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Part I: Alloplastic Procedures, Urodynamics, Surgical Techniques, New Technology, Experimental Oncology

Organisation of the Abstracts: A. Kelâmi, H. Melchior and F. H. Schröder

Alloplastic Procedures

PRESSURE AND GEOMETRY OF URETERIC PROSTHESES

D. Jonas, J. H. Spurk, M. Sellmann, and W. Weber

Urologische Abteilung im Zentrum Chirurgie, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, FRG

Fachgebiet Technische Strömungslehre der Technischen Hochschule Darmstadt, FRG

The urodynamic characteristics of two ureteric prostheses were investigated. One of constant diameter (CD) (3.2 mm internal Scurasil^{R}) and the second (VD) increasing in internal diameter from 3.2 mm to 8.0 mm at the distal end. Pressures in the prostheses were measured during perfusion of a 20 cm length of prosthesis with a peristaltic pump and also with the prostheses implanted into a dog's ureter. These studies showed that the pressure in the VD prostheses was lower (0.3 mm Hg) than in the CD prostheses (2 mm Hg). Viscous resistance is negligible under these conditions and the pressure rise is due to inertial resistance as the bolus entering the prosthesis has to accelerate and displace fluid already in the lumen. If the diameter of the prosthesis increases, the inertial resistance decreases by $\frac{1}{D^2}$.

In a chronic study 5 VD prostheses and 3 CD prostheses were implanted in 5 dogs. Two VD prostheses failed for technical reasons, but two of the three dogs each with one VD and one CD prosthesis showed less dilatation of the upper ureter and pelvis on the VD side, suggesting that a small rise in pressure maintained over a long period may be responsible for significant dilatation of the urinary tract. The geometry and dynamics of the VD prosthesis appear to be superior to the CD prosthesis.

(References can be requested from the authors)

Dr. D. Jonas
Abteilung Urologie im Zentrum Chirurgie
Klinikum der Johann Wolfgang Goethe-Universität
Theodor-Stern-Kai 7
D-6000 Frankfurt/Main 70
Federal Republic of Germany

A PROCEDURE FOR SUBSTITUTION OF THE URINARY BLADDER

A. Hak-Hagir

Urologische Klinik Kassel, FRG

The possible use of the rectus muscle for the replacement of the detrusor following partial or subtotal cystectomy and for the fashioning of a urinary conduit has been investigated. The rectus muscle in dogs was mobilised with preservation of the transversalis fascia, epigastric vessels and nerve supply (XII).

In six dogs the rectus muscle was used to reconstitute the bladder wall following varying degrees of partial cystectomy. One animal (subtotal cystectomy) died post-operatively and one was sacrificed at two weeks, at which time epithelialisation of the muscle surface was clearly visible. The remaining dogs continued

* Further information concerning individual abstracts and reprints is obtainable from the authors.

to void satisfactorilly and one animal is alive at five months following a subtotal cystectomy and rectus muscle cystoplasty. This dog has normal renal function and a bladder capacity of 400 mls.

In four dogs a conduit was fashioned by implanting the ureters into the muscle by a transversalis fascial tunnel and fashioning a conduit over a tube of siliconised human dura. Three of these animals died at 8, 10 and 12 weeks due to obstruction of the lumen due to concretions. The dura dissolves rapidly leaving a conduit lined by granulation tissue only.

(References can be requested from the author)

Dr. A. Hak-Hagir
Urological Clinic Kassel
Terrasse 30
D-35 Kassel
Federal Republic of Germany

URINARY BLADDER WALL REPLACEMENT IN THE CAT BY HETEROLOGOUS SPLIT AND FULL THICKNESS SKIN-GRAFT

R. Pust, M. Butz, W. Weise, G. Jautzke, and G. Karadsic

Urologische Klinik und Poliklinik and Pathologisches Institut im Klinikum Steglitz der Freien Universität Berlin, Bundesgesundheitsamt Berlin, Robert Koch-Institut

Heterologous lyophilised split thickness porcine skin and human skin have been used for replacement of the bladder wall in cats following partial and subtotal cystectomy. The physical properties of these materials compared with cat skin and human dura are shown in the table.

Physical properties of lyophilised graft materials[a]

Material	Breaking strength ($kp \times cm^{-2}$)	Distension (%)
Porcine skin	35	40
Human skin	105	80
Cat skin	12	55
Human dura	55	20

[a] 1 h soak in normal saline at 21° C

Using 1 mm porcine skin four out of eight cats died from urinary extravasation. With 1.5 mm porcine skin, no complications were observed and bladder capacity was 35% of normal twelve months postoperatively. Transitional epithelium was visible at 8-12 weeks and muscle layers within the graft at 3-4 months. Using human skin bladder capacity was 70% of normal at 9 months and epithelialisation and muscle cells were visible at 3-6 weeks and 1-2 months respectively. A microlymphocytic toxicity test showed mild reaction without graft rejection.

Human skin appears to be superior to porcine skin under these circumstances.

(References can be requested from the authors)

Dr. R. Pust
Klinikum Steglitz der Freien Universität Berlin
Urologische Klinik und Poliklinik
Hindenburgdamm 30
D-1000 Berlin 45

REPLACEMENT OF THE URINARY BLADDER WALL BY A SILICONE RUBBER PROSTHESIS

B. Schreiber, B. Brehmer, W. Homann, S. Göbel, and J. Gasch

Urologische Klinik und Poliklinik, Radiologisches Zentrum - Strahlenklinik, Pathologisches Institut des Universitäts-Klinikum Gesamthochschule Essen, FRG

The possibility of using a silicone trigonal prosthesis has been investigated in the pig. Two types of prosthesis were used. One prosthesis was covered on the external surface with a woven textile layer, and the second was covered with Dacron-velour. Both types of prosthesis had two 10 mm lengths of silicone tube for intubation of the ureters.

The prostheses were implanted transperitoneally following excision of part of the base of the bladder and division of the ureters at the uretero-vesical junctions. The prostheses were fixed in position with Dexon sutures taking care to avoid perforation of the silicone layer or inclusion of the mucosal surface. The ureters were intubated and approximated to the textile layer of the prosthesis with Dexon.

In 12 minipigs the trigone was replaced with the textile-lined prosthesis and rejection occurred in all cases. The prosthesis was extruded into the bladder cavity although no

urinary leakage occurred. Six Dacron-velour prostheses were implanted and four of these remained firmly attached to the bladder wall. No incrustation occurred and histological examination showed ingrowth of fibrous tissue into the Dacron mesh.

The type of textile covering appears to be important and a Dacron-velour covered silicone prosthesis provides for satisfactory healing without leakage or incrustation.

(References can be requested from the authors)

Dr. B. Schreiber
Urologische Klinik
Universitätsklinikum der Gesamthochschule
Hufelandstr. 55
D-4300 Essen
Federal Republic of Germany

ALLOPLASTIC SPERMATOCELE FOR THE TREATMENT OF MALE INFERTILITY

L. V. Wagenknecht, A. F. Holstein, and C. Schirren

Abteilungen für Urologie, Anatomie und Andrologie der Universität Hamburg, FRG

Attempts have been made to implant a silicone reservoir into the epididymis to produce a spermatocele from which sperm can be aspirated for artificial insemination.

Silicone-rubber capsules of 10 mm in length with a volume of 0.12 ml and a 2 mm Dacron felt border (Rüsch, Waiblingen/ Stuttgart) were implanted onto the tail and the head of the epididymis in two groups of 15 rats each. The prosthesis was secured within a preformed subcutaneous pouch. Aspirations of the content of the prosthesis 1-1.5 months after operation showed numerous spermatozoa per field in all animals and at 4 months about 30 spermatozoa per field in half of the remaining animals (at weekly intervals two animals were sacrificed for histological examination).

Six similar prostheses of larger size were implanted onto the tail of the epididymis in bulls followed by 2-3 percutaneous aspirations per week. The results were comparable to those obtained in rats. After deep-freezing at -197° C in pellet-form and storage for 6 weeks, the aspirated spermatozoa were inseminated into cows. Two out of four animals became pregnant.

An artificial sperm reservoir within an alloplastic prosthesis can serve for the collection of spermatozoa in rats and bulls. Spermatozoa of satisfactory morphology and motility can be obtained from the prosthesis by percutaneous aspiration. The nearer to the tail of the epididymis the prosthesis is implanted and the shorter the post-operative period of aspiration, the better the results.

Priv.-Doz. Dr. L. V. Wagenknecht
Abteilung für Urologie der Universität
Martininstr. 52
D-2000 Hamburg 20
Federal Republic of Germany

SILICONE RUBBER PROSTHESES IN THE GENITO-URINARY TRACT. PRELIMINARY REPORT

A. Kelâmi and K. Affeld

Abteilung für Urologie, Klinikum Steglitz and Institut für Experimentelle Chirurgie, Klinikum Westend der Freien Universität Berlin

I. Urinary Diversion

Silicone rubber tubes connected to an inner disc which allows satisfactory fixation to the abdominal wall have been used in dogs for permanent forms of intubated urinary diversion. Satisfactory long-term diversion has been obtained by nephrostomy, intubated ureterostomy, and cystostomy. Renal function was not affected and there were no signs of incrustation. These results are encouraging.

II. Epididymal Reservoir

Silicone rubber prostheses have been sutured onto the caput and cauda epididymis of minipigs. They were irrigated and examination of the fluid obtained shows large numbers of live motile sperms. Successful inseminations have been performed.

III. Artifical Urinary Sphincter

A simple, one piece, fluid-filled, implantable urinary sphincter, working on the capillary principal, has been tried in dogs. A sphincter cuff is placed around the urethra and connecting tubes lead to a reservoir in the abdominal wall. The pressure in the cuff is 50 cm of water.

Perineal pressure on the cuff produces a urethral opening time of 30 seconds during which 500-600 ml of urine may be voided. The

initial results with this simple device appear promising.

(Reprints can be requested from the authors)

Prof. Dr. A. Kelâmi
Urologische Klinik der Freien Universität
Klinikum Steglitz
Hindenburgdamm 30
D-1000 Berlin 45

Urodynamics

URODYNAMIC EFFECTS OF URETHRAL OBSTRUCTION. ANIMAL EXPERIMENTS ON FETAL LAMBS

H.R. Osterhage, J.G. Moormann, and H.D. Eggers

Urologische Klinik and Abteilung für Experimentelle Chirurgie der Universität des Saarlandes, Homburg/Saar, FRG

Further experiments on urinary tract obstruction in fetal life have been carried out in lambs.

Intrauterine urethral obstruction was produced in 21 lambs varying from 50 to 122 days of gestation. Silk, catgut and resorbable polyglycolicacid sutures (Dexon) were used to produce varying degrees of stenosis. The urachus was ligated with silk in all cases. All but two lambs continued to full term.

Urachal ligation alone produces no ill effects on the upper urinary tract. The addition of urethral stenosis results in hydronephrosis and hydroureter which appears to proceed in an antegrade manner. Partial ligation of the urethra with Dexon produces a pyelocalyectasis which may disappear later. More severe degrees of obstruction with catgut and silk produce hydronephrosis, hydroureter and megacystis. The new born lambs void very frequently in small volumes.

Histologically the parenchyma was reduced in thickness with dilated tubules. The ureter was dilated with muscular hypertrophy throughout its length. There was an increase of connective tissue within the bladder. The bladder wall may be extremely thin in cases of megacystis.

These experiments may throw some light on the pathogenesis of the megaureter megacystis syndrome occurring in childhood.

(References can be requested from the authors)

Dr. H.R. Osterhage
Urolog. Univ.-Klinik
D-6650 Homburg/Saar
Federal Republic of Germany

THE INFLUENCE OF BARORECEPTOR CIRCULATORY REFLEXES ON BLADDER CONFIGURATION AND INTRAVESICAL PRESSURE

J. Bödeker and H. Urlesberger

Abteilung für Urologie, Klinikum Charlottenburg der Freien Universität Berlin

Having shown that carotid sinus and aortic arch baroreceptor stimulation had significant effect on the micturition reflex and urethral pressure profile, a further study was undertaken to investigate the effects of baroreceptor stimulation on bladder configuration, intravesical pressure and vesicoureteric reflux in rabbits.

25 cystograms were performed in male rabbits and arterial blood pressure, intrarectal and intravesical pressures were recorded. Baroreceptor stimulation was simulated by electrical stimulation of the depressor nerve.

During depressor nerve stimulation arterial blood pressure decreased but there was no change in intravesical or intrarectal pressures. The bladder configuration was altered and the bladder neck became more funnel shaped. Vesicoureteric reflux was not observed at any stage in the experiment.

(References can be requested from the authors)

Dr. Jürgen Bödeker
Urologische Klinik
Klinikum Charlottenburg
Spandauer Damm 130
D-1000 Berlin 19

PHARMACOLOGICAL EXAMINATIONS OF ISOLATED BLADDER WALL STRIPS

R. Stark and A. Schäfer

Urologische Universitätsklinik Bonn, FRG

The pharmacology of isolated bladder wall strips has been studied in vitro in order to assist the interpretation of the pharmacological effects of drugs on the bladder. The muscle strips from different areas of the bladder are placed in Tyrode solution at 37° C and the registration of movement is obtained electronically. The output from an induction coil is amplified 100 times and transferred to a chart recorder.

A characteristic contraction and relaxation curve is obtained at a muscle load of 7.5 g. Contractions are induced by the addition of carbachol, barium chloride and histamine and can be reduced significantly by the prior introduction of atropine or papaverine.

Further studies of alpha- and beta-adrenergic blocking drugs are in progress.

(References can be requested from the authors)

Dr. Roger Stark
Urologische Univ. -Klinik
D-5300 Bonn-Venusberg
Federal Republic of Germany

ELECTROSTIMULATION OF LARGE AND SMALL INTESTINE IN DOGS

D. Hauri

Urologische Universitätsklinik, Kantonsspital Zürich, Switzerland

In view of the problems associated with the attempted stimulation of the neuropathic bladder and with ileo- or colo-cystoplasty, experiments were conducted to see if intestinal segments could be used as a urinary reservoir and stimulated electrically.

Isolated segments of ileum and colon had electrodes implanted in the submucosal layer and the proximal ends closed. The distal end was either brought out onto the surface of the abdominal wall or sutured to the trigone following subtotal cystectomy. In a third group the intestinal segment was inserted into the posterior wall of the bladder and a subtotal cystectomy carried out at a later stage. Intraluminal pressure was measured in the first group by means of a liquid-filled balloon catheter.

Small intestinal segments show frequent and high pressure contraction waves and during electro-stimulation the height of the contraction waves is reduced although frequency remains constant. Following administration of cholinergic agents the intraluminal pressure rises and contractions become irregular. Additional stimulation stabilises these contraction waves and the amplitude increases. Anti cholinergic agents reduce the intraluminal pressure and further electrical stimulation reduces this still further.

Spontaneous contraction waves within the colonic segments appear to be insignificant. Following stimulation, contraction waves up to 60 mm of mercury are seen. This pattern is variable and appears to be stable only after 6-8 weeks. Provided the animal is not curarised the contractions remained constant with repeated stimulation. Cholinergic agents induce high frequency contraction waves of low amplitude. Additional electrostimulation induces rapid high peaks. The frequency of contraction waves is somewhat decreased by the use of anti-cholinergic agents. Beta-adrenergic blocking agents reduce theamplitude slightly and have a dampening effect on electrostimulation.

The primary anastomosis of stimulated isolated intestinal segments to the trigone were not successful due to urinary leaks. The results of a staged operation appeared to be encouraging.

It appears from these experiments that only the large intestine is suitable for the fashioning of a bladder substitute which can be emptied by electrostimulation.

Dr. D. Hauri
Oberarzt der Urologischen Universitätsklinik
Rämistr. 100
CH-8091 Zürich
Switzerland

Surgical Techniques

PREVENTION OF REFLUX WITH INTUSSUSCEPTION VALVES

P. Rüedi, S. Geroulanos, H. Schauwecker, and H. J. Leisinger

Abteilung für Urologie und Chirurgie A., Universitätsklinik Zürich, Switzerland

The possibility of preventing urinary backflow by the use of intussusception valves in the ureter and in intestinal segments have been investigated in dogs.

In 10 dogs the left ureter was exposed and an intussusception valve created. In one case there was obstruction and in another urinary

leak leading to peritonitis. Fifty per cent of the ureteric nipples prevented urinary backflow when examined by retrograde pyelography. Intrapelvic pressure recording showed no difference in intrapelvic pressure between the operated and control kidneys.

In a second group of 5 dogs two intestinal loops were isolated and the proximal and distal ends of each were sutured to the skin as a cutaneous stoma. In one of each pair of loops an intussusception valve was constructed in an isoperistaltic direction. The other was used as control. Radiological investigation showed free flow of contrast medium in an isoperistaltic direction whereas retrograde injection demonstrated that the intussusception valve prevented reflux. There was free flow through the control loop in a retrograde direction. A pressure rise was measured within the valve-containing loop only on filling in a retrograde direction.

A small bowel intussusception valve appears to be satisfactory in preventing reflux without any obstruction to urine flow.

(References can be requested from the authors)

Dr. P. Rüedi
Schiedhaldenstr. 18
CH-8700 Küsnacht
Switzerland

ANTIREFLUX URETEROILEONEOCYSTOSTOMY IN PIGS

F. Tettamanti and R. Tscholl

Urologische Universitätsklinik, Bern, Switzerland

The successful prevention of reflux during substitution of ileum for the lower end of the ureter has been achieved using an intussusception valve in the ileal segment in pigs.

In six pigs a segment of ileum was isolated and substituted for the lower end of the left ureter. An intussuscepting nipple was formed in the ileal segment and implanted into the bladder wall so that the nipple protruded into the vesical lumen. Post-operative studies at 4 weeks by intravenous urography and cystography showed that there was no upper tract obstruction and no reflux. Perfusion studies showed that the ileal segment handled a perfusion of 10 ml per minute with a pressure rise of 2.5 cm water.

In three pigs the procedure was repeated without nipple formations. Follow-up studies showed massive vesico-ileo-ureteral reflux. Perfusion studies of the normal pig ureter shows that the perfusion at 10 ml a minute results in a pressure rise of 10.5 cm of water.

The use of an intussuscepting nipple appears to be a satisfactory method of preventing reflux during ureteroileoneocystostomy.

(References can be requested from the authors)

Dr. F. Tettamanti
Urologische Universitätsklinik und Poliklinik
Anna Seiler Haus
CH-3000 Bern
Switzerland

URETERONEOCYSTOSTOMY WITHOUT TUNNELLING OF THE BLADDER MUCOSA

R. Chiari, W. Gilch, R. Harzmann, and F.H. Lehnhardt

Urologische Klinik des Akademischen Krankenhauses Fulda und Experimentell-chirurgische Abteilung der Fa. Braun, Melsungen, FRG

In irradiated or chronically inflamed bladders, the dissection of a submucosal tunnel for ureteric reimplantation may be impossible. An experimental study was carried out to ascertain whether the implantation of the ureter onto a denuded area of bladder muscle would lead to mucosal regeneration and formation of a submucosal tunnel. One or both ureters were reimplanted onto a denuded area of bladder wall above the trigone in 8 dogs. Two dogs died. The remaining animals were investigated at intervals from three weeks to 16 months after reimplantation. Reflux was absent in all animals (8 ureters). Transient hydronephrosis persisted for periods varying from one week to five months. There was no difference in flow rates between reimplanted or intact ureters. Autopsy studies showed that the intravesical segment of ureter had shortened from 15 mm to 5-8 mm. It was covered with mucosa around 2/3 of the circumference throughout its length. Some ossification was noted in the ureteric wall in two dogs sacrificed at 6 weeks.

In 16 dogs hydroureters were produced by partially obstructing one or both ureters. Following the development of ureteric dilatation, reimplantation was carried out as described. 4 animals died after surgery. Of the remaining 12 dogs two animals showed no

function on intravenous pyelogram. The remaining 10 dogs survived for periods varying between 4 weeks and 16 months. They all showed varying degrees of hydronephrosis which diminished in six animals and a further 4 had normal IVP's at the conclusion of the studies. Reflux was not observed in any of these animals.

This technique would appear to be a satisfactory form of ureteric reimplantation in difficult circumstances. It has been used in two patients with satisfactory results.

Dr. R. Chiari
Urologische Klinik
Akademisches Krankenhaus
D-6400 Fulda
Federal Republic of Germany

New Technology

THE USE OF SHOCK WAVES FOR THE DESTRUCTION OF RENAL CALCULI WITHOUT DIRECT CONTACT

Ch. Chaussy, F. Eisenberger, K. Wanner, F. Forssmann, W. Hepp, E. Schmiedt, and W. Brendel

Abteilung für Urologie und Institut für Chirurgische Forschung der Universität München, FRG, and Dornier System Corp., Friedrichshafen, FRG

The current study was undertaken in order to develop a technique capable of destroying kidney stones by means of extracorporeally produced shock waves. The shock waves were produced at one focus of a water-filled ellipsoid by discharging high voltage (25 KV) sparks. The samples under investigation were exposed to the shock waves at the second focus of the ellipsoid. The distance between the foci was 20 cm. The effect of these shock waves on the following materials was studied:

1. renal calculi - using 25 KV, a pressure amplitude of 1.5 Kbar was produced and human renal calculi of different composition and size were destroyed.

2. mixed lymphocyte cultures - human lymphocytes exposed to the shock wave did not show cytolysis. Stimulation ratio was not altered and there were no significant differences in blast formation.

3. fresh blood - serum haemoglobin concentrations of fresh blood samples increased with exposure. 4 exposures caused the haemoglobin concentration to rise to 430 mg%.

4. rats, intact animal - exposure of the thorax led to massive bleeding into the lungs and was lethal in all cases. Exposure of the abdomen did not appear to produce any lesion.

5. isolated organs- isolated liver, kidney, and intestine did not show any effect when exposed to the shock.

Further studies have shown the successful destruction of human kidney stones implanted in the renal pelvis of dogs.

Dr. Christian Chaussy
Urologische Universitätsklinik
Thalkirchnerstr. 48
D-8000 München 2
Federal Republic of Germany

ULTRASONIC LITHOTRIPSY OF URETERIC STONES

P. Rathert, A. Erichsen, U. Stumpff, R. Pohlmann, and W. Lutzeyer

Abteilung Urologie und Laboratorium für Ultraschall, Rheinisch-Westfälische Technische Hochschule Aachen, FRG

An ultrasonic probe suitable for the treatment of ureteric stones has been developed. A flexible steel probe of 0.8 mm diameter fits into a Teflon sheath and can be introduced into the ureter via a cystoscope. It is connected with an ultrasound converter (27 kc/s, 25 w). The effect of this apparatus on 80 ureteric stones and the temperature rise in the ureter during operation were investigated.

All stones were destroyed. Ureteric temperatures were measured by thermocouples at the probe tip and above and below the probe under different conditions in 10 dogs. Continuous working power for three minutes results in a temperature rise at the probe tip of 16° C. When power is applied intermittently for 2.5 seconds at 2.5 second intervals the temperature rise is never more than 4° C. Under continuous power and drip perfusion (2 drops/sec) the temperature rise is less than 2.5° C. This ultrasonic lithotriptor offers exciting possibilities for the treatment of ureteric stones but further refinements are necessary before it can be used routinely.

(References can be requested from the authors)

Priv.-Doz. Dr. Peter Rathert
Abteilung Urologie
Med. Fakultät der RWTH
Goethestraße 27/29
D-5100 Aachen
Federal Republic of Germany

ENDOSCOPIC IRRADIATION OF THE RABBIT BLADDER USING AN ARGON LASER BEAM

G. Staehler, A. Hofstetter, E. Keiditsch, W. Gorisch, and W. Siepe

Abteilung für Urologie der Universität München and Institut für Pathologie, Städtisches Krankenhaus München-Schwabing, München, FRG

Endoscopic laser application via flexible quartz fibres is now possible. Before the laser can be employed clinically it is important to understand the effect of laser energy on the bladder walls. The following investigations were carried out using an Argon laser because this provides for minimal penetration with good tissue removal. There is satisfactory transmission of the beam through a flexible light guide and there is good coagulation of small vessels.

Areas of tissue in the open rabbit bladder were destroyed using power densities between 150 and 600 joule/cm^2 and durations from 0.25 to 8 seconds. The specimens were examined immediately and at 3-8 days. Further irradiation experiments were carried out transurethrally with two forms of laser endoscope. Any site on the bladder wall could be exposed to the beam with the aid of a movable coated mirror.

Examination of the bladder wall showed that small power densities result in immediate coagulation necrosis. Increasing power densities and duration produce crater-like defects. There are fissures in adjacent areas caused by evaporation of water. Power densities up to 300 joule/cm^2 did not cause perforation of the bladder. Examination at 3-8 days showed similar tissue defects but the area of necrosis had extended beyond the primary area of damage. Widespread irradiation of the bladder produced similar uneven defects. The depth of necrosis could be controlled and irradiation in the region of the ureteric orifice did not lead to hydronephrosis.

The Argon laser appears to be suitable for controlled tissue removal within the bladder and for haemostasis.

(References can be requested from the authors)

Dr. G. Staehler
Urologische Universitätsklinik
Thalkirchnerstr. 48
D-8000 München 2
Federal Republic of Germany

USE OF INFRARED-CONTACTING-COAGULATOR (ICC) FOR HAEMOSTASIS OF KIDNEY PARENCHYMA IN DOGS

A. Hofstetter, G. Staehler, H. Mellin, E. Knott, G. Antes, A. Gebauer, K. Pfeifer, K. Pielsticker, and G. Nath

Abteilungen für Urologie, Radiologie und Pathologie der Universität München and Max-Planck-Institut für Biochemie, München, FRG

An infrared coagulator may be of value during surgery of the renal parenchyma by producing satisfactory haemostasis without the need for renal artery clamping. The ICC is an infrared-emitting coagulator with a cap of perfluoralcorey (PFA) which is transparent for infrared light. This cap is not adhesive to the tissues and transmits 92% of the irradiation without heating up. The beam reaches a light temperature of 3200°K and the spectral maximum is 850 nm. Two coagulators with PFA-contacting surfaces of 10 and 6 mm diameter were investigated. Impulse duration is 1 to 1.5 seconds, and produces energy densities of 66-110 joule/cm^2 for the 10 mm cap and 92-138 joule/cm^2 for the 6mm cap.

Partial nephrectomies without clamping of the renal vessels were carried out in 10 unilaterally nephrectomised beagle dogs. Haemostasis was possible in all cases. The small diameter coagulator with higher energy density was more effective for larger vessels. The larger cap was more effective over a greater area. The animals were followed with serum creatinine and blood urea estimations and scintigraphy and selective angiography were carried out preoperatively and at 8 days and 4-6 weeks postoperatively.

No alterations in renal function were detected post-operatively. When large vessels were coagulated the parenchymal necrosis was seen to extend 1.0 to 1.5 cm along the vessel.

The ICC appears capable of controlling tissue haemorrhage without the necessity for arterial clamping. It may also be suitable for the control of haemorrhage from the liver and spleen.

(References can be requested from the authors)

Priv.-Doz. Dr. A.Hofstetter
Urologische Universitätsklinik
Thalkirchnerstraße 48
D-8000 München 2
Federal Republic of Germany

THE DOG URETHRA AS AN EXPERIMENTAL MODEL FOR TRANSURETHRAL SURGERY

H. Bülow, R. Ackermann, and H.K. Wullstein

Urologische Klinik und Poliklinik and Pathologisches Institut der Universität Würzburg, FRG

The dog urethra has been examined to see if it fulfills the requirements of an experimental model for the human urethra.

The distal urethra is inelastic on account of the os penis and will not allow the passage of an instrument into the bladder. A urethrostomy must therefore be performed in order to carry out studies of the posterior urethra. Following a urethrostomy the posterior urethra of the dog will accept an instrument of 25 FG. However, this segment of urethra is not surrounded by corpus spongiosum and contains only a few layers of striated muscle. The transitional epithelium of this section of urethra is similar to the human.

The posterior urethra of the dog may only be satisfactorily compared with the membranous urethra in man. This limits its experimental usefulness.

(References can be requested from the authors)

Dr. H. Bülow
Urologische Klinik und Poliklinik der Universität
Luitpoldkrankenhaus
Joseph-Schneider-Straße 2
D-8700 Würzburg
Federal Republic of Germany

COMBINED RADIOGRAPHIC-MANOMETRIC INVESTIGATION OF SPHINCTER FUNCTION IN THE FEMALE URETHRA

K.-U. Laval and W. Schäfer

Abteilung für Urologie der Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen, FRG

A combined radiographic-manometric investigation of sphincter function in the female urethra has been developed.

With a fine catheter in the bladder for filling and pressure recording an unelastic cylindrical balloon of 16 mm diameter and 150 mm length is positioned in the urethra. 100 mls contrast medium are introduced into the bladder and the balloon is filled with contrast medium up to bladder pressure. The pressure in the balloon is then varied in stepwise fashion. Bladder neck and urethra are x-rayed and recorded on video-tape, together with the balloon and bladder pressures. Selected pictures are photographed from the tv-screen during replay and used for quantitative analysis.

The contour lines of the balloon represent lines of constant pressure which are in equilibrium with the urethral closure forces. The measured values of urethral closure length as a function of closure pressure and peak closure pressure at the external sphincter correlate well with the urethral pressure profile obtained by conventional methods.

This method has the advantage of examining the whole urethra at varying pressures and diameters compared with the perfusion pressure profile which can measure pressure at only one point in the urethra at a time and at one diameter related to the diameter of the catheter.

Dr. K.-U. Laval
Abteilung Urologie
Med. Fakultät der RWTH
Goethestraße 27/29
D-5100 Aachen
Federal Republic of Germany

Experimental Oncology

LIPID ANALYSIS OF RENAL CELL CARCINOMAS AND NORMAL RENAL CORTEX

G. Popelier, R. Geer s, and G. Verdonk

Urological Clinics and Laboratory for Lipid Research, The State University of Ghent, Belgium

Total lipid extraction from 15 renal cell carcinomas and 15 samples of renal cortex have been performed and subsequently fractioned by thin layer chromatography. Further analysis was carried out by esterification and gas chromatography. The principal findings were:

1. the total fatty acid content of hypernephromas was about 350 % of that of the control renal cortex. - Mean values 3050 mg/100 g wet weight for the tumours and 950 mg/100 g wet weight for normal cortex.
2. concentration of polar lipids in the tumour tissue was decreased compared with

cortex. Values ranged from 7 to 40 % of normal cortical values. Triglycerides and cholesterolesters were always significantly higher in tumour tissue than normal cortex. Free fatty acid levels were variable and alkoxydiglycerides were moderately increased.

3. the lipid composition of tumour tissue is highly variable. The lipid composition of cortical tissue is more constant.

4. the composition of cholesterolesters in tumour tissue is highly variable. The fatty acid composition from tumour tissue is comparable to that of cortex and shows a constant pattern.

Fatty acids represent an important source of energy for renal tissue.

Dr. G. Popelier
Urological Clinics
State University
Ghent, Belgium

CELL KINETIC STUDIES ON THE PROBLEM OF IN VIVO SYNCHRONISATION OF TUMOUR CELLS WITH VINCRISTINE

W. Jellinghaus, B. Schultze, and W. Maurer

Urologische Klinik und Poliklinik and Institut für Medizinische Strahlenkunde der Universität Würzburg, FRG

Chemotherapy of malignant tumours may be improved if cell division within the tumour can be synchronised and cell division arrested at a stage vulnerable to cytotoxic therapy.

Experiments to investigate the possibility of an in vivo synchronisation with vincristine were carried out on the ascites tumour cells of the L1 210 murine leukemia and the jejunal crypt epithelia of the normal mouse. In addition, the mechanism of action of vincristine in vivo was investigated autoradiographically by a double labelling method with H3- and C14-thymidine.

In both cell types it was not possible to obtain a synchronising effect by applying vincristine. Following arrest of cells in mitosis, no further peak of either mitotic or labelling index was observed. Theoretical cell kinetic considerations showed that such maxima were not to be expected. The cells arrested by vincristine in metaphase do not, after vincristine treatment, re-enter the cycle all at one time. They gradually re-enter the cycle during a long time interval (release time = 8 h). The in vivo studies on the mechanism of action of vincristine studies show that in vivo as well as in vitro vincristine affects the interphase cells (S-phase) in such a way that during subsequent mitosis they are arrested as metaphases.

Because of the long release time of arrested metaphases, vincristine is not well suited for use as a synchronising agent. The long release time results from the mechanism of action of vincristine.

(References can be requested from the authors)

Dr. W. Jellinghaus
Urologische Universitätsklinik
Luitpoldkrankenhaus
Joseph-Schneider-Str. 2
D-8700 Würzburg
Federal Republic of Germany

PERFUSION OF TUMOUR KIDNEYS: STUDY OF DNA SYNTHESIS

P. Carl and H. Rabes
Urologische Klinik und Poliklinik and Pathologisches Institut der Universität München, FRG

The kinetics of cell proliferation in human renal cell carcinomas were studied by autoradiography following ^{3}H-thymidine perfusion of the isolated tumour-bearing kidney. The influence of pre-operative irradiation was investigated.

21 tumour-bearing kidneys were perfused with oxygenated blood immediately following nephrectomy for a total of 120-240 minutes. 1.3 Ci ^{3}H-thymidine/ml was added to the perfusate. 11 kidneys had not received pre-operative irradiation. 10 tumours had received a total dose of 1600 R within 48 hours of operation. Following perfusion the kidneys were cut into slices, fixed and autoradiography performed.

DNA-synthesising tumour cells are mostly located in the periphery of the tumour. Non-irradiated tumours showed a labelling index of 0.08 - 5.2 % after two hours, and 1.5 - 11.2 % after four hours' perfusion. 9 of the 11 non-irradiated tumours had a labelling index higher than 1 %. Of the irradiated tumours only 2 of the 10 tumours had a labelling index of greater than 1 %. Of these 10 irradiated tumours 3 contained no labelled tumour cells and 4 of them had less than 20 labelled cells over the total surface of the tumour section.

These studies show that tumour cells of perfused tumour kidneys continue to synthesise

DNA. Temporary inhibition of cell proliferation by pre-operative irradiation is evident.

(References can be requested from the authors)

Priv.-Doz. Dr. P. Carl
Urologische Klinik und Poliklinik der Technischen Universität München
Ismaninger Str. 22
D-8000 München 80
Federal Republic of Germany

TESTING OF BLADDER CARCINOGENS IN MICE BY ORAL ADMINISTRATION FOLLOWING INTRAVESICAL IMPLANTATION OF GLASS BEADS

O. Yoshida, M. Miyakawa, and K. Okada

Department of Urology, Faculty of Medicine, Kyoto University, Kyoto, Japan

The presence of a foreign body in the bladder appears to be necessary for the testing of certain carcinogens in mice. Studies have been carried out using implanted glass beads and the oral administration of 2-naphthylamine, benzidine, 2-acetylaminofluorence (2-AAF), bracken fern, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT), saccharine, sodium saccharine and sodium cyclamate. The mice were killed after 200 days and the bladder and other organs examined histologically.

The incidence of bladder tumours of the mice with glass beads fed with 2-naphthylamine, 2-AAF, and bracken fern was high compared with control animals. In the experiment on FANFT, the time of induction of the bladder tumour was shortened in the mice whose bladders contained glass beads. Benzidine did not induce bladder tumours, only hepatomas. No carcinogenic activities of artificial sweeteners were demonstrated in the experiment.

Osamu Yoshida, M.D.
Department of Urology
Kyoto University
Sakyo-Ku
Kyoto, Japan 606

THE ELECTRONIC VOLUME ANALYSIS OF THE CELL NUCLEUS FOR DIAGNOSIS OF BLADDER CARCINOMA

R. Tauber, St. v. Sommoggy, W. Kaunzner, W. Heinkelmann, E. Hertel, and G. Blümel

Urologische Klinik and Klinik für Experimentelle Chirurgie der Technischen Universität München, FRG

Urine sediments and bladder biopsy material were studied by the technique of electronic nuclear volume analysis. Specimens from 54 patients with tumours, cystitis and normal bladders were included in the study.

Tumour biopsies showed a nuclear volume of 77.8 μ^3. Normal bladder mucosal biopsy had a nuclear volume of 51.9 μ^3. Urine sediment from patients with carcinoma had a nuclear volume of 27.1 μ^3 and for superficial tumours the nuclear volume was 35.4 μ^3. A volume of 29.3 μ^3 was found in cystitis.

(References can be requested from the authors)

Priv.-Doz. Dr. Roland Tauber
Urologische Klinik und Poliklinik der Technischen Universität München
Ismaninger Str. 22
D-8000 München 80
Federal Republic of Germany

RESEARCH ON INDIRECT LYMPHOGRAPHY OF THE URINARY BLADDER

R. Harzmann, R. Chiari, and F.H. Lehnhardt

Lehrstuhl und Abteilung für Urologie, Universität Tübingen, Urologische Klinik, Akademisches Krankenhaus Fulda, and Experimentell-Chirurgische Abteilung der Fa. B. Braun, Melsungen, FRG

Using a particulate contrast medium with a particle size of 1-3 µ and an iodine concentration of 20 % attempts were made to visualise the pelvic lymph nodes in dogs. These lymph nodes are not normally opacified by conventional pedal lymphography.

The injection of 5 ml contrast medium into the intradigital cleft in 5 dogs with and without hyaluronidase produced good opacification of the popliteal lymph nodes in all cases.

In a further 5 dogs 60 ml of the contrast medium were introduced into the bladder lumen for 60 mins. Slight opacification was observed in the lymph nodes in one case. In a third group of 5 dogs the bladder was opened and 5 ml of the contrast emulsion were injected into the submucosa of the bladder wall with and without hyaluronidase and in two cases with warming of the contrast medium to 39 °C. Slight opacification of the paravesical lymph nodes were obtained in 2 cases. There was an intensive inflammatory reaction with occasional

development of necrosis. Hyaluronidase did not appear to influence the result.

(References can be requested from the authors)

Dr. R. Harzmann
Lehrstuhl und Abteilung für Urologie
der Chirurg. Univ.-Klinik
Calwer Straße 7
D-7400 Tübingen
Federal Republic of Germany

SELECTIVE IN-SITU PERFUSION OF RENAL TUMOURS BY CYTOSTATIC AGENTS IN HIGH CONCENTRATION. PRELIMINARY RESULTS OF AN EXPERIMENTAL STUDY

H. W. Asbach, J. Brühmüller, W. Bersch, G. Eickemeyer, R. Daum, and L. Röhl

Abteilung für Urologie und Kinderchirurgie der Universität Heidelberg and Institut für Pathologie der Städtischen Krankenanstalten Ludwigshafen, FRG

In order to increase the tumour dose of antitumour drugs without incurring systemic toxicity experiments have been carried out on the perfusion of kidneys in situ with high doses of chemotherapeutic agents in rats.

The isolated perfusion of normal kidneys and kidneys bearing Walker-Ascites-Carcinoma in the upper pole were perfused with varying doses of Tris-ethylenimino-benzochinon and Methotrexate with suitable controls. Perfusion was continued for 30 minutes with almost complete recovery of perfusion fluid from the venous side and from the bladder. Evaluation of renal function was carried out before and after perfusion by means of ^{131}I-Hippuran scintigraphy and semi-quantitative computerised renogram. Each kidney was examined histologically on the third day following perfusion.

Ringer-Lactate perfusion alone did not produce any functional or structural alterations in the kidney. Cytotoxic perfusion in large doses produced some renal impairment and some histological changes. Regression to tumour size by more than 50% was achieved within 3 days of treatment. Large areas of necrosis were visible histologically. The systemic administration of an LD 50 of the appropriate cytotoxic agent did not produce any tumour control and the tumour enlarged to involve the whole kidney and retroperitoneal tissues over the same period of time.

Dr. H.W. Asbach
Urologische Abteilung des Chirurgischen
Zentrums der Universität
Im Neuenheimer Feld 110
D-6900 Heidelberg 1
Federal Republic of Germany

A HISTOCHEMICAL METHOD FOR THE DETECTION OF PLASMIN IN THE HUMAN PROSTATE

U. Dunzendorfer and W. Weber

Urologische Abteilung im Zentrum der Chirurgie der Universität Frankfurt, FRG

Direct proof of the presence of plasmin within the prostate has been obtained by histochemical techniques. Benzoylarginine-p-nitranilid (BAPA) can be used as a substrate for plasmin and is broken down into benzoylarginine and p-nitraniline. The p-nitraniline inhibits the metachromatic staining of acid mucopolysaccharides with tolonium-chlorides.

Specimens of tissue from hypertrophied prostates (BPH) and the normal prostates of kidney donors were incubated with BAPA and a suitable control provided. Plasmin inhibition was investigated with tranexamic acid. The material was imbedded in methacrylate for 24 hours and sections stained with haematoxylin eosin and tolonium-chloride.

Metachromasia was seen in the BAPA-free incubations with both normal and hyperplastic prostatic tissues. The addition of tranexamic acid showed metachromasia in the BPH tissue only. Following incubation with BAPA metachromasia was absent in both normal and BPH tissue.

This suggests that plasmin activity is localised within the connective tissue of the prostate. Fibrinolytic activity in the plasma was measured post-operatively but no significant change was observed.

(References can be requested from the authors)

Dr. U. Dunzendorfer
Urologische Abteilung im Zentrum Chirurgie
der Johann Wolfgang Goethe-Universität
Theodor-Stern-Kai 7
D-6000 Frankfurt/M. 70
Federal Republic of Germany

THE EFFECT OF CYPROTERONE ACETATE (CA) ON TESTOSTERONE (T) AND DIHYDROTESTOSTERONE (DHT) METABOLISM IN PATIENTS WITH BENIGN PROSTATIC HYPERTROPHY (BPH): IN VIVO STUDIES

G. Hutschenreiter, K. Sinterhauf, and J.E. Altwein

Abteilung für Urologie and I. Medizinische Klinik der Universität Mainz, FRG

The plasma kinetics for tritiated-T and DHT were determined in 20 patients suffering from benign prostatic hypertrophy. The single injection technique was used. Plasma kinetics based on the 2-compartment model, using computer analysis were determined. The patients were treated with 300 mg CA intramuscularly over five days.

CA was followed by a drop of plasma T below 300 mg/ml and LH and FSH below the upper limit of normal (11 mlU/ml). The elimination of both T and DHT is enhanced by CA. The interconversion of T after injection of H^3-DHT is very low. CA resulted in an initial increase of T in plasma. The rate of metabolism (K_2) and the metabolic clearance rate (MCR) rose 344% and 345% respectively, half-life ($T_{1/2}$) decreased 76%. The volumes of the inner (v_1) and outer pool (v_2) and the transfer rate (K_1) remained unchanged. H^3-DHT had a 126% rise of v_2. Rise of v_1, K_1, MCR and $T_{1/2}$ as well as decrease of K_2 were not statistically significant.

Both the uptake of the total radioactivity after the intravenous injection of H^3-T and H^3-DHT and the intraprostatic degradation of these tritiated androgens were not significantly suppressed by the CA pretreatment and remained unchanged.

The enhanced elimination of T after CA pretreatment may be due to an inhibition of androgen ligands in target organs participating in the so-called deep compartment. The increased metabolism of T within the inner pool, which is at least partly due to hepatic enzymatic activity, may be the result of an increased hepatic T degradation.

(References can be requested from the authors)

Dr. G. Hutschenreiter
Urologische Klinik der Universität Mainz
Langenbeckstr. 1
D-6500 Mainz
Federal Republic of Germany

HORMONE DEPENDENT GROWTH OF CLONED EB 33 CELLS IN VITRO AND IN VIVO

W. Jellinghaus, I. Laudenbach, K. Okada, T. Hiei, and F.H. Schröder

Urologische Klinik und Poliklinik der Universität Würzburg, FRG

Single human prostatic carcinoma cells (EB 33) were inoculated into microtiter plates and EB 33 clones developed. Those cells whose growth could be suppressed by more than 50% when cultured in a steroid-free medium were used for further study. 23 clones out of an original total of 111 showed growth suppression. This inhibition could be partially reversed by the addition of testosterone or dihydrotestosterone. The original uncloned EB 33 cells and Hela cells exhibited hormone independent growth.

EB 33 cells were inoculated subcutaneously into "nude-mice" and their growth assessed during daily dihydrotestosterone therapy in castrated animals. Volume increase of the tumours could be increased by daily dihydrotestosterone administration. Tumours from uncloned EB 33 cells and Hela cells were not affected by dihydrotestosterone substitution.

Cloning enables selection of androgen-dependent cell lines from an heterogenous population.

(References can be requested from the authors)

Dr. W. Jellinghaus
Urologische Universitätsklinik
Luitpoldkrankenhaus
Joseph-Schneider-Str. 2
D-8700 Würzburg
Federal Republic of Germany

MEMBRANE ANTIGENS OF A CELL-LINE FROM HUMAN PROSTATIC CARCINOMA (EB 33)

R. Ackermann, T. Okabe, and K. Hempel

Urologische Klinik und Poliklinik and Institut für Medizinische Strahlenkunde der Universität Würzburg, FRG

Antisera were raised in rabbits against the membrane proteins of EB 33 cells. Intensive membrane-fluorescence was seen with all

immune sera on EB 33 cells. Most of this activity was non-specific and similar fluorescence patterns were seen with other target cells. Similar patterns were seen with application of anti-beta-2 microglobulin.

Determination of complement-dependent cytotoxicity showed similar values for EB 33 and Hela cells but following complete antiserum absorption with Hela cells some activity against EB 33 remained.

There are therefore at least two types of antibodies raised against membrane extracts of EB 33 cells.

(References can be requested from the authors)

Dr. Rolf Ackermann
Urologische Klinik und Poliklinik der
Universität Würzburg
Luitpoldkrankenhaus
Joseph-Schneider-Straße 2
D-8700 Würzburg
Federal Republic of Germany

HETEROTRANSPLANTATION OF FRESH TISSUE FROM HUMAN PROSTATIC CARCINOMA INTO "NUDE MICE"

K. Okada, H. M. Heinemeyer, T. Hiei,
K. Wullstein, and F. H. Schröder

Urologische Klinik und Poliklinik der Universität Würzburg, FRG

Fresh tissue from 19 human prostatic carcinomas was transplanted into 84 "nude mice" either subcutaneously or subfascially. The overall tumour survival rate was 73.8%. Carcinoma tissue was recovered histologically from 13 animals. No signs of rejection were seen and the recovered tumour tissue was histologically identical to the tissue of origin. Castration diminished recovery and this could be reversed with testosterone substitution.

It appears that long-term heterotransplantation of human prostatic carcinoma tissue into "nude mice" is possible.

(References can be requested from the authors)

Dr. F. H. Schröder
Urologische Universitätsklinik
Luitpoldkrankenhaus
Josef-Schneider-Str. 2
D-8700 Würzburg
Federal Republic of Germany

ULTRASTRUCTURAL OBSERVATION OF PROSTATIC CARCINOMA AFTER LONG-TERM THERAPY

P. Burchardt, E. Altenähr, and H. Kastendieck

Urologische Universitätsklinik und -Poliklinik
and Pathologisches Institut der Universität
Hamburg, FRG

Ultrastructural observations of prostatic carcinoma cells show two basic types. (1) Differentiated cells with glandular cytoplasm and a dark nucleus. (2) Less differentiated immature cells with pale nuclei and less marked secretory structures in the cytoplasm. Large numbers of free ribosomes suggest high proliferative activity.

Following the treatment of up to 3 years by a variety of techniques including orchiectomy, antiandrogens and irradiation, cells show some different features. The well-differentiated cells have bizarre hyperchromatic nuclei and vacuolated cytoplasms. The less differentiated cells contain small nucleoli in comparison with the primary tumour. The total number of free ribosomes were diminished although plentiful.

The greatest changes appear to take place in well-differentiated cells and appear to correlate with tumour regression over some years.

Priv.-Doz. Dr. P. Burchardt
Urologische Universitätsklinik
Martinistr. 52
D-2000 Hamburg 20
Federal Republic of Germany

Responsible for the text: Prof. Dr. F. Truss, Urolog. Klinik und Poliklinik für Urologie der Univ. Göttingen
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