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I. Operative Technique

THE INFLUENCE OF RADIOOPAQUE MEDIUM ON WOUND HEALING IN EXPERIMENTAL URETHRAL LESIONS

G. Jakse, K. Paulini and M. Marberger

Urethrography may be used to define the extent and position of the lesion following urethral trauma (1), but carries the risk of causing further tissue damage and introducing infection (2).

A standard urethral lesion was produced in the bulbar urethra by scissors under fluoroscopic control in 40 male rabbits in 5 groups. In group A (n=12) and group B (n=12) urethrograms were performed with 10 ml of 30% and 60% diatrizoate respectively. Animals were killed on days 3, 7, 14 and 25 and serial sections of the lesion examined. In group C (n=5) and D (n=5) 10 ml of an E coli suspension (10^6 per ml) were introduced into the urethra following trauma. This was followed by an urethrogram with 30% diatrizoate in group C only. Animals in these two groups were killed on day 7. Group E was a control group in which no urethrogram was performed.

There was no significant difference on histological examination between Groups A, B, D and E. A strong reaction was observed in group C. possibly related to the increased volume of fluid since we had been able to show that 30% diatrizoate is bacteriostatic. Retrograde urethrography appears to be a safe procedure for the demonstration of urethral lesions, but the importance of an aseptic technique and gentle pressure must be emphasised.

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G. Jakse
Urologische Univ. Klinik,
Anichstr. 35,
A-6020 Innsbruck

TRANSURETHRAL RECONSTRUCTION OF THE EXTERNAL SPHINCTER IN POST-PROSTATECTOMY INCONTINENCE

G. E. Bergmann

An operation has been devised for the endoscopic repair of a damaged external sphincter. The necessary instruments for this procedure have been developed in association with Richard Wolf GmbH, Knittlingen. These consist of (1) a long-armed needle which may be passed endoscopically and following transfixion of the external sphincter will release the suture within the bladder.(2) the Bergmann pulley which allows endoscopic visualisation of the sphincter area and transport of an externally tied slipknot. (3) a knotpusher, which in conjunction with the pulley, allows an external knot to be moved proximally and secured. (4) long-armed scissors to trim the completed suture transurethrally.

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The method may be applied transurethrally or transvesically. The external sphincter is first identified endoscopically and seen to contract by external faradic stimulation. Each of the cut margins is then transfixed with a suture and the free ends are released into the bladder. These are then transported externally where a slipknot is formed which is then tightened using the knot-pusher and the Bergmann pulley. This restores the circular continuity of the external sphincter. The transvesical method uses the suprapubic transvesical approach but the same instruments are used. By either method the knot is secured on the proximal surface of the external sphincter.

Using this method the continuity of the external sphincter is restored with correction of urinary incontinence.

Dr. G. Bergmann
Urologische Klinik,
Helmholtzstr. 4-6,
D-5300 Bonn-Duisdorf

AN ARTIFICIAL SPHINCTER FOR URINARY INCONTINENCE

A. Kelami and K. Affeld

The development of a simple, easily implantable device, consisting of a single unit to overcome the disadvantages of current prostheses, is described.

The device (Kelami-Affeld Prosthesis) consists of cuff, reservoir and access port in a single unit. It is implanted through a perineal incision. The cuff is placed around the entire penis subcutaneously and the reservoir placed in the lower abdominal wall. The urethra remains protected by the bulbo-cavernosus muscle and the corpora cavernosa. Pressure on the cuff forces fluid into the reservoir which runs back automatically into the cuff within 30 seconds. This allows sufficient time for the voiding of 600 ml of urine. The prosthesis has been implanted in 22 dogs. In order to test the device the external sphincter was bypassed using an implanted tube running from the bladder to the urethra below the external sphincter.

The prosthesis functioned satisfactorily and there was no evidence of urethral necrosis.

This prosthesis has the advantage of simplicity and ease of implantation. Further development is required before it is used clinically.

Dr. Alpay Kelami
Urol. Klinik, Klinikum Steglitz,
Freie Universität Berlin,
Hindenburgdamm 30,
D-1000 Berlin 45

THE USE OF BIODEGRADABLE TISSUE ADHESIVES

R. Tauber, A. Stemberger, S. Haas, R. Hartung, R. Blasini, I. Wriedt-Lübbe, G. Blümel

Concentrated fibrinogen solutions have been tested for the use as tissue adhesives in urology. These studies were concerned with adhesion, haemostasis, standardisation and compatibility.

Following partial nephrectomy in a series of rats the kidneys were closed using fibrin adhesion and a variety of supportive dressings but without suture. The kidneys were studied histologically at intervals. Fibrinolysis in patients undergoing major surgery on the kidney was examined by thromboelastography, euglobulinlysis time and chromogenic substrates. Cryostat sections were investigated by fibrinolysis autography (Todd) and by a newly developed technique using chromogenic substrates.

Fibrinkleber® and collagen sponges were shown to produce healing with excellent haemostasis. Tensile strengths up to 200 p/cm^2 were measured for these adhesions. The macromolecular structure of the adhesions was studied with the scanning electron microscope. Activation of the fibrinolytic system was demonstrated in blood and in tissue sections.

Both fibrin and fibrin-collagen tissue adhesives have been shown to produce satisfactory adhesion and haemostasis for parenchymatous tissue. The adhesives are non-irritant but a local dose of fibrinolytic inhibitor may be necessary in order to prevent post-operative bleeding and wound dehiscence.

R. Tauber
Urologische Klinik der TU München,
Ismaninger Str. 22,
D-8000 München 80

THE USE OF A FIBRIN ADHESIVE FOR VASO-VASOSTOMY IN THE RABBIT

D. Bach, L. Weisbach, B. Fazel

The possibility that the results of vasovasostomy may be improved by the use of fibrin tissue adhesives has been investigated in an experimental study in the rabbit.

The vasa deferentia of 31 rabbits were divived and reanastomosed using Fibrin-Kleber Human® as a tissue adhesive. The animals were divided into three groups depending upon the form of splintage. Group 1 (n = 7) was splinted with a silastic tube; Group 2 (n = 13) with surgical silk; Group 3 (n = 11) with catgut. A fourth group - Group 4 (n = 5) - were anastomosed using atrau-

matic silk for comparison and with a silk splint. Semen analyses were carried out over a four month post-operative period following which the anastomosis was examined for patency both radiologically and by histological section.

Patency of the anastomosis for each group was as follows: Group 1 - 3 animals; Group 2 - 6 animals; Group 3 - 5 animals; Group 4 - 4 animals. The finding of a patent vasradiologically did not correlate at all with the semen analyses. Histological studies provided some explanation for this discrepancy.

The success of vasovasostomy must therefore be determined by semen analyses and a vasogram will only be helpful if both sides are obstructed. Spermatozoa were found in the ejaculate even in the presence of stenosis. The histological studies were of limited use for studying the effect of adhesive. The best results with adhesive were obtained in Group 2 using a temporary splint for a short period and the ejaculates from these animals showed 100% sperm motility.

D. Bach
Urologische Universitätsklinik Bonn,
D-5300 Bonn-Venusberg

BIOMECHANICAL STUDIES OF CONNECTIVE TISSUE GRAFTS PRESERVED BY DIFFERENT METHODS

R. Pust, W. Weidner, O. Krüger, C.T. Rothauge, U. Schoen

The mechanical properties of fresh, deep frozen and lyophilised skin (split and full thickness) from man, cat and pig have been examined using a fabric testing apparatus (INSTRON Ltd., model TTCM).

The distensibility and elasticity were increased by deep freezing or lyophilisation. This effect was particularly marked with human skin. In all cases breaking strength was higher in the preserved materials compared with fresh human or feline bladder wall.

The mechanical property of a skin graft therefore depends on its species of origin, its basic structure and the method of preservation.

P.D. Dr. Reiner Pust
Urologische Univ.-Klinik,
Klinikstr. 37, D-6300 Giessen

THE CELLULAR REACTION OF THE RAT KIDNEY FOLLOWING LOCAL THERMONECROSIS

B. Helpap and V. Grouls

The left kidneys of female Wistar rats were heat coagulated (740°C/4 sec) and the animals sacrificed at intervals from 12 hours to 30 days. 2.5 μCi/g per mg body weight ^{3}H thymidine was injected intraperitoneally before sacrifice. The labelling indices of the fibroblasts in the granulation tissue and of the interstitial cell and tubular epithelium were determined autoradiographically. A cellular analysis of the granulation tissue was also performed.

At 12 hours a sharply defined zone of thermonecrosis surrounded by haemorrhagic margin is seen. Polymorphs predominate for the first three days following which fibroblasts, macrophages and monocytes appear. Active granulation tissue is still visible at 4 weeks. Maximum labelling indices of mesenchymal and epithelial cells occurred on the second post-operative day. The indices were still above control levels at 4 weeks.

Wound healing is prolonged following thermonecrosis, possibly due to the complete tissue destruction and poor resorbtion of carbonised tissue. If the heat coagulated tissue is excised would healing procedes rapidly in a manner similar to that seen following cryonecrosis.

Prof. Dr. B. Helpap
Pathologisches Institut der Universität Bonn,
D-5300 Bonn-Venusberg

EXPERIMENTAL CRYOCAUTERY OF THE PROSTATE

A.J. Keller, G.E. Schubert and D. Völter

Cryocautery is a method which combines freezing and subsequent extreme heating. The application of this technique to prostatectomy and comparison with cryosurgery alone has been studied experimentally in dogs.

An Erbo-Kryo-OP apparatus was used. Cooling is achieved by evaporation of liquid nitrogen in the probe tip and there is an integral heater. Tissue temperature is measured with a thermocouple. The probe was introduced transvesically and the prostatic adenomas of six elderly male dogs were frozen for 2 minutes at -180°C. In a further six dogs the prostatic adenoma was frozen for 2 minutes at -180°C and subsequently heated for one minute to +170°C. Total prostatectomy was performed at 4 hours, 2 days and 7 days.

The post-operative results following cryocautery were superior. Passage of debris began after two days and there was greater destruction of prostatic tissue. There was less bleeding due to coagulation of both superficial and deep vessels.

Dr. A.J. Keller
St. Trudpert Krankenhaus, Urol. Abt.,
Wolfbergallee, D-7530 Pforzheim

II. Endoscopic Technique and Alloplastic Materials in Urology

CONTINUOUS MONITORING OF THE TISSUE ABSORPTION OF IRRIGATING FLUID DURING TRANSURETHRAL RESECTION: AN EXPERIMENTAL MODEL

K. Naber, H. Kuni and K.H. Bäumler

Intravascular absorption of irrigating fluid during transurethral resection may be monitored continuously (1, 2). However, interstitial absorption cannot be assessed until completion of the operation (1, 2, 3). A method for the continuous monitoring of interstitial absorption has been investigated in an experimental model.

In each of 19 dogs, 200 ml of saline containing ^{133}Xe was infused into the peri-prostatic tissues via the perineum using an infusion pump. ^{133}Xe was determined in the expired air. An intravenous injection of ^{133}Xe served for calibration.

At infusion rates up to 7 ml/min there was a monoexponential decrease of ^{133}Xe activity in the expired air immediately following the infusion. Volume of infused fluid could be calculated from the decline of ^{133}Xe activity. With higher rates of infusion a complex kinetic of ^{133}Xe was observed. The volume of the infusion could be calculated from the second exponential slope. The first slope was complicated by infusion into other tissue compartments.

The principles underlined in these experiments indicate that continuous determination of paravascular absorption of irrigating fluid is possible.

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K. Naber
Department of Urology and Nuclear Medicine,
University of Marburg, D-3550 Marburg/L.

EXPERIMENTAL STUDIES CONCERNING HAEMOLYSIS DURING TRANSURETHRAL SURGERY

The effects of intravenous injection of distilled water, a proprietary irrigating solution (Purisole SM®, osmolarity 177.8 m. osm/litre) and haemolysed blood has been investigated in the monkey. The haemolysed blood was prepared by the addition of approximately equal volumes of distilled water and the animals received either 12.5 ml or 40 ml of haemocytolysate. Total haemoglobin, free haemoglobin, haematocrit, red cell count, LDH, albumin, haptoglobin and haemopexin were measured.

There was an increase in free haemoglobin and LDH and a decrease in haemopexin following the injection of haemolysed blood. The rise in free haemoglobin was higher after injection of blood cytolysate than following Purisole SM. Haptoglobin rose following injection of blood cytolysate and then declined to normal values within 24 hours. Haemoglobinuria was not observed in any case after injection of Purisole SM or distilled water but occurred regularly following injection of haemolysed blood.

These studies suggest that haemolytic episodes during transurethral resection are not primarily dependent upon the use of distilled water but on the intravascular accumulation of haemolysed blood. Complications may be anticipated when large amounts of free haemoglobin contaminate the bladder irrigation.

Prof. K.-H. Bichler
Department of Urology
Calwer Str. 7, D-7400 Tübingen 1

ELECTROHYDRAULIC LITHOTRYPSY OF URETERIC CALCULI, IN VITRO AND IN VIVO STUDIES

A. Doutsias, S. Lymberopoulos, K. Weigner,
G. Lindenfelser and E. Kern

The application of electrohydraulic lithotrypsy of ureteric calculi has been investigated. 83 stones of varying size, shape and composition were implanted in 20 post mortem ureters, 6 ureters obtained at nephrectomy and 24 pig ureters. The stones were disintegrated by electrohydraulic shock waves using a 6-8 FG strong flexible probe. The ureteric wall was examined macroscopically and microscopically for lesions and stone fragment inclusions. Further studies were carried out in 28 rat ureters and the ureteric lesions were observed histologically up to three months post operatively.

78% of the calculi were disintegrated. Lesions in the ureteric wall depended upon the energy applied and varied from slight reversible oedema to clearly visible perforations. Stone fragments within the ureteric wall were observed.

Further experiments and technical refinements of the probe will be required prior to clinical use.

A. Doutsias
Urol. Abteilung des
Knappschaftskrankenhauses Bardenberg,
Hans-Böckler-Platz,
D-5102 Würselen-Bardenberg

DEVELOPMENT OF A CARBON DIOXIDE LASER ENDOSCOPE WITHOUT A MOBILE ARM SYSTEM

H. Bülow and S. Levene

Argon and Neodymium - YAG lasers have been used for endoscopic urological surgery as their beams may be transmitted by flexible light cables. The transmission of a carbon dioxide laser beam to an endoscope would require a mobile arm system using mirrors (1). Further development of a carbon dioxide laser for endoscopic use has been undertaken.

A surgical 20 W hand-held laser (The Israel Electro-Optical Industry, Ltd.) was small enough and light enough to allow direct connection to an endoscope (2). The laser beam was focused into a stainless steel tube of 1.98 mm inside diameter and 235 mm length by a double-convex Germanium lens of 185 mm focal length. This waveguide was carried within an endoscopic sheath with a diameter of 21 FG which included an insert for the viewing optics. The emergent laser beam was coaxial with the waveguide and experimental studies in extirpated dog urethras and bladders have been encouraging. Adequate cutting of fibrous tissue in an experimental urethral stricture was obtained.

Further development of a carbon dioxide laser beam for endoscopic use is required but the initial studies are encouraging.

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Dr. H. Bülow
Urologische Univ. -Klinik,
D-8700 Würzburg

ALLOPLASTIC REPLACEMENT OF THE URINARY TRACT BY VELOUR-COATED SILICONE RUBBER

B. Schreiber, F. Lorentzen, W. Homann, M. Mlynek and P. Mellin

Silicone rubber prostheses have been coated with a layer of Dacron velour in order to provide more secure fixation and leakproof anastomoses. Fibrous tissue grows into the interstices of the Dacron. These prostheses have been implanted in various ways in 30 minipigs.

In 10 animals in which the prostheses were used for ureteric replacement, they have remained in position for up to one year and there was no evidence of leakage, rejection or migration. Only four kidneys showed significant parenchymal loss, anastomoses were intact and there was dense ingrowth of connective tissue into the Dacron coating. In 12 animals the prosthesis was used as a cutaneous ureterostomy. Five animals tore the prostheses off and one was rejected, but six remained firmly attached and functioned well up to 4 months. In 10 animals the prosthesis was used as an urinary conduit. The prostheses remained in position and functioned well over the observation period of eight weeks. Leakage occurred on four occasions. There was no hydronephrosis.

Incrustation was not a problem with any of the 30 prostheses implanted. The coating of Dacron velour over a silicone rubber prosthesis allows the development of a satisfactory watertight junction between organic tissue and the alloplastic material.

Dr. B. Schreiber
Urologische Univ. -Klinik der GHS Essen
Hufelandstr. 55, D-4300 Essen 1

ALLOPLASTIC REPLACEMENT OF THE CANINE URETER BY EXPANDED POLYTETRAFLUOROETHYLENE (GORE TEX®) GRAFTS: A PRELIMINARY REPORT

K. Dreikorn, J. Löbelenz, R. Horsch and L. Röhl

Expanded polytetrafluoroethylene (GORE TEX®) has been successfully used for vascular substitution both experimentally and clinically. Its suitability for subtotal replacement of the canine ureter has been investigated.

The ureter was replaced unilaterally in 8 dogs and bilaterally in 4 dogs with prostheses made of GORE TEX®. Excretory urography has shown the grafts to be well-tolerated and providing free urinary drainage from the kidneys to the bladder.

These successful studies encourage further investigation with this new type of graft.

Prof. Dr. med. K. Dreikorn
Department of Urology, University Hospital
D-6900 Heidelberg

HETEROLOGOUS AND ALLOPLASTIC SEGMENTAL REPLACEMENT OF THE CANINE URETHRA

J. Löbelenz, K. Dreikorn, R. Horsch and L. Röhl

Since human umbilical cords (1), bovine carotid heterografts (Solco®) (2) and expanded polytetrafluoroethylene (PTFE Gore tex®) grafts (3) have

been used successfully for vascular substitution, we have studied their suitability for replacement of the urethra.

3-8 cm of the penile urethra were resected in 22 male dogs and replaced by human umbilical cord (Group I, n = 5), bovine carotid heterograft (Group II, n = 5) and PTFE (Group III, n = 12). Follow-up was by serial urethrograms.

Animals in Group I developed fistulae following infection and stricture formation within 2 weeks. There was extensive stricturing within 3-4 weeks in Group II and this was also followed by fistula formation. Results in Group III were encouraging. Two dogs developed periurethral haematomas and in one animal a urinary fistula developed but this closed spontaneously following insertion of a urethral splint. Graft patency was demonstrated at 13 months. At the end of this time urethroscopy showed no macroscopic evidence of encrustation.

PTFE grafts show encouraging results and these experiments demonstrate their superiority over umbilical cord and bovine carotid heterografts for replacement of the canine urethra.

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Dr. med. J. Löbelenz
Department of Urology, University Hospital,
D-6900 Heidelberg

SCANNING ELECTRON MICROSCOPE STUDIES OF PLASTIC SPLINTING TUBES IN VIVO AND IN VITRO

K. Maar, W. Lenz and R. Blaschke

The encrustation occurring on the surface of plastic splints of various types has been examined following perfusion with urine under a variety of constant conditions. The deposits were analysed by scanning electron microscopy.

These studies showed that polyethylene splints had the roughest internal surface and the smoothest surface was seen with PVC tubing especially siliconised PVC. Encrustation occurred rarely with the PVC splints. When they did occur they formed isolated discrete deposits. Encrustation occurred to a greater extent with polyethylene tubes and these deposits were more homogenous. Examination of the deposits showed an underlying protein layer and a surface calcium phosphate layer. Depositions increased in the direction of flow of the urine.

In vivo studies of splint tubing have also shown an increase of deposits towards the bladder and that beneath a 5 micron thick layer of Calcium-oxalate there was a thin layer (0.1 micron) of calcium phosphate.

Internally siliconised PVC would appear to be the most suitable material for long-term splinting.

Dr. med. Klaus Maar
Urologische Univ.-Klinik Düsseldorf,
Moorenstr. 5, D-4000 Düsseldorf

AN EXPERIMENTAL STUDY OF CRYSTAL AGGREGATION ON CATHETERS OF VARIOUS MATERIALS

H.P. Bastian, L. Weissbach, R. Lunow and M. Gebhardt

The aggregation of crystals on tubing of the following materials in alkaline and acid urine were studied by scanning electron microscopy: Polyethylene, Polypropylene, Polyvinylchloride (PVC), Polytetrafluoroethylene (Teflon), Ethylenacrylacidcopolymerisate, Polyurethane, Silicone and Latex.

The inner surface of the catheters was seen to be smooth except for the Latex and PVC tubes. In acid urine there was heavy crystallisation with Latex. PVC, Polyurethane and Polyethylene showed moderate crystallisation. The best results were obtained with the Silicone catheter. In an alkaline urine crystallisation was heavy with Latex, PVC, Polyethylene and Polypropylene.

Polyurethane and Silicone appear to be the most suitable materials for catheter drainage and Latex and PVC the least suitable.

Priv.-Doz. Dr. H.P. Bastian
Department of Urology, St. Josef-Hospital,
Hollweghstr. 26, D-5000 Köln 91

PHYSICAL CHANGES OF DIFFERENT PLASTIC MATERIALS DUE TO CONTINUOUS EXPOSURE TO URINE

R. Gerlach, K. Weigner, S. Lymberopoulos and W. Bialonski

The changes in the physical characteristics of 16 different plastic materials and encrustation occurring on them as the result of continuous exposure to urine have been studied.

The 16 different tubes were intermittently perfused with fresh urine at 37 C in each of three

parallel circuits. Circuit 1 contained sterile urine from a healthy volunteer. Circuit 2 contained infected alkaline urine and Circuit 3, urine from a person with calculi. Urine was pumped from a reservoir and continuous agitation was used to avoid sedimentation. One tube at a time was perfused in each circuit over a 12 week period and every 4 weeks samples of each tube were tested for changes in their physical properties and examined for deposits and encrustation with the electron microscope.

Minimal encrustation was seen with silicone materials and natural rubber. Isolated islands of crystals occurred, consisting of calcium phosphate, calcium oxalate and mixed crystals. There was loss of elasticity of up to 60% in all silicone materials. The greatest deposits were seen in Circuit 3 and crystals appeared to deposit more frequently on corners and edges. The most satisfactory material was Polystroma which showed no alteration in elasticity and little accumulation. In vivo experiments of over 18 months duration have confirmed this observation.

R. Gerlach
Aerodynamisches Institut der RWTH Aachen,
Templergraben,
D-5100 Aachen

III. Oncology – Prostate

TESTOSTERONE METABOLISM AND CHARACTERISATION REVIEW OF THE HUMAN PROSTATIC CELL LINE EB 33

W. Hoehn, H.-U. Schweikert and F. H. Schroeder

The permanent tissue culture cell libe EB 33 was derived in 1973 from a human prostatic carcinoma (1). Clone 108 of 111 clonal sublines was found to show significantly different doubling rates in medium containing androgens. The testosterone metabolism of EB 33 has been studied further.

Just-confluent monolayer cell cultures of the EB 33 primary line, the clone 108 and HeLa cells (negative control) were incubated for between 2 and 24 hours with 1, 2, 6, 7, -^{3}H) testosterone at a final concentration of 25 nM in Eagles minimum essential medium. The metabolites were extracted with chloroform, separated by thin layer chromatography and assayed for ^{3}H by liquid scintillation.

Testosterone was metabolised mainly to dihydrotestosterone and testosterone concentration was reduced by half after 20 hours. Smaller quantities of androstanediol, androstanedione and andro-4-stenedione were identified. No significant differences could be observed in the metabolism of testosterone by EB 33, clone 108 and HeLa cells.

The metabolic pathways are typical of prostatic cells. However the almost identical metabolism in EB 33 and HeLa cells raises the question as to whether EB 33 is a totally dedifferentiated prostatic cell or has derived from HeLa contamination of cell cultures.

These results, taken together with the previous characterisation of EB 33 (1) limit the scientific interest in EB 33 as a model for human prostatic carcinoma.

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Dr. W. Hoehn
Erasmus University Rotterdam,
Postbus 1738, Rotterdam

IN VITRO STUDIES OF CELL-MEDIATED CYTOTOXICITY IN CARCINOMA OF THE PROSTATE

R. Ackermann, M. Wirth and T. Okabe

In view of suggestions of cell-mediated immunity in carcinoma of the prostate (1) a study was undertaken to ascertain whether cell-mediated cytotoxicity could be monitored in vitro with cell line EB 33 (2), and whether EB 33 cell lysis in vitro was a tumour-specific immunoreaction.

The cytotoxicity of mononuclear effector cells was isolated from venous blood and regional prostatic lymph nodes and was estimated by ^{51}Cr-release assay with EB 33 cells as targets. Lymphocytes were tested from 30 patients with prostatic carcinoma, 9 with BPH and from 10 females.

Cytotoxicity against EB 33 was observed with peripheral lymphocytes on patients with prostatic carcinoma and also from patients with BPH. Reaction with female lymphocytes was significantly weaker. Complete target cell lysis was mostly observed with lymphocytes from patients with Stage B carcinoma and in these cases ^{51}Cr release began after six hours incubation. Circulating lymphocytes were more cytotoxic than those isolated from regional prostatic lymph nodes.

The similar results obtained with lymphocytes obtained from patients with BPH and prostatic cancer may indicate a natural cytotoxicity or suggest that the BPH patients may have had occult carcinoma causing cellular sensitisation. The possibility of an additional specific synergistic cellular component was not elucidated by short term ^{51}Cr release assays or comparative tests with peripheral and regional lymphocytes.

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Priv.-Doz. Dr. R. Ackermann
Urologische Klinik und Poliklinik der Universität,
Luitpoldkrankenhaus, D-8700 Würzburg

EFFECT OF CYPROTERONE ACETATE ON EXPERIMENTALLY INDUCED PROSTATIC HYPERPLASIA IN THE CASTRATE DOG

U. Tunn, B. Schenck, Th. Senge and F. Neumann

Benign prostatic hyperplasia (BPH) in the castrate dog was produced by chronic administration of 5 alpha-androstane-3 alpha 17 beta-diol (3 alpha-diol) alone and in combination with 17 beta-oestradiol (E_2) (1). The influence of the antiandrogen cyproterone acetate (CA) on the development of BPH was investigated.

The inital size of the prostate gland in 23 adult male beagles was estimated from three dimensional measurements following retroperitoneal exploration. Three animals were used as controls (group I). The remaining 20 animals were injected three times weekly for a period of six months with the following dosage schedules: Group II, 3 alpha-diol 75 mg; Group III, 3 alpha-diol 75 mg + E 0.75 mg; Group IV, 3 alpha-diol 75 mg + CA 600 mg; Group V, 3 alpha-diol 75 mg + E_2 0.7 mg + CA 600 mg. The prostates were removed, weighed and examined histologically after six months.

The average increase in prostatic weight for each of the groups was as follows: Group I, 2.5 gm; Group II, 12.8 gm; Group III, 22.1 gm; Group IV, 2.9 gm; Group V, 0.5 gm. Histological features in Group II showed characteristic hypertrophy of the single-layered epithelium. 3 alpha-diol and E_2 induce epithelial proliferation with squamous metaplasia and obstruction of the acini. Activation of the fibromuscular system was also obvious. 3 alpha-diol plus CA caused atrophy of glandular epithelium. 3 alpha-diol plus CA plus E_2 produced activation of smooth muscle fibres but there was no secretory epithelium.

3 alpha-diol causes epithelial hypertrophy. The effect of 3 alpha-diol is abolished by CA. E causes activation of the fibromuscular system.

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Dr. med. U. Tunn
Urologische Klinik,
Josefs-Hospital, D-4690 Herne 1

ANDROGEN METABOLISM IN PROSTATIC CARCINOMA IN RELATION TO TUMOUR GRADING: CYTOPLASMIC AND MICROSOMAL FORMATION OF ANDROSTANEDIOL

G.H. Jacobi, K.H. Kurth, K. Sinterhauf and J.E. Altwein

Prostatic tumours may be initiated and maintained by changes in androgen metabolism. Intracellular 3-alpha-androstanediol formation is increased in hyperplastic prostates of man and dog (1). The necessary enzyme - 3-ketoreductase - is dependent upon testicular function (2). The formation of 3-alpha-androstanediol has been investigated in prostatic carcinoma tissue of untreated patients.

From 8 highly and 14 poorly differentiated adenocarcinoma 160 mg tissue was harvested by transrectal needle biopsy. Tissue preparation and separation of cell fractions by ultracentrifugation was described previously (2). The routine enzyme assay contained 5 uM ^{3}H-DHT, 0.5 mM NADH or NADPH, 0.1 ml cytosol or microsomes, 0.5 mM EDTA, 0.1 M Tris chloride, and 0.1 M Na-citrate, pH 7.5 (cytosol) or 5.5 (microsomes) in in a total volume of 0.2 ml. Incubation and steroid separation by thin chromatography was done as before (1).

3-alpha-androstanediol formation was 6.5 ± 1.1 and 2.5 ± 0.4 nmol/g tissue $^{-1}h^{-1}$ in cytosol and microsimes respectively NADPH was a more potent cofactor than NADH. There was a significant difference of 3-alpha and 3-beta-androstanediol formation in well-differentiated as opposed to poorly differentiated tumour. In the cytosolic, NADPH-linked reaction, 3-alpha-androstanediol formation was not significantly different in normal prostates and well-differentiated carcinoma (7.7 and 9.3 nmol/g tissue $^{-1}/h^{-1}$). The highest activity was seen in BPH (18.4 ± 1.2 nmol/g tissue $^{-1}/h^{-1}$). This was the highest activity of both cell fractions with either cofactor.

As has been demonstrated for 5-alpha-reductase (3), prostatic 3-ketoreductase is also diminished in carcinoma tissue varying with the degree of de-differentiation. This may be related to the hormone-independent growth of undifferentiated or anaplastic tubes.

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Dr. G.H. Jacobi
Urologische Klinik der
Johannes-Gutenberg-Universität,
D-6500 Mainz

DIFFERENCES IN LOCAL ZINC DISTRIBUTION IN HYPERPLASTIC AND UNTREATED AND TREATED CARCINOMATOUS HUMAN PROSTATE. A NEEDLE BIOPSY STUDY

S. Sonnenberg, P. Mellin, S. Nuphaus and I. Rodzek

The local distribution of zinc in hyperplastic and carcinomatous human prostatic cells has been studied. The changes in local zinc distribution in

carcinomatous cells occurring after treatment by orchidectomy, radiation and hormone therapy was also investigated. The methods used were the silver sulphide method described by Timm (3) and staining by May-Grünwald-Giemsa.

The results were as follows: a) Hyperplastic prostate: high concentrations of zinc were found in the nucleus mainly in chromatin. There was less zinc in the cytoplasm with a higher concentration near the cell border. b) Prostatic carcinoma: zinc was found mainly in the nucleus with minimal concentration in the cytoplasm. c) Following orchidectomy almost identical findings to the untreated malignant gland. d) Following hormonal therapy: A general increase in zinc concentrations in carcinomatous and metaplastic cells. There was often rupture of the nuclear membrane with outflow of chromatin particles rich in zinc. e) Following irradiation therapy: large quantities of zinc around necrotic cells. No changes in intact cells.

The sulphide-silver method (1, 2) allows differentiation between hyperplastic and malignant prostatic cells. Treatment with hormones increases the zinc concentration in the cell. Following irradiation local zinc distribution is affected by cell destruction.

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Dr. S. Sonnenberg
Urologische Univ. -Klinik der GHS Essen,
D-4300 Essen 1

INDIRECT REGIONAL LYMPHANGIOGRAPHY OF THE PROSTATE (IRLP): AN EXPERIMENTAL STUDY IN DOGS

N. Pfitzenmaier, M. Blasshofer and K. Möhring

An indirect method of demonstrating the regional lymphatics of the prostate by intraprostatic injection of contrast medium has been investigated in dogs.

In 6 dogs the prostate was injected transcutaneously with 3 to 5 ml of amidotrizoate or Lipiodol UF®*. In a further six dogs the prostate was injected transurethrally using a specially developed instrument** 3 ml of Lipiodol UF and 4 ml of an emulsified contrast medium (AG 52.315***) and isosmotic glucose solution were injected simultaneously in multiple sites.

Water soluble contrast medium proved to be unsuitable for IRLP because of rapid transport by lymphatics. Percutaneous injections demonstrated the regional lymphatics but there was inconplete filling. There was poor distribution of the contrast medium within the prostate. Transurethral injection produced satisfactory demonstration of the regional lymph nodes
tion produced satisfactory homogenous opacification of the prostate and satisfactory demonstration of the regional lymph nodes was seen using Lipiodol UF. However the transport to the node was very slight. Using emulsified contrast medium the regional lymphatics were demonstrated between 12 and 60 hours following injection.

No local or pulmonary complications were observed.

Dr. med. N. Pfitzenmaier
Department of Urology, University Hospital
D-6900 Heidelberg

* Byk Gulden, FRG ** Storz Instruments, FRG
*** André Guerbet, France

IV. Urinarytract Infection and Stone Disease

INTRAVESICAL POLYVINYLPYRROLIDONE - STUDIES OF ITS ABSORPTION AND INFLUENCE ON THE BLADDER MUCOSA IN RABBITS

B. Egger, D. Berg and W. Schmahl

Polyvinylpyrrolidone-iodine solution (Betadine®) has been used in dilute form for the treatment of post-gonoccocal urethritis. As a preliminary to its possible use for bladder instillation, mucosal absorption and local effects of PVP-I have been examined in the rabbit.

The thyroid gland was blocked and the iodine pool determined in 5 rabbits. In 11 animals 10 ml of 7.5% PVP-^{125}-I were instilled in the bladder and radioactivity in the blood determined every ten minutes for 2-3 hours. The bladder was then removed and examined histologically. In 10 animals 7.5% PVP-I solution was instilled into the bladder for one hour daily for 10 days. The bladder was then removed and examined histologically.

The mean iodine pool was 297 ml/kg body weight. 30 minutes after instillation 2.38% kg of the original activity had been absorbed. After 3 hours this figure had risen to 48.5% kg corresponding to 58.2 mg iodine. The resorption rate was 4.47% per 30 minutes and remained constant over 3 hours.

After 3 hours instillation the bladder mucosa showed epithelial defects and oedema. There was considerable eosinophilia. Intermittent instillation over 10 days resulted in granular infiltration of the submucosa and perivascular lymphocytic collection. The epithelium was intact and there was less oedema.

PVP-I is rapidly absorbed from bladder mucosa. Plasma levels are elevated for a short period only due to renal excretion. 7.5% PVP-I is not suitable for instillation as it leads to irritation of the mucosa.

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Dr. Bernd Egger
Urologische Klinik u. Poliklinik
der Technischen Universität,
Ismaninger Str. 22
D-8000 München 80

CONCENTRATION OF CEPHRADINE IN PROSTATIC INTERSTITIAL FLUID

R.-H. Ringert, U. Thiel, and H.-U. Eickenberg

A method for measuring antibiotic concentration in interstitial fluid has been developed (1, 2). This technique has been used to assay cephradine concentration in prostatic interstitial fluid (PIF) and soft tissue interstitial fluid (STIF) and serum.

In four mongrel dogs polypropylene capsules were implanted in the prostate and subcutaneous tissue. 4-5 weeks later PIF, STIF and serum were collected at regular intervals following intervenous infusion of cephradine (20 mg/kg). Antibiotic concentrations were measured biologically.

The initial concentrations of cephradine were higher in serum (82.3 mg/ml) than in PIF (17.7 mg/ml) and STIF (9.3 mg/ml). After 2 hours serum concentration fell to 19 mg/ml, PIF concentration rose to 27.6 mg/ml and STIF to 24.3 mg/ml. Serum, PIF and STIF cephradine concentrations level at 1 1/2 hours. At 2 and 4 hours PIF and STIF show higher cephradine concentrations than serum.

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Dr. R.-H. Ringert
Urologische Univ.-Klinik,
Hufelandstr. 55,
D-4300 Essen 1

LOCAL IMMUNE RESPONSE TO URINARY TRACT BACTERIA IN EXPERIMENTAL CYSTITIS

G. Riedasch, W. Bersch, A. Shackelford, E. Schneider, K. Möhring

It has been suggested that upper urinary tract infections are characterised by the presence of antibody coated bacteria (ACB) (1). This study concerns the presence of ACB in lower urinary tract infection.

Polyacrylamide discs were implanted in the bladders of 30 female Wistar rats. 0.2 ml of an E. coli suspension (ACTT 25922 10 /ml) were injected into the bladder. Urine was collected at 5 day intervals, cultured and examined for ACB (1). 20 rats were sacrificed 22 days later and the bladders and kidneys examined histologically and by immunofluorescence. The remaining 10 animals were given a second injection of E. coli suspension on the fiftieth day. Immediately prior to this second injection and at three day intervals the urine was collected and examined. A control group was injected with E. coli but without foreign body implantation (n = 20). Animals with ascending injection and histological pyelonephritis were excluded.

Over 70% of all urine specimens were ACB positive. Within 24 hours of the second injection on the fiftieth day, 90% of all bacteria were antibody coated. Histology and immunofluorescence demonstrated locally invasive infection with fibrin deposits, plasma cell infiltration. In the control group in which the infection was limited to the bladder lumen without invasion ACB were not seen.

Smith (2) was able to demonstrate 100% ACB in experimental pyelonephritis but Uehling (3) has shown that the urothelium is capable of reacting to bacterial invasion with a local immune response. The results of our study suggest that the presence of ACB is indicative of the invasiveness of local infection rather than the site.

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Dr. med. G. Riedasch
Department of Urology, University Hospital,
D-6900 Heidelberg

INFLUENCE OF DOXYCYCLIN AND CO-TRIMOXAZOLE TREATMENT ON ANTI-LIPID A ANTIBODY RESPONSE. CLINICAL AND EXPERIMENTAL STUDY

M. Westenfelder, C. Galanos and G. Lang

The influence of Doxycyclin and Co-Trimoxazole treatment for urinary infection on the anti-lipid A antibody response has been investigated(1).

Lipid A antibody titres were measured by the passive haemolysis test (2) in:
a) 122 patients with UTI, 58 treated with Doxycyclin and 64 with Co-Trimoxazole.
b) 43 patients with acute pyelonephritis (21 Doxycyclin, 22 Co-Trimoxazole), before, during and after treatment.
c) In 3 groups of rabbits receiving daily 0.9% NaCl, Doxycyclin or Co-Trimoxazole for 36 days and immunised with 200 mg lipid A-vaccine on days 5 and 19.

Study a) revealed anti-lipid A antibodies in 50% of all patients. There was a significant difference between the Doxycyclin group (64%) and the Co-Trimoxazole-group (39%). This difference was independent of sex, diagnosis, infecting organism, kidney function and blood group. Study b) revealed no difference in anti-lipid A antibody response in acute pyelonephritis. In rabbits, antibody response to lipid A vaccine was strongest under Doxycyclin and weakest under Co-Trimoxazole treatment until the time of the second injection. Following this there was no significant difference. The influence of these antibiotics on the humoral immune response to gram negative infection may not be due to antibacterial activity since it occurred following vaccination with dead bacteria and was absent in acute pyelonephritis. This may be unimportant in the treatment of acute infections but long-term prophylaxis should be done with antibiotics which prevent anti-lipid A antibody production to prevent further pathological immune response (3).

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Priv.-Doz. Dr. M. Westenfelder
Abteilung für Urologie der
Universität Freiburg
Hugstetter Str. 55,
D-7800 Freiburg

INFLUENCE OF HYPEROXALURIA AND HYPERURICOSURIA ON CALCIUM OXALATE STONE FORMATION

F. Hering, G. Bigalke and W. Lutzeyer

Hyperoxaluria was induced in male Wistar rats by the administration of 0.8% ethylene glycol in water. Hyperuricosuria was obtained by blocking liver uricase with 2% oxonic acid. Intrarenal precipitates of oxalate and urate were stained histochemically and evaluated by planimetry. Oxalate excretion was determined by gas chromatography. Urate excretion was determined enzymatically. Induced stones were analysed by infrared spectroscopy. The animals were killed at 10, 20 and 30 days.

With the combined treatment a stone frequency of 1.36/animal with an average weight of 53.1 mg was observed. Treatment with ethylene glycol alone produced a stone frequency of 0.56/animal with an average weight of 34.6 mg. Oxonic acid treatment alone produced no detectable stones.

Infrared spectroscopy showed calcium oxalate dihydrate stones. The planimetric evaluation of oxalate deposits in the kidney showed:
1. Significantly greater deposits with combined treatment than with single treatment alone. This effect was independent of the duration of treatment.
2. Significantly more oxalate deposits in the cortex compared with the medulla.

In male rats, hyperuricosuria has a negative effect on calcium oxalate stone formation.

Dr. F. Hering
Abteilung Urologie, RWTH Aachen,
Goethestr. 27/29
D-5100 Aachen

EXPERIMENTAL STUDIES OF THE GROWTH AND DISSOLUTION OF RENAL STONES

M. Gebhardt, H.P. Bastian and J. Kauffmann

The interaction between the urine and the stones of selected stone-forming patients was studied in vitro. Apatite, calcium oxalate and uric acid stones were studied. The stones were examined by scanning electron microscopy. The concentration of calcium, magnesium, uric acid, sodium, potassium and pH in the urine were determined.

Urinary infection led to the crystallisation of apatite and struvite. A urinary pH above 8 promotes dissolution of calcium oxalate crystals. Calcium and magnesium concentrations were decreased at the end of the experiment.

Fresh crystallisation could occur from the

urine of all stone formers and even uric acid stones can develop a shell of apatite or struvite if the pH is over 8.

Priv.-Doz. Dr. H.P. Bastian
Department of Urology, St. Josef-Hospital,
Hollwegstr. 26,
D-5000 Köln 91

V. Oncology – Bladder and Kidney

GLYCOSAMINOGLYCANS (GAG) IN THE NORMAL AND NEOPLASTIC URINARY BLADDER

H. Rübben, H.W. Stuhlsatz and J. Mingers

GAG may be demonstrated within epithelial layers by histochemical stain. They may be involved in the local defence mechanism against bacterial infections (2) and in neoplastic change. The biochemical demonstration of GAG in transitional cell epithelium was undertaken in rat, bovine and human bladders.

The epithelial, submucosal and muscular layers of normal bladders and urothelial carcinomas were separated. Formalin fixed preparations were used as controls for histochemical stains (PAS, colloidal iron, alcian blue 8GS). The tissue underwent proteolysis with papain and chromatography on Dowex 1 x 2 microcolumns eluted with 0.15; 0.50; 1.50 and 3.00 M NaCl solutions. The four fractions were dialysed and hydrolosed. Glucosamine and galactosamine were analysed by means of an amino acid analyser (TSM Technicon) (2).

In the normal urinary bladder the epithelium showed a high concentration of glycoprotein but only traces of GAG could be detected. The submucosa showed high concentrations of GAG in the cell fractions. The muscle layer showed GAG in lower concentrations than in the submucosa. In urothelial tumours the epithelial component showed high concentrations of GAG in the 3.00 M NaCl fraction and low concentration of GAG in the 1.5 fraction. The results did not correlate biochemical analysis and positive staining was observed in the areas shown to be devoid of GAG biochemically.

Histochemical stains therefore appear not to be specific for GAG. The surface coat, involved in the bacterial defence mechanism, does not consist primarily of GAG. Urothelial cancer contains GAG, whose composition differs from connective tissue GAG. Further biochemical analysis is required for identification.

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Dr. med. H. Rübben
Abt. Urologie,
Klinische Anstalten RWTH Aachen,
Goethestr. 27/29,
D-5100 Aachen

STUDIES ON THE PATHOMORPHOGENESIS, INDUCTION AND PROPHYLAXIS OF EXPERIMENTAL URINARY BLADDER CARCINOMA IN RATS

A.H. Adolphs, J. Thiele and H. Kiel

The reliability and selectivity of experimental induction of urinary bladder cancer by feeding 0.188% N-[4-(5-nitro-2 furyl)-2-thiazolyl] formamide (FANFT) has been studied in rats. The histological changes have been documented and the influence of BCG application during tumour induction studied.

Female Wistar rats were fed with 0.188% FANFT for 8 months. Histological and ultrastructural examinations were performed at monthly intervals. The remaining animals were all sacrificed at 12 months. One group of animals received weekly subcutaneous injections with TICE BCG.

All animals developed infiltrating transitional cell carcinomas after 8 months of FANFT feeding. Tumour stages II and III and grades 2 and 3 were most frequently encountered. After prolonged BCG application the tumour weights were significantly lower.

H.D. Adolphs
Department of Urology, University of Bonn,
Venusberg,
D-5300 Bonn

A NEW LONG-TERM TISSUE CULTURE CELL LINE DERIVED FROM A TRANSITIONAL CELL CARCINOMA OF THE HUMAN URINARY BLADDER

P. Dlhos, H. Oerkermann, A. Dlhos and H. Heising

Tissue culture preparations were made from specimens of human urinary bladder tumours. Measurements of cell cycle time measured by time-lapse cinemicrography were compared with cell cycle parameters measured by autoradiography.

Biopsy specimens were minced, trypsinated

and the cell suspensions cultured at 37°C in culture medium containing Streptomycin, Penicillin and 20% human AB serum. Time lapse cinemicrographic studies were performed on monolayer culture for 80 hours taking one picture every 72 seconds. Cell cycle time was determined by counting pictures between successive mitoses. Autoradiographic studies were performed after pulse labelling with Methyl-3H-Thymidine on cultures explanted on tube slips in stoppered ordinary test tubes.

A new long-term cell tissue culture from a human transitional cell carcinoma was established and has been maintained for 7 months over 30 transfer generations. The cells have maintained a completely consistent pattern resembling transitional cell tumour and are epithelial in type. The cinemicrographically measured cell cycle time is 24.9 ± 10.2 hours. The autoradiographically measured parameters were: cell cycle time/T_c/ is 25 hours, S-phase/T_s/ is 9 hours, G_2-phase/T_{G2}/ is 4 hours.

This new cell line corresponds closely with known transitional cell carcinoma cultures. Cell kinetics by the PLM-method are in agreement with the parameters of the MGH-Ul- and T24- cell lines (1, 2).

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P. Dlhos
Eckerstr. 18,
D-5000 Köln 41

CELL KINETIC STUDIES ON IN VIVO SYNCHRONISATION WITH 5-FLUOROURACIL IN THE L 1210 MOUSE LEUKAEMIA

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

The efficacy of 5-Fluorouracil (FU) in producing synchronisation of cell cycles has been studied in vivo.

A wide range of FU doses (0.1-100 mg/g) were studied. The degree of synchrony was assessed by following the course of the mitotic-index and the H-TdR and H-UdR labelling indices autoradiographically after FU administration alone and FU injection followed by cold Thymidine. The reversable accumulation of cells in the S-phase was achieved maximally with 3 mg FU. However, with FU alone no evidence of a synchronised passage of the accumulated cells further around in the cycle was found. This is, at least in part, due to a slow and gradual release of cells from the FU block. When FU injection was followed by cold Thymidine to sharpen the release of blocked cells, a synchronous passage of accumulated cells through the cycle was observed.

The degree of synchrony was small and there was a large variation in the individual response to this treatment.

Dr. med. W. Jellinghaus
Urologische Klinik und Poliklinik
der Universität,
Josef-Schneider-Str. 2,
D-8700 Würzburg

BROWN-PEARCE CARCINOMA AS A MODEL URINARY BLADDER TUMOUR IN RABBITS

R. Harzmann, D. Gericke, K.H. Bichler, E. Altenähr and D. Erdmann

Male rabbits are especially suitable animals for experimental work on urinary bladder cancer. Since induction of genuine urinary bladder carcinoma has always taken at least 2 years in these animals an attempt has been made to develop a technique for implanting a malignant tumour in the bladder more quickly.

Testicular tumour tissue from a Brown-Pearce carcinoma (1) in a rabbit was removed under sterile conditions and transplanted into 160 mongrel rabbits. The transplant was sited intratesticularly (n = 20), subcutaneously (n = 20) and in the wall of the urinary bladder (n = 120). The bladder implants were carried out either by open surgical methods (n = 80) or transurethrally (n = 40) (2, 3). Tumours developed from subcutaneous transplantation in 42.1% of cases. Intratesticular and submucosal transplantation produced tumours in 79-100% of the cases. The tumours ulcerated the bladder lumen and remained in the bladder wall for three weeks. Metastases occurred in the paraaortic lymph nodes and liver. If the transplant was undertaken without separating the mucosal layers peritoneal spread with eye and lung metastases occurred. There was no change in the histological characteristics of the Brown-Pearce carcinoma. The tendency to spontaneous necrosis, ulceration and encrustation was striking.

These studies show that foreign tumour tissue can be transplanted into the urinary bladder and the resulting tumours resemble bladder cancer in terms of growth and metastasis. However, spontaneous necrosis is a disadvantage. This

technique may be suitable for the development of transurethral procedures.

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Dr. med. R. Harzmann
Department of Urology,
University of Tübingen,
Calwerstr. 7, D-7400 Tübingen

INDUCTION OF URINARY BLADDER CARCINOMA IN DOGS

R. Harzmann, D. Gericke, K.H. Bichler, E. Altenähr and H. Grötsch

The latent period for experimental urinary bladder carcinoma induction in dogs is 2 years (2). Attempts have been made to shorten this time.

1.5 ml of a liquid methyl-methacrylate plastic was instilled transurethrally into the bladders of 18 female beagle whelps. An artificial bladder stone was formed. A further 4 animals served as stone-free controls. Three groups of 4 animals were treated with ortho-aminodiphenyl (OADP), FANFT, or both respectively. The animals were examined at monthly intervals including endoscopy and cytological examination. The excretion in the urine of subcutaneously applied carcinogens was measured with Ames' s bacterial mutagenicity test.

No pathological changes were seen in the control animals. Mutagenic substances were found in the urines of the animals who were receiving FANFT but not in those receiving OADP or the controls. FANFT treated animals showed cytological abnormalities after 5 months. At 7 months endophytic and exophytic papillary growths were seen. Carcinomas were present after 12 months. No changes in urinary enzyme excretion were noted.

It appears that the chemical induction of urinary bladder carcinoma in dogs is considerably hastened by the co-carcinogenic impact of artificial urinary bladder stones. The successful induction of carcinoma in pure-bred animals will enable further research to be carried out on transplantation of these experimental tumours.

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Dr. med R. Harzmann
Department of Urology,
University of Tübingen,
Calwer Str. 7, D-7400 Tübingen

THE EFFECT OF LOCAL HIGH FREQUENCY HYPERTHERMIA ON URINARY BLADDER CARCINOMA - EXPERIMENTAL AND CLINICAL STUDIES

R. Harzmann, K.H. Bichler, E. Altenähr and D. Gericke

The clinical use of hyperthermia for the treatment of urinary bladder carcinoma has yielded contradictory data (2, 3). The effect of local hyperthermia on urinary bladder carcinoma has been investigated experimentally. Hyperthermic infusion of the bladder does not produce homogenous warming of the bladder wall and so high frequency local irradiation was carried out by 2 external electrodes (1) and later by means of a transurethral probe. A high frequency long-wave current was used. A transurethrally inserted Teflon-insulated thermocouple was used for temperature monitoring.

The most efficient temperature was found to be 43°C for a period of 30-60 minutes (1). 80 rabbits with implanted Brown-Pearce carcinoma were used in the experiment. The heat-treated animals showed significantly smaller tumour volumes, less frequent metastases and prolonged survival periods compared with controls. Transplantation of previously treated tumours resulted in a regrowth rate of 20% compared with 96% for untreated tumours.

15 patients with urinary bladder carcinoma have been treated by this transurethral high-frequency heat application using an optically controlled probe. Oedema and blanching of the tumour were observed and subsequent reduction in size. In 3 cases the tumour disappeared completely and in a further 8 cases there was substantial improvement. Histology showed cell-cluster necrosis and in 3 cases, hyalinisation of the stroma. The best results were obtained in undifferentiated solid urothelial tumours. Some transient swelling of healthy epithelium occurred but without permanent damage.

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Dr. med. R. Harzmann
Department of Urology,
University of Tübingen,
Calwer Str. 7, D-7400 Tübingen

XERORADIOGRAPHY AND CONVENTIONAL X-RAYS OF EXCISED REGIONAL LYMPH NODES FOLLOWING DISSECTION FOR UROLOGICAL CARCINOMAS

P. Brühl, T. Franken and B. Helpap

Lymphography is the most commonly used diagnostic method for the demonstration of lymph node metastases in urological carcinomas. However a negative lymphogram does not exclude microscopic tumour deposits. When frozen section is used the problem lies in the selection of the appropriate lymph node for examination. This selection may give rise to false negative findings and therefore understaging. Such results may influence treatment.

In cases with a negative lymphogram we have used xeroradiography as a method for the localisation of tumour cells within lymph nodes and suspicious areas are then examined histologically in frozen sections. Xeroradiography increases contrast at margins and makes the selection of lymph nodes for histological examination much more reliable. Another useful technique is the use of needles to label the suspicious lymph nodes after conventional x-ray examination of the excised tissue. Both methods have given good results in the documentation of lymph node involvement after lymphadenectomy in carcinomas of the urinary bladder, prostate, testes and kidneys.

P. Brühl
Urologische Klinik und
Pathologisches Institut der Universität,
Venusberg, D-5300 Bonn

HUMAN RENAL CARCINOMA: DEVELOPMENT OF TWO NEW CELL LINES OF A SERIALLY TRANSPLANTABLE NUDE MOUSE TUMOUR OBTAINED FROM ONE OPERATIVE SPECIMEN - NC 65

W. Hoehn and F. H. Schroeder

Tissue from a human clear cell renal carcinoma and from a renal hilar metastasis containing only granular cells were placed in cell culture and heterotransplanted on nude mice. The resulting cell line was studied by cloning and chromosomal analysis. The primary kidney tumour cell line was cloned and two different sublines were maintained - a spindle-shaped cell and a round cell. Genetically the round cell has developed from the spindle cell. They doubled their number every 28 and 35 hours respectively. These cells could not be grown in nude mice.

A serially transplantable nude mouse tumour was obtained from the hilar node metastasis and maintained the original histology after 21 months.

There was occasional tumour metastasis into mouse regional lymph nodes. The peripheral tumour grew with a doubling rate of 48 hours. On cell culture a round tumour could be identified, genetically derived from the round cell of the primary line, doubling every 53 hours. No tumour resulted when the cell was re-injected into mice. The tumour could not be preserved in liquid nitrogen.

A metastasising nude mouse tumour originating directly from a human renal carcinoma has not been previously described. These cell lines may be useful for further experimental studies of human renal carcinoma.

Dr. W. Hoehn
Department of Urology, Erasmus University,
Postbus 1738, Rotterdam

ALTERED PROFILES OF POLYAMINES IN PROSTATIC HYPERPLASIA AND RENAL CANCER

U. Dunzendorfer, W. Weber and D. H. Russell

Polyamines are low molecular weight compounds found in large quantities in the prostate, compared with other tissues. Elevated urinary excretion of polyamines has been documented in patients with cancer (1, 2). The relationship of spermidine to spermine is highest in very fast growing and undifferentiated cancer tissues. In this study the polyamine concentration in normal human prostate and kidney tissue has been measured and compared with the findings in benign hyperplasia of the prostate and renal carcinoma. Normal prostatic tissue was obtained from kidney donors and young males after accidental death (n = 5). Together with specimens of benign hyperplasia of the prostate (n = 23) and renal tissue samples (n = 16) the tissues were stored at $-20^{o}C$.

Following homogenisation, polyamines were analysed in an aminoacid analyser (3). Polyamine concentrations were very high in the normal prostatic tissue (putrescine 10 $\pm$ 3 nmol/mg protein; spermine 30 $\pm$ 5 nmol/mg protein). In benign prostatic hyperplasia the putrecine content

was reduced and the spermine level elevated (4 ± 3 nmol/mg protein and 60 ± 25 nmol/mg protein respectively). The polyamine concentration was very much lower in renal tissue. In renal carcinoma there was a significant elevation of the spermidine/spermine ratio (0.5-1.3).

Although the polyamine level in the human prostate is very high and the spermine values are significantly increased in benign hyperplasia, the spermidine/spermine ratio is significantly lower. Benign hyperplasia appears to have a different polyamine profile to malignant tissue and a high spermidine/spermine ratio probably represents dedifferentiation in a very malignant tumour.

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U. Dunzendorfer
Abteilung für Urologie,
Klinikum der Johann Wolfgang Goethe Universität,
D-6000 Frankfurt-am-Main 70

ENZYMATIC ISOLATION OF VITAL CELLS FOR PRETHERAPEUTIC TESTING OF HUMAN RENAL CARCINOMAS

H. Bojar, K. Maar, H. Hettwer and W. Staib

A technique is described for the enzymatic isolation of tumour cells for pretherapeutic tumour testing.

Specimens of human renal carcinomas were cooled and cut into small fragments (approximately 1 mm). The particles were dispersed into five volumes (w/v) of Ca-free Krebs-Ringer hydrogen carbonate buffer (pH 7.4), containing collagenase (10 mg/g wet weight tumour tissue). The fragments were digested by a multistep incubation procedure at 37°C. Isolated tumour cells were collected by centrifugation.

The diameter of the isolated tumour cells varied from 10 to 130 µm. The percentage of viable cells, estimated by the trypan blue exclusion test, amounted to about 90%. The ultrastructural integrity of the tumour cells was verified by transmission electron microscopy. The glycogen content of the tumour cells responded only gradually to in vitro manipulations like glucose addition or removal. The glycogen metabolism seems to be deprived of appropriate hormonal control (insulin, glucagon, epinephrine). The isolated cells retained their ability to incorporate radiolabelled amino acids into protein for at least 5 hours.

The investigations suggest that tumour cells isolated by the described procedure may be suitable for testing antitumour drugs. The absence of operative control mechanisms for the glycogen metabolism seems to be an in vitro reflection of the in vivo glycogen accumulation by these tumours.

Priv?-Doz. Dr. H. Bojar
Institut für Physiologische Chemie II der
Universität Düsseldorf,
Moorenstr. 5,
D-4000 Düsseldorf

VI. Urodynamics

URETERIC ELECTROMYOGRAMS IN DIFFERENT SPECIES

Th. Zoedler, U. Geisler, J. Hannappel and C.C.A. Schulman

It has been proposed that the myogenic pacemaker localised in the renal pelvis controls ureteric peristalsis. If the pacemaker frequency is constant, the rate of ureteric peristalsis will be determined by a varying conduction block. Consequently the interval between two successive ureteric contractions should be a multiple of the pacemaker frequency (1,2). This hypothesis and the influence of diuresis on pacemaker activity and conduction blocks have been examined.

Two silver electrodes were placed around the ureter in anaesthetised sheep and rabbits. Bipolar recordings were obtained with the animals awake. Human recordings have been taken intraoperatively.

The intervals between ureteric contractions were found to be in integral numerical proportion. The histograms showed a multimodal distribution of period. The intervals between peaks were exact multiples of a hypothetical basal period - the pacemaker period. This finding was not observed in all histograms in rabbits. The frequency was found to vary with time. The intervals were distributed in a curve. This may indicate that the pacemaker frequency was not constant or that several pacemakers were working independently. The administration of Frusemide increased the conduction rate so that nearly all pacemaker impulses were transmitted to the ureter. In some human subjects a multimodal distribution was observed with a basal period of about 2 seconds.

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Th. Zoedler
Urologische Universitäts-Klinik der RWTH,
Goethestr. 27-29,
D-5100 Aachen

VISUALISATION OF THE URETER BY RADIOISOTOPIC METHODS

K.-U. Laval, F. Höck and Chr. Freundlieb

A radioisotope scan is a valuable alternative to the intravenous pyelogram for examination of the urinary tract in some patients. Ideally scintillation scans should also demonstrate the urine. Comparative studies were carried out in five normal individuals using ^{123}I-hippuran (2mCi), then ^{99m}Tc-DTPA (5mCi) and an infusion urogram using Conray. ^{131}I-hippuran was not used because of its high beta activity and its long half life.

With DTPA the ureter is not easily subtracted from the background activity. Using ^{123}I-hippuran there is only poor background activity which is easily subtracted. The ureter and the renal pelvis can be separated from the surrounding tissue.

When an IVP is contra-indicated ^{123}I-hippuran is the ideal isotopic method for urinary scanning. The radiation dose to the bladder is 100 mrad compared with 500 mrad for an abdominal film. Pregnancy is the only contraindication.

Dr. J.-U. Laval
Abt. Urologie der Med. Fakultät,
Rhein. Westf. Tech. Hoch.,
D-5100 Aachen

CINERADIOGRAPHIC EVALUATION OF URETERIC PERISTALSIS

G. Durben and R. Gerlach

The correlation between bolus geometry and propagation and manometric and myographic measurements has been studied in dogs. Five 20 kg dogs were anaesthetised and x-rayed in the supine position following the injection of Conray 70 (1 ml/kg). Cineradiographic studies were carried out at 25 frames per second and performed for 3 or 4 bolus sequences. The intraureteric pressure was measured and the electro-ureterogram was recorded with a bipolar electrode. Individual frames were analysed paying special attention to the beginning and end of each bolus and its propagation.

The propagation velocity was found to be constant from the kidney and the bladder in any individual animals but varied between animals (3.6-4.5 cms). The electromyographic signal and the maximal intraureteric pressure occurs at the end of the bolus. The propagation velocity of the front of the bolus varies widely.

A muscular contraction ring procedes down the ureter at constant velocity forming the rear of the bolus under low or normal diuretic conditions. This ureteric contraction may be non-occlusive under high diuresis or obstruction but the propagation velocity is unchanged. Under normal conditions the occlusive contraction ring pushes forward a volume of urine which distends the ureter passively. At constant bolus volume, the bolus diameter and length will vary depending upon ureteric elasticity.

G. Durben
Department of Urology, RWTH Aachen,
Goethestr. 27-29, D-5100 Aachen

PRESSURE MEASUREMENTS IN THE URETER DURING THE PERISTALTIC TRANSPORT OF URINE

R. Gerlach and G. Durben

Further investigation of ureteric dynamics has been undertaken and critically analysed.

The pressure was measured in different segments of the ureter and bolus transport was monitored by x-ray cinematography. The volume of a single bolus was measured. A bipolar electrode recorded muscle potential. The frequency response of pressure-catheters was analysed.

The investigation showed that "basic pressure" depends on the ambient pressure. There was a relationship between the bolus pressure and the electrical activity of the muscles. A strict relationship between bolus formation and muscle activity was seen. Under diuretic conditions each bolus is definitely related to the transport of urine. Different catheters have different frequency responses and there may be damping. The pressure curves measured with ureteric catheters need correcting factors.

R. Gerlach
Aerodynamisches Institut der RWTH Aachen,
D-5100 Aachen

THE URETERIC PRESSURE PROFILE

E. Bruijnes

The pressure profiles of the pelvi-ureteric junction, the ureter and uretero-vesical junction have been studied in dogs. Two high density poly-

ethylene catheters (6 FG) were used. One had 8 side openings and the second 2 side openings. Catheter in fusion rate was 2 ml/minute and withdrawal velocity 0.7 cms/second. The graphs were analysed at 0.7 and 0.5 cm intervals in the proximal and distal parts of the upper tract respectively.

No difference was noticed between the two catheter types. Mean pressure varied between 39 ± 5.96 and 54 ± 7.70 cm H_2O. There was a slight increase of pressure at the pelvi-ureteric junction but this was not statistically significant. A significant bi-phasic pressure rise in the distal ureter was seen. The proximal peak was located 1.33 ± 0.13 cm from the ureteric orifice and the mean value was 121 ± 7.14 cm H_2O. The distal peak was located at 0.38 ± 0.02 cm from the ureteric orifice with a value of 111 ± 11.47 cm H_2O. The total functional length of the pressure rise was 2.07 ± 0.16 cm and the length of the distal peak was 0.91 ± 0.09 cm.

These data correlate with the morphological structure of the uretero-vesical junction. The ureteric pressure profile may be easily performed by the cystoscope and may be a useful additional diagnostic method.

E. Bruijnes
Department of Experimental Surgery,
Wilhelmina Gasthuis, University of Amsterdam,
Amsterdam

INFLUENCE OF PRESSOR RECEPTOR STIMULATION ON ELECTRICAL ACTIVITY OF THE URETER IN RABBITS

J. Bödeker and N. Stroh

In previous studies we found that stimulation of the carotid sinus or aortic arch pressor receptors caused a change in bladder configuration. Furthermore urethral pressure profiles were decreased and micturition occurred at reduced bladder volumes (1, 2). The present investigation was undertaken in order to determine the effects of pressor receptor stimulation on electrical activity of the ureter. 66 experiments were performed on 4 male rabbits weighing between 3.5 and 4.2 kg. Anaesthesia was induced with sodium pentobarbital (25 mg per kg). The left ureter was exposed 2-3 cm from the ureteropelvic junction via a flank incision. The electrical activity of the ureter was monitored with the use of a bipolar extracellular wire electrode submerged in 37°C warm paraffin oil. Urine flow rate was measured continously. The depressor nerve was electrically stimulated for 5 min (1, 2).

With a urine flow of 0.2-0.6 ml per min and ureter pressor receptor stimulation caused an increase in ureteric electrical activity. Ureteric impulse frequency was 6.03 ± 0.28 with a urine flow of 0.6 ml per min in the control studies and 7.58 ± 0.28 with depressor nerve stimulation ($P < 0.01$). This shows that with the same urine output an increase in parasympathetic and a simultaneous decrease in sympathetic tone by pressor receptor stimulation caused an increase in electrical activity of the ureter. These results are in accordance with our previous studies in which influences of pressor receptor reflexes on bladder emptying were shown (1, 2).

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J. Bödeker
Urologische Klinik der FU Berlin,
Klinikum Charlottenburg,
Spandauer Damm 130, D-1000 Berlin 19

AUTORADIOGRAPHIC DEMONSTRATION OF ALPHA-ADRENERGIC BINDING SITES IN THE URINARY BLADDER OF THE RAT USING 3H ST 1059

D. Jonas, H. G. Baumgarten and S. Jenner

The autoradiographic demonstration of alpha-adrenergic receptor binding sites has been attempted using 3H ST 1059 (2.5 dimethoxyphenylethanol-HCL, 1.6 Ci/mmol) administered intravenously.

Tracing of radioactivity in freeze-dried or glutaraldehyde-perfused urinary tract tissue (with or without prior ligation of the ureters) processed for conventional or high-speed autoradiography was performed following intravenous injection of 3H ST 1059 to untreated rats or to rats treated with phentolamine (repeated doses of 2-10 mg/rat) or propanol (2 mg/kg rat), or both.

Administration of 1 mg 3H ST 1059 results in a rather unselective labelling of smooth muscle cells, connective tissue cells, fat cells, erythrocytes and the epithelium which is poorly antagonised by beta and/or alpha blockers. Ligation of the ureters and intravenous injection of 0.1-0.2 mg 3H ST 1059 is followed by a selective labelling of the membranes of mainly smooth muscle and connective tissue cells which is strongly suppressed by pentolamine and phentolamine plus propanolol pretreatment.

The results permit the conclusion that low doses of 3H ST 1059 results in a preferential labelling of alpha adrenergic binding sites.

D. Jonas
Urologische Abteilung,
Klinikum der Johann Wolfgang Goethe Universität,
D-6000 Frankfurt-am-Main

ISOMETRIC FORCE CHARACTERISTICS OF URETHRAL STRIATED SPHINCTER PREPARATIONS IN VITRO

A. E. J. L. Kramer

The striated urethral sphincter plays an important role in urinary continence. An exact knowledge of the physical behaviour of this muscle in terms of force, length and energy relations may be of help in interpreting the results of urodynamic measurements in the intact organism.

Part of the striated muscle encircling the urethra was excised from female dogs. The preparation was placed in an organ bath and fixed between a movable clamp and a force transducer. Isometric contractions were elicited by direct supramaximal field stimulation with two silver wires. Active force responses to single shocks (twitch) and multiple shocks (tetanus) as well as the passive force level were studied at different muscle lengths and different temperatures.

The optimum muscle length (L_O), defined as that length where the active force response is maximal, was about 30 mm. At this length the passive force is negligible and rises non-linearly with length if the muscle is elongated. The active force was constant with muscle lengths between 0.95 L_O and 1.05 L_O and fell linearly with length to 0.5 L_O and 1.75 L_O. At 35°C the maximum tetanic force (1.5×10^5 N/m^2 of muscle cross-section) is four times the twitch force. It remains constant down to 30°C and then falls linearly to 0.75×10^5 N/m^2 at 25°C. The time to peak twitch and the half-decay time at 35°C were about 80 ms.

The static isometric properties of the urethral sphincter are similar to those of any striated muscle.

A. E. J. L. Kramer
Department of Urology, University of Leiden,
Leiden, The Netherlands

INTRAVESICAL ELECTROSTIMULATION OF THE BLADDER IN SPINA BIFIDA

J. Seiferth, H. Larkamp and J. Heising

A catheter stimulation device with two electrodes has been developed in co-operation with Messrs. Vygnon (Aachen). The device delivers square waves of 5 ms duration at 35 ms intervals. These pulses continue for 10 seconds at 40 second intervals. The optimum distance between the electrodes was found to be 22 mm. The patients were treated two or three times a week for one hour over a 6-9 month period.

28 spina bifida children who fulfilled the following criteria were treated:

1. incomplete paraplegia.
2. lower motor neuron lesion with normal upper urinary tract and no residual urine.
3. urinary incontinence.
4. a good detrusor response on stimulation.

A good result was obtained in 12 cases. This was indicated by keeping dry for between 1 and 3 hours and micturition in a stream. Prior to treatment these children had permanent urinary dribbling incontinence. The treatment was discontinued in 11 cases primarily because of failure of detrusor muscle response. The method failed with 3 children and in 2 further cases it is too early to assess.

J. Seiferth
Urologische Abteilung des
St. Bonifatius-Krankenhauses
D-4450 Lingen/Ems

TRIGGER STIMULATION FOR BLADDER EVACUATION: TRANSCUTANEOUS ELECTRICAL STIMULATION IN THE DOG

U. Jonas, G. Renschin and H. J. Klotter

Late clinical results following implantation of a bladder pacemaker (MENTOR) showed that 7 out of 8 successful implantations developed reflex evacuation which made further activation of the stimulator unnecessary. Therefore the question was raised if it was possible to trigger reflex arcs by means of transcutaneous electrical stimulation in order to ease voiding in incomplete infranuclear lesions.

In 15 female mongrel dogs, transcutaneous electrical stimulation was performed (parameter: 20 Hz, 1 ms, 5-10-20 mAmp) on 13 selected locations in the ano-genital area. Simultaneously the pressure in bladder, urethra and rectum was measured. The study was based on evaluable recordings of 17 stimulation attempts in 11 dogs. Altogether 235 single stimulations were performed.

It was possible in all cases to provoke a stimulation effect on bladder (51.8%), urethra (52.1%) or rectum (65.5%). However the pressure amplitude did not correlate with the increase of stimulation current, and at the optimal stimulation point, reached an amplitude of 30 to 75 cm H_2O. In 5 out of 17 stimulation attempts (29.4%) a typical physiological micturition curve with selective bladder contraction and simultaneous relaxation of the urethral outlet resistance was achieved. The points of stimulation were: vaginal area (4x) and inner thigh (1x).

Transcutaneous bladder stimulation is possible and provokes micturition in almost 30%. Clinical proof of these data obtained in the dog could lead

to the possibility of provoking reflex evacuation in patients with incomplete infranuclear lesion via transcutaneous trigger stimulation and thus avoid further implantation of a bladder pacemaker.

U. Jonas
Department of Urology, University of Mainz,
D-6500 Mainz

URODYNAMIC INVESTIGATIONS IN PATIENTS WITH COLOCYSTOPLASTY AND THE USE OF ELECTRICAL STIMULATION

F. Fritsch, J. Janez and S. Plevnik

Four patients with a colocystoplasty (sigmoid) following cystectomy were investigated. These patients were continent while awake but wet at night. The patients were investigated by routine radiological methods and urodynamics including cystometry, urethral pressure profile, EMG of the pelvic floor, urinary flow rates and residual urine. Cystometry was performed with cold, cool and room temperature liquids. CMG curves were also examined during the application of electrical stimulation with an anal plus electrode. The effect of parasympathomimetic, sympathomimetic and parasympatholytic agents on the CMG were investigated.

Bladder filling produced a sensation of fullness in the lower abdomen. There was no change with warm or cold fluids. Approximately linear peristaltic activity was observed in all patients during bladder filling. Urinary flow varied from good to very poor. Flow was intermittent. Maximal urethral closure pressure was 70-100 cm H_2O with increase during stimulation.

Considerable variations of the amplitude and form of the peristaltic waves were noted following treatment with a parasympathomimetic agent. Similar results were also seen following sympathomimetic drugs. Parasympatholytic drugs had no effect.

Clinical, radiological and biochemical investigations indicate that the sigmoid colon is not the ideal material for replacement of the bladder (1). This is supported by urodynamic investigations. Stimulation with an anal plug electrode improves nocturnal continence but could have other consequences.

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F. Fritsch
Urologic Clinic, Clinical Centre,
Ljubljana University, Ljubljana, Yugoslavia

VII. Nephrology, Renal Hypothermia and Renal Embolisation

RAT KIDNEY PRESERVATION AT 20°C BY CONTINUOUS PERFUSION WITH A TISSUE CULTURE MEDIUM

R. Horsch, K. Dreikorn and L. Röhl

The adenine nucleotide levels in renal tissue and renal function have been determined after ice storage and continuous perfusion with tissue culture medium at 20°C.

The kidneys of Levis rats were removed en bloc after flushing with cold Collins solution and either stored for 24 hours at 4°C in Collins solution or continuously perfused with oxygenated tissue culture medium at 20°C for four hours. One kidney was then transplanted and the opposite kidney used for the determination of the adenine nucleotides (ATD, ADP, AMP) in the renal tissue.

The total adenine nucleotide level (TAN) in fresh kidney tissue was 3.6 µmol/g wet weight. After 24 hour ice storage the TAN level declined to 1.34 µmol/g wet weight. After 4 hours of continuous perfusion with tissue culture medium the TAN level was 1.4 µmol/g wet weight. Four out of six rats with transplanted ice-stored kidneys survived after transplantation and contralateral nephrectomy whereas none of the 4 rats whose kidneys had been continuously perfused at 20°C with tissue culture medium survived.

The adenine nucleotide level is unreliable as the only indicator of kidney viability.

Dr. med. R. Horsch
Department of Urology, University Hospital
of Heidelberg,
D-6900 Heidelberg

THE INFLUENCE OF INFUSION THERAPY WITH HYDROXYETHYLSTARCH AND RINGER LACTATE ON KIDNEY FUNCTION AFTER TOURNIQUET ISCHAEMIA

A. Tauber, R. Tauber, O. Petrowicz,
G. Wriedt-Lübbe and G. Blümel

Renal function and morphological changes in the kidney were studied after 2 and 3 hours of hind limb ischaemia in rats produced by the application of a tourniquet. These studies were repeated at 0, 1, 2, 3 and 24 hours after restoration of the blood supply to the limb. The effect of infusion therapy with Hydroxyethylstarch and Ringer Lactate were determined after tourniquet ischaemia for three hours. Kidney function was measured using whole body clearance (1). Glomerular filtration rate was

estimated using ^{99m}Tc-DTPA and effective renal plasma flow with ^{131}I-Hippuran. Blood pressure, haematocrit, pH, serum electrolytes, urea and creatinine were determined. The kidneys were studied histologically.

After 2 hours of hind limb ischaemia, no significant functional and morphological changes were seen. After 3 hours of ischaemia ^{99m}Tc-DTPA and ^{131}I-Hippuran clearances were decreased by 50%. Blood pressure was reduced and haematocrit, serum potassium and urea levels increased. Although these changes were reversible, irreversible morphological changes in the tubules could be observed.

Infusion with Hydroxyethylstarch prevented these functional and morphological changes. Treatment with Ringer Lactate was less effective.

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Dr. med. A. Tauber
Ismaningerstr. 22, D-8000 Munich 80

CHANGES IN RENAL PHYSIOLOGY AFTER EXTREME HYPOTENSION OR RENAL ARTERY OCCLUSION

A. Schilling, A. Hofstetter and H. Dahlheim

Renin has been shown to have local intrarenal vasomotor activity (2) and an increase in central venous renin during the oliguric period of acute renal failure has been demonstrated (3). The renin activity of the juxta glomerular apparatus (JGA) has been measured following severe hypotension or renal artery occlusion.

In 200-250 g Sprague Dawley rats the left renal artery was clamped for 60 minutes or systemic hypotension (mean pressure 30 mm Hg) was maintained over 210 minutes. JGA-renin activity was determined 10 minutes after removing the arterial clamp or correction of the hypotension. JGA-renin activity was determined by the method of Dahlheim et al. (1).

The renin activity of the post-ischaemic left kidney was 12.1 ± 3.8 ng/0.1 ml/hr. Control values from the opposite kidney were 5.7 ± 2.0 ng/0.1 ml/hr. The GFR of the left kidney was reduced from 1.0 ± 0.1 ml/min before clamping to 0.2 ± 0.2 ml/min 10 minutes after removal. Following hypotension JGA/renin activity was 13.2 ± 3.8 ng/0.1 ml/hr. Sham operated control kidneys had values of 5.9 ± 2.2 ng/0.1 ml/hr.

These results indicate an increase in renin activity of 100% following ischaemia with even greater increases after hypotension (120%). These results indicate that intrarenal vaso-active control systems may be involved in the pathogenesis of acute renal failure following renal ischaemia.

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A. Schilling
Department of Urology, University of Munich, D-8000 Munich

EXPERIMENTAL TRANSCATHETER RENAL EMBOLISATION WITH AUTOLOGOUS CLOTS IN THE RAT

G. Carmignani, E. Belgrano, S. Zambelli, P. Puppo

When temporary embolisation of the kidney is required, the material used should allow full recovery of renal perfusion. The present study was carried out in order to assess the degree of renal damage following clot embolisation.

Renal embolisation was performed in Wistar rats as follows: Group I (n = 20) 0.1 ml of autologous clot; Group II (n = 20) 0.1 ml of modified clot; Group III (n = 20) 0.3 ml of plain autologous clot. The animals were sacrificed after 24 hours. Histological examination was performed when the kidney appeared grossly normal or partially ischaemic.

In Groups I and II approximately 20% of kidneys showed total infarction compared with 70% in Group III. Of the macroscopically normal or partially infarcted kidneys in Groups I and II less than 50% of the kidney was affected in 75%. In Group III the apparently normal or partially infarcted kidneys were more severely damaged. In some kidneys PAH clearances were determined and these showed that in 7 cases of macroscopically normal embolised kidneys showing less than 20% infarction the mean PAH clearance was impaired by 78% compared with the opposite control kidney.

The degree of recovery appears to be related to the volume of clot injected and the warm ischaemia produces significant loss of renal function even if recanalisation is almost complete.

G. Carmignani
ClinicalUrologica Universita,
Vle Benedetto XV, I-16132 Genova

CONCENTRATION OF ANTIBIOTICS IN LONG TERM EMBOLISED KIDNEYS: AN EXPERIMENTAL STUDY

W. Bischoff, K. Pelz and A. Kloss

The concentration of antibiotics in embolised kidneys has been determined. This is of importance in considering the use of antibiotics for the treatment of infected embolised kidneys.

Unilateral renal embolisation with methyl methacrylate was performed in 7 dogs (1). Six to seven months later 1 gr Cefazolin was given intravenously in a 50 ml NaCl infusion. Two hours later the blood concentration was determined, the dog sacrificed and the amount of Cefazolin in both the embolised and the contralateral control kidney was measured using the agar-diffusion test (2).

Angiograms demonstrated no renal vessels or collateral arteries and histologically there was total or subtotal atrophy of the tubular system and the glomeruli. There were a few small areas of unaltered parenchyma in the subcapsular region and near the hilum. The mean value of Cefazolin concentration in the embolised kidneys was 25.14 µg/mg (SD 6.4) and in the contralateral control kidneys was 60.31 µg/mg (SD 16.5). The serum value was 33.51 µg/ml (SD 8.14).

The Cefazolin level in the embolised kidney is nearly as high as the serum level and was higher than 10 µg/mg in all cases. This concentration is sufficient for a wide range of organisms including many Proteus species.

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Priv. Doz. Dr. W. Bischoff
Urologische Universitätsklinik,
D-7800 Freiburg

CHANGES OF RENOVASCULAR AND GLOMERULAR PERMEABILITY FOLLOWING ACUTE ELEVATION OF PERFUSION PRESSURE

G. J. Mast, R. Dietz, H. Gaebara and M. Ziegler

Vascular lesions in malignant hypertension may be toxic or mechanical in origin. The renal vascular changes following sudden exposure of the kidney to a high perfusion pressure have been studied.

Renal hypertension was induced in rats by constriction of one (group 1) or both (group 2) renal arteries by an 0.2 mm diameter silver clip. 24 days later when hypertension was established one kidney was acutely exposed to the high systemic blood pressure by removal of the renal artery clip (1 clip removed in both groups). Simultaneously 1 ml of a 10% ferritin solution was administered intravenously. Two hours later both kidneys were fixed in vivo by perfusion with 5% glutaraldehyde. Sections of the kidney were stained by the Gomori iron reaction and examined microscopically.

Two hours following sudden exposure of the kidney to an elevated blood pressure ferritin granules were demonstrable as deposits in vessel walls, in the perivascular tissue, in the tubular fluid and in the urine. These findings indicate damage of both the vascular intima and the basement membrane of the glomerulus. In group 1 plasma renin activity fell from high levels to normal following removal of the clip. A fivefold rise of renin activity was observed in group 2.

Sudden exposure of the renal vascular bed to high blood pressure results in rapid damage of the vascular walls and the glomerular basement membrane irrespective of the state of the renin angiotensin system.

Dr. G. J. Mast
Urologische Universitätsklinik,
D-6650 Homburg/Saar

GLOMERULAR FUNCTION DURING AND AFTER RELEASE OF TEMPORARY UNILATERAL OBSTRUCTION IN THE RAT

A. P. Provoost and J. C. Molenaar

After the functional loss of one kidney, the contralateral one quickly responds with an increase in function and weight. According to Hinman's theory of renal counterbalance, correction of the lesion will not lead to restoration of function in the injured kidney. This concept has been modified in recent years. The effect of the presence and removal of ureteric obstruction on glomerular filtration rate (GFR) in rats has been investigated.

Reversible unilateral ureteric obstruction was produced by placing a haemostat on the left ureter close to the pelviureteric junction. The clip was removed after different time intervals.

Complete obstruction of one ureter led to a decrease in GFR of that kidney of 50% within 4 hours. Glomerular function was almost zero after 24 hours. In the contralateral kidney GFR quickly increased, preceding an increase in weight, which was first noted after 48 hours. The long-term effect in the contralateral kidney was an increase in GFR to 70% of the two kidney control values after one week, to 75% after two weeks, and to 80% after three and four weeks. Removal of the ureteric clip after two days of obstruction resulted in a complete recovery of total GFR.

Almost complete restoration was observed after an obstruction of two and three weeks. Removal of the clip with simultaneous contralateral nephrectomy after obstruction of one week caused a recovery of GFR to values greater than that of one control kidney, suggesting a stimulating effect of nephrectomy upon the previously obstructed kidney.

These data indicate that in the rat the possibility for the restoration of GFR after complete unilateral ureteric obstruction is mainly dependent upon the duration of the obstruction. The degree of restoration is, however, influenced by the presence of an intact contralateral kidney.

A. P. Provoost
Institute for Paediatric Surgery,
Erasmus University,
Rotterdam

VIII. Andrology

EFFECT OF OESTROGENS ON THE VAS DEFERENS IN THE CASTRATE DOG

Th. Senge, B. Schenck, U. Tunn and F. Neumann

The vas deferens is derived from the Wolffian duct and its development depends on the presence of androgen. It is therefore a typical androgen target organ and specific androgen binding sites have been demonstrated (1).

In 23 beagle dogs the influence of 3 androstandiol (3-diol), 17 beta-oestradiol (E_2) and cyproterone acetate (CA) on the morphology of the vas deferens was investigated. 3 intact animals served as controls (group I). Groups of 5 castrated dogs were treated with either 3-diol 75 mg per week (group II), 75 mg 3-diol plus 0.75 mg E_2 per week (group III), 75 mg 3-diol plus 600 mg CA per week (group IV) or 75 mg 3-diol plus 0.75 mg E_2 plus 600 mg CA per week (group V).

Androgens and antiandrogens did not produce any morphological changes in the fibromuscular tissue or the epithelium of the vas deferens. In groups II and IV receiving E_2 the fibromuscular stroma was hyperplastic.

These findings suggest that oestrogens stimulate the fibromuscular stroma in the male accessory sex organ. This agrees with findings of fibromuscular hyperplasia in the canine prostate and seminal vesicle in rats following oestrogen treatment (2).

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Priv. Doz. Dr. Th. Senge
Urologische Klinik, Josefs-Hospital,
D-4690 Herne 1

TESTIS AUTOTRANSPLANTATION BY A MICROVASCULAR TECHNIQUE: EXPERIMENTAL STUDY IN THE DOG

G. Carmignani, E. Belgrano, P. Puppo, S. Zambelli and G. Bentivoglio

Autotransplantation of the testis by microvascular techniques has been proposed for the treatment of intraabdominal cryptorchid testes (1, 2). This technique has been studied experimentally in the dog.

Nine testes in seven dogs were autotransplanted to the inferior epigastric or pudendal vessels. The anastomoses were performed using an operating microscope at x16 or x25 using 9/0 or 10/0 nylon. In a further five dogs the spermatic vessels of five testes were divided. In each group biopsies were taken before surgery and compared with post-operative histological patterns at intervals between 7 and 60 days.

Of the five testes with division of the testicular vessels, total necrosis occurred in three and partial necrosis in two. Of the nine testes undergoing autotransplantation six remained normal histologically. In two an occasional mitosis was seen but no sperm. One testis suffered total necrosis with preservation of the epididymis.

This microvascular technique appears to offer a greater chance of fertility following orchidopexy in cases where division of the spermatic vessels would otherwise be required.

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G. Carmignani
Clinica Urologica Universita,
Vle Benedetto XV, I-16132 Genova

A NEW METHOD OF VASECTOMY

A. Hak-Hagir

A new technique of vasectomy has been tested in three rabbits and two dogs. The vas deferens is delivered through a high scrotal incision. The ends are ligated with 3-0 steel wire sutures. The ends are drawn parallel to each other for 3 cm and fixed subcutaneously to the scrotum.

The suture material has proved compatible in all animals. The ends of the vasa remain palpable and are identifiable on x-ray. Sperm granulomata occurred very rarely.

Dr. med. A. Hak-Hagir
Urologic Division of Marienhospital,
Virchowstrasse 135, D-4650 Gelsenkirchen

PRODUCTION OF EJACULATE WITH AN ARTIFICIAL VAGINA AND SEMEN ANALYSIS IN RABBITS

M.Franzen, D. Bach, L. Weissbach and H. Meiling

The production of satisfactory ejaculates for the purpose of experimental studies in fertility was investigated in male rabbits using an artificial vagina.

Semen analysis was carried out every two weeks for four months on 65 male rabbits aged between 4 and 8 months. An artificial vagina was used and its success depends upon the temperature of the artificial vagina, the surroundings and the positioning of the artificial vagina between the legs of the female rabbit.

265 of 294 tests were successful in recovering the ejaculate. The temperature of the artificial vagina appears critical. A count of 20×10^6 to 875×10^6 spermatozoons per ml was found. The average motility was 60 to 100%. Immotile sperms were seen occasionally and never counted for more than 20%. The male rabbit seems to be a suitable animal for experimental studies in fertility because of the predictable production of ejaculate.

M. Franzen
Urologische Universitätsklinik Bonn,
D-5300 Bonn-Venusberg

HISTOMETRIC AND HISTOLOGICAL STUDIES OF TORSION OF THE SPERMATIC CORD IN WISTAR RATS

G. Ludwig, J. Haselberger and R. Münzenmaier

The sequence of changes in the seminiferous tubules and the interstitial cells of the testis following experimental torsion of the spermatic cord were studied in rats.

Bilateral orchidopexy was performed in 45 rats following 720° of inward rotation. Testicular biopsies were obtained at 1, 2, 4, 6, 8, 12, 14 and 24 hours following torsion. Significant oedema of the nuclei was seen within one hour in spermatogonia and spermatocytes but not in spermatids or Sertoli cells. The oedema increased over 6 hours by which time irreversible necrosis of the tubules was seen. The interstitial Leydig cells and the Sertoli cells became necrotic within 8 to 10 hours.

Although the testosterone producing interstitial cells survive longer than seminiferous tubules irreversible damage occurs quickly.

G. Ludwig
Urologische Universitätsklinik und
Pathologisches Institut, Klinikum Mannheim,
D-6800 Mannheim

HISTOLOGICAL AND HISTOMETRIC STUDIES OF DYSTOPIC AND ORTHOTOPIC HUMAN TESTES

M. Stephen, L. Weissbach, W. Wartenberg, W. Hilscher and W. Hilscher

Biopsies of orthotopic and dystopic human testes were examined in order to define further criteria of damage.

100 tubular cross-sections per biopsy were studied to determine mean values for 1) the area A, 2) 6 types of spermatogonia - T_1, T_2, A-pale, A-dark, A-long, B, 3) 2 types of immature Sertoli cells - dark ones and light ones. These criteria were obtained from 75 testicular biopsies in males ranging between 2 and 16 years.

In dystopic testes, the mean values for 1) A were significantly lower, 2) there were fewer spermatogonia, the numbers of T_1 and T_2 were higher. A-pale spermatogonia were seen most frequently in the dystopic testes at any age whereas in orthotopic testes A-dark spermatogonia were more frequent up to the age of 8 years. A-long spermatogonia were the rarest type of A spermatogonia in all cases and did not increase with the patient's age. The numbers of the degenerating dark Sertoli cells were higher in dystopic than orthotopic testes. These findings may be considered as indication of degenerative change in the dystopic testes.

Priv. Doz. Dr. med. L. Weissbach
Urologische Universitätsklinik, Venusberg,
D-5300 Bonn

SPERMATOGENESIS IN THE RAT FOLLOWING EXCISION OF THE TUNICA VAGINALIS

M. Faber and L. Weissbach

The presence of a hydrocoele or the operative procedure to remove it may lead to impairment of fertility (1, 2). The effect of total excision of the tunica vaginalis on spermatogenesis has been examined in rats.

In sexually mature Wistar rats aged 60 days the visceral layer of the tunica vaginalis, the internal spermatic fascia, the cremesteric muscle and the external spermatic fascia were resected with preservation of the cremasteric vessels. The animals were sacrificed at 6, 8, 10, 12 and 16 weeks. Spermatogenesis was assessed by the tubular area, the number of pachytene primary spermatocytes and the number of Sertoli cells (3). There was a reduction of tubular area and the number of pachytene primary spermatocytes in the experimental animal. This difference from control testes was statistically significant. These changes became more pronounced with time. However no

time dependent changes were found in the number of Sertoli cells.

These changes may be the result of reduced motility of the testis, disturbed thermal regulation or immunological factors.

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M. Faber
Department of Urology, University Hospital, D-5300 Bonn

IX. Nephrology, Hydronephrosis, Metabolism

REACTION OF THE KIDNEY VESSELS TO PHARMACOLOGICAL AGENTS AND OSMOTIC CHANGES OF THE PERFUSION FLUID IN HYPOTHERMICALLY PERFUSED DOG KIDNEYS

G. Ruedas, P. Burchardt and H. Huland

Dog kidneys were perfused with a non-pulsatile preparation in vitro at 4°C and 20°C and 60 mm Hg with the following solutions: a) normal Ringer; b) Ringer-Lasix (10 µg/ml); c) Ringer-Acetylcholine (100 µg/ml); d) Ringer-Rogitine (10 µg/ml); e) Ringer-Dopamine (0.2-20 µg/ml); f) Ringer-Mannitol (2% and 4%); g) Ringer-Glucose (2% and 4%); h) Ringer - Urea (0.66% and 1.32%); i) Ringer-Cholin-Chloride (1.72% and 3.44%). The osmolarity of the solutions a)-e) was 300 ± 11 mOsm/l (Normotonic solutions = NS). That of the solutions f)-i) was 400 ± 19 and 500 ± 23 respectively (Hypertonic solutions = HS). With the HS flow increase and vessel resistance decrease was constantly observed. The increase in flow was not dependent on the solute employed but on the osmolarity. The observed flow changes followed the changes of osmolarity in the perfusate within 1 min. No registrable flow change was observed with perfusates containing furosemide or alpha receptor blocking agent. Dopamine induced a slight vasoconstriction at concentrations of 20 µg/ml at 20°C but not at 4°C. In no case was a decrease in vascular resistance with depamine observed.

It is concluded that the use of diuretics or alpha blocking agents in cold perfusates does not improve the flow in the kidney; in contrast to that the use of hypertonic perfusates induces a distinct and reversible decrease of the resistance of the vessels.

G. Ruedas
Institute of Physiology, University of Hamburg, D-2000 Hamburg 20

THE INFLUENCE OF DOPAMINE ON RENAL BLOOD FLOW IN OLIGURIC NEPHROPATHIES

P. Burchardt, H. Huland, G. Ruedas and J. Augustin

Dopamine may result in an increased renal blood flow in the normal kidney. This effect has been studied in kidneys suffering with acute tubular necrosis (ATN), hydronephrosis and acute rejection (AJ).

These studies were carried out using xenon-133 washout techniques. Studies were carried out in 8 patients with ATN, in 7 dogs following allotransplantation with immunosuppression (plus 1 intact kidney) and in 20 dogs with unilateral complete ureteric obstruction. Measurements were carried out 2 and 10 days following transplantation and 7 hours, 1, 2, 3 weeks, 4 and 6 months after ureteric obstruction.

Dopamine 4 µg/kg/min i.v. increased renal blood flow in ATN from 117 to 201 ml/min/100 g kidney weight. A similar response was seen in hydronephrosis even after 6 months of complete ureteric obstruction. The same reaction was seen two days after transplantation but in acute rejection there was no response. In fact the blood flow fell from 20 ml/min/100 g to 16 ml/min/100 g.

Further investigation may allow the development of a "Dopamine-test" for early rejection.

P. Burchardt
Urologische Klinik der Universität Hamburg, D-2000 Hamburg 20

INTRARENAL HAEMODYNAMICS FOLLOWING COMPLETE URETERIC OBSTRUCTION

H. Huland, J. Augustin and P. Burchardt

Intrarenal blood flow and distribution has been studied in the hydronephrotic kidney in an attempt to determine whether hydronephrotic atrophy may be secondary to diminished cortical circulation.

Blood flow was measured in 20 dogs following complete unilateral ureteric obstruction using the xenon-133 washout technique. The contralateral kidney was intact. Measurements were obtained at 3 and 7 hours, 1, 2 and 3 weeks, 4 and 6 months after ureteric obstruction. A diminution in renal blood flow was seen three hours after complete ureteric obstruction. After one week the mean renal blood flow was reduced to 17% of control value. No further decrease was seen up to 6 months. The greatest decrease was seen in the cortex. Cortical flow was reduced to 25% after 1 week (compartment I). In compartment II (juxtamedullary cortex and outer medulla) flow was 51% of controls while in the inner medulla (compart-

ment III) it remained almost unchanged (92%). The compartment I fraction (flow in compartment I as a percentage of total renal blood flow) fell from 90% in controls to 55% at the end of one week of complete obstruction. This figure then remained constant.

No cortical atrophy was seen after 1 week, by which time ureteric pressure had fallen from 80 mmHg to 20 mmHg and cortical blood flow was decreased. Slight cortical atrophy was present at 3 weeks. A reduction in cortical flow appears to play a major role in the pathogenesis of cortical atrophy in the hydronephrotic kidney.

H. Huland
Urologische Klinik der Universität,
D-2000 Hamburg 20

THE RELIABILITY OF DIVIDED HIPPURATE CLEARANCE IN OBSTRUCTIVE UROPATHY

E. Doppelfeld, L. Weissbach, K. Hanische, H. P. Breuel and C. Winkler

Individual renal hippurate clearances have been measured in the chronically obstructed kidney to determine whether impaired urinary flow can result in artificially high readings.

In 8 patients with cutaneous nephrostomies because of chronic obstruction ^{131}I-Hippurate was given intravenously (300 μCi) and urine was collected in 20-second samples for 300 seconds. In 2 patients these studies were carried out before and after occlusion of the fistula. In 14 mongrel dogs individual clearances were measured with ureteric catheters using the ^{131}I-Hippurate and PAH methods with both free urinary flow and unilateral obstruction.

It was found that hippurate appears in the renal pelvis before 120 seconds. This contrasts with the belief that the minimal transit time of hippurate is 120 seconds and that this time is prolonged in the obstructed kidney (2, 3). The results in 2 patients showed that the hippurate clearance resulted in an artificially high figure when measurements were repeated after closing the fistula. Identical results were obtained in the dogs when the hippurate clearance was increased following obstruction. However the PAH clearance showed the well recognised reduction.

It appears that the function of the obstructed kidney may be overestimated by the determination of individual renal hippurate clearance (1) and that in the chronically obstructed kidney hippurate reaches the renal pelvis earlier than has been previously thought.

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Dr. E. Doppelfeld
Institut für klinische und
experimentelle Nuklearmedizin,
Venusberg, D-5300 Bonn

BIOCHEMICAL AND PHYSIOLOGICAL STUDIES OF RENAL INTERSTITIAL FLUID

H.-U. Eickenberg

Renal interstitial fluid has been sampled and its pressure measured by implanting inert capsules into the renal parenchyma in dogs (1). Seven biochemical parameters were measured with the Technicon-Analyser to identify renal interstitial fluid (2).

The results obtained were as follows:

	mEq/L $\bar{X} \pm$ S.E.	g% $\bar{X} \pm$ S.E.	n
T.P.	9.11 ± 4.30	3.74 ± 1.76	12
Alb.	5.49 ± 1.79	2.25 ± 0.73	13
A/G	1.51 ± 0.71:1	0.62 ± 0.29	12
Na+	155.58 ± 2.49	-	6
K+	8.85 ± 2.94	-	13
Ca++	5.54 ± 1.78	-	11
Cl-	117.26 ± 1.00	-	6

Total protein concentration was less than half of the serum level with a relative increase in albumin. Renal interstitial fluid pressure (+ 2.7 mm Hg) was monitored and showed no change during overhydration, but decreased during haemorrhagic shock with a further fall during resuscitation.

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Dr. H.-U. Eickenberg
Urologische Universitätsklinik,
D-4300 Essen 1

EVIDENCE FOR OPTIMIZED ENERGY SUPPLY TO RAT RENAL CORTEX

H. Bertermann and G. Gronow

In rat renal cortex glucose and fatty acids do not provide significant amounts of oxidative energy in competition to other plasma substrates (1, 2). Current results on high oxidative turnover rates

of some carbohydrate substrates from the citric acid cycle (2) induced us to offer a combination of ten substrates to renal cortical tubules to find out the amount of CO_2-production and glucose formation from each of these substrates.

Vital tubular fragments from rat kidney cortex were isolated by collagenase (1, 2) and incubated in an isotonic, O_2-saturated medium containing ten substrates in isomolar (4mM) concentrations. Incorporation of labelled ^{14}C from each substrate into CO_2 and glucose was measured.

High CO_2-formation rates (total CO_2: 2992 nMol/mg DNA/min) were found for alpha-ketoglutarate (524), succinate (475), pyruvate (463) and malate (292), lower rates for glutamate (180), lactate (126), citrate (117), acetate (68), propionate (46) and glucose (10). Though total O_2-consumption, total CO_2-production, and CO_2-production from the ten exogenous substrates remained constant, a decrease of CO_2-formation from alpha-KG (-204), pyruvate (-180), succinate (-63), and malate (-67) was observed. Simultaneously, an increased metabolisation of its redox-partners occurred: glutamate (+224), lactate (+156), acetate (+114), and propionate (+38). The gluconeogenic rate was high: 166 nMol glucose/mg DNA/min, 80% derived from exogenous substrates, a preference was observed as well for alpha-KG, pyruvate, succinate, and malate. Offering these four preferred substrates (6mM) in combination total metabolic activity was even increased, C-incorporation into CO_2 and glucose amounted to about 80%.

In rat renal cortex substrate preferences for alpha-ketoglutarate, succinate, pyruvate and malate were shown. A combination of these substrates may serve as the main energy source for respiration and gluconeogenesis, so that kidney cortex can be protected from a depletion of endogenous energy pools.

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Dr. H. Bertermann
Abt. Urologie, Hospitalstr. 40
D-2300 Kiel

ANALYSIS OF RENAL GLUCOCORTICOID RECEPTORS

H. Bojar, H. Dittmann, H. Hettwer and W. Staib

The influence of glucocorticoids on renal gluconeogenesis has been demonstrated in vivo but not in vitro using kidney slices. This discrepancy raises the question of direct or indirect hormone action. A study has been undertaken of glucocorticoid receptor proteins which if present would definitely indicate a direct target organ action.

Vital renal tubules were obtained by perfusion of the isolated rabbit kidney with collagenase. The affinity and hormone specificity of the receptor molecules were estimated by the dextran-coated charcoal procedure. Sedimentation coefficients were determined by sucrose gradient centrifugation. The synthetic glucocorticoid dexamethasone served as the radio-labelled ligand.

Scatchard analyses of the binding of ^3H-Dexamethasone (^3HD) by kidney cytosol indicated a single class of receptors. The apparent dissociation constant of the ^3HD-receptor complexes amounted to 6.3 ± 2.5 nmol/l. The maximal binding capacity was found to be 161 ± 27 fmol/mg cytosol protein. The binding entities reacted selectively with glucocortoids. The cross-reactivity with other categories of steroid hormones in physiological concentrations was negligible. A biphasic highly specific translocation of the cytoplasmic ^3HD-receptor complexes could be demonstrated, peaking at 30 and 120 min of incubation (30^o). Sucrose gradient centrifugation revealed the cytoplasmic and nuclear binding components to be macromolecules sedimenting in the 4 S region.

The investigations reported here strongly suggest that the ^3HD-binding components in rabbit kidneys are glucocortoid receptors in nature. Despite the fact that significant glucocorticoid effects cannot be shown in vitro, the demonstration of functioning receptor molecules shows the kidney to be a glucocorticoid target organ.

Priv. Doz. Dr. H. Bojar
Institut für Physiologische Chemie II,
D-4000 Düsseldorf