Vesico-Renal Reflux Disease: Genesis and Natural Progression

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It is the knowledge of the origin of a disease that allows us to comprehend morphological and pathophysiological basis correctly. Regarding vesicoureteric reflux there is a contradictory dualism:
The pediatric doctrine points to an exogenous causatory mechanism, a bacterial one. The predominatly urological doctrine sees a more endogenous course and regards the bacterial component as a clinically important secondary disease. Both doctrines represent many correct theories, but are also incomplete.

The dualism can be reversed with a view that there is reflux with and without obstruction, both mechanical and functional, representing different severity grades. In other words, there is simple (non obstructive) and complex (obstructive) reflux. Surely this nomenclature is somewhat outdated as it only offers a hydromechanic explanation. We wish to demonstrate this embryologically. Simple reflux can carry both low or high disease relevance, while complicated reflux is always associated with high disease relevance. Common to both primarily is an endogenously pathologically deformed trigone.

Simple reflux as a result of trigonal malformation

The bladder trigone originates from the Wolffian duct and serves as a communication between detrusor and urethra. Embryogenetically it acts as an organizational centre for all supravesical derivations of the ureteric bud: ureter, renal pelvis, papillae and pyramids. In the next stage they induce and form the metanephros, future renal parenchymal tissue. This old view [21], to transmit from health into disease allows us to assume that an endogenously dysplastic trigone as reflux grading occurs (horseshoe to golfball and megatrigone) can only bring hyper- or dysplastic derivations within a damaged conducting system including fewer malformations in the papillae and pyramids (Fig. 1). The less well formed bud derivate can only produce hypo- or dysplastic renal parenchymal tissue. Increasing trigonal malformation leads to greater degree of renal hypodysplasia, ranging from segmental to global. As a rule, morbidly predominating reflux grades I-II occur with or without minimal hypoplastic diminution. On the other hand, there can be reflux grades IV-V with only marked dysplasia.

Stephens' Pan Bud thesis, an inspiration for many authors, leads to the same result. It's argument is a more speculative one, more mechanical, and assumes aberrations of the ureter cranially in less qualitative metanephros components [36].

It is not possible to confirm one postulated chain between distal trigonal and proximal renal hypodysplasia by ultrasound during fetal life. During this time and during the first postnatal days the kidneys have little function and are not clearly distinguishable from their surroundings. High reflux grades, however, are already at this time associated with a certain degree of ureteric and pelvic dilatation, recognisable by ultrasound from the 20th week onwards and this applies to approximately 10 % of all simple reflux cases [2,13]. They show an obstructive superimposed reflux, a complicated one, the minority of which has high disease relevance. This will be the subject of the next section but one of this paper.

Postnatal causative proof of events between ostial deformation and loss of kidney tissue remains unclear in the majority of simple reflux cases. Following a child's first febrile pyelonephritic episode, or the first as pyelonephritis recognised episode, the child attends a second ultrasound examination (following the perinatal one). The kidneys are now visualised and show a refluxive decrease of renal size in one or both kidneys in over 80 % of cases. One

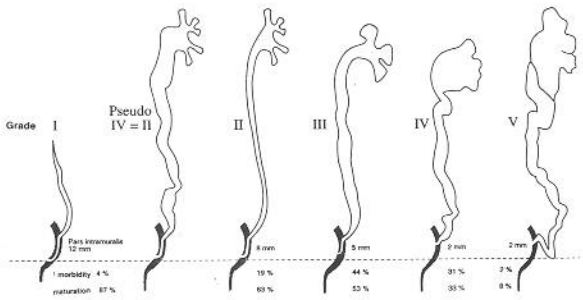

Figure 1. Reflux nephropathy in an embryogenetic system: integrated dependence with greater trigonal-ostial dysplasia increased dysplastic structural loss of ureters and kidneys. Prevesical kink induces a secondary obstructive element.
Below approximate figures of morbidity and maturation.

rarely or never has proof of preceeding normal renal size in these children [2,23,41]. Pyelonephritic reduction in renal size must have occurred within a few days following renal bacterial invasion. This has been proven experimentally, but rarely clinically. It is equally difficult to assess reports of presence of renal scar tissue in up to 30 % of neonates [13,17]. Differentiation between pylonephritic respective hypoplastic or dysplastic renal shrinkage remains constant in further progress. Only marked forms demonstrate dysplasia. Histology can not differentiate hypoplasia from pyelonephritic changes [23,40]. Biopsy would remain unreliable and nephrectomy is rarely indicated in presence of extensive investigations. Nonetheless, nephrectomy indeed contributed markedly in clarifying relationships [25,29,34].

The pediatric teaching doctrine assumes normal parenchymal tissue in all cases initially and explains all parenchymal reduction occurring after infection. It sees it confirmed, as less scar tissue is formed when antibiotic therapy is commenced early. However, this implies a huge neglect of the pediatric doctrine worldwide, as in recent time more scar tissue was formed then was prevented.

Further confusion is added: ascending reflux nephropathy can also occur in normal ostial condition and normal papillae without the ones with a wide broad opening [37]. Incidence is believed to be around 40 %, but appears on average 2 years later [5,12]. As an exception minor (horseshoe) reflux can occur infection free with normal kidneys up to the 6th year of life. This is then followed by septic pyelonephritic events (break-through infections) forming scar tissue, capable of reducing renal parenchymal tissue by 50 % within three weeks. Overwhelming gradual appearance between ostial deformation and nephrorenal diminution has its exceptions. How many is not known.

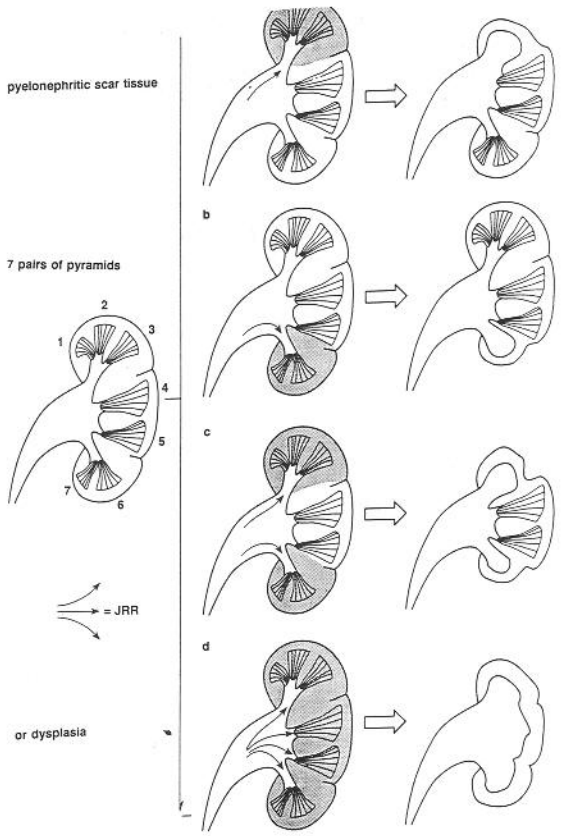

Figure 2. The human kidney usually contains 7 pairs of pyramids, systematically located. Reflux dysplasia can occur segmentally or globally. Concomitant papillae and pyramids (compound) suffer reduction together, always at the poles of the kidneys: either upper pole (a), lower pole (b) or both (c). Generalised reflux nephropathy reduces all pyramids and thus the entire kidney.

Complicated reflux secondary to obstruction

This can be divided into two: The more grave the reflux in children, the greater the likelihood of associated obstruction. One has to differentiate between a simply demonstrated organic obstruction (Valve Syndrome) in boys (A), from a much more difficult proven functional obstruction of bladder outlet which occurs both in boys and girls (B). Half of all valve syndromes occur without reflux and will not be commented upon further. The other refluxive half is mostly associated with gross renal dysplasia [23]. Clarificaton of the different causes thereof is not easy.

A) Reflux due to infravesical bladder obstruction

Deduced from fundamental experiments by Beck (1971) [3] and further thoughts and later confirmations [7,14] it is known that distal bladder obstruction in the first trimester leads to dysplasia, and then renal dysplasia is expressed in pyramidal and nephrorenal loss of induction, combined with known histological criteria of renal dysplasia. The distal obstructive event causes reflux as an integral part of dysplastic potency. Refluxivity of simple reflux, on the other hand, is found in integrated trigonal malformations. Ascendogenesis is the same in both cases. One ends in gross dysplasia (nephrogenic arrest) [7], while the other is limited to hypoplasia or leads to normal renal parenchymal tissue formation (reflux grade I-II). Valvular obstruction adds an obstructive component on top of dysplastic nephropathy, which is expressed in decreased glomerulogenesis in the second and third trimesters [18]. Early embryonic obstruction causes obligatory dysplasia, but is not exclusive [7,24].

Valve syndrome reflux needs further clarification. Valvular obstruction remains ineffective as long as the Allantois tract remains patent. It is now generally agreed that its closure occurs between the 16th and 20th weeks of fetal life [1,10,13,17,19,20,20b]. Valve syndrome should thus occur without dysplastic potency as it occurs in the reflux free half. Reflux cases lead us to assume that detrusor including urodysplasia of the first trimester and that Allantois tract closure occurs prematurely thus leading to obstructive dysplastic potency.

Who, however, sees Allantois closure in 4th to 6th weeks should see valve disease exclusively with reflux dysplasia, which does not happen. Unilateral reflux occurring in bilateral agitating valve syndrome (10-20 %) is difficult to assess. Lastly, it becomes likely that there is a coincidence of two diseases: dysplastic properties with trigonally occurring reflux and infravesical obstructive nephropathy with purely decreased glomerulogenesis [34]. Overall this is a heterogenous composition of reflux nephropathy [20a,31,34] (Fig. 3).

An originally non-refluxive valve bladder can become secondarily refluxive if it is insufficiently de-obstructed (endoscopically), it looses detrusor receptors over a period of years [38].
(Table 1).

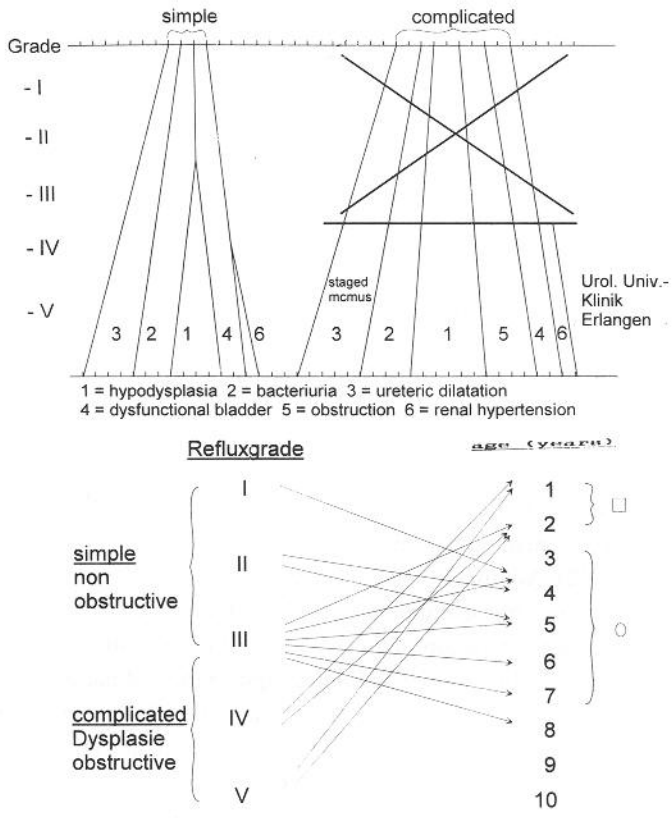

Figure 3 a). Scheme of heterogenous reflux nephropathy, qualitatively and quantitatively, **b)** Low and middle reflux grades (I-III) occurs mainly in girls aged 3 to 7 years. High reflux grades (IV and V) belongs mainly to boys in their first two years of life.

B) Reflux secondary to functional bladder outlet obstruction

B1) Congenital: In vesical, ureteric and renal terms the situation is much the same as in refluxive valvular syndromes, both boys and girls are normal infravesically. As previously, ureteric dilatation becomes sonographically apparent after the third trimester. Histological specimens from suitable nephrectomies and analogue conclusions of fundamental experiments [3] recently performed by Risdon from Great Ormond Street help us to clarify the situation [25,29]. Bladder neck contracture was seen, diagnosed, and operated by YV-plasty successfully in many hundreds of cases in the middle decades of this century. Scarcity of local appearance and insecurity of diagnosis as well as pathophysiological association brought this diagnosis and nomenclature into obsoleteness. Currently we are experiencing a certain didactic renaissance with variations. One extreme form of this disease is the Megacystis Me-

gaureter Syndrome (MCMUS) with its familiar dysplastic kidneys [34]. Very rarely this is also seen in conjunction with a small bladder [9].

Previously mentioned obstructive valvular potency is now analogous to a contracted bladder neck, occurring temporarily during the first trimester. Integrated refluxive dysplasia plus obstructive nephropathy together reduce renal parenchymal tissue bilaterally.

Bladder and ureters are also obstructively dilated, contain residual urine and connective tissue is of poor quality. Who or what relieves distal obstruction remains a matter of speculation. Bladder neck contracture can be induced by experimental lesions to the anterior horn of the lumbar spinal cord [32]. Temporary myelonic immaturity may play a role therein.

B2) Acquired: After mode and time there is a running transformation from temporary intrafetal bladder contracture to later, above all from postnatal to early childhood pathological appearance. What is meant are atypical detrusor contractions, bladder instability, long lasting as well as intermittent short lasting, dysfunctional voiding, with marked appearance of detrusor sphincter dyssynergy (DSDS), all variations of a temporarily increased bladder outlet tone with urinary obstruction. These tend to occur in most refluxive bladders, are causative cofactors of reflux, which realise bacterial pathogenesis of urodynamic reflux [1,12,16,30,33]. It remains open, however, who favors whom to a greater extent: atypical contractions the infection or vice versa.

Pathomorphology of reflux

Uropathy: A simple reflux bladder sustains none or only minimal structural changes. In micturition free intervals ureters are of normal size. During micturition dilatation occurs, as can occur in any smooth muscle. It can range from minimal to marked, radiologically gradable from I toV. It contains errors however, because idiopathic, later spontaneously healing dilatations of ureters and renal pelves can occur with reflux and can be mistakenly identified as a higher grade reflux than actually present (pseudo IV) [2,31,34]. In higher reflux grades the simple reflux ureter has a kink in its opening which can become obstructive. Extravesication is a commonly used term for this and maybe causative for the rarely refluxive isolated megaureter.

Concomitant ureteric dilatation occurring in reflux disease is composed of three factors; these increase with increasing illness relevance. Firstly there is structural tissue lack, secondly hydrodynamic dilatation due to distal obstruction and residual urine and thirdly as a result of bacterial toxins. Much is capable of spontaneous regression later. About 8 % of reflux morbidity [24] have a distal-proximal correlation, where distally disturbed hydrodynamics causes similar disturbance proximally at the pyelo-ureteric junction. Pyelo-ureteric obstruction may also occur incidentally independent of reflux.

Complicated reflux bladder is damaged two fold by early embryonic obstruction from the beginning. The detrusor is dysplastic and has less muscle tissue, which is replaced by connective tissue. Increased volume (seldom decreased) and incomplete bladder emptying follow. Ureters and renal pelves suffer similar circumstances. Residual urine is now constantly present. Formal cause: In order to gain sufficient action potential each muscle fiber is overstretched. Its energy is exhausted prior to complete bladder emptying. Muscular and urodynamic decompensation has occurred. Superimposed infection accelerates this process.

Intrarenal reflux, pyelonephritic reduction and scar tissue formation, occur in parallel with level of previously damaged papillae and pyramids. Histologically this is an interstitial nephritis, which decreases or destroys many nephrorenal elements by hemoobliteration. The cirrhotic process is also ex-

Table 1. Endogenous and exogenous genesis of vesico-renal reflux=A+B

A 1)	Trigonally disorganised local uromorphology - decreased metanephrorenal induction - (1st Trim.). I-normal, II-mild (most cases), III-moderate, IV-V-grave
2)	Temporary bladder outlet obstruction (1st Trim.) obstruction specific urorenal hypodysplasia
3 a)	Valve syndrome (infravesical), obstruction specific, similar to 2) in addition (2nd-3rd Trim.) quantitative diminution of glomerulogenesis
3 b)	Primary non-refluxive, non-dysplastic, purely obstructive uronephropathy, later secondary refluxive due to loss of detrusor receptors if insufficient endoscopic de-obstruction
4)	Prune Belly syndrome, similar to 3a) but only temporarily obstructive
5)	Reflux of congenital neurogenic bladder due to lack of innervation of detrusor and pelvic floor
	1)=simple reflux (majority of cases)-2-5)=complicated reflux (minority of cases)
	in 2 and 3a) hypothetically premature closure of the Allantois tract
B)	Postnatally in addition to 1-5: Recurrent ascending bacteriuria with pyelonephritis and segmental renal shrinkage (scar tissue), symptomatically dominant.

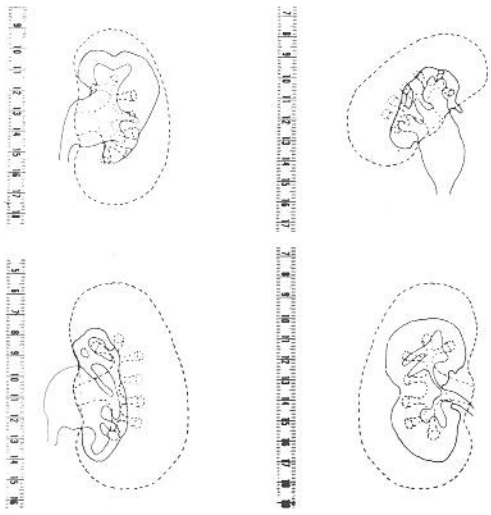

Figure 4.1) 10 year old girl, reflux IV, reflux nephropathy, parenchymal loss 67%, decreased renal length 35%, marked presence of lacunae as sign of pyramidal reduction, renal pelvis dilated by 9%, hypertension. (Upper left)
4.2) 8 year old boy, reflux V, reflux nephropathy, parenchymal loss 78%, decreased renal length 44%, marked lacunae, secondary pyelonic dilatation due to reactive pyelo-ureteric stenosis, hypertension. (Upper right)
4.3) 14 year old boy, MCMUS, urethral valve, bilateral reflux V, renal transplant, parenchymal reduction 88%, extensive lacunae, pyelon, ureters and bladder all dilated, decreased renal length 35%, hypertension, histologically dysplasia. (Lower left)
4.4) 15 year old girl, Ask-Upmark, variation of reflux nephropathy, fibromuscular dysplasia of the renal artery, parenchymal reduction 58%, decreased renal length 31%, typical middle-denting. Sterile urine culture, hypertension (34). (Lower right)

plained by a superoxidase disturbance. An enzyme (NAG) should give quantitative information. Loss of renal parenchymal tissue in simple reflux can lie in the order of 10-80 %, in complicated reflux damage is always considerable (Fig. 4).

Bacterial component of reflux disease

The bacterial component plays a major role in reflux disease. Regularly occurring false diagnoses of urological febrile illness in infancy has grave consequences. Many authors see the first year of life as the decisive one regarding exogenous reflux proportion. Congenital reduction of renal parenchymal tissue as such would be compatible with normal long life expectancy. Hydrodynamically reflux has hardly any damaging effects (waterhammer-effect).

Bacterial invasion of renal tract has its presumptions which are numerous and complex. Bacteria originate from the fecal pool, usually independent of anal hygiene. It is not known whether all colonic bacteria are capable of urological tract invasion. Mainly adhesion potent, fimbriae containing and blood group antigen containing bacteria are believed to be the most pathogen ones urologically. Distal urinary tract mucosa contains several receptors favouring these bacteria. Physiologically one can assume a perianal immunological defence state. In cases of reflux this must be disturbed. Whether influenced by bacteria or not, the female urethra is susceptible to bacterial invasion, by being structurally muscularly immature, or only demonstrates this immaturity in form of a temporary urethral dilatation with concominant unphysiological urinary stream turbulance. Bacteria can thus enter the bladder. Urodynamic reflux then carries them further cranially, which again is not uncomplicatedly simple, but is associated by atypical detrusor contractions, also at rest, associated with increased intravesical pressure. This is also favoured by small volumes of residual urine, which prolong bacteriuria and favor bacterial reproduction. Resulting pyelonephritic action usually heals completely with antibiotic treatment. Frequent recurrence in unpredictable intervals may result from the periodic character of the above mentioned contractions, summarized by the term "unstable bladder".

Characteristic progression of reflux disease

Male dominance occurs in the first two years of life. It's higher disease relevance has several causes. The younger the child, the greater the danger to the urosystem. More aggressive Proteus species tend to predominate in boys. Furthermore mechanical obstructions are far more marked with complicated reflux. Physiological or pathological phimosis also plays its part [41]. At the age of 3 years reflux boys are more or less in a recurrence free state, with variable renal defects [37].

Female dominance: Girls tend to predominate boys by a factor of 6 to 1. Dysplasia potent functional bladder neck obstruction in the first trimester, temporary, rarely persisting, occurs as in boys, but remains a minority. Characteristic reflux disease tends to occur at the age of 3 years in girls, when transformation from reflex to voluntary micturition has occurred. It occurs with disturbances, with immature neuromuscular smooth muscle contractions, within the previously mentioned unstable bladder together with infection predisposing properties and cofactors which are susceptible to spontaneous healing

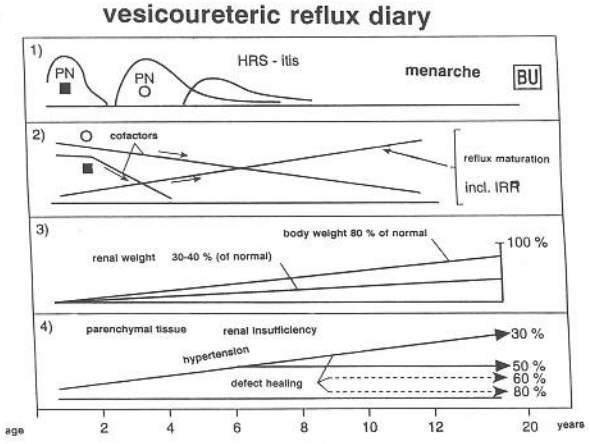

Figure 5.1) Schematic representation of renal reflux events by calendar. Febrile pyelonephritic episodes commence and cease earlier in boys than in girls. After 5th-6th year of life pyelitis is more frequent than pyelonephritis. At menarche all bacterial infections cease. **5.2)** Co-factors disappear earlier in boys than in girls. Maturation of urodynamic reflux begins individually during first year of life and ends at puberty in about 90% of normal.
5.3) In high grade reflux kidney weight may only reach 30-40% of normal, while body weight is 80% of normal.
5.4) If 50% or more of normal parenchymal tissue remains after defect healing renal insufficieny does not occur. If it falls to 40%, or less, clearance demand exceeds capacity of underweight kidneys in the second decade of life.

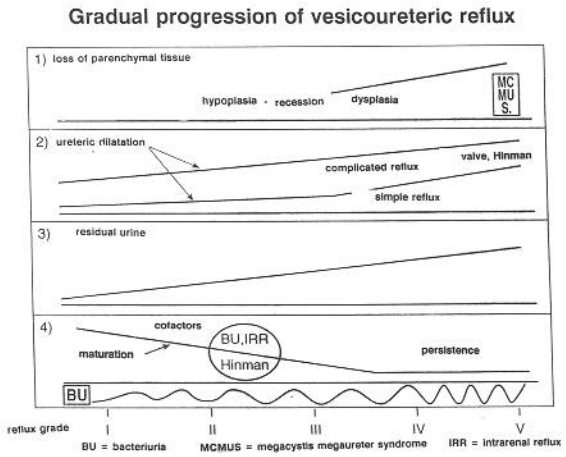

Figure 6.1) Schematic graduation of reflux. I and II occur mostly without parenchymal damage. Hypoplastic decrease occurs with grade III. Maximal grade is compatible to MCMUS.
6.2) Ureteric dilatation is less in simple reflux than in complicated reflux. Greater dilatation in ostial-low reflux is due to coincidental idiopathic dilatation (pseudo IV), which regresses spontaneously.
6.3) With increasing reflux, residual urine increases.
6.4) Tendency of maturation is greatest in grades I-II and decreases in grades IV-V. Cofactors and bacteriuria behave in parallel.

in due course. As long as bladder instability persists medication with anticholinergics is necessary in addition to antibiotics.

Familial predisposition: There appears to be a weak familial predisposition to reflux of 12 % in a large study of reflux children at the Mayo clinic [22]. Disease progress is also more marked in familial predisposition [2].

Maturation of reflux disease - detangling of cofactors

Unnoticed, since having remained without disease relevance, the majority of reflux disappears spontaneously during the first weeks or months of life. An incompleteness from fetal time thus disappears alone. Established picture of illness with ability to spontaneous healing, however, with a renal defect of varying severity, which can amount to 10-80 % of normal parenchymal tissue. Uromechanic maturation, cessation of backflow is indeed a neuromuscular maturation. Functional recovery occurs in parallel, so that the initial entagled cofactors now detangle themselves. Atypical detrusor contractions disappear, dysfunctional voiding disappears, bacteriuria disappears, or remains limited to the distal urinary tract. The nearer girls approach menarche, the more certain it is that the majority of reflux is cured. Prior to reflux cessation there is often a phase of intermittent reflux [2,37]. There is age related as well as gradual occurence of disease, it is not a minority of morbidity (Figure 5,6).

Progression of reflux nephropathy

Concerning previously frequently described progression of scar tissue, with or without persisting blackflow, incidence varies greatly between 5% and 35 % [15,35]. Over 10 % of all adolescent patients are probably not affected at all and hardly anybody is affected seriously. Progression is known to occur independently of disappearing bacteriuria [33].

Persistence of reflux: In 10 % of patients reflux persists into adulthood. Ostial golfhole deformity is the overwhelming proportion. On the other hand there is persistent reflux in grades I-II, which gains disease relevance for the first time after menarche, contributed to by cohabitation, which triggers atypical detrusor contractions, a property, which has not occurred during childhood in this manner. This is more an exception then the rule.

In male morbidity there are bilaterally extremely refluxive megaureters, which are initially noticed during the third or fourth decades of life with

symptoms of renal insuffciency. A bacterial component need never have been present. In unilateral cases it can persist with a little disease relevance till the end of a normal lifespan.

Prognosis of reflux disease: Unilateral reflux, whether recognized or not, whether treated conservatively or surgically, heals spontaneously in the majority of cases at menarche or puberty with its concominant individual parenchymal defects. Disease relevance ceases, providing presence of a normal second kidney. Persistent ostial deformation and transposition can be diagnosed cytoscopically over extended periods of time.

Bilateral reflux does not enter a state of stable parenchymal defect healing, but with a remaining disease relevance as a result of decreased global renal function, it goes in parallel with extent of parenchymal tissue loss. When this reaches 2/3 of the total, the child becomes at risk of renal insufficiency. Unlike the adult, who can lead a perfectly normal life with 1/3 of its total parenchymal tissue, the child enters a difficult contrast between renal and body growth. Body growth continues normally, while renal growth almost entirely ceases. The increased need for renal clearance, parallel with increasing body weight, can no longer be met. Renal insufficiency becomes inevitable.

This occurs in the second decade of life [34]. Dialysis and transplantation then enter in their own right. Nephrologists define terminal reflux nephropathy as a glomerular focal sclerosis, hyperfiltration and overload. A proportion of these children concomitantly suffer renal hypertension. Incidence of this is variable[40]. How many of these children die from cerebrovascular or cardial complications is not known.

With tolerable defect healing future pregnancies are a risk dependent on degree of renal functional loss. Purely unilateral disease has no ill effect.

Unusual forms of reflux disease: Ask-Upmark kidney: This is always hypoplastic, parenchymal tissue reduced by half or more, mostly without bacterial component, causing hypertension, always with abnormal renal artery structure [26].

Duplex kidney: The upper moiety usually perishes due to obstructive aberration of its ureter, almost always dysplastic, the lower moiety suffers high grade reflux with concomitant loss of renal parenchymal tissue, always strongly hypoplastic, not necessarily influenced by bacterial pyelonephritis. Disease of the lower moiety can also occur with a normal upper moiety, which then shows compensatory hypertrophy.

Struvit-kidney: Whether integratedly deformed or normal ostia, urea splitting bacteriuria causes and maintains reflux and leads to extensive kidney damage.

Relations of reflux disease. Congenital neurogenic bladder: Myelodysplasia or sacral dysgenesis are concomitant entities with considerable urological problems. Both belong to complicated reflux conditions. Reflux occurs with all its consequences due to lack of innervation of bladder and pelvic floor.

Prune Belly Syndrome: Genetically, uromorphologically and clinically very similar to the dysplastic valve syndrome. Initial temporary infravesical obstruction must be submitted.

Therapeutic background of reflux therapy

Prompt antibiotic treatment of each pyrexial bacteriuria, together with anticholinergic medication is mandatory. This should be followed by endoscopic bladder de-obstruction of any known outflow hinderances as soon as possible, followed by bladder training.

Invasive therapy

In severe cases prolongation of intravesical ureteric distance by surgical reimplantation or endoscopic injection of inert material (e.g. collagen) is indicated.

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Addenda

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