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The effect of heparinized blood exchange transfusion on endotoxin induced disseminated intravascular coagulation (DIC)

A. Ishikawa, R. Hafter, H. Graeff

I. Frauenklinik der Universität München
Department of Pediatric Surgery, School of Medicine, Chiba University, Chiba, Japan

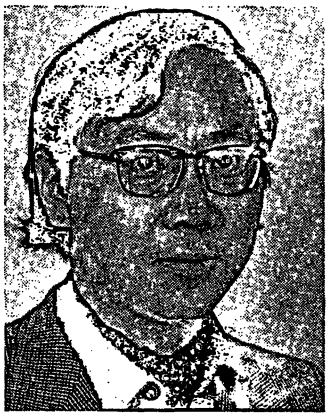
Clinicans are often confronted with cases of DIC in surgery, internal medicine, gynecology and pediatrics. Until now treatment of disseminated intravascular coagulation (DIC) is mostly confined to use of heparin, fibrinolytic agents and occasionally antiplasmin agents [15, 17, 18, 27]. Only recently sepsis of adult or of newborn is treated by heparinized blood exchange transfusion [14, 29]. In sepsis induced by gram negative bacteria endotoxin activates the procoagulant factors in the blood stream [23]. Thrombin action on fibrinogen induces the formation of fibrin monomer complexes which may precipitate in the organs and are the main constituents of the fibrin rich microthrombi which are the morphologic equivalent of DIC [2, 10]. Heparinized blood exchange transfusion is aimed to inhibit thrombin action and to remove activated procoagulant factors and soluble fibrin monomer complexes from the circulation. Hematological in vivo investigations concerning this treatment have not yet been performed. In this study the effect of the heparinized blood exchange transfusion was studied on the rabbit model after an endotoxin induced generalized Shwartzman reaction, generated by two injections of endotoxin spaced 24 hours apart.

1 Material and methods

Animal models: Female non pregnant rabbits weighing between 1.8 and 2.8 kg were used. They were fed rabbit pellet food and water ad libitum. A polyethylene catheter (1.5 mm) was inserted under local anesthesia into a left jugular vein for the first blood sampling and first injection with endotoxin or glucose. Thereafter the catheter was extracted. 24 hours later a new catheter was inserted under local anesthesia via a right jugular vein into the superior vena cava. The second injection with endotoxin or glucose was given and immediately thereafter 5% glucose was infused in all animals at a rate of 2.7 ml/h for a period of 12 hours (Fig. 1).

Six hours after the second injection blood exchange transfusion (200 ml) was carried out by stepwise injection of 10 ml heparinized blood followed by withdrawing of 10 ml blood. The

Curriculum vitae



AKIO ISHIKAWA, *M.D., Born in 1945 in Tokyo. 1972 graduated from University of Chiba, Medical School. 1972–1976 assistant at the Department of Surgery, Chiba University (Director Prof.* H. SATO*). 1976–1977 pediatric surgery, at the Kinderchirurgische Klinik of University of Munich. 1978–1979 biochemical research on intravascular coagulation in the laboratory of Prof.* H. GRAEFF *in I. Frauenklinik of Munich University.*

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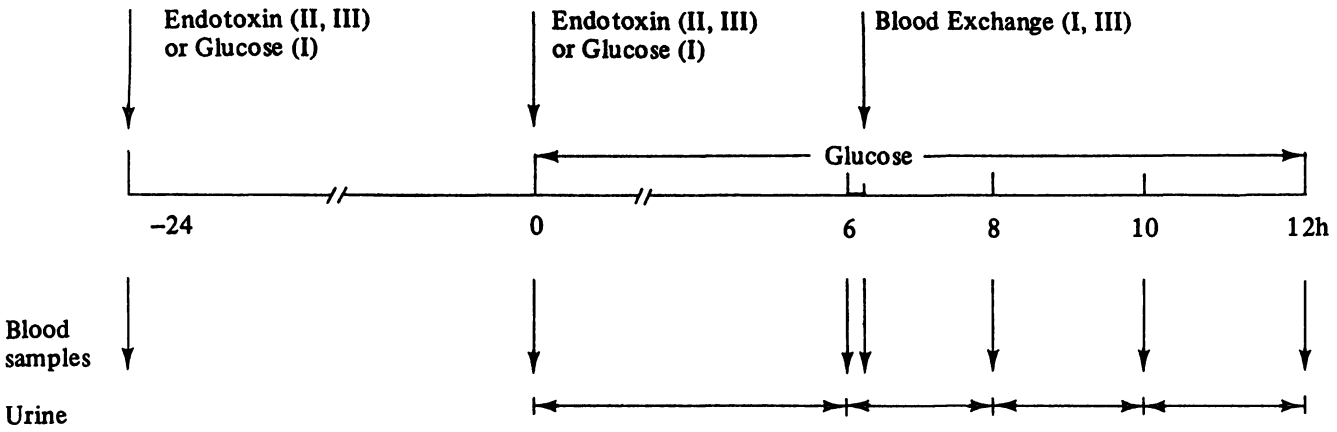

Fig. 1. Experimental design for animal groups I, II and III.

procedure was repeated 20 times in a period of about 40 min.

Blood samples (6.5 ml) were drawn immediately before the first injection and 6, 8, 10, and 12 hours after the second injection. Another sample was taken immediately after blood exchange.

Urine was collected during six hours and thereafter at two hours intervals by a catheter introduced in the vagina (Fig. 1).

Eighteen animals were divided into three groups as follows.

Group I. Six rabbits (controls) received two injections of 5% glucose (5 ml each, spaced 24 h). Blood was exchanged 6 hrs. after the second injection.

Group II. Six rabbits received two injections of endotoxin (75 μg/kg) 24 hrs. apart.

Group III. Six rabbits received endotoxin likewise as group II. Blood was exchanged 6 hours after the second injection.

Endotoxin: Lipopolysaccharide B from E. coli 026:B6 from Difco Laboratories (Detroit, USA) was dissolved in saline (100 μg/ml).

Heparinized fresh blood for exchange transfusion: Blood (100 ml/animal) was collected from male and female non pregnant rabbits (2.5–4.2 kg) from a polyethylene catheter inserted into the carotid artery. 200 units heparin (Liquemin, Hoffman-La Roche) per 100 ml blood were used as anticoagulant. The blood of the donor was tested by cross-matching between donor and recipient before the exchange transfusion.

Hematological studies: Blood (4.5 ml) was drawn into plastic tubes containing 0.5 ml of anticoagulant (0.129 M trisodium citrate, 0.05 M EDTA, 2000 KIU Trasylol (Bayer, Germany) per ml). Hematocrit was measured from the anticoagulated blood in microhematocrit tubes. Platelets were counted by phase contrast microscopy.

Leukocytes were counted on an automatic counter. Platelet poor plasma was prepared by differential centrifugation. The fibrinogen content of the plasma samples was assayed according to BLOMBÄCK [3] slightly modified as described elsewhere [12]. The values were corrected for the hematocrit-dependent dilution with the anticoagulant [22].

Agarose-gel filtration and quantitation of soluble fibrin monomer complexes: β-Alanine precipitation of 2 ml plasma samples and subsequent 4% agarose gel filtration on Biogel A-15 M (Bio-Rad Laboratories) was performed according to the technique of GRAEFF and HAFTER as previously described elsewhere [9, 12].

Fibrin degradation products: Serum samples were obtained from blood (drawn without anticoagulant) after addition of 200 KIU Trasylol and 20 μl Reptilase-Reagenz (BOEHRINGER, Mannheim) per ml. FDP was assayed by the tanned red cell hemagglutination inhibition method of

MERSKEY [24] using anti-rabbit-fibrinogen serum and rabbit red cells coated with tannic acid. The minimum detectable concentration of FDP was 1.8 μg/ml. Anti-rabbit fibrinogen serum was prepared by the intramuscular injection of rabbit COHN fraction I (5 mg) combined with complete Freund's adjuvant into white rats weighing 200–250 g at weekly intervals for 6 weeks. The rats were bled one week after the last injection. The antiserum was repeatedly absorbed with rabbit serum and stored at –30° C.

Pathological studies: All animals of the three groups were sacrificed 12 hours after the second injection by an overdose of sodium pentobarbital and necropsies were performed immediately thereafter. Organs were fixed in neutral 10% formalin. Microscopic sections of kidneys were stained with hematoxylin and eosin.

Statistical evaluation: Mean values and standard deviation were calculated. Student's t-test was utilized for paired observation. A p value of less than 0.05 was considered significant.

2 Results

2.1 Laboratory findings

The data of the determinations are summarized in Tab. I. **Fibrinogen:** The plasma fibrinogen level of the endotoxin treated groups (II and III) was significantly decreased 6 hrs after the second endotoxin injection ($p < 0.005$). It decreased progressively further in the next six hours in group II but returned to the initial or control values, respectively, after blood exchange transfusion (group III) and remained at this level until the end of the experiment.

SFMC: The relative amount of SFMC in per cent of the total fibrinogen content in the endotoxin treated groups II and III was significantly increased six hours after the second endotoxin injection from 3.4% to 13.8% or 2.9% to 14.9%, respectively. It remained at this high level during the next six hours in group II. In group III, however, the values were found strongly decreased after blood exchange, but still higher than the initial value or when compared with the controls. A slight increase was noticed one hour later which persisted through the rest of the experiment in correspondence to the controls (group I).

FDP: A statistically significant increase was observed 6 hours after the second endotoxin injection in groups II and III when compared with the controls and vs. preendotoxin values ($p < 0.05$). The increase persisted throughout the experiment in group II. In group III, however, the values fell during blood exchange to normal but rose slightly again during the rest of the experiment.

Platelets: In groups II and III the platelet counts revealed a significant decline from 344 000 to 92 000 (mean of groups II and III) 6 hrs after the second endotoxin injection. Whereas in group II the counts remained on this low level throughout the experiment, the number in group III recovered after blood exchange significantly from 88 000 to 203 000 and remained at this level which was about 60% of the base value.

Leukocytes: Endotoxin caused a substantial decline in the number of circulating leukocytes, which remained low throughout the experiment. After blood exchange (group III), normal values were found and a gradual increase above the initial level was observed in the next one to three hours. This was at variance with the controls (group I) where the counts remained constant after blood exchange.

Urine. The volumes in the endotoxin treated animals were significantly reduced ($p < 0.05$) in the last three collection periods when compared with the controls. Blood exchange caused practically no recovery in urine excretion.

2.2 Pathological findings

The kidneys of the rabbits of group I revealed microscopically no alterations. The kidneys of the rabbits of groups II and III exhibited multiple petechial hemorrhage. By microscopic examination the glomerular capillaries were found to be filled with fibrin rich microclots.

3 Discussion

Two appropriately spaced injections of endotoxin result in the activation of both the intrinsic and

Tab. I. Laboratory findings in controls (group I) and in endotoxin injected animals (groups II and III). Groups I and III received blood exchange transfusion 6 hours after the second injection. Mean values and standard deviation.

	Group	Before first injection	After second injection					P
		A	B (6 h)	C* (6.7 h)	D (8 h)	E (10 h)	F (12 h)	
Fibrinogen mg/ 100 ml	I	222 ± 16	212 ± 11	213 ± 11	217 ± 15	217 ± 13	227 ± 12	I_B VS. II_B < 0.005
	II	226 ± 27	104 ± 18		91 ± 22	71 ± 17	64 ± 12	I_E VS. III_E n.s.
	III	218 ± 21	95 ± 20	194 ± 31	200 ± 15	206 ± 16	220 ± 14	
SFMC %	I	3.3 ± 0.9	4.2 ± 1.2	3.1 ± 1.1	4.1 ± 1.7	4.7 ± 1.5	4.7 ± 1.3	I_D VS. III_D < 0.025
	II	3.4 ± 0.8	13.8 ± 4.5		14.8 ± 4.3	15.1 ± 3.8	13.1 ± 2.6	I_E VS. III_E n.s.
	III	2.9 ± 0.7	14.9 ± 3.9	5.2 ± 4.9	7.7 ± 3.0	6.9 ± 6.3	6.7 ± 3.3	
FDP µg/ml	I	2.4 ± 0.9	2.4 ± 0.9	2.1 ± 1.1	2.1 ± 1.1	2.4 ± 0.9	2.1 ± 1.1	I_B VS. II_B < 0.005
	II	2.4 ± 0.9	14.4 ± 7.8		18.0 ± 8.8	16.8 ± 5.8	24.0 ± 7.8	I_D VS. III_D n.s.
	III	2.1 ± 0.9	14.4 ± 7.5	2.4 ± 0.9	3.6 ± 2.0	4.8 ± 4.4	5.1 ± 4.6	
PLATELETS × $10^3/\mu l$	I	338 ± 31	329 ± 45	311 ± 20	323 ± 23	342 ± 39	334 ± 14	I_B VS. II_B < 0.005
	II	351 ± 43	96 ± 5		88 ± 8	74 ± 8	77 ± 13	II_D VS. III_D < 0.005
	III	338 ± 21	88 ± 13	203 ± 35	191 ± 22	202 ± 35	221 ± 65	
LEUKOCYTES $10^3/\mu l$	I	7.3 ± 1.5	6.8 ± 0.6	7.7 ± 0.5	7.6 ± 0.7	6.4 ± 0.6	7.0 ± 0.4	I_D VS. III_D n.s.
	II	6.8 ± 1.5	3.2 ± 1.4		3.3 ± 1.7	3.3 ± 1.7	4.0 ± 1.7	I_E VS. III_E < 0.025
	III	6.4 ± 0.5	3.9 ± 2.1	6.8 ± 1.5	7.5 ± 2.4	7.5 ± 2.4	9.1 ± 2.2	III_A VS. III_F < 0.025
Urine	I		19.2 ± 5.0		7.7 ± 3.3	5.7 ± 3.3	7.3 ± 1.8	I_B VS. II_B < 0.05
	II		12.4 ± 5.1		2.9 ± 2.3	1.8 ± 1.8	1.0 ± 0.7	II_F VS. III_F n.s.
	III		16.8 ± 7.3		3.4 ± 1.7	2.3 ± 1.9	2.4 ± 1.6	

*: after exchange transfusion

the extrinsic pathway of the coagulation system [7, 19, 23, 25]. As a result of the increased thrombin action on fibrinogen, fibrin monomer and crosslinked fibrin is formed in the circulation [13]. Polymerisation of fibrin monomer is inhibited to a certain extent by complex formation with fibrinogen and fibrin degradation products [10, 20] resulting in the so called soluble fibrin monomer complexes (SFMC). Furthermore, these fibrinogen fibrin intermediates as well as activated coagulation factors can not be removed from the circulation since the reticuloendothelial system is blocked [5, 16] and the fibrinolytic activity impaired by endotoxin [1, 8]. Hence fibrin and fibrin complexes are deposited in the renal glomerular capillaries and other organs [11, 21, 26] to form microclots. The precipitation of fibrin and fibrin complexes in the kidney plays the key role in the development of bilateral renal cortical necrosis in the endotoxin induced DIC model.

In this study of endotoxin induced DIC model (group II) an increase in SFMC concomitant with a decrease in fibrinogen level and in platelet count was observed six hours after the second endotoxin injection. The observed increase in FDP reflects the activation of both the coagulation and the fibrinolytic system. This shows that intravascular coagulation had been developed at the time six hours after the second endotoxin injection. At this time of the experiment the heparinized blood exchange transfusion was carried out. The exchanged blood volume corresponded to about 1.2 to 1.6 times that of the circulating blood in the rabbit [28, 30]. By the antithrombin enhancing effect of heparin the activity of the coagulation system is inhibited during the course of the blood exchange transfusion [4, 6]. An increase in the platelet count up to 60 to 70% of the initial value could be obtained by the blood exchange transfusion. The SFMC values decreased significantly by blood exchange transfusion yet did not fully reach those of the control animals. In urine volumes, however, no statistically significant difference could be observed between group II without, and group III with blood exchange transfusion. In both groups the urine excretion was diminished by about 60% compared to the controls.

Histological studies of the kidneys revealed significant microclots in the glomeruli of groups II and III. The findings indicate, that heparinized blood exchange transfusion six hours after the second endotoxin injection leads to a hematological improvement, but is without effect on the deposition of fibrin in the organs. Presumably the microclots had already been formed before the blood exchange transfusion was started. The hematological data indicate that the process of DIC was stopped after the exchange transfusion. However, the found microclots were still present at the end of the experiment.

The SFMC values decreased significantly by blood exchange transfusion yet did not fully reach the control values.

The transfusion technique offers advantages over the more limited treatment with heparin alone and seems to be especially indicated when artificial dialysis is difficult to perform as for instance in newborn infants.

Summary

Sepsis of the newborn, induced by gram negative bacteria, especially E. coli is often accompanied by a severe coagulation disorder. It can be treated by blood exchange transfusion (ET) with heparinized blood.

In this study the hematological effect obtained by the exchange transfusion was investigated in rabbits after induction of a generalized Shwartzman reaction by two spaced injections of endotoxin (75 μg/kg) 24 hrs. apart. Three groups of 6 animals each were investigated: group I: without endotoxin but with ET (controls); group II: endotoxin without ET; group III: endotoxin with ET. Fibrinogen, soluble fibrin monomer complexes (SFMC), fibrin(ogen) degradation products (FDP), platelet- and leukocyte counts and urine volume (ml/hr) were estimated.

In group II a decline in the fibrinogen level, and in platelet and leukocyte count, as well as an increase in SFMC and FDP could be observed from 6 hrs. on after the second endotoxin injection. In group III 6 hrs. after the second endotoxin injection, exchange transfusion with heparinized blood was performed.

Variance analysis showed significant differences in all parameters, except in the urine volumes after exchange transfusion between group III and group II. By exchange transfusion an approach of the values towards the values of the controls could be recognized.

The findings indicate, that by blood exchange transfusion the hematological consequences of the endotoxin induced DIC can be corrected, while the dysfunction of the kidneys can be improved only slightly.

Keywords: Blood exchange transfusion, disseminated intravascular coagulation, endotoxin, heparin.

Zusammenfassung

Der Effekt der Austauschtransfusion mit heparinisiertem Blut auf die Endotoxininduzierte disseminierte intravaskulare Gerinnung (DIG).
Bei Sepsisfällen von Neugeborenen, die durch gramnegative Bakterien, besonders E. coli, hervorgerufen werden, wird häufig eine Blutgerinnungsstörung beobachtet. Diese läßt sich durch Austauschtransfusion (AT) mit heparinisiertem Blut behandeln.
Deshalb wurden die Auswirkungen einer Austauschtransfusion auf das Sanarelli-Shwartzman-Phänomen des Kaninchens, welches durch eine zweifache Endotoxin-Injektion von je 75 µg/kg im Abstand von 24 Std. hervorgerufen wurde, an 3 Gruppen zu je 6 Tieren untersucht: Gruppe I: ohne Endotoxin mit AT (Kontrolle); Gruppe II: Endotoxin ohne AT; Gruppe III: Endotoxin mit AT. Fibrinogen, lösliche Fibrinmonomerkomplexe (LFMK), der Gehalt des Serums an Fibrin-Fibrinogen-Abbauprodukten (FDP), Zahl der Thrombozyten und Leukozyten und die Urinausscheidung (ml/Std.) wurden bestimmt.
Bei Gruppe II wurde eine Verminderung des Fibrinogengehaltes, der Thrombozyten und der Leukozyten und ein Anstieg von LFMK und FDP-Gehalt ab 6 Stunden nach der zweiten Endotoxin-Injektion beobachtet. Mikrothromben in den Glomeruli wurden bei der pathologischen Untersuchung nachgewiesen. Die Kaninchen der Gruppe III wurden 6 Stunden nach der zweiten Endotoxin-Injektion durch eine Austauschtransfusion mit heparinisiertem Blut behandelt (200 ml Blut). **Durch die Austauschtransfusion wurde eine Annäherung aller Parameter mit Ausnahme der Urinausscheidung an die der Kontrollgruppe (Gruppe I) erreicht.**

In der Varianzanalyse fand sich ein signifikant unterschiedlicher Verlauf nach der Austauschtransfusion in Gruppe III zu Gruppe II. Lediglich die Urinausscheidung blieb auch nach Austauschtransfusion in der Gruppe III unvermindert niedrig.

Die vorgelegten Befunde zeigen, daß durch die Austauschtransfusion die hämatologischen Folgen der endotoxininduzierten intravaskulären Gerinnung korrigiert werden können, während die Schädigung der Nieren nur wenig verbessert werden kann.

Schlüsselworte: Austauschtransfusion, Endotoxin, Heparin, Intravaskuläre Gerinnung.

Résumé

Effets de la transfusion d'échange de sang héparinisé sur la coagulation intravasculaire disséminée induite par endotoxine
La septicémie du nouveau-né, causée par des bactéries gramnégatives, spécialement E. coli, s'accompagne souvent d'un trouble grave de la coagulation. Elle peut être soignée par une transfusion d'échange (TE) avec du sang héparinisé.
On s'est donc proposé dans cette étude d'observer l'effet hématologique obtenu par la transfusion d'échange chez des lapins après induction d'une réaction Shwartzman généralisée par deux injections espacées d'endotoxine (75 µg/kg) à 24 h. d'intervalle. Trois groupes de six animaux chacun ont été soumis à l'examen. Groupe I: sans endotoxine mais avec TE (contrôles); groupe II: endotoxine sans TE; groupe III: endotoxine avec TE. On a évalué le fibrinogène, les «soluble fibrin monomer complexes» (SFMC), la teneur du sérum en dégradation de fibrine-fibrinogène (FDP), l'énumération thrombocytaire et leucocytaire et le volume d'urine (ml/h).
Dans le groupe II, une baisse de la teneur en fibrinogène et de l'énumération leucocytaire et thrombocytaire ainsi qu'une hausse du SFMC et du FDP ont pu être observées à partir de 6 h. après la seconde injection d'endotoxine. Des microthrombi dans les glomérules sont apparus à l'examen pathologique. Dans le groupe III, on a opéré une transfusion d'échange avec du sang héparinisé (200 ml) 6 h. après la seconde injection d'endotoxine. **A la suite de la transfusion d'échange, on a obtenu un rapprochement de tous les paramètres, à l'exception des volumes d'urine, avec ceux du groupe de contrôle (I).**
Après la TE, l'analyse de variance a révélé une évolution nettement divergente entre les groupes II et III. Seule l'élimination urinaire dans le groupe III est restée d'une constante basse après la transfusion d'échange.
Les résultats montrent qu'une transfusion d'échange sanguin permet de corriger les conséquences hématologiques de la coagulation intravasculaire induite par endotoxine, tandis qu'on ne réussit à améliorer que très légèrement la dysfonction des reins.

Mots-clés: endotoxine, Coagulation intravasculaire disséminée, héparine, transfusion d'échange sanguin.

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Dr. med. Akio Ishikawa
I. Frauenklinik der Universität München
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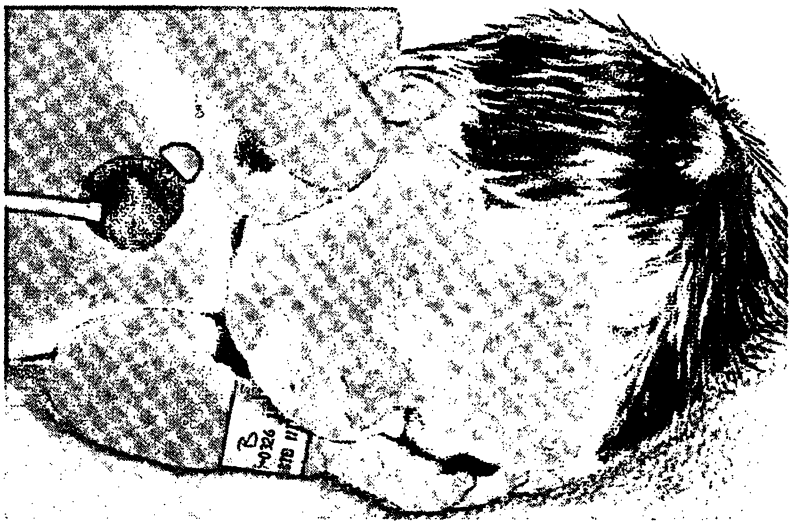

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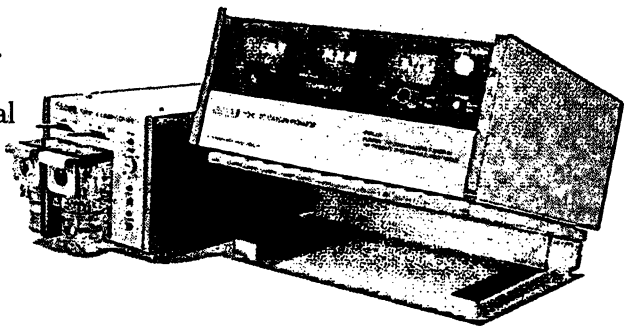

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M. Pecherstorfer

Ausgewählte gynäko-urologische Operationen
Selected Urologic Operations in Gynecology

Anhang:
Durchzugspyelonephrostomie mittels U-Drain
Appendix: U-tube Pyelonephrostomy

Atlas

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Aus dem Vorwort:

Der vorliegende Atlas stellt eine notwendige Brücke zwischen urologischen und gynäkologischen Operationsatlanten dar. Dies deshalb, weil in ihm die dem Gynäkologen am häufigsten widerfahrenden Verletzungen und deren operative Korrektur lückenlos zur Darstellung kommen, so daß auch Operateure mit geringer Erfahrung diese anhand der vorliegenden eindrucksvollen Bilder ohne Schwierigkeiten selbst vornehmen können.

From the Foreword:

The present atlas has filled a definite need in that it combines urologic and gynecologic aspects normally dealt with in separate works. Its purpose has been to give a full account of the most common injuries confronting the gynecologist as well as their operative repair so that even the less experienced surgeon will – guided by the most instructive pictorial material – be able to master surgical problems to which he is unaccustomed.