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The Development and Progress of Urology in Europe

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Based on the data of eminent European urologists, author gives an overview of the development of urology in Europe from the Ancient Times to our days. Reviewing the history, he has attempted to follow the simultaneous events in various countries. In discussing them, the most important events are highlighted. Such milestones in the history of urology were lithotomy and litholapaxy. He attributes no less importance to the development of the individual urological schools. He could not aim at completeness, since it was not easy to gather the historical data. At the end of the paper he expresses his thanks to all those who were of great help in compiling the data.

The history of the development of urology can be divided into three phases.

Initially, the individual urological diseases were treated by unskilled surgeons, i.e. lithotomists or other kinds of quacks.

Later on, urology developed as a part of surgery when the first trained surgeons appeared on the scene.

Finally, urology has become independent of general surgery and one needed a qualification to become a specialist in urology.

In general the establishment of the first specialist department for a special field is considered to be an evidence of its becoming independent. However, before this becomes possible, predecessors have to keep on working for a long time to effect the separation of this special branch of science.

Urology is a relatively recent field which, however has undergone a very long historical development. This is proved by the fact that ancient urological instruments have of en been excavated in the East-Mediterranean region as well as in Persia and India. For example, a scene showing the act of lithotomy dates from 2500 B.C. which was its first pictorial representation and was recovered from the tomb of Teti (in Sakara, near Cairo). Haematuria was already described in vesical schistosomiasis in the Ebers' Papyrus in 1500 B.C.

People suffered from renal or vesical calculi already in prehistoric times. Evidence of this was provided by archaeologists and medical historians by excavating Moorish corpses dating from prehistoric times as well as by the X-ray examination of the mummies. In Egypt vesical calculi were found in a thousand-year old mummy. Although these diseases were heralded by pain, which symptom is as old as mankind, the teaching of the urological diagnostics and therapy of the diseases of the kidney, bladder, the urinary passage and the related organs could become an independent clinical branch of science, i.e. urology, only in the 20th century. It had been a long process until the teaching and research of renal and vesical diseases could become integrated into the body of up-to-date medical sciences.

This is all the more striking because therapeutist were already known for treating stones in the Ancient Times. These so-called 'lithotomists' had already at that time been familiar with a surgical technique of bladder stone operation by which, on operating male patients, they introduced sharp knives and forceps through the perineum into the bladder and removed stones inhibiting micturition. Reference was generally made to medicasters learning their art in a bungling manner since up to the 18th century learned physicians refused to perform this brutal intervention. It is not surprising at all that Hippocrates in his Oath definitely insisted on young physicians leaving those suffering from bladder stones to be operated by lithotomists.

Hippocrates did not, at the same time, refrain from the surgical exploration of the renal region and he described the opening of a renal fistula which he treated by lumbar incision and drainage.

The high mortality due to perineal cystotomy was considered by him as severe as any lethality resulting from each bladder injury. This fact allowed him even to propose the omission of cystotomy to his colleagues by leaving it 'to experts who were experienced in such interventions'.

In the Hippocratic Oath it is as follows:

"I will not cut for stone, even for patients in whom the disease is manifest- I will leave this operation to be performed by practicioners (specialists in this art)".

Lithotomy is looked upon as one of the first interbentions of urological surgery. Transperineal lithotomy had already been practised in Persia and India (Sucruta), too.

Although Hippocrates (460–370 B.C.) was none of a lithotomist, nevertheless he can be regarded as the first urologist. He performed systematic urinary examinations of his patients and wrote several treatises on the diseases of the urinary tract. His ideas on the anatomy and physiology of the urinary passage show evidence of his exact knowledge in urology.

Hippocrates devoted great attention to examining the urine from the points of view of odour, colour, and sediment. He termed the opacities arising in the standing receptable, depending on whether they were seen at the surface, in the middle or at the bottom of it, *nubecula*, *suspensum* and *sedimentum*. Hippocrates was exactly aware of the nature of renal colic. Among his intruments he made mention also of the catheter.

His theory on lithogenesis and his diagnostic explanation of the abnormal components of the urine on macroscopic examination (uroscopy) are valid still today.

At that time, there could hardly be any idea of how urine was produced and of what anatomical structure the urinary organs were. The already mentioned legendary Hippocrates who lived as an itinerant physician from 460 to 370 B.C. in Greece regarded the pair of kidneys as filter organs. The systematic explanation of the process of uropoiesis and the anatomy of the urogenital tract raised the attention of physicians only in the Renaissance. The definition and term of prostate derives from the contemporaries of Erasistratus (300 B.C.) who were students of the School of Alexandria. Some facts may strengthen historical fidelity: We are aware that Hippocrares was not only one person, because several physicians worked under this name and innumerable disciples followed these doctrines throughout the centuries (from the 6th to the 3rd century B.C.). Several of their contemporaries published their observations under the name Hippocrates. Finally, in the 3rd century B.C. they summarized their experience in more than 50 volums (in Greek and Latin). That is why it is called, in general, the School of Hippocrates. The conglomerating material was elaborated by the members of the school according to a uniform principle which comprised the following:

1. Negation of the supernatural forces;

2. Unity of Nature (fauna and flora and Man himself);

3. Nature attempts to restore the upset internal balance of the organism, the physician's task is to support and help (or at least not to hinder) the healing work of Nature;

4. The diagnosis and prognosis of the disease are not based on observation, experience (empiria) and all generalizable factors to be concluded from them;

5. A means of medical healing is the physician's behaviour inspiring trust and the keeping of ethical norms (physician's oath).

6. The physician should avoid any kind of dangerous intervention.

This last point is why Hippocrates left the operation (as also lithotomy) to the barbers and craftsmen. This was partly attributed to the fact that they possessed only a limited knowledge of anatomy. (On the contrary, he considered the immediate life-saving intervention to be necessary, e.g. the morcellation of the fetus if delivery endangered the mother's life).

Despite its several errors (the role of body fluids, humoral pathology), the Hippocratic school has up to the present time been the initiator of medicine instilling a respect and humility for science.

In the Middle Ages a number of lithotomist families emerged as individual societies (guids), their members incorporating great scientists but charlatans as well.

This was the time the first catheter made of parchment paper wa

produced and also when the first suprapubic puncturing of the bladder was performed.

The prostate, a gland in the male under the bladder, was discovered by Herophilus of Chalcedon, a Greek physician living in 300 B.C.

Galenus lived four centuries later in Asia Minor (in 130–200 A.D.). He knew renal calculi to be interrelated with gouty deposits. He differentiates coral calculi and migrating stones and focussed his attention on the bimanual examination of the bladder. Just like Rufus of Ephesus (in 100 A.D.), also Oribasius (325–403 A.D.) was an interesting figure in the history of urology, who invented the indwelling catheter and who lived during the reign of Emperor Julian in Rome. The work of Paul of Aegina (700 A.D.) was mainly of interest in the field of surgery. He was the first to apply bladder lavage.

The quacks settling down in the ancient Rome widened the range of their instruments. The experts practiscing their art had already at that time, possessed bougies of variable size according to the sex of the patient which they could introduce into the urinary tract for catheterization (which was the term also used at that time). Such special instruments were found in the House of Surgeons in Pompeii which were employed for the examination and treatment of patients suffering from bladder stone.

Up to the Migration, the surgeons being active in various parts of the Roman Empire, further improved the treatment of bladder stones and urethral stricture. Oribasius of Greece (325–403 A.D.) already wrote about a catheter made of zinc and lead which could be kept in the urethra for a longer time in urinary retention. Soon afterwards the round-headed bladder probe with a lateral opening was made which inflicted less injury on introduction into the urethra.

Interestingly, already Erasistratus used an S-shaped catheter (in about 300 B.C.) (currently the so-called Béniqué sound). In addition to the straight instruments brought to the surface in the excavations at Pompeii, also a child and a female catheter made of bronze with this double curve were unearthed.

In the period of Hellenism in Alexandria founded at the delta of the Nile by Alexander the Great, who wanted to turn it into the spiritual metropolis of the western world, the technique of lithotomy was improved. This could particularly be attributed to Ammonius, who lived in Alexandria in about 250 B.C. and earned reputation by crushing bladder calculi. The incision made between the testicle and the anus near the perineum did not have to be too large, since the crushed stones could easily be removed with the help of a hook. Mastering this technique the medicaster Ammonius got the nickname of 'lithotomist' (stone crusher).

In Rome, A.C. Celsus (14 B.C–38 A.D) wrote about lithotomy by incision. In this similarly transperitoneal intervention, beside a special knife, only a limited number of other instruments were used. It is not quite clear why the Hippocratic school prohibited lithotomy. There are two explanations. It could have only a poor knowledge of medical skills so it left the 'difficult and dangerous operation being always lethal' to those it consdered to be the adversary of well trained, skilled physicians. It is also plausible, it did not want its students to practise this painful and drastic operation the risk and rate of mortality of which were fairly high, and it was not worthy of the medial profession. Whatever the cause was, it is a fact that Hippocrates is duly considered to be the father of medicine and urology, despite that he has forbidden lithotomy and the performing of the most difficult and most frequent operations and by this he must have delayed the progress of urology.

In the Christian Italy, monasteries and universities undertook the task of training in medicine and surgery up to 1215 when Pope Innocent III in his decree *Ecclesia abhorret a sanguine* (the Church is disgusted with blood) prohibited the practising of surgery. This led to the sinking into oblivion of the considerable medical knowledge dating from earlier times in the central European region. The Arab nations did, however, carry on practising it and spread their knowledge in Spain.

Of the Roman physicians, Celsus was the most important one, whose writings were recovered only in the middle of the 15th century. He was physician and surgeon at the same time. His lithotomic method had been applied quite up to the 18th century. Heliodorus (in 1 A.D.) used a metal tube or a quill caoted by parchment paper for treating strictures. Celsus had already given an exact description of catheterization. Rufus of Ephesus (1st c. A.D.) was the first to give an account of bimanual examination. In his work he refert to haematuria, bladder paralysis as well as to bladder stones.

It was about that time that bladder stone was differentiated from prostatic hypertrophy. Rufus published data on pyuria. Claudius Galenus (129–201 A.D.) considered the urine as an excreted material which is produced from the circulation in the liver, is excreted in the kidney and is emptied through the urinary bladder. Galen (2nd c.) knew about strangury and urinary retention. He considered the latter to be the cause of inflammation, canner, pyuria or bladder paralysis. He demonstrated renal colic, similar to Hippocrates. Paul of Aegina and Alexander of Tralles (525–605 A.D.) reviewed the vesical and renal diseases on the analogy of Galen. The latter attempted to gain a better insight into the diseases of the bladder and kidney and said that nephritis, he regarded fever to be a symptom of crucial importance.

The quality of urine was studied by Alexander of Tralles from the point of view of the differential diagnosis of bladder and kidney involvemeuts. He described with great accuracy the renal colic coused by renal calculus.

Theophilus published his study based on the teachings of Hippocrates and Galen in the 7th century. It rested on the theory of Galen (2nd c.) according to which urine is excreted from the blood. The school of Salerno founded in about 1000 and remained the centre of medicine for two centuries. The *Regulae urinarum* of Master Maurus was widely known. To this circle belonged Trotula, a woman doctor, who used Klysma first as a pain killer.

The School of Salerno produced several works on the urine, such as the *Regulae urinarum* of the young Johann Platearius and the compendium of Master Urso (12th c.).

Up to the 16th century, the didactic poem containing 352 hexametres entitled *Liber de urinis* has won the warmest recognition. In the 12th century, Corbeil transferred the School of Salerno into Paris. He evaluated the sediment and colour of the urine completely on the basis of Galen's theory.

Albucassis' writings (11th c.) are also well known. He propagated bladder lavage and examined the calculus by one or two fingers through the anus. This physician named the 'father of surgery' also refuted to perform the operations by his own hands. He preferred to leave his female and male patients to itinerant lithotomists and midwives. Surgical interventions in female patients for removal of bladder calculi were performed at that time by midwives.

In the 13th century, Bruno Longobardo was the first among physicians to offer litholytic and lithotomy.

In the Middle Ages further progress was made in uroscopy, the diagnostics of urinalysis. To this a great impetus was added by the surgeon Guy de Chauliac (1300–1368) who was educated at the famous university of Montpellier in South France. His work *Grande Chirurgie* was based on his rich anatomical and clinical experience. He tried to give a more exact explanation of the formation of bladder calculi. He had already given preference to the practical use of litholytics. He recommended a surgical intervention using catheter and perineal incision only in cases not responding to conservative therapy.

Guy de Chauliac acquired new and original knowledge in urology. In his book *Chirurgia Magna* (1356) he enriched the Arab and Greek teachings with his knowledge and personal experience. He described the role of the urinary apparatus which purifies the blood.

Uroscopy, the diagnostics of urinary tract diseases, was refined after Chauliac on the basis of the observation and description of the urine. The urine discharged at 'cock-crow' was examined concerning concentration, colour, taste and sediment.

Our first data on the studies of urological anatomy and the first surgical technology derived from the school of Salerno, about which information had been available since the 9th century, and which was prospering in the 12th century.

At that time, catheters were made of the skin of wild and sea animals alloyed with casein, or of metal origin, of tin or lead, which could be adapted to the anatomical curvatures. In Spain the book of J. Gutierrez de Toledo 'The Pain induced by Calculus, Inguinal and Renal Colic' was published in the 15th century (1498). It represented the conception adopted at that time concerning the calculi of the urinary passage including dietetic therapy and water consumption, etc.

The first reference to 'urological' activity derives from about the 1400s from Poland when a surgeon named Gerka removed the bladder calculus of the head cook of the Teutonic Order.

The Mariani method (after Mariano Santo) a technically refined operation was introduced in Rome by Johannes de Romanis, a physician of Cremona, at the beginning of the 15th century. His disciple Mariano Santo wrote about the method presenting also illustrations. After an incision directed at the probe in the urethra, a kind of speculum was introduced into the bladder neck and then assisted by a hook or a spoon, the stone was removed by a lithotriptor.

Kohlreuter (10th c.) openly declared that the disease could not be diagnosed solely from the urine. Some physicians pleaded for the restoration of traditional uroscopy. Following from the 16th century, during the peaks of renaissance and intellectual life, the art of healing started gradually to resist the constraints of the Galenic principles which had formore than thousand years dominated medicine. The progress of the science of anatomy is attached to the name of Vesalius (1514–1564), the discovery of the circulation of blood to that of Harvey (1628). Malphigi (1628–1694) and Leeuwenhock (1632–1723) founded microscopic anatomy. Paracelsus (1493–1541) laid down the foundations of teaching in medical chemistry. Petrus Borellus was the first to study the urine microscopically. Bellini (1643–1704) defined the urine to contain three elements, i.e. water, salt and tartar.

In 1571 the book of Thurneisser, a student of Paracelsus, appeared on 'Iatrophysical Urinalyses' he performed in Berlin. Berlin-Brandenburg was marked by an amazing progress. In this country, first amoung Germanic state, there was a progressive medical system already in 1685. Andreas Laguna is very well known in Europe (Paris 1531, Bologna 1536, Cologne 1546). He wrote his book in 1551 entitled Methodus Cognoscendi Extirpandique Excerentes in Vesicas Collo Carunculas, which was a short monograph dealing with the papillae of the bladder neck, their treatment by cauterization and catheterization. Francosco Diaz was the surgeon of Philip II. His book 'Studies on the Diseases of the Kidney, the Size of the Penis and the Urethra' was published in 1588. He was founder of one of the most famous universities of the Middle Ages, that of Alcala de Henares. The original title of the book was Tratado de todas las enfermedads de los risiones, vexiga y carnosidades de la verga y urina. In Poland Jan Stanko performed a bladder stone operation on Jan Dlugosz, a Polish historian, in the second part of the 15th century. Jan Chrosiejewski, the author of De puerorum morbis (1583) devoted attention to various urological problems (e.g. the chapters on *De clausura meatum urinae et sacrum*, *De urinae incontinentia*, and *De urinae suppressione*).

Papers on urological diseases could be found already from 1717 to 1732 in the *Acta Medicorum Berlinensum*, the first medical journal of Berlin.

Of the lithotomists of the Middle Ages, Eisenbarth (1663–1727) was already a physician and surgeon. To perform the incision of Celsus, he needed a small lancet and a spoon-like instrument, the lapidilum, with which he could extract the calculus following a perineal incision. These methods were used in patients of all age, particularly in children and in cases where the stone had to be felt in the bladder neck.

The operation (i.e. lower-abdominal exposure) becoming later on a routine procedure was called Frankonic method after Nicolaus of Frank, a surgeon of Lausanne. It was applied to particularly large stones. Attempts were made to push the stone through the anus or through the abdomen and to remove it by incision in the right or left transinguinal region. Fabricius Hildanus (Fabry of Hilden 1560–1632) considered this method to be less dangerous using it for particularly large stones. Several surgeons refuted this since injury of the perineum was always lethal.

Due to the deep distrust by which the physicians graduated from universities regarded the surgeons, the development of surgical treatment of urinary calculi was less encouraged. Physicians did not hold the surgeon's activity in great esteem. This was largely due to the fact that the success of on operation was doubtful owing to a lack of disinfectants. For the patient, who could not be anaesthesized quite up to the middle of the 19th century, the operation meant a today hardly imaginable drastic intervention. Even the most experienced quacks restricted themselves to only a limited number of external surgical interventions including, beside bladder puncturing, removal of inguinal and testicular hernias, especially lithotomy. They became specialists in a way that in the 16th and 17th centuries the bladder puncturers and lithotomists as medicasters wandered through the country or as physicians having settled down, installed an operating room in their houses.

Andreas Vesalius (1514–1564), founder of modern anatomy, a professor in Padua, made an essential step in the diagnostics and therapy of the diseases of the renal and urinary tract. In his epoch-making work *De humani corporis fabrica libri septem* published in Basle in 1543, he described the anatomy of the kidney and the urinary organs. His student Gabriele Fallopio (1523–1562), soon developed the method of injection of the renal capsule which enabled its subtle demonstration. Not long after it, the seminal vesicle was discovered by Etienne de la Riviere (died in 1569). Almost at about the same time, the surgical methods were improved by the French surgeon, Ambrois Paré (1510–1590). He devoted three text-books to urology, which were concerned with the behaviour of urine, with bladder stones and gonorrhoea. A memorable event was in the history of urology when, in the 16th century, P. Franco (1505–1570), a French physician, relieved a two-year-old boy of his bladder calculus by removing it anteriorly above the symphisis.

It was described in detail by the English Thomas Willis (1621–1675) in 1674 that the urine of diabetic patients tasted sweet. This added significantly to the diagnostics of internal diseases. Uroscopy developed into a valuable diagnostic procedure which was rated as being equal to the assessment of pulsation. Not much time had to elapse until urinalysis was introduced where the quality of urine was recorded. Still a longer time had to elapse until the fine structure and functional mechanism of the kidney could be explained microscopically first in 1600. Immortal fame was acquired in the research of the physiology of the kidney by the Italian physician, Marcello Malphigi (1628–1694).

It should, however, be noted that, despite the available data on the structure of the uropoietic and urinary organs, both conservative and surgical therapies failed to yield great success in the 16th and 17th centuries. Although quacks developed an ever increasing arsenal of instruments, in lack of hygiene and pain-killer drugs, no particular success could ne recorded. The following instruments were used: scalpel (a kind of razor), dilators, forceps, retractors and spoons. Beside these, various types of operating chairs had already been available in which the patient could be properly placed for the operation. In Paris, there was a possibility in the hospital of the Brothers of Mercy (in 1608 they moved to a new building) that bladder calculi be removed by experts. The textbook *Tractaat vant Steensnyder* of Francois Tolet, a Dutch physician, contains an etching demonstrating such a lithotomy. It was supposed to be performed by Jannot.

Nevertheless, itinerant lithotomists performed the treatment of patients with calculi according to the traditional methods quite up the age of enlightenment. In the Baroque period, Jacques Beaulieu (1656–1714), who published his work in Aachen in 1698, was particularly well known. Jacques Beaulieu, by this master who, practically cannot be considered either a physician or a quack removed over 4000 stones.

Subsequently, a great impetus was given by Giovanni Battista Morgagni (1682–1771), an Italian physician to the medical science of the urogenital organs in his basic work *De sedibus et causis morborum* (The site and causes of the diseases). In 1761, among others, he classified the bladder tumours. In addition, he also wrote about the pathological enlargement of the prostate.

The first mention of the wandering kidney was made by Franziscus of Pedimontium in the 16th century. The symptoms were described by Riolan in 1682.

Bonet was the first in 1679 to discuss the association between nephritis and obstructed urine flow, but this causal relationship was first defined by Petit.

In 1717 the Charité Hospital was founded. From this time on lithotomies were performed here.

Since the first lithotomy in 1728 at the Charité, this operation was particularly cultivated. The first head of the clinic, Eller spent 5 years by mastering its technique at Rau in Amsterdam. According to the methods used at that time, suprapublic incision was used. A favourable portrayal of urological and abdominal operations unfolds from the Charité News published by Eller in 1730 which appeared quite up to the end of the century.

From the point of view of urology, the 19th century in Berlin was hallmarked by an important work, i.e. 'Some Diseases of the Renal and Urinary Tract'. It was published in 1800 by the pathologist Walter. By this work the examinations and study of the urogenital organs assumed considerable importance.

Perineal cystotomy (the internal urethrotomy used in urethral stenosis and ischuria) emerged by the description of Feliciano Almeida on lithotomy from the 17th century which proves that this procedure was regularly performed at that time.

In the 18th century, G. B. Morgagni (1682–1771), the father of histopathological anatomy, reported on benign prostatic hypertrophy, the syphilitic involvements of the bladder, and he was the first to declare the necessity of surgery in tumours of the urinary tract.

In 1774 Bertini wrote about the 'coloumns' of the kidney. The first nephrectomies associated with stones and other diseases were performed in these years.

In the 18th century the first urological wards were established. Then already leading surgeons resorted to complicated operations such as the removal of bladder stones. Still at the middle of the 18th century, out of 812 patients 255 died of bladder calculi.

Lateral lithotomy was reintroduced to France by Jean Baseilhac (1703– 1778), a brilliant clergyman coming from a surgeon's family, who was called Father Come. He adopted and improved the traditional technique, by introducing 'lithotome caché', i.e. concealed lithotomy, by which he could control the incision of the bladder neck by pushing backward of the spatula. He also invented 'sonde á dard' which enabled transurethrally the opening of the bladder interiorly and led to the general acceptence of suprapubic lithotomy.

In 1776 the school of surgeons dealing with calculi of the urinary tract was organized in Moscow by I. P. Venediktov. The manufacturing of urological instruments was started at St Petersburg in 1817.

In 1730 J. Douglas (1675–1742) was the first to describe the position of the peritoneum in the pelvis and in view of this could be pushed down from the bladder intraoperatively.

From the beginning of the 18th century, several Polish surgeons devoted themselves to the special field of urology. The best-known of them were Konstanty Porcyanko (Wilno 1793–1891), Aleksander Le Brun (Warsaw 1803–1868), Julian Kosinski (Warsaw 1833–1914), and Alfred Obalinski (Cracow 1843–1898), professor of surgery at the Jagello University and author of the first urological book the 'Lectures on the Disease of the Male Urinary Tract' published in Poland.

Uric acid was discovered by Sheele in 1770, glucose by Matthias Dobson in 1774, carbamide by Cruikshank in 1799, lactic acid by Berzelius in 1807 and creatinine by Liebig in 1847. The discovery of protein is attached to the name of Cottugno, although Deckers regarded protein as a component of the pathological urine.

Cottugno wrote about protein in 1770. Leube pointed out that Fr. Deckers had already known the component of pathological urine in 1694.

In England in 1750 Mead evolved his theory on diabetes.

In 1774 Matthias Dobson stated that the urine of each diabetic tastes sweet and he established experimetally that urinary glucose shows the properties of the fermentation of wine and vinegar. He was generally recognized only around 1800 as a result of the work of English physicians, like Homes, Cowleys and Rollos. Glucose was chemically produced first by Johann Peter Frank (1745–1821), the famous clinician of Vienna. He was the first to mention impotence in diabetics. In 1838 Boucherdat and Peligot declared uric acid to be equal to glucose.

The various normal and pathological componets of the urine were discovered by Cruikshank, Fourcroy and Vauquelin in 1799 then by Wöhler in 1828.

The method of the physicians of Alexandria, according to which the bladder calculi were crushed then removed by lavage, had already for a long time sunk into oblivion, when this method was adopted by Jean Civiale (1792–1867) who performed such an intervention in 1823. This was called lithotripsy (crushing of a calculus in the bladder), and adequate instruments were developed for penetration into the urethra. This procedure was not only bloodless but was also associated with a lower death rate.

Experiments on the crushing of calculi in the bladder date back into the 9th century. The first one to achieve complete success in performing lithtotripsy was Civiale(1 792–1867). The currently used lithotriptic method derives from Heurtloupe (1793–1864). The final solution was offered by the discovery by J. Bigelow, a physician of Boston (1787–1879), who succeeded in transforming lithotripsy into a safe and convenient intervention.

In 1823 Civiale succeeded in having lithotripsy accepted also by others. It ousted perineal lithotomy having been used for thousand years. By contributing funds, he created the first department of urology in Necker (Paris). Suprapubic cystostomy (sectio alta), was, however, extensively used only after 1870. In 1824, reports appeared on lithotripsy performed by boring into and grasping the stone by a screw-driver-like instrument, but in the majority of cases bladder calculi were still removed by perineotomy.

Baillie (1825) has drawn attention to the characteristic position and size of the dislocated kidney which was verified by Aberles (1826). Hydronephrosis was already described in the 16th century by Felix Plato and Fernet.

In the 18th century, there was a growing number of observations on the changes of the kidney based on a series of pathoanatomical studies. Later the English physicians Brande (1807) and la Scudamore (1823) proved that protein-containing urine contains strikingly little urea.

In 1823 Alison reported in Edinburgh on his findings concerning hard kidneys of uneven surface due to dropsy in several cases.

Based on clinicopathological studies, the scientific description of nephritis was given by Richard Bright (1789–1858). His works appeared in 1827, and brought about marked changes in renal pathology. In his treatise (1827) he stated that dropsy is a cause of renal disease which can be recognized by albuminuria.

The first major monograph on renal diseases is attached to the name of P. F. O. Rayer (Paris 1839–1841). His followers G. Johnson (On the Diseases of the Kidney, London 1852), Jul. Vogel (Krankheiten der harnarbeitenden Organe, in Virchows: Handbuch der speziellen Pathologie, 1856–1865), and Rosenstein (Pathologie und Therapie der Nierenkrankheiten, Berlin 1863) further differentiated the renal diseases based on microscopic findings.

L. Pasteur (1822–1895) elucidated in 1859 and 1860 the cuase of fermentation of the urine. He considered *Torule ammoniacale*, a microbe to be responsible for the change in the quality of urine which was isolated and placed into urine to produce fermentation by his student van Tieghem.

In the years 1855 and 1871 Maissonew and Otis reported on urothrotomy which is also currently in use. Between 1880 and 1892 suprapubic cystostomy was advocated by Peterson in Kiel and by Bazy, Pousson and Guyon in France.

In 1869 the first successful nephrectomy was performed by G. Simon (1824-1876) in a patient with ureteral fistula.

In 1889 a prostatectomy was made by Vincenz Czerny, a professor of Heidelberg.

In 1895 the ureteral catheters and the roentgen tubes were invented. Fuller (1895) described suprapubic transvesical prostatectomy which was later propagated by P. J. Freyer (1851–1921) in 1900. It was first in 1896 that a bladder stone was visualized roentgenologically.

May 9, 1879 was a special date in respect to urology. The first functioning cystoscope was demonstrated at that time. Nitze's cystoscope was considered by many the beginning of up-to-date urology.

In the 19th century, several attempts were made at observing directly the urethra. An equipment was constructed by Bozzini, a physician in Frankfort, termed by him a tube conducting light. In 1826, Ségalas devised his instrument the *speculum uréthrocystique* which was based on different principles. Subsequently in 1827, this was followed by the highly complicated instrument of the American John Fischer and then by that of Acery, in 1840. He published his *Traité d'endoscopie* in 1865 reporting on endoscopic ureterotomy.

Beside the French Guyon (1831-1920) and the British Thomson, Dittel had already at that time been regarded as a urologist of international fame. He could be considered to be the father of urology of the German-speaking world. The first independent department of urology of the word was established in this decade (1872) at the Vienna polyclinic. It was headed by Dittel's student Ultzmann, who further improved cystoscopic diagnostics, primarily concerning bladder tumours. His book 'The Bladder Stones Harboured in the Human Body and the Cause of their Formation' was translated into several languages. His department was a meeting place of physicians concerned with urology from all over the world. From 1873 to 1884, 906 students from 25 countries attended his lectures. In 1887, the first ureterocystoscope was constructed by Leiter-also Dittel's student- according to Brenner's data. This was particularly supported by C. A. Th. Billroth (1829-1894) who reported already in 1884, on the first nephrectomy and pointed out the necessity of functional renal diagnostics. After the untimely death of Ultzmann, his student Frisch became head of the polyclinic. His attention was focussed on the questions of bacteriology. Very soon he started to deal with the major problems of urological surgery, the treatment of bladder tumours and those of bladder stones and prostatic hypertrophy. His paper 'The Diseases of the Prostate' in Nothnagel's manual (1899) is the first fundamental survey of his special field. His urological manual, an exhaustive work of those times, co-authored by O. Zuckerkandl, was published in 1904-1906.

Although there was a number of innovations in the diagnostics and therapy of urolithiasis and other diseases of the urinary tract, they were perfected only by the invention of the endoscope. The visualization of the internal cavities in the living human body could have been a long-cherished dream of physicians until finally Philip Bozzini (1773–1809), a young physician in Frankfurt, reported on a procedure in 1807 by which the bladder could be observed with the naked eye. He tried to make the light of a candle penetrate the bladder with the halp of a light-reflecting mirror. The new procedure was discussed in Vienna, which, however, was first not too promising in lack of a perfect microtechnique. A complicated equiment based on the same principle was devised by Antonin Desormeaux (1815–1852) for illuminating the body cavities. He succeeded by this endoscope in removing an urethral papilloma in 1865. Although methods in ophthalmoscopy (by Hermann Helmholz since 1852), in laryngoscopy (by Manuel Garcia and Ludwig Turk since 1855) projecting into the future, had already been developed from the middle of the last century, there were a lot of anatomical, physiological and physical barriers to be overcome in cystoscopy. Nor Julius Bruck (1840–1902) a dentist in Breslau, was too successful. He devised an urethroscope by which a glowing platinum wire was introduced into the bladder cavity to allow its viewing The question arose how the patient could be protected from the glowing light. Cooling with cold water running in a tube surrounding the platinum tube proved to be too complicated and unimplementable.

Max Nitze (1848–1906), urologist, becoming famous later on, constructed the first usable cystoscope based on Bruck's principle. He presented it in Vienna in 1879. This was much easier to use than the previous one, magnifying the visual field by a system of lenses. The cystoscope could after all be introduced without inflicting burns and causing pain, i.e. not endangering the patient by using the incandescent lamp invented by Thomas Edison (1847–1931). This succeeded finally by applying a so-called miniature lamp bulb which was built into the cystoscope by Joseph Leiter (1830–1892), a technician in Vienna in 1887. By this it became possible to view the interior of the bladder involving no risk for the patient. Soon the cystoscope improved by various eminent urologists – as e.g. Leopold von Dittel (1815–1898) – became accepted all over the world for the detection of each kind of urinary and renal diseases.

In the 20th century, further progress was made in urology. In 1896, the roentgen rays invented by and named after Wilhelm Conrad Röntgen (1845–1923) enabled the visualization of the kidney in a living man.

Surgical technique could also be further improved after anaesthesia had become accepted in 1846 and the introduction of anti- and asepsis made completely sterile operations possible.

The invention of anaesthesia (by Wells and Milton in 1847), the introduction of antisepsis (Ignác Semmelweis (1827–1912) and L. Lister (1827–1912) and the use of asepsis (1886) opened up new vistas in the development of medicine and surgery.

A new scientific era was opened in 1810 in Germany by the foundation of the University of Berlin. The translations of British and French authors appeared soon after the establishment of the university. Another important peak of development was the contribution of Johann Friedrich Diffenbach, the father of plastic surgery. Between 1829 and 1936 he was dealing with the plastic operations of the university tract with special reference to the male urethral fistula as well as to testicular skin grafting. Besides he had been working since 1836 on the closure by plastic surgery of vesicovaginal fistulas.

In 1862 Ernst Fürstenheim was the first to settle in Berlin as the 'physician of the diseases of the genitourinary tract'. After his training in Paris, he introduced with some modifications, Desormeaux's endoscope also in Berlin. In addition to publishing urological papers, he introduced the word 'andrology' coined by him at the meeting of the 'Hofelandsche Gesellschaft' held 26 September 1879.

Maximillian Nitze (1848–1906) carried out most of his work at his private polyclinic. In this field he devised every kind of accessory cystoscope constructions which turned Berlin a centre of European urology. The basic work of Nitze was 'The Textbook of Cystoscopy'. In 1889 the first German urological journal of the Physiology and Pathology of the Genitourinary Organs' (published by Wilhelm Zuelzer in Berlin) appeared. It is due to him that, up to 1894, the first urological manual 'The Clinical Manual of Genitourinary Organs' was published in four volumes.

Between 1890–1897, the first manual of urological surgery in German 'The surgical Diseases of the Male Genitourinary Organs' was published also in four volumes by Paul Güterbock in Berlin.

Although renal surgery is supposed to have been started by G. Simon (1824–1876) in 1869 in connection with a successful case in Heidelberg, its final success is attached to the name of James Israel, who created a usable method. As the head of the Department of Surgery of the Hospital of the Jewish Community (1875) he personally studied in Edinburgh and introduced at his clinic the antiseptic methods of Lister. His classical work 'Experience on Renal Surgery' appeared in 1894.

Robert Kuther was an eminent urologist of this period. He succeeded among the first to take pictures of the interior of the bladder. Ketner had been the initiator since 1900 of the postgraduate training of physicians in Prussia and was the director of the Kaiserin-Friedrich-Haus which had preserved up to 1945 the collection of Nitze's urological instruments.

The first Belgian surgeon to be mentioned as a urologist was André Uytterhoven, a surgeon in Brussels, who published a procedure combining the mutual benefits of lithotripsy and lithotomy in 1863. This comprised the introduction of a lithotriptor through an incision into the bulbar urethra.

As regards renal diseases, French physicians are worth of mention who in the years ofter World War I founded nephrology as a separate branch of science based on the knowledge of outstanding internists and nephrologists, like the German Franz Volhard (1872–1950).

Simultaneously with Sándor Korányi (1866–1944), Franz Volhard (1872–1950) laid down the foundations of the functional approach and introduced the dilution concentration test (specific gravity test for renal function).

Henrique Bastos was born in Portugal in 1874. He was obstetrician, then surgeon at the Civil Hospital of Lisbon. Encouraged by Alfredo da Costa, he became a specialist in urology, learning at Albarran in Paris, at Israel in Berlin and at Freyer in London. He was the first Portugese to perform urethral catheterization and perineal prostatectomy.

Manuel Vincente Alfredo da Costa, the leading surgeon of the Civil Hospital in Lisbon, later professor of pathology, had always been concerned with urology. He was the first Portugese surgeon to perform the first nephrectomy in 1889.

Nevertheless, the first official document on nephrectomy dates from 1891. It was performed by Sabino Coleno in the Sao Jose Hospital.

The name of the Danish L. L. Jacobson (1783–1843) is worth of mention. Two years after J. Civiale (1792–1867) he had devised the triplejawed forceps and constructed a real lithotriptor which had been one of the instruments used for crushing bladdes stones.

Ramm (of Oslo) was aroused international attention in 1893 by presenting the decrease in the size of the prostate and the associated symptoms following castration.

In 1884 the department of urology headed by Suender was established in the Princess Hospital in Madrid. Suender was master of bladder lithotripsy. In 1904 P. Cifuentes (father of our contemporary, L. Cifuentes) followed him in his steps.

In 1889 J. Pages Puig headed the first department of urology in the Hospital del Sagrado Corazon (Hospital of the Sacred Heart) in Barcelona.

The Department of Urology in the Vienna Hospital founded in 1892 was headed first by Robert Ultzmann (1872–1884), the student of Dittel. Up to that time, only a single department of urology had been functioning in Paris. The first perineal prostatectomy was performed by C. A. Theodor Billroth (1829–1894) in 1867. His book entitled 'Nephrectomy' was published in 1884.

The first hospital in Zagreb was opened in 1871 where all operations were done by dr Fon. He is looked upon as the first trained surgeon in Croatia. He performed cystostomies, urethrotomies and closures of vesicovaginal fistulas.

In 1885, a department of medicine was established within the surgery department headed by dr. Wickerbauer at the Zagreb Hospital of 'Sisters of Charity'. The department of surgery became an independent unit in 1849.

The developments of urology in Poland have been similar to those in other European countries. The patients with bladder stones were treated by lithotomists in the 15th, 16th and 17th centuries. Sectio alta became extensively used in the second haft of the 19th century. Nephrectomies were performed only after 1880. In the 19th century medical faculties boomed into prosperity all over Europe. Poland was, however under the rule of three empires (the Russian, German and Austrian), but medical faculties were extablished in Cracow and later in Lwow (Lemberg) only by the Habsburg monarchy. The first urological textbook of Obalinsky, professor in Cracow, was published in 1898. In 1898 Rutkowski was the first in Cracow to report on an intestinal plastic operation in case of exstrophy of the bladder. In 1885, 16 years prior to Coffey, Krynski performed an analogous ureterosigmoideoustomy in dog in Warsaw. There were specialists in urology who were trained in Paris and Vienna, in Warsaw, Cracow, Lwow only at the beginning of the 19th century.

The first department of urology in Russia was established in Odessa in 1863 headed by T. I. Vdovikovsky, while the first department of urology in the university of Moscow in 1866 (headed first by I. P. Matushenkov, then from 1877 by F. I. Sinytsin). Valuable contributions to the development of urology were made by N. I. Pirogov who described the topography of the genitourinary organs and achieved significant success in the field of military urology, by I. F. Bus who pioneered in introducing several urological instruments in Russia.

At the end of the 19th century urological departments were established in Kiev, Kharkhov and other towns and the first textbook of urology was also published by A. G. Podrez in Russia (1887).

In the meantime, Leroy d'Etiolles demonstrated his spiral catheter the bougie à boule. It was similar to those available but did not prove to be too popular at that time. Revbard reported on an inflatable balloon catheter, the predecessor to the Foley catheter. Mercier facilitated catheterization in enlargement of the prostate by inventing coudé and bicoudé. He was also the first to mention hypertrophy of the prostate but he thought the tension of the bladder to be directly due to urine retentions of prostatic origin. The first rubber catheter preventing the patient from the unpleasant feeling of tour de main was described by Nelaton (1807-1875). The name of Béniqué was linked with a new metal sound for dilating urethral strictures and with a modified Charière gauge. The removable spare parts of instruments, all these innovations, were introduced by Maisonneuve and later improved by Phillipis. Maisonneuve utilized this method in creating his urethrotome. This mechanical although still great progress in catheterization was sufficient for performing, on the analogy of J. Civiale (1792-1867), perineal lithotomy and litholapaxy as procedures not involving risk for the patient.

Felix Jean Casimir Guyon (1831–1920) established first the School of Urology in Necker and made official this branch of science. He was the first full professor of urology at the University of Paris. He was surrounded by scientists of various fields of interest who tried to draw upon his special knowledge in urology. In 1889 he founded the French Urological Society and later, in collaboration with Desnos, the International Urological Society. He was so famous that, at the first meeting in Paris of the International Society, professor Israel of Berlin who could hardly be considered as a Francophil stated: 'Urologists from all over the world are in some way or other the disciples of Guyon.' Guyon was the man, who, according to the words of Hugh Young, 'turned Paris the Mecca of students in urology'.

Joaquin Albarrán (1860–1912), who came to Paris through Barcelona from Cuba, was the follower of Guyon at the Hospital Necker. He devised a cystoscope which he provided with an arm facilitating the introduction of the catheter, solving thus the problem of ureteral catheterization. As a result, the state of each kidney could be examined separately and more precise curing methods based on a more exact diagnosis, could be performed. In 1903 Völcker (1872–1915) and Lichtenberg (1880–1928) reported on the methylene blue excretion as a kidney function test and about the visualization of the pelvis by a retrograde collargol sliver preparate. Further progress of endoscopic urology was served by the instrument for transurethral resection developed by McCarth in 1930. The discovery of the school of Alexander Lichtenberg in Berlin in 1929 was of similar importance, namely the description of the roentgenological contrast medium excreted by the kidney, the urogram and their application in practice.

Frisch together with O. Zuckerkandl (1861–1921) published the first manual of urology in 1904. This served for a long time as a basis of this special field. In 1907 he was elected president of the German Urological Association. He was followed by Hans Rubritius (1919–1941) in the director's chair. He had students from almost all over the world, such as de Gironcoli, who was one of the leading urologists in Italy having died just recently. The surgical records show that the leading personalities of East-Europe and the Near-East sought urological consultations and were treated in Vienna. Rubritius was famous for his expertise in performing transurethral operations of bladder neck tumours. In 1953 Paul Deuticke became director of the hospital. Renal tuberculosis was his main field of interest.

O. Zuckerkandl (1961-1921) succeeded in 1889 to find a new perineal route to the prostate and the posterior vesical wall. A classical documentation of this field is provided by his work 'Contributions to the Anatomy of the Hypertrophy of the Prostate' (1922) written in collaboration with the renowned anatomist, Tandler. Despite all efforts, urology became a separate professor in Vienna only a late as 1962. The head of the first university medical school was professor Übelhör. A new impetus was also given to urology in Vienna by Hryntschak, wo published basic works on the ureteral peristaltics, hydronephrosis and the surgical techniques of renal calculi. His comprehensive work 'Suprapublic Prostatectomy with Bladder Closure according to an Individual Technique' is still used today. X-ray diagnostics in urology is due to his successor Deuticke. His book entitled 'The X-ray Study of the Renal and Urinary Tract in Urological Diagnostics' integrates several years of his intensive work of this subject. Chwalla has greately contributed to the understanding of the urinary tract. He published an also internationally recognized work on this topic. Bibus, who was head of the Department of Urology of the Kaiser Franz Josef Spital and whose book published in 1959 deals with the alkalization and litholytic therapy of urinary calculi, is note worthy.

Israel was also known for his 'Folia Urologica' (1907) and the jointly published 'Journal of Urological Surgery' (1913). He was doubtless the Nestor of urological surgery in Berlin up to his death in 1926. He is supposed to be the founder of the Urological Society in Berlin in 1912. With the advance of time, he recognized the importance of sexology for the urologist. His work 'The Hygiene of the Male Sexual Life' published in 1911 is a proof of this. In 1920 he took over the presidency of the Sexologist and Eugenetic Medical Society, establishing a close contact with sexologists in Berlin, among others, with May Hirsch and Iwan Block who had since 1900 been cultivating this field with great success.

Leopold Casper belonged to the most famous urologists in Berlin, who, as a result of his visit to England, familiarized in Berlin modern British urology represented by Thomson, Fenwick and P. J. Freyer (1851–1921). He was also the translator of Thompson's work 'The Diseases of the Urinary Tract'.

Casper's most significant works were the 'Manual of Cystoscopy' in 1890, the 'Textbook of Urology' in 1903 and 'The Manual of Urological Diagnostics' in 1930.

In 1903 Eugen Joseph together with F. Völcker (1872–1955) introduced chromocystoscopy and became the head of the Department of Urology of the Surgical Clinic in Ziegelstrasse unter August Bier in Berlin. The importance of his work lies in the introduction of the chemocoagulation of bladder tumours as well as in constructing the lithotomy forceps named after him. His monograph 'Comments on Pyuria in Childhood' was published in 1931 in which he pointed out the importance of paediatric urology. His further works of interest are 'Cystoscopic Technique' (Berlin 1923). 'Urinary Organs in the X-ray Picture' (1926) and the 'Tumours of the Bladder'. The first prostatic electroresection was performed in his department in Germany in 1932, by using the new method of Maximilian Stern (New York).

In Berlin, Alexander Lichtenberg (1880–1928) also contributed to the development of urology. He had already in 1906 introduced retrograde pyelography together with Völcker (1872–1955). He had been working since 1922 on creating a department of urology in the Hedwig Hospital and developed it to one of the greatest urological clinics of that time. The first experiments with i.v. contrast medium were conducted here.

Coauthored by F. Völcker (1872–1955) and Wildholz, A. Lichtenberg (1880–1928) published their manual of urology in five volumes in 1926 and developed important urological methods in his fruitful collaboration with Walter Hynemann in Leipzig. In 1932 the Lichtenberg–Heywalt bladder neck instrument, a lithotomy forceps and the first German electroresection instrument were presented.

Beside the great personalities of urology in Berlin listed so far, special mention should be made of Nietze's students: Rotschild, Jacoby and Jahr.

Rotschild published a book on Nitze's methods of treatment because Nitze was planning this work, however he could not accomplish it. Jacoby, a Nitze student, earned distinction with experiments in stereocystoscopy discussed in his work 'A Cystoscopy and Stereocystography Atlas'. The youngest of the Nitze students was Rudolf Jahr who was active as a consultant urologist between 1906 and 1921 in the Hedwig Hospital in Berlin.

The last but one Nitze student, Otto Ringleb, essentially improved after Nitze's death the optic system of the cystoscope in collaboration with the firm Karl Zeiss, Jena. In addition, he succeeded in presenting for the first time clear photographs of the bladder in his 'Textbook of Cystophotography' published in 1913.

He reported on his cystoscopic research in 1926 in his 'Textbook of Cystoscopy'. In 1939 he was among the first to take colour pictures of the bladder.

As a result of the two great landmarks of history in 1933 and 1945 and owing to the great personal and material losses, urology in Berlin was again subordinated to surgery. In the period after 1945 a whole generation of urologists had to revive urology.

In Turin, Luigi Ferria was appointed chief surgeon in urology in 1903, followed by Carlo Chiandano in 1932. There were also other schools in Turin: The Rossi Foundation and university chair, where Uffreduzzi was the director of the clinic. The urological patients belonged to Caporale.

At the beginning of the 20th century a department of urology was established by Pavone and in 1932 his son was elected president of the Society.

The Dutch Urological Society was formed March 14, 1908 with a restriction for 25 years. It was later prolonged in 1933 till 1959 for additional 25 years, while in 1979 for an unlimited period. It was founded by H. Brongersma who lectured in urology in Amsterdam in 1906. Zaager did the same in Leyden in 1909. The majority of urological operations were first performed by surgeons, and urology has become independent of surgery only after 1932. Moonen was formally installed in Nymegem in 1964, while Donker in Leyden in 1966. Although urology had initially not been accepted by the universities, it was nevertheless a special branch prospering at the large non-university clinics.

In 1906 J. Mestre was appointed head of the department of urology of the Hospital de la Santa Cruz. In 1911 the Spanish Urological Society was established presided over by Gonzales Bravo. The other founders of the Society were A. Pulido, L. de la Pena and P. Cifuentes.

May 16–18, 1911 was the date of the first congress of the Association of the Spanish Urological Society (Associacion Espanola de Urologia).

Reynaldo dos Santos was the first who, by all means had the greatest impact on urology in Portugal. He was born in 1880 and after graduation he worked together with F. J. C. Guyon (1831–1920), J. D. Albárran (1860–1912), Cathelin, M. Th. Tuffier (1837–1929) and Pinard (1844–1934) between 1903 an 1904 in Paris. In 1905 he visited the leading surgical centres of the USA and worked with Cabot in Boston, with Ochner in Chicago and with Keen in Philadelphia. Ravara was born in 1873 and he became the organizer of outpatient care in 1902 at the age of 29 and head of the first department of urology in Lisbon in 1929. The Portugese Association of Urologists was established in 1923 with Ravara as the president. He was concerned with the whole field of urology and was advocator of subcapsular nephrectomy, particularly in complicated cases of the right side. In 1936, Egas Moniz, the Nobel-prize winner in medicine in 1927, was honoured with the medal of the International Urological Society. He also applied his angiographic method for the abdominal aorta This led to the recognition of the significance of angiography performed by lumbar puncture in urological diagnostics and therapy as well as in other fields of surgery.

Reynold dos Santos retired in 1950 bequeathing a generation's experience to all fields of urology and surgery. It is notable that his son Joao Cid dos Santos, also an urologist, was one of the pioneers in vascular surgery.

At the beginning of the 20th century, S, P. Fedorov played an important role in the development of Russian urology. He was founder of modern urology in his country. He developed several types of operations (i.e. subcapsular, nephrectomy, transvesical prostatectomy, etc.), created new instruments (hilar forceps, etc.) In 1907 he founded the Russian Urological Society. A range of valuable innovations in urology was contributed by F. I. Sinitsin (castration in tumours of the prostate) by B. N. Kholtsov, A. V. Vishnevski, P. D. Solovov, R. M. Fronstein who developed operations of urethral strictures, by P. I. Tikhov, A. V. Martinov and S. R. Mirotvortsev who applied several methods of uretero-enteroanastomosis. From the first years of the Soviet rule, departments of urology were established in all larger towns and urological clinics were organized at the medical universities. Notable textbooks were published by S. P. Fedorov and B. N. Kholtsov. The journal 'Urology' appeared in 1925.

Prominent urological schools were established in Moscow (N. F. Lezhnev, A. P. Frunkin, A. J. Pitel, A. J. Abramyan), in Leningard (A. I. Vasilyev, A. M. Gasparyan), in Kiev (A. A. Tsayka) in Tbilisi (A. P. Tsulukidze) as also in other cities.

Three urological scientific research institutes were organized (in Moscow, Kiev, Tbilisi). The Urological Society with the presidency of N. A. Lopatkin from 1972, held 5 congresses and three conferences (1972, 1978, 1984).

Two journals of urology are published: the 'Urologia i Nefrologia', the 'Urologia i operativnaya nefrologya', a review paper is published in twelve thousand copies.

In Poland the first urological department was organized in Lwow in 1901 by Zenon Lenko (1868–1950), its head until 1927, who was the student of masters such as Marion, Rowsing, Israel and Kümmel. In 1905 an urological department was founded in Warsaw headed by Adam Mincer (1867–1914) who was educated together with Guyon at German and English clinics. The third urological department was founded in Cracow in 1916 headed by Tadeusz Pidarski (1878–1936) who was the first associate professor in the history of urology in Poland and he was student of the school of surgery of the Rowsing Clinic.

After World War II, urology in Poland has undergone rapid development. The first regular chair of urology was organized in Warsaw in 1947 headed by the first Polish professor of urology who was one of the founders of modern urology in Poland.

In 1950 he organized the chair of urology of the Medical Academy of Cracow. Emil Michalowski (1906–1978) succeeded him at the Cracow Chair. The latter was the author of the also currently used textbook of urology. The Urological Society was founded in 1949 by an eminent urologist of Warsaw, Waclaw Lilpop (1884–1949) who won recognition in the field of urology. The Urological Society was founded in 1949 by an eminent urologist of Warsaw, Waclaw Lilpop (1884–1949) who won recognition in the field of urology. The Urologists have their own journal the 'Polish Urology' which has been appearing for 39 years.

In Croatia, urology became independent in 1919. The head of the first department was Blaskovic. The first nephrectomy for tuberculous pyonephrosis was performed December 2, 1899 by Dragutin Schwarz and the first ureterocolostomy by Blaskovic in 1921. In 1905 litholapaxy was made in Sibenik. The third phase of development in the Croatian urology started in 1927-1928. This was the time when mention can be made of the first well-trained urologists. On 22nd October, 1927 the first lecture was read by Blaskovic in the subject of urology to students of the medical university. In 1928 the department of urology at the Hospital of Sisters of Charity in the Vinogradska street became a clinic headed by Blaskovic. This was the first independent urological chair in this part of Europe. At the time of World War II, an urological department was organized in Osijek and in Ryeka in 1947. In 1946 two departments were established in Zagreb at the military hospital and in the clinical centre in Rebron. Another urological department was opened in 1959 in Split. Nowadays. there are two urological clinics in Zagreb and three independent departments in other hospitals.

In Bulgaria the first urological department was established with the leadership of Tanev in 1936. In 1937 a series of urological papers were published by Vladimir Tomov. In 1951 a urological chair was founded headed by Anton Cherven in the postgraduate medical institute. Stojan Lambrev was the head of the urological clinic established at the medical university in 1962.

In 1972 a scientific institute for nephrology, urology, haemodialysis and renal transplantation (INUHT) was founded at the medical academy headed by Nikola Atanassov. The urological clinic at the military medical university was headed by Viktorov for several years and since 1983 it has been done by Todor Patrashka. Nikolao Minkov is the director of the first intensive care and paediatric clinic at the Pirogov University. Since 1983 he has been head of INUHT, while the chair of urology is headed by Christo Kumanov.

The surgeon, Jean Verhoogen, who had introduced prostatectomy and nephrectomy in Belgium, published the first case of total prostatectomy in March 1889. In 1909 he read his paper on total cystectomy at the International Congress in Budapest. The foundation of official urology is due to Albert Hogge. He lived and worked in Liège as a co-worker of Verhoogen. In 1912 he became the first professor at the department of urology in Belgium. Thanks to his ceaseless activity, the first urological institute of the University of Liège was opened on 29th June, 1920. In 1913 Leclerc Dandoy was appointed lecturer in pathology of the urinary tract in Brussels. In 1919 the first department of urology was established in the hospital in Brussels. Urology at the universities in Gand and Louvain developed parallel to that in Liège and Brussels.

In Liège, Charles Phillips had already been early interested in urology and he published a certain number of operative techniques with excellent illustrations in his 'Atlas on Medical-Surgical Knowledge'.

A type of probe has been named after him. The Chair of Urology in Gand was established in 1935 headed by Elaut. In Louvain the Chair of Urology was founded only in 1960. It was led by Jacques Brenev.

The most famous Danish urological surgeon was Th. Rowsin (1862–1927). Prior to him, only a few, such as Axel Iversen and Sylvester Saxtorph, were concerned with the surgery of the urinary tract. A Danish urologist Chr. Fenger (1840–1902) spent the majority of his active years in the USA. Up to his emigration at the age of 35, he made considerable contributions to Danish urology by his thesis on ureteroscopy and acute hydronephrosis. Fenger became later professor in Chicago, and he introduced antiseptic surgery in the USA. By his 60th birthday he had been recognized as the creator of modern surgery and urology. In up-to-date urology in Denmark, Harald Abrahamsen (1885–1955) is supposed to be the greatest personality. He was a versatile surgeon. He worked at the Department D of the Bispebjerg Hospital in Copenhagen. When he payed a vizit to the USA in 1933 he started to deal with urology as a special branch. He introduced several new therapeutic methods into Danish urological surgery.

He founded the 'Travelling (Moving) Club of Scandinavian Urologists' which held its first meeting in 1950 in Copenhagen, in 1950, in collaboration with other Scandinavian urologists. This club formed the backbone of the Scandinavain Urological Society established in Helsinki in 1956. The Danish Urological Society was founded in 1961 and maintained close connections with the Danish Surgial Society and with the other Scandinavian Urological societies. While in Norway some surgeons were particularly interested in urology in the first quarter of the 20th century, the first physician practising in this field was Stain Holst (1891–1955) who founded the urological department in a private (Catholic) hospital in Oslo in 1930 (Var Frue Hospital). His department was the only one quite up to the establishment of the urological unit of Rikshospitalet (Mathisen 1958) and of that of a separate department of the Ulleval Hospital in Oslo (Høeg 1964).

Up to these days, the majority of urological operations were performed by general surgeons in Norway. Urology as a recognized special branch of science was founded in 1947. In 1986 it had about 70 members. Of the urologists, Mathisen introduced several internationally acknowledged new techniques, such as ureterosigmoid anastomosis (1953). Haemodialysis was also introduced by him in his country (1956).

The Finnish Urological Society was established in 1954. Already previously, the majority of professors in general surgery were concerned with urology. For example, Ali Krogium (1864–1939) wrote a useful book 'Surgical Interventions in Urology' and Richard Faltin his thesis on 'Escherischia coli Infections in the Human Organism'. In November 11, 1954 the Finnish Urological Society was set up by four urologists (Oravisto, Pitkanen, Pohjola and Kaunisto) lead by Pauli Tuovinen, the first full professor of urology in whose sauna in Finland the Scandinavian Urological Society was formed in 1956. In 1976 this society which had initially been a travelling club, was reorganized. From this time onwards, its first president has become Olaf Alfthan. The first independent urological department was opened in 1965 in Meilahti at the Central Hospital of Helsinki. Currently, urological training is carried on in Finland at five hospitals.

Jean Hamburger, the internist of Paris (b. 1910) should not be left out of list. He has brought clinical nephrology into being. Like several masters of this field, also this French physician was endowed with artistic gifts, he wrote several books on philosophy and medical history.

It was not long before the first renal transplantation was made (1956) which had already been performed in successful animal experiments by Alexis Carrel (1873–1944), successful animal experiments by Alexis Carrel (1873–1944), another French physician in 1912.

Attempts were made already prior to World War II, to detoxicate the blood of renal patients transperitoneally. It was at that time when the Dutch Willem Kolff (b. 1911) started to construct the first artificial kidney. The professionally supervised ingenious construction of the first manufactured artificial kidney was marketed in the FRG in 1952. An early specimen of these kinds of machines was the so-called Kolff–Watschinger kidney with which human blood was purified extracorporeally. It can be found at the German Hospital Museum in Oldenburg.

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Subsequently, urology rapidly developed in to an essential, autonomous branch of clinical medicine at the German university clinics. The first urological clinic in Aachen at the then still municipal Elisabeth Clinic in the Goethestrasse was founded in 1948 by Carl Heusch (b. 1896) educated in Berlin. Before World War II he laid the foundation-stone of a urological department at the Westend Hospital in Berlin in 1935. In 1950 the first urological chair was organized at the Homburg University of Saarland which was headed by Carl Erich Alken educated in France. Very soon, urological departments were set up in denominational hospitals, as e.g. the St. Antony Hospital in Eschweiler (1968).

The installation of complex equipment by which since 1980 the renal and urinary calculi of 70% of the patients have been crushed by extracorporeal shock wave, has started a new phase in the history of urology. This ingenious medicotechnical invention was made by Egbert Schmied (b. 1902), an urologist in Munich and by his collaborators at the clinic in Grosshadern.

It should not be left unsaid that Alexis Carrel (1873–1944) born in Lyon, opened the era of renovascular surgery by presenting vascular anastomosis, as also that since 1906 he had been known as a pioneer in experimental renal transplantation. (After 1906 he emigrated and worked at the Rockefeller Institute). He anvisaged the role of the lymphocytes and cytotoxic corpuscles of the bone marrow in rejecting the kidney as well as the beneficial effect of radiotherapy on the life-span of the transplanted organ.

Géza Antal, the first head of department of urology in the Rókus Hospital authored the first urological textbook on the 'Surgical Pathology and Therapy of Urinary Tract Diseases'.

In Hungary, the profession found a worthy representative in the person of Professor Géza Illyés (1870–1951) who was founder of the eminent Hungarian school. This great personality of Hungarian urology built the rising reputation of his famous clinic at his small department occupying only the second floor of Rókus Hospital. It was transformed into a center of urology at the middle of the 80s of the last century by Géza Antal. The clinic moved after long years to the Outer Clinical Block of the University of Budapest in 1936.

Géza Illés was born 24 May, 1870, at Marosvásárhely. He wanted to be a clinical and therefore he concentrated on his pathophysiological and pathological studies.

He graduated in 1893, and started to deal with patients at the clinic of Károly Kétly (1839–1927), professor of medicine. After one-and-a-half years, he joined the 1st Department of Surgery of Gyula Dollinger (1849–1937), professor of surgery, where, beside the traditional surgical cases, also traumatological and orthopaedic ones were treated at an up-to-date level. It was then he focussed his attention on urological diagnostics. He took an active part in the development and research of urological diagnostics. In 1899 he published in Orvosi Hetilap (Medical Journal) his 'The State of the Art of Cystoscopy in Surgery'.

The scientific observation of Sándor Korányi (1866–1944) on renal function was put into the practice of urological surgery by Géza Illyés (e.g. the decrease in the freezing point of urine obtained separately from the kidneys).

In May 1900, he already introduced ureteral catheter provided with a 1.5 mm thick silver wire up to the pelvis and he took roentgenograms of it. Then on 13th April 1901, he presented his results at the regular session of the Royal Medical Association in Budapest. He was the first to raise the idea that the renal cavity system can be visualized by bismuth subnitrate suspension through the ureteral catheter. The idea was highly appreciated by Narrath. The substance irritating less the renal pelvis and providing a discernible picture was found by F. Völcker (1872–1955) and A. Lichtenberg (1800–1928) in 1905. Illyés introduced for studying the overall renal function the concentration and dilution test which is in use also today.

He wrote his work on the 'Surgical Ailments of the Genitourinary Organs' the first summarizing booklet of modern urology in 1902–1904. In 1905 he reported on the 'Surgical Treatment of Internal Renal Diseases'.

He dealt with the problem of prostatectomy then, in connection with the surgical solution of hypernephroma, he described the modification of costolumbar incision, the so-called Illyés auxiliary incision.

In 1914 he was assigned a department of 102 beds at the Rókus Hospital and was appointed professor extraordinary at the University Medical School.

On 25th January, 1920, Géza Illyés became full professor at the department of urology at the Rókus Hospital.

Outstanding experts were educated under him including Antal Adler-Rácz, Jenő Borza, Jenő Dózsa, Gyula Minder and Béla Melly.

He wrote his book of 'Urology' of 450 pages in 1930–1931 (he wrote 96 papers) which is invaluable both as a textbook and as a guide for practising physicians.

The topics of urological education and postgraduate training can be well followed in the journal 'Orvosképzés' (Medical Training) up to 1911–1938. During this time summarizing papers appeared written by the great masters and thier students which were presented at postgraduate courses.

Géza Illyés was fighting for long years to have urology recognized as a subject of medical curriculum equivalent to other branches of science.

A decision on the new urological clinic reached in the summer of 1935, which opened at the Outer Clinical Block with 116 beds. Meanwhile Géza Illyés became Corresponding Member of the Hungarian Academy of Sciences.

In Hungary postgraduate specialist training was regulated by an Act in 1924 by the Minister of Welfare and Labour of that time. In this period it was possible to obtain qualifications in 18 branches of science. Among them, urology figured under the heading 'urinary and genital disorders'.

The Act contains provisions as to the setting up of a National Postgraduate Specialist Training Examination Committee.

Antal Babics, the director of the clinic in Budapest had a great share in providing specialist training. He followed in his master's step in applying organ-preserving, tissue-saving procedures. By recognizing the importance of the lymph circulation of the kidney, he has become not only the initiator in Hungary of research into lymph circulation but his observations haven aroused attention all over the world and resulted in a change in approach in the treatment of diseases associated with renal occlusion.

In 1936/37 he went to a visit to Berlin. After his return he soon became the first most important man of his boss. Géza Illyés had envisaged him as his successor already in 1941, however, he became professor only in 1946 and headed the department until 1974.

Another outstanding personality of the period after Illyés was Aurél Noszkay, who started working beside professor Béla Rihmer.

His up-to-date approach to the clinico-pathological assessment and therapy of urogenital tumours was of prime importance for the urology in Hungary in developing regional urological out-patient care and organizing the social worker system and preventive care.

In 1918 he worked already as a medical student at János Hospital. In 1923 he obtained a medical degree then in 1926 an operating surgeon's certificate. At that time the chief physician of the department was professor Rihmer, whose outstanding activity he used to speak about often with great appreciation. He was invited as an assistant to participate in the operations of professor Géza Illyés, his greatly respected professor. Owing to his thorough grounding and comprehensive knowledge, he was appointed head of Department of Urological Surgery at the János Hospital, which he remained for 30 years. He retired in 1973 and died in 1986.

The extension of urological specialist training had become necessary already in the periods between the two world wars, because urology did not exist in the country towns outside the urological clinic of Budapest known all over Europe and some other departments of urology in the capital, not even in the university towns. Urological departments were established, of the country towns, first in 1942 at Szombathely and Kassa. After the liberation the progress in public health and the demands for urology accelerated the development of this field, too. The Urological Clinic at the Pécs University Medical School was founded within the frame works of the 1st Department of Surgery of that times and became independent in 1953. This was followed by the setting up of urological departments in counties Békés, Csongrád, Hajdu-Bihar and Tolna up to 1955, in County Győr-Sopron in 1961, in Veszprém in 1967 and also of additional ones. In 1974 the Department of Urology of the Debrecen University Medical School was opened and the Szeged University Clinic was organized in 1984. At present, urological departments are operating in each county. Regional patient care is provided by urological polyclinics. The Department of Urology of the Postgraduate Medical School functions within the frameworks of the University. It deals with university and postgraduate training.

In compiling the history of urology in Europe I got tremendous help from outstanding urologist colleagues who provided data and who have made me acquainted with the history of urology of their countries.

Grateful acknowledgement is made herewith for their invaluable assistance.

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Herausbildung und Entwicklung der europäischen Urologie

P. MAGASI

Die Arbeit bietet einen Überblick über die Herausbildung der europäischen Urologie vom Altertum bis zu unserer Zeit; die Grundlage der Zusammenstellung bildeten die Daten nahmhafter europäischer Urologen. Im Laufe der Beschreibung der historischen Entwicklung wird versucht die sich chronologisch zur gleichen Zeit abgespielten Ereignisse darzustellen. Auf die besonders wichtigen Geschehnisse wird von Zeit zu Zeit zurückgewiesen. Die bedeutenderen Ereignisse, die Geschichte des Blasensteinschnitts und der Blasensteinzertrümmerung sowie die Entwicklung einzelner urologischen Schulen finden eine ausführliche Besprechung. Ein Anspruch auf Vollständigkeit konnte nicht erhoben werden, da ja die Erkündung der historischen Daten keine einfache Aufgabe war. Am Ende der Mitteilung spricht der Verfasser allen Mitarbeitern, die ihm in der Zusammenstellung der Daten behiflich waren, seinen herzlichen Dank aus.

Возникнование и развитие европейской урологии

п. магаши

Пользуясь данными отличных европейских урологов, автор постарался сделат обзор развития европейской урологии с древних веков до наших дней. Идя по следам истории, он попробовал проследить за событиями, произошедшими в разных странах в одно и то же время. Иногда он возращается к особо важным событиям. Эначительным явгяется более подробный анализ истории исслечения и литотрипсии камней мочевого пузыря. Не менее важным он считает возникновение отдельных урологических школ. Автор не стремится дать исчерпывающую информацию, ведь получение исторических данных было сложной задачей. В конце статьи автор благодарит всех, кто помог ему в получении и составлении данных.

Results on Postcoital and Penetration Test

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Since adequate transcervical passage of sperm is indispensable to the natural fertilization, the sperm-cervical mucus studies provide a new possibility for investigating the marriages infertile due to unknown causes. The behaviour of sperm in the cervical mucus is also important from the point of view of selecting the mode of insemination. Consequently, the comparative evaluation of postcoital, slide penetration and capillary tests were made by the authors.

It is well known that if on examination of a couple desiring children, the andrologist diagnoses normozoospermia, while the gynaecologist does a normal ovulation with patent Fallopian tubes and a hormonal state without any particular alterations, the classical fertility examinations are over. If, however, no pregnancy occurs the couple can be categorized as 'infertile due to unclarified causes' and it becomes evident for the physician that he cannot establish a diagnosis in the traditional way. It becomes neccessary to make a further step in order to clarify the cause of infertility in these cases. A possible way of this is the observation of the behaviour of the sperm in cervical mucus.

The passage of sperm through the cervical canal (penetration) is influenced partly by the motility parametes of the cells and partly by the properties of the cervical mucus. There are several types of sperm-penetration test (postcoital test, slide and capillary penetration tests). By them not only penetration can be studied but sufficient information can be gained concerning the immunoandrological status of the couple examined, since it is well known that cervical mucus contains immunoglobulins and its antisperm antobodies reduce the chance of fertilization.

This could account for the fact that study of the immunological aspects of male infertility and the demonstration of anti-sperm antibodies from cervical mucus [9] or serum by various aimed examinations (1, 2, 6, 7, 8, 9, 13) has become one of the important new trends in andrology.

The value of the examinations used is different. In assessing this, our clinical results were compared with those of the postcoital 'in vivo' test and the simple slide penetration and of Kremer's capillary penetration test (5, 10).

Material and Method

1. Postcoital test (PCT). It is a simple in vivo test for judging the movement and survival of sperm in the cervical mucus. Here, the number and motility of sperms in the cervical mucus obtained postcoitally are observed. The test was indicated in our cases in normozoospermia of subfertile patients (but of a sperm count over 15 millions being, however, non-asthenozoospermic), because the still lower parameters have already previously pointed out the cause of infertility. Table 1 summarizes the 'personal conditions' of the test and the information necessary to perform it technically.

TABLE 1

Postcoital test

Personal conditions

Husband 1. Normozoospermia or a sperm count over 15 million/ml

2. Normal morphological genital status

Ovulation, patent tubes, local inflammationfree state

Technical conditions

- 1. Intercourse after two days of abstinence with the woman in the recumbent position
- 2. The examination is carried out 2 hours after intercourse
- 3. Collection of cervical smear by a tuberculin syringe
- 4. Positive test, with 5 motile sperms per visual field

2. Penetration tests. Here, the ability of the sperm to pass through the cervical mucus is tested. In the Miller-Kurzok test the penetration wedge measured simply on a slide which is formed by the sperms in the mucus smeared. In the Kremer test enabling a more subtle differentiation, the distance covered by the sperms, or the number of motile sperms at a given point of the capillary are evaluated in a closed capillary system under the microscope. In Table 2 the technical devices and the amount of materials necessary to perform the tests are listed. The accurate assessment of the slide penetration test is facilitated by a slide with a millimetre calibration. In the capillary penetration test, proper evaluation is possible only with capillaries of a constantly identical internal diameter (Fig. 1). There are various forms and variations of this test, we performed only the homologous one (10, 11, 13). The capillary test was evaluated by a scoring system. We applied the scoring system proposed by Kremer and accepted also by WHO based on the linear penetration density of the sperm. It is shown in Table 3.

Wife

TABLE 2

Penetration tests

- 1. Slide penetration test (Miller-Kurzok test)
 - a. Slide, 1 drop of mucus, 1 drop of ejaculate
 - b. Examination of penetration wedge (SPIKE)
 - c. Evaluation: 1 cm excellent, 0.5-1 cm weak, no penetration
- 2. Capillary penetration test (Kremer test, sperm penetration meter-SPM test)
 - 1. Homologous (wife) heterologous (standard or normal cervical mucus)
 - a. 50 μl ejaculate, wife's cervical mucus, wife's serum, AB serum
 - b. Sperm penetration meter De Hroot, Harmelen
 - c. Microslide capillary tube constant diameter:
 1 mm (flat for the mucus and cylindrical for the serum) Vitro Dynamics Inc., USA
 - d. Automatic micropipette
 - e. Evaluation: Kremer score (WHO)

In view of this, cases of good, poor and no penetration could be differentiated by thes coring system.

It is to be noted that by the extensive use of penetration tests, new fields of application have been found. Treating the inflammatory diseases by cryocauterization, Gimes et al. measured the effectivity of therapy by the changes of penetration values. We apply the Kremer test as a close system – strictly under the same conditions – for assessing the changes of sperm movement due to chemical substances (3, 12).



FIG. 1

Parameters examined			Scores			
	Score	0	1	2	3	
Linear penetration (cm)		0	0-2	2-5	5	
Penetration density (1 t)		0	1-10	11–5 0	50	
Motility in the upper third of the						
capillary		0	1	2	3	
0 = no p 1 = 25% 2 = 25-50 3 = over	me roceeding proceedin 0% proceed 50% proc	motion ag motion eding motion ceeding r	n otion notion			
	E	valuation	ı			
Sco	ores					
9		excellen	t			
6–9		good				
3-6		poor				
0-3		bad				

 TABLE 3

 Scoring system of the penetration tests

TABLE 4

No. of cases	49		
Positive		30	61.2%
Poor		12	24.4%
Negative		7	14.3%
Total		49	100%
	Slide penetration	test	(M-K test)
No. of cases	49		
Excellent		13	26.5%
Poor		12	24.4%
No penetra	ation	24	48.8%
	Kremer capillary	test	
No. of cases	49		
Excellent		30	61.2%
Poor		13	26.5%
No penetra	ation	6	12.2%
Total		49	100%

Results on postcoital and penetration tests

Results and Conclusions

The results obtained by postcoital and penetration tests are summarized in Table 4. In the postcoital test in 30 of 49 cases positive results were obtained, 12 were poor and 7 negative. During the Kremer test, in 30 cases excellent or good passage was observed, there was none in 6 cases and it was poor in 12 cases.

The agreements in the PCT and Kremer test are so striking that the latter is worth performing in case of poor or negative PCT, the amount of information provided by it, exceeds that of any other tests. The conclusions are summarized in Table 5.

TABLE 5

Conclusions

- 1. Sperm and cervical mucus interactions mean a possible trend of improving the traditional andrological diagnostics.
- 2. The methods applied proved to be useful for assessing sperm motility in the cervical mucus.
- 3. The agreements between PCT and the penetration test are of an extent that they allow a characteristically individual evulation determining the possible site of insemination, too.
- 4. The chronology to be adopted is PCT-penetration test (only in case of poor or negative tests).
- 5. The slide penetration test is in itself not suitable for obtaining the information of a similar quality.

Discussion

It is well known that, concerning fertilization, cervical mucus is one of the most important filtering system of the human organism. The penetration of the sperm through this substance is influenced by several factors. The quality of mucus changes as a result of hormonal disfunction or of the inflammatory processes of the cervix. They may render fertilization impossible even in the case of normozoospermia. According to the classical definition of Kremer 'Good sperm movement in the spermatic plasm does not necessarily imply a good sperm movement in the cervical mucus.' The penetration tests are used for clarifying the causes of infertility in the cervix, too. To detect them, Kremer's capillary penetration test described by him in 1965 is the most suitable and of the best prognostic value (10, 15). The changes of penetration can be increased by increasing the number of sperms (concentration procedures, centrifugation, deepfreeze) and partly by improving the quality of mucus (hormonal treatment, stopping of inflammations) [2, 4]. Currently, the sperm-cervical mucus interactions are complementary andrological examinations prescribed by WHO, their technical performance is regulated by specifications [14]. Their proper performance and precise assessment mean an effective help in recognizing a group of fertility disorders due to unknown causes.

Acknowledgements

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Ergebnisse mit den postkoitalen und Penetrations-Testen

GY. PAPP und R. VAJDA

Zur herkömmlichen Empfängnis ist die transzervikale Spermapenetration von guter Qualität unerläßlich; demzufolge bieten die Spermium-Zervixschleim-Untersuchungen eine neue Möglichkeit zur Durchuntersuchung der unfruchtbaren Ehen, in denen die Ursache der Unfruchtbarkeit ungeklärt ist. Das Verhalten des Spermiums im Zervixschleim ist auch vom Standpunkt der Auswahl der Art und Weise der Insemination von Wichtigkeit. Diesen Ursachen zufolge wurden die im klinischen Material ermittelten postkoitalen, Plattenpenetrations- und kapillären Teste miteinander verglichen und ausgewertet.

Наши результаты с посткоитальными и пенетрационными тестами

ДЬ. ПАПП и Р. ВАЙДА

Поскольку для традиционного оплодотворения необходима пенетрация через шейку матки спермиев хорошего качества, исследования спермиев и шейки матки означают новую возможность для выяснения причин при бесплодных браках. Поведение спермиев внутри маточной шейки важно также и с точки зрения выбора метода инсеминации. По вышеизложенным причинам, авторы производят сравнительную оценку посткоитального, пластинчато-пенетрационного и капиллярного тестов, выполненных на их клиническом материале.

Effect of Operations on Lymphocyte Glucocorticoid Receptors

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The changes in the glucocorticoid receptor count of lymphocytes was studied in diseases requiring various surgical treatments. Based on their studies, authors established that the number of receptors increased in most cases after operation. The increase in receptor count depends on operative stress. As a result, the stimulated receptor count increased to double or triple that of the normal value, decreasing then to normal during the postoperative phase. The change in receptor count can be used in assessing the reactivity of the organism and prognosis.

Following surgical interventions, lymphocytes are of decisive importance in the cellular and immune response of the organism, while glucocorticoids in its neurohumoral reaction [3, 4, 5].

The immunosuppressive effect of operations has been a matter of controversy for a long time. The same is the situation concerning the use of anaesthetics. Immunosuppressive effect was observed postoperatively by some authors [6, 7], while this phenomenon was not demonstrated by others [8, 9, 10].

For measuring operative stress reactions, the determination of the catecholamine [11], cortisol [5] and glucose levels [12] is most often used. Several trials were made for assessing a complex immune response including the best known lymphocyte count [13], blast transformation [14], migration tests, the cutaneous reaction [15] and the determination of the immunoglobulin level [16].

According to more recent observations, the glucocorticoid receptor level assessment of the circulating lymphocytes is of prognostic importance. The change in the number of receptors plays an important role in assessing the function of these cells.

Their number increases in response to immune stimulation, while it is reduced in immunosuppression [2, 17]. The above data serve as a starting point to studying the effect of operative stress on the number of glucocorticoid receptors.

Material and Method

Twenty-eight patients were examined. The patients' age ranged between 30 and 65 years, with a mean age of 45. Six patients were operated for inguinal hernia, 12 for cholelithiasis and 10 for gastrointestinal tumour (in each case, a histologically verified adenocarcinoma). The inguinal hernia was operated in local anaesthesia, while the other operations were performed in intratracheal anaesthesia according to the same method. Blood samples were collected first preoperatively, then one day and, in part of the cases, seven days after the operation.

The lymphocytes were isolated according to Boyum [22] from heparinized blood by centrifugation of the Ficoll-uromiro concentration gradient. The separated lymphocytes were placed in Hanks' solution in a concentration of $0.8-5 \times 10^7$ lymphocytes per ml. The receptors were measured in a cellular system according to the modified method of Kerepesi and Arányi [23]. The separated lymphocytes were incubated at 37 °C for 40 min in the presence of 3 H triamcinolone in a saturated concentrate. Then the steroid unbound to the cell was washed out from the system. Incubation was repeated also in the presence of the 100fold surplus of unlabelled triamcinolone acetonide for establishing the aspecific binding. The cell-bound radioactivity was also measured. The difference between the radioactivity values in the absence and presence of unlabelled triamcinolone acetonide was accepted as the specific binding and the number of receptors per cells was calculated from it. Statistical analysis was made by the Student *t*-test.

Results

In most of the cases, the lymphocyte count was normal preoperatively. In patients with malignant tumour or in inoperable changes it decreased. In response to operations it decreased. Our results are presented in Tables 1 and 2.

The number of glucocorticoid receptors of the lymhocytes ranged in most cases between 3200 and 3800 receptor per cell. In operable gastrointestinal tumour patients an elevated mean value of 4104 ± 583 was obtained. In inoperable changes, there was a significant decrease of 1346 ± 326 . In some cases no estimable receptors were found in patients in a very poor general condition.

There was a significant increase in the number of receptors in response to operation (i.e. from 3200 ± 252 to 5477 ± 1027 , P < 0.01) in the patients operated for inguinal hernia. In cholecystecomy, this increase was more explicit (i.e. from 3877 ± 1049 to 9481 ± 3171 , P < 0.01). Repeating the measuring one week after cholecystecomy, an average value approaching the preoperative value (i.e. 3378 ± 861) was obtained. Following operations for gastrointestinal tumour, the receptor count increased significantly in the operable cases (from 4104 ± 583 to 6846 ± 1523 , P < 0.01). At the same time, in the operable cases, the invention was associated with the decrease in the number of receptors (from 1346 ± 326 to 869 ± 301 , P < 0.05).

TABLE	1
	-

Change in lymphocyte glucocorticoid receptor count after hernioplasty and cholecystectomy

	Inguinal he	Inguinal hernia $(n = 6)$		Cholelithiasis $(n = 12)$		
Diagnosis	preo perative	postoperative	preopertaive	postoperative	7 days postoperatively	
Glucocorticoid receptor receptor/cell	3206 ± 525	$5477 \pm 1027*$	3877 ± 1049	9481 ± 3171	33 78±816	
Leucocyte count cell/mm ³	5800 ± 696	7100 ± 109	$7200\!\pm\!2069$	10717 ± 1508	6533 ± 1072	
Lymphocyte count cell/mm ³	2004 ± 430	$1642 {\pm} 269$	$2275\!\pm\!860$	1648± 39 8	2150 ± 222	

*P < 0.01

TABLE 2

Effect of operations on the glucocorticoid receptor count in gastrointestinal tumours

	Gastrointestinal	tumour $(n = 10)$	
OI	perable	Inoperable	
preoperative	postoperative	preoperative	postoperative
4104 ± 583	$6846 \pm 1523*$	1346 ± 326	869± 3 01**
6558 ± 527	12317 ± 1745	5105 ± 427	7025 ± 450
2487 ± 302	2053 ± 186	1640 ± 112	986 ± 177
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*P < 0.01; ** P < 0.05

Discussion

Changes due to operative stress belong to the reactions of the organism. Based on the results of the investigations made so far, it was established that after surgical interventions there is an increase in the glucocorticoid, catecholamine, blood glucose and free fatty acid levels, with a decrease in the insulin level.

Observations on the majority of cellular and humoral reactions are mainly aimed at lymphocytes. Clinical and experimental studies were carried out with in vitro and in vivo methods. Several questions have remained unclarified and the results are sometimes contradictory. The glucocorticoid receptor count of the circulating lymphocytes increased significantly after the operations. These changes in values were equally noted in local and general anaesthesia. Our further investigations have verified that the postoperatively increased receptor count returned to the preoperative value within a week.

In operable tumours, the number of receptors increased significantly after operations, however in the inoperable cases, there was rather a decrease. It is noteworthy that in gastrointestinal tumours the preoperative values were significantly lower in the inoperable than in the operable cases. The mechanism of this phenomenon is unknown. It can be assumed that the change in receptor count is related to cell division or the reactivity of the organism.

The receptor count can be used in assessing the reactivity of the organism and the prognosis of the disease. The reproduction in animal experiments of these investigations is in progress. Our data obtained so far seem to confirm the results gained in humans. By these investigations we would like to provide data on the changes in the glucocorticoid receptors of lymphocytes in patients with the above disease, which can play an important role in judging the function of these cells as well as the reactivity of the organism.

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Über die Wirkung der Operationen auf die Lymphozyten-Glykokortikoidrezeptoren

A. KRASZNAI, P. KRAJCSI, P. ARÁNYI und I. HORVÁTH

Im Laufe der Untersuchung der Gestaltung der Zahl der Rezeptoren der Glykokortikoide der Lymphozyten in verschiedenen, eine chirurgische Behandlung beanspruchenden Krankheitsbildern, wurde festgestellt, daß sich die Rezeptionzahl nach den Eingriffen in der Mehrzahl der Fälle signifikant erhöhte. Der Anstieg der Rezeptorenzahl ist die Funktion der Grundkrankheit und der operativen Belastung. Unter Wirkung des Operationsstresses hat sich die stimulierte Rezeptorenzahl auf das zwei- dreifache des Normalwertes erhöht sodann, in der postoperativen Phase normalisiert. Die Gestaltung der Rezeptorenzahl bietet eine Hilfe zur Beurteilung der Reaktionsfähigkeit des Organismus sowie der Prognose der Krankheit.

Влияние операций на глюкокортикоидные рецепторы лимфоцитов

А. КРАСНАИ, П. КРАЙЧИ, П. АРАНИ и И. ХОРВАТ

Авторы изучали динамику изменений числа глюкокортикоидных рецепторов лимфоцитов при различных патологиях, требующих хирургического вмешательства. Результаты исследования показали, что после операций число рецепторов в большинстве случаев достоверно увеличилось. Увеличение числа рецепторов зависит от основного заболевания и операционной нагрузки. Число рецепторов, стимулированных под влиянием операционного стресса, увеличивается в два — три раза по сравнению с нормальным значением, затем, в постоперативном периоде, нормализуется. Динамика изменения числа рецепторов может быть использоване для оценки реактивности организма, а также прогноза заболевания.



Segmental Spinal Instrumentation in the Early Fixation of the Fracture-dislocations of the Dorsal and Lumbar Spine (S.S.1)

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A total of 24 patients were admitted to the Department of Neurosurgery and Traumatology between April 1, 1985 and March 31, 1987 for fracture-dislocation of the dorsal and lumbar spine. Review of the observation of the patients is given from their hospitalization to the surgical indication. The patients with unstable spinal fracture were operated independent of their neurological status. The operative technique which contains in fixing the spine according to the operative technique elaborated by Edwardo Luque is reviewed in detail. The advantage of their method is that bent Steinmann rods are used for fixation of the spine. A detailed review of the postoperative treatment and the complications is given.

The dislocation-fractures of the dorsal and lumbar spine are complex injuries that may be associated with severe injuries of the spinal cord or cauda equina. Most fractures are unstable and call for urgent operative or conservative treatment.

There has been a controversy concerning the early management of dislocated, unstable fractures for 150 years. The present paper was aimed at the assessment of the results of decompression laminectomy and simultaneous operative fixation as regards the improvement of the patients and the duration of hospital treatment.

Patients and Operative Method

From April 1, 1985 to March 31, 1987 a total of 24 patients were admitted to the Departments of Neurosurgery and Traumatology of the Al-Thawra Hospital in Sana'a. The injured patients were examined by a traumatologist and neurosurgeon right after their admittance, and they were classified on the basis of the clinical and neurological status as well as the X-ray study. All patients with an unstable spinal fracture were operated independent of their neurological status. Following decompression laminectomy, surgical fixation involving at least 5 or 6 segments was performed in each case. The operative finding was mostly as follows: a torn intervertebral disk or one with pulsion,



FIG. 1a. X-ray picture of L-Sspine, AP-L2 fracture. b. L-S spine, lateral-L2 fracture

bone fragments, dislocated minor joint, destroyed dura and roots, as well as their compression by the dislocated vertebral bodies.

The segmental fixation of the vertebrae from a posterior incision was performed initially in neuromuscular scoliosis or in some cases in dorsal and lumbar vertebral fractures.

We applied a stainless steel double rod with an L-shaped bend at one end and wires introduced for fixation extradurally and sublaminarly according to Luque's method.

Stages of the Operation

1. Postoperative exposure

2. Dissection of the soft parts, decompression laminectomy

3. Introduction of a sublominar extradural wire below and above the injury involving at least 2 segments each

4. Facetectomy

5. Fixation of the double L-rod with the wires introduced into the extradural space

6. In some cases, implanation of spongy bone grafts from the iliac crest

The advantages of our vertebral fixation involving at least 5–6 segments and performed from a posterior exposure set against those of the Harrington method, the Merique–William plate, the Weiss' spring and the screwing of the vertebral arch can be as follows:

1. A stable, rigid fixation at a segment of the spine exposed to the greatest mechanical strain which is capable of warding-off and dividing the elevating power impilses manifesting at several points.

2. There is no need of a postoperative fixation by a plaster jacket or corset. Surgical fixation enables early mobilization. The time of hospital care can be considerably reduced. Bedsores can be prevented as well as other complications associated with a prolonged bed-rest. These issues are of particular importance in the regions where there is no possibility for the organized care of patients with spinal injuries.

The more important data (age, sex, course and date of injury, hospital admittance and operation, the level of injury and neurological status) of patients treated by us were summarized in Table 1.

Results

Reposition of the fracture

The appropriate statics of the spine could be restored in all patients. The preoperative kyphosis ceased, and no considerable deformity resulted in any of the cases even after a 6-month out-patient follow-up.



FIG. 2a. X-ray picture of L-S spine, $Ap-L_1$ fracture. b. L-S spine, lateral-L₁ fracture

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TABLE 1 24 patients were admitted to the Al-Thawra Hospital, Sana'a (April 1, 1985—March 31, 1987)

Neurological status

Three of our patients were operated without pre- or postoperative pathological neurological change. Mild preoperative paraparesis without incontinence was found in two patients. They gradually improved further after the operation. In ten cases the preoperative paraplegia did not change even after the operation. A patient with paraplegia before the operation started to move voluntarily both lower estremities five days after laminectomy and surgical fixation. Some months postoperatively, seven patients improved gradually, their sensory disturbance decreased and they could actively move both of their lower extremities. The incontinence of one patient normalized within three months.

Mobilization

Mobilization by walking or by using a wheel-chair could follow in each case within two weeks.

Duration og hospital care

The longest hospital care lasted for four months, while in the rest of the cases for an essentially shorter time. Five patients could be disharged two weeks postoperatively.



Fig. 3. Transection of the ligamentum flavum-opening of the extradural $\mathop{\mathrm{space}}$



FIG. 4. Passing wire through the extradural space



FIG. 5. Facetectomy

Complications

Infection. Wound suppuration in the operative region was found in one patient, two weeks after excision, his state returned to normal.

Metal substance. The slipping of the fixing rod occurred three weeks postoperatively due to the loosening of the sublaminar wire when the patient had already been able to move by wheel-chair. In one case loosening of the rod was found one year postoperatively. It was therefore removed.

Medical. One patient was lost due to pulmonary embolism, three weeks after operation although he was rehabilitated in a wheel-chair.

Discussion

Surgical solution for the early rehabilitation in dorsal and lumbar dislocation fractures has come into the foreground in the recent 20 years, although this is not followed, in the majority of cases, by a noteworthy improvement in the neurological status [5, 6.]

The paraplegic patient cannot expect neurological improvement by the surgical fixation itself. It depends on decompression, independent of whether it had been made from an anterior or posterior exposure. Recently, decompression has been regarded as being more successful if made from the anterior exposure [9], however the roots can be released much favourably from a posterior one [2, 3, 7].

Flesch et al. [5] proved an essential improvement, in certain cases, in the functions of cauda equina and the medullary cone.

Jacob observed the earlier and more marked regeneration of the cauda equina and the nerve roots in patients subjected tosurgical fixation [7, 8].

According to E. Shannon's opinion, the early operation of paraplegic patients by open reposition and fixation enabled the potential neurological regeneration and helps effectively prevent comsication due to a prolonged hospital care [12]

In patients with cauda equina injury, improvement in the neurological state was observed merely by the stabilizing operation without decompression. On the contrary, there are several reports on the late complications induced by bone fragments and slipped disk [1, 4] associated with stabilizing operation twihout decompression.

The main argument against posterior decompression is the increasing instability and further potential neurological impairment. However, the immediate stabilization after decompression may create more favourable conditions for neurological regeneration even in the case of a cauda equina injury [9, 10, 11].

The hardly more than one-year follow-up is still insufficient for drawing precise conclusions as to the late results. We believe, however, that the method used may be suitable for offering further expectations to our injured patients categorized as the so-called 'hopeless ones' and by this we can provide them with more than just an approach confining them for good to wheel-chair.

According to Sir Robert Jones, the orthopaedist's aim is the restoration of function. The operation itself means only the beginning of therapy and whatever brillian it may be, its value is attached to the functions regained.

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Chirurgische Behandlung der Luxationsfrakturen der dorsalen und lumbalen Wirbelsäule

E. R. DE LUNA, M. KORDÁS und Z. RISKÓ

Zwischen dem 1. 4. 1985 und dem 31. 3. 1987 wurden wegen der Luxationsfraktur der dorsalen und lumbalen Wirbelsäule auf die neurochirurgische und traumatologische Abteilung des Krankenhauses 24 Patienten aufgenommen. Beschrieben wird die Öbservation der Patienten von der Einlieferung bis zur Entscheidung der Operationsindikation. Die, eine instabile Wirbelsäulenfraktur erlittenen Patienten wurden, unabhängig vom neurologischen Zustand operiert. Im Laufe der Eingriffe wurde die Wirbelsäule, der von Edwardo Luque entwickelten Operationstechnik entsprechend fixiert. Als vorteilhaft erwies sich die Anwendung gebogener Steinmann-Stäbe zur Fixierung der Wirbelsäule. Abschließend finden die postoperative Behandlung und die Komplikationen eine ausführliche Besprechung.

Хирургическое лечение переломков с вывихом спинного и поясничного отделов посвоночника

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В период между I опреля 1985 г. и 31 мартом 1987 г., авторы приняли в нейрохирургическое и травматологическое отделения больницы 24 больных по поводу травмы с вывихом спинного и поясничного отделов позвоночника. Они знакомят с наблюдениями за больными, начиная с момента поступления до решения относительно показания к операции. Больные с нестабильным переломом позвоночника были прооперированы, независимо от их невропатологического статуса. Подробно описывают оперативную технику, суть которой заключается в том, что позвоночник фиксируется в соответствии хирургической техникой, разработанной Эдуордо Луке. Достоинством метода является то, что для фиксации позвоночника авторы пользовались согнутыми стержнями Штейнмана. В статье подробно описываются послеоперационное лечение и осложнения.



The Method of Early Postoperative Alimentation by Needle-catheter Jejunostomy

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It is well established that the nutritional state greatly influences tolerance during the operation. Authors present a new procedure for the early postoperative enteral alimentation having not been used in Hungary so far. Twelve hours after operation, a pump-operated, gradually increasing amount of oligopeptide foodpreparation and concentrate is introduced continuously into the second jejunal loop intraoperatively. Using this method, a caloric intake of 9572 kJ can be achieved already from the fourth postoperative day onwards. Based on our experience gained from 32 patients, the method can be recommended for an up-to-date postoperative enteral alimentation.

The therapeutic success in each branch of surgery is decisively defined, in addition to the nature of the disease to be operated and the skills of the surgeon, also by the actual tolerance of the patient. The patient's tolerance and thereby the risk of the operation is markedly influenced by the patient's nutritional state [7]. Albert reported already at the end of the last century on the use of catheter jejunostomy for postoperative alimentation [1]. However the spread of the method has been limited by the fact that the theory of early postoperative atony affecting the entire gastrointestinal tract had formerly been generally accepted. So, from the middle of the 60s, parenteral alimentation was almost exclusively given preference in postoperative alimentation therapy [9]. In recent years, however, the consistent results of the experimental and clinical studies of various authors have verified that after laparotomy, postoperative atony primarily affects the stomach and the colon [10]. At the same time, the motility and absorbing capacity of the small intestine is almost undisturbed a couple of hours after operation [5]. This entirely new observation has opened up new vistas for postoperative enteral alimentation, in so far as it does not involve the stomach.

The method of needle-catheter jejunostomy was described by Delany in 1973 [4]. At our clinic the procedure modified by Heberer in 1983 is used [6]. For introducing the food preparation the Jejunokath-kit (Pfrimmer and Co., Erlangen) is applied. First, the polyurethane catheter, 1.5 mm in diameter, is introduced by a puncturing needly through the abdominal wall into the abdominal cavity. The optimal size of introduction is the mid-third of the line connecting the navel with the left costal arch. Subsequently, a submucous channel is made in the antimesenterial intestinal wall by a catheter-guide (Figs 1a-d). The importance of the submucous antireflux channel lies in that it prevents, after removal of the catheter, the formation of a fistula. Finally, the intestinal loop is fixed by 2-3 stitches to the peritoneum. The small silicon plate preventing the catheter from slipping is fixed with two stitches to the abdominal wall. The silicon-caoutchouc connection at the end of the catheter



FIG. 1a-d. Various phases of applying needle catheter jejunostomy



FIG. 2. Scheme of enteral alimentation

ensures communication with the disposable Nutriset (Pfrimmer and Co., Erlangen) sac containing the food-preparation. The continuous 24-hour introduction of the food-preparation is secured by easy-to-manage, small, portable enteral pump, Nutromat (Pfrimmer and Co., Erlangen). For a foodpreparation, a chemically defined lactose-free oligopeptide diet is employed (Peptisorb, Pfrimmer and Co., Erlangen). A food-preparate of a caloric value of 4187 kJ contains 45 g protein, primarily oligopeptide, 14 g fat, decisively a medium-carbon-chain, as well as 175 g carbohydrate, mostly oligo- and polysaccharide.

Alimentation is started on the first postoperative day after controlling filling with a contrast medium the site of the catheter. By gradually increasing the volume introduced, the building up of alimentation lasts up to the fourth postoperative day. Then already a caloric intake of 9572 kJ can be achieved with a daily amount of 2400 ml (100 ml/h) food-preparation. The energy introduced can be further increased by increasing the concentration of the food-preparate. In the phase of adaptation no peripheral complementary parenteral feeding is employed (Fig. 2).

This form of alimentation was used in 32 patients having undergone major surgery at the 1st Department of Surgery between 01, 02, 85 and 31, 12, 85 (Table 1). The effectiveness of the method was proved by the absence

TABLE 1

Distribution of patients fed enterally

Pancreatic resection-chronic inflammation	9
-tumour	6
Oesophageal resection	9
Gastrectomy	5
Oncotomy, necrectomy (acute pancreatitis)	3
Total	32



FIG. 3. Change in body weight during postoperative enteral alimentation after operation



FIG. 4. Change in postoperative total serum protein level during enteral alimentation after the operation



FIG. 5. Change in postoperative N equilibrium during enteral feeding after the operation

of postoperative weight loss experienced almost always after the similar major operations in the previous cases, by the rapid elevation of the total protein level and by the positivity of the N balance following the fourth and fifth postoperative days (Figs 3, 4, 5) [2]. The majority of the complications could be controlled by an adequate intervention. Alimentation had to be

TABLE 2

Distribution of the complications of postoperative enteral alimentation

	Feeding	
	Total	Interruption
Diarrhoea	10	1
Distension	3	1
Hyperglycaemia	8	0
Technical causes	2	0

TABLE 3

Indications for alimentation by needle-catheter jejunostomy

Oesophageal operations Gastrectomy Pancreatic resections Pancreatic cyst operations Liver resections and transplantations Expectable postoperative complications

TABLE 4

Contraindication for alimentation by needle-catheter jejunostomy

Crohn's disease Peritonitis Ascites Radiation enteritis Ileus due to adhesions

TABLE 5

Advantages of enteral feeding

Less expensive Involves less risk Simpler Imposes less strain More physiological Prevention of intestinal atrophy Gastrointestinal bleeding occurs less frequently More adaptable to permanent feeding

interrupted only in two cases because of uncontrollable diarrhoea and distension (Table 2).

According to our experience, early postoperative enteral feeding is useful when postoperative care is expected to exceed 5 days and when, beside the restitution of peroral feeding, complementary artificial feeding cannot be dispensed with (Table 3). Naturally, the procedure can also be contraindicated. These are summarized in Table 4.

The literature on the comparison of parenteral and enteral alimentation lists several advantages of enteral feeding over the parenteral one (Table 5). All this considered, enteral alimentation by early postoperative needlecatheter jejunostomy can be recommended with the indications outlined above being an adaptable method for meeting the postoperative energy requirement.

Acknowledgement

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Postoperative Frühernährung durch den jejunostomischen Nadelkatheter

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Die Literaturdaten haben es eindeutig bewiesen, daß durch den Ernährungszustand der Patienten ihre operative Tragfähigkeit in bedeutendem Maße beeinflußt wird. In der Arbeit wird eine neue, in unserem Land bisher nocht nicht angewandte, zur postoperativen enteralen Frühernährung dienende Methode dargestellt. Durch einen, in die zweite Jejunumschlinge intraoperativ eingeführten Kacheter werden dem Patienten kontinuierlich, mit einer Nährmittelpumpe gesteuert oligopeptide Nährmittel in stufenweise ansteigenden Mengen und Konzentrationen zugeführt. Mit dieser Methode können bereits vom 4. postoperativen Tag an 9572 kJ Energien dargeboten werden. Die Methode hat sich, wie darauf die in 32 Fällen ermittelten Erfahrungen hinweisen, zur zeitgemäßen postoperativen enteralen Ernährung als geeignet erwiesen, so daß ihre Anwendung empfehlenswert ist.

Метод раннего постоперативного энтерального питания с помощью игольчатого катетера

дь. Бокоди и л. харшани

Литературные данные однозначно доказывают, что состояние упитанности больных в большой степени влияет на перенесение ими операционной нагрузки. Авторы представляют новый, не применявшийся до сих в Венгрии, способ энтерального питания в ранний послеоперационный период. Во время операции, во вторую петлю тощей кишки вводится катетер, через который, начиная с 12-го послеоперационного часа, вводят в больного олигопептидный питательный раствор, количество и густота которого постепенно повышаются. Раствор вводится непрерывно, с помощью насоса. С помощью этого метода, уже начиная с 4-го постоперативного дня, больной может получать 9572 К J энергии. На основании полученного опыта (32 больных), авторы считают, что этот метод может быть рекомендован для современного постоперативного энтерального питания.

Use of Laser Knife in Thoracic Surgery

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 $\rm CO_2$ laser knife was applied in 18 thoracic operations. The laser knife can be used for the sterile and ablastic cutting of skin, soft parts, ribs, sternum, bronchi and lung parenchyma. By its use intraoperative bleeding is substantially diminished.

The formulation of the theoretical principles of laser is attached to the names of Townes, Schawlow, Basow and Prokhorov (cit. Jakó [3]). They were awared the Nobel prize for this work in 1964. Laser was first used in medical practice by Jakó, Tigyi and Pollányi [3] in Boston in 1964. The first surgical laser which was a CO_2 laser, was constructed by Tamás Pollányi.

Severall kinds of laser devices were developed such as ruby-, Nd-glass, Nd-YAG, He-Ne, Cd-, CO_2 , nitrogen-, gallium, aluminium-arsenic-, dye-, etc. lasers.

The laser beam is monochromatic with a large spatial and temporal coherence, and power ful radiation. The almost parallel laser beam enabled its focussing at close range with a minimum loss to be performed. Thus the so-called 'laser-light knife' can be produced which renders it an excellent device for different operations.

In endoscopic surgical practice first Nd-YAG lasers developed by Kiefhaber, Nath and Hofstetter (cit. Jakó [3]) in Germany, have extensively been used. The wavelength of the Nd-YAG laser is 1.064 μ m. The Nd-YAG and CO₂ lasers are both employed in surgical practice [5, 6, 10].

Material and Method

We have been working with the type RT TLS_{61} CO₂ laser (TUNGSRAM) since 1986. The power of the equipment is 60 watts. The well-sweep like manipulating arm of the equipment is easily and freely movable in all directions. It can be focussed on the site of the operation after its isolation by an appropriate sterile sac (Fig. 1). Through the sterilizable tube-like end-piece which can be gasped like a pencil, the laser beam can be focussed on the site of the operation. The shutter can be released by a pedal.

The CO_2 laser light is invisible. Focussing of the guide light is ensured by a He-Ne-laser built into the equipment which produces a well-visible violet light. The power of the guide light is altogether 1 mW, i.e. it does not damage tissues but only serves for focussing.

This equipment was used in performing a total of 50 operations during a period of 4 months in the fields of thoracic, gastroenterological, general



FIG. 1. Surgical application of TLS₆₁ TUNGSRAM CO, laser

and dermatological surgery. The majority of laser operations were thoracic, i.e. a total of 18 interventions. During the operations tissues were severed by a laser light knife or only some partial tasks were performed, such as the transection of ribs, bronchi and lung parenchyma.

Data of our 9 patients, in whom lung surgery was made by a laser knife, are presented in Table 1. Operations were made for lung tumour, tuberculoma and lung cyst. The laser knife was applied for the severing or dissection of bronchi, main bronchus, lung parenchyma and for that of the interlobar space.

The bronchus or the main bronchus were always transected after a preliminary suturing by a stapler. Lung parenchyma was cut after previous suturing by a stapler or without it.

Table 2 shows the patients who were operated on in the thoracic wall, trachea or mediastinum by a laser knife. Skin, adipose tissue, muscle, fascia, rib, pleura and sternum were transected in the chest wall. The laser knife is also suitable for the sterile cutting of bones.

 TABLE 1

 Use of laser knife in thoracic surgery. Operations of the lung

No.	Name	Age (yrs)	Diagnosis	Operation	Use of laser
1.	Cs. Z	24	Left pulmonary tumour (thymus metastasis)	Wedge resection of the left lung	Cutting of lung parenchyma
2.	Cs. G.	8	Left pulmonary tumour (sarcoma)	Left upper lobectomy	Dissection of interlobar space
3.	В. Е.	14	Right pulmonary tumour (chondroma)	Tumour excision	Cutting of lung parenchyma (without suturing by stapler)
4.	V. J.	72	Left pulmonary tumour (cc)	Wedge resection of the left lung	Cutting of lung parenchyma
5.	Gy. J.	63	Right pulmonary tumour (cc)	Bilobectomy + wedge resection	Cutting of lung parenchyma
6.	K. Gy.	63	Right pulmonary tumour (cc)	Right upper lobectomy	Cutting of lobar bronchus
7.	P. A.	15	Left pulmonary cyst	Wedge resection of the left lung	Cutting of lung parenchyma
8.	L. Zs.	64	Left pulmonary tuberculoma	Wedge resection of the left lung	Cutting of lung parenchyma
9.	Р. В.	14	Left pulmonary tumour	Biopsy, thoracotomy	Cutting of tumour, thoracic wall

TABLE 2

Use of laser knife in thoracic surgery. Operations of the thoracic wall, trachea and mediastinum

No.	Name	Age (yrs)	Diagnosis	Operation	Use of laser
1.	S. I.	51	M. Raynaud	Thoracal sympathectomy	Thoracotomy, evaporation of the sympathetic nerve
2.	Z. G.	39	TOS	Right costal resection	Axillary exposure
3.	М. В.	14	Costal tumour (chondroma)	Partial costal resection	Thoracotomy, rib resection
4.	Sz. A.	14	Costal tumour (cartilaginous exostosis)	Partial costal resection	Thoracotomy, rib resection
5.	к. і.	31	Sternal and costal osteomyelitis	Partial resection of 7th and 9th ribs and of sternum	Sternum resection, rib resection
6.	H. S.	33	Mediastinal tumour	Biopsy	Excision from tumour
7.	к. і.	25	Empyema necessitatis	Partial resection of 4th, 5th ribs	Rib resection, sterilization with defocussed beam of empyema cavity
8.	Cs. J.	46	Left pulmonary tumour (cc)	Pulmonectomy	Resection of left main bronchus
9.	К. Е.	14	Oesophagotracheal fistula	Tracheotomy	Cutting of trachea and cervical soft parts

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Results

The laser knife has proved to be useful in our thoracic surgical practice. There is less bleeding on severing than on dissection by a sharp instrument and the bones do not bleed at all. The operator has to devote less attention to haemostasis. Only vessels of a diameter over 0.5 mm bleed. This bleeding is arrested by ligation, electrocatuerization or by a defocussed laser knife.

Cutting is sterile, bacteria and tumour cells are destroyed in the line of incision. Wound suppuration was not observed following thoracotomy by a laser light knife.

The bronchi and the lung parenchyma can be well severed by laser knife. On cutting of lung parenchyma, without suturing by a stapler, only major vessels are liable to bleeding but not parenchyma.

Opening of a bronchus, secondary bleeding and pulmonary collapse were not observed after operations performed by laser knife. As a result of its use, the alveoli, minor bronchioli and vessels are closed. The bronchial tissues are not necrotized along the incision line (Fig. 2). There is no risk of loosening of stotches or sutures inserted into the bronchus.

Also the sternum and the ribs can readily be resected by laser knife.

A defocussed laser knife can be used with the benefit of arresting oozing bleeding after adhesiolysis of the thoracic wall.

The skin cut by laser knife heals adequately (Fig. 3).

Discussion

The literature on the surgical use of lasers is fairly extensive [11, 12, 13, 14, 15, 16]. A total of one million laser operations per year are performed in the USA. In the USSR one thousand surgical lasers are in use.

In Hungary, the use of laser in medicine has been introduced by Mester [7, 8, 9]. His first report was published in 1966 [7].

In our clinic, a total of 50 operations and treatments have been made so far. The number of thoracic interventions has been 18.

The basis of the biological and surgical use of the laser light of a wavelength of 10.6 μ m is that it is absorbed rapidly at a depth of about 0.2 mm in water as also in tissue of a large water content. Consequently, the water content of the tissues boils, and the affected cells explode as pressure is built up and part of the cells are burnt. Temperature does not exceed 100 °C in the focus and no rise in temperature can be observed at a distance of 2 mm from the incision. In the surrounding of the focus a 1 or 2 mm wide crater is formed surrounded by a narrow 50–150 μ m wide coagulation-necrotic zone.

The question may arise why laser knife is better than the tradition methods. Ribs and the sternum have formerly been resected by scissors and


FIG. 2. Histological section from the adjacent region of the resection line from a main bronchus severed by a laser knife. The chondrocytes are destroyed and there is no evidence of an extensive necrosis



Fig. 3. Healing of the wound of thoracic symphatectomy after thoracotomy with a laser knife

saw. The soft parts can be cut well with little bleeding by electric knife. Bronch can be transected by scalpel, etc.

Based on our experience, the benefits of the laser knife can be summarized as follows:

The laser light knife is the first universal cutting device for severing skin, soft parts, bone, bronchus and lung parenchyma, etc. The electric knife is an excellent device, but skin, bone and bronchi cannot be transected with it. For cutting skin, also currently a scalpel is usually applied, which may be a means of introducing infection. The subcutaneous tissue is liable to bleed which can be arrested by electrocauterization. This sometimes may give rise to a circumscribed skin necrosis. The transection of bronchi is made by a scalpel, this method being, however, non-sterile and non-ablastic. The laser knife is suitable for cutting bronchi and lung parenchyma.

It is extensively used in the USA for removing multiple lung metastases. We have had no experience in this respect.

Transection of the sternum and ribs is usually performed by scissors, electric saw, or other sharp metal instruments. This method may be associated with bleeding, fragmentation and infection. Cardiac surgeons sometimes observe sternum osteomyelitis, with occasional necrosis which is considered as a severe complication. Based on our experience and the data in the literature, it seems that this complication can be considerably reduced or even eliminated by the use of a laser knife.

A research group in the USA [14] proved that, following tumour removal by a laser knife, there were less local recurrences than after the use of a sharp instrument or electrocautery. These results require further experimental and clinical support but they can have far-reaching implications concerning future practice.

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Über die Anwendung des Lasermessers in der Thoraxchirurgie

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Das CO₂-Laser-Lichtmesser fand bei 18 Thoraxeingriffen eine Anwendung. Das Lasermesser eignet sich zum sterilen und ablastischen Schneiden der Haut, der Weichteile, der Rippen, des Sternums, der Bronchien und des Lungenparenchyms. Vorteilhaft erweist sich ferner, daß die intraoperative Blutung geringer ist.

Применение лазерного ножа в хирургии грудной клетки

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При 18 операциях на грудной клетке авторы применили СО2-лазерный световой нож. Лазерный нож пригоден для разрезания кожи, мягких тканей, ребер, грудины, легочной паренхимы стерильным и абластическим образом. Кровотечение во время операций бывает слабым.

Surgical Solution of Femoral Fibrosarcoma. Experience Obtained by a 9-year Follow-up

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Biopsy followed by tumour removal and replacement by autologous bone tumour at the distal end of the femur were performed. Histologically, the tumour proved to be benign. Three years later progression was observed and epiphyseodiaphyseal resection was made because of on excessive tumour. Histology revealed a fibrosarcoma. Consolidation was hindered by osteomyelitis and fracture, recovery could be achieved only by a series of operations. These histological and operative difficulties are documented and the importance of extremity-saving operations is discussed. Our patient has been free of complaints 9 years after epiphyseodiaphyseal reseaction.

The primary fibrosarcoma of the bone belongs to the less frequent bon^e tumours. It occurred in 10 out of the 215 primary bone tumours removed a^t the National Institute of Rheumatology and Balneotherapy between 1956 and 1980 (incidence rate 4.7%) [1]. In the material of the Mayo Clinic 3.3% of overall tumours was fibrosarcoma [6]. Fibrosarcoma occurs in each age and in both sexes with almost the same frequency. In half of the cases it is localized at the distal metaphysis or epiphysis of the femur or at the proximal end of the tibia. Rarely it can be multifocal. The clinical symptoms, such as pain, swelling or an occasionally palpable hyperplasia, are not characteristic.

Radiologically, an inhomogeneous bone destruction is visible without reformation of bone and calcification.

Histology reveals spindle-shaped tumour cells corresponding to fibroblasts and fibrocytes. The stroma is composed of collangenous fibres. The highly differentiated forms are characterized by an almost complete absence of atypia, while in the un-differentiated forms polymorphia, polychromia and several mitotic phases are seen.

Case-Review

P. Gy., a 30-year old male patient was admitted to the Department of Radiology and Radiotherapy of the National Institute for Oncology for pain in the left knee joint having persisted for some months. Based on the examinations performed there, suspicion of neoplasm was raised (Figs 1 and 2). He was therefore transferred for biopsy to the Department of Orthopaedics Surgery of the Korányi National Institute for Tuberculosis and Pulmonology on 8th July 1974. The result of histology of the biopsy material was as follows: Microscopically, a fibrous connective tissue could be recognized with granulation foci. The granulation was composed of histiocytes, macrophages and of a giant cell containing several nuclei. Tissue changes indicative of tumour could be found. Histologically, the change corresponded to a reactive granulation (Dr. E. Vincze). The tumorous part was removed one week after the biopsy. At operation a fibrous tumour tissue was found excavating the bone surface focolly and detachable from the bone. Being removed, it was coagulated with diathermy then the lateral condyle was replaced by autologous bone taken from the crista and fixed with a screw (Figs 3 and 4).

Histology. Tissue specimens excised from several places were studied microscopically. The histological picture was structurally the same everywhere, i.e. a connective tissue of a considerable matrix, rich in collagenous fibres and of a moderate cell density. In some places the matrix was fairly abundant. The cells corresponded to fibroblasts. The nuclei were in general of the same size with some larger less compact nuclei at some places. The chromatin content was also moderate. In view of these findings the cells appeared to be well-differentiated fibroblasts. The change was fairly extensive, with no evidence of reactive inflammatory phenomena beside it. In the hyperplastic region, however, in several places there were diapedetic, haemorrhagic and pigment-containing regions. Pigment was found mostly extracellularly. However, some multinuclear but also well-differentiated fibroblasts appeared around the pigmented regions. The stroma did not produce either cartilaginous or osseous tissue. Some spongy bone trabeculae could be observed in the fibrous connective tissue with loosened and considerably disintegrated bone tissue and calcium absorption at some places. No osteoblastic activity could be observed around the bone trabeculae. The border of the pathological and intact tissue could not be defined precisely with adipose tissue recognizable in some places beside the fibrous connective tissue.

No evidence of malignancy could be demonstrated either on the basis of cell structure or on that of tissue structure. Cellular packing density was rather low.

The size of the change and the process destroying the cortical bony substance and almost occupying the distal epiphysis of femur mars raise the suspicion of the malignant nature of the alteration, however, the tissue structure did not show any evidence of malignancy despite the extremsive destruction. Consequently, it was not considered to be an ossifying fibroma, but the possibility of a well-differentiated central fibrosarcoma could also be contemplated. For the latter no decisive proofs were found not even after studying a number of sections. Diagnosis: Non-ossifying fibroma (Dr. E. Vincze) (Fig. 5).



FIGS 1-2. X-rays taken in 1974 serving as bases for biopsy followed by on extended operation



FIGS 3-4. Replacement and fixation of the lateral condyle Acta Chirurgica Hungarica 30, 1989

Postoperatively, the patient received grid irradiation of 4×3000 r at the National Institute of Oncology.

In December 1974, the screw was removed. The autograft had been incorporated, there was no tumour recurrence. Subsequently, the patient was free of complaints for two and a half years.

In May 1977, during his control at the Department of Orthopaedics of the National Institute of Rheumatology and Balneotherapy, X-rays revealed



FIG. 5. Surgical material from 1974. Tumour tissure rich in cells and poor in fibres. The tumour cells are immature, monomorphous, they correspond to fibroblasts. Mitotic forms occur only sporadically. H&E, 40×6.3

progression (Fig. 6). The patient felt no pain, there were no norphological or functional changes. Since in view of the advanced high-dose irradiation, further irradiation therapy was not recommended, on 29 April 1977, reoperation was made (epiphyseodiaphyseal resection: EDR). Once being convinced that the structures of the popliteal fossa could be isolated although with some difficulty, the distal 23 cm part of the femur was resected. The frozen sections of the biopsy specimen taken from the resection line (surrouding the soft parts, periosteum, the 'soft tissue' corresponding to the medullary space of the bone) did not reveal any tumour. The tibia was halved and the lateral half was elevated like an inlay at a length of 20 cm for replacing the femur then osteosynthesis was performed by using bolts and malleolar screws. Subsequently, the missing portions were replaced by preserved bone trabeculae (National Institute for Traumatology). Nailing was performed by using a special Küntscher nail (Fig. 7). After operation a pelvi-extremital plaster of Paris was applied. The histological result of the complete operative material was a well-

differentiated fibrosarcoma (Fig. 8). Postoperatively, the patient received a walker with a pelvic basket and a tuberal support in which he could be exposed to load.

In June 1978 he was readmitted for pain in the malleolar region. Since his X-rays disclosed the slipping of the Küntscher nail, it was pulled back by 3 cm. Subsequently, he had a permanent purulent discharge from the opening of the



FIG. 6. May 1977. Recurrence can be observed, block dissection is planned

fistula for about three years. In December 1978, exploration, removal of the nail, cleansing of the focus and plaster fixing were made, for the three fistular openining having not responded to conservative treament. In May 1979, cleansing of the focus was repeated and an aimed antibiotic treatment was administered. The process did not, however, normalize. Therefore the Küntscher nail was removed in October 1979 and a pelvi-extremital plaster was applied.

The X-rays taken on changing the plaster following removal of the Küntscher nail showed fracture. Then osteosynthesis by metal splint was performed (Figs 9 and 10). However, due to instability then, too, a suppurating



FIG. 7. Picture after epiphyseodiaphyseal resection



FIG. 8. Histological picture of the surgical specimen obtainde in 1977. Cell-poor, tumour tissue conspicuously rich in fibres, the tumour cells partly correspond to fibrocytes. Beside them, several polymorphous, polychrome and mitotic forms are visible. The histological picture corresponds to a differentiated fibrosarcoma, H & E, 40×6.3



FIGS 9-10. Fracture and osteosynthesis by plates

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fistular opening remained. In April 1981, after cleansing, an autologous bone grafting was made. During operation the loosening of nails was observed.

In July 1981, reoperation was decided upon for non-controllable osteomyelitis having persisted for three years and requiring permanent local treatment. The metal substances were completely removed. External pin fixation was applied under a TV amplifier which secured a fairly good stability (Figs 11, 12 and 13). The foci were cleansed and an open therapy was started. In November 1981, after healing of his osteomyelitis and with no evidence of suppuration an autologous spongiosa plasty was made in a reoperation. On operation the bone was found to be surprisingly strong and thickened. The roentgenogram taken in April 1983 revealed complete consolidation. Then the pin fixation was removed.

Discussion

Reviewing our case is considered important from several aspects. Paretly for our conscious attempts at an extremity-saving operation.

Concerning the treatment of the semimalignant and malignant tumours of the extremities, the question often arises whether amputation is necessary or by resecting the extremity, then restoring its continuity, it can be saved altogether. [5]. The presented case was a relatively benign slowly progrediating fibrosarcoma.

The view of D'Aubigné [9] in the question of indication is that a resection can be indicated if after excochleation of the tumour there is a recurrence. In his opinion, the survival rate after resections approximates that of amputations. The patient's life expectations are improving after operation, therefore maintenance of function is of an increasing importance in deciding the tasks during operation [14].

In the first case, the plastic reconstruction was proposed by Juvara [8]. This technique was modified by Merle D'Aubigné [9]. In our case, this modified procedure was applied.

The operative results of EDR in 12 cases were reported by Riskó et al. [13] In 1961 Riskó [12] already reported on 50 cases of bone tumour of which 11 were of extremital localization.

The technical questions and the experience obtained is reported by several authors [2, 3, 4, 5, 8, 9, 10, 11, 12].

In the present paper we have not aimed at comparing and criticising the various surgical solutions. It should, however, be noted that amputation coulc have led earlier and without a series of operations appearing to be heroic efforts in retrospection, to a satisfying solution, however, our patient was resolutely against the idea of amputation. As a result of the extremity-saving operation, although because of a 4 cm shortening, he wears orthopeadic shoes, he can walk without any appliance (Figs 15 and 16).



FIGS 11-12. The picture of external pin fixation



FIG. 13. The external pin fixation fixes the very weak bone



FIG. 14. Picture of the consolidated femoral segment (1983)



FIGS 15-16. X-rays of the formerly operated, healed extremity of the patient

The case is also rendered interesting by the fact that diagnosis could be established only on the basis of the complete resection material, although the suspicion of malignancy was raised already on partial removal. Particular importance is attached to our case by the elected, relatively rarely performed operation, the EDT. The incorporation of the graft taking a longer time during which an appropriate fixation is required is a decisive question concerning recovery. In the present case, the development of osteomyelitis delayed recovery, since until the infection could not be eliminated, bony consolidaton could not occur. Refracture indicated the weak point of healing; the junctions between the graffed and own bones and between the distal end of the femur. Initially, facilities for an external fixation were not available. Finally, however, the problem was solved by fixing it in a completely extrafocal resting position. The multiple autologous bone grafting promoted recovery.

The use of a long forgotten device which seems to have currently its revival has markedly contributed to recovery. Finally, it should be pointed out that a precondition of successful curing of the patient is the close cooperation between the oncologist, histologist and orthopaedic surgeon.

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Chirurgische Lösung des Femur Fibrosarkoms. Erfahrungen anhand 9jähriger Follow-up-Untersuchung eines Falles

Z. SZABÓ, T. RISKÓ, I. UDVARHELYI, G. JAKAB, L. KOVÁCS und M. BÉLY

Erläutert wird die chirurgische Lösung eines am distalen Femurende sitzenden Fibrosarkoms. 9 Jahre nach dem Auftritt der Veränderung ist Patient beschwerdefrei. Es werden die Operationsserie dokumentiert, die diagnostischen Schwierigkeiten dargestellt, die ermittelten Erfahrungen besprochen sowie die Bedeutung der extremitätenerhaltenden Eingriffe betont.

Оперативное разрешение фибросаркомы бедренной кости — в связи с 9 летним наблюдением одного случая

З. САБО, Т. РИШКО, И. УДВАРХЕИ, Г. ЯКАБ, Л. КОВАЧ и М. БЕЙ

Авторы описывают случай хирургического разрешения фибросаркомы, расположенной на дистальном конце бедренной кости. Спустя девять лет после появления опухоли у больного нет жалоб. Авторы документируют серию операций, указывают на диагностические трудности, знакомят с собственным опытом лечения этого заболевания. Они подчеркивают значение значение операций, сохраняющих конечность.

Book Reviews

George H. A. Clowe, jr.: Trauma, Sepsis and Shock in the series 'Science and Practice of Surgery', Marcel Dekker Inc., pp. 587, with 49 black-and-white drawings, 129 figures and 79 table, \$ US 150.

In the introduction of the book the term shock, which has been the result of a mistranslation and is so firmly rooted in medical usage, is discussed. The expression 'choc' in the study on bullet wounds of the French le Dran published in 1743 was mistakenly used by the unknown translator for characterizing the severe state, the circulatory failure due to bullet wounds, although it had been used by the author in its original sense for expressing a kick or blow.

The book consists of four parts and 18 chapters on some aspectes of the currently substantial body of scientific knowledge concerning the management of patients in a state of traumatic or infectious shock. The dynamic balance between the cellular lesions of various origin and the protective responses is discussed. The physiological, biochemical and immunological implications of processes resulting in the preservation of life and healing are dealt with drawing useful therapeutic conclusions from the scientific results.

Of the chapters so well constructed both in their contents as well as proportionally, Chapter 3 on the macroscopic and ultrastructural appearance of traumatic and inflammatory cellular lesions and Chapter 11 on the practical aspects of the combined insufficiency of several organ systems are to be pointed out. In the highly didactically written Chapter 18, including also short case studies, the monitoring and practical aspects of treatment of the patients are discussed. A separate chapter is devoted to the theoretical and practical aspects of antibiotic therapy.

It is to the credit of the editor and the coautorhs that they impart practical advice well utilizable in the everyday medical routine in addition to presenting the most up-to-date scientific research results relying on the conclusions to be drawn from them.

The book has been primarily intended for candidate specialists and specialists, mostly for those who are concerned with the management of the patient in traumatic or septic shock.

M. Ihász

K. Pape: Knochen- und Knorpeltransplantationen im Kiefer-, Gesichts- und Schädelbereich. Johann Ambrosius Barth, Leipzig 1983, pp. 244 with 132 figures and 6 tables, DDM 74.

The regularly appearing volumes of ACMF (Acta Chirurgie Maxillo-Facialis) always treat some actual and well-circumscribed field of head surgery. They include the papers of the congresses organized by the Internationale Gesellschaft für Kiefer-Gesichts-Chirurgie concerned with a definite topic.

In the sixth volume of the series published in 1983 the possibilities of bone and cartilage transplantation performed in the faciomaxillary region are discussed. The book was edited by Prof. Klaus Pape (Cottbus), the individual chapters were written by the most prominent experts from several countries. Accordingly, in the majority, German, but in some parts also English and Russian, texts are presented. The book is addressed to surgeons, but it does not êither lack the theoretical bases indispensable to physicians concerned with bone transplantation. In the first two chapters the specificities of the physiological functions of bones and the immunological reactions following their transplantation are reviewed. Following the theoretical part, the up-to-date bone and cartilage to germ-free state and 'biological value' of the material to be implanted. The additional chapters include operative technical descriptions related to the removal and the way of application of the transplant. The site and mode of removal of the cartilage and bone are also illustrated, besides detailed description, by perceptive figures. The reader can learn, besides the up-to-date possibilities of transplant removal, also about the mode of their reconstruction. Articular transplantations are discussed by a separate chapter and the results are evaluated by histological studies.

In the subsequent part of the book, precise methodological descriptions follow on the replacement of the body and cartilaginous defects of the head. The reconstructive operations of the anatomical regions including the mandibles, the skull, the nose, the orbit and the auricle are analysed in detail by the authors. Among the operative-technical descriptions the up-to date methods of the reconstructive surgery of congenital abnormalities can be found. A special case of articular and bone transplantation is when the transplantation is performed for promoting the fixability of removable dental prostheses. The procedures used for this purpose are summarized by a separate chapter. The text is throughout illustrated by numerous figures, roentgenograms and photos, with a list of references and glossary at the end of each chapter.

Gy. Szabó

Harry Warnke: Chirurgie der koronaren Herzkrankheiten (Surgery of Coronary Diseases). J. A. Barth Verlag, Leipzig 1983, pp. 244, DDM 69.

The book edited by Prof. H. Warnke contains the chapter on the surgical implications of coronory heart diseases written by physicians of the Humboldt University of Berlin, the well-famed Charité (such as H. Warnke, K. Lindenau, and R. A. Parsi, cardiologists and J. Kunz, pathologist).

Several chapters in books and monographs have appeared on this important subject. The epidemiology of coronary heart diseases have still made it necessary for several authors to publish the possibilities of surgical therapy and their results achieved in two decades. It particularly refers to those who, as the students of the recently deceased Prof. Porstmann, have pioneered in the invasive diagnostics of the heart and its vessels, and in the particular building at that where the first heart catheterization was performed 55 years ago.

The book is divided into six chapters on the anatomy of the coronary system (30 pages), the pathology of coronary heart diseases (30 pages), the hacmodynamics of coronary circulation (15 pages), on the clinical aspects of ischaemic heart diseases, with particular regard to pre- and postoperative diagnostics (50 pages), the invasive radiomorphological and haemodynamic diagnostics of ischaemic heart diseases (50 pages) and, finally, on the surgical procedures (88 pages). The above chapters are followed by extensive but not redundant lists of references. The references from the world literature may guarantee that the authors' views are in concert with international experience. Although the 3000 coronarographies and the 248 aortocoronary bypasses presented do lag behind the American figures of several ten thousands (data published in 1978), this does not at all mean that the conclusions drown, the indications, the guidelines to be followed, the operative résults and the quality of the laborated material would be worse or of less value.

A large number of figures and well-constructed tables enable this not too voluminous book of 294 pages to contain everything what is currently to be known about coronary heart diseases and theirs surgical management. The layout and editorial work of the book are of high standard. It can be easily consulated and its simple structure and reasonable price make it desirable to be studied by as many GPs and cardiologists as possible. It will be a source of preparation for cardiologists and would-be specialists in cardiac surgery and one of repetition for the graduates.

Z. Szabó

Gerhard Horman and Winifred Hutschenreiter: Herz- und Gefässchirurgie. Grundlagen und Praxis. Part IV. Gefässe. Johann Ambrosius Barth, Leipzig 1983, DDM 140.

'Vascular Surgery' published as the fourth part of the series of 'Heart and Vascular Surgery' produced by the prominent publishers in Leipzig in 1983 has promised for a long time to come to be the most popular handbook of the diagnosis and management of

vascular diseases. The main chapters include surgery of the arteries, surgery of the veins, lung embolism, vascular dysplasias and vascular tumours as well as lymph vessel surgery.

For illustration it contains 151 excellent drawings and roentgenograms and a list of 375 references.

The didactic structure of the book is ideal. Its typography makes it easy to handle. It provides ample stage classifications and clear and well-formulated operative indications. The most voluminous part the 'Surgery of the Arteries' deals with injuries, chronic arterial stenoses and occlusions, acute arterial occlusions, the aneurysms, arteriovenous fistulas (including also haemodialytic shunts) as well as with congenital arterial anomalies. Each chapter is of a similar structure starting from generalities going through symptomatology up to surgical treatment and indicidual specificities. In the chapter on 'Surgery of the Veins', venous injuries, varicosity, very extensively thrombophlebitis and phlebothrombosis, the post-thrombotic syndrome and the insufficiency of perforating veins as well as erural ulcer are discussed. The subchapter on the chronic lymphoedema of the extremities is an invaluable part of the chapter on 'Lymph Vessel Surgery'. The cahpters are built up according to the easy-to-use decimal system.

Repeated mention should be made of the lucid and beautiful drawings of Gerd Ohnesorge.

The publishing in Hungary of an illustrated vascular surgery of such scope and structure would be desirable most fortunately perhaps by translation into Hungarian of this publication.

E. Kisida

Matzen-Matzen: Orthopädie fur Studierende. Johann Ambrosius Barth Verlag, Leipzig 1981, 5th edition, pp. 498, with 359 figures. DDM 36.

Generations of students have profited from the textbook of Prof Matzen. In the fifth edition his son, too, has contributed to the repeated publishing of the most important information about orthopaedics and about the injuries which are taught within the scope of tramatology in the German-speaking countries. The didactic classification and the traditions of the book account for the fact that our professional 'heritage' has perhaps been more extensively reviewed than the present or future prospects and possibilities. The book is structured according to the decimal system. Following the examination

The book is structured according to the decimal system. Following the examination methods and the specific methods of treatment of orhopaedics, the various disease groups are treated then the clinical aspects and management of the individual diseases are discussed according to the anatomical regions.

Numerous photos, roentgenograms and sketches help in understanding the text Thereby this volume goes beyond the scope of the usual textbooks and it offers the reader knowledge on locomotor diseases carrying on the high traditions of German orthopaedics. This is also referred to by the authors when mentioning in the preface that the book has been intended for medical students, but it can also be of value to those who, during their clinical activities, would like to have rapid information on some topics. Currently, it is for sure that the rich contents of the book could hardly be considered to be a teaching material in medical training, the volume can keep on being an invaluable reading for those dealing with locomotor diseases.

The volume has been presented to the reader with the meticulous care so much charcteristic of the publishers.

Gy. Berentey

Karl Fritz: Funktionelle Methoden der ästhetischen Gesichtschirurgie. Johann Ambrosium Barth, Leipzig 1981, pp. 210, with 220 partly coloured drawings, DDM 88.

Karl Fritz, assistant professor, is head of the unit of plastic surgery of the 2nd Department of Otorhinolaryngology of the Vienna University School of Medicine. He intended his book for would-be specialists and for beginners in plastic surgery.

He discussed all aesthetic corrective possibilities of the face and the operations of the nasal septum. For didactic reasons, in order ot provide sound bases for the students, he frequently reviews the only and most simple solution or the one most effective according to his own experience. The selection of the method is subjective so it is subject to dispute but is always based on restoration or preservation of function.

Book Reviews

The book is divided into nine parts. The first five chapters can be looked upon as the general part. They are devoted to the preoperative information of the patient and documentation, anthropometric data, to the bases of profile-plastics, rhinomanometry and atraumatic operative technique. Of them, the chapters on profile-plastics and rhinomanometry are to be pointed out because the findings allow important therapeutic conclusions to be drawn.

The detailed part is divided into four chapters. One-third of the book is made up by discussion of the operations of the nasal septum. The essential anatomical data are reviewed as wells as the possibilities for correcting the bony and cartilaginous portions of the nose. An important observation of his is that the horrective operation of the nasal septum and the outer nose should be made in one seesion. His view does not, in all its aspects, agree with the Hungarian practice, as e.g. he always uses cartilage for correction of saddle nose and he does not even make mention of the method applying the ridge of the nose. The potential complications are discussed in detail as well as the cause of undesirable postoperative change of form.

The correction of the ear is dealt with less extensively. Besides the methods, the reasons for the poor results are also given account of.

The chapter on the ageing face in naturally more spacious. Review of the anatomical bases is connected with the description of the possibilities of dissecting out of the various regions. In addition to the rhytidectomic procedures of the face, forehead, neck and the eyelids, the correction of the lips and the nasolabial fold is also treated. The chemical elimination of wrinkles and dermabrasion are discussed at a length signifying its importance. The final part on operative and postoperative documentation is elaborately detailed and up to the point.

A partical solution is the emphasizing of the important details by a vertical red line before the text.

The largely coloured drawings excellently serve comprehension of the text.

The book is completed by a reference list and a subject index. The reference list has been conscientiously limited, it contains only reports and volumes considered to be of particular importance by the author.

The work meant to be a compendium, based on the author's great experience, is a good summary of the up-to-date knowledge on the easthetic surgery of the face. It offers good bases for would-be specialists and beginners in plastic surgery, but it may also be of benefit to advanced learners.

L. Ménesi

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Vein Valve Transplantation Segmental Transposition: a Case Report

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(Received: August 8, 1987)

A patient with chronic venous insufficiency of the right lower extremity caused by total valve incompetence was operated. A 2.5 cm long segment of basilic vein with intact valve was transplanted as an 'interpositum' into the popliteal vein. Postoperative control was performed with venous occlusion plethysmography, radionuclide venography and Doppler US. As a result of the well-functioning implanted valve the complaints of the patient diminished.

Chronic venous insufficiency (CVI) is caused by deep venous thrombosis or congenital valvular incompetence. The classical symptoms like leg pain, edema, varicose veins, pigmentation and stasis ulceration are due to reflux of blood in the venous system.

When the conventional management is not enough and the patients suffer from a severe clinical syndrome of venous insufficiency, and a major degree of deep vein incompetence demonstrated by descending and ascending phlebography, deep vein valve reconstruction is considered [6, 7].

Case Report

I. T., a 50-year-old man. Previously surgery of the varicose vein was performed in 1972 and 1986 on the right side. In the history there was a deep vein thrombosis in 1983 on the same side. Since then, he has had severe edema and leg pain with recurrent ulcer. Before the second operation (1986) an ascending phlebography was performed. This time the deep venous system was found to be patent, however, total absence of valves could be demonstrated at descending phlebography (Fig. 1).

Doppler ultrasound examination also verified the total deep vein incompetence (Fig. 2).

The stripping of the great saphenous vein and the ligatures of the perforting veins did produce the expected result, and the condition of the limb remained unchanged.

A brachial or axillary vein segment transplantation into popliteal vein was planned. However, during the operation in January 1987 we could not



FIG. 1. The reflux can be confirmed to the upper third of the calf during the Valsalva manoeuvre by descending phlebography (white arrow-head)

find valve in either of these veins. There was a well-functioning valve in the basilic vein just before it drained into the brachial vein (Fig. 3). Thus, this venous segment was resected in a length of 2.5 cm and was implanted into the popliteal vein below the major adductor muscle.

There was a fibrotic thickening of the wall of the popliteal vein with a patent lumen as a remnant of a previous thrombosis. The luminal difference of the veins was corrected and end-to-end anastomoses were made with 7/0 Prolene sutures. Figure 4 shows the well-functioning valve within the transplanted segment.

After intra- and postoperative heparinization a longterm anticoagulation treatment was started with dicumarol. The wound healed by first intention.



FIG. 2. Doppler examination proves durable and/or high velocity reflux at full length of the extremity during the compressions and the Valsalva tests. This indicates total deep venous valvular insufficiency: all valves are incapable of closing. The venous escape pressure is 35 mm Hg

During hospitalization in the postoperative period the edema, painfulness and the superficial leg ulcer diminished. The patient had no complaints during the 2 months follow-up period.

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		Venous reflux with valsalva manoeuvre	
1	(measured	by means of venous occlusion plethysmograp	hy)

	Preoperative –	Postoperative		
		1 day	1 week	2 months
Reflux volume [ml/12s/100 ml tissue]	5.2	1.6	1.7	1.6
Maximal reflux flow [ml/min/100 ml tissue]	39.8	7.2	8.8	8.3



FIG. 3. Schematic view of the intraoperative situation



FIG. 4. The intraoperative view of the implanted vein segment. After distal compression the vein is emptied above the level of the valve. After stopping of the proximal compression the blood reflows only to the valve (white arrow-heads). Below the valve the wall of the vein remains collapsed

At the 2nd month check-up there was normalization of the preoperative high venous reflux volume and flow decreased considerably. The maximal venous outflow became normal as shown by the venous occlusion plethysmography (Table 1).



FIG. 5. The postoperative radionuclide venography with Valsalva manoeuvre. In the region of ROI N° 1 and 2 the visible decrease of the activity demonstrates that the crural vein valves are incompetent further on. In the region of ROI N° the activity increases continuously which indicates a satisfactory function of the valve [8]

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FIG. 6. The Doppler curve of the common femoral vein remains unchanged after the operation. There is only a short nonpathological reflux after the compressions without reflux above the popliteal vein during the Valsalva test. The crural deep vein valve malfunction persists (durable reflux after DD and PC above the posterior tibial vein). The venous escape pressure is 30 mm Hg

Preoperative backflow with the Valsalva manoeuvre became insensible above the implanted valve, but more distally a periferal type of reflux could be detected at the 4th month follow-up study by radionuclide venography (Fig. 5).

This reflux could also be demonstrated by Doppler ultrasound examination (Fig. 6).

Phlebography was not performed in the follow-up period, because the noninvasive tests were convincing.

Discussion

The notion that venous insufficiency is due to valvular incompetence was first described by Homans in 1917 [3]. Haimovici in 1970 was the first to report an experimental attempt of venous autografting [2]. In patients whose deep vein valves were incompetent due to primary valve incompetence, the first series of surgical valve correction was reported in 1975 by Kistner [4]. Vein segment transposition was described in 1979 in patients who had incompetent valves due to postphlebitic valve damage because after phlebitis a direct repair of the valve is not possible [5]. The procedure consists of anastomosing to an adjacent segment that has not been affected by the phlebitis and still has competent valves. Other possibility is transplantation of segments of vein from an upper extremity containing a competent valve. This may be necessary in those in whom a direct valve repair or a segment transposition is not possible due to the absence of valves of the profound and saphenous veins [9].

Who are the candidates for deep venous valve surgery? Patients whose preoperative radiological, haemodynamic and clinical findings indicate a severe clinical syndrome such as abnormal venous pressure dynamics, normal outflow, patent tibial-popliteal-femoral-iliac veins and an advanced degree of incompetence in the femoropopliteal segment with a considerable venous reflux [7].

In the early eighties autogenous brachial or axillary vein segments were transplanted into the superficial femoral vein. Later, however, it was realized that a competent valve at the level of the popliteal vein is sufficient to alleviate the symptoms of CVI. In addition, the intraluminal diameters of the brachial and popliteal veins are comparable in size. The donor basilic valve was transplanted into the popliteal vein, because the patient had no brachial valve.

In addition to thorough preoperative examinations, also postoperative follow-up is important. As noted by Taheri et al. the noninvasive evaluation in this case does not correlate well with invasive testing [10]. It was found that noninvasive venous Doppler examination [1], venous occlusion plethysmography and dynamic radionuclide venography are optimal monitoring methods without risk. Thus, we do not share Taheri's opinion that venography is essential in the follow-up period.

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Venenklappen-Transplantation mit Segmenttransposition. Falldarstellung

V. MÁRK und Z. FÓRIS

Operiert wurde ein, an chronischer venöser Insuffizienz der unteren Extremität leidender Patient, bei dem totale Klappeninsuffizienz bestand. Das 2.5 cm lange Segment der V. basilica mit intakter Klappe wurde als «Interpositum» in die V. poplitea transplantiert. Zur postoperativen Kontrolle kamen Okklusionsplethysmographie, Isotopenvenographie und Doppler-US-Untersuchung zur Anwendung. Als Ergebnis der Transplantation der gut funktionierenden Klappe hörten die Beschwerden des Patienten auf.

Трансплантация венозного клапана трансплантацией сегмента: Описание одного наблюдения

Б. МАРК и З. ФОРИШ

Авторы прооперировали одного больного, страдающего хронической венозной недостаточностью правой нижней конечности, у которого наступила полная недостаточность клапанов. В подколенную вену они трансплантировали — как «интерпозит» — сегмент длиной 2,5 см интактного клапана внутренней поверхностной вены предплечья. Послеоперационный контроль был выполнен методами окклюзионной плетизмографии, изотопной венографии и с помощью ультразвукового исследования (Допплер). Жалобы больного прекратились вследствие хорошего функционирования трансплантированного клапана.
A Simple Method for Intraoperative Autotransfusion in Cardiac Surgery

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(Received: September 15, 1987)

Authors present a simple, safe and inexpensive method of intraoperative autotransfusion (ATF) for open-heart surgery. A brief comparison is given with other techniques already in use.

Asanguinous open-heart surgery has become a routine practice by the eighties. Among others, this brilliant achievement is due to the introduction of the modern techniques of autotransfusion (ATF). Several methods applying different devices have been described for intraoperative ATF. A simple technique is presented for this purpose.

Technique

Bentley 10TM oxygenator and Bentley-3500 cardiotomy reservoir with filter (20μ) are used in our institution. Having finished the cardiopulmonary bypass and removed the venous cannula(s) but with an aortic cannula in place and before neutralizing the heparin with protamine, coronary suction is stopped for one or two minutes and the tube running from the bottom of the reservoir to the oxygenator is cross clamped (see Fig. 1). At this moment two units of standard citrate-phosphate-dextrose (CPD) solution (i.e. 126 ml) are filled into the reservoir through port A (see Fig. 1). When this is accomplished, coronary suction is restarted and protamine is given to the patient according to the general practice. The mediastinally shed blood is removed from the surgical field by coronary suction into the reservoir up to the end of the operation. Having closed the thorax the suction is connected to the chest tubes and the blood is aspirated through them. Two units of CPD are capable of anticoagulating 850 ml of blood in case of an optimal (i.e. 7 to l) blood to citrate ratio. When this volume is reached the blood is delivered into transfusion bottles by gravity through a standard transfusion set with filter. If severe bleeding occurs, the blood is first transferred into the oxygenator and



FIG. 1. Schematic drawing of the cardiotomy reservoir (type Bentley BCR 3500) and its connections for intraoperative autotransfusion

from there into transfusion bottles, and two units of CPD are filled into the reservoir again. After the end of the operation the reservoir is connected to the chest tubes to accomplish postoperative ATF.

Comment

We have already practised this technique successfully in more than 100 consecutive cases and found it effective and safe. It is important to follow accurately recommendations in the timing and mode of filling the reservoir with a CPD solution to prevent clot formation in the reservoir under the filter. In some cases this may occur when the CPD is filled after the protamine has already been given or when CPD is delivered through port B (see Fig. 1) because in this way it will not contact the filter.

Comparing our intraoperative ATF technique with others already in use. we judged it advantageous for open cardiac procedures. The cell saver system (e.g. Haemonetics) [3], the Sorenson ATF unit [2] and several other systems [1, 4,] are expensive, while our method saves money by applying the cardiotomy reservoir from the same operation. This technique does not need regional heparinization, so there is no increased risk of bleeding. The endproduct is whole blood anticoagulated with citrate which does not need further processing. The avoidance of blood dilution with crystalloid solutions save patients from additional fluid load.

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Eine einfache Methode der herzchirurgischen Autotransfusion

J. SZÉCSI, J. ARANYOSI und Á. PÉTERFFY

Beschrieben wird eine zuverläßliche, einfache und wirtschaftliche herzchirurgische Autotransfusionsmethode. Das Verfahren wird kurz auch mit den sonstigen, bisher gebräuchlichen Autotransfusionsmethoden verglichen.

Простой метод аутотрансфузии в сердечной хирургии

Я. СЕЧИ, Я. АРАНЁШИ и А. ПЕТЕРФФИ

Авторы знакомят с надежным, простым и экономичным методом аутотрансфузии в сердечной хирургии. Они делают краткое сравнение своего метода с другими, до настоящего времени использовавшимися трансфузионными методами.

-

Resection Arthroplasty of the Rheumatoid Forefoot

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(Received: April 10, 1987)

After discussing the term of resection arthroplasty of the rheumatoid forefoot, the problem of indications and contraindications for surgery is dealt with. Experience obtained by operations is presented together with the recommended operative technique.

The clinical picture of rheumatoid arthritis also includes involvement of the foot which is a progressive, destructive inflammation of the foot joints. Due to the frequent involvement of the foot, the developing deformities and the characteristic consequential impairment in function, the term rheumatoid foot has also been accepted on the analogy of rheumatoid hands. The rheumatoid foot can manifest in the form of a diverse clinical syndrome including pain, sensitivity to pressure, sensory defect and deformity, limited movement of the joints and also their functional disorder [4].

In treating rheumatoid foot, beside the conservative treatments, surgical procedures are becoming more extensively used aimed not only at the correction of the deformities but also at prevention of further impairments. To the latter group of operations belong the synovectomies, tenosynovectomies as well as the operations restoring the normal posture of the tarsus which may prevent deformity of the forefoot.

Resection arthroplasty of the forefoot is a generic term. By this is meant the operative procedure where simultaneously several or all metatarsophalangeal joints, but at least the heads of the 2nd, 3rd and 4th metatarsal bones are resected. Therefore, these operations are aimed at correcting an affeted toe or joint but practically at treating the entire forefoot. Concerning the essence of the intervention, perhaps Hehne's [6] designation is the most precise one, who uses the term resection arthroplasty of the metatarsophalangeal joints.

Several types of operative procedures are known. The individual methods differ from each other in the site of exposure, as well as in the extent of dissection of the soft parts and of the bone resection [1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12]. The primary goal of the resection arthroplasty of the forefoot is the mitigation of metetarsalgia as well as the reduction in the subluxation, claw foot

and lateral deviation of the lateral toes, the diminishing of the limited movement of the forefoot and thereby the improvement in the functions of the foot. The removal of the metatarsal bone heads serves primarily the treatment of metatarsalgia, while resection of the proximal phalangeal bases of the toes that of hammer toes.

The resection arthroplasty of the metatarsophalangeal joints is the basis of the surgical solution of a complex forefoot deformity occurring in rheumatoid arthritis patients, which can be completed by additional operative procedures.

Indications for surgery are first of all pain which occasionally can even be of an extent that it endangers the patient's ability to walk. In addition to pain, the resulting functional disorder is also important from the point of view of indication for surgery. Therefore, if impairment of the forefoot considerably limits the patient in standing, walking or wearing shoes, operation is also indicated. A deformity not causing pain or functional disorder does, generally, not call for an operation.

Contraindications for surgery are the patient's poor general condition, the circulatory disorder of the leg in addition to the acute manifestation of the disease, its neurotrophic impairment, real and suspected infections, as well as the circumstance that the patient does not wish to be operated even despite being informed about the nature of his disease.

Material and Method

The resection according to Hybinette or Clayton of the metatarsophalangeal joints was performed in a total of 119 patients with rheumatoid arthritis during the 14 years between 1969 and 1983, While Hybinette [7] resected only the 2nd, 3rd and 4th metatarsal heads, Clayton performed resection in all metatarsal bone heads completing it, if necessary, by the resection of the proximal phalangeal bones.

The majority of the patients were females (female to male ratio: 20:1), with a mean age of 53 years. Their primary disease had been persisting for on average of 15, while their metatarsalgia for 11 years. Follow-up time after operation was on an average 8 years.

During our operations, several modifications were used. Namely, in cases where the extension of the big toe persisted even after the resection of the metatarsal head, the long extensor tendon of the big toe was lengthened in a Z shape. For reducing the twisted position of the big toe, medially a capsular incision was made. Following bone resection for a hammer toe deformity and dissection of the soft parts, in some cases, instead of splinting of the medullary space, the lateral toes were sutured downwards to the skin

of the sole for securing the corrected position, while in the cases where an excessive resection had previously been made for a hammer toe deformity, the neighbouring toes were partially sutured with each other.

Results, Experiences and Recommended Operative Technique

In the first year after operation it was generally observed that the regions previously exposed to an increased pressure were released from the extreme pressure, metatarsalgia diminished or even ceased completely. The soft parts having shrunk due to the shortening of the bony frame of the foot relatively lengthened, which resulted in the reduced rigidity of the foot.

In the subsequent years it was found that gradually new surfaces became to be loaded, a pseudohead formation started which provided a possibility for the development of metatarsalgia. As a result of the scarring and shrinkage of connective tissue structures, contracture began to develop.

The effectivity of the operation was assessed by considering the metatarsalgia occurring on standing and walking. On this basis, 69% of our operations were considered to be successful.

Failure was supposed to be due to a resection of or soft part dissection of an inadequate degree.

In two patients the wound suppurated. In the majority of our patients, protracted healing of the wound and secondary healing were observed. Reoperation had to be made in 6 cases.

In 30 patients data processing was made where metatarsalgia, claw toe deformity, wearing of shoes and the patient's opinion were recorded and scored from 1 to 3. For analysing significance the chi²-test was used (Table 1).

Our data showed that the patients' metatarsalgia and claw toe deformity were diminished significantly. The patient's ability to walk also improved. This must have been influenced also by the condition of the other points of the lower extremity because of involvement of several points. There was no change in the wearing of shoes. The majority wore orthopaedic shoes with an arch support before and after the operation.

	Before	After	Р	Commont	
5	operation		(%)	Comment	
Metatarsalgia	2.48	1.53	0.1	strongly significant	
Clow toes	2.10	1.30	1.0	significant	
Ability to walk	1.96	1.36	10.0	not significant	
Wearing of shoes	2.17	2.17	-	unchanged	
The patient's opinion				1.22 = generally satisfied	

Т	A	р	т	F	1
л	A	р	1	r.	



FIGS. 1-2. Prior to the operation both forefeet were painful and deformed

In the patients' subjective opinion, 2 of 30 patients were completely satisfied, 21 satisfied, 6 dissatisfied and one completely dissatisfied with the result of the operation.

Summarizing the experience gained by the postoperative follow-up studies, it was established that a permanently good result was seen in the cases where both resection and the soft part dissection were of an adequate extent (Figs. 1–5). In cases, however, in which resection and/or dissection of the soft parts was performed to an inadequate extent, early reappearance of complaints and symptoms was observed.

In the cases, however, where the forefoot had been rigid preoperatively, after the intervention pain did primarily abate without the lasting diminishing of the rigidity of the forefoot.



FIGS. 3-4. Immediate postoperative state

Asit has been mentioned earlier, pain is the first from the point of view of indications for surgery and taking this into consideration, in assessing the effectivity of the operation particular importance was attributed to the patients' opinion.

Concerning the operative technique, the following is recommended. Resection arthroplasty of the forefoot can be performed equally from a transverse plantar, or a transverse or longitudinal dorsal incision [1, 2, 7]. Accord-

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FIG. 5. As a result of resection arthroplasty of the forefoot, the painful deformity permanently diminished

ing to our experience, the least disorder in wound healing was observed in the exposure made by this latter method [8]. An additional advantage of the incision in the dorsum of the foot that it provides a possibility for resection of the proximal phalangeal bases as well as for resection of the extensor digitorum and for the plastic lenghtening. Inflamed plantar, bursal and rheumatoid nodes can also be removed from a plantar incision.

We have found the practice unacceptable which neglects the detailed analysis of the type of foot and the changes developed and therefore practically always the same "well-established" surgical procedure is performed. It is essential that the degree of bone resection as well as of soft part dis-



FIG. 6. The length of the bone to be resected is on an average one and a half or 2 cm Acta Chirurgica Hungarica 39, 1989

section should, in each case, be adjusted to the nature and extent of the existing deformity. The degree of necessary resection is influenced by the type of the foot and also by the extent of postoperative contracture. In the cases, however, where the foot had been more limited in motion, less was resected than in the case of a rigid one. Similarly less was resected in the 'loose' form of Clayton than in the 'stable' type of foot. The length of resection averaged one and a half to two centimetres (Fig. 6).

The extent of the resection of a given metatarsal bone also depends on the length of the metatarsal bones relative to each other. Following an operation using the appropriate technique, the metatarsal stumps will form a lateral, gradually shortening arch so that the stumps of the first and second metatarsal bones are of approximately the same length. If the first metatarsal stump is essentially longer than the second one, the development of the fibular deviation of all toes should be reckoned with.

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Resektionsarthroplastik des rheumatischen Vorfusses

G. GÁSPÁRDY und JULIA ZSENGELLÉR

Nach Beschreibung des Begriffs der Resektionsarthroplastik des rheumatischen Vorfusses, finden die Operationsindikationen und Kontraindikationen sowie die mit der Operation ermittelten Erfahrungen und anschließend die Operationstechnik eine Besprechung.

Резекционная артропластика, произведенная на ревматической ноге

Г. ГАШПАРДИ и Ю. ЖЕНГЕЛЛЕР

После ознакомления с понятием резекционной артропластики, произведенной на ревматической ноге, авторы занимаются вопросами показаний и противопоказаний к операции.

Они знакомят с опытом, приобретенным при выполнении этой операции, и описывают рекомендуемую хирургическую технику.

Do Steroid Hormones Influence the Concentration of PGF_{2α} Receptors of the Uterine Muscles?

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Uterine contractions are largely regulated by steroid hormones. The receptors which are important from the point of view of uterine contractions (such as oxytocin, alpha- and beta-adrenergies) are also influenced by steroid hormones. In this paper the regulation by steroids of $PG_{2\alpha}$ receptors was studied in vivo. Due to ovariectomy, the concentration of $PG_{2\alpha}$ decreased significantly in rats without a change in affinity. As a result of in vivo progesterone treatment, the $PG_{2\alpha}$ receptor concentration decreased to its third as compared to that of the ovariectomized control also without a change in affinity. $PG_{2\alpha}$ receptor concentration was not changed by in vivo estrogen treatment in comparison to that of the ovariectomized control but a high-affinity, low-capacity binding-site appeared. Our experiments revealed the in vivo regulation by steroid hormones of the $PGW_{2\alpha}$ receptors of the rat myometrium.

Introduction

Estrogens are generally considered to exert a stimulatory, while progesterone, an inhibitory effect on spontaneous uterine contractions. The progesterone level in rabbit and rat during pregnancy is high and it decreases to the non-pregnant values only prior to labour [6]. Therefore, these two species are suitable endocrinologically for enlarging on problems connected with the 'progesterone block' theory, such as the role of progesterone in maintaining pregnancy or inducing labour [4]. In view of the complicated mechanism of uterine contractions, the exclusive role of progesterone in inhibiting the spontaneous activity of the myometrium as well as in giving rise to automatic contractions due to a decrease in its production around or prior to labour is improbable. Nevertheless, the most important regulators of the mechanism of uterine contractions are the steroid hormones, namely estrogens and progesterone.

Under physiological conditions, the rat uterus is inactive even if the estrogen level is high, as in proestrus or around labour. However the contrary may also be true, when estrogen levels, are low as in estrus, metestrus and diestrus, and in the first half of pregnancy. Under such circumstances the rat uterus displays permanent contractions. In proestrus, ovariectomy results in

permanent uterine contractions [5]. Progesterone exerts, in general, a suppressive effect on both mechanical and pharmacological stimulations. At the same time, estrogens enhance the effect of these stimuli. After progesterone suppression the response of the uterus to oxytocin increases. At the same time, a preliminary progesterone suppression influences less the effect of agents activating the uterus. Based on the investigations of Soloff et al. [15], the mechanism of uterine response to oxytocin, which is mainly regulated by ovarian hormones, has become better known. Specific oxytocin receptors were shown to be present in the myometrium, which are also controlled by the ovarian hormones. The uterine response to oxytocin largely depends on the concentration of the oxytocin receptor of the uterus [15]. It is known that in rabbit myometrium, estrogen treatment increases the number of oxytocin receptors, while progesterone considerably decreases the receptor concentration [12]. In rabbit, the extent of response to oxytocin changes parallelly to the number of receptors. This correlation is even more significant in rat. It has been proved that alpha- and beta-adrenergic as well as angiotensin receptors are equally controlled by steroid hormones [13, 17]. Our earlier experiments have verified that the alterations of hormone levels in the pregnant rat affect the sensitivity of the myometrium to prostaglandin and oxytocin [8]. Increase in receptor concentration could be detected in the rat on the day of labour without any change in receptor affinity [9].

All these considered, steroid hormones can be assumed to play a role regulating the concentration of PGE_{2a} receptors. Investigating another aspect of the question, in vivo experiments were performed. Ovariectomized rats were treated by estrogen and progesterone, then following treeatment, prostaglandin receptors were determined from the myometrium. According to our studies, they affect the PGF_{2a} receptor concentration of the rat myometrium.

Material and Method

Ovariectomy

Young Sprague–Dawley female rats, weighing 200-300 g, were ovariectomized under general anaesthesia. Anaesthesia was provided by the i.m. administration of 90 mg/lg Ketamine and 10 mg/kg Rompun for 30-40 minutes. The ovariectomized rats were observed for a week then treated with the hormones.

Treatment of Ovariectomized Rats by 17-Beta-Estradiol, Probesterone and their Combination

During estrogen treatment, the ovariectomized rats received 1.0-10.0and 50.0 μ g 17-beta-estradiol intramuscularly in oily injections twice daily

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for two days, then on the third day prostaglandin was determined. In the course of progesterone treatment, the ovariectomized rats were administered i.m. 0.5–1.0 and 5.0 mg progesterone twice daily for two days and prostaglandin receptor was assessed on the third day. Combined treatment included wo days of estrogen followed by two days of progesterone treatment during which the ovariectomized rats received 10 μ g twice daily, 17-beta-estradiol for two days, then twice 1 mg progesterone for the subsequent two days. On the 5th day prostaglandin was meesured. In both groups 12 rats were used.

PGF_{2a} Receptor Determination

The rats were anaesthetized with ether then exsenguinated. The uterine horns were removed and cleaned of adhering connective tissue and fat. The cleaned myometrium was washed in buffer at 0 °C (0.25 M) sucrose, 10 mM TRIS-HCl, 1 mm mercaptoethanol of a pH 7.5 and 1 mm CaCl₂). The tissue was cut to small pieces, then homogenized in a 5-6-fold volume of buffer in a Polytron PCU-2 homogenizer. To prevent endogenous prostaglandin synthesis during preparation, the buffer contained indomethacin. The homogenate was filtered through four layers of gauze, then the filtrate obtained was differential-centrifuged. From the myometrial homogenate a rough plasma membrane fraction was produced by differential-centrifugation (1000 g for)15 min. 10,000 q for 15 min, 105,000 q for 60 min). The final pellet was suspended in TRIS-HCl buffer and was regarded as a rough membrane fraction for the binding experiments. All manipulations were carried out at 0 °C. To determine PGF_{2n} receptors, the earlier used and reviewed method developed by us was employed. Labelled PGF_{2a} was incubated at 37 °C for 60 min in an end-volume of 0.2 ml without PGF_{2a} not labelled by a membrane fraction containing 100–200 μg protein. The bound and free prostaglandins were separated by filtration (0.45 μm Millipore). The residual radioactivity on the filter paper was measured by a scintillation counter. The specific binding was calculated from the difference in bindings measured in the absence and presence of cold prostaglandin. The results were analysed by Scatchard linear regression analysis and the binding capacity and the dissociation constant were calculated. In our experiment saturation analysis was applied during which the amount of labelled PGF_{2a} ranged between 0.25 and 25 pmol. (For the detailed description of the method see Ref. [10].)

Protein Determination

The protein content of the membrane preparate was assessed according to the Bradford procedure using serum albumin for standardization [2]. 112 F. Lintner et al.: Do Steroid Hormones Influence the Concentration of PGF 24

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Results

Young female rats were ovariectomized then, after one week, the PGF_{2a} receptors of the ovariectomized rat myometrium were compared with those of the untreated controls in either stage of the cycle. A high-affinity binding site was found in both the untreated control as well as in the ovariectomized animals, the affinity being of a magnitude of $10^{-8}M$. The Scatchard analysis of the PGF_{2a} receptors of the control and ovariectomized rat myometria are shown in Fig. 1. After ovariectomy the PGF_{2a} receptor concentration without a change in affinity decreased considerably. The receptor concentration of the myometrium of the untreated control animal was 450 fmol/mg protein by contrast to the 310 fmol/mg protein value in the ovariectomized rat. The difference was significant, i.e. p < 0.05.

The ovariectomized rats were treated by 0.5–1, 0–50 mg progesterone twice daily for two days and on the third day the myometrial PGF_{2a} receptors were determined. There was no difference after progesterone treatment applied in different doses. The Scatchard analysis of the results is shown in Fig. 2. In response to progesterone treatment, the PGF_{2a} receptor concentration decreased significantly almost to one-third of that of the ovariectomized control animals. Progesterone treatment did not influence the affinity of the prostaglandin receptors. A similar decrease was observed in the number of prostaglandin receptors without a change in affinity during combined treatment, i.e. when the ovariectomized rats were given estrogen for two days or progesterone subsequently for two days.

In another series of investigations the ovariectomized rats were treated with 17-beta-estradiol for two days in a dose range of 1.0–10.0, 0–50 μ g. The



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FIG. 2. Effect of progesterone treatment on $PGF_{2\alpha}$ receptors



FIG. 3. Effect of 17-beta treatment on $PGF_{2\alpha}$ receptors

difference between the dose limits examined couod not be established. Consequently, Fig. 3 shows the Scatchard analysis of the experimental data after a typical estrogen treatment (10 µg estradiol). The prostaglandin receptor concentration did not change in comparison to the ovariectomized control animals, however, a high-affinity, low-capacity binding site, appeared of a concentration of 25 fmol/mg protein and of an affinity of $\sim 0.7 \times 10^{-9}$ M. The dissociation constant of the low-affinity binding site was the same as that of the ovariectomized control animal.

Discussion

Our results indicate that PGF_{2a} receptor concentration is influenced by steroid hormones in the rat myometrium in vivo. In young female animals after ovariectomy a high-affinity PGF_{2n} binding site was found. The decrease of angiotensin II receptor, concentration following ovariectomy has already been observed, where after castration the amount of the receptors measured decreased in proportion to the time elapsed [14]. During our experiments, receptor measurements were made only one week after ovariectomy when the above decrease was observed. The decrease was probably due to a lack of circulating steroids, primarily that of the estrogens which manifested also in the decrease in the mass of the uterus. Following ovariectomy, the plasma estradiol, estron and progesterone levels of the rat decreased significantly [3]. It is known that estrogens stimulate glucose oxidation and protein, RNA and lipid synthesis as early as 24 hours after their administration, they increase mitotic activity in the uterus [11]. All these can account for the reduced binding capacity. Although dose-dependence could not be demonstrated after progesterone and estradiol treatments, most likely due to a non-adequate dosage and absorption or to the fact that the required local steroid concentration is more difficult to be reached in vivo. Similar to previous experience, an antagonism was observed in the effect of both hormones. Following in vivo progesterone treatment, the amount of prostaglandin receptors decreased to about its third without a change in affinity. A similar decrease was noted, if estrogen was administered two days prior to progesterone treatment. In response to progesterone treatment, the progesterone and estrogen receptor concentration of cytosol is reduced [1] with a simultaneous decrease in the angiotensin receptor concentration in the rat uterus as a result of an adequate progesterone treatment [14]. Progesterone, the fundamental effect of which is to ensure the inactive state of the uterus during pregnancy, exerts its effect by way of several mechanisms. Perhaps the most important of them is the reduction of the amount of hormone-specific receptors (oxytocin, alpha--adrenergics and prostaglandin) playing a role in almost all smooth muscle contractions. The decrease of receptor concentration may imply, at the same time, the decrease of sensitivity to uterotonics which is supposed to be the biological effect of progesterone [13, 15, 17]. Estrogen treatment is of an opposite effect, increasing, in general, the amount of receptors (estrogen, progesterone, angiotensin) mostly dose-dependently. Nevertheless, a decreasing effect was also observed since estrogen treatment may also inhibit the uterine protein and DNA synthesis [16]. Subsequent to permanent estrogen treatment, the formerly increased receptor concentration may decrease to the initial value which is explained by the so-called down-regulation or desensitization.

Estrogens increase the amount of their own receptors and that of progesterone, as also the receptor concentration of oxytocin and of alpha adrenergics. In our investigations, such an effect could not be demonstrated by in vivo treatment in the rat uterus concerning PGF_{2a} receptors, the appearance of a high-affinity binding site which, in agreement with the biological effect of estrogen, can increase myometrial contraction.

The effect of ovarian steroids on uterine contraction is fairly complex. The spontaneous activity, i.e. the coordination of pharmacological responsiveness and uterine contraction is individually regulated by the sexual steroids. Ovarian hormones exert their diverse effects time- and dose-dependently on a large scale. For the manifestation of the primary effect of estrogens, protein synthesis is required including also the uterus-contracting proteins and enzymes which provide the contractive mechanism with energy. As part of the complicated mechanism, there is also a change in membrane potential, pacemaker activity, cyclic AMP level and in several other properties not considered here [6]. The molecular bases of the opposite effects of estrogen and progesterone are not known. It has been verified by morphological experiments that the so-called gap-junctions are regulated, beside several other factors, also by sexual steroids [7]. During pregnancy the contraction of the myometrium and its regulation are still more complex.

In the pregnant rat uterus (following ovariectomy performed on the 17th day) its spontaneous activity in vitro, on the day of labour, was lower as compared to uteri of sham-operated animals, although the extent of prostaglandin release was the same in both groups. If the ovariectomized pregnant animals were given estrogen treatment on the 19th and 20th days, spontaneous uterine activity on the day of labour was of a higher amplitude and intensity as compared to that of the ovariectomized animals. Based on this, estrogens seem to be fundamental in eliciting spontaneous contraction [5].

The prostaglandin receptor concentration without a change in affinity is influenced in opposite ways by estrogen and progesterone in the rat uterus. The prostaglandin receptors of the rat myometrium are, as a consequence, directly affected by ovarian steroids. These data support our previous assumption that, during pregnancy and labour, sexual steroids play an essential role in the contractive mechanism of the myometrium partly in the regulation of receptor concentration and partly in that of the contraction mechanism (gap-junctions, enzymes, calcium concentration).

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Wird die Konzentration der PGF_{2 Alpha}-Rezeptoren des Myometriums durch die Steroidhormone beeinflußt?

F. LINTNER, F. HERTELENDY und B. ZSOLNAI

Die Uteruskontraktionen werden in bedeutendem Maße durch die Steroidhormone geregelt. Die vom Standpunkt der Uteruskontraktionen wichtigen Rezeptoren (Oxytozin, Alpha- und Beta-Adrenerge) stehen ebenfalls unter dem Einfluß der Steroidhormone. In vorliegender Arbeit wird über die in vivo Untersuchung der Steroidregelung der PGF 2Alpha-Rezeptoren berichtet. Bei der Ratte hat sich unter Wirkung der Ovariektomie die Konzentration der PGF_{2Alpha}-Rezeptoren ohne Änderung der Aktivität signifikant verringert. Der in vivo Progesteronbehandlung zufolge verringerte sich die PGF_{2Alpha}-Rezeptor-Konzentration, ohne Änderung der Affinität um ein Drittel. Durch die in vivo Östrogenbehandlung wurde die PGF_{2Alpha}-Rezeptorkonzentration im Vergleich zu den Kontrollen nicht geändert, es erschien aber eine Verbindungsstelle mit großer Affinität und kleiner Kapazität. Im Laufe der Versuche konnte nachgewiesen werden, daß die $\mathrm{PGF}_{2\mathrm{Alpha}}\text{-}\mathrm{Rezeptoren}$ des Rattenmyometriums in vivo durch die Steroidhormone geregelt werden.

Влияют ли стероидные гормоны на концентрацию PGF₂ рецепторов в миометрии

Ф. ЛИНТНЕР, Ф. ХЕРТЕЛЕНДИ и Б. ЖОЛНАИ

Сокращения матки в большой степени регулируются стероидными гормонами. Важные с точки зрения сокращения матки рецепторы (окситоциновые, альфа- и бета-адренергические) также оказывают влияние через стероидные гормоны. В настоящем сообщении излагаются результаты исследований регуляции, осуществляемой посредством простагландиновых рецепторов (PGF_{2x}). У крыс, под влиянием овариэктомии, концентрация рецепторов достоверно уменьшилась при отсутствии изменений аффинности. В результате воздействия прогрестерона *in vivo*, концентрация простагландиновых рецепторов (PGF_{2x}) уменьшилась на одну треть у животных с удаленными яичниками по сравнению с контрольными, без изменения аффинности. Воздействие в условиях *in vivo* эстрогеном не изменяло концентрацию рецепторов PGF_{2 альфа} у крыс с овариэктомией по сравнению с контрольными, но появилось место связи с высокой аффинностью и малой емкостью. В своих экспериментах нам удалось выявить регуляцию *in vivo* рецепторов PGF_{2x} миометрия крысы через стероидные гормоны.

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Management and Care of the Precanceroses of the Stomach in the 11-Year Material of our Clinic

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The present paper surveys over the past 11 years the cases of the endoscopic laboratory of our clinic which, according to criteria accepted all over the world, were considered as precancerous states of the stomach. According to the authors' experience, an advance in the management of malignant diseases can only be expected by referring to operation the cases in their early stage, if the examination and regular control of the patients are carried out with the predisposing factors being considered by a team involving the surgeon, endoscopist and pathologist.

The currently routine endoscopic examination of the upper gastrointestinal tract has provided an opportunity for the early detection of the even currently only surgically treatable gastric cancer thereby increasing the chances of recovery. Similarly routine endoscopy with the simultaneously performed serial biopsies plays a decisive role in the detection and follow-up of the morphological changes which predispose to the development of carcinoma and, according to view accepted all over the world, can be looked upon as precursors to malignant changes.

Patients and Method

At the 3rd Department of Surgery of Semmelweis University Medical School a well-equipped endoscopic laboratory has been operating for 11 years. Here not only the patients of the clinic are examined but health service and control are provided for by neighbouring in — and out — patient departments. Thus there is a possibility for the evaluation of not only the surgical patients material proper.

The number of gastrointestinal endoscopies performed between 1976 and 1987 approached 8000. In 0.8% of our cases gastric examination was prevented by the disease of the oesophagus. In about 10% of the above patient

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material endoscopy was performed during or after gastrointestinal bleeding or acute endoscopy was made when assessment of the subtler morphological structures was not possible. Collection of biopsy specimens is expedient only at a later date at the so-called second-look examination. Biopsy was performed on account of the capacity and the time-consuming nature of the workup only when it had been justified by the macroscopic picture, localization or any other findings.

In evaluating our material the clinicomorphological classification of Bajtai and Fink [1, 9] was taken into consideration. According to it, the precancerous states of the stomach are as follows.

1. Chronic atrophic gastritis with intestinal metaplasia;

2. Adenomatous polyps of the stomach;

3. Chronic ventricular ulcer;

4. Mucous hyperplasia with giant gastric folds (Menetrier's disease);

5. Changes arising in the operated stomach;

6. Mucous lesions in pernicious anaemia.

Results

1. In chronic gastritis biopsies were performed in 730 patients. In 95 of them intestinal metaplasia was detected. These patients are controlled every year. A 'relatively' early cancer was detected in two patients in this group in whom the tumorous infiltration did not involve the muscles. One of them was observed after three, the other after six, years' follow-up. In both cases the tumour appeared on the greater curvature of the pyloric antrum.

2. Of a total of 8000 examinations 96 adenomatous polyps were found in 82 patients. Earlier these patients were referred to places where endoscopic

Precancerosis	Biopsy or polypectomy	Malignancy 2
Chronic gastritis	730 intestinal metaplasia 95	
Ventricular polyp (elsewhere 61)	35	1
Gastric ulcer	405	15
Hypertrophic gastritis with mucosal lesion	74	_
Menetrier syndrome	1	-
Operated stomach total 645	58	11
Pernicious anaemia	3	—

TABLE 1

polypectomy was available or the polyps were removed by surgery if indicated by their size or morphological appearance. A total of 4 polyps were removed by operation of which three corresponded to tubulovillous adenoma. It has been possible to perform endoscopic polypectomy only since three years and, consequently, the number of such cases is not yet sufficient to draw conclusions. A total of 31 polyps were so removed in 31 patients. Histologically, 21 have proved to be adenomatous polyps, while 10 tubulovillous adenomas. Malignancy was found in one surgically removed polyp. The latter case is reviewed in more detail also for its other interesting aspects.

Case Report

A. Sch., a 73-year-old female patient was admitted to the 4th Department of Medicine of the István Hospital in October 1986 for symptoms of an acute inability of gastric emptying, with colicky pains localized to the upper abdominal half and for voluminous repeated vomiting. In response to conservative treatment, she rapidly became complaint free. X-ray performed one or two days later revealed in the antrum a polypoid structure, almost of the size of a tennis-ball, which migrated, due to the patient's change of posture, either into the fornix or the duodenal bulb. The biopsy, then the repeated gastric X-ray (Fig. 1) unambiguously disclosed a nut-sized polyp with a long pedicle on the junction of the corpus and the fornix. Another, and still bigger one of the same surface but of a wide base was located in the middle third of the stomach on the lesser curvature. The pedicled polyp was removed by a diathermic loop (Fig. 2) and biopsy was performed from the other. Both proved to be adenomatous polyps. In the pedicled polyp removed in toto there was no



Fig. 1. Double contrast study of the stomach. The pedicled polyps arising in the fornix and those of a wider base localized on the lesser curvature of the corpus are well discernible



FIG. 2. Endoscopic polypectomy with the GIF-type 2 device

evidence of malignancy. It was obvious that complete removal of the other polyp was also necessary, therefore after preparation, the wide-based polyp, the size of a baby's palm, was excised in gastrotomy in the patient with several associated diseases. Histology revealed the carcinomatous change of the base of the polyp (!) Control endoscopy and biopsy with negative results were performed three months later in the patient with a complication-free recovery.

3. Endoscopy has disclosed ventricular ulcers in 405 patients in the past 11 years. Hundred-forty-five of them were operated for acute recurrent bleed-



FIG. 3. Macroscopic picture of an endoscopically removed polyp



FIG. 4. Relatively early stump carcinoma developing after Billroth II resection involving the mucosa. The surgical specimen

ing [49] or ulcer refractory to a 6 to 9-week conservative treatment. Sixtyeight patients did not recover after a short conservative treatment but their general state was so poor that endoscopic observation and control by biopsy were decided upon or the patient was referred for operation.

In 9 patients biopsy, while in six the histology of the surgical specimens verified ulcer carcinoma. Naturally, patients whose X-ray had revealed ulcer or this was assumed on the basis of the macroscopic picture but histology disclosed some other but not ulcerous carcinoma, were not included in this group.

4. In several cases, mucous folds (hypertrophic gastritis) thicker than usual were encountered. Biopsy in these cases was only made in loss of epithelium over the mucosa. Histology did not reveal malignancy in any of the cases and the control indicated intact mucosal surface in all instances.

In our own case [6], gastroscopy was made in the young male patient after a haemorrhage inducing shock. Extremely thickened, vulnerable mucous folds were found. Histology did not disclose malignancy but the gastritis with huge folds—Menetrier's disease—was proved. Gastrectomy was performed at an elective time.

5. In the recent 11 years, a total of 645 gastric stumps have been examined. Histology verified the development of carcinoma in 11 gastric stumps operated according to Billroth II. In 8 of them already the macroscopic picture was indicative of malignancy. In 50 cases, tissue samples were collected for an anastomositis more marked than usual and a negligible mucosal defect, of which three proved to be carcinomas (Fig. 4). The latter were all early cases [14] and operable, while three of the former 8 cases were operated in an inoperable stage. The first operation of patients with stump carcinoma had been 4 to 36 years earlier. In one-third of the cases resection for ulcer had preceded the development of stump carcinoma by 15 to 18 years.

6. Only three patients with documented pernicious anaemia were examined. Their biopsies revealed mucous atrophy without malignant transformation.

Discussion

Among the precancerous states of the stomach, as regards their significance and frequency, by all means chronic ventricular ulcer is to be mentioned in the first palce. Although the relationship between gastric carcinoma and chronic peptic ventricular ulcer is a matter of controversy also today, we [7], in concert with authors in Hungary [1, 8] and the Editorial Report of the British Medical Journal [13], believe that of the patients at risk, just this group can be regarded to be the one in need of the strictest control. Also conservative treatment, of gastric ulcer verified by biopsy (!) is looked upon, to some extent, to be risky and can be recommended to be continued only for some weeks. Unless marked regression or complete recovery occurs after 6-8 weeks of intensive medication, operation is justified. It is obligatory to perform the endoscopic examination and a series of biopsies of the gastric ulcer detected by X-ray. Biopsy can be omitted only in the case of acute haemorrhage.

Sample collection of 405 patients with ventricular ulcer was made in 527 cases of which carcinoma was unexpectedly detected in 15 cases. This implied a 4% carcinoma incidence rate in this group, which is 6.5 times higher than the incidence rate of gastric cancer of the average population. It is necessary to follow up and control ulcer patients up to their complete recovery, and immediate control on repeated appearance of gastric complaints is indispensable.

Another important patient group is the one having undergone gastric operation for ulcer. As to the development of gastric cancer, those with a gastric stump operation according to Billroth II are supposed to be at risk. Doneloff [4, 5] and Nichols [15] consider the incidence rate of cancer 2 to 6 times higher in the operated stomach than in the intact one. The incidence rate of the development of cancer increases about 5 to 15 years after resection. Therefore, it is necessary 5 years after gastric resection to refer the patients to regular yearly controls or to perform double contrast study of the gastric stump. Thanks to this follow-up strategy, in three patients early-stage gastric cancer could be detected in the gastric stump. The examination of 645 gastric stumps revealed malignancy in 2% which is a three times higher morbidity rate than the usual one. Except for one case, the resections had been made more than 10 years earlier.

According to the overall statistics of Crespi [3] and Figus and Simon [8], in chronic atrophic gastritis in patients with hypo- or achlorhydria, the number of glands in the stomach decreases considerably or is missing occasionally. The gastric mucosa is replaced by acini resembling the glands of the small intestinal mucosa. After 20 years of follow-up malignant change occurs in 10%of these patients, while in the normal population—during a similar observation period—only in 0.6%. Intestinal metaplasia was found in 95 out of 730 chronic gastritis patients (i.e. 13%). In the relatively short (maximum 10 years') follow-up period, 2.1% of these latter were found to show cancer development. More than half of our cases were, however, not followed up even for 5 years. It can be extrapolated that during the 20-year follow up of the whole patient material a 10% incidence rate would prevail also in our patients, a rate reported on in international statistics. Consequently, the yearly control of the patient group seems to be by all means justified [16].

Blackstone [2], King [11] and Seifert [18, 19] analysed in their work the cases of more than 1000 patients with adenomatous gastric polyp. Ten per cent of the polyps were removed surgically, the other by the endoscope. Five per cent of those, 2 cm or more in diameter, proved to be histologically malignant. In cases where endoscopic removal was not complete, the tumour cells were situated in the peduncle or near the surface of the incision, operation was indicated. The type of operation, if biopsies performed in the environment had not been pathological, can be excision in toto. Gastric resection gastrectomy can be considered only in extensive polyposis or in case of an extremely large sessile polyp [12].

Due to an earlier lack of technical facilities, the number of gastric polypectomies is relatively modest. In the period when the conditions of endoscopic polypectomy had still not been provided, according to the up-to-date view, the detected gastric polyp cases were not biopsied but were referred to institutes where in toto endoscopic removeal was possible. We got feedback relatively rarely and so these cases could not be included in to our present material. The only case of malignancy during the 31 polypectomies of 25 patients was not assessible statistically because of the relatively low number of cases. It seems, however, justified by all means to remove the gastric polyps in toto, considering also the literary data [2, 11, 12, 14, 18, 19]. Our case reported in detail allows to draw several conclusions. On the one hand, it proved that two polyps of almost the same surfaces can have different histological characters in the same patient. That is why each seemingly similar polyp has to be re-



FIG. 5. Endoscopic picture of gastric polyposis by the JFB-type 2 device

moved, and it will not suffice to make the histological study of a polyp in a given case. In extensive polyposis (Fig. 5), where obviously only some polyps can be removed by the endoscope, resection is the method of choice. In patients at a considerable risk and of a poor general condition, endoscopic polypectomy performed in several steps can be considered with the removal of 3 to 6 polyps on one occasion. Another message of the reviewed case was that a long-ped-icled polyp can be drifted into the bulb by the peristaltics which may cause an obstructed passage.

Menetrier's syndrome and pernicious anaemia were rare findings during our study so we can not comment on them.

Scharschmidt [17] collected 120 cases of giant hypertrophic gastritis (Menetrier's syndrome). He observed some degree of malignancy in 10% of the cases. It should, however, be noted that these cases were operated relatively early for other severe complications of the disease such as electrolyte and protein loss and bleeding [6].

Zamchek [20] detected gastric tumour in 10% of the fairly large number of necropsies of patients with pernicious anaemia. According to him, carcinoma was due to achlorhydria. Others, like Hoffmann [10] do not agree with this.

One of the most strenuous but, at the same time, most promising tasks of the endoscopic laboratory is to control patients. Our experience, in agreement with the opinion of other teams studying a larger material, shows that a team including a surgeon, endoscopist and pathologist can hope for curing the malignant disease of the stomach more effectively than at present because of operation of cases detected earlier.

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Behandlung und Betreuung der Magen-präkanzerosen im 11jährigen Material der Klinik

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Analysiert werden jene Fälle des seit 11 Jahren in Betrieb stehenden endos-kopischen Laboratoriums der Klinik, die laut der in aller Welt anerkannten Auffassung als Präkanzerosen des Magenkarzinoms betrachtet werden können. Die Erfahrungen sprechen dafür, daß in der Heilung der malignen Magenkrankheiten - durch frühere chirurgische Behandlung der Patienten — nur dann ein Fortschritt zu erwarten ist, wenn das aus Chirurg, Endoskope und Pathologe bestehende Team die aktuellen Untersuchungen unter Berücksichtigung der prädisponierenden Faktoren durchführt und die Patienten regelmäßig kontrolliert.

Лечение прекарциноза желудка по 11-летним материалам нашей клиники

Й. ФАЛЛЕР, И. ШУГАР, Ф. ЯКАБ, Ю. МОХАЧИ и П. ОНДРЕЙКА

Авторы исследовали те случаи, отмеченные за 11-летний период деятельности эндоскопической лаборатории в нашей клиника, которые, согласно принятому во всем мире мнению, можно считать прекарцинозом желудка. Как показывает накопленный ими опыт, шаг вперед в лечении злокачественных заболеваний желудка можно ожидать лишь тогда — посредством операций в ранней стадии заболевания, — если рабочая группа, состоящая из хирурга, врача, производящего эндоскопию, и патолога, принимая во внимание предрасполагающие факторы выполняет актуальные исследования и осуществляет регулярное наблюдение за состоянием больного.

Clinicopathological Problems of the Local Tissue Effect of the Copper-releasing Intrauterine Contraceptive Device (IUD)

I. General Characteristics of the Copper-containing IUD (Clinical Study)

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As a first part of their series, authors discuss the clinicopathological problems of the tissue effects of copper-containing IUDs. They stress the possibilities of local injury caused by copper ions which play a role in enhancing the contraceptive effects.

Based on experience obtained so far, the clinicopathological problems of copper-containing IUDs are discussed. The occurrence in their direct vicinity of the effects which can be followed morphologically are surveyed. In the present paper the general characteristics of the copper-containing IUDs are dealt with.

According to their material and effect, two main types of IUDs are distinguished.

1. Inert devices made of a tissue-compatible material and/or a neutral metal,

2. Bioactive plastic devices medicated with some biochemically active additives.

The local effect of the devices on the endometrium not affecting its cycling function depends on the material of the device, on the contacting surface between the device and the endometrium (the size of the surface and the nature of the contact). In the tissues around the IUD, changes due to a sterile inflammation or foreign body effect can be observed (accumulation of macrophages and leukocytes which can become chronic subsequently). That bacterial effects do not play a role is proved by the fact that in experimental animals grown in a germ-free environment, the same reaction, i. e. sterile inflammation, is induced by the IUD.

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Beside the physical, chemical and biological relationships between the surface of the device and the endometrium, the contraceptive effect can be further enhanced by chemical and biochemical methods [4].

Zipper et al. were the first to observe that among metals studied (Ag, Cu, Mn, Sn), even traces of cytotoxic copper exert a strong contraceptive effect [5, 7, 24, 25, 26, 27, 29].

Their observation was utilized in a new bioactive generation of IUDs, i. e. the device was provided with a thin copper wire coil [2, 17, 18, 20, 21, 22, 23, 25], and later a cylinder-jacket made of copper plate of a copper surface of 200-380 m². The local effect of copper has also been confirmed by the neutron activation (serum, cervix mucus, endometrium) measurements of Orojan [19]. The decrease in the copper content of Copper T 200 with time was followed by Turay [28] by his polarographic method.

The oxidation of copper depends on several factors in the uterus (such as acid-base equilibrium, concentration of amino acids, oxygen level, amount of secretion, quality and size of the copper surface). A large copper surface is considered to be favourable. Dissolution of copper is explained by Kosonen [12] by the fact that copper is first oxidized on the surface of the wire then black copper oxide is dissolved by the amino acids of the uterine fluid.

According to Mensing [14], in the uterine fluid, i. e. a solution containing ions, metals have an electric field of force which may cause a change in pH. Consequently, the activity of pH-sensitive enzymes also changes. On the examination by the Kremer test of cervical mucus formed while using coppercontaining ('copper') devices, Orojan [17] found that a fairly small amount of copper ion blocks spermatocytes. According to Koch [9], copper inhibits transtubal sperm migration preventing zygote-formation. The presence of copper considerably enhances the effectiveness of devices made exclusively of plastic.

Copper is oxidized in utero, it is blackened and later on a moth-hole-like erosion and fragmentation of the wire are notable. In utero copper corrosion is dealt with in detail in the papers of Kosonen [10, 11, 12]. In the months following insertion, copper release from the wire of the IUD is 1.6–4.7 μ mol/d (100–-300 μ g/d), however this value decreases rapidly and after 3 to 5 months the value of 0.16–0.63 μ mol/d (10–140 μ g/d) is hardly diminished. A recent report of Chantler et al. [3] contains similar data for the Gravigaard device, i. e. the speed of copper release decreases exponentially with time, while during the average 41 months time of use the amount of copper per IUD decreases from 1.4 to 11. mmol. First organic material contacts the copper surface, forming an incrustate on it, followed by calcium salts. All these influence Cu²⁺ release, the electrochemical corrosion of copper. After the initially high copper release, the copper surface accessible to bio-oxidation is rapidly reduced independent of how much copper is retained on the device. In view of this, Elstein [5] arrived

at the conclusion that calcified IUDs should be replaced after two years or they should be left in the uterus for more than three years [1]. The in utero corrosion of the copper wire can be so marked that the wire is broken to pieces [15]. To prevent this fragmentation, first the wire diameter was increased to 0.25 then 0.3 mm (Multiload 250), then in utero a 0.1 mm thick non-corrosive silver thread (Nova T) was introduced into the wire in the hope that silver prevents its fragmentation and thereby the device can be used for at least six years [11, 13].

Theoretically, copper dissolution is accelerated if uterine fluid reaches silver, namely in heterogeneous alloys the electrochemical dissolution of copper of a lower potential is more rapid than that of pure metal. These earlier observations have been summarized in this paper to review the results of our further investigations concerning the several unknown effects of copper ions useful for contraception as compared to our earlier observations.

Later, the detrimental effect due to copper-containing IUDs undoubtedly useful from the point of view of contraception will also be presented.

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Klinikopathologische Probleme der lokalen Gewebewirkung kupferhaltiger intrauteriner Instrumente (IUI). 1. Allgemeine Charakterisierung der kupferhaltigen IUI (Klinische Studie)

K. PATAI, I. BALOGH und Z. SZARVAS

Im ersten Teil der Studienserie finden die klinikopathologischen Probleme der Gewebewirkung der kupferhaltigen Instrumente eine Besprechung. Damit im Zusammenhang wird auf die Möglichkeit der durch die Kupferionen verursachten lokalen Schädigungen aufmerksam gemacht, die in der Intensivierung der Antikonzipientwirkung eine Rolle spielen.

Клиникопатологические проблемы локального воздействия на ткани медьсодержащего внутриматочного средства (IUE = BMC) I. Общая характеристика содержащего медь ВМС (клиническое исследование)

К. ПАТАИ, И. БАЛОГ и З. САРВАШ

В первом сообщении своей серии авторы обсуждают клиникопатологические проблемы тканевого действия внутриматочных средств, содержащих медь. Они обращают внимание на возможность вызывания местных поражений ионами меди, которые играют роль в усилении противозачаточного действия.
Clinicopathological Problems of the Local **Tissue Effect of Copper-containing IUDs**

II. Electron-microscopic Study of the Endometrial Scraping

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For assessment of the tissue effect of copper-containing IUDs routine electron microscopic study was made of the endometrial scrapings. It was established that there was evidence of severe, degenerative changes not only on the IUD but also in the endometrial cells and, occasionally, also in the muscle layer of the uterus. These were characterized by pyknosis of the endometrial cells and alterations of the intracellular components. In this material of the study of 22 endometrial specimens obtained from beside IUDs, relatively few microtubuli were found in the endometrial cells. The changes seemed to be too severe to be ascribed to a sterile inflammation. The sporadic changes in the endothelial cells were found to be non-specific.

The ultrastructural study of the endometrium surrounding an IUD has started simultaneously with the first insertions of the devices [1, 3, 4]. The interpretation of the results of early electron microscopic studies has not been critical enough in the early phase. The changes detected were directly associated with IUD. Cellular damage connected with sample collection was only rarely considered and the erythrocytes found were evaluated as evidence of haemorrhage due to IUD. The present investigations were aimed at the electron microscopic study of 22 specimens of endometrial scrapings from areas close to IUDs performed for bleeding, to establish whether the subcellular changes were responsible for the appearance of clinical symptoms.

Material and Method

The 22 specimens of endometrial scrapings adjacent to IUDs collected for bleeding were studied electron microscopically. Fixation was made by immersing them into 2.5% glutaraldehyde (buffered by cacodylate), then the material was postfixed in 1% osmium tetroxide. Following dehydration and embedding, the ultrathin sections (Reichert U OM2 ultratome) stained with toluidine blue were used for orientation to exclude the mechanically destroyed cells from the evaluation. The ultrathin sections were studied by a JEOL 100 B

electron microscope (Central Electron Microscopic Laboratory of Semmelweis University Medical School) at an accelerating voltage of 60kV.

The duration of the use of the IUD was 1, 3 and 5 years, the age of the patients ranged between 19 and 36 years.

Results

The electron microscopic patterns of the 22 specimens of endometrium adjacent to IUDs did not differ from each other. There were severe pyknotic changes in the endometrial cells, which were characterized, beside nuclear changes, also by lipofuscin granules, lipid droplets, mitochondrial impairment and occasionally by the appearance of smaller amounts of microfilament bundles (Figs. 1–4). In the immediate vicinity of endometrial cells, closely connected to them, connective tissue cells were present as a partial phenomenon of cellular reparation (Figs. 5–8). Erythrocytes were rarely detected in the destroyed cells (Fig. 7). As a matter of course, extracellularly, several erythrocytes were present in the scrapings.

Discussion

In this material 22 specimens of endometrial scrapings collected for bleeding were processed electron microscopically. The specimens were obtained by routine curettage, which in itself can be associated with the direct damage of the endometrial epithelium as well as of the damage of the tissue adjacent to the device. Therefore, for orientation, semithin sections were used and the mechanical damage associated with curettage was excluded from the evaluation. As a matter of fact, acute cellular damage and acute necrosis were ignored. Beside the normal endometrial cells, the presence of an endometrial cell of a markedly pyknotic nucleus, occasionally with increased electron-density was characteristic in all 22 cases. Beside the endometrium in its immediate vicinity, signs of tissue reparation were apparent. The endothelial cells contained several osmiophils, intracellular structures surrounded by membrane, glycogen granules, lipid droplets, lipofuscin, damaged mitochondria and, occasionelly, widened sacs of endoplasmic reticulum, and microtubules. Since sample collection itself causes bleeding, the presence of erythrocytes was considered to be pathologic if they had already been organized or were closely connected with the cells.

Several inflammatory cells were also noted. Compared to date in the literature [1, 3, 4], relatively few microfilaments were found in the cells. Muscle changes in the endometrial muscle itself were also rarely found, which support the optimal pressure exerted by the device [2]. Vascular changes were



FIGS. 1–4. Pyknotic endoscopic cells. Electron microscopic study of the endometrial scrapings. In the cells, lipofuscin (lf), dilated rough endoplasmic reticulum (rer), mitochondrial (m) impairment and relatively few microfilaments (f) were found, X12.000



 FIGS. 5-6. In the reparation tissue, close to the device, connective tissue cells appeared, Fig. 5: X9600, Fig. 6: X12.000
 FIG. 7. Erythrocytes in the destroyed cells (rbc), X18.000
 FIG. 8. Pyknotic endometrial cell with destroyed mitochondria, X9600

detected only due to IUDs having been used for a long time in the uterus and causing complaints. These changes however, were non-specific in the endothelial cells and could have been caused by the effect of copper ions but also as a partial phenomenon to inflammation or connective tissue reaction.

It is of common knowledge that any kind of tissue-compatible metal or any other foreign body in the organism may trigger a defense reaction which induces connective tissue formation [2]. In the case of IUDs, the signs of sterile inflammation could be observed with various degree of changes of the endometrial cells. These changes seemed, however, to be graver and, in our opinion, could not be solely ascribed to sterile inflammation. Therefore, investigations were made for the ultrastructural cytochemical visualization of copper ions.

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Klinikopathologische Probleme der lokalen Gewebewirkung eines kupferhaltigen intrauterinen Instruments (IUI). 2. Elektronenmikroskopische Untersuchung des Gebärmuttergeschabsels

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Im Interesse der Auswertung der Gewebewirkung der kupferhaltigen intrauterinen Instrumente wurde das Gebärmuttergeschabsel elektronenmikroskopisch untersucht. Nebst den, auf dem IUI beobachtbaren Inkrustaten waren in den endometrialen Zellen und fallweise auch in der Muskelschicht der Gebärmutter, schwere durch die Pyknose der Endometriumzellen und die Veränderungen der intrazellulären Bestandteile charakterisierte degenerative Veränderungen nachzuweisen. Im Material waren anläßlich der Untersuchung der neben den intrauterinen Instrumenten liegenden Gebärmutterschleimhaut-Abschnitten in den endometrialen Zellen relativ wenig Mikrotubuli vorzufinden. Die Veränderungen schienen schwerer zu sein dazu, daß sie allein mit einer sterilen Entzündung zu erklären gewesen wären. Die in den Endothelzellen fallweise gefundenen Veränderungen zeigten keinen spezifischen Charakter.

Клиникопатологические проблемы локального воздействия на ткани медьсодержащего внутриматочного средства (IUE = BMC) II. Электронно-микроскопическое исследование маточного соскоба

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Для оценки воздействия на ткани внутриматочного средства, содержащего медь, авторы провели рутинные электронно-микроскопические исследования соскобов слизистой матки. Установили, что не только на внутриматочном средстве, но и в клетках эндометрия, а иногда и в мышечном слое матки обнаруживались тяжелые изменения дегенеративного тица, которые характеризовались пикнозом клеток эндометрия, изменениями внутриклеточных включений. При исследовании маточной слизистой около 22 ВМС было обнаружено в клетках эндометрия относительно малое количество микроканальцев. Изменения кажутся слишком тяжелыми, чтобы их можно было объяснить просто стерильным воспалением. Изменения, обнаруженные в некоторых случаях в эндотелиальных клетках, считаются не имеющими специфического характера.

Clinicopathological Problems of the Local Tissue Effect of IUDs Containing Copper

III. Cytochemical Study of the Endometrial Scrapings

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The clinicopathological problems of the tissue effect of copper-containing IUDs are discussed. In the third part of their series, authors present the cytochemical analysis of the endometrial scrapings. For the investigations, dithizone, salicylaldoxime, rubeanic acid as well as dimethylglyoxime were used. The reaction precipitate, the copper dithizone complex, could be visualized partly intracellulary and intramitochondrially and partly interstitially. The technical problems of copper demonstration are also dealt with.

It has been a long endeavour of clinical cytochemistry to be able to demonstrate in the normal and pathological processes, the site of enzyme functions, the permeability disorders as well as the foreign materials accumulating in the cells. It can be stated, in general, that for the cellular localization of the various enzyme functions, only an adequately pretreated, incubated and, sometimes fixed material is suitable (depending on the sensitivity of the enzyme). This basic requirement is, in most cases, not met by the surgical preparations, since, depending on the nature of the material, its placing in the appropriate medium (or its fixation) cannot be ensured during sample collection. Consequently, improved technical facilities are required as compared to traditional electron microscopic sample collection. In the electron microscopic and/or electron microscopic-cytochemical study of the endometrial scrapings, fortunately enough, it is possible to perform the preparative process immediately. Nevertheless, critical evaluation is also of prime importance. In our material the cytochemical demonstration of copper ions in the endometrial scrapings was attempted.

Material and Method

From the endometrial scrapings discussed in detail in the second part of our series, beside electron microscopic studies, the material fixed in 2.5% glutaraldehyde (dissolved in 70% ethanol) was treated by dimethylglyoxime,

salicylaldoxime, rubeanic acid as well as by dithizone for 5 min, then it was postfixed in 1% osmium tetroxide. The reaction precipitate was examined by X-ray diffraction and energy-dispersive analysis.

Results

Electron-dispersive metal-dithizone complexes were found in the endothelial cells of the scrapings (Figs. 1, 2, 3, 5, 6) intracellularly and intramitochondrially, in between the cells interstitially (Figs. 1, 5, 6), as well as in the connective tissue cells (Figs. 4, 8) in the material adjacent to the copper coil. The complexes could not be detected by dimethylglyoxime, salicylaldoxime or rubeanic acid.

Discussion

For the detection of trace elements, various materials have been used for a long time [14]. They have been demonstrated electron microscopically quite recently. The histochemical detection is aimed chiefly at demonstrating a large amount of extracellular copper. In a ligh microscopic magnitude, beside haematoxylin, ammonium sulphide, potassium ferrocyanide, hydrobromic acid, ammonium polysulphide, rubeanic acid dissolved in water, p-dimethylaminobenzylidene, rodanine, diphenylcarbazide, haematoxylin dissolved in ethanol, sodium diethyldithiocarbamate, rubeanic acid dissolved in ethanol, silver sulphide, rubeanic acid dissolved both in ethanol and sodium acetate, benzidene, o-toluidine as well as their combinations were used [14]. The electron microscopic dimension does, however, exclude several roughly aspecific reactions from the above series. Dithizone reaction is suitable for detecting 0.03 μg copper. In the literature, the majority of authors agrees that, under normal conditions, similar to other trace elements, copper ions cannot be detected cytochemically. In case of pathological, accumulated copper ions, however, there is a fair chance of detecting copper compounds, precipitate, etc. of some magnitude higher concentrations.

Control examinations were performed by using various reagents reacting with other trace elements. No reaction precipitate was observed when applying salicylaldoxime, rubeanic acid or dimethylglyoxime. In addition, the energydispersive as well as X-ray analyses of the sample were also performed for other elements. (It is well known that the material of copper grid renders impossible the determination of copper in the sample also during energydispersive analysis, and we had no possibility to use nylon grids. Peaks corresponding to other elements were not detected.) On this basis, we feel justified to assume that in the system examined by us, the reaction precipitate found was a copper-dithizone complex.



FIG. 1. Endometrial scrapings. Junction of endometrial cells. Electrocytochemical study. The metal-dithizone complexes (arrow) can be seen interstitially, X24.000

FIG. 2. Endometrial scrapings. Endometrial cell. Dithizone-metal complex is seen intracellularly, X24,000
 FIG. 3. Endometrial scrapings. Endometrial cell. Metal-dithizone complexes are noted intracellularly (arrow) and intramitochondrially (m). In the nucleus (n) there are no complexes, X12,000
 FIG. 4. Endometrial complexes and connecting tigue cell. The arrow is a set of the set of the

FIG. 4. Endometrial scrapings. Endometrial call and connective tissue cell. The arrow indicates the metal-dithizone complexes localized intracellularly, X24.000



FIG. 5. Endometrial scrapings. Endometrial cell. Intracellularly metal-dithizone complexes are noted (arrows), X18.000 FIG. 6. Endometrial scrapings. Endometrial cell. The arrow indicates the metal-dithizone

complexes of intracellular localization, X18.000

FIG. 7 and 8. Connective tissue cells from the region close to the copper coil. Metal--dithizone complexes can be seen both intracellularly and inter titially (arrows), X1800 for both figures

Detection of cytochemical trace elements has not been made so far in endometrial scrapings or in a sample derived from tissue adjacent to an IUD made of copper. Our material has supported our assumption that a chronic copper IUD while ensuring contraceptive effect interacts with endometrial cells, i. e. it induces connective tissue formation. Locally absorbed, the copper ions entering the circulation may influence or block several enzymatic reactions [5, 6, 7, 10, 11, 12]. It was shown by us that in isolated perfusion marked ultrastructural impairments occur dose dependently in the myocardium which also change the endothelial cells, the mitochondria of the heart muscle and probably also the contraction-relaxation mechanism [9]. The present investigations have supported that, during the increase of the local copper ion flux, the metal (copper) ions forming a complex with the reagent, dithizone, used by us penetrate the region around the cells, or the cells themselves. According to our hypothesis, not only the presence of a device but also copper ions damage the endometrium. It deserves special attention that a traceful amount of copper ions entering locally or probably also via the circulation, may influence other trace element metabolisms so e.g. the copper-cadmium balance in the kidneys, liver and intestinal mucosa, the copper-zinc balance, a. o. in the kidneys, liver, plasm as well as in the breast milk, and the iron, nickel and copper balance in the liver, the iron, copper and cadmium balance in the erythrocyte, by the upsetting of which impairments can be triggered in the organism on the basis of the domino principle [1, 2, 3, 4, 8, 13, 15, 16, 17]. The route by which copper ions enter the endometrium is still unknown. Intracellular accumulation by way of direct membrane impairment can also be supposed but even a competitive antagonist mechanism of action on the calcium metabolism cannot be excluded either, similar to the myometrium. To decide this, still further investigations are needed (membrane, tracers, labelled copper ion, etc.).

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Klinikopathologische Probleme der lokalen Gewebewirkung kupferhaltiger intrauteriner Instrumente (IUI). 3. Zytochemische Untersuchung des Gebärgeschabsels

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Die Arbeit befaßt sich mit den klinikopathologischen Problemen der lokalen Gewebewirkung der kupferhaltigen intratuterinen Instrumente. Im dritten Teil der Serie wird die zytochemische Analyse der Gebärmuttergeschabsel dargestellt. Zu den Untersuchungen wurden Dithizon, Salizylaldoxim, Rubeansäure sowie Dimethylglioxim angewandt. Das Reaktionssediment und der Kupferdithizon-Komplex waren teils intra-zellulär und intramitochondial, teils im Interstitum sichtbar. In den Zellkernen ließen sich keine Komplexe beobachten. Abschließend finden die technischen Probleme des Kupfernachweises eine Besprechung.

Клиникопатологические проблемы локального воздействия на ткани медьсодержащего внутриматочного средства (IUE = BMC) III. Цитохимическое исследование маточного соскоба

К. ПАТАИ, И. БАЛОГ и З. САРВАШ

Авторы обсуждают клиникопатологические проблемы действия на ткани внутриматочных средств, содержащих медь. В своем ІІІ-м сообщении авторы знакомят с результатами цитохимического анализа меточного соскоба. В этих исследованиях они применяли дитизон, салицилальдоксим, рубеановую кислоту и диметилглиоксим. Реактивный осадок, комплекс медь-дитизон можно было увидеть отчасти внутри клеток и митохондрий, отчасти в интерстиции. Комплексы не были обнаружены в клеточных ядрах. Авторы занимаются техническими проблемами обнаружения меди.

Longitudinal and Vertical Ultrastructural Lesion of Crural Muscle in Post-thrombotic Syndrome

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The vertical and longitudinal ultrastructural changes of the crural muscle (triceps surae) were studied in a selected patient material of 18 patients suffering from post-thrombotic syndrome. The transmission and scanning electron microscopic method helped in revealing that the damage had affected the contractile system, the mitochondria and the endoplasmic reticulum and in addition marked degenerative phenomena occurred.

It was shown that vertically the impairments of the fine structure were localized in foci and involved the muscle layers to the same extent. Longitudinally — distally — the muscle changes displayed an increasingly aggravating diffuse appearance.

Of the several factors responsible for the development of the pathological ultrastructural picture, tissue hypoxia and metabolic disorder, as well as a decreased microciruclation (hypoperfusion) and chronic inactivity are to be emphasized.

The understanding and interpretation of pathological processes developing in post-thrombotic syndrome are attempted primarily by the haemodynamic examination of the insufficient venous flow as well as the study of the metabolic disorders of the muscle tissue [10, 15, 16, 24]. Further progress can be expected by studying the consequential fine structural lesions arising in the extremital muscles. Based on them, new vistas can be opened up in conservative and surgical treatment as well [2, 3, 11, 12].

Formerly, marked ultrastuctural changes in the superficial layers of the post-thrombotic crural muscle have been demonstrated [20].

Our paper aimed at studying the longitudinal and vertical ultrastructural damages developing in the crural musculature in patients suffering from post-thrombotic syndrome.

Material and Method

Selection of Patients

In the first stage, patients were selected according to the characteristic symptoms and clinical manifestation of post-thrombotic syndrome.

In the second stage of the selection, haemodynamic and morphological examination procedures were applied.

The methods of selection were as follows:

1. Ascending phlebography;

2. Venous occlusive plethysmography.

The technical applicability of both methods and their calculation were treated in previous studies [20].

The ultrastuctural investigations were performed in 18 patients (11 females and 7 males) with a disease approximately identical in severity (mean age: 45.5 years).

Electron Microscopy

Collection of muscle samples was made under sterile conditions from a skin incision of a few millimetres, under local anaesthesia.

a. The examination of the vertical muscle impairment was made from a specimen taken from the upper third of the triceps muscle of the calf from depths of 5-6, 10-12 and 20-24 mm.

b. The longitudinal damage was studied by muscle samples collected from the upper middle and lower thirds of the leg from a depth of 5-8 mm.

The specimens were processed by transmission (TEM) and scanning (SEM) electron microscopic techniques.

Transmission electron microscopy. 10–15 mm long muscle pieces of a width of 2–3 mm were fixed at inactive length or in a slightly stretched state atraumatically on a bent glass rod. Then the samples were placed in a mixture of glutaraldehyde and 0.1 M phosphate buffer (pH 7.2) of a ratio of 1 to 3, for two hours. They were then postfixed in a buffered solution of 1% osmium tetroxide and, finally, after dehydration through graded alcohol, they were embedded in Araldite. The contrasting of the ultrathin sections was made by uranyl acetate and lead citrate. Sections were viewed and photographed under a JEOL 100 C electron microscope.

Scanning electron microscopy. As compared to TEM, a larger material was collected which was processed similar to TEM. The fixation was modified by placing the samples into glutaraldehyde for 24 hours. After dehydration, the samples were saturated with Araldite without polymerization. Following freezing, they were broken then the synthetic resin was dissolved in propylene oxide. After critical point drying the samples were gold-coated in a vacuum vaporizer and they were studied under a JEOL 100 C electron microscope at an accelerating voltage of 20 kV.

Results

For clarifying the problem, investigations were carried out in two directions.

a. Vertical muscle damage. The muscle samples collected from all three depths displayed fine structural lesions. Characteristic changes were shown by the contractile elements, mitochondria as well as the transversal and longitudinal tubules of the sarcoplasmic reticulum. Interfibrillarily, degenerative phenomena occurred.

Of the changes of the contractile elements, the impairment of the I--segment, i. e. partial, more rarely complete rupture, can be considered to be characteristic. The A-segments often showed overstretching. The Z-band widened, became serpiginous and occasionally fragmented (Fig. 1). The myofibrils were separated by oedema.

The moderate dilatation of the T-tubule system belonging to the sarcoplasmic reticulum could be considered to be of the same degree for each muscle layer examined. The subsarcolemmar space was dilated with the appearance of oedema. The sarcolemma was occasionally fragmented.

Their increase in number, the morphological deformity and the change of density were characteristic of the mitochondrial damage of all muscle layers. The development of various forms, ranging from giant round or flattened to the lobular, small forms, could be due to tissue oedema (Fig. 2). There was also an intramitochondrial damage, i.e. decrease, in other places, of density



FIG. 1. Muscle sample obtained from a depth of 10 mm. Irregular Z-bands, with moderate hyperplasia, X12.000



FIG. 2. Muscle sample taken from a depth of 10 mm. Cumulative polygonal mitochondria. Accumulation of glycogen granules, X19.000

with rupture or occasional disappearance of the internal lamellar system. Also amorphous dense granules appeared.

The nuclei were not changed. A characteristic alteration was the accumulation of interfibrillar glycogenic granules in foci. Cumulatively round or oval lipid vacuoles were seen which often compressed the sarcomeres (Fig. 3).

Hyperplasia separating the myofibrils was present in all three muscle layers studied.

According to our observations, the impairments detected appeared in foci, i.e. intact substance could be noted adjacent to the damaged muscle tissue. Otherwise the changes involved all three muscle layers to the same extent.

b. Longitudinal muscle damage. The contractile elements, mitochondria as well as parts of the sarcoplasmic reticulum were severely impaired in the tissue samples taken from all three regions. Beside them, a marked hyperplasia and necrosis appeared.

There was evidence of disorganization in the myofibrils. Along the I-segment fragmentation and lysis were notable. Beside being extended. The A-segments were fragmented and lysis appeared. The Z-bands widened and disappeared. The M-line was serpiginous with the H-zone missing in several places. Severe interfibrillar oedema was observed.

The already described deformity of the mitochondria became more accentuated. Intramitochondrially, the characteristic picture showed, beside the fragmentation of the internal lamellar system and the decreased density



FIG. 3. Muscle sample taken from a depth of 20 mm. There are several round lipid vacuoles in between the myofibrils. Dense mitochondria, X20.000



FIG. 4. Impairment of the sarcomere with interfibrillar oedema. Disintegration of the internal lamellar system of mitochondria, X18.000

of the matrix, the disappearance of cristae (Fig. 4.). Intramitochondrially, inclusions were noted. The longitudinal and transversal tubules of the sarcoplasmic reticulum and of the triads were considerably dilated. The subsarcolemmar space was filled by oedema.

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There was an accumulation of the sharp-contoured, round lipid vacuoles appearing interfibrillarily (Fig. 5). The glycogen granules were also accumulated.



FIG. 5. Z-band deformity. Lipid vacuoles compressing the sarcomere. Hyperplasia, $$\rm X17.000$$



FIG. 6. Marked hyperplasia with cumulatively occurring polymorphous mitochondria, X17.500





As a sign of degenerative change, marked hyperplasia could be seen replacing the myofibrils in continuous regions (Fig. 6). Adjacent to them, necrotic phenomena could be observed.

The capillary impairment was easily discernible by SEM. Their lumina were filled with unidentified structures, walls were fragmented and had become patent to tissue fragments, and ecchymoses developed. Red blood corpuscules occurred cumulatively in the perivascular space (Fig. 7.). The swelling of the capillary endothelial cells narrowed the lumen. The severe morphological picture was indicative of a microcirculatory disorder.

In the nuclei of the muscle cells, the chromatin substance was fragmented. The nuclei were enlarged and oedematous.

According to our observations, the severity of the fine structural changes detected increased distally and became diffuse.

Discussion

In the past decades the frequency of diseases due to the venous circulatory disorder of the lower limb increased. The pathological picture recognized only late or an inadequate therapy can by all means contribute to the development of chronic venous circulatory insufficiency. Among others, the clinical importance of post-thrombotic syndrome is considerable. It can be stated that our knowledge concerning the pathophysiological and haemodynamic features of post-thrombotic syndrome and the morphological damage of the vascular wall has been considerably enriched [1, 4, 9, 13, 14, 22]. At the same time, there are no data available on the nature, extent and severity of the fine structural changes.

The ultrastructural damage developing in the superficial layers of the post-thrombotic crural muscle has earlier been demonstrated [20]. Of them, the changes of the contractile system, of the mitochondria and of the endoplasmic reticulum were found to be the most characteristic. In the present material, the vertical and longitudinal fine structural alterations developing in the crural muscle were studied.

Among the impairments of the samples taken from three different depths, the injury of the contractile system i.e. the fragmentation of the I-segment, the widening and serpiginousness of the Z-band as well as myofibrillar oedema are to be emphasized. Similar ultrastructural changes may be associated also with other pathological processes. Similar observations were made by Józsa et al. [7] following tendon injuries. Trout et al. [25] studied the phenomeonon of degeneration in the latissimus dorsi muscle. The thickening of the Z-band, the decrease and rupture of the myofibrils are regarded as characteristic. Ingjer [5] compared untrained healthy people with skiers: the muscle samples collected from the quadriceps muscle revealed a significant difference in the fibre type A II. In their investigations the importance of inactivity is emphasized. Sjöström et al. [17] demonstrated Z-band alterations and glycogen accumulation in the biopsy material obtained from the anterior tibial muscle of patients with arterial stenosis. According the the animal experiments of Kurasz and Andrzyewska [8], local injury with cold in the anterior tibial muscle causes myofibrillar destruction and membrane lesion. Jakubiec--Puka and Kulesza [6] described the reduction in the diameter of the soleus muscle one or two weeks following denervation of the rat hindlimb. Taheri et al. [21] studied light microscopically and histochemically the fibres of the gastrocnemius muscle in venous insufficiency. According to their statement, the development of muscle fibre atrophy and necrosis are largely due to ischaemia.

As observed by them, several factors can be made responsible for the pathological structural change of the contractile elements among them, the chronic inactivity, as well as the effect of tissue hypoxia. This latter may induce local metabolic disorders.

In our material, of the mitochondrial damages—in all three proximal layers—the change in density and shape, while in the distal regions of the leg the rupture and lysis of the internal lamellar system are predominant. Józsa et al. [7] found mitochondria with swollen fragmented lamellae being shrunk in other places in human muscles with rupture of the tendon. The injury of the mitochondria indicates the disorder of the cellular energy metabolism. In giving rise and maintaining the pathological mitochondrial processes, hypoperfusion and the consequential tissue hypoxia as well as a regional metabolic disorder may play important roles.

In the vertical studies a moderate dilatation of the transversal and longitudinal tubules of the sarcoplasmic reticulum, while a severe one of the samples from the distal regions were found. Somogyi et al. [19] described the impairment of the sarcotubular system as a consequence of hypoxia in animal experiments in a biopsy material obtained from the quadriceps muscle. Józsa et al. [7] found dilatation of the sarcoplasmic reticulum in muscle inactivities of various duration. In post-thrombotic syndrome, both alterations may exist.

According to our investigations, lipid vacuolization appearing vertically in foci and occurring diffusely in the distal muscles, as well as the interfibrillar hyperplasia can be assessed as signs of the degenerative process. The pathological haemodynamic relationships exert probably their effect more in the distal muscles. Sjöström et al [18] emphasize the possibility of immobilization in the development of the process.

The impaired capacity of the capillary network has a great share in the development of the fine structural injuries. The demonstrated endothelial damage narrowing the lumen and the rupture of the capillary wall resulting in the perivascular and interfibrillar appearance of unidentified structures undoubtedly induce tissue hypoperfusion.

Our investigations have proved that marked fine structural changes arise in the post-thrombotic crural muscles; transversally in foci and to the same extent, while longitudinally in an increasingly aggravated and diffuse form.

Our investigations have not clarified the reversibility of the detected pathological ultrastructural alterations and whether the conservative and/or surgical interventions performed at an elective time are capable of exerting a favourable effect. These questions are still to be answered by clinicomorphological investigations in progress.

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Longitudinale und vertikale ultrastrukturelle Schädigung der Unterschenkelmuskulatur bei postthrombotischem Syndrom

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Bei einem, aus 18, an postthrombotischem Syndrom leidenden Patienten bestehenden, ausgewählten Krankengut wurden die vertikalen und longitudinalen ultrastrukturellen Veränderungen der Unterschenkelmuskulatur (M. triceps surae) untersucht. Mit den Transmissions- und Scanning-elektronenmikroskopischen Methoden wurde festgestellt, daß sich die Schädigung auf das kontraktile System, die Mitochondrien und auf das endoplasmatische Retikulum erstreckte, daneben aber auch bedeutende degenerative Erscheinungen auftraten.

Es wurde nachgewiesen, daß sich die feinstrukturellen Schädigungen in vertikaler Richtung in Herden befanden und die Muskelschichten in identischem Ausmaß betrafen. In longitudinaler Richtung — distal — zeigten die Muskelveränderungen stets schwerere, diffusere Formen.

Unter den zahlreichen Faktoren, die für die Entwicklung des pathologischen ultrastrukturellen Bildes verantwortlich sind, ist vor allem der Gewebehypoxie, der Metabolismusstörung sowie der verringerten Mikrozirkulation (Hypoperfusion) und der chronischen Inaktivität eine Bedeutung beizumessen.

Продольно и вертикально направленные ультраструктурные изменения мышц голени при посттромботическом синдроме

т. смоленский, б. марк, т. кишш и к. тромбиташ

У 18 отобранных больных, страдающих посттромботическим синдромом, авторы изучали вертикальные (глубинные) и лонгитудинальные (продольные) ультраструктурные изменения мускулатуры (*m. triceps surae*) голени. С помощью методов трансмиссивной и электронной микроскопии установили, что повреждение затронуло сократительную систему, митохондрии и эндоплазматический ретикулум, и наряду с этим появились признаки значительной дегенерации.

Было показано, что в вертикальном направлении тонкоструктурные повреждения располагались в виде очагов и в одинаковой степени затрагивали мышечные слои. В продольном направлении — дистально — обнаружили все усиливающиеся, диффузные изменения мышц.

Среди многих факторов, играющих роль в возникновении патологической ультраструктурной картины, надо выделить тканевые гипоксические и метаболические нарушения, а также ухудшение микроциркуляции гипоперфузия/ и хроническую неактивность.

Aimed Application of Antibiotics in Treating Hand Infections

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Surgical exploration is of prime importance in treating hand infections. In addition, it is essential to apply up-to-date and adequate antibiotic treatment. Authors employed antibiotics during the treatment of hand infections of 65 various actiologies and types by considering the antibiotic sensitivity spectrum of the most frequent pathogens as also the effective concentration of the antibiotic acting in the inflammatory focus. For assessing effective antibiotic concentrations, samples were collected during exploration from the inflammatory tissues, and based on their essessments, it was pointed out that an adequate inhibitory antibiotic concentration cannot be reached by each antibiotic by applying it in the usual dose and way.

The use of certain antibiotics is recommended in view of the most frequent pathogens of hand infections, of the spectrum of the antibiotic selected by the authors as well as in that of the measured tissue antibiotic concentrations in the dosage used by them. The effective application as well as dosage are also published.

Regarding that, in practice, antibiotic treatment should be started according to the nature of the disease without knowing the spectrum of resistance and the pathogen, it is considered important for them to select initially, beside the surgical treatment, an antibiotic which is probybly effective and is capable of entering in a sufficient amount the focus of inflammation.

Currently, several antibiotics of excellent pharmacokinetic properties and of a broad spectrum are available which are extensively applied in treating inflammatory diseases. Although early surgical management plays an undisputably decisive role and this cannot be replaced by any other method, the basic rules of applying antibiotics as a complementary treatment cannot be neglected either. An antibiotic treatment being (i) therapeutic, (ii) aimed and (iii) used for a sufficient time is required.

Of these requirements, the implementation of the aimed treatment is the most difficult one since no resistance test is available in the first days of treatment.

In clinical practice, therefore, in general, a broad-spectrum antibiotic is prescribed or an antibiotic combination which is capable of affecting the most frequent pathogens based on in vitro investigations. After assessing the bacteriological findings of a previous period, the bacteria were determined which could be effective with a high probability in clinical practice (Table 1).

Using an aimed antibiotic, an antibacterial effect can only be expected if an effective antibiotic concentration can be achieved not only in the blood

Г	A	R	T.	E	1
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Streptoc. beta haemolyt.	<i>Streptoc.</i> alpha haemolyt	Staph. zur.	Staph. albus	E. coli	Klebsiella
10	12	78	8	5	6
	S	Sensitivity	y(n)		
9	11	22	6	-	
9	5	64	7		-
6	5	27	3	3	3
7	5	31	2	1	_
5	5	70	6	_	
8	9	51	4		
5	7	74	5		
10	10	60	7	3	3
9	6	68	5		
1	7	72	6	4	4
	1	68	6	4	2
	Streptoc. beta haemolyt. 10 9 9 6 7 5 8 5 10 9 1	$\begin{array}{c cccc} Streptoc. & Streptoc. \\ alpha \\ alpha \\ haemolyt \\ \hline 10 & 12 \\ \hline 9 & 11 \\ 9 & 5 \\ 6 & 5 \\ 7 & 5 \\ 5 & 5 \\ 8 & 9 \\ 5 & 7 \\ 10 & 10 \\ 9 & 6 \\ 1 & 7 \\ - & 1 \\ \hline \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c c c} Streptoc. \\ beta \\ haemolyt. \\ \hline \\ 10 \\ 10 \\ 12 \\ \hline \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 $	$\begin{array}{c c ccccccccccccccccccccccccccccccccc$

Overall microbiological results of 100 patients treated for hand infections

*The antibiotics, which were marked out for further investigation. Cefuroxime (Zinacef) was studied on the basis of its optimal spectrum (3, 5).

but in the inflammatory tissue as well. It is known from pharmacokinetic studies [5, 6, 7] that, during an antibiotic treatment of routine dosage, an effective tissue concentration cannot be reached by each antibiotic and consequently antibiotic concentrations were defined during data collection.

Material and Method

Our investigations were carried out in recent years during the management of 65 patients presenting with hand infections and treated at our clinic.

Administration of the antibiotics listed below had been started prior to surgical exploration:

Cephalothin (Keflin, E. Lilly) 15-20 mg/kg. i.m.

Cefuroxime (Zinacef, Glaxo) 20-25 mg/kg i.v.

Clindamycin (Dalacin, Cleocin UpJohn) 8-10 mg/kg i.m.

The patient received the first dose of the selected antibiotic 1 to 4 hours prior to surgica exploration. This period is the waiting time for the patient to be ready for anaesthesia which elapses between the establishment of surgical indication and the exploration. Intraoperatively, samples were taken from the inflammatory tissue and the peripheral blood for assessing antibiotic concentration. The values were obtained counting from the administration, at various times. The antibiotic concentrations were determined by a microbiological method by the diffusion procedure according to Grove-Randall [2]. A strain



FIG. 1A, B. The tissue and serum concentration values of the chosen antibiotics plotted against time. The MIC values of the individual antibiotics were indicated by a horizontal line. (For details see text)

ATCC 6633 Bacillus subtilis was used as a test bacterium. (The examinations were carried out in the Institute of Microbiology.) The obtained values were plotted against time. For each antibiotic 20–25 blood or tissue samples were collected. The concentrations in the peripheral blood and the tissue samples in the 1st, 2nd, 3rd and 4th hours were calculated from the concentrations obtained in such a way. Based on these data, a column diagram was constructed (Figs. 1a,b).

The tissue concentrations were compared with the minimal-inhibitory concentration (MIC) of the individual antibiotic against Staphylococcus aureus [1, 3, 4, 5]. The tissue concentration measured by us was considered to be effective if it had reached or exceeded the known MIC levels against Staphylococcus aureus.

On surgical exploration, specimens needed for the standard microbiological tests were also obtained from which bacteriological culturing and resistance test were made.

Results

The antibiotic concentrations measured following administration of Cephalothin and Cepiroxime are shown in Fig. 1 α plotted against the hours elapsed from administration. As seen, during Cephalothin treatment, with acceptable blood levels, no effective antibiotic concentration was found in the inflammatory tissues, so this drug, we believe, cannot be used in this form for treating several hand infections. Using Cefuroxime, however, fairly favourable concentrations were observed in the inflammatory tissue. One or three times higher concentrations than MIC values lasting for 4 hours were found.

Also favourable observations were made following the i.m. administration of 600 mg Clindamycin. This antibiotic in the selected dose reached an effective level in the focus of inflammation for 4 hours (Fig. 1*b*). The tissue concentrations exceeded 1 to 5 times the value of MIC and in case of this bacteriostatic drug, this was sufficient for a bactericidal effect as well.

Discussion

In the present paper we do not wish to consider the detailed surgical management of hand infections, but it should be emphasized that early exploration for curing the disease cannot be replaced by anything else. This treatment strategy did not imply that we declined from adopting the general rules of antibiotic treatment. In treating hand infections aimed antibiotic treatment in a therapeutic dose and prolonged for the elimination of the

inflammation should also be employed. The possibilities of an actually effective antibiotic treatment feasible in clinical practice were studied. According to literary data and to our own investigations, for the Staphylococcus and Streptococcus-like strains causing most frequently hand infections, the antibiotics used by us [3, 8] are effective (Table 1). This fact gains importance if we consider that in everyday practice the antibiotic treatment following the management of the infected hand must be started without knowing the pathogen and the spectrum of its resistance. The antibiotic is also expected to ensure an effective drug level in the inflammatory focus. Therefore, neither the mode of application nor dosage, can be indifferent. We thought that after the apposite selection of the antibiotic, it is the simplest way of being convinced about the effectiveness of the drug if the antibiotic concentration is measured in the focus of inflammation thereby eliminating the differences arising from the absorption, distribution, metabolic and elimination properties of the individual drugs and and so we obtain highly relevant data. Therefore the serum and tissue antibiotic concentrations were measured simultaneously. The tissue antibiotic levels were followed up in time from the administration and compared with the MIC levels against Staphylococcus aureus. (These values for the given antibiotic are known from the literature [1, 3, 4, 5]). Effective concentrations were looked upon those exceeding MIC concentration, since this pathogen was most often encountered during microbiological investigations.

As can be seen from the measurement results, certain antibiotics in certain dosage ensure with high probability the expected clinical results after surgical exploration while others seem not to be suitable for treating hand infections of the antibiotics used by us. Based on our investigations, the i.m. administration of 600 mg Clindamycin at every 8 to 12 hours and the i.v. administration of 1,5 Cefuroxime 6 to 8 hour intervals are recommended. The usual dose of 1 g of Cephalothin at intervals of 6 hours is not considered effective for treating hand infections.

It should be noted that the standard microbiological tests should be performed in each case and treatment should be changed in view of the antibiogram.

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Gezielte Anwendung der Antibiotika bei der Behandlung der Handinfektionen

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Bei der Behandlung der Handinfektionen ist die chirurgische Freilegung von entscheidender Bedeutung, gleichzeitig ist aber auch die richtige Anwendung der zeitgemäßen Antibiotika fast obligatorisch. Im Laufe der Behandlung von 85 Handinfektionen mit unterschiedlicher Ätiologie und von unterschiedlichem Typ wurde die antibiotische Behandlung unter Berücksichtigung des Antibiotikumempfindlichkeits-Spektrums der am häufigsten vorkommenden Krankheitserreger sowie der effektiven (im entzündlichen Herd wirkende) Konzentration des betreffenden Antibiotikums eingesetzt. Zwecks Bestimmung der effektiven Antibiotikumkonzentration wurden im Laufe der Freilegung aus dem entzündlichen Gewebe Proben entnommen; anhand der Meßergebnisse wird darauf hingewiesen, daß die geeignete, bakteriostatische Antibiotikumkonzentration mit der üblichen Dosierung und Applikation nicht mit allen Antibiotika erreicht werden kann.

In Kenntnis der häufigsten Krankheitserreger, des Wirkungsspektrums der ausgewählten Antibiotika sowie der nebst der angewandten Dosierung gemessenen Gewebe-Antibiotikumkonzentrationen wird die Anwendung gewisser Antibiotika, ihre wirksame Applikationsweise sowie ihre Dosierung empfohlen.

In Anbetracht dessen, daß in der Praxis die antibiotische Behandlung der Eigenart der Krankheit gemäß ohne die Kenntnis der Resistenz, des Spektrums und des Krankheitserregers begonnen werden muß, ist es von Wichtigkeit, daß bereits am Anfang ein Antibiotikum gewählt werde, welches mit großer Wahrscheinlichkeit wirksam ist und in genügenden Mengen in den entzündlichen Herd eindringen kann.

Целенаправленное применение антибиотиков при лечении заражения рук

М. КУБАТОВ, Р. ЛАКИ и Б. КОЧИШ

В лечении инфекции рук решающее значение принадлежит хирургическому вскрытию, наряду с этим необходимо также правильное применение современных антибиотиков. При лечении 85 инфекций рук разного типа и различной этиологии авторы применяли антибиотитическую терацию таким образом, что принимали во внимание сцектр чувствительности к антибиотикам наиболее часто встречающихся патологических возбудителей, а также эффективную для данного лица концентрацию антибиотика (действующую в очаге воспаления). С целью определения эффективных концентраций антибиотика, при вскрытии очага брали образцы воспаленных тканей; на основании измерений, авторы обращают внимание на то, что соответствующая тормозящая концентрация антибиотика при обычном дозировании и способе применения может быть достигнута не любым антибиотиком.

Зная наиболее часто встречающиеся при инфекции рук возбудителей, спектр действия выбранных ими антибиотиков, а также определенные при данной дозировке концентрации антибиотиков в тканях. авторы рекомендуют применять определенные антибиотики. Знакомят с эффективным методом применения, указывают соответствующие дозы.

Принимая во внимание, что на практике приходится начинать терапию антибиотиками исходя из характера болезни, но еще не зная спектр резистентности и возбудителя заболевания, авторы считают важным, чтобы — наряду с хирургическим лечением уже в самом начале лечения был бы выбран такой антибиотик, который с большой долей вероятности является эффективным и способен в достаточном количестве попасть в воспалительный очаг.

Multiple Primary Malignant Tumours of Patients Treated for Colorectal Carcinoma (Clinical Analysis of 61 Cases)

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Multiple primary malignant tumours were found by the authors in a population of 543 patients treated during 10 years for colorectal cancer at an incidence rate of 11.2%. Thirty-nine of 69 patients had tumours of metachronous and 22 of synchronous appearance. Of patients treated for multiple tumours, the ratio of women (p < 0.1) was much higher, the average age was much (2 years) higher and occurrence of malignant disease in the family was more frequent than in those with a solitary tumour. Based on the high incidence reported on in the literature and in their own material, they draw attention to the practical, clinical aspects of the problem. The difficulties in diagnosing multiple colonic tumours are described in detail, pointing out the importance and possibility of pre- and intraoperative examinations aiming at completeness. Based on survival data, it is stated that multiple malignancies do not by all means imply incurability. An improvement of therapeutic results is expected, beside the improvement of surgical results, of the introduction of up-to-date examination methods, of the care and continuous follow-up of the patients at risk.

Multiple primary malignant tumours have been known in the circle of experts concerned with research and treatment of tumours since the last century [20]. The first comprehensive case report is attached to the name of Billroth, who, by presenting three of his own cases, established also the criteria which serve as a basis for diagnosing multiple primary tumours. Accordingly, the tumours are supposed to be of different histological structure, different in origin and having their individual metastases [5]. According to our current views, the latter condition is not valid while the first two, however, proved to be permanently valid. At present, the characteristics of multiple primary malignant tumours are formulated according to the report of Warren and Gates published in 1932, however, somewhat modified as follows: The tumours should be (i) truly malignant; (ii) differing in histological structure, (iii) in csse of identical localization, they should be removed from each other at an adequate distance, and (iv) they should not be metastatic or recurrent tumours.

These principles are equally valid for synchronous (simultaneous) and, asynchronous (metachronous, heterochronous) tumours. The incidence rate of primary multiple malignant tumours was found to be 1-12% in collected

data [15, 17, 18, 21]. Accordingly, it can be stated that the clinical importance of the issue goes beyond the level of pathological rarity and it can also be assumed that the study of multiple tumours may also help in clarifying the problems of carcinogenesis and of natural antitumour immunity.

Patients

Between January 1, 1970 and December 31, 1979, a total of 543 patients were treated for colorectal cancer at the 1st Department of Surgery, Semmelweis University Medical School. Patients suffering from primary multiple malignant tumours were selected from this material. Our cases included therefore exclusively those whose 'index tumour' was colorectal in origin. Patients with multiple tumours arising from familial colonic polyposis were excluded from the study, i.e. synchronous ones localized within a distance of 10 cm from each other or metachronous tumours developing in the vicinity within 10 cm of an earlier site or operation (anastomosis).

In view of the published data, metachronous tumours were considered those developing after a time longer than one year. Our retrospective analysis incorporated also necropsy results. The study was closed on 31, December 1985.

Results

In our material of 543 colorectal tumour patients, primary multiple malignant tumours were found in 61 cases. In the 61 patients a total of 129 tumours were detected. It is noteworthy that among those treated for multiple tumours, the ratio of women was much higher, average age was higher and the malignant disease of the immediate family members was more frequent (Table 1), but the differences are not significant.

Of the patients with synchronous tumours, two were lost during operation. The average survival time of the others was 44 (3-76) months. The

	Tumour						
	Solitary			Multiple			
	n	%	Age (yrs)	n	%	Age (yrs)	
Male	237	49.2	61.7	22	36.1	64.8	
Female	245	50.8	62.3	39	63.9	63.4	
Total	482	100.0	62.0	61	100.0	64.0	

TABLE 1

Distribution of patients according to sex and age

metachronous tumours were, on average, detected 65 (12–216) months after the first operation, the survival time of these patients calculated for the latest tumour was 16 (2–57) months. On termination of the investigation four patients were living (6.6%), of them two each had syncrhonous or metachronous tumours. Of the synchronous tumours, preoperative examination had revealed only 18 cases. Intraoperatively, the second tumour was detected in two cases and additional two were only revealed by autopsy, 63.0% (39 patients) of multiple tumours were metachronous. Treatment for a malignant process appeared in the histories of 21 of them. These, as tumours preceding index tumours are summarized in Table 2. The table also shows the localization and histological structure of tumours appearing after treating index tumours. Of these, 11 developed in the colon and 8 in other organs. Of the synchronous tumours, amounting to 36.1% (22 patients), of all cases four were not colorectal

TABLE 2

1st tumour	Index tumour		2nd tumour Colon and rectum $7 + (2)$		3rd tumour		4th tumour	
SKIN basocellular carci- noma					Colon	(2)	Colon	(1)
LARYNX planocellular c.	2		Lip planocellular	1 c.	Ovaries adenoc.	1		
BREAST medullary c. intraductal c.	3 + (2)		Lung anaplastic c.	1				
OVARIES adenoc. cystoc.	3		Breast Paget c. Ovaries	(1)				
UTERUS adenoc.	3 Co re 35	blon and tum	Small bowel gelatinous c.	(1)				
KIDNEYS hypernephroma	(1)		Thyreoid adenoc.	1				
PROSTATES	2		Haemopoietic and lymphatic	1 c system				
STOMACH adenoc.	2							
BILE DUCT adenoc.	1							
HAEMOPOIETIC AND LYMPHATIC SYSTEM CLL	1							

Distribution of metachronous tumours

Note: In brackets: triple and quadruple metachronous tumours. Each of the colorectal tumours is an adenocarcinoma.

T	ARTE	3
	ADLL	J

Synchronous tumous Heamo-Des-Ascenpoietic cending Transding Index tumour lympn Rectum Sigmoid Caecum Lungs Prostate colon colon verse hatic colon and flex. 1. flex. h. system 1 1 Rectum 12 1 7 1 1 4 + (1)1 (1)1 Sigmoid 1 (1)1 Descending colon flex. 1. 2 1 1 1 Transverse colon 1 Ascending colon + flex. h. 1 1 1 1 Caecum

Distribution of synchronous tumours

Note: In brackets triple synchronous tumours; each of the colorectal tumours are adenocarcinomas; the lung tumour is a planocellular tumour; the prostate tumour is an adenoarcinoma; the lymphatic tumour is a malignant lymphoma.

in origin. The distribution of these tumours is shown in Table 3. Three patients had (4.9%) triple, and two patients (3.3%) quadruple tumours

Comparing the blood group according to Wolff's method [20] of our patients with that of those with a solitary tumour and with that of a control group of blood donors also used as controls in a previous study [26], no significant difference was found.

Discussion

The increasing number of multiple tumours has been due to the increase in average age, to the ever widening circle of patients cured from a tumorous disease as well as to the improving diagnostic possibilities. The accumulating reports raise the question of the increase in the absolute number of multiple tumours, too [1-4, 6-14, 19, 21, 24-25, 29-30]. In our material a high incidence rate being in the upper range of that published in the literature was found. It can be established that the incidence of primary multiple malignant tumours is not only a rarity worth reporting, but a constant danger to be aware of in our everyday diagnostic activity and in the care of our operated patients.

By presenting our data, we would like to draw attention to the importance of pre- and postoperative diagnostics aiming at completeness, namely on the routine examination of colonic diseases (irrigoscopy, colonoscopy), a

distal tumour causing stenosis may render unrecognizable the second tumour localized more proximally. Careful surgical exploration in these cases is of paramount importance According to the evidence of the two cases lost, extensive adhesions deriving from previous operations may also delimit the scope of intraoperative physical diagnostics. Currently, intraoperative colonoscopy may help also in these cases. The instrument can usually be passed by the surgeon through the distal stenosis, and so the oral-otherwise inaccessiblecolonic segment can also be examined. Similarly, intraoperative ultrasonography, may be of help in some improving our results.

Based on survival data, it can be stated that multiple malignancies do not in themselves mean incurability. It should be noted here that one of our patients living free of complaints even 16 years after his first tumour is one of the cases with a quadruple tumour. It is a textbook evidence that in patients operated for mammary tumour, there is a possibility of the development of a malignant process in the contralateral breast. According to our data, there is a similar or (even increased) risk of metachronous colorectal tumour formation. That is why the necessity of the continuous monitoring of the once operated and cured tumour patients and the importance of care should be emphasized, since the improvement of therapeutic results can only be expected even in multiple tumours, of treatment of cases detected in the early stage.

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Multiple primäre maligne Tumoren bei wegen eines kolorektalen Karzinoms behandelten Patienten

(Klinische Analyse von 61 Fällen)

A. TÓTH, L. HARSÁNYI und A. SZÉCSÉNY

Unter den 543 Patienten, die im Laufe von 10 Jahren wegen eines kolorektalen Karzinoms unter Behandlung standen, war mit einer 11,2% igen Häufigkeit ein multipler, primärer, maligner Tumor vorzufinden. In 39 der 61 Fälle handelte es sich um einen metachronen und in 22 Fällen um einen synchronen Tumor. In der Gruppe der mit multiplen Tumoren behandelten Patienten waren im Vergleich zu den an einem solitären Tumor leidenden eine höhere Proportion der Frauen (p < 0,1) ein höheres durchschnitt-liches Lebensalter (um 2 Jahre höher) und ein häufigeres familiäres Vorkommen der malignen Erkrankungen vorzufinden. Aufgrund der Literatur und der Inzidenz des eigenen Materials wird auf die praktische klinische Bedeutung der Frage hingewiesen. Die Schwierigkeiten der Diagnostik der multiplen Dickdarmtumoren, die Wichtigkeit und die Möglichkeiten der prä- und intraoperativen Untersuchungen finden eine aus-führliche Besprechung. Anhand der Überlebensdaten wird festgestellt, daß die mehrfache Malignität nicht unbedingt eine Unheilbarkeit bedeutet. Die Besserung der therapeutischen Ergebnisse wird – nebst der Besserung der Ergebnisse der chirurgischen Behandlung – von der Einführung der neuen Untersuchungsmethode und der Betreuung bzw. laufenden Kontrolle der gefährdeten Patientengruppen erwartet.
Множественная первичная злокачественная опухоль у больных, леченных по поводу колоректальной карциномы (Анализ 62 клинического случая)

А. ТОТ, Л. ХАРШАНИ и А. СЕЧЕНИ

Из 543 больных, которых авторы лечили по поводу колоректального рака за 10летний период, у 11,2% нашли многократные первичные злокачественные опухоли. У 39 больных из 61 были опухоли метахронного появления, у 22 синхронного. Среди больных, леченных по поводу многократных опухолей, пропорция женщин была значительно выше (р *ж* 0,1), выше средний возраст (на два года) и чаще встречались в семьях злокачественные заболевания, чем среди больных с однократной опухолью. На основании высокой встречаемости таких опухолей, как показывают данные литературы и собственный материал авторов, они обращают внимание на практическое и клиническое значение данного вопроса. В статье подробно обсуждаются трудности диагностики мультиплексных опухолей толстой кишки, важность и возможности пре- и интраоперативных исследований, стремящихся к полноте. На основании данных переживания авторы установили, что многократная злокачественность не обязательно означается неизлечимость. Улучшения результатов терапии — наряду с улучшением результатов хирургического лечения они ожидают от введения новых исследовательских методик, от патронирования и постоянного контроля находящихся в опасности групп больных.

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Preoperative Ultrasonic of Common Bile Duct Stones and its Importance to Surgical Management-Result of a Prospective Controlled Trial

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The biliary tract was examined by sonography in 192 nonselected surgical patients with clinically suspected gallbladder stone disease. This study was carried out to assess the potentiality of ultrasonic examination in the detection of common bile duct stones. All patients were operated on with sonographic monitoring during surgery. Common bile duct stones can be detected with high accuracy only in patients with an obstructive jaundice and a dilated common duct. In these, the sensitivity was found to be 70%, whereas that for the whole group of patients was as low as 28%. Accuracy in the ultrasonic detection of common bile duct stones is limited, and operative cholangiography seems to retain its position as the most reliable method of exploring common bile duct stones.

Introduction

Cholelithiasis is accompanied by common bile duct stones in 10% of patients and is known to entail further complications [2, 8]. Jaundice, pancreatitis, biliary cirrhosis, or cholangitis can be avoided only by early surgical treatment.

During the past decade the diagnosis of gallbladder diseases has changed. Sonography has been favoured and accuracy in the diagnosis of cholecystolithiasis was found to range from 96 to 99% [5, 9, 15]. Accuracy in ultrasonic detection of common bile duct stones is limited [10, 13]. Even though sonography is a form of sensitive detection of biliary dilation [1, 13] its diagnostic value in recognizing common duct stones is restricted [2, 3, 4, 10].

The purpose of the present work was to assess the potentiality of sonography in the detection of common bile duct stones in nonselected surgical patients with cholecystolithiasis. The results of this investigation were supposed to elucidate important issues of ultrasonic findings with regard to surgical management.

Methods and patients

Our studies were performed in 192 nonselected patients diagnosed by sonography as suffering from gallbladder stones. All of them were operated on at the Surgical Clinic of Magdeburg Medical School during the period from January 1984 to December 1985. The series included 68 males and 124 females

TABLE 1

Clinical diagnosis	Number of patients	%
Cholecystolithiasis (relapsed colics, relapsed chronical-inflammatory culluladan discusses)	141	73
Acute cholecystitis	34	18
Obstructive jaundice	17	9
	192	100

Clinical diagnoses of our patient group

aged 20 to 83, the average age being 47 years. The clinical diagnoses are shown in Table 1. Two patients with carcinoma of the gallbladder were excluded. Ultrasonic examinations were performed on a Toshiba SAL 35 A real-time scanner with a 5 MHz linear transducer.

Ultrasonic assessment of the biliary tree and the common bile duct is established, being well described recently by Taylor [14].

When expanded beyond 7 mm the common bile duct has been considered dilated [2, 4, 13, 14]. All our examiners had a long-term experience in abdominal ultrasonic evaluation.

The sonographic findings were compared by operative cholangiography performed through infusion of 20 ml contrast solution (Visotrast $290^{\rm R}$) via a drain tube into the cystic duct and common bile duct. The procedure was observed through an X-ray monitor (Siemens Arcoskop 110-OP) and documented by two X-ray pictures at the beginning and at the end of these examinations. In comparison with the sonographic findings were the surgically verified common bile duct stones. The common duct stones obtained by surgery were compared to both the width of the common duct and the calculi observed by ultrasonography.

The sensitivity and specificity of sonography were calculated, and conclusions were drawn as to the importance of surgical management.

Similarly, the occurrence of jaundice in a pentient's case history was correlated with the site and frequency of occurrence of common bile duct stones.

Results

In our series of 192 patients, only one case of gallbladder stone could not be confirmed during operation (accuracy: 99%). In eight cases (4.2%) the common duct was not visualized by sonography. The first criterion — the dilated duct (\geq 7 mm) — was not in a correlation with choledocholithiasis in our nonselected group of patients. Only 53% of cases with common bile duct stones were associated with dilated ducts (Table 2), whereas in 17 patients with preoperative dilation no pathological signs were seen during surgery.

Seventeen patients had developed a progressive obstructive jaundice and had to be operated on immediately. In 16 of these cases the common bile duct was dilated (≥ 7 mm) and in twelve of them common duct stones were correctly diagnosed by sonography (Tables 2 and 3).

On the other hand, there was no significant difference in either stone detection or duct diameter between the non-jaundice patients and those with a previous history of jaundice (Table 3).

The overall sensitivity of sonography to reveal common bile duct stones was rather low, being only 28% in our group of nonselected patients. As little as two false positive results were noted and, therefore, the account led to 99% specificity.

TABLE 2

Coincidence of common bile duct stones and dilated ducts in different patient groups

	Group of patients with choledocholithiasis and obstructive jaundice during surgery n = 17	Group of patients with surgically confirmed com- mon bile duct stones n = 40
Coincidence of common duct stones and dilated ducts $(\geq 7 \text{ mm})$	$94\%{0}(n=16)$	53% ($n = 21$)

TABLE 3

Sensitivity and specificity of sonography in detecting common bile duct stones in different patient groups

	Group of patients with obstructive jaundice during surgery n = 17	Group of patients with a previous history of jaundice n = 30	Group of patients without a previous history of jaundice n = 145	Whole patient group $n = 192$
Sensitivity of sonography in detecting common bile duct stones	70%	3.7%	No stones detected	28%
Specificity of sonography in detecting common bile duct stones	100%	100%		99%

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	Number of patients	Surgically confirmed common duct stones	No common duct stones
Obstructive jaundice during surgery	17	17	_
Previous history of jaundice	30	13	17
No history of jaundice	145	10	135
	192	40	152

Importance of jaundice in relation to choledocholithiasis

The sensitivity rate was 70% in patients who had an obstructive jaundice verified during surgery (Table 3). Most of the stones observed sonographically were located in a dilated common bile duct in patients with obstructive jaundice. It was only in one case that a stone was spotted in a nondilated duct.

On the other hand, jaundice in case histories had no real relevance to the prediction of choledocholithiasis in our series (Table 4).

Discussion

Cholecystectomy has become one of the most frequent operations in Europe and the USA [1, 4] and sonography has developed into an important noninvasive technique in examining biliary tract diseases [13-15]. The use of ultrasonography in detecting gallbladder stones and distinguishing obstructive from nonobstructive jaundice is well established [3, 13].

The sensitivity of sonography in the detection of common bile duct stones had an outcome of 28% in our series. This result is consistent with those obtained by other workers [2, 4, 11, 14] who found sensitivity to range from 13 to 20%. Börsch et al. [1] and Seitz [13] reported higher sensitivities of 60 to 70%.

The diagnostic accuracy was as high as 70% (Table 3) in jaundice patients, whereas the coincidence of duct dilation and common duct stones turned out to be 94% in this group.

A previous history of jaundice had less importance than expected (Table 4). In 17 of those patients we did not find duct stones or any other pathological signs during surgery. But ten patients with choledocholithiasis had never had a jaundice in their history.

Only half of all patients in whom surgery revealed the presence of stones had a dilated common bile duct (Table 2). However, in 17 patients with dilated common ducts these signs were not confirmed by cholangiography. Taylor [14] and other workers [6, 12] pointed out these discrepancies between contrast cholangiography and ultrasonic measurements.

Sonography is of limited capability to depict choledocholithiasis (28%) sensitivity), but only two false positive results were diagnosed so that the specificity turned out to be 99%. These findings were confirmed by other investigators [1, 2, 13]. Ultrasonic accuracy was higher in patients with dilated ducts and obstructive jaundice (70% sensitivity). Only in one case was a stone observed in a nondilated duct. Taylor [14] and Myllyä et al. [11] confirmed these observations and stated that when stones are demonstrated in dilated ducts the obstructing cause is usually more distally situated.

Ultrasound examination of the biliary tree is well established as a screening method including the assessment of the common bile duct. However, the surgeon should be aware of the limits of diagnostic accuracy in detecting common bile duct stones. In spite of conflicting opinions [7], operative cholangiography seems to retain its position as the most reliable method of exploring common bile duct stones [11].

Conclusions as to surgical management

1. Common duct calculi can be detected by sonography with high accuracy only in patients with an obstructive jaundice and a dilated common bile duct (70% sensitivity). In those cases, primary surgical exploration of the common duct is a reasonable approach [2, 11, 14], but at the end of this procedure operative cholangiography through the T-tube should be compulsory.

2. The obstructing cause is usually more distally situated than the duct stone which is detected by sonography [11, 14].

3. A previous jaundice in a patient's case history had less importance than expected in the prediction of choledocholithiasis in our series.

4. The diagnostic accuracy of sonography in detecting common duct stones in the whole nonselected patient group was rather poor (28% sensitivity) and for a proper surgical strategy [4, 10].

5. Twenty-five percent of patients with choledocholithiasis had had no histories of jaundice and 45% had a normal-sized common duct. Currently, operative cholangiography is the most reliable method in exploring common duct calculi [8, 11].

6. Both the monitoring of cholangiography and assessment of two X-ray pictures guarantee a high accuracy of this method, prolonging the operation time by ten minutes only.

7. Computed tomography, hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiography should be used as diagnostic procedures to determine abnormalities along the patient's history or other suspected clinical signs [5, 9, 10, 11].

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Präoperative Ultraschalluntersuchung von Choledochussteinen und ihre Bedeutung in der chirurgischen Versorgung. Ergebnisse einer prospektiven kontrollierten Untersuchung

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Um die Möglichkeiten der Ultraschalluntersuchung bei der Detektierung der Choledochussteine bestimmen zu können, wurde der Choledochus von 192 randomierten chirurgischen Patienten, bei denen klinisch der Verdacht eine Cholezystensteines vorlag, mittels Ultraschall untersucht. Da sämtliche Patienten operiert wurden, bot sich zur intraoperativen Kontrolle der Ultraschallbefunde eine Möglichkeit. Der Choledochusstein kann mit großer Genauigkeit nur bei Patienten erkannt werden, die einen weiten Choledochus besitzen und an Verschlußikterus leiden. In diesen Fällen betrug die Sensitivität 70%, während sie auf die ganze Gruppe projiziert nur 28% ausmachte. Die Genauigkeit der Feststellung der Choledochussteine ist beschränkt, so daß die zuverläßlichste Methode auch weiterhin die operative Cholangiographie zu sein scheint.

Предоперационное ультразвуковое исследование камней общего желчного протока и его значение в хирургическом обслуживании. Результаты проспективного контролируемого исследования

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Авторы исследовали ультразвуком желичные протоки 192 хирургических больных, взятых без выборки, у которых клиническое обследование указывало на наличие желичных камней. Ультразвуковое исследование сделали для того, чтобы определить возможности этого метода в обнаружении камней общего желчного протока. Все больные были прооперированы, благодаря чему была возможность в ходе операции проверить данные ультразвукового исследования. С большой степенью точности определить наличие камняя в общем желичном протоке можно только у тех больных, у которых развилась обструкционная желтуха при расширенных общих желчных протоках. В этих случаях чувствительность составила 70%, тогда как в масштабах всей группы только 28%. Точность определения камней общего желчного протока ограниченна, и по-прежнему оперативно холангиография кажется самым надежным методом обнаружения камней общего желлного протока.

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Diagnosis and Treatment of Inflammatory Intestinovesical Fistulas

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The histories of 3 patients operated for inflammatory intestinovesical fistulas are reviewed. Two of them were treated for colovesical, one for ileovesical fistula. The questions concerning the development, diagnostics and surgical management are discussed in detail. The importance of cystoscopy in diagnosis is emphasized. In all three patients one-session operations were performed with good results.

An abnormal communication between the intestinal tract and the urinary conducting system may be caused by various pathological processes. As a result, intestinal content may enter the urinary tract or, more rarely, urine may enter the intestines. Intestinovesical fistula formation is due, most often, to severe, necrotizing inflammations, malignant tumours (of the colon, uterine cervix, urinary bladder), trauma, foreign bodies, but iatrogenic fistulas are not rare either [4, 8, 9].

Of the fistulas communicating with the alimentary canal and the urinary tract, the colovesical fistula occurs the most frequently [2, 12]. The colovesical fistulas of inflammatory origin are mostly caused by diverticulitis of the sigmoid colon but they may also be induced by ulcerous colitis, periappendicular abscess, or irradiation enteritis [8, 12]. Ileovesical fistulas are, in most cases, complications of Crohn's disease.

During a period of two years three inflammatory intestinovesical fistulas were diagnosed at our Department of Urological Surgery, which were successfully solved by operation.

Case Reports

Case 1. K. B., a 37 year-old male patient, was admitted for the suspicion of a vesical tumour. He had a history of ulcer established 15 years earlier causing complaints from time to time. His urological symptoms had started half a year before his admission, presenting with a frequent urge to void, terminal alguria, perivesical pain and subfebritily. His complaints were ascribed to chronic prostatitis and treated accordingly. Within two months he had lost 15 kg. Two days prior to his admission, right inguinal pain, terminal



FIG. 1. Cystogram: the right upper margin of the bladder shows a triangular density extending upwards $\label{eq:FIG}$

haematuria and subfebrility appeared. He had not defaecation complaints. On admission the sensitivity to pressure in the ileocaecal region and pyuria were the characteristic symptoms. Of his laboratory tests his moderately high erythrocyte sedimentation rate (28 mm/h), as well as the urinary sediment (4–5 leukocytes) showed pathologic alteration. Urinary bacterial culture: $E.\ coli$. His i.v. urogram disclosed roentgenologically intact anatomical and functional conditions with no pathological change of the bladder picture. Cystoscopy: In the right upper portion of the posterior wall of the bladder an opening of 2 mm was seen in hyperaemic environment with a drop of pus. Retrograde cystography: on the right side of the upper margin of the bladder a triangular density with a border extending upwards was observed, the fistulous tract showed an incomplete filling (Fig. 1). Irrigoscopy demonstrated normal radiological conditions.

At the Department 'A' of Surgery of our hospital surgical exploration was made from a lower median incision, when in the right iliac fossa a fist--sized inflammatory conglomerate was found including the caecum and the terminal ileal loop, too. The latter strongly adhered to the pesterior wall of the bladder, and on separation from it, an almost pencil-thick fistula was opened. On the posterior wall of the bladder the fistular opening was closed in two layers. The terminal ileal loop showing evidence of very grave inflammation was resected together with the caecum. The ileum was anastomosed end-to-side to the ascending colon and the wound was closed with drainage.

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FIG. 2. Histological picture of the mucosal membrane of the removed segment: terminal ileitis

The histology of the removed intestinal segment disclosed inflammation involving all layers of the intestinal wall. The extensive scarring, the marked dilatation of the lymphatics and the characteristic fissure of the mucosa verified Crohn's disease (Fig. 2).

The catheter was removed after two weeks. Healing of the wound was uneventful. According to the control one year later, the patient had gained weight, ha had no defaecation and voiding complaints. Urinary sediment and bacterial culturing were negative.

Case 2. M. J., a 52-year-old male patient, was admitted for pyuria. Beside, pyuria having persisted for months and been refractory to treatment, he had macroscopic haematuria on one occasion. He complained about abdominal distension, and diarrhoeal stools. Urinary sediment: 3-4 WBCs, 4-5RBCs. Urinary bacterial culturing: *E. coli*. The other laboratory tests yielded normal results. I.v. urography showed normal conditions. Cystoscopy revealed the posterior wall of the bladder to be moderately protruded with an oedematous proliferation on the left side, in region, 2 cm in diameter, at the mid portion of the bladder. In the middle of at a fistular opening was found from which a mucous fibrillar substance was discharged. A 3 Ch ureteral catheter was introduced into the fistular opening which got stuck after 3 cm and the tract could not be filled even by contrast medium.

By irrigoscopy an inflamed sigmoid colon of a thickened wall was visualized from which several tiny diverticula were filled. Orally to this, the colon did not show any pathological change. Rectoscopy disclosed an intact colon.

For suspicion of colovesical fistula, surgical exploration was made from a lower median incision. The sigmoid colon was thickened, its inflamed midsegment adhered planularly by scarring to the left side of the posterior surface of the bladder. After separation of the bladder, peritoneum and the simoid colon, the fistula was closed in both directions. The wound cavity was drained extraperitoneally. The catheter was removed after 10 days. The patient was discharged two weeks postoperatively, complaint free and with pus-free urine. The control irrigoscopy three months after the operation disclosed sigmoiditis and some diverticula. His urine was sterile.

Case 3. P. I., a 48-year-old female patient, was admitted for cystitic complaints having persisted for months and not responded to antibiotic treatment, for macroscopic haematuria occurring several times, lower abdominal pains and subfebrility. An examination carried out three years earlier for abdominal pains revealed diverticulitis of the sigmoid colon. On admission, he was markedly obese, with a lower abdominal tenderness to pressure, his urine was cloudy and foul smelling, containing a fibrillar substance. Of his laboratory finding, the high erythrocyte sedimentation rate (46 mm/h) and urinary sediment (15-20 WBCs, 1-2 RBCs) changed pathologically. Urinary bacterial culture test: E. coli. I.v. urography revealed the roentgenological signs of chronic pyelonephritis on both sides. The bladder was of a homogeneous contour. Cystoscopy: on the left side of the top of the bladder, there was a bullous, oedematous protruding region, from the midregion of which a vellowish, ointment-like material (faeces) was discharged at a width of about 2 mm. Irrigoscopy: the descending colon was narrowed at its lower segment at a length of 7-8 cm, it was rigid, and it did not dilate with a slightly inhomogeneous contour. The radiological picture indicated tumour of the descending colon. Abdominal ultrasonography: a cystic mass, 13 cm in diameter, was visualized behind the bladder.

Surgical exploration was performed at our department of surgery from a low midline incision. In the abdominal cavity on the left a conglomerate filling the iliac fossa was detected, which involved the anterior and posterior walls of the bladder, the 15 cm segment of the sigmoid colon and the 10 cm segment of the ileum as well as the anterior surface of the uterine fundus. The frozen section examination of the tissue sample taken from the conglomerate showed inflammation. The ileum and the colon were separated, from the latter a fistula of the thickness of a pencil, led into the bladder. The vesical wall and its environment was considerably inflamed, oedematous and fragile, therefore the bladder was not sutured but its vicinity drained with an indwelling catheter. The livid, oedematous ileal segment of indurated wall was resected, then a side-to-side anastomosis was constructed. Due to a change of the sigmoid colon simulating a fist-sized tumour, a 25 cm long sigmoid segment was removed, then an anastomosis was performed end-to-end between the sigmoid colon and the upper third of the rectum. Between the anterior wall of the uterus, the bladder and the abdominal wall, an egg-sized abscess containing

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thick pus was found which was emptied. The wound cavity was drained. Histology revealed a considerable accumulation of connective tissue and nonspecific granulation tissue. There was no evidence of malignancy. After operation the patient's urine cleared and he was discharged with a healed wound. Five months postoperatively he was free of complaints, his urine did not contain pus.

Discussion

Enterovesical fistulas occur most frequently in the 5h-8th decades of life [4]. This is due to the fact that diseases giving rise to fistula appear also at this age. The incidence rate of intestinovesical fistulas among males and females is 3 to 1 and 5 to 1 [5, 12]. The higher ratio of men is accounted for by the fact that the uterus localized between the bladder and the sigmoid colon inhibits fistula formation [4, 12]. This is also supported by the observation that in 61% of females with sigmoidovesical fistulas hysterectomy had previously been made [7].

Among the clinical symptoms of intestinovesical fistula faecaluria is the reliable diagnostic sign. It appears in the more advanced stage of the disease when the fistula is already larger [2]. Pneumaturia is also a specific sign. Although it may be produced by urinary tract infection due to gas-producing microorganisms. If it occurs, an enterovesical fistula should always be considered [8]. A solitery symptom for a long time can be the permanent urinary tract infection unresponding to treatment. Mostly $E. \ coli$ is cultured from the urine. Subfebrility is frequent, a recurring febrile state, shivering, chills, moreover, septic shock may occur [8]. In addition to dysuric complaints, micro- or macroscopic haematuria may develop. In a progressive case, part of the urine may be passed via the rectum [8].

It is often difficult to detect enterovesical fistulas radiologically, because the thickened mucosa may act as a valve closing the passage [10]. Diagnosis could be established by i.v. urography only in a fairly small part of the cases. Retrograde pyelography reveals the bladder contour to be inhomogeneous and deformed. The 'beehive' sign is also supposed to be characteristic, the margin of the bladder shows a triangular density extending upwards (Fig. 1). A useful sign may be the cystographic visualization of gas intravesically [2, 10]. A completely normal cystogram may also occur. In our examinations the cystogram showed pathological alteration only in one case.

X-ray and irrigoscopy play a role in detecting the pathological process leading to fistula formation.

According to Amendola et al. [2], the Bourne test can well be applied in diagnosis. During it, in the roentgenogram taken of the centrifugate of the urine sample following irrigoscopy, only a neglectable amount of the radiopaque barium is well discernible. This examination is more sensitive than the use of peroral dy indicators [2].

Of the endoscopic diagnostic tests, cystoscopy is the most useful one. Based on the examination results of 280 patients [8, 13], the sensitivity of cystoscopy in enterovesical fistula is estimated between $27\frac{3}{4}$ [1] and 57% [5]. The fistular opening itself can be observed relatively rarely, it is rather the indirect signs of the fistula which predominate. These include the hyperaemia, bullous, oedema, polypous change of the circumscribed area of the bladder mucosa. Naturally, the appearance of faeces makes diagnosis unambiguous. The cystoscopic change should primarily be differentiated from cystic cystitis, granular cystitis or primary or secondary vesical tumour. On suspicion of the latter, the tumorous origin of the disease can be excluded by TUR biopsy [10]. In our own cases, the enterovesical fistula was recognized by cistoscopy in all cases.

The spontaneous closure of enterovesical fistulas occurs very rarely, only in 2% of the cases, mainly due to traumatic causes. The 12 enterovesical fistulas due to inflammation should be treated surgically by the collaboration of urologist and abdominal surgeon. There is no unanimous view on the most appropriate way of closing a fistula. It should be emphasized that rigid rules should not be imposed during operation. Actiology, the patient's age and general condition, the extension and severity of the inflammatory change should all be considered at the decision [12, 13]. In Corhn's disease, in general, the macroscopically affected intestinal segment is resected by anastomosis [6] as well as by the extirpation of the fistulous tract. It suffices to close the vesical end of the fistula by sutures, segmental vesical wall resection rarely becomes necessary [10].

The surgical solution of colovesical fistulas due to diverticulitis is also the extripation of the fistulous tract and the resection of the colon as required by the severity of the inflammatory change [12, 13]. Closure of the fistula may require operation in one or two session. In case of the latter a decompression colostomy is performed which can be eliminated in the third operative phase after closure of the fistula and intestinal resection. A three-session operation is recommended in intestinal stricture or pericolic abscess [11].

A one-phase operation can be performed in case of a 'mature' fistula, if intestinal stricture, abscess or free abdominal perforation are not present, and the fistula does not involve a third organ [4]. A further precondition is that the part of the intestine adjacent to the affected segment be intact in both directions [9]. In colovesical fistula, it is important to apply the pre-operative preparation used in colorectal surgery [3].

In two of our three patients, intestinal resection was performed with immediate anastomosis, without ileo- or colostomy. In the third one, the inflammatory change in the sigmoid colon was not so marked as to necessitate resection and so the fistula was closed.

The prognosis of inflammatory enterovesical fistulas is, in general, very good.

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Diagnose und Therapie von Darm-Blasenfisteln entzündlichen Ursprungs

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Dargestellt wird die Krankengeschichte von drei, wegen einer entzündungsbedingten Darm-Blasenfistel operierten Patienten. In zwei Fällen handelte es sich um eine kolovesikale und in einem Fall um eine ileovesikale Fistel. Die mit der Entstehung, der Diagnostik und der chirurgischen Behandlung der Krankheit verbundenen Fragen finden eine kurze Besprechung. Die Zystoskopie bietet eine bedeutende diagnostische Hilfe. In allen drei Fällen, fand mit gutem Erfolg eine einzeitige Operation statt.

Диагностика и терапия кишечно-пузырных свишей воспалительного происхождения

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Авторы знакомят с историями болезни трех больных, оперированных по поводу кишечно-пузырного свища воспалительного происхождения. Двух больных лечили в связи с коловезикальной, одного больного в связи с илеовезикальной фистулой. Авторы кратко обсуждают вопросы, связанные с возникновением, диагностикой и хирургическим лечением болезни. Подчеркивают значение цистоскопии в диагностике заболевания. У всех трех больных была выполнена одноэтапная операция, с хорошим результатом.

Schistosomal Granulation Masquerading as Testicular Tumour

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The case of a 7-year-old boy is reported in whom the *Schistosoma haemato-bium* infection manifested as the clinical picture of metastisizing testicular tumour. The correct diagnosis was established by the postoperative pathohistological examination. No similar observations was found in the literature studied.

Urogenital bilharziasis is endemic in several countries of Africa and the Near-East. The most frequent pathogen is *S. haematobium*, but rarely *S: mansoni* infection, may also cause a disease of urogenital localizaton [4]. The infection, most often, manifests in the bladder, this is followed in frequency by the bilharziasis of the ureters, the urethra and of the renal cavity system. The involvement of the testicles and the pididymis may very rarely result in infertility [1]. Studying a total of 150 patients with bilharziasis of the urinary tract, Umerah et al. [7] found none with manifestation in the testicles or the epididymis.

In the countries where this disease is not prevalent, even the typical form of the disease may often pose diagnostic difficulties [3, 5], while the rare manifestation of bilharziasis, as presented in this report, may even be problematic for physicians working in the endemic regions.

Case Report

It was told by the parents of A. H. A., a boy, aged 7 years, that the child had been having a testicular tumour for 2–3 months.

The child's development was appropriate for his age, his general condition was good. On physical examination, a considerably enlarged, compact, nodular testicle, 6 by 4 by 5 cm in size, was palpated on the left side. The right spermatic funicle was thickened to the size of a thumb, it was compact with uneven surface.

The right suprainguinal lymph nodes were considerably enlarged. They were not tender to palpation and moderately fixed.

The patient's parents had made no mention of any previous disease. The neccessary laboratory tests and X-ray studies were performed for the suspicion of testicular tumour, then the patient was admitted for operation at the department of urology.

Labofatory Findings

Hb: 11.6 g/dl, WBC: $10,200/\text{mm}^3$, Se: 63%, Ly: 29%, Mo: 1%, Eo: 7%, We: 16 mm/h. Urine: alb: neg., glucose: neg. Microscopically 3-4 WBCs and 4-6 RBCs per visual field were found.

Chest X-ray: No pathological change with no evidence of metastasis.

 $Plain \ renal \ X$ -ray: Positive shadow of a calculus or calcification were not noted.

I.v. urography: The state and size of the kidney were normal, excreting the contrast medium in due time and with adequate intensity. The renal collecting system was diffusely and evenly dilated, the ureters were almost dilated to the size of a little finger, the midsegment of the right ureter formed a strong lateral arc, its left course being slightly serpiginous. It was striking that on both ureters several arcuate impressions were visible (those due to an enlarged retroperitoneal lymph node) (Fig. 1).



FIG. 1. I.v. urography: The midsegment of the right ureter is arcuate, pushed aside laterally, which is probably caused by the retroperitoneal mass

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FIG. 2. Macroscopic picture of the removed organ. The testicle is enlarged, nodular, the funicle is thickened with a group of plum-sized lymph nodes

Based on the physical examination the laboratory and X-ray findings, operation was made for the suspicion of testicular tumour. In general anaesthesia the inguinal canal was explored from a 'slipped' suprainguinal incision and the spermatic funicle was compressed at its upper orifice. Then the testis and its appendages were lifted from the scrotum. The testicle was of the size as described earlier, it was of a roughly nodular surface. The spermatic funicle was also nodular and infiltrated (Fig. 2). High castration was performed, then, proceeding stepwise, the ipsilateral inguinal lymph nodes, 3 to 5 cm in diameter, were removed.

To our greatest surprise, the histopathological finding verified schistosomal granulation. In possession of this finding, a series of urinalyses and examinations of stools were made for schisostomiasis but all results were negative. After repeated questioning of the parents, it turned out that the boy had received antibilharzal treatment for *S. haematobium* about one-and-a-half years earlier. They could, however, provide no information on the drug administered.

In view of the positive histopathological finding, *Schisostoma* antigen test was requested which disclosed the presence of species-specific antibodies against *S. haematobium*.

The patient's recovery was uneventful, and he was discharged in a good general condition.

He reported again half a year after his discharge from hospital. At the control examination, beside the moderately enlarged left inguinal lymph nodes and a moderate (6%) eosinophilia, no pathological change was noted.

Discussion

The S. haematobium infection starts with bathing in infected water by the percutaneous penetration of the cercariae. Entering the veins, the parasites drift via the right heart to the pulmonary arteries where they cause inflammation of the vessels and the perivascular tissues. In this stage, S. haematobium may induce pulmonary infiltration with inflammatory symptoms [6]. The pathogen migrates from the arterioles to the veins, it enters the portal system via the left heart where it develops into a mature worm which is carried into the pelvic venous plexuses. Here it is embedded in the tissues, it mates and the eggs produced by the female are transported, with the help of their tissue-dissolving enzymes, via the tissues into the bladder, intestines and other places of the urogenital organ system, while inducing reaction, fibrosis then granulation in the affected tissues.

In our case, a rare, unusual manifestation of S. haematobium developed which, masquerading as testicular tumour, induced diagnostic difficulties preoperatively, even if the absence of lung metastasis, the patient's good general condition and the eosinophilia did not fit in with the picture. It should be noted that in North-Yemen, parasitic diseases are frequent, in childhood, helminthic disease, such as eosinophilia is a routine finding.

According to literary evidence and our own results, a fairly high recovery rate, about 90-97% can be reached with the up-to-date anti-bilharziatic treatment (Biltricide, R-Bayer) [2]. There is no explanation in the literature to the phenomenon why the granulation process progressed after the successful drug treatment even in the parasite-free state.

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Im Bilde eines Hodentumors erscheinende Schistosoma-Granulation

T. LUKÁCS, L. PAJOR, L. HAMZA und A.-A. EL-SEAGHY

Dargestellt wird der Fall eines 7jährigen Knaben, bei dem sich die Schistosoma-Haematobium-Infektion im klinischen Bilde eines metastatischen Hodentumors meldete. Die richtige Diagnose lieferte die postoperative pathohistologische Untersuchung. In der einschlägigen Literatur war keine, sich mit einem ähnlichen Fall befassende Mitteilung vorzufinden.

Появляюшаяся в картине опухоли яичка шистозомная грануляция

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Авторы описывают собственное наблюдение, когда у 7-летнего мальчика заражение фся. saema_sob⁷um проявилось в клинической картине тумора яичка. Правильный диагноз был поставлен на основании патогистологического послеоперационного анализа. В изученной специальной литературе рни не встретили опиания подобного случая.

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Use of CO₂ Laser Knife in Gastroenterological Surgery

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Favourable results obtained by using the RT TLS₆₁ CO₂ laser of TUNGS-RAM, of a performance of 60 W are reported. It is emphasized that the device has several advantages in surgical gastroenterology over the traditional cutting instruments. The light of the device coagulates the smaller than 0.5 mm vessels during cutting. On opening the gastrointestinal tract-contrary to electrocautery-the necrotic zone is narrower, which may be of importance from the point of view of suture insufficiency. The device provides more favourable conditions for ablastic operations than do the traditional cutting instruments.

During gastrointestinal operations, the opening or transection of the alimentary canal for resection or anastomosis is also currently made by scalpel, scissors or electrocautery.

The use of sharp instruments in humans with the aim of healing dates back to several thousand years, and it is sure that both the scalpel as well as scissors will be applied for still a long time to come.

The electrocauteries were developed in 1920 [11]. Their main field of application is the severing of tissues and coagulation of minor vessels. The use of electrocautery incurs some risk both for the surgeon as well as the patient. Despite that, it is sure that these devices will be in use for still a long time to come.

Various lasers have been used by surgeons for separation and severing of tissues for over 20 years. It is imaginable that these devices will be used in some respect as an alternative to electrocautery and sharp instruments.

Material and Method

A total of 105 operations have so far been made by the TUNGSRAM RT TLS₆₁ CO₂ laser of a performance of 60 watts (Fig. 1). These operations include chest, bone, vascular, plastic and gastrointestinal interventions. Complete operations, too, were performed by laser, although they were used for solving partial tasks, such as opening of the intestine and lung resection.



FIG. 1. Cutter of a TLS₆₁ laser

When used, the device is operated continuously, mostly being focussed, when the energy is concentrated on a small surface and the tissues are vaporized, i.e. it serves for function similar to cutting. Being defocussed, it can be applied for the vaporization of minor tumours and haemostasis.

At laser operations, certain safety regulations have been introduced. The vapours produced are absorbed by a suction appliance and the team performing the operation is provided with goggles.

The technique of the laser operation differs from that of the classical operation. The laser beam proceeds, after transection of the tissue, and if there is a larger vascular structure, biliary tract, intestine, etc. in the background, it may get damaged. Therefore, the region behind the operated area should be protected by discs absorbed in sodium, or metal probes.

The beam emitted by the device is directed through a manipulating arm under sterile conditions, to the operative site. The beam is pedal-operated. Accurate focussing is ensured by a He-Ne laser built into the device, the light of which is invisible to the naked eye.

Results

So far about 30 gastrointestinal operations have been made by laser knife (Table 1), including gastric resection, choledoduodenostomy, pyloroplasty, ileal and colonic resection, etc. Rectal polyps, chondylomas and minor malignant tumours can be removed by focussed beam.

TABLE 1

Tot	al	31
15.	Rectal condyloma acuminatum (evaporization)	2
14.	Rectal polyp (excision)	1
13.	Rectal villous adenoma	3
12.	Rectal carcinoma (excision)	1
11.	Sigmoid resection	2
10.	Right hemicolectomy	2
9.	Ileal resection	2
8.	Hepatic cyst (excision)	1
7.	Cholecystectomy	4
6.	Cholecystojejunostomy	1
5.	Cholecystoduodenostomy	1
4.	Jejunostomy (Marwedel's operation)	2
3.	Heinecke-Mikulitz pyloroplasty	3
2.	Gastrostomy	3
1.	Resection of ventricular segment according to Billroth II	3

Use of CO₂ laser knife in gastrointestinal surgery

It was used for removal of rectal carcinoma only if the patient's age and general condition and/or other caused had not allowed radical removal.

The light of the CO_2 laser coagulates the vessels smaller than 0.5 mm during transection and, consequently, at opening or resection of the ileum or rectum, there is no bleeding from the intestinal wall. The larger vessels in the mesenterium should be ligated because these vessels are not closed even when being severed by laser. The major vessels of the gastric wall are also liable to bleed on opening the wall, but it is generally necessary to ligate only a single vessel. Less bleeding creates more convenient conditions for performing the operation, such as e.g. an intestinal anastomosis.

In such cases, no swabbing is needed at inserting the sutures which is also beneficial to sterilization.

A new way of application has also been developed by us. The mesenterial wedge which is to be removed, is closed prior to resection by a defocussed beam. For closing vessels and lymph vessels, before manipulation on a tumour, it can be of benefit to prevent the dissemination of tumour cells. On resection the closed vessels are naturally also ligated.

 $\rm CO_2$ laser can also be employed for Marwedel's jejunostomy: with sufficient experience a seromuscular fossa is created by the beam without injuring the mucosa.

Discussion

These use of lasers in medicine [1] has been started in the middle of the 60s in the USA [6] and the Soviet Union [12]. The first surgical laser, being a CO_2 laser, was constructed by Pollányi in Boston (cit. Jákó [6]). It has since been widely applied in surgery. It was believed to be the ideal surgical cutting device, because cutting was sterile, with limited anaesthesia the wounds would not, or would hardly bleed, because the beam of the CO_2 laser closes the vessels smaller than 0.5 mm. The initial enthusiasm went to the other extreme, i.e. its opposers declared the device to be cumbersome, expensive (a scalpel costing 2.5 million forints !), and healing of the wound was none the better than by a sharp instrument, moreover it was in fact worse in some cases. Comparative studies were made in experimental animals which documented objectively by histological examinations the advantages and drawbacks of the individual cutting instruments [4, 11].

The wound healing of incisions made on the skin is supposed to be the best after cutting with a metal instrument. Lasers, however, can in certain respects, be more favourably used in surgery. For instance, the beam of the Ar and Nd-YAG lasers can be introduced through an endoscope to the body cavities for haemostasis, cauterization of tumours and tumorous obstructions, etc. After tumour removal by CO_2 laser, less local recurrences were found than by a sharp instrument or electrocautery [9].

Schoeder [11] studied the advantages of a sharp instrument and electrocautery for the various organs. He found that the necrotic zone of incisions made on the stomach and the small bowels was the narrowest while using CO_2 laser. This device is fairly suitable for removing haemangiomas but it can be used successfully also on operating haemophilias, too.

Since CO_2 laser has been available, a wide variety of human tissues were cut by it. A total of 105 operations have been made so far. Our experiences are in agreement with the experimental data. It is supposed to be particularly useful for performing special tasks. It is of great benefit in gastrointestinal surgery to open or resect stomach or intestine. On transection, the intestinal wall does not bleed, it does not need swabbing and this is favourable for sterility. The necrotic zone along the incision line is narrow, since temperature in the focus does not exceed 100 °C. In this respect, it is preferable to electrocautery. Using a defocussed laser beam, the mesenterial vessels can be closed without transecting the mesentery. This maneouvre can be performed prior to manipulation on tumour, creating more favourable conditions for an ablastic operation. The anastomosis cases healed well, without suture insufficiency.

Naturally, we are aware that suture insufficiency is also influenced by several other factors, and that our case number is not high. However, our favourable results have undoubtedly shown that CO_2 laser can, in some cases, be applied with benefit also in gastroenterological surgery.

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Anwendung des CO₂-Laser Lichtmessers in der gastroenterologischen Chirurgie

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Berichtet wird über die vorteilhaften Erfahrungen mit dem CO₂-Lasergerät, Typ TLS₈₁, Leistung 60 Watt, Herstellungsfirma TUNGSRAM AG. In der chirurgischen Gastroenterologie verfügt das Gerät, im Vergleich zu den herkömmlichen Schneidewerkzeugen über zahlreiche Vorteile. Durch das Licht des Geräts werden die kleineren als 0,5 mm Gefäße während des Schneidens koaguliert und dadurch auch die Blutung in bedeutendem Maße gestillt. Bei der Öffnung des Magen-Darmtrakts ist — im Vergleich zu dem Elektrokauter - auch die nekrotische Zone schmäler, welcher Umstand vom Standpunkt der Vorbeugung der Nahtinsuffizienz aus von Bedeutung ist. Das Gerät schafft auch zu den ablastischen Operationen günstigere Bedingungen als die herkömmlichen Schneidegeräte.

Применение СО₂-лазерного светового ножа в гастроэнтерологической хирургии

Т. ТОТ и М. ИХАС

Авторы знакомят с благоприятным опытом применения CO_2 -лазерного аппарата типа *Tungsram RT TLS*₈₁, можностью 60 Ватт. Они подчеркивают, что данный прибор имеет много преимуществ в хирургической гастроэнтерологии по сравнению с традиционными режущими инструментами. Свет прибора коагулирует при разрезании сосуды диаметром меньше 0,5 мм, что в значительной степани уменьшает кровотечение. При вскрытии желудочнокишечного тракта — в противоположность электрокаутеру — зона некроза также бывает более узкой, что имеет значение с точки зрения предотвращения шовной недостаточности. Данный аппарат создает более благоприятные условия также и для абластических операций, чем если используются обычные режущие инструменты.

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Cytochemical Detection of Nickel in Endometrial Carcinoma during Progestogen Treatment

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During progestogen treatment, nickel ions were detected in the human endometrial tissue of patients with endometrial carcinoma by the dimethyloxime cytochemical method. In this paper, the mechanism of action of nickel is dealt with and, because nickel ions have earlier not be detected in human endometrial carcinomatous tissues, the question arises as a result of what kind of cell biological processes, nickel ions appear in the cells of endometrial carcinoma. It is still to be answered whether the progestogen treatment applied can be correlated with the appearance of the trace element in the carcinomatous cell.

Nickel is an essential trace element [1, 2, 3, 6]. In adults, the average nickel uptake is 165 $\mu g/dav$ but uptake in a given case can even reach 900 μg if food is rich in nickel. Of the nickel content of drinking water coming from the watermains of various nickel concentrations, even an uptake of 1 mg nickel/day can be calculated. One to 5% of the nickel uptake is absorbed while the residual amount is excreted from the organism. In the case of nickel inhalation the daily nickel uptake ranges between 0.4 and 0.2 μ g. The difference reflects urban and rural environment, respectively. About 35% of the inhaled nickel is absorbed. Cigarette contains a considerable amount of nickel, so that the inhaled value per packet of cigarettes can even attain 4 μ g, although serial measurements could not so far detect a significant difference between the sera and whole blood of non-smokers and smokers. The nickel divalent cation is transported to the blood, primarily to serum albumin but, it is bound, to a lesser extent, to the other ultrafiltrable parts of the serum, such as histidine. Although serum nickel is bound in the largest fraction to nickeloplasmin, which is an alpha-macroglobulin, the nickel content of nickeloplasmin cannot infrequently be replaced by exogenic divalent nickel ions and the nickeloplasmin has been proved not to play an important role in the process of divalent nickel transport [8, 15, 17]. The divalent nickel ions are largely extracted from the serum and are excreted from the urine. In the milk of healthy lactating mothers, nickel concentration is considerably higher than the whole blood or serum nickel content of that of healthy non-lactating women.

The serum nickel concentration is higher in myocardial infarction. In severe myocardial ischaemia, acute stroke, or in patients with massive burns the serum nickel level decreases as also in liver cirrhosis probably due to the marked hypalbuminaemia [13, 14]. Rubányi et al. [16] found higher nickel concentrations following vaginal delivery. In those working with nickel malignant diseases of the nose and the lungs occurred cumulatively. The workers were exposed to increased nickel levels. The accumulation of not only the above tumours but, in general, that of malignomas (such as larvngeal, prostatic, gastric tumours, particularly sarcomas) were also observed. Nevertheless, there was no documentable statistical significance between nickel exposure and the cumulative appearance of tumours [7]. Beside the tumours, other diseases due to nickel exposure, such as interstitial pneumonitis, hypertrophic rhinitis, nasal polyposis, perforation of the nasal septum, adrenal failure or even stroke occurred [18]. Hypernickelaemia developing during extracorporeal haemodialysis may induce, or contribute to, the development of hypersensitivity following dialysis, encepalopathy or osteoporosis [11].

There is an extensive literature on studies concerning the in vitro genotoxic effect of the nickel ion. It was found that chromosomal impairment, sister-chromatid exchange and cellular transformations arise due to nickel ions [9, 10].

By various nickel compounds, adenoma and adenocarcinoma can be induced under experimental conditions. Malignant epithelial tumour formation was also observed in persons exposed to nickel.

Our team has been systematically dealing with the study of organ impairment due to nickel, i.e. with the cytochemical examination of intracellularly detectable nickel ions under pathological conditions [1, 2, 3, 4].

Although the fact of tumorous change caused by nickel is accepted in the literature, the detection by cytochemical methods of nickel ions has not been made so far. Our present studies aimed at the cytochemical tracing of nickel ions in human biopsy material in adenocarcinoma of the uterus.

Material and Method

The highly differentiated surgical materials of two cases (H. T. and S. L.) studied light- and electron microscopically were fixed in 2.5% glutaraldehyde, then postfixed in 1% osmium tetroxide. For the cytochemical examination of nickel, 0.1% dimethylglyoxime (dissolved in 70% ethanol) was used for incubation for 10 min [1]. The reaction precipitate was verified, on the one hand, by energy-dispersive microanalysis, while on the other by X-ray diffraction. Both patients (aged 62 and 66) were in the menopause. They were characterized by the specific signs of the 'syndrome of the car-



FIGS. 1–4. Human endometrial carcinoma. Biopsy sample. Electron microscopic cytochemical study. Note the dimethylglyoxime complexes intracellularly and mitochondrially (arrows); m = mitochondrion, n = nucleus. Figs. 1,2,4×12,000, Fig. 3×18,000

cinoma of the uterine body' i.e. they were markedly adipose, obese, one of them was diabetic. They received antihypertensive treatment, but they had had no previous history of nickel exposure.

Results

Intracellularly in the tumour cells, in the cytoplasm or the mitochondria as well as interstitially, characteristic, concentrically arranged nickel-dimethylglyoxime complexes were notable, which were proved by the microanalytical studies to be particles containing nickel (Figs. 1-4).

Discussion

Nickel ions can be visualized subcellularly by the cytochemical dimethylglyoxime technique. The inracellularly localized nickel ions were detected by our team both under normal and pathological conditions, in the myocardium, in smooth and skeletal muscle as well as in cerebral tissue [3, 4, 15]. Dimethylglyoxime forms a complex binding with nickel ions. This shows a concentric, electron-dispersive pattern in the tissue which is accessible to both X-ray diffraction as well as energy-dispersive microanalytical methods and in this way nickel can be verified in the intracellular reaction precipitate.

Nickel ions have not been detected cytochemically so far. In our cases nickel exposure at the workplace could not be shown in the patients' history, which could have been related to the development of adenocarcinoma, i.e. to the presence of the nickel ions detected.

According to our hypothesis, the nickel detected in the cells would just indicate the tumorous nature of this process and, at the same time, it can be supposed that regression of the tumour tissue due to progestogen treatment may contribute to the appearance of the trace element. The aim of earlier investigations was to decide how the cellular regression induced by progestogen treatment aimed at influencing carcinoma therapeutically and the nickel ions detected are interrelated.

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Zytochemischer Nachweis von Nickel bei Endometriumkarzinom im Zusammenhang mit Progestogenbehandlung

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Im Zusammenhang mit Progestogenbehandlung wurden in den karzinomatösen Geweben des Endormetriums der menschlichen Uterusschleimhaut mit der zytochemischen Dimethyloxim-Methode Nickelionen nachgewiesen. Die Mitteilung befaßt sich mit dem Wirkungsmechanismus von Nickel und da in den karzinomatösen Geweben des humanen Endometriums bisher keine Nickelionen nachgewiesen wurden, erhebt sich die Frage, welche zellbiologische Prozesse es zur Folge haben, daß in den Karzinomzellen des Endometriums Nickelionen erscheinen. Eine weitere noch unentschiedene Frage ist, ob zwischen der angewandten Progestogenbehandlung und der Erscheinung der Spurelemente in den Karzinomzellen irgendein Zusammenhang besteht?

Цитохимическое определение никеля при карциноме эндометрия в ходе лечения прогестероном

қ. патаи, з. сарваш и и. балог

Авторы, с помощью цитохимической методики с диметоксимом, показаги наличие ионов никеля в карциноматозных тканях человеческого эндометрия в связи с лечением прогестероном. В настоящем сообщении они занимаются вопросом механизма действия никеля, и, поскольку ионы никеля ранее не были обнаружены в тканях карциномы человеческого эндометрия, встает вопрос: в результате каких клеточно-биологических процессов появляются ионы никеля в клетках карциономы эндометрия? Также ждет своего решения вопрос: связано ли появление микроэлемента в клетках карциномы с примененным лечением прогестероном.

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The Use of Nonspecific Esterase in Assessing the Effectivity of Cryotherapy on the Uterine Cervix

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Cryotherapy of the uterine cervix can produce tissue damage of various depths. It is very important to be familiar with the extent of tissue damage in standardizing the treatment and assessing its effect. In the present work nonspecific esterase reaction was applied for the early study of tissue damage. It was found that this method can be used with benefit in the early assessment of the effect of freezing. The enzyme reaction was primarily a sensible marker of cell damage in the cervical cells.

Enzyme-histochemical studies, including also the reactions demonstrating the changes in nonspecific esterase activity, have gained momentum from several respects in judging pathological alterations. The change of activity can be detected also prior to the appearance of light-microscopic changes and can be reliably localized in the cryostat sections by using various substrates.

The enzymes decomposing esters are of ubiquitous appearance and are known to be present in several species and tissues. Their activity changes during pathological events, in which lysosomes and breakdown processes are of importance. Thus, the reactions were studied in degenerative vascular changes [1] and inflammations as far as the participations of monocytes or leukocytes or their activity played a role [3].

This reaction has been employed in several tissues for the early diagnosis of prenecrotic cellular changes [2], and its electron microscopic version has also been developed.

In the present paper, the early changes of the cervical glandular epithelium of human uterine cervix subjected to cryotherapy and of their superficial epithelium were followed by the routine light-microscopic staining techniques as well as by studying the modifications of nonspecific esterase reaction.

Material and Method

Two to three hours prior to a tracheloplasty planned for laceration of the cervix, cryotherapy was applied by 5 min freezing in fertile women in 8 cases, some days after termination of their periods (mean age: 32.3 years). An Erbokryo-Amoils 40/a freezing device was used, with a perfusion pressure of the N_2O gas being 3.8-4.4 MPa. The surface temperature of the cryoprobe ranged between -75 °C and -85 °C. Postoperatively, the removed tissues were cut, partly unfixed, by a Leitz 1720 cryostat (at temperatures of -22 °C of the support and at -20 °C of the knife), and was partly fixed in 4% glutaraldehyde and 8% formaldehyde. The 10 μ m thick cryostat serial sections were partly stained after a 10 min Baker's formalin fixation at 4 °C by haematoxylin-eosin and partly incubated in a phosphate buffer containing alpha--naphthyl acetate and hexazotylated fuchsin adjusted at pH 7.2 for 20 min at room temperature. Then the sections were covered with glycerinated gelatin and were studied by a Leitz-Lumival microscope the following day. Later the material fixed in glutaraldehyde was embedded for processing in resin (Durcupan ACM, Fluka). After paraffin embedding of the material fixed in formaldehyde, routine histological studies were made. The activity of the glands and epithelia of the regions not exposed to freezing at the marginal parts of the cervix was regarded as normal or as the control of the frozen parts. Fur studying the specificity of enzyme-histochemical reactions, sections incubated without a substrate and denaturated by heat treatment, were used.

Results

In the intact regions the cervical glands were lined with a regular columnar epithelium with a basal nucleus. The poor lymphocytic infiltration focally under the epithelium indicated slight chronic inflammation (Fig. 1*a*). The non-specific esterase reaction made on parallel sections showed marked polarization within the epithelial cells, inasmuch as the reaction precipitate can be predominantly found between the nucleus and the basement membrane, and it is of finely granular structure (Fig. 1*b*).

In the regions exposed to freezing the epithelium of the cervical glandular lumina became totally desquamated near the surface, the epithelium in the deeper lumina became detached only on the side facing the surface, while it appeared to be intact on the contralateral side by staining it with haematoxylin-eosin (Fig. 2a). The enzyme-histochemical reaction performed on parallel sections revealed complete loss of activity in the desquamated regions, and in comparison to that in the intact tissue, it greatly differed both in its localization and distribution in the preserved epithelium. The polarity of enzyme activity changed in the latter epithelial regions, with its centre of gravity in the individual segments shifting to the side of the lumen facing the epithelium. In other places it showed a roughly uneven distribution varying by cells. The enzyme activity detectable in the segmentally preserved epithelium was of irregular or homogeneous distribution. The focal and intensive enzyme



FIG. 1A. Slight chronic inflammation in the surroundigs of the cervical glands lined with intact epithelium, H & E, $\times 100$. (b) Serial section of the region seen in Fig. 1a, showing a finely granular nonspecific esterase activity of basal localization of the intact epithelium, $\times 100$

activity in the periepithelial region corresponded to the monocytes of an inflammatory reaction (Fig. 2a, b).

There was no reaction precipitate on the heat denaturated section immersed into hot water and incubated without a substrate.

Discussion

Esterases hydrolyse short-chain fatty acids and so they play an important role in several vital processes. Due to their lysosomal and cytoplasmic localization and their role in the hydrolytic processes, they are especially suitable for examining the functional state of the cells and are sensitive enough for diagnosing the early changes.

As to the normal occurrence of enzyme activity and its pathological change, no data have been found on the cervix in the gynaecological literature. Since the reaction employed yielded good results in also bradytrophic tissue, [4] it was found suitable for examining the early cervical changes subjected to cryotherapy as well as for judging the effective depth of the treatment.



FIG. 2A. The part facing the epithelium of the epithelial lining of the glandular lumen 3 mm deep in the frozen region has become desquamated, in other places preserved. Detached epithelial cells embedded in the precipitated mucus can be found in the lumen, its environment showing lymphocytic-leukocytic infiltration, H & E, $\times 100$. (b) In the lumen seen in Fig. 2a, the enzyme activity of the parts facing the surface is not visible. In the preserved epithelial cells, activity appears partly on the side of the lumen and partly it displays a roughly granular and irregular, but mostly homogeneous, distribution in the desquamated epithelial cells of various intensity and uneven structure. The adjacent cells showing intensive activity correspond to monocytes belonging to inflammatory infiltration, $\times 100$

The basal activity observed in the intact cervical glandular epithelium is likely to be bound to lysosomes, which seems to be supported by its granular structure. In the partially damaged cervical glandular epithelium having been subjected to cryotherapy, in the depth of the demarcation zone, granular activity has partly become inhomogeneous with a change in its localization and it partly ceased or homogeneous activity was noted in the whole cell. These changes include the partial enlargement of lysosomes, a partial change in their localization and they partly refer to their opening or to the homogeneous distribution of their content in the cytoplasm. This enabled us to conclude that all the regions of the glands in which an irreversible damage of the lysosomes occurs, later become necrosed, autolysed and desquamated.

Due to its simplicity, the non-specific esterase reaction seems to be suitable for the early detection of tissue damage during the gynaecological application of cryotherapy.

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Anwendung der nicht spezifischen Esterasereaktion zur Beurteilung der Effektivität der Kryobehandlung der Zervix

S. MATÁNYI und T. KERÉNYI

Durch die Kryobehandlung der Zervix können Gewebeschädigungen unterschiedlicher Tiefe zustandegebracht werden. Die Kenntnis der Ausbreitung der Gewebeschädigung ist zur Beurteilung der Standardisierung und Wirkung der Therapie von großer Bedeutung. Die zur Frühuntersuchung der Gewebeschädigung angewandte nicht spezifische Esterasereaktion hat sich zur frühen Beurteilung der voraussichtlichen Wirkung der Kryobehandlung gut bewährt. Die Enzymreaktion war in erster Linie in den zervikalen Drüsen ein empfindlicher Indikator der Zellschädigung.

Использование неспецифической эстеразной реакции для оценки эффективности криотерапии шейки матки

Ш. МАТАНИ и Т. КЕРЕНИ

Криотерапия шейки матки может вызывать провеждения тканей различной глубины. Для того, чтобы стандартизировать лечение и оценить его эффективность, важно знать степень распространения тканевого повреждения. В нашей практике, для раннего определения тканевого повреждения, мы применили несспецифическую эстеразную реакцию и нашли, что она вполне годится для ранней оценки ожидаемого от криотерапии эффекта. Энзимная реакция была чувствительным индикатором, в первую очередь, клеточного повреждения в цервикальных железах.

Ultrastructural Alterations in the Ectocervical Epithelium after Cryotherapy

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The central problem of the cryosurgery of the uterine cervix in gynaecological practice is the extension in depth of the tissue impairment. The ultrastructural alterations were studied in the surgical material of portioplastics performed two hours after cryotherapy of the non-malignant ectocervical changes of fertile women. For control, the un frozen regions of the same cervix were used. The vacuolization of the cytoplasm and partial fragmentation of the mitochondria appear to be detectable and reversible changes. Parallelly, severe irreversible nuclear impairments can be demonstrated in the basal and parabasal layers of the cervical epithelium. The relative connective tissue insensitivity, in contrast to the damage of the epithelium, verifies the advantage of cryosurgery in the therapeutic applicability.

Cryosurgery of the uterine cervix in gynaecological practice is an extensively used therapeutic intervention. Its importance is emphasized by the fact that it grants several benefits over the other physical ways of treatment. It is inexpensive, painless and can be performed in out-patient departments. It is not associated with by-effects and complications, healing is without scars.

Hardly any data are available on the ultrastructural study of the early changes due to cold in the ectocervical tissue [9]. In the present paper the early ultrastructural alterations of human uterine cervix occurring due to a type of freezing most often applied in clinical practice are described.

Material and Method

Cryotherapy was performed in fertile women prior to tracheloplasty immediately after their periods, with negative cytological findings. The perfusion pressure of NO₂ gas was 3.8-4.4 MPa, the superficial temperature of the probe was from -75 to -85 °C, the duration of therapy was 5 min. An Erbokryo-Amoils 40/a equipment (Spembly Ltd., Andover, England) was used. Freezing was performed partly in the fornix and partly intracervically by the use of a probe of 9.5 mm, in diameter with a cone-shaped end. The tissue temperature of the ectocervix contacting the probe was continuously recorded by a needle placed immediately on the epithelial surface, containing a copper-constant an thermocouple. The average value of cooling velocity was 0.25 °C/s, that of warming 0.45 °C/s.

The operation was carried out two hours after freezing. The removed cervical tissue was immediately rinsed with a physiological saline solution after 4-6 h of fixation (in 0.1 M phosphate buffer, pH 7.4), 2 cm² blocks were cut from the intact and superficial parts of the cervix, both from the frozen and unfrozeen epithelia for electron microscopic study and embedding. After dehydration in graded alcohol series, they were embedded in DURCUPAN ACM (Fluka). The regions for ultrathin sectioning were selected in semithin sections. After staining with toluidine blue, the semithin sections were studied under a ZETOPAN microscope. Ultrathin sections were stained with uranyl acetate and lead citrate under a JEOL 100B electron microscope.

Results

The ultrastructural alterations after cryotherapy were studied in semithin and ultrathin sections.

In semithin sections, the superficial layers of the epithelium were more compact and stained intensely, while in the basal-parabasal layers, vacuolization of the cells was striking. Erythrocytes embedded in fibrin were attached to the surface of the epithelium. Focal bleeding appeared subepithelially. The boundary between the epithelium and the connective tissue was sharp



FIG. 1. Under the superficially desquamated, haemorrhagic, condensed cell layers, the spinocellular cells seem-to be intact. Vacuoles appear contacting the nuclei of the basal and parabasal cells. Subepithelially, haemorrhage is seen in the connective tissue. Semithin sections, toluidine blue staining, $\times 200$

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FIG. 2. Squamous cells are present over the surface of the epithelium under the cell debris embedded in fibrin. Their plasm contains no organelles, their plasm membrane is partly missing. Contrast staining with uranyl acetate and lead citrate, × 9600



Fig. 3. The interstitial spaces in the deeper layer of the planocellular cells have widened with an accumulation of a finely granular, weakly electron-dense material. The plasm of the cells contains tonofilaments, glycogen granules, the intercellular junctions are intact. Contrast staining with uranyl acetate and lead citrate, $\times 18,000$



FIG. 4. Floccular material and cell debris in the interstitial space of the basal-parabasal cells widened to various extents. Besides the nucleus of the basal cell, in the vacuole of low electrondensity and filled with granular substance, there is an osmiophilic clot resembling a myelin figure. A similar one is seen in a smaller vacuole, also beside the nucleus. The cristae of mitochondria are fragmented, the structure of the nucleus is well preserved. The basement membrane is intact with slight edema in the subepithelial connective tissue. Contrast staining by uranyl acetate and lead citrate, × 9600

everywhere (Fig. 1). The control section showed a normal layered epithelial structure without any sign of condensation and vacuolization.

In the ultrathin sections cell debris was found between the superficial fibrin bundles of fascicular structure. The plasma membrane of the cell layer under the fibrin was absent in several places. Cell debris occurred also under the fibrin layer (Fig. 2). The spaces between the epithelial cells were substantially widened with the accumulation of a weakly electron-dense, finely granular substance containing osmophilic clots (Fig. 3).

In the spinous layer of the epidermis the intercellular spaces were widened only focally and inhomogeneously, the cells retained their shape. The most conspicuous ultrastructural changes occurred in the nucleus, where cavities developed with one or two loculi, situated within the nuclear membrane or protruding from the nucleus and filled with a flocular, slightly electrondense substance. Chromatin was partly condensed at the nuclear membrane, the eu- and heterochromatin, as well as one or two nucleoli were well differentiable within the nuclear substance (Figs. 4–5). The cytoplasm contained



FIG. 5. In the nucleus of the basal-parabasal cells vacuoles of one or two loculi developed. Some chromatin is found condensed on the nuclear membrane, the nucleoli are differentiable. The vacuoles in the cytoplasm are partly connected to the mitochondria. Contrast staining with uranyl acetate and lead citrate, $\times 6000$

large amounts of glycogen, the endoplasmic reticulum was occasionally widened, the cristae of the mitochondria showed focal fragmentation.

The cells of the germinative layer of the epidermis retained their connection with the basement membrane. In the interstitial space widened in the environment of the cells, a slightly electron-dense, flocular material, cell debris and osmiophilic clots were present (Fig. 4).

Discussion

The tissue damaging effect of freezing has been studied in several in vitro and in vivo experiments [4, 7, 8]. Tissue alterations depended, besides the freezing and thawing velocity, on the depth of cooling and also on the type of tissue [1, 2, 3, 10, 15].

On freezing the uterine cervix, a considerably heterogeneous tissue is cooled. The extent of damage is affected by the differentiation of cells, their water content and distance from the surface of the cryoprobe.

Just for orientation, the cooling and warmin velocities were given in average values. During cooling, however, the decrease in temperature is not

homogeneous, initially being rapid then later on increasingly slower. This applied to warming as well. In the first minute a cooling velocity of 1.17 °C/s and a warming velocity of 0.84 °C/s, in the fifth minute a cooling velocity of 0.12 and one of 0.12 °C of warming velocity were measured. These values refer to the most superficial tissue temperatures. Naturally, the cooling of deeper tissue layers is slower, their thawing velocity is, however, faster. There are no data on the ultrastructural implications of tissue damage of this kind. According to several authors, rapid cooling and slow thawing in the superficial layers inflicts nuclear damage [13, 14, 15]. In our case such ultrastructural changes appear mostly in the basal and parabasal layers. At the same time, also mitochondrial damage, described in different tissues had previously been observed by others in in vitro experiments [11, 13]. The sensitivity of the basal layer is connected with its active metabolism and high water content.

The superficial epithelial layers were hardly damaged. There was evidence of damage only in the widening of intercellular spaces and the accumulation of floccular material.

There were no estimable subepithelial changes in the connective tissue. The intensitivity of the connective tissue, as opposed to the explicit damage of the adjacent epithelium, proves the selective epithelium-damaging effect of freezing beneficial from many aspects. The selective epithelium damaging effect of freezing has earlier been verified by enzyme-histochemical studies also in the deeper cervical glandular lumina [6].

Our results do not fully agree with the findings of investigations published earlier [9]. This is probably due to the differing type, depth and velocity of freezing, the size of the frozen region, to the characteristics of the cryoprobe used, to the quality of the cooling contact and to the two hours elapsing from the termination of freezing to obtaining the sample.

No obvious conclusions can be drawn from our experiment as to the reversibility of ultrastructural alterations, but considering the importance of intranuclear vacuolization known from general pathology, it can be duly assumed that this implies an irreversible cell damage.

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Ultrastrukturelle Änderungen im Epithelgewebe des Gebärmutterhalses nach Kryobehandlung

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Das zentrale Problem der Kryochirurgie des Gebärmutterhalses ist in der gynäkologischen Praxis die Tiefenausbreitung der Gewebeschädigung. Im Operationsmaterial der 2 Stunden nach der Kryobehandlung der nicht malignen, pathologischen Zervixveränderungen von sich im fertilen Alter befindlichen Frauen durchgeführten Portio-Plastiken wurden die ultrastrukturellen Veränderungen untersucht. Als Kontrolle dienten die nicht gefrierten Gebiete desselben Gebärmutterhalses. Die Vakuolisation des Zytoplasmas und die partielle Fragmentierheit der Christen der Mitochondrien können nachgewiesen werden und scheinen reversible Veränderungen zu sein. Gleichzeitig sind in den basalen und parabasalen Schichten des zervikalen Epithels schwere, irreversible nukleare Veränderungen zu beobachten. Die relative Unempfindlichkeit des Bindegewebes gegenüber der Schädigung des Epithelgewebes ist ein Beweis für die vorteilhafte therapeutische Anwendung der Kryobehandlung.

Ультраструктурные изменения в эпителиальной ткани шейки матки после криоскопии

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Центральной проблемой криохирургии шейки матки в гинекологической практике является распространение в глубину тканевого провеждения. В хирургическом материале пластики влагалщной части маточной шейки, производимой через два часа после криотера» пии патологических изменений шейки матки не злокачественного характера у женщин репродуктивного возраста, мы изучали ультраструктурные изменения. Контролем служили не подвергавшиеся замораживанию участки той же самой шейки матки. Выявились вакуолизация цитоплазмы и частичная ломкость митохондриальных крист, которые кажутся обратимыми изменениями. В то же время, обнаруживаются тяжелые, необратимые ядерные повреждения в базальном и парабазальных слоях цервикального эпителия. Относительная нечувствительность соединительной ткани сравнительно с повреждением эпителиальной ткани подтверждает достоинство применения криотерапии.

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Endoscopic Removal of Residual Calculi from Horse-shoe Kidney and Ureter

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Ureteroscope and pyeloscope were used for removing residual calculi following open operation of horseshoe kidney. Endoscopic nephrolithotomy is suitable for preventing complications of

Endoscopic nephrolithotomy is suitable for preventing complications of open operations.

Following the open operations of multiple stones, staghorn calculi, it is not rare that residual calculi are retained in the renal calyceal system or they slip into the ureter. According to literary evidence, if there is no intraoperative roentgenographic control by ultrasound or endoscope, there may remain residual stones in 25–30% of the cases [1, 2, 4]. Reoperations for residual stones have always belonged to the technically difficult operations, they entail strain and risk for the patient and they are often associated with a considerable loss of parenchyma. Endoscopic nephrolithotomy offers, also in this respect, a new means to prevent these complications. In our case worth of presentation, a total of 21 residual stones were found following pyelotomy in the right calyceal system and dilated ureter of a horseshoe kidney containing particularly numerous stones.

Case Report

N. H., a 30-year-old male patient, was examined for right lower back pain and sensitivity having persisted for years. Haematopyuria was detected in the urine and $E. \ coli$ was isolated bacteriologically. Urography revealed a horseshoe kidney in the left renal pelvis of which one calculus, while in the right renal calyceal system of which over 20 bean- and nut-sized positive calculi were found. Excretion on this side was delayed and weaker (Figs. 1, 2).

Owing to the obstruction by stone of the right kidney and the patient's complaints on his right side, it was decided that his right side was to be operated on. The kidney was exposed from a downwards lumbotomy and after an extensive pyelotomy 26 stones were removed. The patency of the



FIG. 1. Plain film of a horseshoe kidney with a bean-sized positive stone in the left half, and over 20 bean- or nut-sized positive stone in the right half of it



FIG. 2. I. v. urography. Characteristic stones of the collecting system of a horseshoe kidney with an only suspectable dilatation due to the weak excretion on the right side

ureter was checked by a ureteral catheter of 5 Ch which could be freely introduced up to the bladder. At the end of the operation, X-rays were taken for possible residual stones, but there were none. Nehphrostomy was performed for the dilated calyceal system via the lower calyceal system. To our greatest surprise, the postoperative control roentgenogram revealed 18 residual stones in the lower ureteral segment situated like a row of pearls, and two beanand nutsized stones even remained in the dilated calyceal ends, too (Fig. 3). The possible explanation could be that this portable X-ray apparatus could not take pictures of appropriate quality and the lower ureteral segment had not at all been taken by the picture because we thought that free passage had been amply verified by the introduction of the ureteral catheter. It was not, however, taken into consideration that the ureter was dilated enough to contain both the calculi as well as the catheter. After the 7th postoperative day, following dilatation of the orifice by a rigid ureteroscope, 14 calculi were removed from the ureter (Fig. 4). By using an indwelling ureteral catheter, the following day a pyeloscope was inserted through the nephrostomic channel into the calvceal system, but no stones were found. The sterile fluid injected through the ureteral catheter drifted the stones having entered the upper segment of the ureter, under our eyes, into the renal pelvis. These were removed by pyeloscopy. The control roentgenogram taken after one open and two



FIG. 3. Postoperative plain renal film. A string of beads is formed of stones in the right ureter but there are two residual stones even in the collecting system



FIG. 4. Plain film after stone removal by ureteroscopy with no calculus in the right ureter



FIG. 5. Following one open and two endoscopic operations the right half of the kidney is free of stones

endoscopic operations disclosed no stone on the right side (Fig. 5). Nephrostomy was removed on the day after the last operation and the patient was discharged free of stones and cured.

Discussion

The ureterorenoscope is being successfully used for diagnostic and therapeutic purposes [3]. It is of particular importance in removing fragments, so-called 'Stein-Strasse' having developed due to extracorporeal shock-wave lithotripsy (ESWL) and been trapped in the ureter.

In our case the stone piled up like a string of beads-this cannot be actually regarded as a 'Stein-Strasse', since they were not really fragments but intact stones. It is of interest that the residual calculi of the collecting system had slipped into the ureter and they had to be washed from the upper renal pelvis to be removed by the pyeloscope. For removing the stones in the collecting system the track of the transrenal drain could be excellently used. In Hungary and in the Yemen Arab Republic, apposite equipments are available at an increasing number of urological departments and, consequently, experience concerning endoscopic nephrolithotomy has been accumulating in the recent years [5]. Parallelly, however, open surgery, is also employed for treating calculi. The two procedures can supplement each other in a way that the endoscopic method is recommended for residual stones.

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Endoskopische Entfernung der Residualsteine aus der Hufeisenniere und aus dem Ureter

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Nach offener Hufeisennierenoperation kamen zur Entfernung der Residualsteine Ureteroskop und Pyeloskop zur Anwendung.

Die endoskopische Steinchirurgie eignet sich zur Verhütung derartiger Komplikationen der offenen Operationen.

Эндоскопическое удаление резидуальных камней из подковообразной почки и мочеточника

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Дгя удаления остаточных камней вслед за открытой операцией подковообразной почки авторы пользовались уретероскопом и пиелоскопом. Эндоскопическая хирургия камней применима для устранения осложнений после открытых операций.

The Effectiveness of Venous Hypothermia in the Left Kidney

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Twenty renal parenchyma operations of the left kidney were performed in venous hypothermia. The hypothermic solution was perfused via the spermatic (ovarian) vein, outflow occurred through the vessels opened by the incision. The effectiveness of venous hypothermia was measured by the probe of an electrical thermometre inserted into the renal tissue. The temperature of the cooled kidney became constant between 20 and 23 °C by using a perfusion solution of 4–5 °C. The method can be used for its simplicity and safety also in extensive renal parenchyma operations, its only limitation is that it can be performed only on the left kidney.

Prolonged renal parenchyma operations requiring a time longer than 20 min and causing ischaemia, can be performed without impairment of function by hypothermia [1, 2, 3, 4]. Cooling may be superficial or intravasal, this latter can be made via the venous system of the kidney [11]. The use of any of the hypothermic methods is justified in practice, the procedure of choice should be adjusted to the operated kidney [7]. An essential point is that hypothermia should provide an effective help in the operation and the hazards and risks of operative activities required by cooling should be proportional to the advantages gained. The risk of superficial cooling is low, its effectiveness is smaller, however the placing of the ice bag or cooling plastic bag around they kidney is not time consuming [4]. The prerequisities of perfusion hypothermia are the exposure of the renal or spermatic artery or vein, puncture of the vessels or introduction of a cannula-which all increase the time of operation. It is true that perfusion hypothermia is more effective and more homogeneous as well as it has the advantages of washing the blood out of the vessels and so during expulsion, no intravasal clotting is likely to occur.

The thorough cleaning, 'denuding' of the renal artery and vein is associated with the destructuion of the perihilar lymph vessels and neural plexuses, the role of which factors cannot be ignored in the delicate process of physiological regulation. Puncture and cannulation of the vessels may induce thrombosis, later vascular stenosis and the patient may become hypertensive. Retrogade venous hypothermia can also be made via the left (ovarian) vein. The theoretical principle of venous hypothermia is that, in contrast to the segmental distribution of the arteries, the venous system of the kidney is unbroken and, being opened at any place, continuous flow is achieved. According to the literature, the perfusion solution must be circulated after careful compression of the renal pedicle by a pressure of 80–100 water cm, and for avoiding tension in the kidneys, simultaneously an incision should be made in the parenchyma, and so the perfusion solution can flow out through the open vessels [5, 6]. The optimal composition of the perfusion solution is the Collins or the Euro-Collins solution.

Material and Method

Perfusion hypothermia via the (ovarian) vein at the left parenchyma operations of 20 patients was performed at the Department of Urology of Semmelweis University Medical School and of the Al-Thawra Modern General Hospital of Sanaa. Indication for operation was required in patients with coral or multiple calculi where, beside stone removal, an anatomical correction, resection of the calculus nest and calyceal plastics was necessary. In three cases tumour resection was made in a solitary kidney by applying venous cooling. The aim was to assess the effectiveness of venous cooling. The left kidney was exposed by transverse lumbotomy, which makes possible the exploration of the renal pedicle and its environment. The vessels were never denuded but efforts were made at preserving the perivascular tissue. The vein was transected at 2-3 cm from the inflow and the distal stump was ligated, introducing a 8 Ch infant feeding tube into its proximal end in a way that its tip should hang into the renal vein, but should not injure the opposite wall (Fig. 1). The probe of the electric thermometer was pricked into the upper pole up to the corticomedullary junction and so the change in temperature, i.e. the effectiveness of hypothermia, could be continuously measured intraoperatively. The renal pedicle was clamped proximal to the inflow of the spermatic vein and incision of the parenchyma was performed simultaneously with perfusion of the fluid cooled to 4-5 °C (Fig. 2). The difference in pressure maintaining the flow, i.e. 100 water cm, and the length and calibre of the tubes were standardized. During operation the amount of cooling fluid was measured used as well as the time needed for the renal parenchyma to achieve the 30 °C and 23 °C representing a 50% and 30% oxygen consumption, respectively. The nuclear temperature of the cooled kidney did not fall under 20 °C, but became constant between 20 and 23 °C. This phase was celled 'isothermic ischaemic time'. Inference to the mass of the kidney was made from its width and thickness, based on the autopsy data of healthy kidneys.

The kidney size measurements (length, width and thickness) of 100 randomly selected individuals died of non-renal diseases were multiplied and



FIG. 1. Cannula introduced at 3 cm from the inflow of the left testicular vein



FIG. 2. Marginopolar wedge resection by venous perfusion cooling of the kidney with stone in the opened renal calyceal system

the ratio of volume and weight obtained was called the 'density of the kidney'. Density was used as a coefficient for calculating the mass of the kidney. (For the data our thanks are due to Dr. F. Brittig, Head of Department of Pathology, Markusovszky Hospital, Szombathely).

Results

Our patients tolerated the operation well without exception. In 6 patients, after stopping of ischaemia, an enhanced blood pressure of amout 20 mm Hg, lasting for some minutes, was observed. The renal function values did not increase, although it is true, that there were no azotaemic cases among the patients. Three months postoperatively the patients were controlled by urography and half of them by dynamic scintigraphy. The intervention did not, in any of the cases, involve any impairment of function detectable by the above examinations.

Under standardized conditions, the amount of fluid perfused through the venous system of the kidney during one unit of time is practically constant — independent of the mass of the kidney — and if the two extreme values were omitted, it ranged between 23.4 and 26.3 ml/min (Table 1). In our opinion,

TABLE 1

Calculation of average weight of the operated kidneys: 210 g Average amount of cooling fluid used: 845 ml Average duration of cooling: 35 min (two extreme values: 19 and 60 min, resp.) Average speed of perfusion (by omission of the two extreme values): 25 ml/min Fluctuation of perfusion without the two extreme values: 23.4–26.3 ml/min Average duration of isothermia: 23 min Average time of warming up: 4.9 min Average time of cooling to 23 °C: 11.25 min

it is due to the fact that the narrowest cross-section of the system was the lumen of the opened vessels and the nephrotomic wound surface was the widest at the two extreme values. The effectiveness of venous hypothermia means that 30% was achieved on average during 4.37 min and 23 °C on average during 11.25 min.

It is interesting but logical that if the dynamism of cooling is calculated for 100 g of renal tissue, this two time periods do hardly change, i.e. they are 2.2 ± 0.6 and 56 ± 0.5 min.

Discussion

It is easy to achieve a rapid increase in temperature by perfusion hypothermic through the (ovarian) vein. Cooling is homogeneous and mechanical lesion and perniosis of the environment and of the kidney are excluded. The method is simple, it is more rapid than other intravasal procedures and is much easier to perform. The operative region is easier to survey, on the cut surface the perfusion fluid makes the open blood vessels visible even without staining and the eluent coming 'from the inside' may drift even minor calculi.

The disadvantage of the method is that it can be used only in operations of the left kidney. In an earlier renal or retroperitoneal exposure such perihilar scarring may occur which makes the exposure of the vein immpossible. Venous hypothermia can be well applied in extensive renal parenchyma operations of the left side, because it does not require much equipment, it is simple, cooling is effective and harmless. In our opinion, even with the extensive use of endoscopic nephrolithotomy and shock-wave lithotripsy, certain renal calculi can be removed optimally by open surgery and the organ-preserving operations of renal tumours have opened up new vistas for parenchyma operations.

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Effektivität der venösen Abkühlung in der linken Niere

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20 linksseitige Nierenparenchymoperationen wurden in venöser Abkühlung durchgeführt. Die Kühlflüssigkeit strömte durch die V. spermatica (ovarica) ein und durch die bei der Freilegung geöffneten Gefäße aus. Die Effektivität der venösen Abkühlung wurde mit der Verlegung geornioen Genergewebe gestochenen elektrischen Thermometers gemessen. Die Temperatur der gekühlten Niere stabilisierte sich bei Anwendung einer Kühlflüssigkeit mit einer Temperatur von 4–5 °C zwischen 20 und 23 °C. Wegen ihrer Effektivität, Ein-fachheit und Ungefährlichkeit kann die Methode auch bei ausgedehnten Nierenparenchymeingriffen eine Anwendung finden, ihr einziger Nachteil ist, daß sie nur auf der linken Seite durchgeführt werden kann.

Эффективность венозного охлаждения в левой почке

т. лукач, д. франг, л. пайор, а.-а. эль-сиги и л. хамза

Авторы выполнили 20 операций на паренхиме левой почки в условиях ее венозного охлаждения. Охлаждающую жидкость пропускали через семенную (яичниковую) вену. Вытекала жидкость через вскрытые в ходе разрезов сосуды. Эфективность венозного охлаждения измеряли электическим термозондом, воткнутым в повечную ткань. Температура охлажденной почки устанавливалась между 20 и 23°С, при использовании 4-5 градусной охлаждающей жидкости. Вследствие эффективности, простоты и безопасности метода, он может применяться и при распространенных операциях на почечной паренхиме, единственный его недостаток — годится только для левой стороны.

Pacemaker Twiddler's Syndrome (Rotation of the Pacemaker around the Electrode Cable, a Rare Complication of Pacemaker Therapy)

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Rotation of the pacemaker generator around the electrode cable (i.e. twiddler's syndrome) was observed by the authors in six cases during the implantation of 4250 pacemakers. Twiddler's syndrome developed in three cases following implantation and in three cases after the replacement of the pacemaker. As a result of the rotation of the device, displacement of the electrode occurred in all cases. The factors predisposing to rotation of the device were as follows: (*i*) a loose, dilated pocket in 5 cases; (*ii*) seroma formation around the device in 2 cases; (*iii*) manipulation with the pacemaker in one case.

For treating twiddler's syndrome, reimplantation was performed, 'fashioning a small and tight pocket for the device and fixing it by transfixing sutures. After reimplantation, the patients became complaint free, no recurrences occurred.

Twiddling of the pacemaker in the pocket of the device results in its rotation around the electrode and it usually leads to displacement or other disorders in the function of the pacemaker. This syndrome was described by Bayliss et al. in 1968 [2] and since then 30 cases have been reported in the literature [1-12]. In our patient material 6 cases of twiddler's syndrome were observed during a total of 4250 pacemaker implantations.

The present study aimed at reviewing the peculiarities of twiddler's syndrome and the factors predisposing to rotation of the device.

Case Report

Case 1. T. L., a 76-year old, thin male patient had pacemaker implantation in 1968 for complete A-V block (3rd degree A-V block). For an electrode, bipolar endocardial electrodes with a ring at their end were used which was introduced via the left cephalic vein into the right ventricle. The left pectoral subcutaneous region was used as the pocket for the pacemaker. Rotation of the device developed three months after the implantation. Ineffective pacemaker electric signs (signs of ineffective electric cardiac stimulation) and slipping back of the electrode into the right auricle, drew attention to the above complication. The pacemaker twiddled around the catheter as a cable and made triple rotations in the vertical plane. Pacemaker reimplantation followed and the new device was fixed by transfixing muscle sutures in the pocket. On inquiry the patient told us that he moved and twisted the device several times after implantation.

Case 2. B. J., a 62 year-old, thin, male patient. Pacemaker implantation was made in 1969 for sinus-node diseases and bradyarrhythmia. His device was implanted in the right pectoral subcutaneous region by applying a unipolar 'flanged' electrode which was fixed via the cephalic vein in the apical part of the right ventricle. Following pacemaker implantation, transitionally seroma was found to form around the device. The symptoms of twiddler's syndrome appeared after six months. Ineffective electric pacemaker signs, defective demand function and stasis of the diaphragm called attention to the complication. The device rotated twice horizontally around the electrode cable. The pacemaker was reimplanted, then the patient became complaint--free.

Case 3. W. J., a 67-year-old, obese female patient. Pacemaker was implanted for complete A-V block and Adams-Stokes attacks in 1972. Unipolar electrode was applied, which was introduced into the left cephalic vein. The pocket of the device was in the left subcutaneous pectoral region. In 1978 the pacemaker was replaced followed in 4 months by the appearance of the twiddler's syndrome. The device rotated three times around the cable as the axis, the electrode slipped from the apical part of the right ventricle and electric cardiac stimulation became ineffective. Pacemaker reimplantation was performed resulting in the disappearance of symptoms.

Case 4. M. J. female patient, aged 68 years. Pacemaker was implanted for sinus-node disease and second-degree A-V block. Unipolar, tined electrode was employed, introduced via the left cephalic vein and fixed in the apical region of the right ventricle. The device was implanted into the left pectoral region subcutaneously. The complication arose two months after implantation, i.e. ineffective electric signs, twitching of the diaphragm. The device rotated four times in the pocket along the vertical axis. The cable broke at the side of the rotation. Pacemaker reimplantation was made in a new pocket deep in the right pectoral region.

Case 5. J. K., obese female patient, aged 51 years. Implantation of pacemaker was made for complete A-V block in 1979 with a unipolar tined electrode. The electrode cable was introduced by puncture of the right subclavian vein into the right ventricle. The device was implanted subcutaneously into the right pectoral region. In 1984 the device was replaced which was followed by seroma formation. Symptoms developed after five months, i.e. ineffective electric signs, defective demand function. The device rotated twice around the horizontal axis and the electrode slipped back to the right auricle.



FIG. 1. In the chest X-ray (anteroposterior view), the pacemaker and the electrode cable can clearly be visualized. The device rotated around its vertical axis and is localized perpendicular to the frontal plane. The cable has been twisted twice in the pocket. The electrode was renained in the right ventricle (microdislocation)

The pacemaker was reimplanted by fixing the device in a new pocket deep in the left pectoral region.

Case 6. L. S., a 81-year-old, thin female patient. Pacemaker implantation was made for sinusnode disease and a second-degree A-V block. Unipolar tined electrode was inserted via the left cephalic vein which was fixed in the apical region of the right ventricle. The pocket of the device was in the left pectoral region. Symptoms appeared eight months after implantation including ineffective spikes and deficient demand function. The end of the electrode was displaced from the site of implantation, but it remained in the right ventricle. The device rotated twice vertically around the cable as an axis. Reimplantation was performed, the new device was fixed by transfixing sutures deep in the right pectoral region.

Discussion

Twiddler's syndrome is a relatively rare complication of pacemaker therapy. In our patient material twiddler's syndrome occurred at an incidence rate of 7.1% after pacemaker implantation. Although twiddler's syndrome occurred in the patient material of Ellringmann and Schmitt [6] relatively frequently, at an incidence rate of 6.3%, their data were not confirmed by other teams. It is notable that, while the frequency of pacemaker complications is decreasing with the advancement of pacemaker technology, the incidence rate of twiddler's syndrome has actually not changed.

The pathomechanism of twiddler's syndrome is not precisely known as yet, but undoubtedly, the primary cause is rotation of the device in the pocket. This leads to twisting of the electrode cable which results in displacement and retraction from the place of fixation of the electrode. The macrodislocation of the electrode (its slipping back to the auricle) is a frequent phenomenon, while its microdislocation from the site of fixation can be less often observed. Electrode dislocation gives rise to the most important clinical symptom of twiddler's syndrome, i.e. electric stimulation becomes ineffective. In cases of microdislocation, electric stimulation is usually ineffective only periodically. An additional clinical sign of twiddler's syndrome is defective demand function. The development of diaphragmatic contractions may also occur in twiddler's syndrome, four cases are cited in the literature; in our material further two were observed. A rare complication is the breaking of the electrode cable at the site of the rotation. In our material one such case was observed.

Getting familiar with the factors predisposing to pacemaker rotation would be equally important from both the clinical as well as from the practical points of view. Twiddler's syndrome seems to occur relatively more frequently in older, obese patients. The accumulation of prepectoral subcutaneous adipose tissue and pendant breasts predispose to the rotation of the device. The loose subcutaneous tissue around the pocket of the device makes rotation of the device possibly easier but this is supposed not to be the main cause of the development of twiddler's syndrome. Among our patients with twiddler's syndrome, there were three explicitly thin patients and in one case (Case 6) rotation of the device occurred after their losing weight. Presumably with a loose, dilated pocket, the device tends to rotate more easily. Fluid accumulated in the pocket may also promote twisting of the pacemaker. Transitional minor seroma with occasional development of haematoma is not rare after pacemaker implantation. In our material, considerable transitional seroma formation preceded the development of twiddler's syndrome in two cases.

The moving, twiddling of the pacemaker can also facilitate rotation of the device. Ellringmann and Schmitt [6] often found that the patient had manipulated the device prior to the development of the twiddler's syndrome. Surveying the relevant literature, however, it seems probable that moving of the pacemaker is rarely the sole cause of twiddler's syndrome. The type of the pacemaker electrode cable and the site of introduction seem to play no role in producing the rotation of the device.
It should also be pointed out that in our material (Cases 3, 5, 6) rotation of the device occurred after replacement of the pacemaker with the use of a newer type and smaller and narrower device. It is probable that the narrower. small and streamlined device, i.e. an up-to-date pacemaker, can more easily slip or twist in its pocket. This is supposed to be responsible for the fact that the frequency of twiddler's syndrome has, in fact, not decreased despite the progress in pacemaker techniques and technology. As far as the management of twiddler's syndrome is concerned, the only task is to reimplant immediately the pacemaker. It is advisable to fix the new device by transfixing sutures in its pocket to prevent the rotation of the newer device.

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Pacemaker Twiddler's Syndrom

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Im Laufe von 4250 Pacemaker-Implantationen wurde die Rotation des Pacemakergenerators um das Elektrokabel herum — Pacemaker Twiddler's Syndrom — in 6 Fällen beobachtet. In 3 Fällen entwickelte sich das Twiddler's Syndrom nach der Einpflanzung des ersten Pacemakers und in 3 nach dem Wechsel des Pacemaker-Geräts. Die Rotation des Geräts bewirkte mit der Zeit die Verschiebung der Elektrode. Zwerchfell-Zuckung war in 2 Fällen zu beobachten. Was die zur Rotation des Gerätes prädisponierenden Faktoren anbelangt, waren folgende vorzufinden: 1. Lockere, weite Gerätetasche (5 Fälle), Serombildung in der Umgebung des Gerätes (2 Fälle), Manipulation mit dem Pacemakergerät (1 Fall). Zur Behandlung des Twiddler's-Syndroms wurde Reimplantation vorgenommen, wobei nach Ausbildung einer kleinen, engen Gerätetasche das Gerät mit einer Naht fixiert wurde. Nach der Reimplantation wurden die Patienten beschwerdefrei, Rezidive kamen nicht vor.

Pacemakep TWIDDLER'S SYNDROMA

Ф. ШОЛТИ, Э. МОРАВЧИК, Ф. РЕНИ-ВАМОШ и З. САБО

В ходе имплантации 4250 водителей сердечного ритма, авторы в 6 случаях отмечали ротацию пейсмекерного генератора вокруг электродного кабеля — т. н. синдром пейсмекерного вращения. Этот синдром в трех случаях возник вслед за имплантацией первого водителя ритма, и еще у трех больных после смены прибора. Во всех случаях к вращательному движению прибора позже присоединилось смещение электрода. В двух случаях наблюдали диафрагмальные подергивания. Следующие причины предрасполагают к ротации прибора: 1) рыхлый, широкий карман прибора: 5 случая. 2005 случая. З Манипуляции приборан 1 случай.

Для устранения симптома вращения произвели реимплантацию, создав маленький, тесный карман для аппарата и сделав надежный сетжок для фиксирования его. После реимплантации жалобы прекратились, рецидивы не отмечались.

Ovulation Induction with Pulsatile Administration of Human Menopausal Gonadotropin

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Ovulation induction was performed by the pulsatile administration of subcutaenous human menopausal gonadotropin (hMG). Treatment was started with a daily dose of 75 IU hMG (in a 90% distribution), then it was increased to 150 IU depending on the oestradiol level of the plasm and on the result of folliculometry. Of 10 cycles treated ovulation was induced in 7 cases and two pregnancies occurred. In two cases, following a previous unsuccessful intramuscular hMG treatment, ovulatuon was induced. Hyperstimulation did not occur. The pulsatile s.c. administration of hMG seems to be an adequate ovulation-induction method in ovulatory disorders of hypothalamo-hypophyseal origin and is a good substitute for the missing, endogenous gonadotropin secretion of inadequate pace.

Disorder of absence of ovulation occurs in 15–25% of infertile couples [1]. One of the preconditions of ovulation is the intact functioning of the hypothalamus and the pulsatile secretion of gonadotropin releasing hormone (GnRH) [2]. This peculiarity of hypothalamic control is reflected also by gonadotropin secretion [3, 4]. The inadequate GnRH secretion results in anovulation and amenorrhoea. The pulsatile infusion of GnRH has recently been effectively used in treating hypo- and normogonadotropic anovulatory states [5].

From the mid-1960s, disorder of hypophyseal FSH and LH secretion was corrected by the i.m. administration of human menopausal gonadotropin (hMG) [6]. It is known that also ovarian hyperstimulation, an undesired consequence of the induction treatment, can be induced by the i.m. administration of hMG [7]. Otherwise, i.m. hMG is not always effective.

The new type of pulsatile administration of hMG subcutaneously or intravenously by an automatic infusion pump offers a means to induce ovulation in due time with a lower risk of hyperstimulation even in cases resistant to the treatment by i.m. hMG administration [8, 9].

Patients and Methods

Of those presenting at our out-patient department treating female infertility, 9 oligo- and amenorrhoeal patients participated in the study with an age range between 21 and 31 (mean age 27.2 years). Prior to treatment ovulation could not be induced by other inductory methods (by clomiphene, clomphene + hCG in two cases by the i.m. administration of hMG). After a careful history-taking and admission, tubal patency was evaluated by hysterosalpingography. Plasma prolactin and testosterone levels were normal in all cases. The FSH and LH values determined prior to treatment, fell in the low or normal range. Other endocrine diseases were excluded. The husbands had normal sperm patterns. Except for one patient, they wanted to have a child.

Human menopausal gonadotropin (Pergonal[®], Serono) was given subcutaneously into a subepigastric region by pulsatile administration with the help of a computerized infusion pump operated by a small battery (Zkylomat[®], Ferring, Kiel and Autosyringe[®], Ayerst) at every 90 min. Treatment was in most cases started with a daily dose of 75 IU of hMG (distributed in 16 pulses) and later it was increased to 150 IU depending on the plasma oestradiol level and the result of folliculometry.

During treatment, basal temperature, plasma oestradiol and progesterone levels and the state of cervical mucus were checked and sonographic folliculometry was performed. The hormone determinations were made according to the RIA methods of the 'WHO Matched Reagent Program 1986'. Folliculometry was performed by the Picker 3000[®], USA, ultrasonograph. Ovulation was documented by a progesterone level over 15 nmol/l and an ncreasing waking temperature.

Case	Age	Before treatment			Bleeding in response to	Clomiphene induced		
		FSH IU/l	LH IU/l	Prl. mU/l	E ₃ pmol/l	gestagen test	(without ovulation)	Comment
1	32	2.10	24.53	174	137	+	-	Sterility I, oligo-amenorrhoe, hypertrichosis
2	30	3.50	17.74	165	214	+	-	Sterility I, amenorrhoea II, obesity
3	21	2.51	15.44	235	185	-	—	Sterility I, oligo-amenorrhoea, hypertension
4*	30	2.13	4.56	346	2 64	+	-	Oligo-amenorrhoe, (she did not want to have a child)
5	26	1.67	7.67	45 6	82	+		Sterility II, amenorrhoea II
6	26	2.57	6.90	524	105	+	+	Sterility I, oligomenorrhoea
7	27	4.56	13.45	356	118	-	-	Sterility I, amenorrhoea II, obesity
8*	26	2.86	9.65	298	89	+		Sterility I, amenorrhoea II
9	28	3.81	14.35	579	134	+		Sterility I, amenorrhoea II, hypertrichosis

TABLE 1

Case historic and	l clinical a	lata of	the patients
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Results

The pulsatile subcutaneous hMG treatment was carried out in 10 cycles of 9 patients. The important anamnestic and clinical data of the patients are summarized in Table 1.

The hMG treatment was continued for 16–29 days. Ovulation was successfully induced in 7 cases and two pregnancies resulted (Table 2).

Case	hMG dose/day (IU)	Duration of administration (day)	Ovulation	Menses	Pregnancy	Oestradiol peak	Duration of luteal phase (day)
1	75-150	29	_	+	_	486	_
2	75-150	19		_	-	344	_
3	75-150	16	+	+	-	1288	11
4	75-150	17	+	+	_	1492	13
5	75-150	17	+		+	1965	
6	75-150	18	+		+	1654	_
7	75-150	21		+		586	_
8	75-150	23	+	+		1231	9
	75	19	+	+	_	1145	11
9	75-150	17	+	+		1678	13

 TABLE 2

 Effectivity of pulsatile hMG administration

Figure 1 shows the ovulatory cycle occurring as a result of pulsatile hMG treatment.

Hyperstimulation did not occur during the treatments. Ovulation did not result in three patients, their oestradiol peaks remained at a low level.

Luteal insufficiency was found in one case.

Discussion

Human menopausal gonadotropin treatment by pulsatile administration was carried out in anovulatory conditions of hypothalamo-hypophyseal origin. Except for three patients, ovulation could be induced successfully in all cases, in two instances also when the previous i.m. administration of hMG had been ineffective.

The greater risk of i.m. administration of hMG is hyperstimulation [7]. Namely, hMG administered in a single daily dose, does not mimic the gonadotropin secretion characteristic of the normal hypophysis, which occurs in pulsations at about every 90 min. This non-physiological mode of application can induce hyperstimulation via the switching off of the endogenous feedback



FIG. 1. The basal body temperature and the plasma progesterone levels indicated that ovulation occured.following pulsatile hMG administration

mechanism. The pulsatile administration of hMG tries to restore the physiological state and so a pace of follicular maturation characterizing the normal female cycle occurs.

In the initial phase, human choriogonin (hCG) was not administered, luetal insufficiency occurred on one occasion.

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This method is also effective in patients not responding to conventional (i.m.) treatment and in lack of GnRH. The pulsatile administration of hMG can also be attempted in cases requiring GnRH.

As a complication of the treatment, in one case an inflammatory skin reaction arose around the subcutaneously inserted needle, which made reinsertion of the subcutaneous cannula necessary. No other by-effects were encountered. The treatment was well tolerated by the patients, it did not disturb their everyday life.

The method is not suitable for inducing 'superovulation', because during treatment only the dominant follicle matures and also later, the i.m. administration of hMG is needed for in vitro fertilization.

The pulsatile s.c. administration of hMG is a suitable inductory method for treating ovulatory stater and it is a good substitute for the lacking endogenous gonadotropin secretion or for a secretion of inadequate pace.

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Mit in pulsatorischer Form verabreichtem humanem menopausalem Gonadotropin durchgeführte Ovulationsinduktion

S. KOLOSZÁR, G. BÁRTFAI, G. GODÓ und M. SAS

Mit in pulsatorischer Form, subkutan dosiertem humanem menopausalem Gonadotropin (hMG) wurde Ovulationsinduktion durchgeführt. Die Initialdosis betrug 75 NE hMG/Tag [in einer 90minütlichen Verteilung], wonach die Tagesdosis wurde vom Plasma-Östradiolspiegel und dem Ergebnis der Follikulometrie abhängig auf 150 NE erhöht. In 242 S. Koloszár et al.: Ovulation Induction with Human Menopausal Gonadotropin

7 der 10 behandelten Zyklen entstand eine Ovulation und zwei Frauen wurden schwanger. In 2 Fällen traf nach vorangegangener erfolgloser hMG-Behandlung eine Ovulation ein. Hyperstimulation kam nicht vor. Die pulsatorische subkutane Verabreichung von hMG scheint im Falle von Ovulationsstörungen hypothalamo-hypophysealen Ursprungs eine entsprechende Ovulationsinduktionsmethode zu sein, die die fehlende oder nicht in erforderlichem Rhythmus verlaufende Gonadotropin-Ausscheidung in geeignetem Maße ersetzt.

Индукция овуляции, произведения пульсирующим дозированием человеческого менопаузного гонадотропина

Ш. КОЛОСАР, Г. БАРТФАИ, Г. ГОДО и М. ШАШ

Авторы индуцировали овуляцию с помощью подкожного введения, в пульсируюшей форме, человеческого менопаузного гонадотропина (hMG). Лечение начали с введения 75 МЕ гонадотропина ежедневно (каждые 90 мин), затем — в зависимости от уровня эстрадиола в плазме и от результатов фолликулометрии — повышали дозу до 150 МЕ. В 7 случаях из 10 произошла овуляция, а в двух случаях наступила беременность. В двух случаях овуляция наступила после безрезультатного предыдушего лечения внутримышечным введением гонадотропина. Симптомов гиперстимуяции не наблюдали. Пульсирующее, подкожное введение гонадотропина кажется подходящим методом индукции овуляции при ее нарушениях гипотеламо-гипофизарного происхождения, и хорошо замещает недостаточное выделение эндогенного гонадотропина, или выделение в не сответствующем темпе.

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Feminizing Genitoplasty: One-stage Genital Reconstruction in Congenital Adrenogenital Syndrome

A. PINTÉR

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(Received: January 11, 1989)

Complete one-stage genital reconstruction was made in five children with congenital adrenogenital syndrome. Removal of the cavernous body of the clitoris was made by preservation of the glans with its vascular and neural supply. The lesser lips of the pudendum were fashioned from the skin of the penis and the prepuce. During the same operation, the vaginal orifice was created by the inversion of an U-shaped flap taken from the perineum into the introitus vaginae. There were no surgical complications. The patients recovered with good cosmetic results. It is necessary to regularly dilate the new vaginal orifice.

Introduction

Feminine pseudohermaphroditism due to congenital androgenital syndrome is the most frequent form of childhood intersexuality. Masculizination of the external genitalia is likely to be associated with the amount of androgen production in the foetus and with the exposure time. In these girls the internal genitalia (uterus, tubes, ovaries, proximal vagina) are normal, however, the external ones show various degrees of severity in virilization. In the milder forms of the change, only an enlarged clitoris is observed with a normal vaginal orifice, while in the severe forms a penis approximately normal in appearance is present, the proximal end of which opens into the urethra. The majority of cases range between two extremes: the external orifice of the urethra can be found on the proximal part of the hypertrophic clitoris, with fusion of the hypoplastic lesser lips and with absence of the vaginal orifice (Fig. 1).

Inadequate selection, then later on alteration, of the sex after birth pose a very serious emotional and psychosocial problem. Children reared up to their puberty as males are particularly subject to great psychic shock when examination of their haematuria reveals it to have been menstruation and the child to be a male not a female.

1*

Earlier Surgical Solutions

Operation performed at an early age-at that of 2 or 3 years – prevents the infection of the urogenital tract and helps the parents, siblings and relatives in accepting and breeding their child as a female. A further advantage of operations performed at an early age is that the child is still not aware of the abnormality of the genital organs.

The clitoridectomy performed earlier is currently not accepted because the clitoris plays an important role in the normal development of psychosexuality [11]. Accordingly, the more recent surgical solutions, such as the recession and relocation of the clitoris, its plication preserve its sensory function, however, due to its unchanged size, the cavernous bodies swell painfully [1]. Therefore, by preserving the glans of the clitoris with its vascular and neural supply, the cavernous bodies are removed. By this, the organ is reduced with simultaneous preservation of its sensory function [2]. Marburger [9] recommended for shaping an introitus vaginae of normal appearance, i.e. for construction of the missing lesser lips of the pudenda, the use of the penile and preputial skin. Formerly, for enlargement of the vaginal orifice, the longitudinal incision of the adhering lesser lips covering the introitus was proposed, which, however, often resulted in a secondary stricture. Fortunoff et al. [4] recommended the inversion of a U-shaped flap obtained from the perineum into the vaginal orifice (V - Y plasty). The perineal skin flap folded into the posterior wall of the vagina does not only provide a much wider introitus vaginae, but it also prevents narrowing of the vaginal orifice during the child's growth. If the vagina opens high, near the bladder neck into the urogenital sinus, it is advisable to wait with the operation until the size of the anatomical structures creates more favourable conditions for perform - in the pull - through vaginoplasty [6, 7].



FIG. 1. Congenital adrenogenital syndrome. a: Frequent form, when the vagina opens distal to the external sphincter urethrae into the urogenital sinus (a vaginal orifice can be formed by an U-shaped perineal flap) b: A rarer, more severe form when the vagina opens into the urethra proximal to the external sphincter urethrae (shaping of the vagina can only be solved by a pull-through operation)

Recommended Operation

Synder et al. [10] reported in 1983 an operation which unites the three operative steps performed in adrenogenital syndrome, i.e. resection of the cavernous body by preservation of the glans with its vascular and neural supply, shaping of the lesser lips and, formation of a wide introitus vaginae. Since this report the above surgical procedure has been performed in five children. According to our experience, the one-stage complete genital reconstruction is a relatively simple operation yielding good cosmetic results.

The feminizing genitoplasty has to achieve three goals:

1. Removal of the cavernous body should be made by not injuring the vascular and neural supply of the glans.

2. Shaping of the lesser lips of an approximately normal appearance from the penile and preputial skin.

3. Fashioning of a vaginal orifice of an adequate width.



FIG. 2. One-stage feminizing genitoplasty (scheme). a: U-shaped incision line for fashioning of the introitus vaginae; b: Construction of a perineal flap; c: Forming of a vaginal orifice; d: Preservation of the dorsal neural and ventral vascular supplies of the glans; e: Fixation of the glans to the public bone after crural resection with a median incision on the skin of the prepuce and the penis; f: Construction of the lesser lips from them

This one-stage operation can be made if the vaginal orifice is situated distally by the folding of a U-flap taken from the perineum (Fig. 2a).

Before operation, a Foley catheter is to be introduced into the bladder for the protection of the urethra. On mobilizing the U-flap from the perineum with its preserved subcutaneous tissue, care thould be taken of the rectal wall underneath it (Fig. 2b). Then a long median incision is made on the posterior wall of the urogenital sinus up to the vagina with the incision line involving also its posterior wall. The perineal flap (V-Y-plasty) is placed and fixed, between the the incised vaginal edges pulled apart, with supporting sutures (Fig. 3c). This is followed by clitoroplasty. By making two parallel longitudinal incisions alongside the ventral phallus, a skin flap is left over being as wide as not to damage the vessels underneath it, supplying the glans (Fig. 3d). Subsequently, the incision is carried around the glans corresponding to the coronary sulcus in a way to enable the complete mobilization of the penile skin and the separation of the nerves passing along the dorsal clitoris from the cavernous bodies lying under neath it (Fig. 3d). On removing the cavernous bodies, care must be taken of the vessels as well as the neural structures securing the sensitivity of the glans. According to Bissida et al. [3], the neurovascular bundle can be preserved more safely if dissecting out of the structures is made together with the Buck's fascia. Mobilization of the cavernous bodies should involve the pubic bone and the resection should be performed right at the bones. The clitoris with its preserved vascular and neural supply should be fixed to the fascia underneath it by an unabsorbable suture. If the glans is too large it can be reduced by wedge resection.

The penile skin pieces separated from the cavernous bodies are halved longitudinally (Fig. 3e) and they are folded back along both sides of the glans for the lesser lips (Fig. 3f). The sides of the skin flaps slong the glans are sutured to the glans.

Regular dilatation of the vagina is started two weeks postoperatively and it is advisable to carry on for 6-12 months.

If the vagina opens high into the urogenital sinus, proximal to the external sphincter of the urethra (Fig. 1b), clitoroplasty and the fashioning of the lesser lips can be made at an early age, however vaginal pull-through operations are recommended only later.

Case-report

Infant born spontaneously with an Apgar score of 10–10, on gestational week 40, from the fourth pregnancy of the mother, weighing 4000 g. At birth, she was assumed to be male and was given appropriate name.

At the age of 6 days, she was referred to the Department of Paediatrics for 'doubtful sex' examination. The investigations (chromosome, genitography,

vaginoscopy) unanimously proved a female genotype. Based on masculinization of the female external genitalia, the low serum sodium, the high potassium, the salt loss with the urine, the elevated urinary 17-ketosteroid level and the high 17-OH-progesterone level, a proneness to dehydration as well as the stagnation of somatic development, the salt-losing form of 21-OH-ase deficiency was established.

Following an acute normalization of the salt and water balance, for substitution of mineralocorticoids, initially DOCA implantation tablet was administered complemented by daily 1 g of sodium chloride. For reducing the extreme secretion of sex steroids, daily 12.5 mg (half a tablet) of Adreson was received by the patient. The optimal dosages of the medicine were defined by considering the children's pace of growth, the age of bones, the 17-OH progesterone and urinary 17-ketosteroid levels, securing their normal pace of development and, at the same time, protecting them from premature puberty.

Anatomical reconstruction of the genitalia was performed at the child being 3 years of age (Fig. 3a-d).



FIG. 3. One-stage feminizing genitoplasty a: Hypertrophic clitoris at the proximal part of which the orifice of the urogenital sinus is seen; b: The nerves supplying the glans are separated from the dorsal, while the vessels from the ventral side of the cavernous bodies; c: Immediate postoperative state. The clamps expose the fashioned vaginal orifice; d: The external genitalia two weeks after feminizing genitoplasty

Results

Five patients were subjected to the above operation. The children's age ranged between 2.5 and 8 years. There were no postoperative complications. The regular vaginal dilatations were performed at every 2-3 weeks without anaesthesia. The patients' follow-up time ranged between 14 and 42 months (mean value: 26 months). The external genitalia largely resemble the normal female genitalia.

Discussion

The surgical solutions fashioning the female form of the abnormal genitalia of girls with congenital adrenogenital syndrome have undergone considerable development in the past two decades [1, 5, 6, 8, 11]. Nowadays, total clitorectomy is regarded as unacceptable.

If the penis is small, plication of the clitoris may provide satisfactory results in itself. In case of a larger clitoris, none of the surgical solutions removing the cavernous bodies can be accepted not only for cosmetic reasons but since they result in the painful swelling of the cavernous bodies during erection. The surgical procedure yielding the best result is the resection of the cavernous bodies with conservation of the vascular and neural supply of the glans [9, 10].

Shaping of a wide vagina fit for sexual life can be made by the inversion of a perineal flap of adequate size and thickness into the introitus vaginae. In absence of this, operation may result in the persisting stenosis of the vaginal orifice requiring surgical correction.

Some authors recommend the postponement of a plastic operation forming a vaginal orifice up to puberty, in order that the regular dilatation necessary after operations performed at an early age be avoided. In our opinion, dilatation after childhood vaginoplasties does not impose a psychic stress as if the child were to wait long years for the operation, being constantly aware of her abnormal external genitalia. Our view agrees with that of Hendren according to whom the advantages of the surgical correction performed at an early age are more marked than the drawbacks of a plastic operation [6, 7] performed aroud or after puberty.

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Feminisierende Genitoplastik: Einzeitige, totale genitale Rekonstruktion bei angeborenem Adrenogenitalsyndrom

A. PINTÉR

Bei 5, an angeborenem Adrenogenitalsyndrom leidenden Kindern wurde einzeitigetotale genitale Rekonstruktion durchgeführt. Die Entfernung der Corpora cavernosa erfolgte nebst Beibehaltung der Glans mitsamt ihrer Gefäß- und Nervenversorgung. Zur Ausbildung der kleinen Schamlippen kam die Haut des Phallus und des Präputiums zur Anwendung. Der Scheideneingang wurde im Laufe desselben Eingriffes durch Eindrehung eine aus dem Perineum entommenen U-förmigen Lappen in den Introitus vaginae ausgeformt. Operationskomplikationen meldeten sich nicht, die kosmetischen Heilergebnisse waren gut. Postoperativ ist die regelmäßige Dehnung des neuen Scheidenengangs erforderlich.

Феминизирующая генитопластика: одноступенчатая полная генитальная реконструкция при врожденном адреногенитальном синдроме

А. ПИНТЕР

Автор произвел одноступенчатую полную генитальную реконструкцию у пяти детей, страдающих врожденным адреногенитальным синдромом. Уделение пещеристого тела производилось с сохранением головки члена, при интактном сосудистом и нервном снабжении. Формирование малых губ производилось из кожи фаллоса и крайнем плоти. В ходе этого же хирургического вмешательства формировался влагалищный вход повертыванием взятого из промежности U-образного лоскута ко входу во влагалище. Осложнений после операции не было, больные выздоровели с хорошим косметическим результатом. Необходимо производить регулярное расширение входа в сформированное новое влагалище.

Factors Influencing the Vascular Action of Dopamine in the Canine Mesenteric Bed

I. Dóbi^{1, 2} and VIOLETTA KÉKESI¹

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(Received: February 12, 1988)

The effect of dopamine on the mesenteric arterial bed was investigated in dogs anaesthetized with pentobarbital sodium. The vascular responses to dopamine in a branch of the superior mesenteric artery supplying a segment of the small intestine were measured with a flowmeter probe and visualized by infrared telethermography or, in a separate series of dogs, were obtained by the direct determination of arterial resistance-changes during perfusion with constant flow. It was found that the mesenteric action of dopamine (given i. v. in the submaximal dose of $16\mu g \cdot kg^{-1} \cdot min^{-1}$ or intraarterially up to a dose of 40 $\mu g \cdot min^{-1}$) is primarily mediated via dopaminergic vasodilator and a alpha-adrenergic vasoconstrictor receptors, the net result of this competition usually being moderate vasodilation under natural conditions. The contribution of beta-adrenergic vasodilation to the mesenteric dopamine action is minimal as evidenced by beta-blockade with oxprenolol. By blocking the alpha-component with phentolamine $(1.0 \text{ mg} \cdot \text{kg}^{-1})$ an almost threefold increase of the vasodilation was obtained in resistance. Be-cause of the concomitant reversal of the systemic hypertensive dopamine action to hypotension, the net flow increase remained essentially unchanged. It was concluded that unless the degree of alpha-stimulation is restrained and proper control of blood pressure is eusured, it is not possible to recommend that dopamine be used in the therapy of mesenteric vascular disorders.

In a great variety of surgical situations a mild to severe degree of intestinal ischaemia may develop as a result of mechanical obstruction of flow (e.g. atherosclerotic reduction of vessel lumen), decreased perfusion pressure head (e. g. circulatory shock), augmented responsiveness to vascular spastic influences (e.g. cardiac glycoside toxicity), and, more importantly, the combination of some of these or other factors. Although pharmacologic treatment with vasodilators may benefit these patients, the appropriate selection of drugs is hampered by the still imperfect understanding of their local mechanisms of action on the mesenteric vascular bed.

It was our intent to document the precise relation of factors (especially of those involved in adrenoceptor stimulation) relating to the intestinal vascular effects of dopamine, one of the most widely used drugs in cardiovascular emergency states.

Methods

Mongrel dogs of either sex, weighing 13–27 kg and fasted overnight were anaesthetized with pentobarbital sodium (30–35 mg \cdot kg⁻¹ i. v.); subsequent small doses (15–30 mg) were given as needed. After tracheal intubation the abdomen was opened in the midline, a suitable segment of the small intestine was exteriorized, and the branch of the superior mesenteric artery supplying this segment was prepared free for application of a flow probe or cannulation. A femoral artery was dissected for pressure measurement; when the intestinal segment was to be perfused artificially a common carotid was also isolated.

Two types of experimental preparations were used. In five dogs (type 1) an electromagnetic flow probe (Statham SP 2201) was fitted around the mesenteric arterial branch. Phasic as well as electronically integrated (mean) blood flow levels were continuosly recorded together with the arterial blood pressure (Statham gauge). In this experimental series computer-assisted telethermography of the bowel segment was simultaneously performed according to the technique developed in our laboratory and fully described elsewhere [10, 11, 12). Briefly, thermograms were taken with the aid of an AGA 750 Thermovision camera which senses the infrared rays in the 2 to 5.6 μ m wavelength range. These rays projected by a rotating prism on an indium-antimonide crystal cooled with liquid N_2 to -196 °C are converted continuously to electric signals. Next, the signals are transmitted to the monitoring unit of the device working on the principle of a closed colour television chain (where they can be photographed) and/or to the computing unit, where the signals are converted from analogue to digital, classified and evaluated by a special program. Knowing the total extension of the thermographic image and the distribution of the respective temperature ranges (colours), the ratios of these ranges to the whole image can be described and the mean temperature characterizing the rate of blood flow [10, 13] can be calculated. (The latter procedure is analogous with the determination of the average concentration of a given tracer in the organs.) In this study the sensitivity of detection was chosen so that each colour represented a 0.2 °C step, the whole scale thus being 2.0 °C. In the thermographic images the warm and cold ranges are represented by white-red and blue-green colours, respectively.

In another five dogs (type II) a closed artificial circuit was created between the cannulated central and peripheral stumps of the carotid and mesenteric arteries, respectively, then the bowel segment was perfused with constant flow utilizing two parallelly connected fingertip pumps which were coupled in a shifted phase angle to ensure a practically constant perfusion. The initial level of the pressure head was chosen within a range different by less than 10 mm Hg from the mean systemic blood pressure of the animal. Since the output of the pump was kept constant, any change in the perfusion pressure, as measured with

a Statham gauge distal to the pump, was directly related to the alteration of the local vascular resistance. These dogs were given heparin (500 IU kg⁻¹) before cannulations.

Dopamine doses were infused continuously for 3–5 min to obtain steady state responses. In preparation type I the agent was administered intravenously in a dose of 16 μ g · kg⁻¹ · min⁻¹ which, according to the earlier studies of one of us [6] elicits submaximal stimulation of cardiovascular beta-adrenoceptors. In preparation type II the maximal vascular response was determined by infusing the drug in increasing doses (2 to 20–40 μ g · min⁻¹) directly into the tubing of the perfusion circuit. The response was considered maximal when it remained unchanged by doubling the preceding dopamine dose. Beta-adrenergic blockade was obtained in both series with i. v. administration of oxprenolol (Trasicor[®], Ciba, 0.5 mg · kg⁻¹), while the alpha-adrenoceptors were subsequently blocked by i. v. phentolamine (Regitin[®], Ciba, 1.0 mg · kg⁻¹). In three dogs of the first series (type I) the dopamine action was repeatedly tested after subjecting the intestinal segment to complete ischaemia of 2 h duration and then re-establishing blood flow.

Circulatory variables were recorded in a four- or six-channel Hellige multiscriptor and chosen for data analysis immediately before dopamine administration and at steady state levels of the infusion periods. Statistically evaluated numerical data are given as mean values \pm S. E. M. The significance of results was calculated by using Student's *t*-test for paired and unpaired data.

Results

The basic haemodynamic data of experiments performed with unopened mesenteric vessels (preparation type I) are summarized in Table I. Three successive experimental phases were evaluated. Initially, dopamine was administered to untreated dogs, then to the same preparations with blocked beta-adrenoceptors, and finally, to those with combined (beta + alpha) auto-

TABLE I

	Untreated		Beta-blockade		${\it Beta} + {\it alpha} \ {\it blockade}$	
	C	DA	C	DA	C	DA
Mean arterial pressure	149.4	168.4	138.6	144.6	128.8	86.0 ^a
(mm Hg)	\pm 12.4	\pm 20.4	\pm 14.8	\pm 19.2	\pm 9.4	\pm 8.7
Mesenteric blood flow	49.5	68.9 ^a	42.2	55.2	41.6	58.5
$(ml. min^{-1})$	\pm 2.6	\pm 6.3	\pm 4.4	\pm 5.6	\pm 8.1	± 12.1

Effect of dopamine (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on mesenteric circulation*

* Means values \pm S.E.M. ^Significant change (p<0.05) from control; C=Control; DA = dopamine

nomic blockade. Mesenteric blood flow was found to increase in each experimental phase. However, this reponse was accompanied by hypertension in the first two phases, and by hypotension in the third one.

The local vascular action of dopamine is best demonstrated by calculating arterial resistance in the mesenteric bed. As shown in Fig. 1, this variable decreased in all experimental phases indicating vasodilation. However, a considerable degree of vasodilator response was obtained only after blocking the alpha-adrenoceptors (third phase), while the moderate vasodilation of the initial phase was remarkably little affected by beta-blockade alone (second phase). In fact, beta-blockade reduced the dopamine-indiced mesenteric vasodilation in only two cases out of all observations. Treatment with the autonomic blockers in itself did not elicit characteristic changes in resting mesenteric vascular resistance: its level was 3.09 ± 0.38 , 3.50 ± 0.58 and 3.66 ± 0.80 mm Hg ml⁻¹ min (mean \pm S. E. M.) in the control state, after beta-blockade, and after combined autonomic blockade, respectively. These changes were statistically not significant and their slightly increasing tendency appeared to follow the concomitant moderate hypotension.

An essentially similar picture emerged from simultaneously taken thermographic pictures. Dopamine administration elicited a warming of the mesentery when the flow was actually increased by more than 15-20% and this reaction was also accentuated when the complete autonomic blockade enhanced



FIG. 1. Dopamine-induced changes of calculated mean mesenteric vascular resistance (MVR). Mean values \pm S.E.M. Asterisks refer to significance of resistance changes



FIG. 2. Effect of dopamine on the mesenteric circulation. From above downwards: Phasic and mean mesenteric blood flow (MBF), blood pressure (BP), A untreated, B after betablockade, C after combined (beta + alpha) autonomic blockade. In each block the druginduced percent change of vascular resistance is also indicated. Numbers (1, 2, 3) refer to thermograms in Fig. 3

the flow response. In the experiment depicted in Fig. 2, the marked flow-augmenting action of dopamine in the control phase (A) was exceptionally reduced and retarded by oxprenolol, although this effect was still prevalent enough to result in vasodilation (B). On blocking alpha-adrenoceptors the response beca-



FIG. 3. Mesenteric thermographic images of the experiment shown in Fig. 2. (Signs as in Fig. 2.) Each colour-band of the calibration scales corresponds to $0.2 \, {}^{\circ}$ C. (From above downwards: decrease of temperature.) Figures refer to computer-aided evaluation of the mean temperature. Note the potentiation of warming (dopaminergic vasodilation) after combined autonomic blockade (C)

me considerably accentuated and also characterized by a rapid onset (C). These changes, as shown in Fig. 3, were clearly parallelled by the thermographic images. The warming of the mesentery was more rapid and more pronounced in the third phase of the experimental observation (C). Direct evidence of this phenomenon, although it was apparent to the naked eye, was provided by the computerized evaluation (see numerical values in Fig. 3).



FIG. 4. Dopaminergic thermographic response in normal state (A) and after mesenteric ischaemia of 2 h duration (B). Note the reduction of dopamine-induced warming after ischaemic stress. Signs as in Fig. 3 (1 control, 2 dopamine). In the middle: ischaemic thermogram and photo of the bowel segment. Simultaneously measured flow increases and vascular resistance decreases (not shown) also indicated a reduced vasodilator capacity $(+31 \text{ vs. } +4 \text{ ml} \cdot \min^{-1} \text{ and } -67 \text{ vs. } -24\%$, respectively)

TABLE II

Dopamine-induced maximal resistance changes in the perfused small bowel segment*



* Mean values \pm S.E.M., n = 5

In the same series of experiments the dopamine-induced decrease of vascular resistance was reduced from $53 \pm 6\%$ to $22 \pm 9\%$ (n = 3) after a transitory local ischaemic stress of 2 h duration. This change was found to be also parallelled by simultaneously recorded thermographic images (Fig. 4).

Similar tendencies of changes were demonstrated in another series of experiments (preparation type II) performed with an artificially perfused mesenteric bed. At the same time, the character of the dopamine response of the perfused vessels differred from that of the vessels carrying normal flow: the dopamine-induced response was characterized, instead of vasodilation, by vasoconstriction in the first two experimental phases, while combined autonomic blockade unmasked significant vasodilation. Similar to the former experimental series, there was no significant difference between the reactions of the untreated and the oxprenolol-treated vessels, and, on the other hand, both of the latter reactions sharply differed from the dopaminergic vasodilation elicitable in the third phase after treating the animals with phentolamine (Table II).

Discussion

The experiments demonstrated, in agreement with earlier observations [5, 9, 16, 17], the vasodilator action of dopamine in the mesenteric vascular bed. The principal finding of this work was that under normal conditions the dilator potency of the drug, evidently "dopaminergic" in origin [5, 9], competes with a concomitant vasoconstriction resulting from the simultaneous activation of alpha-adrenoceptors which curtail the flow increase. Although the usual response to dopamine administration is the reduction of calculated local vascular resistance, after blocking the alpha-adrenoceptors a much greater resistance decrease was unmasked. At the same time, the expected double competition (alpha-responses competing with beta *and* dopaminergic ones) was only exceptionally observed (Fig. 2). Thus, the activation of beta-adrenoceptors

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does not seem to play an important role in the dopamine-induced mesenteric vascular reactions. Principally similar but quantitatively transformed results were obtained while infusing dopamine directly into autoperfused small intestinal segments. In this case the whole spectrum of dopamine responses was shifted towards the vasoconstrictor range of the drug-potency, the latter being obviously accentuated by the well-known impairment of physiologic autoregulatory capacity of mesenteric vessels subjected to an artificial type of circulation [4]. However, the *relation* of local sensitivity to autonomic blockers remained the same: the beta-blocker oxprenolol failed to influence the dominant vascular reaction which was then reversed by a subsequent alpha-blockade with phentolamine. This is in sharp contradiction with the sensitivity to the same blockers of dopamine-induced coronary vasodilator responses that exhibit a complete reversal after beta-blockade and practically disappear after combined autonomic blockade [6, 15]. Moreover Kékesi et al. [6] have shown the net augmentation of the dopamine-induced coronary beta-response after alpha--blockade. The apparent conclusion to be drawn from these observations is the presence of true dopaminergic vascular receptors in the mesenteric, and the absence of similar receptors in the coronary circulation. It should be noted that in these investigations, as in former studies [6, 15], all dopamine-induced vascular responses that manifested themselves after combined autonomic blockade were considered "dopaminergic". This a priori assumption seems to be justified by the uncertainties involved in the action of so-called dopamineantagonists.

Although there was a potentiation of drug-induced vasodilator tendencies in the phentolamine-treated mesenteric vascular bed, the resting tone of vessels was remarkably little affected by the blocker. This finding indicates a small degree of resting sympathetic tone on these vessels, and corroborates recent evidence obtained by Lehmann et al. [8] in rabbits. Thus, despite the precapillary mesenteric constriction elicitable by sympathetic nerve stimulation [1, 2, 3], it is doubtful whether a clinical benefit related to an improved blood supply in the abdomen can be expected simply by blocking alpha-responses.

As a first approximation, dopamine with alpha-blockade seems to be the most advantageous combination for obtaining the ideal stimulatory level of adrenergic receptors. However, the evidence described in this paper (namely the sometimes unusually marked systemic hypotension characterizing the latter state), also indicates the potential hazards involved in the above combination. In order to prevent the attempted therapy to be self-defeating, great caution is needed to proceed to use these drugs without continuously monitoring arterial pressure.

All of these observations were confirmed in this study by direct thermographic visualization of the above-mentioned phenomena. The technique, as developed in the hands of Papp and his team [10, 11, 12], proved to be a very convenient tool for demonstrating the time course and the characteristic features of vascular alterations, especially their homogeneity [14] under surgical conditions. This method has recently been shown by Krever et al. [7] to be even more informative while revascularizing totally obstructed vascular segments.

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Die vaskuläre Wirkung von Dopamin beeinflussende Faktoren im mesenterialen Kreislauf beim Hund

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Bei mit Na-pentobarbital narkotisierten Hunden wurde die den mesenterialen Kreislauf betreffende Wirkung von Dopamin untersucht. Die durch die Droge ausgelöste vaskuläre Antwortreaktion wurde mit einem, an ein, ein Dünndarmsegment versorgenden Zweig der A. mesenterica superior angebrachten elektromagnetischen Meßkopf registriert und mit infraroter Thermographie sichtbar gemacht, oder — in einer besonderen Ver-- durch direkte Bestimmung der arteriellen Resistenz, bei mit konstanter suchsserie -Strömung herbeigeführter künstlicher Perfusion gemessen. Es wurde festgestellt, daß die den mesenterialen Kreislauf betreffende Wirkung von Dopamin (die in den Untersuchungen mit einer submaximalen Dosis von 16 μ g kg⁻¹·min⁻¹ i. v., oder mit einer ganz bis zu einer Dosis von 40 $\mu g \cdot \min^{-1}$ erhöhten intraarteriellen Infusion herbeigeführt wurde) primär durch die Dopaminerg-Vasodilatator- und Alpha-Adrenerg-Vasokonstriktor-Rezeptoren mediiert wird; als netto Ergebnis der zwischen den beiden bestehenden Kompetition wird unter Normalverhältnissen im allgemeinen mäßige Vasodilatation zustandegebracht. Wie das mit der Zufuhr des Beta-Blockers, Oxprenolol bewiesen wurde, ist die Teilnahme der Beta-Adrenerg-Vasodilatation in der durch Dopamin ausgelösten mesente-rialen Antwort, nur minimal. Durch die Phentolamin (1 mg \cdot kg⁻¹)-Blockade der Alpha-Komponente wurde die (resistenzherabsetzende) Wirkung des Dopamindilatators fast auf das Dreifache erhöht; gleichzeitig blieb infolge der Verschiebung des hypertensiven Effekts des Mittels in hypotensive Richtung, der netto Strömungsanstieg im wesentlichen unverändert. Die Ergebnisse führten zur Folgerung, daß ohne der Zurückdrängung des Maßes der Alpha-Adrenerg-Stimulation und der entsprechender Kontrolle des Blutdrucks die Anwendung von Dopamin in der Therapie der mesenterialen Kreislaufstörungen nicht empfehlenswert ist.

Факторы, влияющие на васкулярное действие дофамина в мезентериальном кровообращении у собак

И. ДОБИ и В. КЕКЕШИ

В экспериментах на собаках под Na-пентобарбиталовым наркозом авторы изучали влияние дофамина на мезентариальное кровообращение. Вызванные этим средством сосудистые реакции симультанно регистрировали электромагнитным датчиком, помещенным в ветвь верхней брыжеечной артерии, снабжающей один из сегментов тонкого кишечника, кроме того эти реакции стало можно видеть с помощью инфракрасной термографии, или же в отдельное экспериментальной серии — их измеряли напосредственным определением артериального сопротивления наряду с искусственной перфузией при постоянном токе жидкости. Было установлено, что действие дофамина на мезентериальное кровообращение (которое вызывали либо вжутривенным введением субмаксимальной дозы 16 мкг/кг/мин, либо внутриартериальной индузией дозы, повышенной до 40 мкг/мин) первично осуществляется через дофаминаргические вазодилататорные и альфа-адренергические вазоконстрикторные рецепторы, результатом компетиции между которыми в нормальных условиях обычно бывает умеренная вазодилатация. Участие бета-адренергической вазодилатации в мезентариальной реакции на дофамин минимально, как это доказали опыты с введением бета-блокатора окспренолола. Блокирование альфа-компонента фентоламина (1 мг/кг) почти в три раза усилило дилататорное (снижающее сопротивление) действие дофамина в то же время чистое усиление кровотока почти не изменилось вследствие перехода гипертен зивного эффекта препарата в гипотензивное. Авторы проходят к выводу, что, без уменьшения степени альфа-адренергической стимуляции и соответствующего контроля за кровяным давлением, не рекомендуется применение дофамина в терапии нарушений мезентериального кровообращения.

Motility, Haemodynamics and Responsibility to Vasoactive Agents after Revascularization of Autotransplanted Small Intestine Segments in the Dog

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Functional and haemodynamic changes occuring after revascularization of an autotransplanted small intestine segment were studied in acute experiments performed in 10 dogs under pentobarbital anaesthesia. Intestinal motility and mesenteric blood flow of the segment were measured with intraluminal pressurized balloon and electromagnetic flowmeter, respectively. The time-course of observations was divided, according to the findings, into three main periods (phases 1 to 3). In the initial phase (1) the bowel exhibited very slight spontaneous motility which was found to increase moderately but significantly after denervation and isolation of the graft still left in situ before transplantation (phase 2). After declamping of anastomoses of the retransplanted graft (which was protected by cooling to $4 \,^{\circ}\text{C}$ after being removed from the body) a short period ($\sim 2 \,\text{min}$) of reactive hyperaemic flow increase was observed in association of vigorous bowel movements lasting for a more prolonged (~ 15 min) period of time (phase 3a and 3b). Reactivity of the retransplanted vasculature as compared to the denervated control revealed a marked relative shift in adrenergic balance, tested by dopamine, to the vasoconstrictor range, but it showed no change in responses to general haemodynamic or haemorheologic interventions, tested by veratrine and pentoxifylline, respectively. However, the basic levels of blood supply (controlled also by thermography) and systemic blood pressure remained unaltered after transplantation. Regarding the critical role of functional changes immediately after transplantation in determining the survival of bowel grafts, these observations may contribute to a more effective monitoring of surgical interventions.

Transplantation of the small intestine has proved to be an alternative therapy for the complex failure of intestinal functions [13]. Under up-to-date conditions of immunosupressive therapy a wide clinical application of this intervention is expected at an international scale. Besides the technical and immunological aspects, pathophysiological and functional problems have to be considered: events of such type, especially in the first hours after revascularization of the graft, determine function and survival of the transplanted intestine. Knowledge of pathophysiological mechanisms and functional values may ensure an effective monitoring of this phase. The preparation of a bowel segment for allograft results in its total denervation. Because of the intrinsic nervous system in the intestinal wall, a regulation of motility and haemodynamics is possible [8]. After revascularization this local regulation interferes humorally with the regulating mechanisms of the recipient body. The aim of this study was to examine the two-phasic process — —reactive hyperaemia and stabilization period — of changes after restoration of blood flow by characterizing motility and haemodynamic parameters quantitatively.

Materials and Methods

We evaluated intestinal grafts by utilizing a model of autologous small bowel transplantation described by Luther et al. [13]. Ten mongrel dogs of both sexes, weighing 21 kg on the average (range: 17-25 kg), were used after overnight fasting. A saphenous vein was cannulated for infusion and drug administration. Under pentobarbital sodium anaesthesia (30 mg kg⁻¹ b. w.) the right femoral artery was dissected and a heparin-filled catheter connected to a Statham gauge (P 23 Db) was inserted for continuous pressure measurement. The traditional balloon technique was used for bowel movement recording: after median laparatomy, a thin-wall rubber balloon was led 10 cm into the oral end of the intestinal segment assigned for autotransplantation (75 cm oral of the ileocaecal valve) and cannula of the balloon was connected to another pressure transducer (Medexinc, 02 3319). After determining the pressure optimum for spontaneous bowel movements, these signals were recorded on a four--channel Hellige multiscriptor. Thereafter, the artery and the vein of the segment were dissected free, the segment was cut orally and aborally (3 cm from the ileocaecal valve), the lymph nodes as well as the nerves leading to the graft were resected. An electromagnetic flow probe (Statham SP 2201) was applied to the segmental artery and instantaneous (phasic) and electrically integrated (mean) flow were measured alongside with motility of the denervated graft and blood pressure. The next steps were cutting of the vessels, perfusion and preservation of the graft with physiological saline solution at a temperature of 4 °C [13]. In 3 dogs we performed end-to-side anastomoses of the segmental vessels to the intrarenal abdominal aorta/vena cava inferior, in 7 dogs the vessels were anastomosed end-to-end in orthotopic position. After restoring the circulation, motility and blood flow were measured up to the stabilization of the values. For the quantitative analysis of bowel movements we used the motility index:

Motility index = $\frac{\text{summa contraction amplitudes} \times \text{contraction frequency}}{\text{time (min)}}$
Intestinal motility was monitored in 8 dogs: conclusions were drawn from 7 successful experiments. In two dogs of this group revascularization was also detected thermographically according to the principles originally described by Papp et al. [15, 16] and adapted to the mesentery in former experiments [5, 12]. The sensitivity of the Thermovision equipment (AGA 750) was set to cover a range of 10 °C. Reactivity of the denervated and retransplanted vessels was tested by rapid bolus i. v. injections of three drugs. Dopamine was given in two different doses (4 and 8 $\mu g \cdot k g^{-1}$), veratrine (Merck) in a dose of 10 $\mu g \cdot k g^{-1}$ and pentoxifylline (Trental[®], Hoechst) in a dose of 30 mg. Responsiveness to drugs was characterized by flow and calculated vascular resistance (mean pressure/mean flow) changes. For these tests 6 dogs were used.

Values quoted in the tables and figures (except individual ones) are means \pm S. E. M. The results were examined statistically by using Student's *t*-test. For the comparison of successive experimental phases paired data were used, except comparing phase 2 with phase 3a (v. i.); in this and all other instances *t*-values for umpaired data were calculated. A probability index less than 5% was considered the limit to reject the O-hypothesis.

Results

The original tracings of a typical experiment (Fig. 1) depict the principal phases of our investigations. Under the conditions of pentobarbital anaesthesia and laparatomy only discrete contractions were seen (phase 1), even after some time of waiting. We did not measure blood flow in this phase because of the inevitable partial denervation while dissecting the artery. After complete denervation of the small bowel segment (phase 2) we found a significant increase of contractile activity. Our main interest was focussed on the time after revascularization called phase 3. By comparing motility and blood flow values with the given data from phase 1 and 2, respectively, we defined two parts of phase 3. At first we observed maximal contractile activity coinciding with a reactive hypaeremic response in blood flow (phase 3a). This hyperactivity was followed by a stabilization period (phase 3b); at the end of the latter motility decreased to a level which was not discernible from that of phase 1.

Table I summarizes the statistical evaluation of results. In respect of intestinal motility there were marked differences between the successive principal phases. After a short-lived and usually moderate reactive hypaeremia developing synchronously with the warming of the retransplanted bowel segment, blood flow returned to a level which, although slightly lower than the control, was not statistically different from it. The sufficient technical quality of revascularization was also indicated by thermographic measurements which showed the prompt and homogeneous refilling with warm blood of the



FIG. 1. Consecutive phases of the investigation. From above downwards: intestinal motility (IM), phasic and mean mesenteric blood flow (MBF), blood pressure (BP). For explantation see text

TABLE I

Spontaneous bowel movements, blood pressure, and mesenteric blood flow during the principal phases of investigation*

	Bowel movements (units)	Blood pressure (mm Hg)	$\begin{array}{c} {\rm Blood\ flow}\\ {\rm (ml\ min^{-1})} \end{array}$	
Normal				
a) Control (phase 1)	$124 \pm 12^{ m bc}$	$170 + 9^{b}$		
b) Denervation (phase 2) Autotransplanted	$352 \pm 40^{\mathrm{abd}}$	$187 \pm 12^{ m acd}$	80 ± 7	
c) Reactive hyperaemia				
(phase 3a)	$1572\!+\!376^{ m abd}$	$153 + 6^{b}$	90 ± 8^{d}	
d) Stabilization period				
(phase 3b)	$114 + 10^{bc}$	$159+4^{ m b}$	$67 \pm 7^{ m c}$	

* Mean values \pm S. E. M., n = 7; a, b, c, d, denote, as indexed, significantly different (p < 0.05) changes from a, b, c, and d, respectively

mesenteric vasculature (Fig 2). On the other hand, the duration of phases 3 depended on the types of the vessel anastomoses. As shown in Table II, we found a significant correlation between the duration of phase 3b and the blood flow deficit occurring after revascularization.

In six dogs we tested the vascular responses to pharmacological interventions of characteristically different mechanisms of action. The drugs were given in phases 2 and 3b. Figure 3 demonstrates the basic features of these reactions, while the diagram of Fig 4. summarizes statistical evaluation of the



FIG. 2. Thermographic record of revascularization. Each colour of the calibration-scale (left) corresponds to 1 °C. Reconstructed artery to the autotransplanted bowel segment was declamped at 0 s. White arrowheads indicate the border between the mesentery and the bowel tissue. Note the homogeneity of reflow and the change in size of the lightcoloured pattern after 90 s indicating vigorous bowel contractions

results. As shown, in the typical biphasic flow response of dopamine we found a practically total disappearance of the second (vasodilator) phase after revascularization. The vasoconstrictor potency of the agent also diminished. However, this change was not statistically significant. Vascular responses elicited by the receptor-stimulant veratrine, were similar both before and after revascularization: there was no local vasodilation of considerable degree (except an equivocal tendency for it after revascularization) during the Bezold–Jarisch reflex. In contrast, we observed a short, transitory increase of vascular resist266 I. Kreyer et al.: Motility, Hemodynamics and Responsibility to Vasoactive Agents

				Dog No.					Unit
	1	2	3	4	5	6	7	$Mean \pm S.E.M.$	
Duration of phase 3a (reactive hyperaemia)	70	100	200	150	65	200	180	$138\!\pm\!22$	s
Duration of phase 3b (stabilization period)	40	6.5	23	20	8	10	8	16.5 ± 4.4	min
Blood flow deficit (phase 3b minus phase 2)	-40	-10	-30	-10	0	0	0	-12.8 ± 6.1	$ml \cdot min^{-1}$



TABLE II



FIG. 3. Responses to vasocactive drugs before (above) and after (below) bowel transplantation. Signs as in Fig. 1

ance accompanying the initial blood pressure drop. Finally, pentoxifylline administration produced almost identical responses in flow and resistance during both experimental phases, i.e. the virtual vasodilator action of the drug remained unchanged after retransplanting the bowel segment.



FIG. 4. Statistical comparison of vasoactive responses in the denervated (normal) and the retransplanted mesenteric bed. Asterisks refer to significance of drug-induced changes

Discussion

A minimal degree of basic motility was found in phase 1 of our experiments because of overnight fasting and laparatomy which are known to inhibit resting cyclic motor activity for the duration of surgery and several hours after it [3, 4]. Although the central nervous system does not control directly the motor activity, it does have an effect on enteric oscillatory mechanisms [8, 17]. After denervation (phase 2) motility increased slightly which may be due to neural effects and to a discrete increase of intestinal perfusion [12]. Is seems therefore, that denervation leads to a loss of neural down-regulation of resting motor activity. During the preservation of the allograft, despite the protective effect of cooling, acidic metabolites cumulate and tissue pH decreases [9]. Thus, in response to revascularization, some degree of blood flow enhancement was 268 I. Kreyer et al.: Motility, Hemodynamics and Responsibility to Vasoactive Agents

observed (reactive hypaeremia = phase 3a). The rapid onset of this phenomenon after a very short (≤ 30 s) period of latency was also indicated by thermography which is a particularly suitable technique for detecting homogeneity of the flow-dependent temperature distribution during the rewarming of artificially cooled tissues [14, 19]. Simultaneously with the increasing blood flow an activation of small bowel motility was seen, However, the normalization of blood flow did not go conform which normalization of motility (phase 3b). On the contrary, phase 3b exceeded phase 3a manifoldly. This relation might have been due partly to hypersecretion [10] and activating effects of intraluminal metabolites [18]: In 2 dogs we found an extremely long-lasting stabilization because of closed intestinal segments. In the other cases we drained intestinal content via a tube. As seen in Table II, there was also a correlation between the duration of phase 3b and the blood flow difference before and after revascularization.

The alteration of vasoreactivity which was tested with drugs possessing totally different mechanisms of action is of considerable interest. Since dopamine, a general activator of a wide spectrum of adrenoceptors, failed to induce vasodilation after revascularization, a significant change of balance of the adrenergic regulatory mechanisms is suggested in the latter state. The disappearance of vasodilation, apparently dopaminergic in origin [5], shifted this balance to the constrictor range, despite the fact that the vasocinstrictor potency of the drug also moderately decreased.

As expected, the vessels of the denervated bowel segment did not respond even before transplantation with characteristic vasodilation to the administration of veratrine which is known to elicit a reflex decrease of vasomotor tone in the periphery by stimulating, principally, coronary venous [11] and arterial [2] as well as left ventricular [6] mechanoreceptors. However, a local reflex effect cannot be excluded considering the complexity of the enteric nervous system where the functional features of the elements are only partially understood [8] and several morphologically classes of neurons can be discerned [7]. The initial vasoconstrictor response after veratrine may be attributable to such a local effect, or alternatively, it may reflect the nonlinearity of the flow/pressure relation during sudden hypotension.

In contrast, the flow-augmenting effect of pentoxifylline which acts through a haemorheologic rather than a direct vasoactive mechanism [1] remained unchanged after the transplantation of the bowel suggesting a potential therapeutic benefit of its administration to patients undergoing surgical interventions of this type.

Despite some changes in reactivity, the most conspicuous feature of the revascularized mesenteric bed was the stability of its basic blocd supply. When expressed in terms of calculated resistance reflecting the vascular tone as a whole, the values measured before and after transplantation were 2.52 ± 0.35

and 2.56 + 0.32 mm Hg ml⁻¹ min, respectively. The mean of percent difference between these values was +4.1 + 8.1 (p > 0.6) which is negligible. Taken together, our haemodynamic measurements also indicated the essentially favourable state of the graft.

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Postrevaskularisations-Motilität Hämodynamik und Antwortbereitschaft gegenüber den vasoaktiven Agentien in autotransplantierten Dünndarmsegmenten beim Hund

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Im Laufe von, bei mit Pentobarbital narkotisierten Hunden (n = 10) durchgeführten akuten Versuchen wurden die nach der Revaskularisation des autotranspantierten Dünndarmsegments auftretenden funktionellen und hämodynamischen Änderungen untersucht. Die Motilität des Segments wurde mit einem, unter Druck gestellten intraluminären Ballon und die Durchblutung mit einem auf den entsprechenden Zweig der A. mesenterica superior applizierten elektromagnetischen Meßkopf registriert. Die Chronologie der Beobachtungen wurde den erhaltenen Daten entsprechend in 3 Hauptphasen geteilt periodisiert. In der Anfangsphase (1) zeigte das Darmsegment eine nur sehr schwache spontane Motilität, die nach der Denervierung und der chirurgischen Isolierung (2), im noch in situ belassenen Segment, mäßig aber signifikant anstieg. Auf das Auflassen der Gefäßanastomosen reagierte das retransplantierte Graft (welches nach der Entfernung aus dem Körper auf 4 °C abgekühlt protektiert wurde) mit kurzer reaktiver Hyperämie $(\sim 2 \text{ min})$ und mit synchron damit auftretenden, aber wesentlich länger dauernden $(\sim 15 \text{ min})$ kräftigen Darmbewegungen (3a und 3b). In der mit Dopamin getesteten adrenergen Gefäßreaktivität des retransplantierten mesenterialen Gefäßbettes war im Vergleich zur Kontrolle eine relative, aber bedeutende Verschiebung in Richtung des vasokonstriktorischen Bereiches zu beobachten, während sich die mit Veratrin bzw. Pentoxifyllin getesteten allgemeine hämodynamische oder die auf die hämorrheologische Eingriffe erhaltene lokale Kreislaufsanwort nicht änderte. Die Grundblutversorgung des Grafts (auch mittels Thermographie kontrolliert) bzw. der systemische Blutdruck der Tiere zeigten indessen im Vergleich zu den vor den Transplantation bestimmten Werten, keine signifikante Abweichung. Angesichts der kritischen Rolle der sich direkt nach der Transplantation abspielenden funktionellen, Änderungen betreffs der Beurteilung der Lebensfähigkeit der Dünndarmgrafte, dürften die angeführten Beobachtungen zur effektiveren Monitorierung der chirurgischen Eingriffe beitragen.

Двительная активность, гемодинамика и реактивность к вазокативным агентам после реваскуляции в аутотрансплантированных сегментах тонкой кишки у соваки

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В острых эксперимантах на наркотизированных пентобарбиталом натрия собаках (n = 10) авторы изучали функциональные и гемодинамические изменения, наступающие в аутотрансплантированном сегменте тонкой кишки после реваскуляризации. Двигательную активность сегмента регистрировали с помощью баллона, размещенного под давлением в просвете киски, а кровоток измеряли электромагнитным датчиком, помещенным в соответствующей ветви верхней брыжеерной артерии. Хронологию наблюдений периодизировали, разделов на три главные фазы, в соответствии с полученными данными. В начальной фазе (1) обнаруживается лишь очень слабая спонтанная двигательная активность участка кишечника, которая после денервации и хирургического изолирования (2-я фаза) умеренно, но статистически значимо возрастает в оставленном пока еще *in situ* сегменте. На освобождение сосудистых анастомозов ретрансплантированный графт (который после удаления из тела сохраняют при +4 °C) реагировал кратковременной (2 мин) реактивной гиперемией и одновременно с этим возникающими, но значительно более продолжительными (15 мин) сильными движениями кишечника (фазы За и Зb). В адренергической сосудистой реактивности ретрасплантированного мезентериального сосудистого ложа по сравнению с контролем отмечали относительное, но значительное отклонение в сторону вазоконстрикции при тестировании дофамином, тогда как локальная реакция кровообращения в ответ на тестированные вератрином или пентоксифиллином общие гемодинамические или гемореологи-

ческие вмешательства не претерпела изменений. В то же время, базальное кровоснабжение графта (что было проверено также и термографией) или системное кровяное давление у животных не отличались достоверно от предтрансплантационного уровня. Принимая во внимание критическую роль функциональных изменений, следующих непосредственно за трансплантацией, в отношении оценки жизнеспособности трансплантата, надо полагать, что полученные авторами результаты могут способствовать более эффективной мониторизации хирургических вмешательств.

Effects of *a*₁-Adrenoceptor Blocker Prazosin on Microcirculation in Terminal Rabbit Ileum

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The influence of the specific α_1 -blocker prazosin on the microcirculation of the terminal ileum was examined in 10 rabbits. For this purpose an isotope clearance test was carried out by administering ¹³³-Xenon solution into the intestinal wall before and after the intra-arterial injection of prazosin (1.0 mg) via the superior mesenteric artery. These experiments were supplemented by haemodynamic and thermographic measurements in a further group of 5 rabbits. Due to the systemic circulatory effect of prazosin, i.e. the drug-induced hypotension, the bowel segment exhibited, contrary to expections, significantly delayed values for isotope elimination indicating a reduced local tissue clearance and blood supply. Thermographic observations also confirmed the impairment of mesenteric blood flow after prazosin. Therapeutic applicability of α_1 -adrenoceptor blockers to treat intestinal circulatory disturbances in diseases of vascular genesis thus remains dubious.

Athough the small intestine is richly innervated by sympathetic and parasympathetic fibres, only a dense adrenergic plexus has been demonstrated in the intestinal vessels: the parasympathetic vegetative system seems to have no direct influence on intestinal blood flow. Because of the dominance of α -adrenoceptors in the splanchnic region, sympathetic nerve stimulation leads to vasoconstriction and reduces intestinal blood supply [2, 5].

In search of selective pharmacological tools to improve intestinal circulation the possibility of α -adrenoceptor blockade has been discussed [8]. α_1 -adrenoceptor blocking drugs such as prazosin have been reported to cause vasodilation in the innervated intestine and this was probably due to the reduction of sympathetic influences on the vessel tone [10].

The aim of our study was to further evaluate the effect of prazosin related to vasodilation in the intestinal circulation. In order to minimize the systemic circulatory action, we injected the α_1 -blocker directly into the superior mesenteric arteny. In rabbits thes main branches of this artery supply the terminal ileum, which is very sensitive to circulatory disturbances [12]. For this reason, we examined pharmacologically induced microcirculatory changes in this region, while the generalized intestinal effects were assessed by thermography.

Materials and Methods

A total of 15 rabbits of both sexes were used in the experiments. In 10 rabbits, weighing 3.5 kg on the average, isotope clearance determinations were carried out. Preoperatively the animals received Ursonarcon (2 mg/kg b. w.), diazepam (25 mg) and atropine (1 mg) intramuscularly. The anaesthesia was continued by administration of ketamine (5. mg) i. v. After median laparatomy 0.2 ml (= 9 MBq) of 133-Xe-solution was administered into the wall of the terminal ileum. The recording of the decrease in radiation with a scintillation probe VA/S 968 type 2700 connected to the radiation measurement instrument 20046 MK 8 (both VEB Messelektronik, Dresden), lasted 4 minutes. After that 1 mg prazosin was injected into the superior mesenteric artery near to its origin, and the isotope clearance test was repeated immediately.

In another group of 5 rabbits the time course of the generalized haemodynamic action of prazosin was analysed. These animals were anaesthetized with Inactin (25–30 mg/kg b. w.) intravenously followed by pentobarbital sodium (50 mg/kg b. w.) i. m.

Systemic blood pressure was continuously recorded with a Statham gauge (P 23 Db) connected to a heparin-filled catheter in the femoral artery. In 3 rabbits the blood flow-dependent infrared irradiation from the exposed mesenterial region was recorded with computer-assisted telethermography according to the technique developed by Papp et al. [14, 15, 16, 17] as it has recently been adapted for the investigation of the mesenteric circulation [6]. The sensitivity of the AGA 750 Thermovision equipment was set to cover a 2.0 °C temperature range. Because of the smaller body weight of rabbits in this group (2.5 kg on the average), the close arterial injection of prazosin was also effected in a proportionally reduced dose (0.7–0.8 mg).

Statistical evaluation of the results was made by using Student's *t*-test for paired data, a stochastic probability of 0.05 being taken as significant.

Results

Table I lists the variations in half-life of ¹³³Xenon before and after prazosin administration, while Fig. 1 shows an example of the ¹³³Xe clearance curves in a typical experiment. We were able to demonstrate a considerable variability of the isotope clearance in the terminal ileum. These deviations might have been partly due to the variability of blood flow itself and partly to the difficulties involved in obtaining uniformity of intramural isotope application. After injecting prazosin we found an increase of the half-life in four-fifth of cases. The average clearance delay was significant compared to the pretreatment control

TABLE I

Experiment No.	Half-time of 133	Half-time of 133 < Xenon (min)				
Experiment No	Before prazosin	After prazosin	 Change in flow (%) 			
1	2.0	4.0	-50			
2	4.5	4.8	— 6			
3	6.5	5.2	+25			
4	3.6	6.9	-48			
5	4.0	6.4	-38			
6	2.5	3.0	-17			
7	5.7	8.2	-30			
8	4.5	3.4	+32			
9	3.5	4.7	-26			
10	2.6	7.0	-63			
lean + S.E.M.	3.94 ± 0.45	$5.36 \pm 0.54^{\mathrm{a}}$	-22.1 ± 9.9^{b}			

Effect of prazosin on blood supply to terminal ileum

^a significant difference (< 0.05) from control; ^b nearly significant change (≥ 0.05)



FIG. 1. A typical example of the alteration of 133 Xenon clearance in the terminal ileum after prazosin (ordinate: logarithmic scale)

values, and corresponded to a more than 20% decrease of the estimated tissue blood flow.

Table II summarizes the alterations of systemic circulation. These data show that mean arterial pressure decreased after prazosin administration by one-third of its initial value. Since heart rate remained unaffected, a direct cardiac action of the drug seems improbable. In the same series of experiments the dynamics of prazosin-induced changes were visualized by infrared thermography. Figure 2 shows two different thermographic patterns obtained in the whole mesenterial region by depicting the original colour-coded images (A) and describing their computerized evaluation in histograms (B). In one of the experiments where prazosin was only slightly hypotensive, the drug elicited a



FIG. 2. Original thermograms (left) and their computerized evaluation (right) in two experiments (No. 3 and No. 5). White arrows denote the region of terminal ileum Each colour-band of the calibration scales corresponds to 0.2 °C. (From above downwards: temperature decrease.) The histograms describe percent distribution of the same colour-bands. (From left to right: decrease of temperature.) Systolic/diastolic arterial pressure levels are also indicated. Note the mesenteric warming after prazosin when the blood pressure was preserved (exp. No. 3) and the cooling parallelled by hypotension in the other experiment (No. 5)

TABLE II

	Before prazosin	After prazosin	Change	
Systolic blood pressure (mm Hg)	$108.0\pm~7.8$	$72.5\pm$ 5.9	$-35.5 \pm 8.7^{ m a}$	
Diastolic blood pressure (mm Hg)	$50.4\pm~2.8$	$33.0\pm~4.4$	$-17.4\pm~5.4^{ m a}$	
Mean blood pressure (mm Hg)	$66.5\pm$ 4.4	$42.4\pm$ 4.6	$-24.1\pm$ 8.4 ^a	
Mean blood pressure $\binom{0}{0}$	100 ± 0	66.4 ± 10.7	$-33.6 \pm 10.7^{\mathrm{a}}$	
Heart rate (beats $\cdot \min^{-1}$)	308 ± 13	$307~\pm~7$	-1 ± 8	

Effect of intraarterial prazosin on systemic circulation*

* Mean values \pm S. E. M., n = 5; * Significant change (p < 0.05)

transitory warming which indicates vasodilation; the more typical example was, however, the regressive cooling seen in the set of images corresponding to the hypotension-dependent decrease of flow.

Discussion

The validity of prazosin-related blockade of α_1 -adrenoceptors has also been demonstrated for the rabbit as a species [3, 8]. We anticipated, therefore, on injecting prazosin, an effective augmentation of mesenteric flow. Contrary to this expectation our experiments demonstrated that the tissue perfusion at the microcirculatory level declined after prazosin administration. By using the isotope clearance the blood flow per tissue volume, BF/TV, is known to be in inverse proportion to the half-life, t(1/2), of a defined quantity of 133-Xenon, actually determined in our investigations. The exact formula is:

 $BF/TV = constant \cdot 1/t(1/2)$

Since under the present experimental conditions the precise value for the TV is undefined, the results were expressed in terms of the directly measured half-life of ¹³³Xe which was delayed, and the percent value of BF which, accordingly, was reduced after prazosin. The assumed BF increase was seen only in exceptional cases (Table I). Since after prazosin mean arterial blood pressure decreased by one-third and blood flow by one-fifth of their original levels, the alteration of local vascular resistance, blood pressure/blood flow, can be approximated as follows: 2/3 per 4/5 = 10/12 which roughly corresponds to a 15%decrease of resistance, i.e. a very moderate degree of vasodilation. This slight vascular response (indicating an almost negligible resting sympathetic tone in the mesenteric vessels) could have meant effective improvement of blood supply only with an adequate level of driving pressure, and this, in the majority of experiments, had clearly not been the case. The above conclusions were fully confirmed by our thermographic observations which revealed an augmentation in flow-dependent infrared irradiation (warming) provided the blood pressure was comparatively well preserved after prazosin, and an unequivocal cooling when the hypotensive prazosin action prevailed (Fig. 2). Thermographic visualization demonstrates mesenterial distribution rather than tissue perfusion [6], and this situation discriminates the anatomical territory of bowel from the heart tissue where the methodology was originally developed by Papp and his associates [14, 15, 16, 17]: In the latter organ the medium for blood flow distribution (the epicardium) lies close to and is thermally supported by the main bulk of the supplied tissue itself. Notwithstanding, the thermographic technique seems suitable to record also the overall changes of local flow in the mesenterial region.

As evidenced by our present studies, these local flow effects are dominated by the hypotensive action of prazosin even in the case of its close arterial administration indicating the escape into the systemic circulation of a substantial percentage of the drug. Several factors can be accounted for the generalized hypotensive effect. (i) The consequences of α_1 -blockade in the skin and muscle vessels may be of primary importance [4, 19]. Even the slight intestinal vasodilation may cause an additional effect. It should be added that under resting conditions, the splanchnic region gets 12-15% of the cardiac output. This value increases, e.g. during postprandial hypaeremia to 25-30% [18]. (ii) The venodilator action of prazosin [9] may reduce venous reflow to the heart and thus decrease cardiac output, an important determinant of blood pressure. (iii) Prazosin, unlike the direct vasodilators, fails to enhance plasma renin activity [1], and inhibits rather that augments, unlike nonselective α --blockers, the sympathetic outflow from the central nervous system [13]. Thus there is no compensatory humoral pressor response and sympathetic stimulation, after injecting the drug.

In summary, we conclude that the therapy with α_1 -adrenoceptor blockade of isolated circulatory disturbances in the intestine seems not to be effective. Apparently, the ideal approach to improve intestinal circulation would be the application of selective drugs without considerable influence on the vessels of other organs. In that respect the agonist-induced stimulation of dopamine receptors which elicits selective redistribution of systemic flow to this region seems promising [7, 11]. Such a therapy might find its application in clinical states were the intestinal blood flow is impaired, e.g. in chronic inflammatory bowel diseases, especially of vascular origin. However, as shown by the recent work of Dóbi and Kékesi [6] even the latter type of approach has its own limitation, and dopamine, as a specific vasodilator of the splanchnic region, should probably be selected on a comparatively narrow basis.

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Über die Wirkung des Alpha₁-Adrenorezeptor-Blockers, Prazosin auf due Mikrozirkulation des terminalen **Ileums beim Kaninchen**

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Bei 10 Kaninchen wurde die Wirkung des Alpha₁-Adrenorezeptor-Blockers, Prazosin auf die Mikrozirkulation des terminalen Ileumabschnitts untersucht. Zu diesem Zweck wurden Isotopenclearance-Untersuchungen vorgenommen und zwar mittels Verabreichung der ³³Xenon-Lösung in die Darmwand, vor und nach der intraarteriellen (in die A. mesenterica superior) Prazosin-Injektion (1 mg). Ergänzungshalber wurden bei weiteren 5 Tieren hämodynamische und termographische Messungen vorgenommen.

Als Folge der Wirkung von Prazosin auf den systemischen Kreislauf bzw. der durch die Droge herbeigeführten Hypotension war im Darmsegment wider Erwartung eine signifikant verzögerte Isotopenelimination — als Zeichen der verringerten lokalen Gewebeclearance und des niedrigen Durchblutungsniveaus — zu beobachten. Die thermographischen Beobachtungen bekräftigten die Möglichkeit der durch Prazolin herbeigeführten Störungen der mesenterialen Blutversorgung. Demnach scheint der Einsatz der Alpha,-Adrenerg-Blocker in der Therapie der vaskulär bedingten Darmkreislaufstörungen zweifelhaft.

Влияние блокатора альфа₁-адренорецепторов празозина на микроциркуляцию терминального участка подвздошной кишки у кроликов

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В экспериментах на 10 кроликах авторы изучали воздействие празозина, блокирующего альфа₁-адренорецеторы, на микроциркуляцию терминального участка подвздошной кишки. С этой целью были выполнены исследования с клиренсом изотопа ксенона (Xe), путем введения его в стенку кишки до и после интеррартериальной (в верхнюю брыжеечную артерию) инъекции празозина (1 мг). Эти исследования были дополнены в экспериментах еще на пяти животных, с гемодинамическими и термографическими измерениями.

В кишечном сегменте, под влиянием празозина на системное кровообращение, то есть, в результате вызванной этим препаратом гипотензии, наблюдали — в противоположность ожиданию — достоверно растянутую во времени элиминацию изотопа, что означало пониженный локальный тканевой клиренс и уменьшенный мезентериальный кровоток. Термографические наблюдения подтвердили возможность возникновения нарушений мезентериального коровоснабжения после введения празоина. Авторы приходят к выводу, что применение альфа₁-адренергических блокаторов в терапии нарушений кровообращения в кишечнике сосудистого происхождения кажется сомнительным.

Prenatal Diagnosis and Management of Chondrodysplasias*

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Thorough ultrasound examination of fetal limbs and fetal movements allows us to recognize several types of osteochondrodysplasia, both in high risk pregnancies (with a family history of chondrodysplasia) and up on routine screening. Correct diagnosis of growth retardation requires nomograms for bone length, and we have developed our own standards for the humerus, ulna, femur and tibia. Since some types of osteochondrodysplasia are compatible with life and others not, it is important to make the correct diagnosis using several differential diagnostic criteria. Only in this way can we decide the further management of a pregnancy. At our Prenatal Diagnosis Centre 8 cases of osteochondrodysplasia have

At our Prenatal Diagnosis Centre 8 cases of osteochondrodysplasia have been diagnosed. We discuss the differential diagnosis and the pregnancy management for some of thes cases.

Recent development of ultrasound technology has made it possible to detect a large number of fetal malformations prenatally and a relatively small fraction of these abnormalities are osteochondrodysplasias. By the through examination of fetal limbs and movements these anomalies can be relatively easily recognized both in high risk pregnancies [1, 2, 7, 8, 9, 10] (with a family history of chondrodysplasia) and by routine ultrasound [4, 5, 6, 8, 11] screening. This way we have diagnosed at our Prenatal Diagnosis Centre 8 cases of osteochondrodysplasia and in this report we would like to present some of these cases in order to demonstrate not only the possibility of prenatal diagnosis but some differential diagnostic criteria and the management of these pregnancies as well.

Case Reports

Zs. T., a 20-year-old achondroplastic woman, was referred to us for genetic counselling and prenatal diagnosis during the 13th weel of her first pregnancy. Her husband was normal. She was told to have a 50% risk of recurrency of heterozygous achondroplasia and she decided to ask for a prenatal diagnosis and for termination of pregnancy in evidence of fetal achondroplasia. Measure-

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ments of the fetal long bones were normal both at the 13th and 19th gestational weeks, but proved to be significantly shorter at the 26th gestational week. On her request the pregnancy was terminated and the histological examination of the femoral epiphysis showed typical features of heterozygous achondroplasia.

M. J., a 22-year-old primigravida, was referred to our Genetic Counselling Clinic in the 15th gestational week because she had polydactyly on both upper and lower extremities. By physical examination it was also remarkable that she was only 132 cm tall and had shorter and bowing extremities. These signs raised the possibility of some type of osteochondrodysplasia and for this reason radiographic examination of the limbs and sella was performed. As these showed typical signs of heterozygous achondroplasia she was told to have a 50% risk of recurrence. At the first ultrasound examination of the fetus no abnormality could be revealed. At gestational week 21 the ultrasound scanning was repeated and then the fetal long bones proved to be significantly shorter than the normal standards and were bowing as well. On the basis of these signs, the gravida was informed that the risk of having a baby affected with heterozygous achondroplasia was 100%. Inspite of this fact she decided to keep her pregnancy as she did not feel that she was affected by any illness and she was 'informed' of this fact at our Genetic Counselling Clinic for the first time. Further ultrasound scans at the 25th, 30th and 35th gestational weeks also



FIG. 1. The radius and ulna are not only shorter than normal but are bowing as well Acta Chirurgica Hungarica 30, 1989

supported the prenatal diagnosis of fetal achondroplasia (Fig. 1) and at the 38th gestational week, a 2510 g female newborn was delivered by Caesarian section. The infant also had polydactyly and she was confirmed to be affected with heterozygous achondroplasia, as well.

B. A., a 23-year-old gravida 3, para 2, was referred to us because of severe polyhydramnios for ultrasound examination in the 36th gestational week. The ultrasound scanning showed polyhydramnios, remarkably short limbs, macrocephaly, and a protuberant fetal abdomen while the thorax was depressed (Fig. 2). On the basis of these findings, the intrauterine fetus was diagnosed as a thanatophoric dwarf. Because of the severe polyhydramnios preterm delivery induction was performed and the fetus died during labour. The necropsy showed typical signs of thanatophoric dysplasia.

H. GY., a 33-year-old gravida, was referred to our Prenatal Diagnosis Centre during the 21st gestational week of her second pregnancy because the ultrasound examination performed in another ultrasound laboratory indicated fetal malformation. Her first child was healthy and there was no family history of chondrodysplasia. The ultrasound scan showed a Bpd within the normal



FIG. 2. The thorax is narrow

range but the fetal limbs were so short that the first impression was that the fetus had tetraphocomelia. After the thorough examination the extremly short extremities could be visualized and a narrow thorax could be proven, as well. The forehead was prominent. These signs supported the diagnosis of thanatophoric dwarfism and the couple, upon being informed about the severity of the condition, agreed upon the termination of pregnancy. The necropsy confirmed prenatal diagnosis.

Discussion

Several authors have already proved that ultrasound makes the measurement of fetal bones in utero possible, facilitating the diagnosis of osteochondrodysplasia characterized by short and/or deformed extremities. Fetal bones can be visualized with ultrasound as soon as they become calcified. Cartilaginous structures are usually not visible, but the fetal long bones start to ossify from the ninth gestational week and or measurable a few weeks later [2, 6]. Nomograms for the growth of the humerus, ulna, radius, femur and tibia have been made by several authors. These standards can be used not only to assess the correct gestational age, but in the diagnosis of intrauterine growth retardation and skeletal dysplasias, as well. The examination of fetal extremities and long bones is essential in prenatal diagnosis of disturbances of mineralization and also in differential diagnosis of multiple malformation syndromes. In our ultrasound laboratory we have also made our own nomograms of the fetal long bones by a linear scanner (Picker LS 2000) on the basis of the measurement of several fetuses from normal pregnancies. As suggested by other authors, only the shaft of the long bones was measured and not the distal and proximal epiphyses because it is not adaequately ossified for visualization [2, 6].

In cases where one of the parents is affected with any type of osteochondrodysplasia, if the length of the fetal long bones is significantly shorter than normal, a definite diagnosis can be made [1, 3, 5]. This has already been proved by several authors and is supported by our first two cases. The situation is the same if a previous child had suffered from an autosomal recessive type of osteochondrodysplasia and in a subsequent pregnancy short fetal limbs can be detected [2, 3, 7, 9, 10].

In cases of heterozygous achondroplasia, the prenatal diagnosis is possible often only at the end of the second trimester as earlier abnormal femoral length cannot be demonstrated. This was found by other authors [1, 2, 3] and our first case also supports this finding. In cases when a routine ultrasound examination detects the disorder of fetal limb growth and the pregnant woman has had no family history of chondrodysplasia, finding the correct diagnosis is much more difficult. Since, besides short limb dwarfisms, there are other multiple malformation syndromes which affect fetal limbs, a thorough investigation of the whole fetus is very important after the recognition of short limbs. It is necessary to exclude macro- or microcephaly, as well as hydrocephaly.

The thorough examination of the face is also necessary in order to judge or rule out prominent forehead, micrognathia, cheilognathopalatoschisis, hypo-, or hypertelorism, and microphthalmia. By the examination of the thorax, thoracal hypoplasia and as a consequence, pulmonary hypoplasia, can be proved or excluded. Investigation of the ribs, vertebral bodies, and fingers is also essential [4, 5, 6]. On the basis of these signs, short limb dwarfisms can be differentiated from other malformations and these features can be used for the differentiation between various types of chondrodysplasias as well. Since nowadays 21 types of osteochondrodysplasia are known and most of them are compatible with life, it is important to make the correct diagnosis of tetramicromelias. Only this way can further management of a pregnancy be decided.

In our third and fourth cases the narrow thorax was the differential diagnostic sign which led us to conclude that this form of tetramicromelia was incompatible with life. Other types of chondrodysplasias associated with hypoplastic lungs could be excluded by the absence of postaxial polydactyly (Ellisvan Creveld syndrome, Majewsky and Saldino-Noonan syndromes) and severe dysplasia of tubular bones and vertebrae ruled out asphyxic thoracic dysplasia as well. In this way the diagnosis of thanatophoric dysplasia could be determined in both cases.

As in these lethal conditions, termination of pregnancy can be suggested, all cases where short limbs can be detected by routine ultrasound examination should be referred to a specialized centre that frequently deals with fetal malformations in order to determine the correct diagnosis.

In connection with our first two cases, it is also worth mentioning that we consider it to be necessary to give the parents the right to decide the management of the pregnancy in those situations when one or both of the parents suffer from an autosomal dominant type of chondrodysplasia.

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Pränatale Diagnose und Versorgung von Chondrodysplasien

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Die gründliche Ultraschalluntersuchung der Fötusextremitäten und der Kindsbewegungen ermöglicht die Erkennung einzelner Typen der Osteochondroplasien sowohl in der high Risk Schwangerschaften (in der Familie kam bereits Chondrodysplasie vor) als auch im Laufe der Routine-Reihenuntersuchung. Zur genauen Diagnose der Wachstumretardation sind die Nomogramme der Röhrenknochen nötig, weshalb die Standarde des Humerus, der Ulna, des Femurs und der Tibia angefertigt wurden. Da einige Typen der Osteochondrodyplasien mit dem Leben vereinbar, andere dagegen nicht vereinbar sind, ist die genaue Diagnose, unter Verwendung der verschiedenen diagnostischen Kriterien von ausschlaggebender Bedeutung, zumal über die weitere Versorgung der Schwangerschaft nur in Besitz dieser Diagnose eine Entscheidung getroffen werden kann. In dem pränatalen diagnostischen Zentrum wurde die Osteochondrodysplasie in 8 Fällen diagnostiziert. Die differentialdiagnostischen Probleme und die Art und Weise der Versorgung der Schwangerschaft werden erläutert.

Пренатальный диагноз и лечение хондродисплазий

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Тщательное ультразвуковое исследование конечностей плода и двигательной активности плода позволяет диагностировать отдельные типы остеохондродисплазий как при беременностях с высокой степенью риска (в семье уже встречалось заболевание ходнродисплазией), так и в ходе рутинных обследований. Для точной диагностики замедления роста необходимо делать номограммы длинных костей, поэтому авторы изготовили стандарты плечевой, локтевой, бедренной и большой берцовой костей. Поскольку некоторые типы остеохондродисплазий совместимы с жизнью, в то время как другие несовместимы, важно поставить правильный диагноз, используя различные диагностические критерии. Только таким образом можно решить вопрос о дальнейших мерах, которые необходимо принять при беременности. В центрах пренатальной диагностики остеохондродисплазию диагностировали в восьми случаях. Авторы обсуждают дифференциальный диагноз в этих случаях и способы патронирования беременных.





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Nomograms 1–6, case I x, case II o, case III A, case IV

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Routine Prenatal Screening Policy of Fetal Malformations by Both Maternal Serum Alpha-fetoprotein and Ultrasound in Eastern Hungary*

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Since January 1979, at our Genetic Counselling Unit in Debrecen all pregnancies at high risk for any reason have been screened sequentially by serum alpha-fetoprotein estimation (at the 16th week) and by ultrasound examination (18th week). This screening policy covered 1200–1500 consultations per year. From July 1983, the same prenatal screening policy has been extended to cover the *whole pregnant population* ot two large counties in Eastern Hungary. In a six-year period over 300 fetal malformations were diagnosed. Details of the screening policy and the main groups of malformations diagnosed prenatally are demonstrated.

Fetal malformations are among the most common causes of perinatal fetal wastage and because these defects occur mainly in pregnancies without any known risk factor, a need emerges for an effective prenatal screening policy.

Based on published studies and personal experience we have developed a protocol for prenatal screening of fetal malformations in all pregnancies in Eastern Hungary [1, 4].

Material and Results

Between 1st January 1979 and 31st December 1984 we screened 9261 highrisk pregnancies referred to our Genetic Counselling Centre in Debrecen, by maternal serum AFP estimation at the 16th gestational week, and by ultrasound examination at the 16th and 18th weeks. The main reasons for referral are listed in Table I.

If the serum AFP level was normal, ultrasound examination showed no fetal abnormality, and the risk for the particular genetic disorder provoking consultation was not high, pregnancies were allowed to continue to term. [2]. If prenatal diagnosis by amniotic fluid analysis was required, amniocentesis, with biochemical or cytogenetic analysis of amniotic fluid cell cultures, was performed.

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Genetic Counselling Centre, Debrecen: January 1979 to December 1984. Pregnances screened for fetal malformation by combined maternal serum AFP and ultrasound

Reason for referral	Pregnancies screened	Fetal malformations detected before the 24th week of gestation (in parentheses the reason for referral)
 Family history of disease or malformation (a) autosomal dominant inheritance 	93	1 achondroplasia (maternal achondroplasia) 1 hydrocephalus $+$ spina bifida (familial poly- and syndactyly)
(b) autosomal recessive inheritance	202	2 early meconium ileus (pregnancies at 1 in 4 risk for cystic fibrosis)
(c) X-linked recessive inheritance	103	=
(d) neural tube defects	533	8 anencephaly 1 exencephaly 2 anencephaly + spina bifida 3 hydrocephalus + spina bifida 1 occipital encephalocele
(e) congenital malformations (excluding neural tube defects)	1621	 anencephaly + spina bifida (previous exomphalos) hydrocephalus (previous cleft lip and palate; renal agenesis) hydrocephalus + spina bifida (previous cleft lip and palate) iniencephaly (previous congenital heart disease) renal agenesis (previous renal agenesis)
(f) teratogenic	66	
(g) chromosomal	284	1 ascites $+$ hepatic cirrhosis (previous trisomy 21)
(h) others	341	 2 anencephaly (previous mental retardation; cerebral palsy) 1 hydrothorax + pulmonary hypoplasia (previous microcephaly) 1 thanatophoric dysplasia (previous leukaemia)
(2) Exogenous effects during pregnancy	3035	 exencephaly (X-ray exposure) hydrocephalus (rubella exposure; antibotic treatment of influenza) spina bifida (2 rubella exposure; 1 drug treatment of colpitis) hygroma colli (drug abuse - attempted suicide) ascites + viral hepatitis (rubella exposure; drug abuse - attempted suicide) renal agenesis (X-ray exposure)

Total	9261	86 fetal malformations
(8) Anxiety (no serious previous history)	1253	5 anencephaly 1 anencephaly + spina bifida 1 hydrocephalus 2 hydrocephalus + spina bifida 1 spina bifida 1 ectopie cordis 1 calcific meconium peritonitis
(7) Long period of infertility and/or seminal fluid abnormalities	203	 anencephaly (oligospermia) hydrocephalus (oligospermia and a long period of secondary infertility) hydrocephalus + spina bifida (pregnancies conceived after a long period of primary infertility)
(6) Recurrent pregnancy wastage	1015	 2 anencephaly (previous recurrent abortions; previous stillbirths) 1 hydrocephalus + spina bifida (previous recurrent abortions) 1 spina bifida (previous recurrent abortions) 1 iniencephaly (previous recurrent abortions) 1 hydrothorax + pulmonary hypoplasia (previous deceased child) 3 exomphalos (previous recurrent abortions) 1 intestinal atresia (multiple) (previous deceased child) 1 multicystic kidney disease (previous recurrent abortions) 1 ADAM complex (two previous abortions)
(5) Maternal diabetes mellitus	36	1 exencephaly (isolated) 1 exencephaly + holoprosencephaly + cyclopia 1 polycystic kidney disease
(4) Advanced maternal age (35)	422	 2 spina bifida (ages 38 and 39) 1 iniencephaly (age 42) 1 diaphragmatic hernia (age 39) 1 exomphalos (age 36) 1 Mayer-Rokitansky-Küster-Hauser syndrome (age 39)
(3) Parental consanguinity	54	because of rheumatoid arthritis)
		 polycystic kidney disease (X-ray exposure) megacystis-microcolon-hypoperistalsis syndrome (X-ray exposure) persistent cloaca (drug treatment with Peritol) non-immune hydrops (drug abuse – attempted suicide: drug treatment

If serum AFP was elevated but ultrasound showed no abnormality, a repeated serum AFP estimation was performed at the 18th week. Amniocentesis was carried out when either *two* AFP levels were above 2.5 MoM or ultrasound examination indicated fetal malformation. The amniotic fluid samples were tested for AFP and examined by exfoliative cytology. For abnormal pregnancies terminated at parental request we used extra-amniotic instillation of 100–120 ml 0.1% Rivanol solution. The prenatal diagnosis was confirmed by embryopathological study (Table I).

From July 1983 a slightly modified form of this prenatal screening policy has been employed to cover the whole pregnant population of Debrecen and two large neighbouring counties in Eastern Hungary. The serum AFP estimation was made at the 16th week of gestation, and oltrasound examination was carried out at the 18th gestational week; this initial screening was carried out at one of the three ultrasound laboratories, depending on the place of referral [3, 5]. All pregnancies with high serum AFP and/or any suspicion of fetal malformation on ultrasound performed elsewhere in the region were then referred for a second opinion at our Genetic Counselling Centre in Debrecen. From 1st of July 1983 till 31st December 1984, 12/131 pregnancies were screened within the region.

Fetal malformations diagnosed prenatally before the 24th week of gestation, and the effectiveness of maternal serum AFP and ultrasound screening, are summarized in Table II. Occurrence of malformations in the different groups can be seen in Table III. The detection rates of the different screening methods are documented in Table IV.

Conclusions

1. The policy of universal maternal serum AFP screening and the scanning of women with raised serum AFP levels is useful for the detection of open neural tube defects but fails to detect most other types of malformations.

2. A more effective screening policy for fetal malformations would be the use of *maternal serum AFP estimation with subsequent ultrasound*, in all pregnancies:

- ultrasound provides a high detection rate for both neural tube defects and other malformations

- *AFP estimation* will detect some pathological situations, in addition to open neural tube defects (e.g. threatened abortion, fetal distress, Down's syndrome etc.).

TABLE II

Malformations	High-risk pregnancies counselled at the Genetic Counselling (11979-1984) (9261 cases)	Pregnancies without any demand for counselling screened routinely (1983-1984) (12 131 ca- ses)	Total	Maternal serum AFP was above 2. 5 MoM	Abnormal ultrasound
CRANIOSPINAL DEFECTS					3
Anencephaly (isolated) Anencephaly + spina bifida Hydrocephalus (isolated) Hydrocephalus + spina bifida Spina bifida (isolated) Hydranencephaly Exencephaly (isolated) Exencephaly + holoprosence- phaly + cyclopia Cebocephaly + holoprosencephaly Iniencephaly Occipital encephalocele	$ \begin{array}{r} 18 \\ 4 \\ 6 \\ 10 \\ 11(1) \\ - \\ 3 \\ 1 \\ - \\ 3 \\ 1 \end{array} $	7 6 10(2)* 15 3(4) 1 6 1 3 3(1)	$25 \\ 10 \\ 16(2) \\ 25 \\ 14(5) \\ 1 \\ 9 \\ 1 \\ 1 \\ 6 \\ 4(1)$	$23 \\ 9 \\ 3 \\ 20 \\ 15 \\ - \\ 9 \\ 1 \\ 6 \\ 3 \\ 3 \\ $	25 10 16 25 11 1 9 1 1 6 4
Sacrococcygeal teratoma		$\frac{3(1)}{2}$	$\frac{4(1)}{2}$	1	4 2
Total	57(1)	57(7)	114(8)	90(73.8%)	111(90.1%)
CERVICOTHORACIC DEFECTS					
Hygroma colli Diaphragmatic hernia Cystic adenomatoid malformation Hydrothorax + pulmonary hypoplasia	1 1 2	$\frac{4}{1}(1)$ 2	$5 \\ 1(1) \\ 1 \\ 4$	2	5 1 1
Eetopia cordis	1	2	3	1	3
Total	5	9(1)	14(1)	3	14
GASTROINTESTINAL ANOMALIES					
Exomphalos (most with multiple malformations) Gastroschisis Intestinal atresia Ascites + hepatitis/cirrhosis Meconium peritonitis and/or ileus	4 1 3 3	9(1) 1 1 2	13(1) 1 2 5 3	8 1 	$13 \\ 1 \\ 2 \\ 5 \\ 3$
Total	11	13(1)	24(1)	9	24
UROGENITAL MALFORMATIONS					
Renal agenesis Polycystic kidney disease Multicystic kidney disease Urethral obstruction Megacystis-microcolon-hypoperistal- sis syndrome Persistent cloaca Mayer–Rokitansky–Küster- Hauser syndrome	2(1) 2(1) 1 1 1 1 1	5 2 2 2	$7 \\ 4(1) \\ 3 \\ 2 \\ 1 \\ 1 \\ 1$		7 4 3 2 1 1 1
Total	8(1)	11	19(1)	1	19

Fetal malformations diagnosed prenatally before the 24th week of gestation (Debrecen, January 1979 to December 1984)

Table II (continued)

Malformations	High-risk pregnancies counselled at the Genetic Counselling Clinic (1979-1984) (9261 cases)	Pregnancies without any demand for coun- selling screened rou- tinely (1933-1984) (12 131 cases)	Total	Maternal serum AFP was above 2.5 MoM	Abnormal ultrasound
MISCELLANEOUS					
Achondroplasia	1		1		1
Thanatophoric dysplasia	1		1	_	1
ADAM complex	1	1	2		2
Cheilognathopalatoschisis	-(2)	1(2)	1(4)		1
Non-immune hydrops	2(1)	3	5(1)	-	5
Total	5(3)	5(2)	10(5)		10
TOTAL	86(5)	95(11)	181(16)	103	178

* Undetected malformations, in screened pregnancies, are shown in parentheses.

TABLE III

Distribution of malformations between the different referal groups, and in the screened group without special request for counselling

Group (as in Table I)	Pregnancies screened	Fetal malforma- tions detected (undetected mal- formations in parentheses)	Ratio [detected/screened (%)]	Pregnancy prevalence of malformations [malformations/preg- nancies (%)]	
SPECIAL REFERRAL:COUNS	ELLED GROU	JP			
la	93	1*	1/93 (1.07)		
1b	202	-* (1)	-/202 (-)		
1c	103	_	-/103 (-)		
1d	533	19 (4)	1/28 (3.56)		
1e	1621	6	1/270 (0.37)		
1f	66		-/66 (-)		
lg	284	1	1/284 (0.35)		
$1 \mathrm{h}$	341	4	1/85 (1.17)		
2	3035	15	1/202 (0.49)		
3	54		-/54 (-)		
4	422	6	1/70 (1.42)		
5	36	3	1/12 (8.33)		
6	1015	12	1/85 (1.18)		
7	203	4	1/51 (1.97)		
8	1253	12	1/104 (0.95)		
Total	9261	83*(5)	1/112 (0.89)	1/105 (0.95)	
WITHOUT ANY DEMAND FO	R COUNSELLI	ING			
	12 131	95 (11)	1/128 (0.78)	1/114 (0.87)	
TOTAL	21 392	178* (16)	1/120 (0.83)	1/110 (0.90)	

* Excluding achondroplasia and the two cystic fibrosis cases; these pregnancies were already known to be at high risk.

TABLE IV

Detection rates of different screening methods for fetal malformations

Malformations			Detec	tion rate		
	Maternal	serum AFP	Ultr	asound	Both serun ultra	n AFP and asound
Open neural tube defects	79/93	(84.9%)	84/93	(90.3%)	87/93	(93.5%)
Craniospinal defects including neural tube defects	90/122	(73.8%)	111/122	(90.1%)	114/122	(93.4%)
Fetal malformations excluding craniospinal defects	13/75	(14.2%)	67/75	(89.3%)	67/75	(89.3%)
Total of fetal malformations	103/197	(52.3%)	178/197	(90.3%)	181/197	(91.8%)

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Routine pränatale Reihenuntersuchungspraxis fötaler Anomalien durch Bestimmung der Alpha-Foetoprotein-Konzentration im mütterlichen Serum und gleichzeitiger Ultraschalluntersuchung in Ostungarn

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In unserer genetischen Beratunsstelle, Debrecen werden seit Januar 1979 unabhängig von dem Charakter der Beratung — bei allen Schwangeren in der 16. Woche Serum Alpha-Foetoprotein-Bestimmungen und in der 18. Woche Ultraschalluntersuchungen durchgeführt.

Dieses Reihenuntersuchungsprogramm bedeutet 1 200–1 500 Beratungsfälle pro Jahr. Von Juli 1983 an wurde dieses pränatale Reihenuntersuchungsprogramm auf die ganze Schwangerpopulation von zwei großen Komitaten Ostungarns ausgebreitet. Im Verlauf von sechs Jahren wurden mehr als 300 fötale Malformationen diagnostiziert. In der Arbeit finden die Einzelheiten des Reihenuntersuchungsprogramms sowie die Hauptgruppen der pränatal diagnostizierten Malformationen eine Besprechung.

Практика рутинного пренатального обследования для выявления нарушений развития плода в восточной венгрии с помощью одновременного применения альфа фетопротеина материнской сыворотки и ультразвука

М. САБО, З. ТОТ, О. ТЁРЁҚ, Л. ВЕРЕШШ, Э. БЕДЭ, Ф. НАДЬ и З. ПАПП

В дебреценской Генетической Консультации с января 1979 года — независимо от консультативного характера — у всех беременных на 16-й неделе определяли содержание в сыворотке альфа-фетопротеина, а на 18-й неделе делали ультразвуковое исследование. Эта профилактическая программа охватывает ежегодно 1200–1500 консультационных случаев. С июля 1983 года эту программу пренатального профилактического обследования распространили на всю популяцию беременных двух больших областей Восточной Венгрии. На протяжении шести лет были диагностированы больше 300 плодных мальформаций. В настоящем сообщении демонстрируются подробности профилактической программы и главные группы пренатально диагностированных мальформаций.
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Ventral Spondylodesis: Basic Method in the Treatment of Cervical Spine Injuries

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Ventral spondylodesis or ventrofixation is the most important surgical method for the treatment of severe cervical spine injuries accompanied by instability. Its wide indications include fracture-dislocations, compression fractures of the vertebral body, injuries to the disc, luxations, 'tear drop fractures' as well as 'hangman's fractures'. The essential parts of its technique: previous reduction by traction, anterior cervical approach, removal of the injured parts of vertebral body and disc(s), replacement by corticocancellous bone graft with subsequent plate-screw fixation. The authors performed in their Institute nearly 100 operations of this type, in a 10-year period of which; detailed accorunt is given. Good results of surgery can be expected only by ensuring adequate technical conditions and professional knowledge, performing the operations in centres having sufficient experience.

In the last 20 years specialists all over the world engaged in surgical treatment of cervical spine injuries – neurosurgeons, traumatologists, orthopaedic surgeons – can be divided on the basis of supporting dorsal or ventral spondylodesis. Dorsal spondylodeses, predominating in the early period [17, 22, 25, 26, 31, 36] have generally been replaced by ventral spondylodeses since the development of the ventral technique [1, 4, 7, 14, 19, 23, 24, 34] and its numerous variations [5, 12, 13, 40, 15, 29, 30, 36]. This tendency can be observed in our practice as well but falling behind the European frontline [20, 27, 28].

As a matter of fact, in Hungary ventral spinofusions have been started quite early [38, 39], but not with the current up-to-date technique accepted all over Europe. We are aware of the fact that ventral spondylodeses were performed for traumatic cases in several Hungarian Institutes but these were either far smaller in number, or have not been published, or were performed only in cases of inveterated injuries, or — apart from those quoted above — did not meet the requirements of up-to-date stabilization.

^{*} Place of work at present: Department of Neurosurgery, Military Hospital, Győr.

Why has anterior fusion become so popular? Our aim was to make clear this question analysing the 10-year ventrofixation material of the N. I.T. hoping that our experience can partly contribute to the perfection of the ventral spondylodeses.

Material, Method and Results

Ninety-five operations with ventrofixation technique were performed at the N. I. T., Department of Neurosurgery, during a 10-year period from 1976 till 1985. Of course, treatment of herniated cervical discs with severe spondyloses made also by ventral cervical approach, are not included; these were carried out in 37 cases during the above period (20).

Indications of ventral spondylodesis cover quite wide range of cervical spine injuries; practically, it is applicable in most severe cervical spine injuries with instability at the level from C2 to Th2. These are: fracture-dislocations, compression fractures with big dislocation, severely comminuted or burst fractures, tear drop fractures, luxations, injuries to the discs and the certain types of 'hangman's fractures'; all of them in cases without neurological injury as well as with partial or total spinal cord injuries or root lesions [14, 32, 33, 35].

Surgical technique. In our institute the Smith-Robinson or the Caspar technique is applied [14, 22, 23, 24, 36]. After conservative reduction (Crutchfield traction: 8, 9; or halo extension: 11, 18, 21) the patient's neck is reclined, exposure is made on the anterior surface of the neck, mostly on the right side with a transverse skin incision, controlled under lateral image intensifier. Passing backward between the carotid vessels and the cervical viscera the anterior surface of the cervical spine is exposed, the level of injury is identified under the image intensifier, and the injured vertebral body and discs are removed. Similarly, the bone and disc parts, that have ruptured or compressed into the spinal canal, are removed and decompression of the dural sac and roots is made. The corticocancellous bone graft taken from the patient's iliac crest and formed to be adequate in shape and size, is placed in the site of the removed disc and/or vertebral body so, that there should be a large junction interface of the fresh cancellous bone. If necessary, a complementary reposition manoeuvre is made and afterwards the injured spine segment is stabilized with H-plate and screws in that position. (Other types of plates can be used as well, e.g. trapezial plate: 5.) In order to assure good stabilization 2-2 screws each should hold 4 corticalseach in the vertebral bodies above and below the boneblock and one screw should fix the block. Wound closure is made by muscle and skin sutures, suction drainage is maintained for 24 hours.

Postoperative external fixation is unnecessary in our opinion. A soft sponge collar is applied for 1-2 weeks to decrease neck pain, muscle spasm.

Mobilization begins from the day after surgery, rehabilitation treatment is started also as early as possible after surgery if it is necessary.

Bony union occurs during several months, monitored by clinical and X-ray examinations monthly. The comfort feeling of the patients recovers quite early in most cases. Neurological symptoms of the patients with incomplete spinal-cord or root lesions have been regressed generally. (The detailed analysis of the injured nerve system-regeneration in the spine injuries will be given in another publication.)

The removal of metal implants was performed generally one year after surgery in the past, following established bony union. Recently, routine metal removal is not performed only in special cases, since the metal left in, does not cause any functional disorder and the removal of the implants in the operated scarry tissues implies increased risk of complications [20].

Figure 1 shows the levels of ventral spondylodeses. Operations have been performed between the vertebrae C5–6 and C6–7 in the majority of cases. Besides the operations represented on the diagram, in further 12 cases one or two vertebral bodies had to be completely removed and replaced by bony block, thus fusion was made not between the adjacent vertebral bodies. Among the vertebral bodies C5 and C7 were injured most frequently, they had to be totally removed and replaced in 5 cases each. The same happened to the C4 body once, and to the C6 body twice. In one case we had no other choice but a double vertebral body replacement (C6 and C7), so fusion was done between C5–Th1.



FIG. 1. The levels of the ventral spondylodeses. Complete removal of the vertebral bodies in further 12 cases: C 4 in 1 case; C 5 in 5 cases; C 6 in 2 cases; C 7 in 5 cases (double removals of C 6–7) in 1 case)



FIG. 2. Distribution of ventral spondylodeses per years. Total number: 95



FIG. 3. Distribution of dorsal spondylodeses per years. Total number: 25

Figure 2 shows the distribution of operations per year. They have ben performed in our routine practice since 1978; their number has constantly been growing in the recent years, in contrast to the dorsal spondylodeses, which have been diminished to the minimum (the latter see in Fig. 3).

The age of patients operated on ranged from 14 to 72 years, the majority being in the 3rd-5th decades. Average age: 38 years, the male-female ratio: 58-37.

Injuries, treated with ventrofixation, were caused most frequently by car accidents, diving into shallow water and falling from heights.

Complications. After surgery transient unilateral paresis of the recurrent nerve was seen in 12 cases, that ceased after several days or weeks. There were no carotid or vertebral injuries as well as injuries to the trachea. In one case the oesophagus wall was perforated by the shifted bone block and screws. The thin pharyngeal wall opened during the high cervical exposure (C2-3) in two cases. They were treated with suturing without fistulous or inflammatory consequences. Intraoperative lesion of nerve structures (spinal cord, roots) did not occur. In three cases the shift of the bone block, dislocation of the screw and plate with or without partial redislocation of the vertebra was observed. Two of them were caused by unsatisfactorily stable desis made in the first period, in the third case the screws disengaged in the fractured vertebral body. In these cases removal, repeated reduction and external fixation (Plaster collar, cervical support, halo) were performed. Septic complication occurred also in 3 cases, one of them was the suppuration of soft tissues, and two of them were inflammatory processes involving bony substance as well. Their treatment consisted of reoperation, cleaning and removal, specific antibiotic treatment and local irrigation-suction drainage. There were no intraoperative or late fatal cases caused by surgery in our material; 8 out of the patients operated on died because of severe spinal cord injury and its consequences (thrombophlebitis, pulmonary embolism, inflammatory pulmonary complications, bleeding from gastric ulcer, etc.). Because of the very bad general condition caused by spinal cord lesion, 17 patients could not be operated on although their spine injury required ventrofixation.

Characteristic cases of ventrofixation are illustrated in Figs 4, 5, 6 and 7.



FIG. 4. Ventrofixation with removal of the injured disc and stabilization by means of H-plate. Dislocation between C5–6, fracture-dislocation of the left articular process with the symptoms of partial lesion of the left C6 root. Complete reduction by Crutchfieldtraction with subsequent ventrofixation removing the injured disc and inserting the corticocancellous bone block, stabilization with H-plate and screws

Discussion, Conclusions

On the basis of our clinical experience and the results of our statistical evaluation, also confirmed by literature, we can sum up the advantages of ventrofixation as follows:

Out of all surgical methods (excluding combined fusions) it ensures the most reliable stabilization of the cervical spine [3, 33, 37], it can be applied for all kinds of vertebral body injuries from C2 to Th2, it is also suitable for the treatment of disc injuries [20, 23], it ensures the very important ventral decompression of the spinal canal [2, 16, 34], it allows bilateral root decompression, it makes unnecessary the external fixation in general, it provides conditions of early mobilization and rehabilitation giving good body union, it does not hinder subsequent cervical motor functions, it restores quickly the patients' comfort, providing the best conditions for the regeneration of nervous elements during rehabilitation treatment. Considering all these advantages it is easy to understand why this technique could become the basic method in the surgical treatment of cervical spine injuries while dorsal spondylodeses have become less popular. In our material, e.g., ventrofixations give 70% of all operations in the treatment of cervical spine injuries.



FIG. 5. Ventrofixation with partial removal of two vertebral bodies and double H-plate stabilization. Compression fracture of C4–5, subluxation, disc injury with significant kyphotic formation of the spinal canal, defect of filling in the myelogram, symptoms of partial but severe spinal-cord lesion. After Crutchfield-reduction ventrofixation: removal of the destroyed parts of both vertebral bodies and implantation of a large corticocancellous bone-block, fixation with double H-plate and screws. Bony union in the good reduction-state, effective rehabilitation with the regression of the neurological lesion 4 months after operative treatment

Of course, besides the advantages, there are some disadvantages as well as in all other methods. Reduction can be made either only partially, or with difficulties or not at all during the operation, the method is not suitable for a wide exposure of the spinal canal, not good for exploration, posterior treatment, or the proper treatment of dura-lacerations, it cannot be performed in tracheotomized patients and can potentially cause the complications mentioned above. Nevertheless, these are outweighed by the advantages.

Other surgical techniques (dorsal spondylodesis, laminectomy, duraplasty, lateral exposure, screwing of the odontoid process, combined deses, etc.: 20) or different conservative methods are naturally maintained for the less frequent injuries required other kinds of treatment. Good results essentially depend on surgery made only upon appropriate indications, individually con-



FIG. 6. Treatment of 'hangman's fracture' with ventral spondylodesis. Anterior luxation of the axis, double fractures of the arch with significant dislocation, injury to the disc between C2–3 without neurological lesion. Reduction with Crutchfield-extension, removal of the injured disc from a high anterior approach, implantation of a corticocancellous bony block and ventral desis with H-plate and screws. The fractures of the arch generally do not require surgery unless they cause spinal space occupation or neurological signs. Bony union 3 months after operation sidering the potential contraindications arising from the type of local trauma or general condition of the patient.

Concerning operative complications we should stress that in the majority of cases they can be prevented by thorough professionalism knowledge. In our cases the complications could be well treated,, they were not fatal and did not cause deterioration of the neurological state. Being aware of these facts, we recommend to consider some special circumstances or factors as relative contraindications or even indications (e.g.: not to perform this operation in professional singers, to perform it preferably in epileptic patients, etc.).



FIG. 7. Combined dorsal and ventral spondylodesis. Fracture-dislocation between C6-7 with the signs of partial lesion of the spinal cord (central spinal-cord syndrome). Reduction could not been achieved even by means of traction up to 25 kg with Crutchfield-extension. The first operation was done from posterior approach, open reposition of the articular processes and fixation with wire. The second operation was performed by anterior approach, ventrofixation in the reduced but instable position: removal of the injured disc, implantation of a corticocancellous bony block and stable desis with H-plate and screws

The time of surgery is a very important factor. In acute trauma after reduction by conservative methods it is advisable to perform the stabilizing operation as soon as possible, before the deterioration of the patient's general condition. If the reduction cannot be made by conservative methods—either in cases of acute or inveterated injuries—we should not rash in performing ventral desis ! In these cases it is recommended first to make surgical reduction from a posterior approach, to maintain temporarily the reduced position by posterior desis with a wire loop or plates, and in the second step to assure the final stabilization by ventrofixation (combined dorsal and ventral desis; Fig. 7) [10, 20, 12].

In many cases we have to treat inveterated cervical spine injuries which have not been treated at all or have been treated with poor result i.e., progressive neurological symptoms or unstable cervical spine. Also in these cases ventrofixation is unfit for monotherapy, we had better to use the combined variation mentioned above. However, in these difficult cases we should especially take into consideration the possibilities of the combined surgical treatment with halo [6, 11, 21] as the modern conservative method giving the best stabilization.

Finally, on evaluating ventral spondylodeses, we have to mention also some organizational and economic factors. Regarding circumstances in our country this surgery should be performed only in *centres* of spinal surgery, since adequate technical and professional conditions can be ensured only there. All the conditions necessary to the treatment of acute and chronic trauma-cases should be fulfilled in these centres, and also quite important economic aspects make it imperative that the management of non-traumatic spinal pathologies (cervical spondyloses, herniated discs, tumors, etc.) should also be concentrated here (Fig. 8). The theoretical conditions of the further development of ventral spondylodeses, education, postgraduate courses and research work also depend



FIG. 8. Distribution of the cervical herniated discs treated from ventral approach. Total number: 37. This is about 40% related to the number of traumatic ventrofixations. However, in the last years their number came close to the frequency of traumatic ventrofixations and in the future we have to consider this tendency in the surgical material of the spinal surgical centres

on the existence of these centres. Although the first Hungarian thesis on ventral spondylodeses [28] has already been published, we still have a lot to do in this respect as well for advancing toward the international first line of spinal surgery.

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Ventrale Spondylodese: Basismethode in der Therapie der zervikalen Wirbelsäulenverletzungen

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Die ventrale Spondylodese, oder Ventrofixation ist die wichtigste und erfolgreichste chirurgische Methode zur Versorgung der mit Instabilität einhergehenden schweren zervikalen Wirbelsäulenverletzungen. In ihr breites Indikationsgebiet gehören die Luxationsfrakturen, die Kompressionsfrakturen, die Bandscheibenschädigungen, Luxationen, die sog. «Tränenfrakturen sowie die Hangman' fracture-Fälle. Technik: In vorangehend reponierter Lage Entfernung der verletzten Wirbelabschnitte und der geschädigten Knorpelscheibe (oder Knorpelscheiben) aus ventraler, zervikaler Freilegung, ihr Ersatz mit autologen kortikospongiösen Knochenblöcken, Fixation mit Plattenschrauben. In der Arbeit findet sich die ausführliche Bearbeitung und Bewertung der im Laufe von 10 Jahren durchgeführten nahezu 100 derartiger Eingriffe. Die Kriterien der erfolgreichen Operation sind: Entsprechende technsche Bedingungen, Fachkenntnisse, über genügende Erfahrungen verfügende chirurgische Zentren.

Вентральный спондилодез: базисный метод в лечении травм шейного отдела позвоночника

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Вентральный спондилодез, или вентрофиксация — лучший метод хирургического лечения тяжелых травм шейного отдела позвоночника, сопровождающихся нарушением стабильности. Этот метод дает лучшие результаты. Широкая область показаний к его применению включает в себя переломы с вывихом, компрессионные переломы, повреждения и вывих диска, т. н. «слезнокапельные переломы» и hangman's fracture. Суть техники метода: удаление травмированных частей тела позвонка и хрящевого диска из вентрального шейного доступа, в предварительно вправленном положении, замещение аутологичными кортико-спондиозными костными блоками и пластиночно-винтовая фиксация. Авторы за 10-летий период произвели в своей больнице около 100 таких операций, результаты обработки полученных данных и их оценка приводятся в настоящем сообщении. Хорошие результаты от описываемого метода можно ожидать только при наличии соответствующих технических и профессиональных условий, при проведении операция в имеющих соответствующий опыт работы центрах.

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Intensive Treatment and Prognosis of Patients with Sepsis of Gynaecological Origin

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The treatment of 16 patients with severe sepsis of gynaecological origin admitted to the Institute of Anaesthesiology and Intensive Therapy of Albert Szent-Györgyi Medical University, Szeged between 1980 and 1985 is reported.

According to the scoring system described by Elebute and Stoner, [2] based on the clinical and laboratory findings typical of the septic state, efforts have been made to assess the severity of sepsis and to give prognostic sings for the chances of survival. The species and incidence of pathogenic agents isolated from different discharges of the patients are also reported.

As a result of the complex intensive care only 3 died of the 16 female patients with severe sepsis.

The management of septic patients and the establishment of prognosis represent a serious problem all over the world. There is no universally accepted method for the unequivocal assessment of grading the severity of the disease or its progress and prognosis. Several attempts have been made to solve this problem [1, 2].

Elebute and Stoner [2] devised their scoring system on the basis of the clinical picture and laboratory diagnosis in which the deviation from the normal was represented by a higher score in each grade.

We applied the scoring system developed by the latter authors to a selective retrospective group of patients. Our aim was to assess the severity and outcome of sepsis in our group of patients and to test the validity of the abovementioned method.

We draw attention to pelvic abscess and peritonitis which play a decisive role in the outcome of the septic state and they are thus presented by weighting of the scores.

Of the 15 patients with sepsis of different origin (thoraco-abdominal) treated by Elebute and Stoner [2], 5 died of whom 4 had more than 20 scores while only one of the 10 survivors had scores above 20.

Schaffer and Széll [3] published their results in 104 septic patients using Elebute and Stoner's sepsis grading. Fourty-seven patients died (45.1%). In only 5 patients was the sepsis gynaecological in origin. Therefore, their results are not comparable with our data on 16 septic patients where the sepsis in all cases was of gynaecological origin.

Patients and Methods

The grading system mentioned above has been applied by us to patients with septic diseases of gynaecological origin (Table I). From 1980 to 1985, 16 patients with septic diseases arising from the pelvis were treated at the Institute of Anaesthesiology and Intensive Therapy of Albert Szent-Györgyi Medical University Szeged,. The youngest of them was 16, the oldest patient was 71 years old. Nine of the cases were associated with pregnancy or delivery. In order to remove the evident septic focus each of them had to be operated on, 13 of them were subjected to reoperation and in 3 cases multiple reoperations became necessary. Of the 16 female patients only 3 died (Table II).

TABLE I

Patients treated for pelvic sepsis

N of cases	Age (yr) (range)	Pregnancy de- livery (n)	Complications (n)	Operation (n)	Reoperation and drainage (n)	$\begin{array}{c} \text{Multiple} \\ \text{reoperation} \\ (n) \end{array}$
16 (100%)	35 (16-71)	9 (56%)	7 (44%)	16 (100%)	13 (81%)	3 (19%)

		Т	ABLE II	
Patients	treated	for	pelvic sepsis	(1980-1985)

Patient No.	Age (yr)	Operation	Source of sepsis	Reoperation	Outcome
1.	50	Uterus exstirpation	Sigmoid injury	Suture of large intestine and drainage	survived
2.	16	Delivery	Atonic bleeding	Uterus exstirpation	survived
3.	54	Appendectomy and drainage	Tubo-ovarial abscess	_	survived
4.	47	Uterus exstirpation	Haematoma	Evacuation and drainage	survived
5.	71	Uterus exstirpation	Generalized purulent peritonitis	Drainage	survived
6.	32	Caesarean section	Haematoma	Evacuation and drainage	survived
7.	41	Uterus exstirpation	Tubo-ovarial abscess	Adhesiolysis and drainage for mechan- ical bowel obstruc- tion	survived
8.	20	Appendectomy. Me- chanical bowel ob- struction. Small in- testine resection Ileostomy	Small bowel necrosis	_	survived
9.	35	Removal of Intra- uterine Device (IUD)	Uterus perforation with IUD	Small bowel resection for mechanical bo- wel obstruction Adhesialysis and	survived

drainage

Table II (continued)

Patient No.	Age (yr)	Operation	Source of sepsis	Reoperation	Outcome
10.	31	Caesarean section	Periappendicular infiltration	Adhesiolysis for me- chanical bowel ob- struction and drain- age	survived
11.	29	Caesarean section	Intraperitoneal abscess	Adhesiolysis for me- chanical bowel obstruction	survived
12.	29	Appendectomy	Gangrenous appendicitis	Relaparotomy for Douglas abscess	survived
13.	21	Spontaneous delivery	Purulent endometritis	Relaparotomy, hysterectomy	survived
14.	32	Curettage	Uterus perforation, peritonitis	_	died
15.	34	Shirodkar operation (20 weeks pregnancy)	Purulent endometritis	 Spontaneous abor- tion completed by instrumental labour Total abdominal hysterectomy, haemorrhage Bilateral adnexec- tomy, haematostasis 	died
16.	22	Interruption of pregnancy	Arteficial uterus perforation	 Reabrasion Hysterectomy and left adnexectomy 	died

TABLE III

Patient		Septic co	omplications		Georg	Days in
No.	Circulatory	Kidney	Liver	Lung	- Score	hospital
1.	+	+	+	+	2 0	3
2.	+	+	+		19	8
3.				+	13	3
4.	+	+		+	16	5
5.	+	+		+	19	5
6.					15	6
7.			+	+	18	22
8.	+	+	+	+	26	18
9.			+		13	8
10.					13	3
11.			+		18	4
12.		+			21	9
13.		+	+	+	23	20
n (%)	5 (53.8)	7 (53.8)	7 (53.8)	7 (53.8)	$18 \pm 4*$	$8.8 \pm 6.7*$

Surviving septic patients (n = 13)

Results

The distribution of the septic complications in the surviving patients according to organ lesions is shown in Table III. Circulatory disturbance occurred in 5 cases, kidney-lung-liver lesions were found each in 7 cases. In accordance with the scoring system, the scores of each patient are represented on a striking spot in the table. The lowest score for survival was 13, the highest 26. In our group the scores of 3 patients rose above 20. The mean score was 18. The average number of days spent in the intensive care unit was 9.

Each of our 3 non-surviving patients had circulatory failure, kidneyliver-lung lesion as well as DIC proved by haemostasis examination. Their scores were high, exceeded 30 in every case (Table IV).

Patient No. 1. 2. 3.		Ser	9	TT			
	Circulatory	Kidney	Liver	Lung	DIC	- Score	Hospital days
1.	+	+	+	+	+	32	7
2.	+	+	+	+	+	34	2
3.	+	+	+	+	+	37	2
						$34.3 \pm 2.5*$	$3.7 \pm 2.9*$

TABLE IV

Non-surviving septic patients (n = 3)

$\mathbf{\bar{x}} \pm \mathrm{SD}$

TABLE V

Patient No.	Respirator	Antibiotic	Inotropic drug	Steroid	Immune globulir
1.	+	+	+	+	+
2.		+	+	+	
3.					
4.	+	+	+	+	+
5.	+	+	+	+	
6.		+			+
7.	+	+			+
8.	+	+	+	+	+
9.		+			
10.		+			+
11.		+			
12.		+		+	
13.	+	+	+	+	+
14.	+	+	+	+-	+
15.	+	+	+	+	+
16.	+	+	+	+	+
n (%)	9 (56.3)	16 (100)	9 (56.3)	10 (62.5)	10 (62.5)

Main treatment strategies (n = 16)

Table V shows the applied basic therapy. Respirator treatment became necessary in 9 cases and, of course, antibiotics were administered to each patient according to the bacteriological findings.

Positive inotropic agents were used on 9 occassions, high dose of methylprednisolone was needed in 10 cases and gamma globulin was also adminstered in 10 cases.

Samples taken from the patients' discharge were sent for bacteriological analysis every day (Table VI). Pathogenic agents could be isolated from blood

TABLE VI Bacteriological results*

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Positive	n	%	
Haemoculture	6	(37.5)	
Drain-fluid and wound discharge	16	(100.0)	
Throat- and tracheal secretion	12	(75.0)	
Urine	8	(50.0)	

*No of patients: 16

TABLE VII

Frequency of aerobic pathogens

Haemoculture	$E.\ coli$	8	(50.0%)
	Micrococcus	6	(37.5%)
	Staphylococcus alb.	4	(25.0%)
	Enterobacter aerogenes	3	(18.7%)
Wound discharge	E. coli	11	(68.7%)
	Proteus mirabilis	10	(62,5%)
	Micrococcus	8	(50.0%)
	A cine to bacter	8	(50.0%)
	Streptococcus haem.	7	(43.8%)
	Pseudomonas	6	(37.5%)
	Blastomycetes	4	(25.0%)
Fracheal secretion	$E.\ coli$	10	(62,5%)
	Pseudomonas	8	(50.0%)
	A cine to bacter	8	(50.0%)
	Streptococcus faecalis	7	(43.8%)
	Staphylococcus aureus	6	(37,5%)
Urine	Proteus	8	(50.0%)
	Streptococcus faecalis	7	(43.8%)
	E. coli	6	(37.5%)
	K leb siell a	6	(37.5%)

in 37.5% of the cases, whereas the drain and the wound discharge contained pathogens in every case. From pharyngotracheal discharge microorganisms could be identified in 75% of the patients, from urine in 50%. As for the incidence of aerobic pathogens it can be stated that (Table VII) the most frequently detected bacteria from haemoculture, wound discharge, tracheal secretion and urine were in the order of frequency E.coli, Proteus mirabilis, Pseudomonas and the Klebsiella pneumoniae. Most of the pathogens were found to be Gram-negative intestinal bacteria.

The antibiotics used in our study group were as follows: cefalosporins, aminoglycosides and metronidazole, or their combinations.

Discussion

It is the merit of Elebute and Stoner that they tried to make measurable such a complex process as sepsis in which a lot of factors are involved affecting one another. We are aware of the fact that sepsis as a severe state cannot be described by numbers, using the language of mathematics, yet, as a summary of our examinations we can state that the scoring system by Elebute and Stoner could well be applied also to our patients with sepsis of gynaecological origin and by using this scoring we were able to make a prognosis that help to predict the outcome of the disease. Presumably, the age factor cannot be neglected either, though no data have been found concerning this, nor such a correlation has been sought in our study group.

In our opinion the tablet can be improved or modified by weighting the scoring. We consider it the deficiency of the score that parameters as important as those referring to the circulation or respiration (RR, P, CVP, respiratory rate, values of blood gas, etc.) are missing. By the daily analysis and scoring of the clinical and laboratory findings of sepsis we can establish a more exact prognosis of the course of the disease. The simple scoring system, which should be readily available at general hospital level, proved to be useful but in agreement with other authors, the examinations should be extended to a larger number of patients and, as a result of further improvement, other septic states, such as burn or trauma, could also be involved.

It is important to emphasize that in our study group the mortality was only 19%, which is much more favourable than that in other septic cases of abdominal origin with complications. This suggets that a septic focus in the pelvis can be more easily eliminated and located than some surgical complication or an abdominal process causing diffuse peritonitis.

In conclusion, it is worth drawing attention to the ethical point of view saying that it cannot be allowed to lose hope in treating patients even with permanently high scores.

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Intensive Behandlung und Prognose von, an gynäkologisch bedingter Sepsis leidenden Patientinnen

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Berichtet wird über 16, an schwerer, gynäkologisch bedingter Sepsis leidenden Patientinnen, die zwischen 1980 und 1985 im Anästhesiologischen und Intensivtherapeutischen Institut der Medizinischen Universität Szeged, unter Behandlung standen. Mit Hilfe eines, anhand der charakteristischen klinischen und Laborbefunden zusammengestellten Punktsystems werden Versuche zur Beurteilung der Schwere der Sepsis und der Prognostierung des wahrscheinlichen Überlebens unternommen. Erläutert werden die Typen und die Häufigkeit des Vorkommens der aus den verschiedenen Körperextrakten der Patientinnen gezüchteten Krankheitserreger.

Als Ergebnis der komplexen Intensivtherapie starben insgesamt 3 der an schwerer Sepsis leidenden Patientinnen.

Интенсивное лечение и прогноз при септических заболеваниях гинекологического происхождения

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Авторы знакомят с лечением 16 тяжелых больных с сепсисом гинекологического происхождения в Отделении анестезиологии и интенсивной терапии Сегедского медицинского университета в период между 1980—1985 гг. На основании характерных для септического состояния результатов клинического обследования и лабораторного анализа разработана система баллов (*Elebute и Stone, Br. J. Surg.* 70: 29, 1983), в соответствии с которой авторы делают попытку оценивать тяжесть сепсиса и прогнозировать вероятность выживания. Знакомят с видами патогенных возбудителей, высеянных из различных жидкостей тела больных, с частотой их встречаемости. В результате комплексной интенсивной терапии из 16 тяжелых больных с сепсисом они потеряли в общей сложности трех пациенток.



Change of Tissue Temparature of the Uterine Cervix during Double Freezing

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The tissue temperature of the uterine cervix was measured at a distance of 5 mm from the cryoprobe by using the double-phase freezing technique. It was established that by this method a deeper cold effect and tissue necrosis can be achieved than by one-phase freezing. In view of the linear extension and the extension in depth of CIN, as well as of its fairly frequent localization in the transformational zone, the method is mainly suitable for curing minor CIN lesions of young patients.

 \mathbf{F} rom the point of view of cryotherapy it is of prime importance, how deep cryonecrosis occurs and whether the pathological change has been destroyed including also the process at the bottom of the cervical crypts.

It is known from the literature that rapid freezing and slow thawing influence the cell the most destructively [8]. However, in addition to this, maximal freezing temperature, is also important [8]. All live tissues, if cooled to or below -20 °C, are subjected to cryonecrosis at least for 1 min [3, 4, 15]. It was shown by Stone et al. that the range between -10 and -40 °C can be the critical, lethal range for cells. Being cooled down below this range, their survival may increase. According to Stone et al. [15], the freezing-thawing-freezing cycle reduces the survival for cancer cells more than that of benign cells.

In the present study it was investigated how at a distance of 5 mm from the edge of the cryoprobe, tissue temperature changes during the double-phase freezing technique.

Material and Method

To benign changes of the uterine cervix the freezing-thawing-freezing method was applied in eight patients in a way that the 2 mm ice-ring around the probe was kept on being frozen for additional 5 min in both freezing phases. The thawing period lasted for 5 min. Prior to the intervention, cervical mucus was carefully removed. A thin layer of water-soluble pointment improving heat contact was applied to the surface of the probe and freezing was started only after insertion of the probe. The adequately high pressure of the gas bolloon



FIG. 1. Size of the cryoprobe

(3,7-4,2 MPa) ensured the appositely low temperature of the surface of the cryoprobe, which is one of the most important requirements of the effective freezing procedure. Simultaneously with applying the cryoprobe, a thermocouple made of copper and constantan was introduced at 5 mm from its edge into the tissue of the portio and tissue temperature was registered by a line-recorder. The same cryoprobe was applied in all cases with a tip protruding into the cervical canal (Fig. 1). Before freezing, the gas bolloon was kept at a room temperature of +20-+25 °C for a long time.

Results and Discussion

The results are summarized in Table I. The first figure of column 't'means the time elapsed up to the development of the ice-ring of 2 mm, followed by the freezing time of 300 s. By the thickness of the ice zone are meant the values measured from the edge of the cryoprobe.

No	1	1st freezing phase		2r	nd freezing phase	
No.	t (s)	thickness of ice zone (mm)	tissue temperature (°C)	t (s)	thickness of ice zone (mm)	tissue temperature 9 (°C)
1.	90 + 300	$8\mathrm{mm}$	-18	20+300	9	-20
2.	120 + 300	7	-11	25 + 300	8	-15
3.	45 + 300	10	-19	20 + 300	10	-20
4.	84 + 300	8	-20	18 + 300	12	-20
5.	90 + 300	8	-10	30 + 300	8	-12
6.	120 + 300	7	— 6/0	20 + 300	9	-18
7.	20 + 300	8	-20	10 + 300	10	-20
8.	60 + 300	6	-15	25 + 300	9	-15
Mean	\pm S.D.	7.75 ± 1.16			9.37 ± 1.30	

TABLE I

Change of cervical tissue temperature during double-phase freezing

It can be stated that on average 78.75 ± 35.1 a have elapsed in the first freezing period up to the appearance of the 2 mm ice-zone, while only 21 ± 5.92 s in the second one.

The thickness of the ice-ring encircling the margin of the probe was 7.75 ± 1.16 mm in the first and 9.37 ± 1.30 mm in the second phase of freezing.

In the first phase of freezing, temperature did not sink below -10 °C at 5 mm from the edge of the probe in the servical tissue, while it showed -20 °C in four cases. In patient No. 6, after changing the position of the thermocouple, a tissue temperature of -6 °C, instead of one of 0 °C was measured, which indicates a difference in the local blood supply, and it is plausible that the value of 0 °C meant the proximity of a larger blood vessel.

The results have revealed that by using the double freezing technique, a deeper cryonecrosis can be achieved, so this kind of treatment yields better results. This is supported by several data on the double phase cryotherapy of CIN [13, 14].

The pre-invasive lesions of the uterine cervix have their site in the transformational zone in the majority of cases [1, 5, 6, 9, 11]. Only about 9.7% of them are localized endocervically and 3.1% of them ectocervically [1]. In the material of Johnson et al. [6] only 2% of them appeared ectocervically. Richart states that CIN develops rarely also multifocally but only within the transformational zone [12]. The average linear extension of the CIN III change ranges between 9.02 + 4.37 mm and 6 and 11 mm increasing with advancing age [10, 11]. The average depth of crypts affected by CIN varies according to some authors, it ranges between 0.73 and 1.6 mm. In their material, Reagan and Hicks give a value in in situ carcinoma of 1.6 mm [10]. Reagan and Patten [11] established in severe dysplasia a value of 0.73 mm, while Anderson and Hartley one of 1.24 mm in the case of CIN III [2]. In the investigations of Abdul-Karim et al. [1], this value is 1.35 in CIN III. In a CIN lesion of a more advanced stage a greater than the average depth can be found in the crypts to be affected by the process. Taking the greatest average depth of the crypts affected by the CIN process for a basis, i.e. a value of 1.6 mm, it appears that the process does not exceed a depth of 3.6 mm at least in 95% of the patients (mean \pm 2 S. D.). Considering also the linear extension, i.e. a 4 mm deep cryolesion along a segment of 15 mm, which corresponds in its localization to the transformational zone, may be sufficient from the point of view of the cryotherapy of the CIN. This cryolesion can be produced under adequate freezing conditions in young patients where the process is more superficial and is localized in a smaller linear extension [10, 11].

Figure 2 shows the change of tissue temperature in the immediate proximity of the surface of the probe in function of time (Erbokryo–Amoils 40/ freezing equipment, N_2O gas). In the initial phase of freezing a rapid reduction in temperature can be noted. Later it slows down and the curve approaches the



FIG. 2. Change of tissue temperature in the immediate proximity of the surface of the probe during the thawing-freezing cycle

horizontal line. Here 80 s have elapsed up to the formation of the 2 mm ice-ring. In the subsequent five minutes tissue temperature decreased, but this value was maintained over a prolonged period of time. Following this it hardly changed. This indicates that the heat balance between the substance of heat uptake and the one of heat loss has already almost completely developed and by a further increase in freezing time, a further reduction in temperature can hardly be achieved, i.e. the extension of the ice-zone has achieved its approximately maximal size. Thus, with this prolonged freezing time, the almost maximal possible extension of cryolesion is achieved, which practically means that after development of the 2 mm ice-ring, freezing is performed for additional five minutes. After the cessetion of freezing, the initial stage of tempeature reduction is the result of mechanical defrosting which lasts for 60 s and terminates by the stopping of the adherence of the probe to the tissue. This is revealed by the rapidly thawing ice layer from the surface of the probe. In the subsequent 4 mm, the warming of the tissue in the immediate proximity of the probe is due to the amount of heat conducted by the blood, the tissue temperature gradually increases achieving +27 °C by the end of the fourth minute.

Based on topometric studies on the localization of CIN and its extension in depth and linearly [1, 2, 9, 10, 11], it can be stated that a cryonecrosis of a depth of 4 mm produced in more than 95% of the cases along a 15 mm segment, corresponding to the axis of the cervical canal proximally to the most caudal point of the portio, destroys the tissues to a sufficient extent from the point of view of curing CIN. This statement presupposes that cases where the boundaries of the transformational zone and the pathological change are not differentiable to their full extent, or they involve the endocervical canal, should be treated as unfit for cryotherapy, similarly to those where the histological study had revealed a positive endocervical currettage. A further condition is that there should not be fissures on the cervix, in which the pathological epithelium concealed at the bottom is not sufficiently exposed to the cold effect as well as there should not be Nabothian follicles which can deeply penetrate even the stroma and can, although rarely be involved in CIN. A necessary condition is that the surface of the cryoprobe should evenly and directly contact the surface of the tissue to be treated, and the heat contact should be suitable and the surface of the probe should completely cover the cervical region under treatment. It is not enough if the complete region to be treated falls only into the forming ice-zone. Important points are an equipment of an adequate freezing performance, the adequate gas pressure and other technical conditions. It is useful in the justitution providing the cryotherapy of CIN to measure for establishing the technical performance of the freezing equipment, the tissue temperature produced during cryotherapy at an adequate distance from the surface of the probe.

Considering that in young multiparae, in CIN lesions of lower degrees, only minor changes of an extension both in depth and linearly, should be reckoned with [1, 2, 9, 10, 11], really promising results can be achieved by the cryotherapy of the CIN I-II lesions by coincidence of the appropriate selection of the patients, an accurate diagnosis and the criteria of a reliable follow-up.

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Gestaltung der Gewebetemperatur der Zervix im Laufe der Anwendung der zweiphasigen Kryotechnik

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Im Laufe der Anwendung der zweiphasigen Kryotechnik wurde die Gewebetemperatur der Zervix 5 mm vom Rand der Kryosonde entfernt gemessen. Die Erfahrungen zeigten, daß mit dieser Methode tiefere Kältewirkung und Gewebenekrose erreicht werden kann als mit der einphasigen Kryotechnik und angesichts der linearen und Tiefeausbreitung der CIN und ihrer häufigen Lokalisation in der Transformationszone eignet sich das Verfahren zur Heilung der CIN-Läsionen niedrigeren Grades junger Patientinnen.

Vom Standpunkt der Kryobehandlung der präinvasiven Läsionen der Zervix aus ist es von grundlegender Bedeutung bis zu welcher Tiefe die Kryonekrose zustandekommt und ob die pathologische Veränderung in ihrer ganzen Ausbreitung — auch die sich tief in den zervikalen Krypten abspielenden Prozesse inbegriffen — zerstört wird.

Динамика температуры тканей шейки матки в ходе применения техники двойного замораживания

Ш. МАТАНИ

В ходе применения техники двойного замораживания автор измерял температуру тканей шейки матки, на расстоянии 5 мм от края замораживающего зонда. Он установил, что с помощью этого метода достигается более глубокое действие холода и отмирание ткани, чем при однофазном замораживании, и, принимая во внимание линейное и глубинное распвостранение CIN, а также довольно частую локализацию в зоне трансформации, он считатет, что метод годен для применения, главным образом, для лечения более низкой степени поражений CIN у молодых женщин.

С точки зрения криотерапии преинвазивного поражения шейки матки очень важно знать, до какой глубины доходит крионекроз и целиком ли уничтожено патологическое изменение, понимая под этим также глубоко находящийся процесс цервикальных крипт.

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Cryotherapy during Pregnancy

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Bening cervical alterations causing complaints in 44 pregnant women were cured by cryosurgery in all three trimesters of their pregnancy. Recovery resulted in 41 cases after a single and in three extensive chondylomatous changes, after two treatments. The painless out-patient treatment did not influence pregnancy and the course of delivery. Cryosurgery has advantages over traditional surgical interventions, or using chemical caustic agents and it can be applied throughout pregnancy.

During pregnancy cervical polyps causing and maintaining cervicitis and associated with bleeding may interrupt pregnancy due to the consequential cervicitis and amnionitis [3]. Their removal is an indicated and necessary intervention.

In clinical practice silver nitrate treatment or painting with chemical caustic or other agents (Vagothyl, Albothyl) is extensively applied, often ineffectively. Frequent bleedings persist even after several treatments, there is a copious vaginal discharge and even pregnancy may terminate. Occasionally, they can be removed by surgery which requires institutional care.

In our study it was examined how successfully cryosurgery can be performed during pregnancy in treating benign cervical alterations.

Material and Method

In the period between 1982 and 1987, a total of 44 pregnant women received cryotherapy at the out-patient unit of the 2nd Department of Obstetrics and Gynaecology, Semmelweis University Medical School for vaginal discharge, frequent bleeding, occasionally for a cervical change causing hypogastric pain. Treatment was performed in all three trimesters of their pregnancy, in one part of the cases following some other kinds of unsuccessful conservative treatment (Table I).

The conditions of treatment included a negative cytological finding, the preliminary elimination of vaginitis, documentation by ultrasonography of a live foetus and exclusion of any forms of abortion.

		1	Symptom	s	Unsuccessful		Cryotherapy		
Indication	No	hypogas- tric pain	dis- charge	bleeding	conservative therapy	once	twice	unsuccessful	
Cervical polyp	7		6	5	1	7		-	
Decidual polyp	23	1	19	22	5	23	_	_	
Papilloma of the portio	1			_	_	1		_	
Condyloma acuminatum	12	2	12	1		9	3		
Ectropion with a bleed- ing tendency	1	1	1	1	1	1	_	_	
Total	44					41	3	—	

 TABLE I

 Cryotherapy of benign cervical changes during pregnancy Clinical data

The age of patients ranged between 21 and 36 years, with a mean age of 28.2–3.2 (S. D.). Among the treated patients there were 4 primiparae, 17 nulliparae having earlier been pregnant and 23 pregnant multiparae. The average number of abortions was 1.2 ± 1.06 (S. D.), the average number of deliveries was 0.45 ± 0.46 (S. D.).

Deep freezing was performed by using the Erbokryo–Amolis 12/a equipment (Spembly Co.) which freezes on the basis of the Joule–Thomson effect by utilizing N₂O gas. During treatment the working pressure of the gas remained in the effective range. The surface temperature of the probe moved between -60and -65 °C. Four-six weeks after the intervention, cohabitation had to be abstained from. The effectiveness of treatment was checked by a control examination four-six weeks subsequently. Recovery was considered in cases with no evidence of changes treated by cryotherapy and the pregnant woman being also free of complaints.

In the first phase of treatment, the base of the peduncle of the polyp, i.e. the mass to be removed, was frozen for 3 min by a so-called 'cervical' probe and then removed together with it by utilizing the cold adhesive effect, or in the case of a tissue piece larger than a bean, it was unscrewed by corn-tongs after defrosting of the probe. In such cases bleeding was not observed, or only minimal bleeding occurred. In the second phase, after two minutes, the base of the removed tissue was repeatedly frozen for 3 min. The second phase of treatment, beside ensuring perfect haemostasis, resulted in a safe cryonecrosis of the still not removed region. The size of the ice-ring formed during treatment beyond the boundaries of the mass to be removed, reached but never exceeded, a depth of 2–3 mm in the intact tissue. Treatment ensured in all cases a material suitable for histological study.

The prerequisite of successful treatment is that prior to it, the superfluous mucus should be removed from the region to be frozen. Freezing is started only

after application of the probe, and the working pressure of the gas must not decrease during treatment. The time phases of double freezing have been shaped after several experiments with an attempt to make the intervention to last for the shortest time possible, however, with retaining its neccessary effectiveness. The first phase of the defrosting period was mechanical defrosting (for about 1 min), the adhesive cold effect disappeared at the end of this minute, then, due to the blood flow, spontaneous warming of tissue followed. If the frozen mass was removed together with the probe at the end of the first phase of freezing, no mechanical defrosting was performed.

The first cryosurgical interventions were made by close observation of pregnant women on an in-patient Unit in the Institute. Colposcopy was performed initially weekly then four-six weeks following treatment. In the case of three extensive chondylomatoses, two treatments were effective, the second one performed four weeks after the first one.

The course of pregnancy could be followed up in 29, while it could not in 15 cases.

Results and Discussion

In 30 of the pregnant women treated by cryosurgery, intervention was made for cervical polyp causing complaints. Histology revealed decidual polyp in 23 cases, while cervical polyp in 7 cases. The most frequent complaints were a copious vaginal discharge and bleeding. Hypogastric pain occurred only sporadically. In a part of the cases cryotherapy was preceded by ineffective conservative treatments (such as treatment with caustic silver nitrate, painting with Albothyl). A single treatment by freezing was effective in all cases.

In our material papilloma of the portio healed in one case and condyloma acuminatum in 12 cases after cryosurgery. In 3 of them, repeated cryosurgical treatment was required in extensive condylomatosis. Changes in other places than on the portio, were also treated, taking a good care that the base of the alteration be frozen in a deoth of 2–3 mm also in the intact tissue because, according to our experience, this was necessary to prevent recurrence. By pressing the probe to the condyloma during the three minutes of freezing, even the base is frozen in a depth of 2–3 mm and this is not accompanied by pain in the case of vaginal or vulvar changes. Even a prolonged treatment in the portio does not cause any pain.

The cryosurgery of condylomatous changes in the first trimester of pregnancy is of particular importance, since the administration of Podophyllin of a teratogenic effect is not indicated either during this period, nor throughout pregnancy. In the perinatal period the condylomatous change of the birth canal means an indication for caesarean section. By applying cryotheraphy operation can be avoided.

Indication	Term of pregnancy on treatment trimester			Ab	ortion	Premature	Mature	delivery	Ceasarean	Not kno
	I	п	III	artificial	spontaneous	denvery	spontaneous vaginal	vacuum extraction	- section	
Cervical polyp	6	1	_	1	-	_	3	-	1	
Decidual polyp	10	8	5		_	1	12	1	-	9
Papilloma of the portio	1		—			—	—	_		1
Condyloma acuminatum	5	3	4		1	1	6	_	1	3
Ectropion with bleeding ten- dency	1	-	-		_	_	1	-		-
Total	44				2	2		25		15

TABLE II Outcome of pregnancy after cryotherapy

TABLE III

Delivery data of patients receiving cryotherapy during pregnancy and those of controls

	No	Spontaneous vaginal delivery	Caesarean section	Vacuum extraction	Cervical rurupture	Cervical stenosis	Cervical insufficiency —	Duration of labour (hrs)			Apgar score
	N0.							6	6-12	12-18	(5 min)
Group with cryotherapy	27	25	2ª	1 ^b	1	_		19	7	1	9.51 ± 0.64
Control group	27	24	—3°	—	2	_	-	16	9	2	$9.48 {\pm} 0.70$

a —fetopelvic disproportion (1) postponed labour, primary uterine inertia (1)
 b —threatened intrauterine fetal asphyxia, umbilical cord anomaly (1)
 c —fetopelvic disproportion (2) threatened intrauterine fetal asphyxia (1)

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In one case a proliferating cervical ectropion with a bleeding tendency in the first trimester of pregnancy, healed after a single application of cryotherapy. Initially, it was treated several times by painting with Vagothyl. In general, cervical ectropion, if vaginitis is remedied, produces complaints only rarely during pregnancy, and it is unnecessary to treat. In individual cases when ectropion is subjected to cryotherapy for occasional bleeding and the persisting inflammation, a safe recovery can be anticipated.

In 15 out of the 44 pregnant women given cryotherapy, the course of pregnancy could not be followed up, 25 out of 29 pregnancies had term deliveries producing mature foetuses. There were two premature births on the 29th and 34th weeks (placenta previa + premature rupture of the amnion or preterm labour pains and tocolysis yielding no results). There was one induced abortion, one spontaneous abortion terminated on the 10th–11th gestational week accompanied by the symptoms of a febrile grippe. Cryotherapy had been performed six weeks previously (Table II).

Fourteen pregnant women out of the 29 followed up were multiparae. Comparing the course of pregnancy and labour prior to cryotherapy as well as the subsequent course of pregnancy and labour, in 9 of them no pathological conditions indicated a changed physiological function of the cervix.

The 27 cases terminating with labour were matched with the same number of controls of corresponding age, parity and fetal weight and there was no significant difference in the frequency of obstetric operation, of cervical rupture, in the duration of labour and in the 5 min Apgar scores. Nor did cervical stenosis or insufficiency occur in any of the groups (Table III).

Monaghan and Davis [8] studied the course of 33 pregnancies after cryotherapy applied for benign or preinvasive lesion of the neck of the uterus, while Laubstein and Petrie [4] did the same in 136 pregnancies. They did not find any disadvantage of cryotherapy, which did not find any disadvantage of cryotherapy, which they preferred to electrocautery and to the traditional surgical conization. Hemmingsson [2] analysed the course of pregnancy of 500 women administered crytotherapy for the CIN lesion of the neck of the uterus. He compared the deliveries of 115 women after cryotherapy with those of 69 women of the same group before it and he did not note any significant difference between the two groups in premature birth, caesarean section, premature rupture of the amnion, cervical insufficiency and stenosis, perinatal mortality and intrauterine death.

There are only fragmentary data on cryosurgical interventions performed during pregnancy.

Ong et al. [9] applied cryotherapy by using CO_2 in 50 patients for vulvar and vaginal 'warts'. Of them 9 were pregnant with no by effects at all. Bergman et al. [1] used cryosurgery for treating condyloma acuminatum in 34 pregnant women in the third trimester. No maternal, fetal or neonatal complications occurred either during treatment or subsequently. Cryotherapy precluded the neccessity of elective caesarean section in patients with extensive condylomatosis. Sommer et al. [10] applied successful crytherapy in 43 pregnant women between gestational weeks 12 and 32 for condyloma acuminatum and repeated freezing was required only in 14 cases. Von. J. Könnecke et al. [7] followed up the pregnancies of 26 women in whom cervical cryotherapy had been applied prior to, or during their pregnancies. The results were compared with those of traditional interventions on the portio. The benefits of cryosurgery are stressed by them. It was revealed by Leiman et al. [6] as well as by Lee [5] that conization by cryocautery is detrimental to pregnancy. The number of mid-term spontaneous abortions and of premature deliveries increases after surgical conization and this is related to the size of the conus. Producing cervical stenosis, the incidence rate of caesarean section also increases.

According to our experience, cryotherapy of the portio during pregnancy does not affect its course and labour, independent of the fact in which stage of the pregnancy treatment is administered. Healing is without scars, the elasticity of the tissues of the portio is retained. It is more advantageous than surgical resection after chlorethyl freezing or excision by electric knife.

During or after cryosurgery, no complications occurred. During treatment the pregnant women did not complain about pain, except for the slight dull feeling resembling a menstrual cramp arising in half a minute after starting the first phase of freezing, but this did not last longer than a minute in any of the cases. Since, due to the cold effect, the impulse conduction of the sensory nerve fibres stop very soon, moreover it is known that the innervation of the portio is very poor, it can be assumed that at the off-setting of the cold effect, the endogenous prostaglandins released in the cervical tissue are responsible for the phenomenon observed. During the second phase of freezing the patients did not report about a menstrual cramp-like sensation.

In one-third of the cases, 5 to 10 min after termination of the treatment, flushing of the face appeared with a slight sensation of warm which stopped spontaneously after some minutes. This was the same, harmless phenomenon, also well known during the cryosurgery of non-pregnant patients.

Following cryotherapy, in some cases a gradually decreasing amount of thin, watery or pinkish vaginal discharge was observed for 2-3 weeks which was connected with the cellular-type colliquation of cryonecrosed tissue.

During pregnancy, cryosurgery of the neck of the uterus is an intervention primarily indicated and required for treating cervical polyps and condyloma acuminatum. It is more advantageous in this field than any other hitherto known therapeutic intervention. Being used for an adequate time and appropriately, it is not associated with complications and makes also histological study possible. By its use the therapeutic arsenal is enriched.

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Kryochirurgie benigner Zervixveränderungen während der Schwangerschaft

S. MATÁNYI

Bei 44 schwangeren Frauen wurden die Beschwerden verursachenden gutartigen Zervixveränderungen in allen drei Trimestern der Gravidität mittels Kryobehandlung geheilt. Die Heilung traf in 41 Fällen nach einmaliger und in 3 Fällen mit ausgedehnten Kondylomveränderungen nach zweimaligen Behandlungen ein. Durch die schmerzlose ambulante Behandlung wurden die Austragung der Gravidität bzw. der Verlauf der Entbindung nicht beeinflußt. Die Kryochirurgie ist ein vorteilhafterer Eingriff als die chemische Kaustika oder die chirurgischen Verfahren und kann mit entsprechender Technik während der ganzen Schwangerschaftsdauer ein Anwendung finden.

Криохирургия доброкачественных изменений шейки матки во время беременности

М. МАТАНИ

Автор излечил с помощью криотерапии изменения шейки матки у 44 беременных, вызвавшие у них жалобы, применяя это лечение во все периоды (триместры) беременности. В 41 случае выздоровление наступило после однократного применения лечения, в трех случаях с распространенным кондиломным поражением лечение пришлось применять дважды. Безболезненное, амбулторное лечение не повлияло на вынашивание беременности и на протекание родов. Криохирургия имеет преимущества как метод вмешательства по сравнению с традиционным применением химических вяжущих средств, или по сравнению с хирургическим вмешательством. При соответствующем методе может применяться в течение всего перода беременности.

New Possibilities of Recognizing Early Endometrial

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Ultrasonographic examinations completed by electron microscopic study were made with transvaginal head in 15 cases. According to the authors, the combined use of these two methods can improve the chances of detecting and recognizing early hyperplasia, preblastoses as well as endometrial tumours.

Changes of the endometrium are not seldom detected too late. Diagnosis is often hampered by the fact that, by using the current diagnostic methods, the extension of the changes does not reach the lowest range of recognizability. Both ultrasonography as well as electron microscopic biopsies have been known for a long time in obstetric-gynaecological pathology. The application of both methods has its benefits and drawbacks. Being aware of the cycle-dependent morphological changes of the endometrium, the pathological changes associated with its thickening or with other structural changes can be differentiated.

Ultrasonography can ideally be completed by the ultrastructural study of the endometrium. We are now reporting cases where early diagnosis was established by the use of two techniques theoretically independent of each other.

Materials and Method

Examination were carried out by using the Toshiba Sonolayer, SAL 38B equipment with a 5 MHz ultravaginal head. The transducer was coated with a liquid gel, covered exteriorly by a rubber cot or then repeatedly smeared with a contacting agent. The transducer head was introduced into the vaginal fornix.

The material for electron microscopic study was obtained by curettage. It was fixed in 2.5% glutaraldehyde then postfixed in 1% osmium tetroxide. Following embedding, the ultrathin section were prepared with Reichert U/OM 2 ultramicrotome, then studied by the JEOL 100B electron microscope (at the 2nd Central Electron Microscopic Laboratory of Semmelweis University Medical School, Head of Department: Anna Kádár).



PICTURES 1-4. Carcinomatous infiltration of the endometrium

PICTURE 1. Boundary of the intact and pathological region. lu = lumen, \times 16.200 PICTURE 2. Carcinomatous region. n = nucleus, l = lipid, \times 10.800 PICTURE 3. Centre of the necrotic region. l = lipid, \times 10.800 PICTURE 4. Cell debris in the tumorous cell (d). \times 16.200


PICTURES 5–8. Hyperplastic endometrium. Dilated endoplasmic reticulum (er) with several granules (g). n = nucleus, Picture 5 — $\times 10.800$; Pictures 6,7,8 — $\times 16.200$

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Results

Light- and electron microscopic studies were made from a material obtained by curettage in 15 cases. Light microscopically, proliferative and secretory endometrium was found in 13 cases. In one instance, carcinoma could already be detected by light microscopy. In this case, electron microscopy revealed tumorous cells (Pictures 1-4) infiltrating the endometrium. The tumorous cells were found to contain degenerative changes, necrotic regions, lipid granules



PICTURE 9. Case 3. The endometrium is markedly thickened and of an inhomogeneous contour, with a blurred boundary towards its surroundings



PICTURE 10. Case 12. Widened endometrium

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No.	Age (yrs)	Sonography	Histology
1.	38	normal uterus size, shape and position, normal endometrium	proliferative endometrium
2.	43	normal uterus size, shape and position, normal endometrium	secretory endometrium
3.	48	widened, thickened endometrium	endometrial adenocarcinoma
4.	30	normal uterus size, shape and position, normal endometrium	proliferative endometrium
5.	46	normal uterus size, shape and position, normal endometrium	proliferative endometrium
6.	42	normal uterus size, shape and position, normal endometrium	secretory endometrium
7.	50	widened endometrium of inhomogeneous contour	endometrial hyperplasia
8.	47	normal uterus size, shape and position, normal endometrium	proliferative endometrium
9.	54	normal uterus size, shape and position, normal endometrium	endometrial hyperplasia
10.	58	widened endometrium	endometrial hyperplasia
11.	53	normal uterus size, shape and position, normal endometrium	proliferative endometrium
12.	33	widened endometrium	endometrial hyperplasia
13.	56	widened endometrium	proliferative endometrium
14.	50	normal uterus size, shape and position, normal endometrium	secretory endometrium
15.	51	normal uterus size, shape and position, normal endometrium	secretory endometrium

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In all cases, examinations were carried out for prolonged and irregular bleeding

as well as cell debris, myelin figures and pathological nuclear patterns (Case 3). Hypertplasia of the endometrium was found in Case 12 where dilated endoplasmic reticulum and numerous granules were seen (Pictures 5-8). In this case there was no evidence either of light- or of electron microscopic tumorous change.

The results of ultrasonography are shown in Case 3 by Picture 9 and in Case 12 by Picture 10.

Discussion

Transabdominal (TA) ultrasonography is a routine procedure in gynaecology. In the majority of cases, clinical complaints, and/or a pathological physical finding cell for ultrasonography. The accuracy of the method is limited by technical-anatomical factors (the applied frequency, size and shape of the transducer head, repletion of the bladder, thickness of the abdominal wall, etc.). Similarly often, pathological pelvic and, consequently, endometrial changes

are 'accidentally' found when performing TA studies for other reasons [1, 2, 3]. Ultrasonography is suitable for detection of the various changes in the structure and thickness of the endometrium. However, the most divergent changes underline the morphological changes [3, 4, 7, 9]. Of the detectable pathological alterations, endometrial carcinoma, hyperplasia, adenomatosis, chronic endometritis and pyometra occur the most frequently, which may produce thickening and irregularity of the endometrium – their picture is non-specific.

At the same time, it should be stressed that hyperplasia or the initial stages of endometrial carcinoma do not necessarily produce the changes in thickness that can be visualized by ultrasonography. Sonography in itself cannot detect minimal endometrial changes [1, 2, 6, 8].

In Hungary, transvaginal head for endometrial sonography was first employed by us.

The use of transvaginal (TV) ultrasonography is indicated as a second step for its numerous benefits, e.i. (i) visualization of the uterus does not require a full bladder. (ii) a better resolution can be achieved by a high frequency and (iii) the structure and thickness of the endometrium can be evaluated more precisely.

Besides other indications, increasing importance is certainly attached to TV sonography (like an early pregnancy, extrauterine gravidity, ovarian process, etc.) in diagnosing the pathological processes of the uterus. In assessing the character and extension of the process, TV sonography is valuable together with the clinical and, naturally, with the histological studies.

Sonography with electron microscopic biopsy, the combinated use of these two theoretically different methods largely increased the sensitivity of detection.

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Neue Möglichkeiten zur Diagnostizierung der Frühveränderungen des Endometriums

K. PATAI, ZS. JAKAB, Z. HARKÁNYI und I. BALOGH

Die in 15 Fällen mit dem transvaginalen Kopf durchgeführten Ultraschalluntersuchungen wurden mit elektronenmikroskopischer Auswertung ergänzt. Die Ergebnisse führten zur Feststellung, daß durch die gleichzeitige Anwendung der beiden Methoden die Möglichkeiten der Frühdiagnose der Hyperplasie, der Präblastosen sowie der Endometriumtumoren gebessert werden können.

Новые возможности ранней диагностики изменений эндометрия

К. ПАТАИ, Ж. ЯКАБ, З. ХАРКАНИ и И. БАЛОГ

Авторы в 15 случаях выполнили ультразвуковое исследование трансвагинальным наконечником, которое дополнили изучением ткани под электронным микроскопом. По их мнению, одновременное применение этих двух метовод улучает возможности ранней диагностики гиперплазии, пребластозов и опухолей эндометрия.

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Abbreviations should be spelled out when first used in the text.

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References

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