhorn's	46, XX(XY), 4p−	Loss of the short arm of chromosome 4
Orbeli's	46, XX(XY), 13q− or 46, XX(XY), r(13)	Loss of the short arm of chromosome 13 or ring chromosome 13
"Cat eye"	47, XX(XY), mar+	Trisomy for small additional marker

Table 2. Main abnormalities of urinary system in autosomal syndromes

	Syndrome						
General frequency of abnormalities of urinary system	Patau's 109/172	Edward' 118/209	Down's 14/112	Wolf's 8/14	"Cat cry" 3/9	Orbeli's 10/13	Triploidy 15/21
Renal abnormalities							
Horseshoe kidney	5	46	—	—	1	—	—
Unilateral agenesis	1	—	—	1	1	3	1
Hypoplasia	1	5	4	2	—	6	2
Simple dysplasia	—	29	7	2	—	—	4
Cystic dysplasia	—	—	—	—	—	1	2
Excess of lobulation with cysts	72	—	—	—	—	—	—
Simple dystopia	3	3	—	1	—	1	—
Crossed ectopy with fusion	—	5	—	—	—	—	—
Hydronephrosis	28	14	2	—	—	2	2
a) obstructive	10	2	2	—	—	2	1
b) unobstructive	18	12	—	—	—	—	1
Duplication of ureters	9	30	—	—	1	—	—
Megaloureter	2	5	—	—	—	—	—
Hydroureter	11	3	—	—	—	2	—
Dilatation of ureters	4	11	3	1	—	—	—
Atresia, stenosis and aplasia of ureters	8	6	1	—	—	2	2
Hypospadia[a]	8/83	—	—	16/19	—	12/29	7/14
Persistence of urachus	4	5	—	1	—	—	1

[a] The frequency of hypospadia is presented on clinical data.

Bilateral Renal Agenesis

Bilateral renal agenesis is very rare in chromosomal disorders. This malformation was mentioned in one case of 4p-syndrome (Mikelsaar *et al.*, 1973) and in one case with additional chromosomal fragment (Ferrandez and Schmid 1971). Karotype in other cases of bilateral renal agenesis was normal (Passarge and Sutherland, 1965; Schlegel *et al.*, 1966; our observations).

Unilateral Renal Agenesis

Unilateral renal agenesis is more frequent in Wolf-Hirschhorn's syndrome (Giorgi *et al.*, 1965; Taylor *et al.*, 1970), in Orbeli's syndrome (Masterson *et al.*, 1968; Cagianut and Theiler, 1970; Hoo *et al.*, 1974), in "cri du chat" syndrome (Lejeune *et al.*, 1964); trisomy 8 (van Eys *et al.*, 1970); partial trisomy 11 (Francke, 1972); trisomy 13 (Giovanucci *et al.*, 1969); trisomy 18 (Stoll *et al.*, 1972); 18q- (Law and Masterson, 1969); and "cat eye" syndrome (Schachenmann *et al.*, 1965).

Left-side renal agenesis with cystic dysplasia of the right kidney was observed in one case of Orbeli's syndrome with the karyotype 46, XY/45, XY,-D/45, XY, Dq+ (Lazjuk *et al.*, 1973).

Renal Hypoplasia

Renal hypoplasia is usual in Orbeli's syndrome, where it was found in 6 out of 13 autopsied children; in Wolf-Hirschhorn's syndrome; in some cases of triploidy (Schmickel *et al.*, 1971; Papiernik-Berkhauer, 1968), partial trisomies 4 (Surana and Conen, 1972) and 10 (Yunis and Sanchez, 1974); trisomies 18 (Schepens *et al.*, 1967; Terplan *et al.*, 1970; Schinzel and Schmid, 1971) and 22 (Hirschhorn *et al.*, 1973).

The weight of kidneys in Down's syndrome is usually decreased, but a true renal hypoplasia was found only in 4 of our cases. In these the decrease of the weight was accompanied by the decrease of the number of calices. Microscopically, no structural abnormalities were seen in these small kidneys. A rare small glomerular cysts, less than 220 μ in diameter were found which were located in subcapsular zone and lined by cuboidal epithelium. However, such cysts were also observed in the controls (more often in premature newborn). We believe that this feature can not be considered pathologic.

Abnormalities of Form

Abnormalities of the form of kidneys are very typical for Edwards' syndrome, where they are found in 25% of cases (51 out of 209). The most common type of these anomalies is the horseshoe kidney, less commonly the L- and cake-like kidneys. Horseshoe kidneys in Edwards' syndrome have not been studied in detail but Butler *et al.* have reported glomerular cysts in such cases (Butler *et al.*, 1965). Horseshoe kidneys were found in 2 of our cases with trisomy 18, and L- form in one. There were small glomerular and rare clusters of tubular cysts lined by tall columnar and cuboidal epithelium and surrounded by connective tissue.

Horseshoe kidneys were also found in rare abnormalities of the autosomes (Shaw *et al.*, 1965; Pfeiffer, 1968).

Abnormalities of Location

Ectopia of kidney, mainly the pelvic kidney, was found in Patau's (Huttova *et al.*, 1971), Orbeli's (McIntyre *et al.*, 1964), r(4) (Hsu *et al.*, 1970; Witkowski, 1972) and 9p- (Leisti, 1971) syndromes. Crossed renal ectopia with fusion was observed in autopsied cases of trisomy 18. The frequency of this anomaly in consecutive autopsies is about 1:12000 (Pytel, 1969). This malformation was not found in other types of chromosomal disorders.

Renal Dysgenesis

One of the most frequent abnormalities of the urinary system is renal dysgenesis, where clusters of hyaline cartilage and primitive ducts are usually observed. The persistence of metanephric blastema, cysts (not caused by inflammation and sclerosis) may be also considered as evidence of dysgenesis. Renal dysgenesis may be simple or cystic, uni- and bilateral, focal, segmental or total (Kissane, 1966). The kidneys with simple dyplasia are diminished with small cysts on a surface (Kravtzova and Lazjuk, 1975). Many cysts of different sizes are seen in cases of cystic dysgenesis in which normal renal parenchyma is usually absent. Cystic dysgenesis is frequently accompanied by ureteral malformations (atresia, stenosis, hypoplasia, aplasia etc.). Our analysis of literary and own data revealed that simple dysgenesis was mentioned in 4 of 21 cases of triploidy, in 2 of 14 cases of Wolf's-Hirschhorn's syndrome and in 15% of cases of Edward's syndrome. This malformation is described also in trisomy 8 (Saint-Rome *et al.*, 1972), partial trisomy 1 (van den Berghe *et al.*, 1973), ring-9 chromosome (Butler *et al.*, 1967), and other chromosomal anomalies.

We found a simple renal dysgenesis in 4 of 28 cases of Down's syndrome and in 3 of 7 cases of Edwards' syndrome. In all, the size and weight of kidneys were decreased and histological examination revealed primitive ducts, tubules and ductules; glomerular, ductal and tubular cysts, persistence of metanephric tissue and proliferative stroma (Fig. 1a–d).

Cystic renal dysgenesis is described in some cases of triploidy, trisomy C (10?) (Reinwein *et al.*, 1966; Juberg *et al.*, 1970; Beaudoing *et al.*, 1972) and rarely in cases of r (22) (Picciano *et al.*, 1972), Bq+ (Prats *et al.*, 1967) and some other abnormalities. We found unilateral cystic dysgenesis in case of Orbeli's syndrome (Lazjuk *et al.*, 1973) and bilateral dysgenesis in case of partial B trisomy due to maternal rearrangement.

Some authors attribute the malformations of kidneys in Patau's syndrome to dysgenesis (Blanck *et al.*, 1964) believe that renal anomalies in this syndrome are a peculiar type of polycystic kidney disease.

Analysis of 151 autopsy cases of Patau's syndrome from the literature (Bocquet, 1968; Pfeiffer, 1968; Taylor, 1968; Lazjuk *et al.*, 1971) and 24 of our own revealed that abnormalities of urinary system occur in 63%. The most typical malformation in the increase of embryonal lobulation and the weight of kidneys and the presence of small, usually cortical cysts (Fig. 2a).

The relative weight of kidneys in Patau's syndrome was $1{,}43 \pm 0{,}05\%$ of whole body weight (compared to controls—$1{,}06 \pm 0{,}01$; $p < 0.02$). The excess of embryonal lobulation was a common malformation, the number of lobules was usually

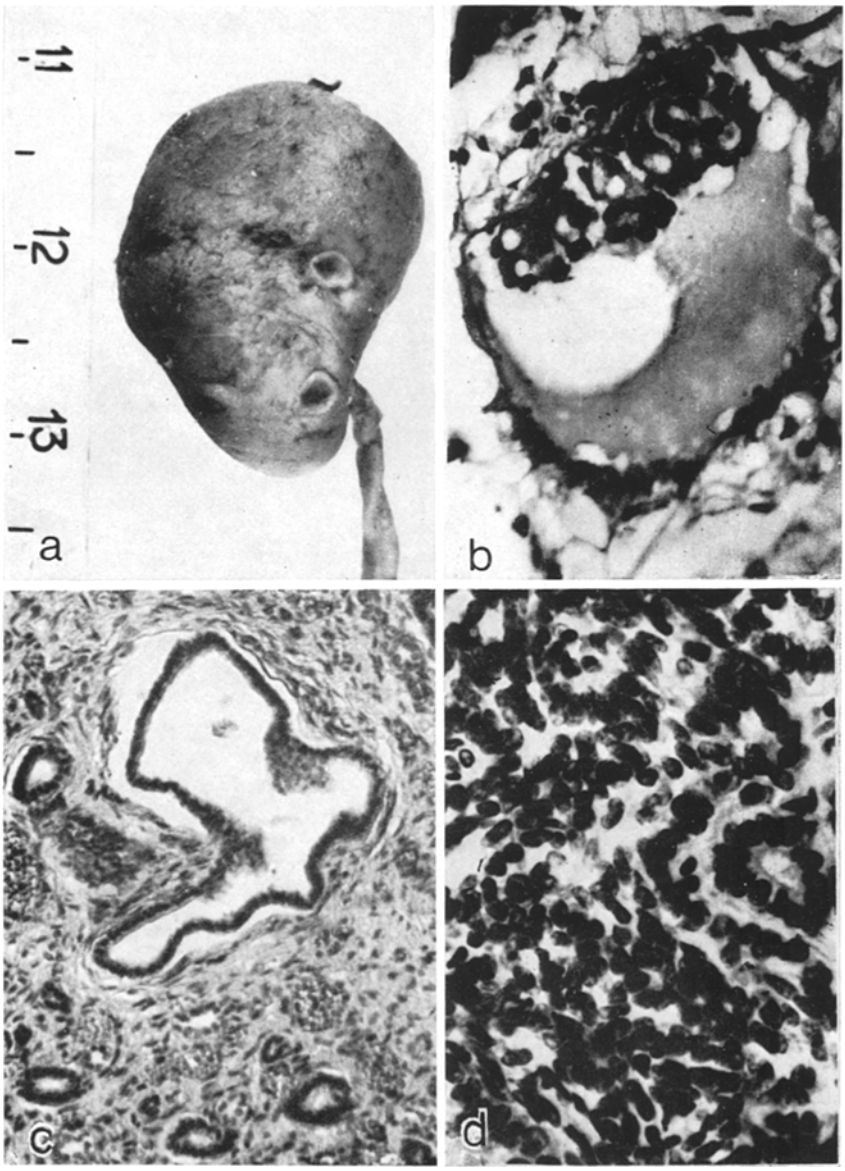

Fig. 1 a—d. Renal anomalies in Edward's and Down's syndromes: (a) small dysplastic kidney with two cysts on the surface (Down's syndrome); (b) glomerular cyst lined by cuboidal epithelium (Down's syndrome) H & E, ×240); (c) primitive tubules and cyst surrounded by a fibromuscular collar in medulla (Edward's syndrome) (H & E, ×60); (d) metanephric blastema in full term infant (H & E, ×240)

40–60 and more (15–20 lobules are normal for newborn). Small cysts, 1–2 mm in diameter, were observed on the surface of cortex, and less frequently in medulla. Larger cysts (more than 5 mm in diameter) were found only once in our cases and reported in one case by Mottet and Jensen (1965). There were glomerular, tubular

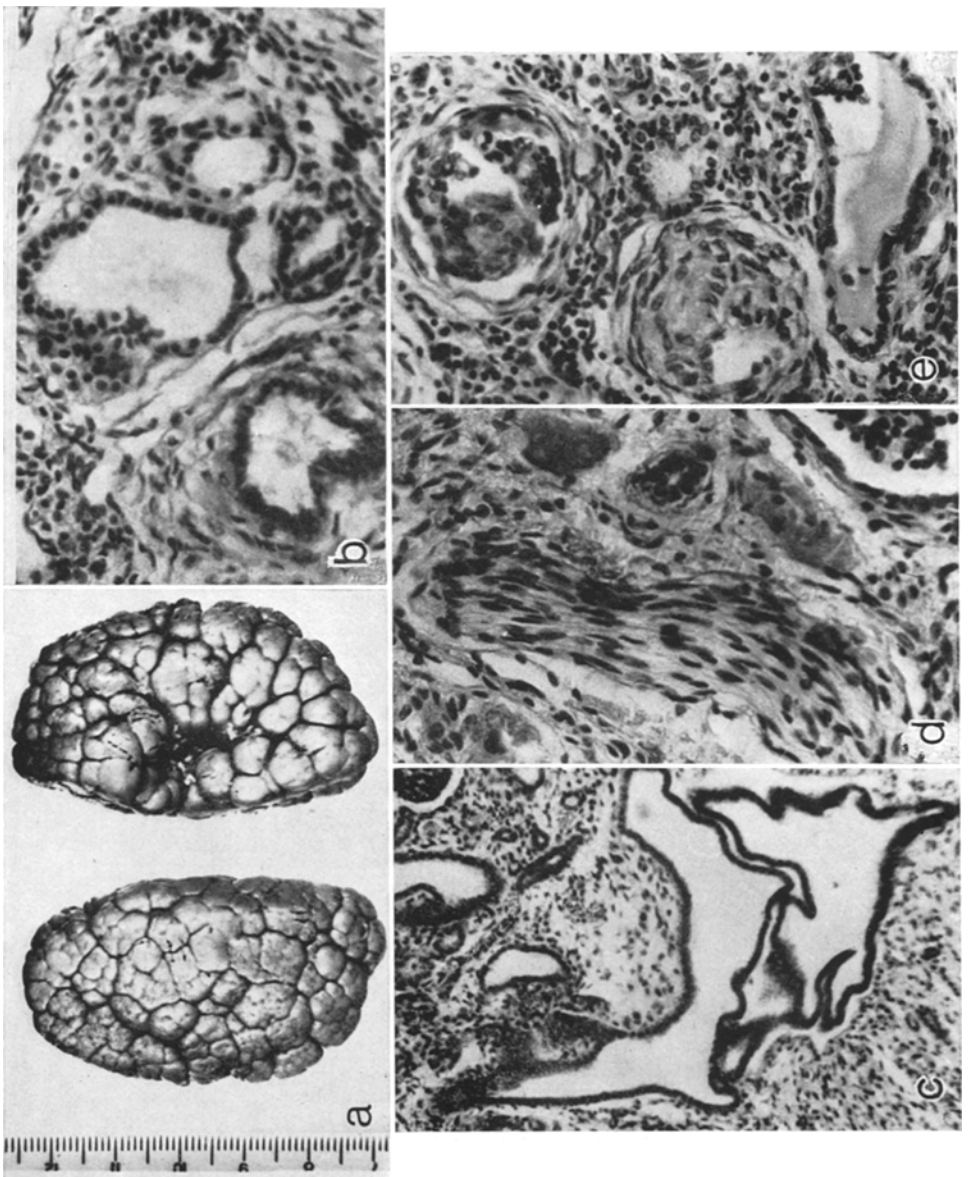

Fig. 2 a—e. Renal anomales in Patau's syndrome: (a) an excessively lobulated kidney with small cysts; (b) and (c) tubular cysts and primitive ducts in cell-rich medulla (H & E, ×140); (d) a cluster of smooth muscles in cortex (H & E, ×140); (e) glomerulosclerosis and tubular cyst in cell-rich stroma (H & E, ×140)

and ductal cysts in cortex and medulla (Fig. 2b, c). Persistence of metanephric blasteme with primitive ducts, ductules, glomeruli, tubules, clusters of smooth muscles in cortex were also found in our cases of Patau's syndrome (Fig. 2b–d). There were also glomerular, arterial and arteriolar sclerotic and hyperplastic changes (Fig. 2e). These abnormalities (excess of embryonal lobulation with increase of weight and cystic changes) have not been reported in other chromosomal disorders or in the control group.

Renal abnormality in Patau's syndrome is a distinct malformation not found in other syndromes.

Infantile polycystic kidney disease and medullary "sponge" kidney have not been described in chromosomal abnormalities. Karyotypes have been normal in such cases (Hole, 1967; own observations).

Hydronephrosis

Hydronephrosis occurs virtually in all types of autosomal aberrations. It is most common in the "cat-eye" syndrome (28,5%) and trisomy 8 (Malpuech *et al.*, 1972; Jacobsen *et al.*, 1974). Hydronephrosis is usually secondary to an organic obstruction of the urinary tract. According to the literature obstructive changes in urinary tract were observed only in one-third of the cases of hydronephrosis in chromosomal diseases. Nevertheless, it is impossible to speak about a primary non-obstructive hydronephrosis, when ureters have not been histologically examined.

The degree of hydronephrosis can vary from the dilatation of pelvis and calyces to almost complete atrophy of parenchyma with the formation of sack-like structure. The latter occurs usually in stillborns.

Other Abnormalities

Other abnormalities of the urinary tract are as frequent as malformations of kidneys. Most common of these are duplication of ureters, hydroureter and hypospadias.

Duplication of ureters is usually accompanied by duplication of the pelvis and kidneys. It is the most frequent type of malformations of the urinary system. This anomaly occurs in 15% of cases of Edwards' syndrome, where it is usually complete. In some cases it is associated with ureteral fusion. We have observed this abnormality in one case of Edwards' syndrome and in two cases of Patau's syndrome. The histological changes in kidneys were typical for these syndromes.

Megaloureter is not associated with chromosomal disorders.

Hydroureter is accompanied usually by hydronephrosis. It is caused by the obstruction in the lower urinary tract, as in non-chromosomal diseases.

Ureteral dilatation (diameter more than 0,5 cm in newborns without apparent obstruction in the lower part) must be distinguished from the primary megaloureter and hydroureter. We have observed this abnormality in 9 cases. Hypoplastic changes of musculur filaments of the longitudinal layer and reduction of epithelium were seen in all cases. Instead of the common muscle layer there were only thin filaments of muscle divided by connective tissue. In 5 cases neural

cells were hypoplastic. Whether these are primary or secondary is difficult to determine.

The cause of ureteral dilatation is possibly persistence of embryonal-like ureter, where muscular hypoplasia is common. This view confirms the opinion that most congenital malformations in chromosomal disorders are due to cessation or delay of normal development.

In an older age ureteral dilatation may lead to a pathological reflux, pyelonephritis and hydronephrosis.

The most common type of abnormalities of the urethra is hypospadia. It was found in 84% cases of Wolf-Hirschhorn's syndrome, in 41% cases of Orbeli's syndrome and in 33% of cases with triploidy. Abnormalities of bladder (mostly as the persistence of urachus) are rare.

Discussion

Abnormalities of urinary system in chromosomal disorders occupy the third position in frequency following malformations of central nervous and cardiovascular systems. Most frequently this system is involved in "cat-eye", triploidy, Orbeli's (13q-) and Patau's syndromes. Nearly all known malformations of the urinary system are observed in children with chromosomal diseases, but the frequency is not the same in different syndrome.

Some abnormalities (*e.g.*, simple dysgenesis) occur virtually in all chromosomal disorders. These are regarded as nonspecific. Other abnormalities are characteristic for certain chromosomal diseases and may be regarded as specific: unilateral renal agenesis observed in 4p- and 13q- syndromes, a crossed renal ectopy with fusion and horseshoe kidney seen in Edwards' syndrome, hypospadia found in 4p-syndrome and an excess of embryonal lobulation of kidneys with the increase of its weight and cystic changes seen in Patau's syndrome.

The pathogenesis of malformations of the urinary system in chromosomal disorders is complex and has not been adequately investigated.

The urinary system consists of two components: the secretory (metanephric blastema) and the excretory (ureteric bud). Normal morphogenesis of kidneys is possible only if both are present.

The mechanism of development of the majority of abnormalities of the urinary system in chromosomal diseases is connected with the delay of development of nephrogenic blastema and ureteral bud. Depending on the time of such delay agenesis, cystic dysplasia, duplication, abnormalities of form, ectopy and ureteral dilatation may be observed.

Bilateral renal agenesis can be due to a deficiency of the nephrogenic ridge which fails to show any potentiality for differentiation as renal tissue. In such cases the genitalia are usually absent (Ashley and Mostofi, 1960). In 4p- and 13q-syndromes renal agenesis is believed to be due to a different mechanism: inhibition of metanephric blastema and (or) the ureteric bud up to 32nd day of embryonal development. It is very likely that teratogenic influence of these deletions affect renal morphogenesis very early.

Pathogenetically, cystic renal dysgenesis may be primary or secondary. The former is caused by the damage of differentiation of metanephric blastema.

Teratogenic terminational period (TTP) of primary cystic dysgenesis ends by the 32nd day of embryonal development, so the embryos of 32 days have formed nephrons (O'Rahilly and Muecke, 1972), but there is not a single formed nephron in primary cystic dysgenesis. Secondary cystic dysgenesis is due to an obstruction in the lower urinary tract (Bernstein, 1968; Osathanondh and Potter, 1964). TTP of ureteral and urethral atresia must be considered in the discussion of the time of teratogenic influence in this malformation.

Renal dysgenesis results from disturbance of differentiation and delay in development of metanephric blastema. Normally nephrogenesis continues up to 34th week of intra-uterine development (Osathanondh and Potter, 1964). Therefore, the influence of teratogenic factors during different stages of this period can have different manifestations. Thus dysgenesis with hyaloid cartilage and persistence of primitive ducts and renal hypoplasia found in triploidy is the earliest malformation. Renal dysgenesis with primitive structures and small cysts in cortex, which are typical of autosomal trisomies, may be a consequence of such influences in later periods.

Double ureters were detected in early human embryos of maximal length 8–10 mm, the 37th day of development (Tondury, 1973) and therefore TTP of this malformation is limited to the end of the 5th week of development.

Renal ectopy is the result of disturbance of renal elevation from the pelvis, where the kidney is located until the 37th day. The kidneys complete their ascent by the 51st day (O'Rahilly and Muecke, 1972), therefore factors that affect this process must act up to that period.

According to Tondury (1973), TTP of a horseshoe kidney is 28–30 days. Therefore a teratogenic effect of extra chromosome 18, where a horseshoe kidney is frequent, affects renal development before the 28th day of pregnancy.

Formation of cysts is due either to hyperplasia of tubular interstitial parts or inhibition of ampula (Baxter, 1965; Osathonondh and Potter, 1964). The earlier a teratogenic factor acts, the more pronounced are the cystic changes. Cysts in chromosomal diseases are usually small, they lie in external parts of cortex and, more probably, they are formed after the 8th week of embryonal development. The mechanisms are probably not the same in different cases.

Formation of excessively lobulated cystic kidneys in Patau's syndrome is probably related to the acceleration of the division of the ureteral bud. This leads to excess lobules and cystic appearance. Glomeruli are formed by the cell masses of blastema, and if these are insufficient to form glomeruli the blind tubules become cystically dilated. Other mechanisms for cysts' formation are also possible.

The formation of lobules begins at the 7th week. In a 51-day-old embryo the surface of kidneys is slightly lobulated (O'Rahilly and Muecke, 1972), and the 56-day-old embryo has well formed lobules (Osathanondh and Potter, 1964), so the influence to form excess lobulations lasts until that time.

The specificity of different renal abnormalities in different chromosomal diseases allows us to postulate a scheme of sequence of the realization of chromosomal imbalance upon the morphogenesis of the kidneys and the urinary tract. Apparently, the results of 4p-, 13q- and triploidy, leading to renal agenesis or cystic dysplasia, affect morphogenesis in very early development. Phenotypic realization of supernumerary chromosome 18 reveals itself later and leads to

abnormalities of the form and cross renal ectopia with fusion. The effect of supernumerary chromosome 13 is realized still later. Absence of accurate information on interrelationship between different types of renal malformations, the possibility of development of different malformations at the same time (malformations which may be divergent rather than consequential) and the deficiency of our knowledge about TTP or renal abnormalities do not allow a more precise scheme of phenotypic realization of chromosomal imbalance upon renal morphogenesis.

The morphology of abnormalities of the urinary system in chromosomal diseases does not differ from renal anomalies in nonchromosomal syndromes. However, the structure of renal malformations in chromosomal disorders is different. The most common malformation in chromosomal disorders is simple renal dysgenesis indicating an unspecific delay of development and it appears in all types of chromosomal abnormalities. At the same time not a single case of infantile polycystic kidney was found in chromosomal disorders, whereas its frequency in general population is, according to our data, about 1:11000 births. On the other hand, not a single case of excessively lobulated cystic kidney, as is found in Patau's syndrome, was observed in non-chromosomal disorders.

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Dr. Garina I. Kravtzova
Department of Pathological Anatomy
Minsk Medical Institute
Minsk 220000, USSR