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Effect of Transtympanally Applied Lidocaine on the Cochleovestibular Function

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(Received June 12, 1984)

Twenty-two patients with recurring attacks of tinnitus, hearing loss and dizziness were treated with transtympanally injected lidocaine. The tinnitus improved in 19, and the pure tone and speech audiometric thresholds decreased in 15 cases. The dizziness and latent spontaneous nystagmus disappeared in all subjects where these symptoms were manifest before treatment.

Introduction

Recurring attacks of tinnitus, hearing loss and dizziness drive patients to despair. The oldest surviving written account of this clinical entity originates from 400 B.C., when Hippocrates made an attempt to alleviate the symptoms of patients suffering from tinnitus [24]. The aetiopathogenetic background of the complaints can be elucidated in certain cases (labyrinthine hydrops, virus infection, disturbance of blood circulation, etc.), but it remains undiscovered in others [13]. In spite of the uncertainty in the genesis of the symptoms, one has to make an effort to develop a successful regime for treatment and prophylaxis. The broad scale of recommended therapeutic procedures makes it evident that this problem, too, is far from having been solved.

During the past few decades, numerous publications have reported the cochleovestibular effects of local anaesthetics. In 1935, Bárány published his pioneering observation concerning the relief of tinnitus after the local application of procaine hydrochloride during intranasal surgery [1].

His report inspired the first clinical experiment to test the presumed beneficial effect of intravenously administered procaine, dibucaine hydrochloride, and a combination of quinine and urethane [18].

Subsequently, a vast number of workers have described various intravenously injected local anaesthetics to eliminate or reduce tinnitus temporarily [6, 7, 8, 10, 11, 15, 16, 17, 19, 20, 24].

Transtympanic injections of pantocaine and lidocaine have been tried in humans by Ristow [21] and Sakata and Umeda [22, 23]. Lidocaine was given intratympanally via iontophoresis by Gillespie et al. [12] in animal experiments.

We have recently made therapeutic attempts to reduce the symptoms of Ménière's disease by means of intratympanic lidocaine administration. The clinical and otoneurological effects are summarized in this communication.

Patients and Methods

Twenty-two patients (13 females and 9 males) with an average age of 42.5 (31 to 55) years were examined and treated for recurring attacks of tinnitus, hearing loss and dizziness. Their histories started 1.5 to 22 years before the initiation of the present study. The attacks of their symptoms were repeated every 3 weeks to 4 months, and the acute phases were not followed by complete recovery. The course of the disease could not be influenced by the previously attempted conservative means (vasodilators, vitamins B₁ and B₆, diuretics and antiemetics). The ophthalmological, neurological, medical and radiological examinations (lateral roentgenogram of the cervical vertebrae, and the Stenvers X-ray examination) revealed no pathognomonic signs.

The treatment was carried out in an attack-free period of the disease. Two ml of 2% lidocaine hydrochloride was injected transtympanally into the tympanic cavity and the same intervention was repeated 4 days later. The injections were followed by intense rotational dizziness for a few seconds and nystagmus directed to the side of drug application. Change in the position of the head evoked similar symptoms, with nausea and occasionally with vomiting for further 3–4 hours. Audiologic and vestibular examinations were performed before the treatment and on the third day after the 1st and 2nd injections. Check-ups were repeated 1 and 3 months later.

The examinations involved pure tone and speech threshold audiometry, tinnitometry, and the investigation of recruitment. The subjects were checked for spontaneous vestibular symptoms and for induced (optokinetic, positional, rotational and caloric) nystagmus. The caloric reactions were tested by the method of Cawthorne–Fitzgerald–Hallpike with electronystagmographic recording (EEG type 4751), according to the criteria and principles of evaluation established by the Hungarian Ophthalmo-Otoneurological Section [3].

Results

Tinnitus. All the patients complained of unilateral tinnitus before the lidocaine treatment. After the first transtympanic injection, improvement was reported by 12 subjects and complete disappearance of tinnitus by additional 5 subjects. After the second application of the drug, a marked diminution in the severity of tinnitus was observed in 10 of the previous 12 patients and

this result was maintained until the end of their follow-up study. In 9 further cases, tinnitus was eliminated totally after the second lidocaine injection and the effect proved permanent in all but one of them. Three patients were non-responders; their histories had started 10 to 22 years prior to the present therapy.

Hearing loss. Pretreatment hearing ability was normal in one case only, while the audiological examination revealed a unilateral hearing loss of neural origin with recruitment in all the others. The pure tone and speech thresholds improved simultaneously in 15, and did not change in 7 patients. The average pure tone threshold values of the responders before treatment and their post-treatment changes are demonstrated in Figs 1 to 5. A trend to improvement

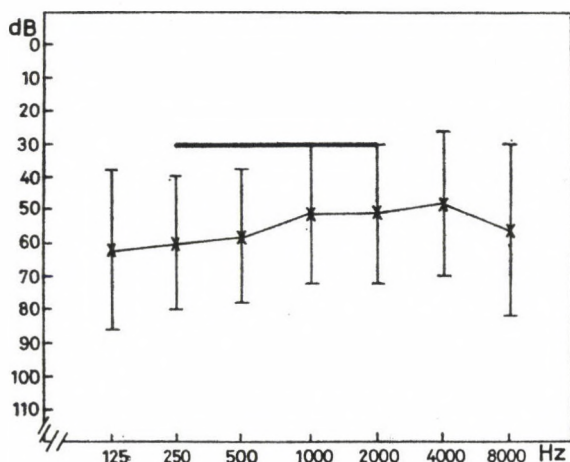


FIG. 1. Pure tone threshold audiogram before lidocaine treatment. Mean dB \pm S. D. ($n = 15$). Air conduction

can be observed after the first treatment. A significant beneficial effect resulted after the second administration of the drug when the threshold curves improved in the frequency zone from 125 to 1000 Hz in 3 days, and a further amelioration was to be seen later. However, the therapeutic effect was more marked at lower frequencies.

Vestibular symptoms. Sixteen out of 22 patients had complained of dizziness before treatment. This subjective symptom disappeared totally after the first trial with lidocaine in all of them and did not return until the end of their observation period. Latent spontaneous nystagmus, directed contralaterally to the impaired ear, which was recorded in 8 cases, was eliminated by the first injection (Fig. 6a,b). During caloric tests, unilateral canal paresis was recorded in all cases and it could not be influenced by lidocaine intervention.

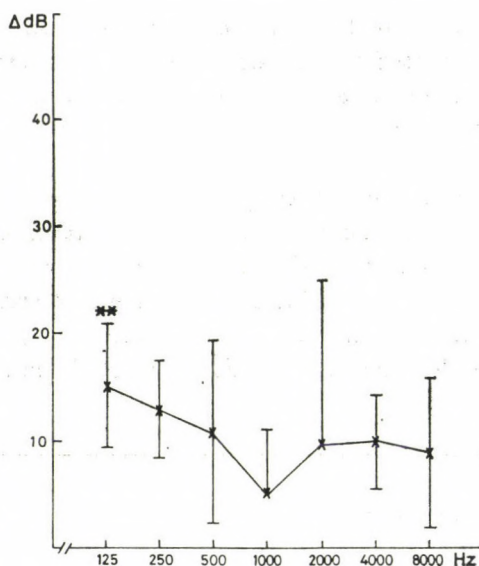


FIG. 2. Improvement of the pure tone audiometric threshold on the 3rd day after the 1st transtympanic lidocaine injection. Mean Δ dB \pm S. D. ($n = 15$). Air conduction. ** significant change exceeding 10 Δ dB was recorded at the frequency of 125 Hz ($p < 0.01$; Student's 1 sample t test)

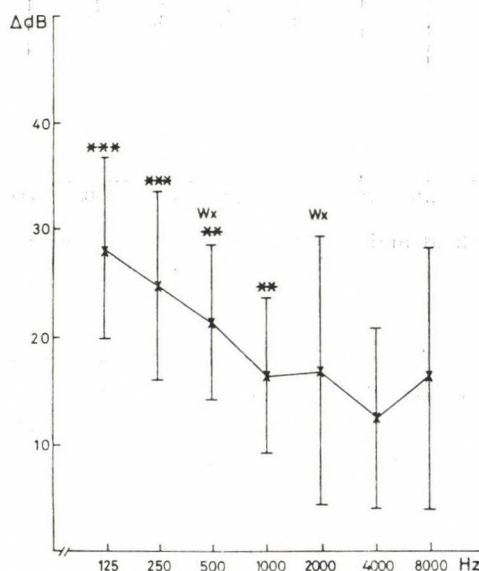


FIG. 3. Improvement of the pure tone audiometric threshold on the 3rd day after the 2nd transtympanic lidocaine injection. Mean Δ dB \pm S. D. ($n = 15$). Air conduction. A significant beneficial effect exceeding 10 Δ dB was demonstrated in the frequency zone 125–1000 Hz. (** $p < 0.01$, *** $p < 0.001$. Data were analysed by the signed rank test indicated by Wx and by Student's 1 sample t test at all the other frequencies.) The therapeutic effect was more marked at lower frequencies ($p < 0.001$; 125 vs. 500– and 250 vs. 1000 Hz, ANOVA)

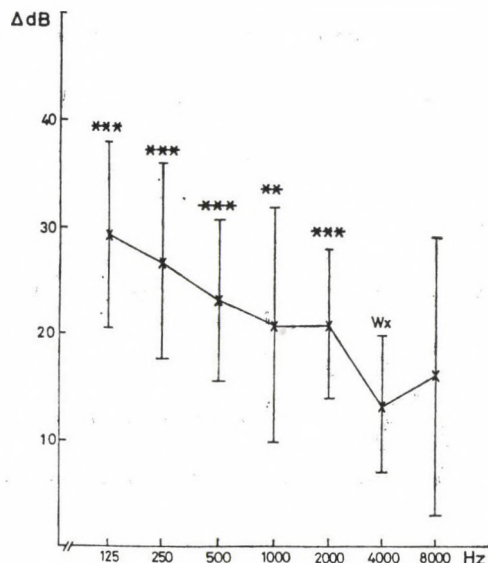


FIG. 4. Improvement of the pure tone audiometric threshold 1 month after the 2nd transtympanic lidocaine injection. Mean Δ dB \pm S. D. ($n = 15$). Air conduction. A significant effect exceeding 10 Δ dB can be observed in the frequency range 125–2000 Hz. (** $p < 0.01$, *** $p < 0.001$; Student's 1 sample t test and signed rank test.) The therapeutic effect was more marked at lower frequencies ($p < 0.001$; 125 vs. 500-, 250 vs. 1000-, 125 vs. 2000- and 250 vs. 2000 Hz, ANOVA)

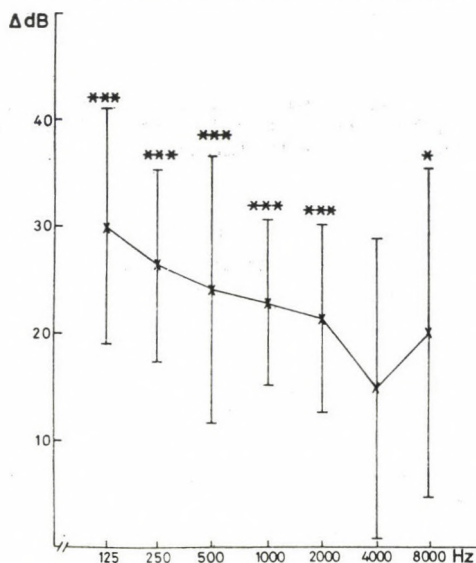


FIG. 5. Improvement of the pure tone audiometric threshold 3 months after the 2nd transtympanic lidocaine injection. Mean Δ dB \pm S. D. ($n = 15$). Air conduction. A significant effect exceeding 10 Δ dB was demonstrated at all the investigated frequencies except 4000 Hz (* $p < 0.05$, *** $p < 0.001$; Student's 1 sample t test). The therapeutic effect was more marked at a lower frequency ($p < 0.001$; 125 vs. 1000-, 125 vs. 2000- and 125 vs. 8000 Hz, ANOVA)

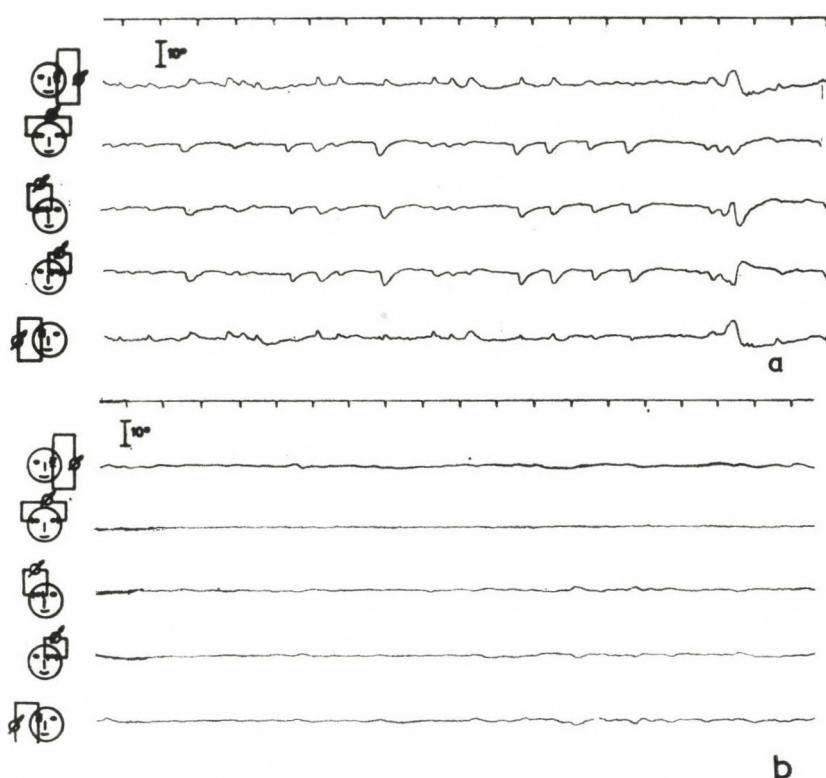


FIG. 6. G. J., 36 year-old woman. Latent spontaneous horizontal nystagmus, directed to the left, was eliminated by the first transtympanal lidocaine injection. *a.* Before treatment. *b.* After the first treatment

Ménière attacks recurred in 7 patients 4 months after treatment. Their complaints and the changes in the parameters were less severe than earlier, and the condition remaining after the attack could again be affected positively with lidocaine.

Discussion

Apart from its local anaesthetic effect, lidocaine has been widely applied systemically for various medical purposes: as an antiarrhythmogenic and anti-convulsive agent, for pain relief, etc. [2, 5, 14].

Although numerous data are available as to the mode and site of its action, the actual mechanism of its cochleovestibular effect still remains to be elucidated. As a membrane stabilizer, lidocaine inhibits the uptake of amino acids into the cells, and this action cannot be altered by increase of the calcium concentration in the milieu [4, 25]. By inhibiting the sodium-potassium trans-

port through the cell membrane, lidocaine causes hyperpolarization and decreases the action potential [5, 7, 17, 19, 25]. It also blocks oxidative phosphorylation in the mitochondria [25], and dramatically decreases the ATP content of the cells [9].

Lidocaine inhibits central nervous activity [2], and has therefore been used to control epileptic seizures. Consequently, the therapeutic effect of intravenously employed lidocaine on tinnitus has been attributed to a blockade of the central nervous system [16].

However, Lyttkens et al. and others [7, 17, 19] have demonstrated that lidocaine readily accumulates on the melanin of the modiolus, whereas its related compounds exert an affinity for the melanin content of the modiolus, stria vascularis and vestibulum. Moreover, a quaternary ammonium derivative of lidocaine, which does not penetrate the blood-brain barrier at all, is also able to eliminate tinnitus in man. These recent results indicate that the site of cochleovestibular action of lidocaine is mediated by a peripheral rather than a central mechanism. Either lidocaine attached to melanin represents a pool that is able to act on the statoacoustic nerve, or the altered quality of the melanin itself can influence the hearing process directly [17, 19].

Our study was not scheduled to investigate the theoretical basis of lidocaine action, but rather to evaluate its therapeutic usefulness in Ménière's disease. The temporary alleviation or elimination of tinnitus following systemic administration of local anaesthetics has been reported by various groups [1, 2, 7, 8, 10, 11, 15, 16, 18, 19, 20, 24]. About 80% of their cases proved to be responders to the treatment. However, Cathcart was sceptical about the effectiveness of orally administered tocainide, a lidocaine analogue [6]. Gejrot [10] observed a prompt diminution or elimination of nausea, vomiting and tinnitus when lidocaine was injected intravenously during Ménière attacks. The effect on tinnitus was only transient, while the trial did not influence the nystagmus and hearing ability of these cases at all. Sakata and Umeda [22, 23] have reported the successful treatment of tinnitus by transtympanic lidocaine injection. We have studied the therapeutic value of intratympanic lidocaine administration in the treatment of permanent cochleovestibular disorders remaining after attacks of Ménière's disease. As far as the relief of tinnitus is concerned, our results are in good agreement with those of Sakata and Umeda, who applied a therapeutic regime similar to ours. They also harmonize with the experience of the majority of authors who employed the drug orally or intravenously.

The effects of lidocaine on impaired hearing ability and on equilibrium disturbance have received little mention in the literature. Thus, we consider that our data on the improvement of the pure tone and speech audiometric thresholds and on the disappearance of the latent spontaneous nystagmus may be worthy of attention.

This study has provided further and more detailed arguments for the usefulness of intratympanic lidocaine application in the treatment of objective and subjective symptoms caused by Ménière's disease.

Acknowledgement

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Wirkung des transtympanal verabreichten Lidokains auf die cochleovestibuläre Funktion

É. SZABADOS, E. NAGYMAJTÉNYI, O. RIBÁRI und K. BODA

22 Patienten mit einem aus anfallsartig auftretenden Ohrensausen, Hörverlust und Schwindeln bestehenden Syndrom wurden mit transtympanal verabreichtem Lidokain behandelt. In 19 Fällen meldete sich das Ohrensausen nach der Therapie in mäßigerer Form, während bei 15 Patienten die Reinton- und sprachaudiometrische Schwelle abnahm. Der vor der Behandlung beobachtete latente spontane Nystagmus und das Schwindeln hörten bei sämtlichen Patienten auf. Die Ergebnisse sprechen für die vorteilhafte therapeutische Wirkung des Verfahrens.

Влияние введенного транстимпанально лидокаина на кохлеовестибулярную деятельность

Э. САБАДОШ, Э. НАДЬМАЙТЕНИ, О. РИБАРИ и К. БОДА

Авторы лечили 22 больных транстимпанально введенным лидокаином, которые страдали от приступов шума в ушах, понижения слуха и головокружения (симптомо-комплекс). В 19 случаях шум в ушах стал слабее, в 15 случаях снизился аудиометрический порог чистого звука и речи. Головокружение и отмечаемый до лечения латентный спонтанный нистагм прекратились у всех больных. Результаты, полученные авторами, подтверждают положительное действие данного способа терапии.

Anaesthesiological Problems of Patients Undergoing Prostatic Operations

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(Received 8 May, 1984)

The author reports on the problems of preparing and anaesthetizing patients in 204 prostatic operations made in 1983 at the Department of Urology of the Postgraduate Medical Institute, Budapest. These are related to the age distribution and the underlying and associated diseases of the patients.

Two hundred-four prostatic operations were performed with anaesthesiological cooperation at the Department of Urology of the Postgraduate Medical Institute, Budapest. Of them 129 adenomectomies were made by transvesical operation and 79 were transurethral resections. The average age was 71.5 years as opposed to the average age of 63 patients undergoing other urological operations. The age distribution of those subjected to prostatic operation has changed even in the recent two years. In 1981 the ratio of patients over 61 years was 86% which had increased to 92.2% by 1983. The number of anaesthesiological interventions of aged patients has increased both in relative and absolute numbers, as reported by Greenfield and Lazar [9]. They implied that with a larger number, a higher percentage of the patients can be operated than earlier. In our own material—in addition to the above—it can also be ascribed to the fact that cryosurgery, too, is applied at the department. Thus patients are referred here from several places, who have been found unfit for prostatectomy. A considerable part of these patients become able to surgery with a detailed physical assessment, preoperative preparation, considerate surgical technique, careful anaesthesia and after-care—and 70% of them undergo a successful operation.

The distribution of the 204 operations according to the anaesthesiological method used was as follows.

Prostatectomy:	105 in epidural anaesthesia (51.4%)
	24 in neuroleptic anaesthesia (11.7%)
TUR:	75 in i.v. anaesthesia (36.7%).

Each patient undergoing an operation is subjected to a detailed physical examination. At the same time, an aimed and effective reparative treatment of the detected pathological changes (anaemia, hypoproteinaemia, etc.) is started.

In addition to the patient's general state, the actual circulatory, respiratory and metabolic status is assessed.

According to our present standpoint, concerning the cardiovascular state, digitalis pretreatment is only given to decompensated patients or if impulse formation or impulse propagation disorders make it necessary. Treatment was always individual, it did not depend on stereotypes and was applied in 20% of the patients.

Pretreatment of hypertension is also considered necessary. The high blood pressure can be returned to normal by administration of diuretics and beta-blockers. Depressors with prolonged action (Rausedyl) and ganglion-blockers (Dopegyt) are not administered to avoid an unexpected fall in blood pressure during operation.

Prevention of thrombosis, particularly in case of a positive history, is considered to be fairly important. Patients with varices are transferred to the operation room with a bandage on. Movement of the extremities after the operation and mobilization of the patient on the first postoperative day may well serve this purpose. In case of an increased risk, a small dose of heparin or dextrane is given although in some cases a proneness to bleeding of the operative region was observed [8]. Epidural anaesthesia itself may diminish the risk of thrombosis [21].

Recovery from a heart attack is not considered to be a contraindication if the patient is otherwise compensated. Patients having had several heart attacks tolerated the operation well. Patients with recent heart attacks are possibly not operated on within half a year after the attack. Neither is insertion of a pacemaker an obstacle, but it is rather a precondition of the operation.

With advancing age, changes in the respiratory system appear cumulatively. Patients are characterized partly by the rigidity of the thoracic wall and partly by changes of the lungs themselves and of the respiratory tract, respectively (emphysema, bronchitis), some of them have had several diseases. That is why it is important that 81.3% of prostatectomies have been performed under epidural anaesthesia. Thus the mechanical (tube) and chemical (anaesthetic gases, vapours) irritating effects on the respiratory tract and the deterioration of the condition of the patient with a reduced respiratory capacity, as a result of the possible prolonged curarization, are eliminated. Besides, pain is still absent for one hour to three hours and thus the patient is not prevented from adequate breathing and from expectoration [14].

An important issue is to teach the aged patients for practising deep breathing exercises and forced coughing possibly before operation. Though not an aesthetic sight, it may be vital for the patient.

The metabolic changes are associated partly with the underlying disease (e.g. in 60% of the patients there was an increased serum creatinine level) and partly by their advanced age. Of these, the deficiency states are of great

importance as, e.g. hypovolaemia, hypoionia (Na, K), decreased serum protein level, anaemia, as well as diabetes still playing an important role at present [12, 18].

Concerning diabetes, those in need of daily one tablet or two tablets are subjected to operation without changing their dose. Patients requiring a larger dose of antidiabetics are changed over to insulin even today. This helps avoiding the difficulties in adjusting the upset glucose balance during intensive care which imposes a great strain on both the patient as well as on the physician.

The time of preoperative preparation is suitable for normalizing the metabolic changes, the time of operation is already too late.

Fluid replacement should be made immediately before operation by giving a 1000 ml crystalloid solution. Prolonged deprivation of the patient of drinking should be avoided. Our own investigations have confirmed [3, 4] that, while the adequate preparation may improve, the drastic intervention (e.g. powerful purgatives given several times) may considerably worsen, the patient's condition. Fluid replacement can be continued during the operation, too, partly for replacing the loss of fluid and partly for counteracting the blood pressure-decreasing effect of vasodilatation due to the anaesthesia [19]. The amount of fluid depending on the duration of the operation, is 1500 to 3000 ml. None of the patients was influenced by its strenuous effect.

As regards transfusion, our standpoint is positive. In view of the advanced age of the patients and their limited vital capacities, i.e. that they react to a minor blood loss by producing a fall in blood pressure, blood is transfused even in case of a bleeding of 500 ml [12]. In our opinion, this is bound to adequately influence the patient's condition, oxygenation, that means, his cerebral state. Transfusions were performed in 30% of prostatectomies made under epidural, and 48% of operations made under general anaesthesia. The average amount of transfused blood was 500 ml and 800 ml, respectively. In TUR, no transfusions were needed intraoperatively.

A considerate surgical technique and precise haemostasis may help the patient tolerate the operation more easily and recover more rapidly. This can be effective only with stable blood pressure values. This is provided, in addition to the continuous and attentive monitoring of the patient, by a good preoperative preparation, a careful replacement of losses (fluid, blood, protein, etc.) and by an adequately selected and performed anaesthesiological procedure. An adequate postoperative care may also be an effective aid.

Beside the direct anaesthesiological care of the patient, maintaining of a contact with him, providing him with detailed information and letting him know about the actual phase of the intervention are all considered highly important issues. It particularly refers to operations made under epidural anaesthesia. Although this anaesthetic procedure is also of a stress-reducing effect [5, 7], it can be still more easily tolerated by administration—if needed—of 5

to 10 mg Diazepam. The extensive use of epidural anaesthesia, the intervention imposing the least strain on the aged patient is prevented by the absence of personal conditions.

General anaesthesia, with careful monitoring of the patient performed by adequate skills may also yield good results, however postoperative management requires more care and this should not be the method of choice in these cases.

None of our patients was lost on the operating table, neither postoperatively nor as a result of the anaesthesiological method used.

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Über die anästhesiologischen Probleme von vor Prostataoperationen stehenden Patienten

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Im Zusammenhang mit 204, an der Klinik im Jahre 1983 durchgeführten Prostataoperationen finden die mit dem Alter sowie mit den Grund- und Begleitkrankheiten der Patienten verbundenen Probleme der Operationsvorbereitung und Anästhesie eine ausführliche Besprechung.

Об анестезиологических проблемах больных с операцией простаты

Ч. БАРАБАШ

Автор сообщает о подготовке и анестезии больных в связи с 204 операциями простаты, которые были произведены в 1983 г. в Урологической клинике Государственного института усовершенствования врачей. Проблемы связаны с возрастным составом больных, а также с их основным заболеванием и сопровождающими болезнями.

Introduction of Anaesthesia in Caesarean Section by Using Ketamine and Fazadinium

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The evaluated data of the anaesthesia protocols of 91 caesarean sections are presented. The narcosis of caesarean sections was introduced by using 1 mg/kg ketamine. Relaxation was achieved by administration of 1 mg/kg fazadinium. To maintain anaesthesia, fentanyl or repeated doses of histamine, were used after removal of the fetus. Anaesthesia was adequate in each case, the patients were amnesic concerning the operation. They recovered well. During anaesthesia, circulation was characterized by the elevation of pulse rate and of systolic pressure. The mean value of the above parameters kept on differing significantly from the initial values throughout the anaesthesia. However, the extent of increase had not reached the difference observed by other authors.

The method is considered to be safe and easy to perform since ketamine and fazadinium are anaesthetics well adaptable for use just in this sort of patient material. The analgetic, anaesthetic and amnesic effect of ketamine is fairly good. It does not generally produce circulatory depression rather acts inversely. It does not depress the vital functions of the fetus either and, at the same time, due to its long action, it provides adequate anaesthesia for prolonged removals as well. The rapidly acting fazadinium produces fast relaxation similar to that produced by succinylcholine, while its effect is not associated with the side-effects of the former agent, i.e. hyperkalaemia, fasciculations. As a result of the latter, it is a useful aid in preventing the always threatening aspiration in the anaesthesia of caesarean sections.

There are special requirements in the anaesthesia of caesarean sections. Pregnancy gives rise to changes in the maternal circulation and is associated with the decrease of peripheral resistance and tachycardia and often with hypotension. Each caesarean section, including the elective operations, too, may involve the risk of a full stomach. Therefore, the initial anaesthetic is required to provide, in addition to hypnosis and amnesia, also analgesia. It should not depress the maternal circulation and fetal respiration, and the fetal central nervous functions either. Neither should it be toxic for the mother or for the fetus. Induction of anaesthesia should ensure a good abdominal relaxation and prevention of aspiration, too.

Similar to other data in the literature, the use of ketamine-fazadinium is considered to be the agents best fulfilling the above requirements. In the present study our experiences gained by this method are reported.

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Material and Method

The data of the anaesthesia protocols of a total of 91 caesarean sections were elaborated. The mothers' age ranged between 16 and 45, with a mean age of 28.3 ± 6.5 years. Thirteen elective and 78 urgent operations were made. Twin pregnancies occurred in two cases. In the histories there was one caesarean section in 10 cases and two in two cases. Among the indications of the operation 12 cases of placenta praevia and 6 cases of toxicosis of pregnancy should be pointed out.

For induction of anaesthesia, following an i.v. premedication of 0.5 mg, 1 mg/kg ketamine (in 89 cases Ketanes, Parke-Davis, in 2 cases Calypsol, Chemical Works of Gedeon Richter, Ltd., Budapest), then immediately 1 mg/kg fazadinium (Fazadon, Duncan and Flockhart) were administered. The patients were made to inhale a mixture containing 70% oxygen and 30% N_2O during introduction of the anaesthesia and after intubation up to the removal of the fetus. Later the ratio of the gases was changed to 1 : 3. Anaesthesia was maintained by 0.05 to 0.20 mg fentanyl in 88 cases. Three patients with spastic bronchitis were repeatedly administered ketamine. At the end of the operation as usual decurarization was achieved by administering a mixture of 0.5 to 1.25 mg atropine and 1.0 to 2.5 mg neostigmine.

In order to assess the effects on the circulation of the drugs used on induction of anaesthesia, the blood pressure and pulse rate before premedication and induction of anaesthesia, and after intubation and removal of the newborn and following awakening were compared.

Results

Induction of anaesthesia by ketamine and fazadinium helped, in each case putting the patient to sleep within one minute, and achieving her complete relaxation within one minute. Five to 15 minutes elapsed up to the removal of the fetus. The time of removal of the newborn was, on an average, 6.69 ± 2.35 min. In 10 cases, it took 10 minutes or more. Anaesthesia proved, in these cases, too, to be adequate.

During the caesarean sections 91 living neonates were delivered. The mean of 1 min Apgar scores was over 7.

In the course of induction complications developed in one case, i.e. an anaphylactic reaction which returned to normal as a result of the adequate treatment and did not entail subsequent consequences. The phenomenon occurred on administration of Calypsol.

The systolic pressure averaged 123.63 ± 1.67 mm Hg, the mean diastolic values were 88.57 ± 1.13 mm Hg. Following intubation a statistically signifi-

cant elevation of systolic pressure was observed. The average value was 130.33 ± 1.91 mm Hg. ($t = 2.647$, degree of freedom = 180, $p < 0.01$). The mean diastolic pressure— 81.21 ± 1.20 mm Hg—was higher than the initial value but this was an unassessable difference. The blood pressure values after removal of the newborn did not differ significantly from those obtained before the introduction although they were indicative of elevated mean values, i.e. systemic mean values of 129.89 ± 2.14 mm Hg and diastolic mean values of 78.79 ± 1.37 mm Hg were found. The systolic pressure after termination of the anaesthesia, after awakening exceeded again significantly the initial value by a mean of 131.32 ± 1.69 mm Hg ($t = 3.248$, degree of freedom = 180, $p < 0.01$). The diastolic value did not increase significantly with a mean of 80.55 ± 1.13 mm Hg. The blood pressure values during and after anaesthesia did not differ from each other significantly.

The mean pulse rate prior to the introduction was 95.36 ± 1.13 mm Hg. After the intubation there was a significantly increased value, i.e. 107.50 ± 1.82 per minute ($t = 3.803$ m degree of freedom = 180, $p < 0.01$). On measuring after the removal of the fetus, the mean values further increased ($t = 4.397$, degree of freedom = 180, $p < 0.01$). The mean value after awakening significantly exceeded the initial value, i.e. 106.07 ± 2.23 per minute ($t = 3.128$, degree of freedom = 180, $p < 0.01$). The values recorded in the latter three cases did not significantly differ from each other.

The values obtained after intubation and following removal of the fetus reflected the haemodynamic effect of atropine premedication, of the ketamine-fazadinium combination as well as of that of ventilation, of the start of the intubation manoeuvre and of the operation. The ketamine- N_2O anaesthesia was suitable for 10 to 35, on an average 17.3 ± 3.7 min. Additional medication was made subsequently.

Discussion

For introducing anaesthesia in caesarean section, currently barbiturates are most often used. Thiopental has been applied also for this purpose since 1936. This method does not, however, produce an adequate hypnosis. The transport of the drug through the placenta cannot be reliably calculated: it cannot be directly related either to the dose or to the time of administration [3]. Following removals taking more than 10 minutes, fetal depression may frequently occur [6]. It is indicated by urgent caesarean sections due to fetal asphyxia where the cerebroprotective effect of barbiturate can be reckoned with [3]. The drawback of propanidid and Althesin both soluble in Cremophor EL is a frequently occurring allergy to the solvent and also that both anaesthetics promote the development of fetal acidosis [3, 6]. Ketamine is the intravenous hypnotic which, at the moment, may best fulfil the requirements of an

ideal hypnotic being an analgesic, an anaesthetic and a hypnotic in itself and having also an amnestic effect [11]. It has been used in obstetrics since 1968. It does not, in general, depress the newborn but may rather induce hypertension and hyperexcitability [3]. It may also exert an oxytocin-like effect, but an elevated uterine tone is actually characteristic only of the first trimester. In the third trimester, this effect can only be traced to be assessed in doses over 1 mg/kg [11]. According to White et al. [11], the rapid introduction of caesarean section by ketamine is particularly indicated in hypovolaemia, bleeding and in bronchospasm.

As stated by Patschke et al. [9], fazadinium is an almost ideal relaxant since it has a rapid effect which can be prolonged only for a relatively short time. It can be suspended by cholinesterase-blockers and it has only mild side-effects even on administration of a dose providing complete relaxation. This is how it blends the advantages of depolarizing and non-depolarizing relaxants: its effect is triggered as rapidly as that of succinylcholine, being at the same time, neither associated with an elevated serum potassium level nor with fasciculation. This latter essentially diminishes the risk of aspiration. Its circulatory effect is characterized by a decrease in peripheral resistance which was found to occur in 15% by the above authors. This is compensated by the 11% increase of heart rate combined with the increase of the cardiac index producing thereby only an insignificant decrease in tension. The observations concerning the extent of tachycardia are different: Rowlands and Fidler [10] observed a slight increase in heart rate in 60.8, and a more severe one in 4.4% of the patients. Montanini et al. [8] described an elevated heart rate of 12–14 per minute. Based on our earlier findings and on our studies on other patient materials, on an average, an increase in heart rate of 14 per minute was found corresponding to an increase of 14–15%. This was associated, on an average, with a decrease of 12 mmHg of systolic pressure which corresponded to 8% [1].

Fazadinium is ideal for use in the anaesthesia of caesarean section for its three properties, i.e. its rapid effect almost equalling that of succinylcholine; a lack of side-effects associated with the use of succinylcholine which may largely facilitate the prevention of aspiration and also for the fact that it does not, or does only partially, infiltrate through the placenta [4, 5, 7, 8, 9, 10]. Its total relaxant effect is estimated to be 30 to 75 seconds [5, 7, 8]. In 7 out of 8 cases, it could not be traced in the umbilical blood by Blogg et al. [4], in one case a concentration corresponding to about 40% of the maternal blood level was measured. A concentration gradient was found between the myometrium and the endometrium, the placenta and the fetus.

Using a fairly similar method as ours in anaesthetizing caesarean sections, after the introduction, on an average, a pulse rate of 153.8 ± 9.8 per minute was found by Cane and Sinclair [5], which decreased to a value of 114.0 ± 8.5

per minute, on an average, during 12.6 ± 3.2 minutes not reaching again, however, the initial level. In addition, unchanged blood pressure values were found in 62% of the patients, and an increase of 12.5 ± 4.2 mm Hg in 38% of the cases.

In 50 of our earlier cases, where partially even higher ketamine doses, i.e. of 1.5 to 2.0 mg/kg, were administered, the initial increase in heart rate was on an average 10.4 per minute. The heart rate observed after removal of the fetus exceeded the initial value by 13.7 per minute, the value at the end of the anaesthesia exceeded the value prior to introduction by 7 per minute. The systolic pressure increased, on an average by 11.2 mm Hg at the termination of anaesthesia. The diastolic pressure did not initially show any changes exceeding the average value by 7.9 mm Hg when taken for the third time, and by 4.4 mm Hg at the end of anaesthesia [2].

Comparing our present results with the data of Cane and Sinclair [5], it is revealed that even the combined use of atropine, ketamine and fazadinium did not induce such an intensive tachycardia in our patients as described by the above authors. The increased pulse rate immediately after the introduction persisted even later on. The systolic pressure did not change in 31 cases (34%) after intubation it increased in 45 cases (49.5%), and decreased in 15 cases (16.5%). Compared with our earlier data [2], as a result of administering the uniform ketamine doses of 1 mg/kg, a greater degree of tachycardia could be observed, however, with an essentially smaller elevation in blood pressure. Diastolic pressure did not practically change.

The method proved clinically to be very good. Putting the patient to sleep was, in each case quick and without excitation. The relaxation required for the intubation was always achieved within 40 to 60 seconds. The patients were without exception amnesic. After using fentanyl in a very small dose, no antidotes were required in any of the cases. Vomiting and regurgitation did not occur. The only more serious complication was the already mentioned anaphylactic reaction following the administration of Calypsol. The duration of action of ketamine proved to be sufficient even during prolonged deliveries. Longer action was found in very short patients of small body weight, while one of about 10 minutes in patients of over 70 kg body weight. The low number and small dosage of the drugs used were also considered advantageous. Prolonged anaesthesia or relaxant effect did not occur. The patients woke up rapidly and comfortably and promptly showed adequate behaviour. There were no postanaesthetic complications. All these considered, the method can be regarded as good and safe in using it in elective and urgent caesarean sections.

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Einleitung der Anästhesie des Kaiserschnitts mit Ketamin und Fazadinium

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Der Arbeit liegen die Daten der Anästhesie-Protokolle von 91 Kaiserschnitten zugrunde. Die Einleitung der Kaiserschnittnarkose erfolgte mit 1 mg/kg Ketamin, die Relaxation mit der Gabe von 1 mg/kg Fazadinium. Zur Aufrechterhaltung der Narkose wurde nach Heraushebung der Frucht Fentanyl bzw. eine wiederholte Ketamindosis verabreicht. Die Anästhesie erwies sich in sämtlichen Fällen als befriedigend, die Patientinnen waren im Zeitpunkt der Operation amnestisch und wachten am Ende der Narkose munter auf. Die während der Narkose beobachteten charakteristischen Kreislaufänderungen waren die Erhöhung der Pulsfrequenz und des systolischen arteriellen Drucks. Der Durchschnittswert der erwähnten Parameter unterschied sich zwar stets signifikant von dem Ausgangswert, das Maß des Anstiegs blieb aber unter den von anderen Autoren angegebenen Werten.

Angesichts der sich gerade bei dieser Gruppe der Patientinnen manifestierenden Vorteilen von Ketamin und Fazadinium hat sich die Methode als zuverlässig und nützlich erwiesen. Durch das über intensive analgetische, anästhetische und Amnesie herbeiführende Wirkungen verfügende Ketamin werden im allgemeinen weder Kreislaufdepression verursacht — das Mittel wirkt eher in entgegengesetzter Richtung — noch die Vitalfunktionen der Frucht deprimiert, außerdem wird seiner Wirkungsdauer zufolge sogar im Falle sich verzögernder Heraushebungen die nötige Anästhesietiefe gewährleistet. Da sich die Wirkung von Fazadinium sehr rasch entfaltet, wird durch das Pharmakon eine dem Sukzinylochin ähnliche rasche Relaxation herbeigeführt, ohne daß sich die Nebenwirkungen des erwähnten Mittels — Hyperkaliämie, Muskelfaszikulation — melden würden. Diesem letzterwähnten Effekt zufolge bietet das Pharmakon auch zur Prophylaxe der bei der Kaiserschnittnarkose stets drohenden Aspiration eine nützliche Hilfe.

Введение анестезии кетаминот и фазадиниот при кесаревом сечении

М. АНТАЛ и М. БЕНКЕ

По отношению к анестезии при кесаревом сечении существуют определенные требования. Беременность изменяет состояние кровообращения матери, сопровождается уменьшением периферического сопротивления сосудов, тахикардией, часто гипотензией. При любой операции кесарева сечения — включая также и elective операции — приходится считаться с риском полного желудка. К требованиям, предъявляемым к вводному снотворному средству, относится обеспечение хорошей аналгезии наряду с гипнозом и амнезией, оно не должно вызывать депрессию материнского кровообращения и дыхательной функции плода, угнетать функции центральной нервной системы плода, быть токсичным ни для материнского организма, ни для организма плода. Наряду с введением в наркоз средство должно также обеспечивать хорошее расслабление брюшных мышц и аспирационную профилактику.

Подобно другим авторам, мы считаем, что вышеупомянутым условиям скорее всего соответствует кетаминотфазадиниотый вводный наркоз. В настоящей статье мы знакомим с собственным опытом применения этого метода.

Correlation between the Results of Carcinoembryonal Antigen (CEA) Test and the Clinical Stage of Colorectal Carcinoma

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Correlation between results of CEA test and clinical stage of colorectal carcinoma is described. No correlation was found between the different stages and the actual CEA titre. Normalization of an increased preoperative serum CEA level indicated, however, nearly always the radical character of the intervention. Critically high (above 30 ng/per ml) CEA value observed in Dukes' stages C and D can be considered bad prognostic signs. Patients like these died within one year. Results of CEA tests are also useful complementary data contributing to the diagnosis of recurrence or distant metastases.

Gold and Freedman [5] described in 1965 a glycoprotein of 200,000 molecular weight occurring in high amount in the gastrointestinal tract of the embryo and in the serum of adult patients suffering from gastrointestinal endodermal tumour. The substance is absent or can be revealed only in very low concentrations in other normal tissues. The substance has been called carcinoembryonal antigen (CEA). Thorough investigations indicated that CEA was not tumour-specific. High CEA levels were detected in other cases, too [14, 18, 25], like in 19% of smokers, in 57% of patients with obstructive pulmonary emphysema, in 70% of cases of alcoholic cirrhosis of the liver, in 30% of patients with ulcerative colitis, while endodermal malignant tumours of the alimentary tract were accompanied by an increased CEA level in 73% of the cases. According to some authors [1], CEA level depends on the volume of the tumour or on its secretion type [15]. Experience of almost two decades suggests that CEA determination, in spite of its limits and errors, is still a valuable complementary indicator in the evaluation of the state of the patient with colorectal carcinoma [6, 11, 22, 23].

In Hungary, mortality rate of colorectal carcinoma is 14 per 100 000 in males and 13 per 100 000 in females (Annual of Statistics, 1977). Despite this high mortality rate, relatively few investigations are in progress in the field.

Patients and Methods

In our Institute CEA determinations have been performed since 1977 in patients with colorectal, gastric, mammary, testicular and pulmonary tumours. The aim of the present work is to reveal the correlation, if any, between CEA values and the stage of the colorectal tumour observed.

As far as staging is concerned, several classifications were described in the literature (Dukes, Astler-Coller, Kirklin, Ecker, Cass, TNM). In the present study the Dukes specification has been used partly because our material originates from a period when this was the most widely used schedule and partly because it is considered suitable for the evaluation of our results. Dukes originally distinguished only A, B and C classes. In our work we applied the up-to-date international A, B, C, D stages. For the present study 100 patients were randomly selected from those treated for colorectal carcinoma at the Department of Surgery of the National Institute of Oncology (Budapest) between 1977 and 1982 and who underwent CEA determination. Patients were divided into two groups. In the first group of patients, systematic CEA determinations were performed both before and after surgery, while in 37 patients of the second group only postoperative determinations were made.

For the double parallel CEA tests CIS, CEAK-M, RIA Kit (¹²⁵I) was used [21] (CIS-CEA-SORIN). Calibration curve was plotted in a linear system. Values were considered normal below 10 ng per ml. Anamnestic data concerning alcohol and nicotine abuse, chronic obstructive emphysema and other inflammatory diseases were taken into consideration. In such cases increased CEA values under the limit of 30 ng per ml were evaluated only, if observed repeatedly.

Normal control value fell between 0 to 5 ng per ml for each Kit. Postoperative CEA determinations were made in every 6 months, patients were followed for a period of 3 to 72 months.

Results

Majority of our patients were older than 50 years, mean age being 66.9 years (23 to 78 years). Their distribution, according to age, sex and Dukes' stages is shown in Table I. Distribution according to tumour localization is indicated in Table II. Seventy per cent of the patients suffered from rectal carcinoma, 44% displayed significant symptoms of obstructive emphysema, 12 patients were chronic alcoholics and 9 heavy smokers. Non-tumour factors possibly modifying CEA results are included in Table III. Out of the 100 patients one refused surgical treatment, in the 99 remaining patients 103 interventions were made. Types of operation are presented in Table IV. Opera-

tions in 84 cases appeared to be radical, in 18 cases no more than palliative interventions could be made. CEA values, in dependence of stage distributions are illustrated in Table V.

From the patients belonging to Dukes' stage A in 14 cases both pre- and postoperative, in 2 cases only postoperative CEA determinations took place.

TABLE I

Distribution of patients according to sex, age and Dukes' stages

Age (years)	Clinical stage									
	A		B		C		D		Total	
	16 patients		50 patients		19 patients		15 patients		100	
	male	female	male	female	male	female	male	female	male	female
20-29	—	—	1	1	—	—	—	—	1	1
30-39	—	1	2	1	—	1	—	1	2	4
40-49	—	2	3	2	4	4	1	1	8	9
50-59	3	4	7	8	2	1	4	—	16	13
60-69	2	2	8	7	2	1	4	1	16	11
70-79	1	1	4	6	1	3	1	2	7	12
Total	6	10	25	25	9	10	10	5	50	50

TABLE II

Distribution of tumours according to localization

Localization	Dukes' stages				Total
	A	B	C	D	
Rectum	14	35	10	11	70
Sigma + colon descendens	2	4	1	2	9
Colon transversum	—	5	1	—	6
Colon ascendens + coecum	—	7	7	1	15

TABLE III

Non-tumour factors modifying CEA results

Factors	Dukes' stages				Total
	A	B	C	D	
Alcohol	1	7	1	3	12
Nicotine	3	4	—	2	9
Emphysema	4	24	8	8	44
Inflammation*	2	3	1	—	4

* (pyelitis, polyarthritis, colitis)

TABLE IV

Distribution of our own patients according to the type of operation

Type of operation	Dukes' stages				Total (103)
	A	B	C	D	
Abdominoperineal extirpation of the rectum	10	26	9	2	47
Dixon's operation	2	7	4	—	13
Hartmann's operation	—	3	—	—	3
Right hemicolectomy	—	9	7	1	17
Segment resection	1	6	—	—	7
Polypectomy	2	—	—	—	2
Posterior rectotomy	1	—	—	—	1
Explorative laparotomy + preternatural anus	—	—	—	10	10
Explorative laparotomy	—	1	—	2	3

TABLE V

CEA values in dependence of Dukes' stages

	A (15 patients)			B (25 patients)			C (9 patients)			D (15 patients)			Total
	<10	10-30	30<	<10	10-30	30<	<10	10-30	30<	<10	10-30	30<	
<i>Before operation</i>	5	8	1	9	8	8	2	3	4	3	4	8	63
<i>After operation</i>													
6 months	8/1*	5		16/3	4/3	5/1	3	3	3	4	3	8/1	
12	11/1			17/7	3/2	3/1	4	1	3	4	2	4/1	
18	8/1			13/8	3/2	3/1	2		2	2		2/1	
24	7/1			11/10	2/1	1			2	2		/1	
36	5/1			9/16	1/1				1				
48	6			6/13	1/5		/1		/1	1			
60				3/12			/7	/2	/1				
Local recurrence	0			2/3			1			4			
Death	0			/2			3/2			9/1			

* Before operation/after operation

Increased preoperative values were encountered in 9 patients out of whom in 5 cases CEA values were normalized 6 months after radical surgery. In 3 patients the transient rise of postoperative CEA level also normalized after 6 months. Patients of this group are alive, tumour-free 24 to 60 months after surgical intervention.

From the 50 patients of Dukes' stage B preoperative CEA determinations were made in 25 cases. Increased values were found in 16, normal values in 9 cases. After operation the previously increased CEA values were normalized in 13 patients while 3 patients died two weeks, three weeks and two months, respectively, after the operation. In these 3 patients no evaluable control examination was performed. The remaining 22 patients have been clinically free of symptoms and complaints during 5 to 31 months after surgery.

In the 25 patients of Dukes' stage B classified in the so-called retrospective group, the postoperative CEA determinations revealed normal levels (lower than 10 ng per ml). Repeated control tests indicated the elevation of CEA values in 3 cases. Out of them local recurrence occurred in 2 patients after abdominoperineal extirpation of the rectum and recurrence in the anastomosis after Dixon's operation was observed in one patient. Due to these observations the first patient was submitted to radium therapy (1.11×10^8 Bq \times 10 per 24 h) and the second one to chemotherapy (5-FU, in a total dose of 1000 mg). These treatments were followed by a lowering of the CEA values. Because of the recurrence following Dixon's operation we applied Hartmann's operation and postoperative chemotherapy. Three patients are alive with tumour residue, 22 patients have been clinically tumour-free for 6 to 65 months.

Nineteen patients were grouped into Dukes' stage C. Preoperative serum CEA determinations were made in 9 of them revealing enhanced values in 7 cases (the serum CEA value being higher than the critical 30 ng per ml level in 4 patients). Three patients died within 6 to 14 months. One patient is alive and clinically tumour-free but constantly displays high CEA levels. In 10 patients of this group CEA was measured only in the postoperative period. Out of them 9 patients are alive and appear to be tumour-free for 6 to 108 months, their CEA values being lower than 10 ng. In one patient increased serum CEA level was observed 24 months after surgery; this patient died 4 months later due to the progression of the disease.

From the patients of Dukes' stage D preoperative CEA measurement was made in 15, revealing values over the critical level in 8 cases. All these 8 patients died within one year. In the other patients of this stage significant increase in CEA concentration was observed within 5 to 12 months due to the progression of the disease. Of this group 3 patients are alive, 6 to 42 months after surgery.

Discussion

The carcinoembryonal antigen is not a specific tumour marker. Repeated examinations, however, contribute to the selection of groups among colorectal tumour patients whose tumour disease is of higher risk and of worse prognosis. Several authors take preoperative CEA values into consideration in evaluating

the stage of the disease [4, 10, 13, 26]. Other authors take this value as a prognostic factor in colorectal and pulmonary carcinomas [1, 13, 20]. It appears that current literature generally accepts CEA determinations in the follow-up of colorectal carcinoma patients, in the monitoring of the course of the disease [1, 8, 12, 17]. Authors presenting large patient material [7, 13, 19, 24] warn that increase in the CEA titre precedes the clinical manifestation of tumour progression by 3 to 6 months. CEA values may be important not only in determining operability but also for the late therapy. Surgery is sometimes followed by a transient enhancement of CEA concentration. Its rapid normalization is a favourable prognostic sign [7].

In a fortunate case radical operation is followed by quick normalization of the CEA value which then remains at a low level. If surgery was not radical and tumour tissue was retained in the organism CEA level usually remains high. Local recurrence and development of distant metastases also give rise to enhanced CEA concentrations.

As CEA determination is not tumour-specific (inflammatory processes, smoking, alcohol abuse) increased CEA levels can be evaluated only after repeated tests in comparison with the clinical signs. If the enhanced pre-operative CEA titre is followed after radical surgery by a normalization of the antigen level then a repeated increase in serum CEA level usually indicates progression or recurrence of the process. Some authors consider re-laparotomy necessary even in cases appearing clinically tumour-free in order to detect and treat early the recurrence ('second-look') if serum CEA values are higher than normal [2, 16].

Many authors analyse the correlation between CEA titre and the stage of the colorectal tumour [4, 10, 13, 26]. According to Chaupuis et al. [4], increased CEA values are obtained in 59% of patients in Dukes' stage C and in 94% of those in stage D.

Analysis of our patient material did not allow us to detect such a close correlation between the stages and CEA titre. Normalization of an increased preoperative serum level indicated, however, nearly always the radical character of the operation. Critically high CEA values (over 30 ng per ml) in Dukes' stages C and D can be considered bad prognostic signs. Patients like these died within one year. A repeated increase of CEA level, which had normalized after surgery, indicates a recurrence also in our experience. It is known that efficacy of chemotherapy was proved in certain cases also by the decrease in the CEA titre [8]. In one case we also succeeded in observing the lowering of the previously increased CEA level after a successful chemotherapeutic treatment of a local recurrence.

Comparing literary data and our own experience, we can conclude that high CEA levels have prognostic significance in inoperable cases but they do not entirely exclude the possibility of surgical intervention. Normalization of

CEA level after radical operation is a good prognostic sign. Although systematic CEA control cannot replace careful clinical observation of the patient, it still provides useful complementary data on the diagnosis of recurrence or distant metastases. Signs of local recurrence or metastases must be searched for in case of repeated increase in CEA values after their previous normalization following radical surgery. In selected cases the so-called 'second-look' operation must also be performed in order to remove recurrence in due time.

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Korrelation zwischen den Ergebnissen der Karzinoembryonalen-Antigen (KEA)-Untersuchungen und dem klinischen Stadium des kolorektalen Karzinoms

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Die zwischen den Ergebnissen der KEA-Untersuchungen und dem klinischen Stadium des kolorektalen Karzinoms bestehende Korrelation wurde unter die Lupe genommen. Zwischen dem aktuellen KEA-Titerwert und den verschiedenen Stadien ließ sich kein Zusammenhang nachweisen, die Normalisierung des präoperativ erhöhten KEA-Spiegels sprach indessen fast ausnahmslos für den radikalen Charakter des Eingriffs. Die in den Dukes-Stadien C und D beobachteten kritisch erhöhten (über 30 ng/ml) KEA-Werte zeugen für eine schlechte Prognose: Alle in diese Gruppe gehörenden Patienten starben binnen 1 Jahr. Die Ergebnisse der KEA-Untersuchungen liefern nützliche Daten zur Diagnostizierung von Rezidiven oder Fernmetastasen.

Взаимосвязь между результатами определения карциноэмбрионального антигена (СЕА) и клинической стадией колоректальной карциномы

Л. МОЛНАР, П. РАХОТИ, Э. БАУЭР, П. РОНАИ, И. БЕСНЯК и С. ОТТО

Авторы описывают взаимосвязь между результатами исследований СЕА и клинической стадией колоректальной карциномы. Корреляцию между актуальным титром СЕА и различными стадиями не обнаружили. Однако, нормализация повышенного перед операцией уровня СЕА почти всегда доказывала радикальный характер вмешательства. Критически высокие (30 нг/мл и выше) значения СЕА, отмеченные в стадиях С и D по *Dukes* могут считаться плохим прогностическим фактором. Смерть таких больных наступает в течение одного года. Результаты определения СЕА также могут служить полезными данными для диагностирования рецидивов или отдаленных метастазов.

Current Problems of the Diagnostics of the Retroperitoneum

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The authors discussed the examinations yielding optimal results in revealing the pathological retroperitoneal processes. Among those were bilateral dorso-pedal lymphography, ultrasonography and computed tomography. They evaluated these examinations in detecting the retroperitoneal lymph node metastases of 15 non-seminoma patients.

They describe their 4 cases of extragonadal germ-cell and testicular tumours and speculate on their development. They suppose that the 'unexplainable' renal colics of the older male patients can possibly be due to primary retroperitoneal germ-cell tumours.

The combined examination procedures for revealing the pathological retroperitoneal processes (lymphography, ultrasound and CT) will be discussed. All these procedures have been applied at our clinic for years. These examinations will be evaluated in view of the detection of the retroperitoneal lymph node metastases of 15 non-seminoma patients as well as in that of the examinations of 4 patients with primary extragonadal germ-cell tumours.

Forty per cent of our testiculoma patients were represented by the 'pure' seminoma patients that also underwent the combined retroperitoneal examination. Since retroperitoneal lymphadenectomy (RLA) of these patients is not performed but they are referred to irradiation therapy, this evaluation cannot be made.

We want to emphasize that renal colics of old patients with no obvious cause may be the consequence of ureter compression due to retroperitoneal tumour.

Method

Examination methods used in most of the cases for approaching the retroperitoneum are as follows:

1. Intravenous or infusion urography
2. Arteriography (aorto- or cavography)
3. Lymphography
4. Ultrasound

5. Computed tomography

6. Retroperitoneal air insufflation (O₂).

In the present paper, examinations under points 3, 4 and 5 are dealt with in detail, the others are discussed only superficially.

1. In addition to examining the morphological and functional state of the kidneys, intravenous or infusion urography may call attention to the presence of other retroperitoneal processes. These 'indirect' signs can be as follows. (i) The kidneys themselves, or their lower poles, can be displaced generally laterad. (ii) The ureters can be dislocated both mediad or laterad; in case of lymph node metastases, generally laterad. (iii) Obstructed ureteral flow producing expressed occlusive symptoms without obvious reasons (e.g. stone tumour, abnormal vessel, etc.).

2. Total abdominal or pelvic arteriography is performed in two particular cases: (i) If the suspicion of retroperitoneal tumour could not be confirmed by other examination. (ii) Cavography can be performed if the relationship of the retroperitoneal process or tumour to the vessels is to be clarified or suspicion of a tumorous invasion arises.

3. Lymphography. Although the examination takes a long time and its results are doubtful in some cases, it is still the examination yielding the most complete information on mapping the retroperitoneum.

In 1692 Nuck [cit. 5] was the first to delineate the lymphatic system by injection of mercury. The next step was made at the beginning of the 20th century when Braitwate then Hudack and MacMaster [cit. 5] used indigo carmine stain. After the discovery of X-rays, in 1859, experiments were made by the subcutaneous and intracavitary introduction of radiopaque materials. In 1952 Kinmonth et al. [5] elaborated the technique of bilateral dorsopedal lymphography used also today. The contrast material Lipiodol Ultrafluid (Ethiodol) used today was worked out in 1959 by Fischer and Zimmermann [cit. 5] then five years later by Koehler, Wohl and Schaffer [cit. 5].

The contrast medium injected by cannulation of the lymphatic vessels on the dorsum pedis fills the external inguinal lymph nodes, after passing through the lymphatic vessels of the lower extremity. Then it reaches the retroperitoneum after passing upwards via the external iliac vessels and alongside the great vessels.

The lymphatic system surrounds the vessels by a complicated network, the lymph nodes creating an approximately regular chain before and behind the vessel on both sides. Using this method neither the lymphatics of the perineum, the rectum, the prostate, the bladder, the uterus and the testicles up to their joining the iliac vessels nor the most distal members of the deep inguinal lymph node group coming from the penis are visualized.

Lymphography includes the early filling phase (lymphangiograms) (Fig. 1), and the late storage phase (lymphadenograms) made after 24 hours (Fig. 2).

On evaluating the lymphograms, the morphological changes appear as direct or indirect signs. The angiograms show the course and patency of lymph vessels. Changes are indicated also by the tortuous course of some of the lymph vessel segments or by the dilatation of the lymph vessels suggestive of a flow obstacle.

In the adenograms filling defects are considered direct signs (Fig. 3). For forming a safe diagnosis they should at least be of a diameter of 5 mm. Filling defects can appear in several forms. They can be found in the interior of the lymph node (central defect) in the marginal sinus (marginal defect) and defects can be multicentric within one lymph node. By growing expansively, the process may push the intact part containing the contrast medium towards the marginal sinus and, as a result of the compression, the part of intact tissue adjacent to the alteration may produce a more intensive shadow in a ring-like manner, i.e. the 'rim' or 'halo' sign. If the process has completely destroyed

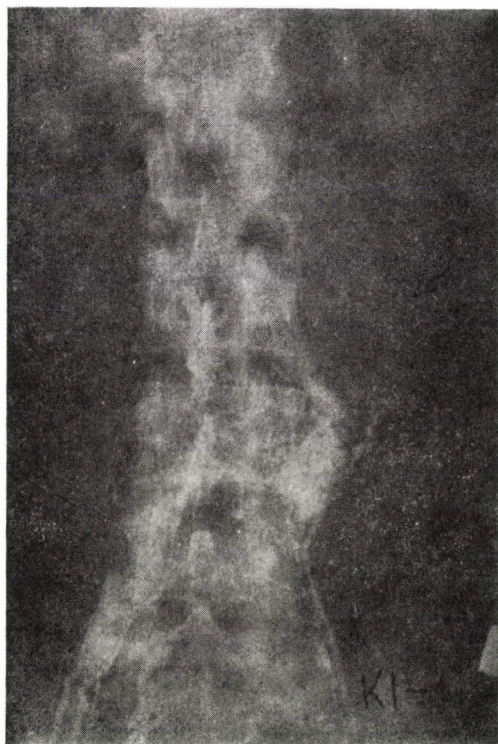


FIG. 1. Lymphangiogram with conglomerate

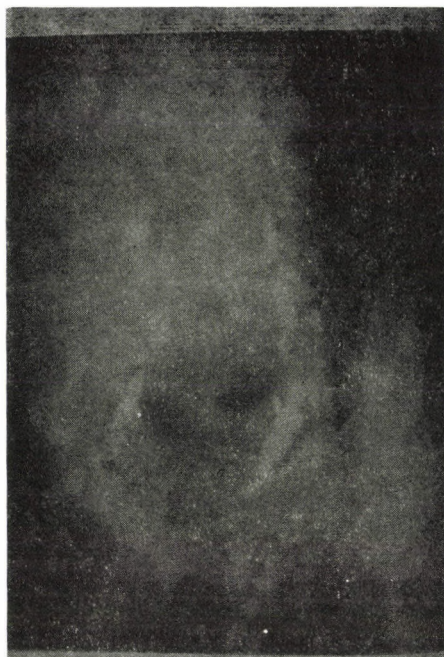
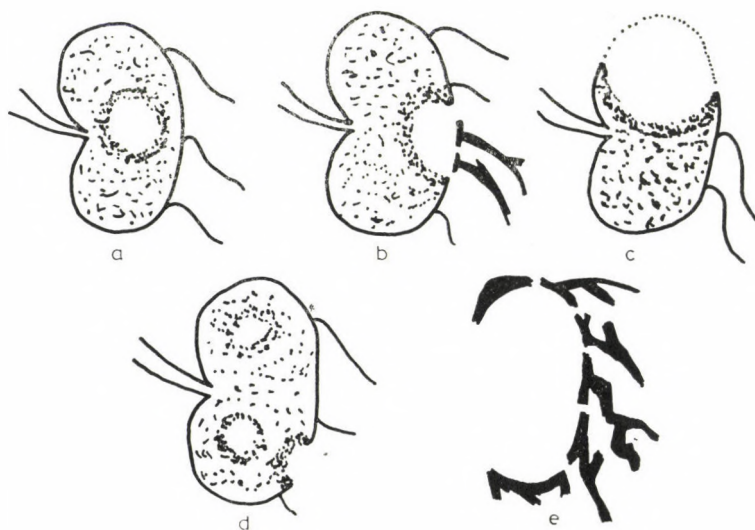


FIG. 2. Lymphadenogram

FIG. 3. Filling defects of lymph nodes. *a.* central, *b.* marginal, *c.* egg-cup sign, *d.* multi-centric, *e.* damaged

one-half of the lymph node, the so-called 'egg-cup' sign develops. The lymph node is not filled by the contrast medium when it is totally infiltrated and its sinus-system obstructed and destroyed by the process. It may also occur that also the afferent vessels of the lymph node are obstructed by the process. In these cases, the enlarged lymph node storing no contrast medium can be diagnosed on the basis of the dislocation produced in the surrounding lymph vessels, moreover, in the surrounding organs, e.g. in the ureter [6, 11].

Each roentgenological symptom suggestive of impeded lymph flow (dilatation of lymph vessels, congestion, extravasation of contrast medium, interrupted lymph vessel, development of collateral circulation, lymphovenous shunt, etc.) can be regarded as an indirect sign indicating pathological alterations.

In view of the above, lymphography is performed in each patient with testicular tumour and in every case when some symptoms or signs may raise the suspicion of a retroperitoneal change. In cancers of the prostate, bladder or penis, lymphography is made only on a well-founded suspicion of metastasis, since, because of the differences between the lymphatic systems of these organs and their dorsopedal lymphographic visualization, lymphograms would play a staging role only.

Earlier inflammatory process of the lymph node and the so-called lipid degeneration, too, may produce inhomogeneity of the storing structures, or minor filling defects. An incorrect evaluation of the defects produced by these changes may result diagnostic errors.

Though rarely, primary Hodgkin's disease, too, may occur in the retroperitoneum. In this case, the characteristic lymph nodes of a 'foamy' structure are to be found [5].

4. Ultrasound. The equipment used for the examination is a Brüel-Kjaer gray-scale static scanner.

Among the retroperitoneal pathological processes and lymph nodes, the larger tumours, cysts, lymphadenomegaly, malignant lymphomas and metastatic lymph node conglomerates can be visualized by echosonography. The enlarged pre- and para-aortal lymph nodes are generally visualized, because of their homogeneity, as round trans-sonic solid structures. They can be relatively well visualized between the liver and the aorta. The iliac region can, however, be approached by ultrasound very inadequately (Fig. 4).

The echogram of lymph node metastases is not homogeneous. In the early phase a strongly reflecting (echogenous) centre is visualized within the trans-sonic mass due to the presence of perivascular adipose tissue (the so-called 'sandwich-sign'). With the advance of the process, the picture is becoming irregular. The method appeared to be best suited for revealing greatly enlarged lymph node conglomerates incapable of storing contrast medium as a result of the tumorous infiltration. These latter structures cannot be visual-

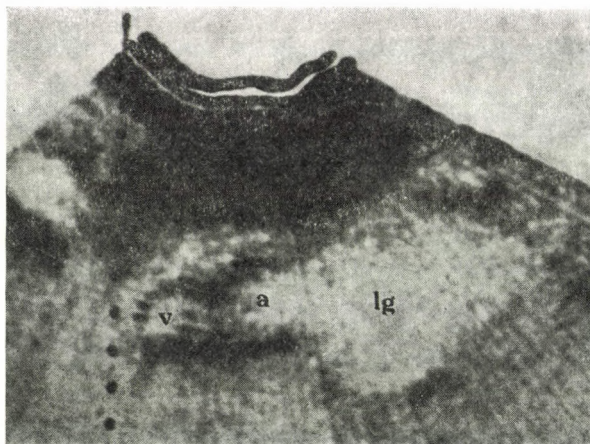


FIG. 4. Ultrasound. a: aorta, v: vena cava, lg: lymph node

ized by lymphangiography. The examination is not influenced either by the presence or the absence of the contrast medium in the lymph nodes.

This method of noninvasive character has been used extensively and it has reduced the importance of examinations used so far, as e.g. retroperitoneal air insufflation. It often renders arteriography superfluous, too (e.g. in case of unambiguous cysts).

5. Computed tomography. The equipment used for the examinations is a Medicor-Pfizer-0100 first generation scanner. Scan time: 6.5 min, matrix: 256×256 , scans: 7 mm thick sections.

Computed tomography is an excellent supplement to lymphography since by its nature it delineates structures from another view. Lymph nodes of a size over 2 cm can be visualized only by the equipment used by us, in the absence of contrast medium. Lymph nodes of the size between 4 to 5 mm can also be localized if they are filled with contrast medium. Therefore CT has been performed always after lymphography.

CT is a valuable aid in assessing the relationship between the lymph nodes with metastases and their surroundings, primarily the aorta and the inferior vena cava. This problem is of great importance in operability (Fig. 5).

Similar to ultrasonography, CT can reveal the lymph nodes or lymph node conglomerates with metastases of the regions which are not reached by the lymphographic contrast medium, e.g. the lymph nodes of the renal hilus.

6. Retroperitoneal air insufflation (O_2) is very rarely performed partly due to its strongly invasive character and partly to the ultrasound possibilities. Today, it can be of importance only in the case of some adrenal tumours, therefore it is rather of historical character.

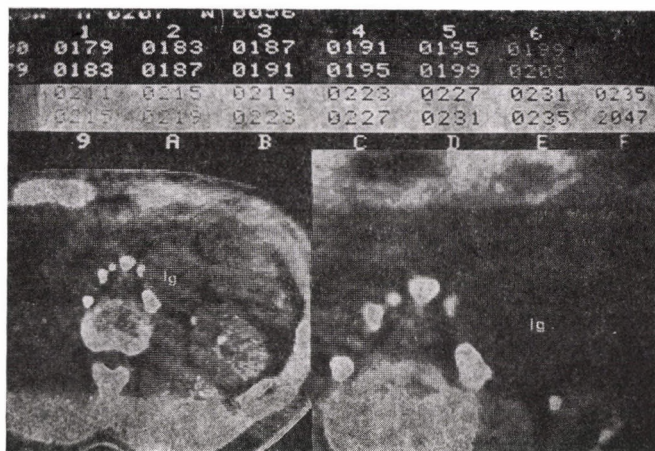


FIG. 5. lg: conglomerate pushing lymph nodes aside

Results

Table I is a summary of the combined retroperitoneal examination of 15 non-seminoma patients. It appears that in 4 cases indirect signs are already shown by the urograms.

TABLE I

Comparison of the data of retroperitoneal testicular tumour metastases

Case No.	Infusion urography	Lymphography	Ultra-sound	CT	RLA	RLA histology
1	neg.	pos.	pos.	pos.	operable	neg.
2	neg.	pos.	—	—	inoperable	metastasis
3	neg.	pos.	pos.	pos.	operable	metastasis
4	neg.	neg.	pos.	neg.	operable	neg.
5	neg.	pos.	neg.	neg.	operable	metastasis
6	dislocated ureter	neg.	neg.	pos.	operable	metastasis
7	dislocated ureter	pos.	pos.	pos.	inoperable	metastasis
8	dislocated ureter	pos.	pos.	pos.	operable	metastasis
9	neg.	pos.	neg.	neg.	operable	metastasis
10	dislocated ureter	pos.	pos.	pos.	inoperable	metastasis
11	neg.	pos.	neg.	neg.	operable	metastasis
12	neg.	neg.	neg.	neg.	operable	neg.
13	neg.	neg.	—	—	operable	metastasis
14	neg.	pos.	pos.	pos.	operable	metastasis
15	neg.	neg.	neg.	pos.	operable	neg.

TABLE II
Primary extragonadal

Case No.	Age	Symptom	I. v. pyelography	Localization
1	52	pain in lower extremities, walking disturbances	right ureteral dislocation	retroperitoneal
2	62	right inguinal lymph node enlargement	neg.	right inguinal
3	51	renal colic on left side, fever	left ureteral dislocation, congestion of renal pelvis	retroperitoneal
4	74	renal colic on right side, haematuria	partial occlusion of right lower ureteral portion	retroperitoneal

The value of lymphography is 80 %, with a 10 % false-positive and 40 % false-negative error.

The value of ultrasonography is 54 % with a 29 % false-positive and 67 % false-negative error.

The value of CT is 62 % with a 25 % false-positive and 60 % false-negative error.

Evaluating all three examinations reveals that there is no more false-negative error, the false-positive one moves, however, around 20 %. On assessing the combined examinations together, it is considered to be a positive examination if the result of only one examination is positive. So the accuracy of diagnosis for all examinations is around 80 %.

Table II summarizes our patients with primary extragonadal germ-cell tumours. The process was primarily retroperitoneal in cases Nos 1, 3 and 4. Only one patient—No. 3—was preoperatively examined. Patients No. 1 and 2 were transferred from the Department of Surgery with preoperatively known histological results. On palpation, the testicles were normal in every case. In the first two cases, biopsies of the testicles were also normal. RLA was also made in patient No. 2 with negative histological results. This patient has so far been free of symptoms and complaints. He received chemotherapy, too. Despite the immediate combined chemotherapy in cases Nos 1 and 3, and the immediate irradiation in case No. 4, the patients were lost some weeks post-operatively.

erm-cell tumour cases

Operation	Histology	Lymph- ography	Ultra- sound	CT
inoperable	Leyding-cell testiculoma metastasis	postop. pos.	postop. pos.	postop. pos.
operable	germ-cell testiculoma metastasis	postop. neg.	postop. pos.	postop. pos.
nephrectomy on left side, inoperable	embryonal-cell carcinoma	pos.	pos.	pos.
nephrectomy on right side, inoperable	seminoma (embryonal form)	postop. pos.	postop. pos.	postop. pos.

Discussion

The combined examination including bilateral dorsopedal lymphography, ultrasound and CT is sufficient for morphologically examining the retroperitoneum after urography. These examinations should be evaluated not separately but together to achieve the almost optimal diagnostic accuracy.

Attention should be paid to the appearance over the fifth decade of primary extragonadal germ-cell tumours of testicular origin, primarily in the retroperitoneum [2]. Primary retroperitoneal germ-cell tumours can be of three origins [1, 7]. (i) It developed from a congenitally misrouted germ-cell; (ii) It was growing as a metastasis of an occult undetected testicular tumour; (iii) It was growing as the metastasis of an undetected testicular tumour in the retroperitoneum, then, after development of the metastasis, the primary testicular process regressed.

According to our experiences, these tumours start to grow rapidly after operations, should any treatment be applied. This observation does not correspond to the data of Munro et al. [7] who describe these to be well-reacting tumours.

Naturally, no far-reaching conclusions can be drawn from the three described cases.

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Zeitgemäße Fragen der Diagnostik des Retroperitoneums

L. SCHMIDT und G. VYDRA

Zur Diagnostizierung der pathologischen Prozesse des Retroperitoneums kam das kombinierte, beidseitige Fußdrücken-Lymphographie, Ultraschalluntersuchung und Computer-Tomographie in sich fassende, als das optimalste betrachtete Untersuchungsverfahren zur Anwendung. Anhand der Erfahrungen mit der Diagnostizierung der retroperitonealen Lymphknotenmetastasen von 15 nicht seminomatösen Patienten findet die Auswertung der angeführten Untersuchungen einzeln und auch gemeinsam statt.

Im Zusammenhang mit der Darstellung von 4 Fällen mit extragenitalem embryonalem Hodengewebetumor wird — unter Berücksichtigung der Literaturdaten — die sich auf die Entwicklung der Neubildungen beziehende Hypothese erläutert. Schließlich wird darauf hingewiesen, daß im Hintergrund der »unerklärlichen« Nierenkolik der älteren Männer unter Umständen ein primärer, retroperitonealer, embryonaler Tumor stehen kann.

Актуальные вопросы диагностики ретроперитонеальных процессов

Л. ШМИДТ и Г. ВИДРА

Авторы обсуждают комбинированное обследование, которое они считают самым оптимальным в наши дни для выявления патологических процессов забрюшинного пространства. Это комплексное обследование включает в себя двустороннюю лимфографию тыльной поверхности стопы, ультразвуковое исследование и компьютерную томографию. Результаты каждого исследования они оценивали отдельно и вместе, сравнивая с данными, полученными в ходе поисков метастазов в ретроперитонеальных лимфатических узлах у 15 больных, не имевших семиномы.

Авторы описывают 4 наблюдения экстрагенитальных, с зародышевыми клетками, опухолей, происходивших из ткани семенников, излагают свои представления относительно их возникновения, которые они сравнивают с литературными данными. Обращают внимание на то, что, на заднем плане «необъяснимых» почечных коликов у мужчин пожилого возраста, может быть первичная ретроперитонеальная эмбрионально-клеточная опухоль.

Importance of the Urodynamic Examination of Aged Patients

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(Received May, 5 1984)

Urodynamic studies have been made since 1980 in aged patients treated for micturition disorders. Impaired micturition reflex action was found in 37% of the cases. The importance of the combined use of cystometry with sphincter electromyography is emphasized.

Urinary complaints appear in old age in the form of impeded micturition, frequency and urgency of micturition and overflow incontinence. Male patients are admitted because of hypertrophy and cancer of the prostate, sclerosis of the bladder neck and stenosis of the urethra; female patients present with cystocele. Urological surgery has undertaken the care of patients over 75 years to a growing extent. In this age peripheral and central changes due to atherosclerosis (malattia, apoplexy), neurological disorders [13] (parkinsonism), systemic diseases (diabetes mellitus) occur cumulatively [7, 8, 11]. The prerequisite of a successful operation is the intact state of the innervation of the lower urinary ducts. Disturbances of the urinary reflex may arise from anywhere, from the cerebral cortex to the lower urinary tract [3, 4] (Fig. 1).

Material and Method

In our clinic, urodynamic examinations have been made regularly since 1980 by the Browne UD 4E equipment examining old age micturition disorders. The equipment is suitable for CO₂ cystometry, external sphincter electromyography combined with filling of the bladder, urethral pressure profile examination and for uroflowmetric recording. This procedure is used for revealing urological dysfunctions and for measuring the effectiveness of medication [1, 5]. As a matter of course, urodynamic detection is preceded by urinalysis for revealing infection, by infusion urography, miction and retrograde ureterography and cystography for clarifying the anatomical changes. In certain cases (bladder tumor, stones) cystography is performed.

In the urodynamic laboratory a total of 460 tests have been made so far, in 118 of them for old age micturition complaints. Owing to the acute or chron-

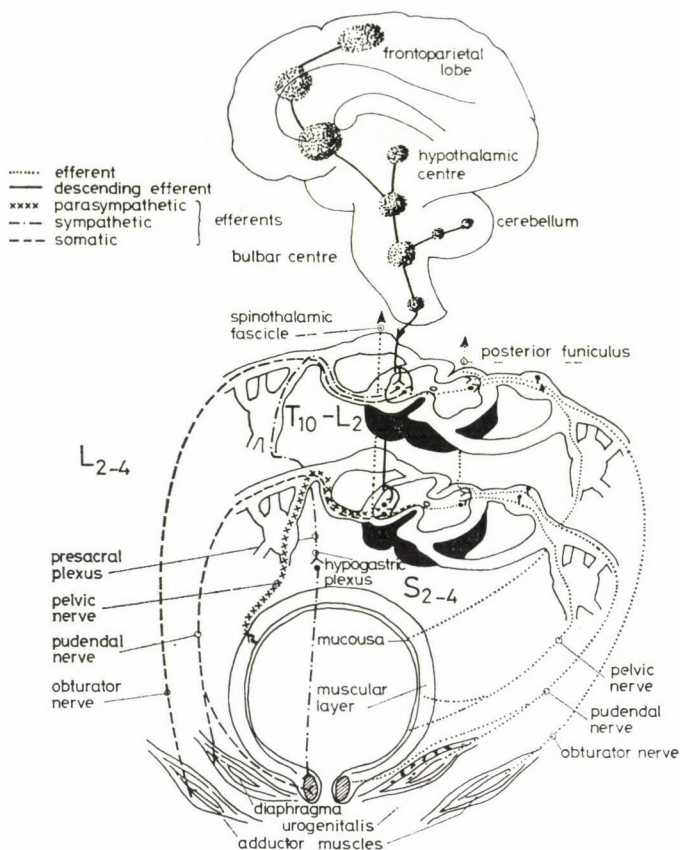


FIG. 1. Neural regulation of micturition

ic inflammation of the bladder, the detrusor muscles contract strongly and frequently and an urgency of micturition was the dominant symptom of the pathological picture (Fig. 2). The bladder of a small volume having lost its compliance often causes painful micturition.

The involvement of the autonomous nervous system of the bladder often accounts for the micturition disorder. Parasympathetic stimulation induces contraction of the detrusor.

Blockade of the alpha-sympathetic fibres stimulates the opening of the neck of the bladder and the relaxation of the posterior urethra. Stimulation of the beta-sympathetic fibres decreases urethral pressure and relaxes the neck of the bladder. Disorder of the adjacent sensory nerves (pudendal nerve, presacral plexus, hypogastric nerve) lead, in diabetes mellitus, to continuous dribbling [2] (Fig. 3).

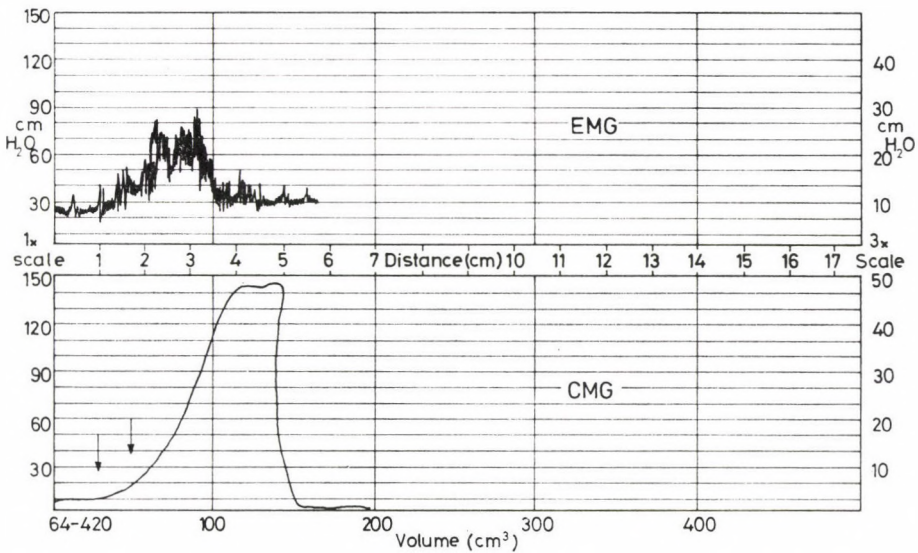


FIG. 2. EMG and CMG pictures of chronic cystitis developed after TUR due to sclerosis of the bladder neck. Urgency of micturition appears at a low bladder pressure. The maximal bladder tension is higher than normally. Sphincter function is normal

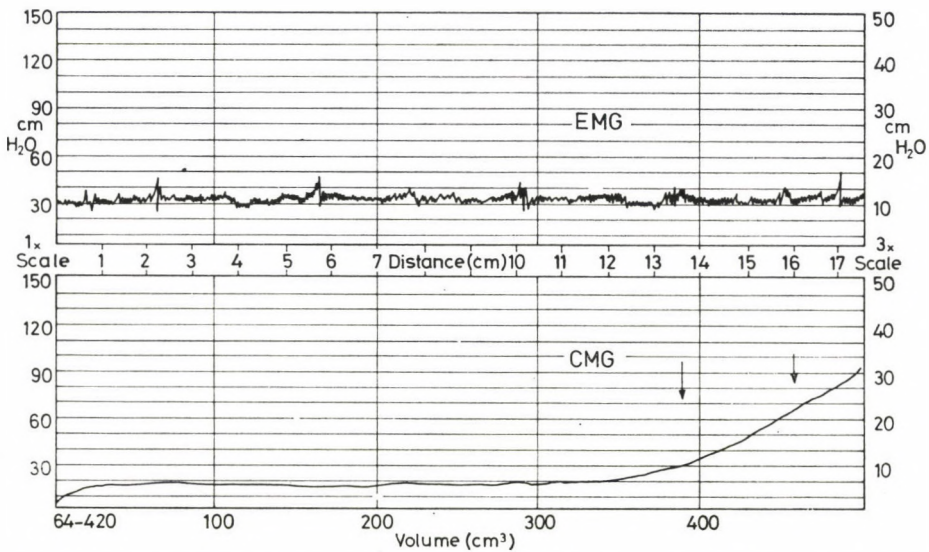


FIG. 3. Urinary retention of 200 to 250 ml in a patient presenting with dysuric complaints. The diabetes mellitus having persisted for 12 years has caused a peripheral innervation disorder of the bladder

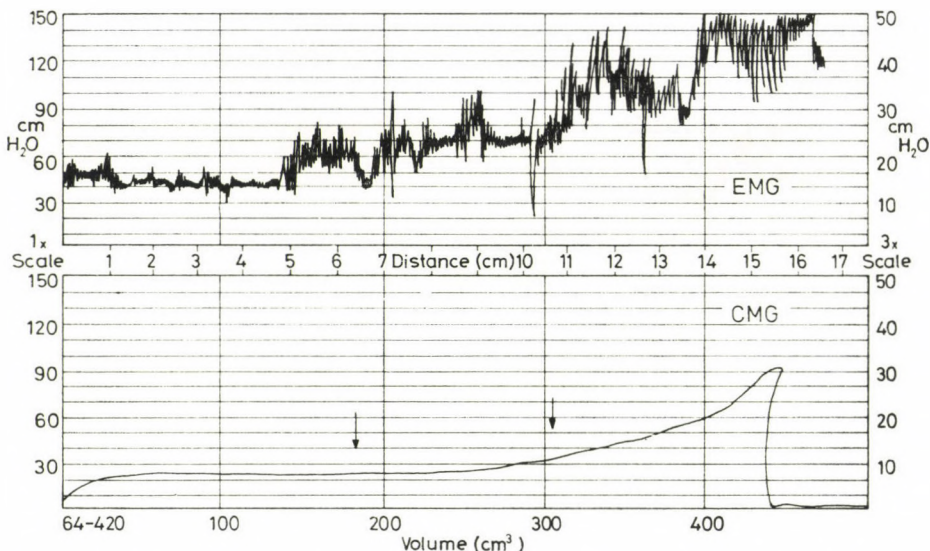


FIG. 4. Central motor innervation disorder. The patient was admitted because of prostatic hypertrophy. Bladder dysfunction had been caused by herpes zoster

Involvement of the sacrospinal centres (S_2 , S_3 , S_4) produces atony of the bladder (Fig. 4; prostatic hypertrophy and herpes zoster).

Disturbance in the central inhibition of the spinal bladder reflex centres may produce detrusor-sphincter dyssynergia (Fig. 5; sclerosis of the bladder neck, meningocele) [9, 10].

Involvement of the grey nuclei of the brain stem and of the frontoparietal part of the brain may provoke bladder spasm with intensive pollakiuria. The isolated frontal lesions may cause precipitant urination, however, the voluntary sphincteric control is normal. Bilateral diffuse cerebral lesions evoke non-inhibited detrusor contractions with an inhibited sphincteric reflex (Fig. 6; prostatic hypertrophy, state after cerebral thrombosis).

Thirty-seven per cent of micturition disorders are due to neurological changes.

Discussion

The innervation system of the lower urinary tract can be divided into four functional circles [6]. The first connects the motor detrusor-centre situated in the frontal lobe with reticular formation in the height of the diencephalon. This circle is connected with the thalamus, the basal ganglia and with the limbic system. The reflex is stimulated by the thalamus and is inhibited by the basal ganglia and the limbic system. Besides, the cerebellum, too, controls and

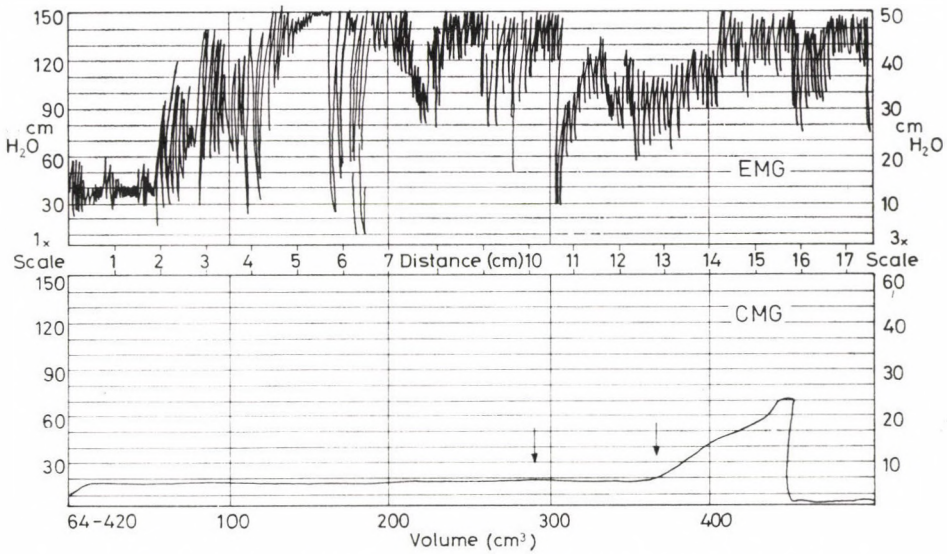


FIG. 5. EMG and CMG pictures of detrusor-sphincter dyssynergia

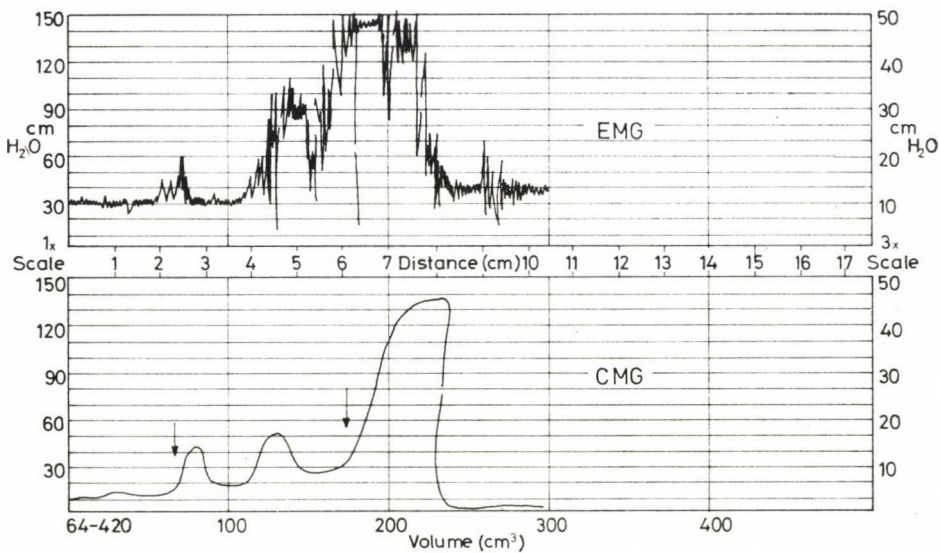


FIG. 6. The patient admitted due to prostatic hypertrophy has had a history of cerebral thrombosis. His frequent urge to micturate was caused by contractions of the non-inhibited detrusor

modulates the functioning of the first circle. In case of an intact reflex arc, the detrusor contractions can be voluntarily suppressed, in case of a disturbance the stimulus threshold of micturition will decrease.

Central detrusor hyperreflexia may be due, in old age, to brain tumour, parkinsonism or mental deterioration. Cystometry indicates the disorders of the first circle [12].

The second circle of innervation includes the sensory nervous paths (running from the receptors of the bladder wall to the miction centre of the reticular formation), and also the motor fibres in the intermediolateral column. This circle contains proprioceptive afferents and motor efferents which, like the preganglionic neurones of the motor detrusor centre in the sacrospinal cord, are situated in the grey matter. The circle is responsible for the coordinated transmission of the miction reflex.

The third innervation circle contains afferents which arise from the intramural stretch receptors of the detrusor and pass to the motor neurones of the pudendal plexus to the sacrospinal cord. The motor impulses of the pudendal nucleus are inhibited by this reflex and the striated, periurethral muscles become relaxed. The intactness of the reflex arc can be evaluated by the combined use of cystometry and electromyography. Its disturbance may be due to arachnoiditis and diabetes mellitus [12].

The fourth circle of innervation is responsible for the supraspinal and segmental innervation of the striated sphincter muscles. The supraspinal part of this circle contains sensory nervous paths in the posterior column which connect the muscle spindles of the pelvic floor with the ventrobasal nucleus of the thalamus. From here additional axons pass to the pyramidal cells of the pudendal area to the sensory brain cortex. The motor impulses run in the corticospinal tract through the internal capsule to the sacrospinal grey matter. The functional capacity of the fourth circle can be studied by electromyography. Tearing of the supraspinal part may lead to sphincter spasms, injury of the adjacent region, to relaxation of the sphincter.

In diagnosing micturition disorders in the aged patients, urodynamic examinations are of importance. Particularly cystometry and the summation electromyography of the external sphincter may provide valuable information on the intactness of the bladder reflex. It is not always difficult to interpret the records. Neurological changes due to individual or systemic diseases may appear as mixed dysfunctions. Diabetes mellitus may impair the associated micturition centre. The second or third innervation circles, too, may be affected. Cerebromalacia and mental deterioration as a result of atherosclerosis may produce disturbances at both the first and fourth levels of innervation. Only a careful history taking, the consideration of the neurologist's opinion, and necessary, complementary examinations (bidirectional spinal roentgenograms, EEG, cranial CT, isotope carotography, etc.) may aid in detecting the disturb-

ances of the micturition reflex. When operation or drug treatment of micturition disorders in old age result in failure, an altered function of the nervous system should also be considered.

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Bedeutung der urodynamischen Untersuchung von bejahrten Patienten

E. SZÜLE und Zs. SIMON

Bei wegen Miktionsbeschwerden behandelten Patienten werden seit 1980 urodynamische Untersuchungen vorgenommen. In 37% der Fälle waren Störungen des Miktionsreflexes zu beobachten. Anhand der ermittelten Erfahrungen wird die Wichtigkeit der simultan mit der Zystometrie durchgeführten Sphinkter-Elektromyographie betont.

Значение уродинамических исследований у пожилых больных

Э. СЮЛЕ и Ж. ШИМОН

С 1980 г. авторы производят уродинамические исследования у пожилых больных, которые лечатся по поводу жалоб в связи с мочеиспусканием. Нарушения мочеиспускательного рефлекса отмечались у 37% больных. Авторы подчеркивают важность выполнения электромиографии сфинктера одновременно с цистометрией.

Primary Retroperitoneal Tumours and Cysts

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The authors give a summarizing report on retroperitoneal tumours and cysts. They review the origin and classification of tumours and cysts, their diagnostic and differential diagnostic possibilities as well as the therapeutic measures. Finally, their own 3 cases are reported.

Retroperitoneal tumours and cysts develop behind the peritoneum or among the serosal layers of the mesentery and are not connected with the retroperitoneal organs. These are called primary or genuine tumours and cysts, respectively.

Retroperitoneal tumours and cysts occur rarely and cannot easily be traced at an early stage not even by the current up-to-date diagnostic procedures. Lobstein [11] was the first to describe in 1829 retroperitoneal tumours, making, however, no distinction between the cyst and the solid tumour. The tumours arise from nerve fibres and ganglia as well as from mesenchymal adipose and connective tissues [1, 2, 6, 8, 11, 13]. Fibroma, lipoma and myxoma occur the most frequently [3], teratoma is less frequent [9, 11], while neurogenic tumours occur fairly infrequently [1, 8].

The age and sex distribution of these tumours shows great fluctuation [3, 12, 13]. According to some authors, the male to female ratio can be estimated to be almost identical, while to others, the ratio is 1 to 3 [3]. Age distribution ranges between 30 to 50 and 40 to 70 years, respectively [3]. Occurrence of malignant tumours greatly differs.

According to the classification of Frang and Pákozdy [5, 13], primary retroperitoneal tumours and cysts can be grouped as follows.

Pathology

Group I: Solid tumours.

1. Adipose-tissue tumours.

2. Connective-tissue tumours. They occur in varying number and size. They can often mix with other tissue elements.

3. Smooth muscle tumours, partly benign and partly malignant; leiomyosarcoma giving metastases via the blood mainly to the liver and the lungs.

4. Striated muscle tumours. They arise from the mesenchymal tissue and are fairly malignant.

5. Lymphangiomas and lymphomas of the lymphatic tumours, are benign. Malignant are the lymphogranulomas, lymphosarcomas and reticulomas.

6. The neurogenic tumours of the retroperitoneum are as follows.

a. Neurinomas arising from the peripheral nerves, neurofibromas and neurosarcomas.

b. The sympathetic nervous system may give rise to ganglioneuroma and gangliocytoma which can both be benign and malignant.

c. Paragangliomas arising from the chromaffin tissue of the paraganglions producing norepinephrine.

7. Retroperitoneal carcinomas metastasize into the lungs, liver and the brain.

Group II: Non-differentiable, immature sarcomas causing early death.

Group III: Cysts classified as follows.

1. Embryonal urogenital cysts.

2. Dermoid cysts containing the elements of all three germ layers.

3. Cysts arising in the mesocolon.

4. Traumatic cysts that are smaller and devoid of epithelium.

5. Parasitic cysts occur rarely in Hungary.

6. Lymphatic cysts with a yellowish content.

Symptoms

The symptoms of retroperitoneal tumours and cysts are not characteristic and appear only with the advancement of the process. The first complaints are due to the compression of the large size cyst or tumour on its environment. Vague abdominal, lumbar pain, occasionally gastric and intestinal disorders, nausea, a sensation of repletion are possible to appear. Dyspnoea can occur if the tumour compresses the diaphragm but this may also be due to lung metastasis. The compression of the common bile duct may lead to icterus, that on the inferior vena cava to the swelling of the lower extremity. Ureteral compression may produce renal colic. In case of infection of the cysts septic fever may develop.

Diagnostics

On palpation a fixed tumour or an elastic or mobile cyst was observed. It is important to perform intravenous urography. If this fails to provide the necessary information on the relationship between the kidneys, the pelvic

cavity, the ureter and the tumour or the cysts, it is important to perform retrograde pyelography or X-ray diagnostics of the stomach and intestine. A frequently used examination is pneumoretroperitoneum being a most helpful diagnostic aid. In the recent years computed tomography, ultrasonography and angiography have assumed importance in the diagnosis and differential diagnosis of retroperitoneal space occupying processes. These examinations help demonstrating, in the majority of cases, the tumours or the cysts.

A safe recovery can only be expected of an early operation which, as a result of delayed and non-alarming complaints, is often performed too late. Operation can be made trans- and retroperitoneally. Exploration is always made according to the site, nature and size of the tumour.

As a supplement to surgical treatment, X-ray irradiation may also be considered. In certain cases, following irradiation, an inoperable tumour may become operable [3].

Of a total of 12,031 operations performed at our clinic between 1974 and 1984, 3 retroperitoneal tumours have occurred. These 3 cases will be presented here.

Case Report

T. E., a female patient, aged 22, was referred to our clinic from the urology section of one of the county hospitals in 1982 with the suspicion of right renal tumour revealed by intravenous urography and angiography (Fig. 1). The patient underwent physical examination due to gastric pains, nausea and vomiting. Esophagogastroboscopy revealed extraventricular impression. Subsequently, retrograde pyelography of the right side was performed which enabled the visualization of the caudad and laterad dislocation of the right renal cavity system. The abdominal CT delineated the cystic change of the liver or an extrahepatic space occupying process compressing the liver.

Laboratory findings: haemat.: 38%, WBC: 8000, Hg: 65 g/l, BUN: 4.7 mmol/l, SER: 62 mm/h. Subsequent transperitoneal exploration revealed a 4500 g tumour anchoring on the kidney but arising from the retroperitoneum, compressing the liver and the stomach and connected through connective tissue bands with the inferior vena cava and the diaphragm. The tumour was removed together with the kidney.

Histology: Fibrosarcoma (Fig. 2). For after-care she was referred to the National Cancer Institute.

K. J., a female patient, aged 76 was transferred to us from one of the medical departments in January 1983, where she had been admitted to because of weight loss, gastric pains and tympanites. The palpation finding was suggestive of a fixed space occupying process.

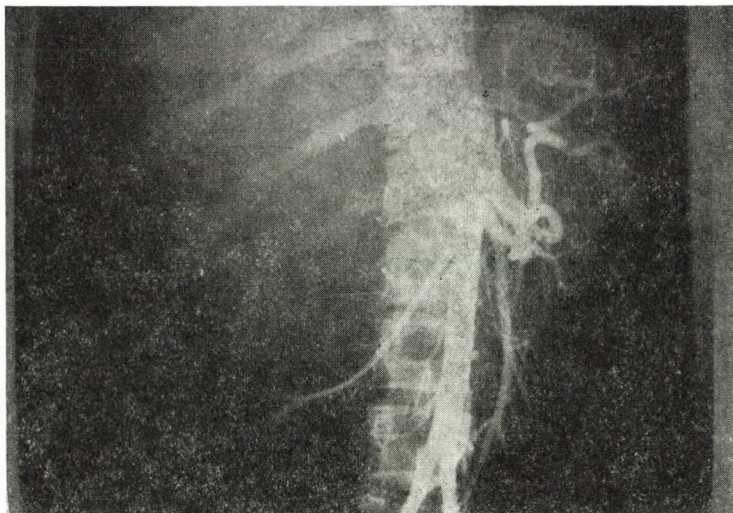


FIG. 1. Aortography: the abdominal aorta is moderately dislocated to the left. The right renal artery is elongated and shows a caudal dislocation. Above it an avascular mass can be seen



FIG. 2. Macroscopic picture of a 4500 g retroperitoneal tumour removed together with the kidney

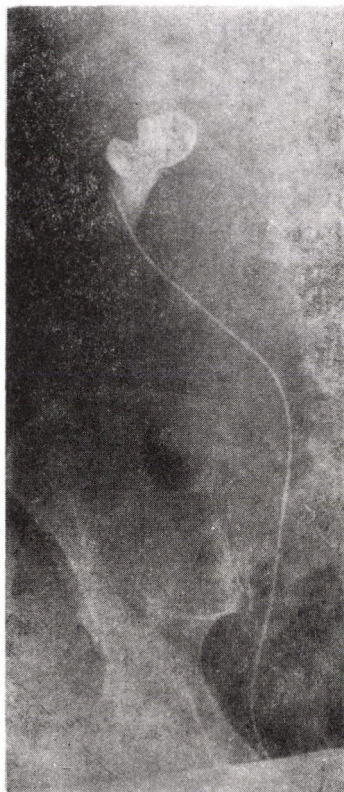


FIG. 3. Retrograde pyelography of the right side. The right ureter shows a dislocation laterad cranially from the fourth lumbar vertebra. The pelvis and the lower pole of the right kidney are also dislocated laterad

Laboratory findings: haemat.: 38%, WBC: 8500; Hg.: 117 g/l, BUN: 5,5 mmol/l; SER: 112 mm/h.

The intravenous urography demonstrated the caudal dislocation of the right kidney and of the proximal third of the pelvic cavity, arousing the suspicion of a retroperitoneal space occupying process. Retrograde pyelography on the right side confirmed our suspicion (Fig. 3). In the course of retroperitoneal exploration, a tumour arising from the retroperitoneum, enveloping the kidney, compressing the vena cava inferior and occupying the whole retroperitoneal space was removed (Fig. 4).

Histology: Myogenous tumour showing the signs of regressive atypia. The patient died 4 months after the operation.

B. I., a 15-year-old boy was transferred to our clinic from the urology section of one of the hospitals in October 1983 with a retroperitoneal tumour confirmed partly by palpation and partly by intravenous urography. Intravenous urography also showed a silent kidney on the left side. Ultrasonography

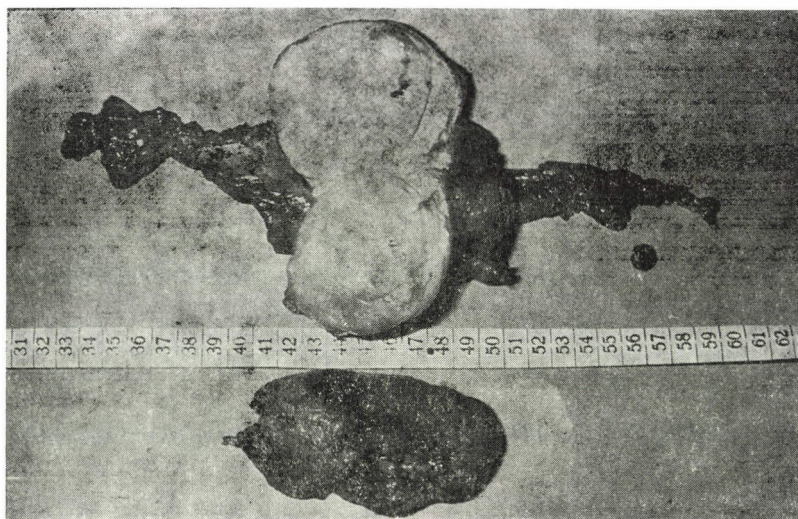


FIG. 4. Removed right non-functioning kidney and a 2500 g retroperitoneal tumour

confirmed the suspicion of the retroperitoneal tumour dislocating the left kidney and causing stasis of the pelvic cavity.

Laboratory findings: haemat.: 47%; WBC: 9200; Hg.: 140 g/l, BUN: 5.1 mmol/l; SER: 32 mm/h.

During surgical exploration the tumour was removed together with the kidney (Fig. 5).

Histology: myxofibrosarcoma.

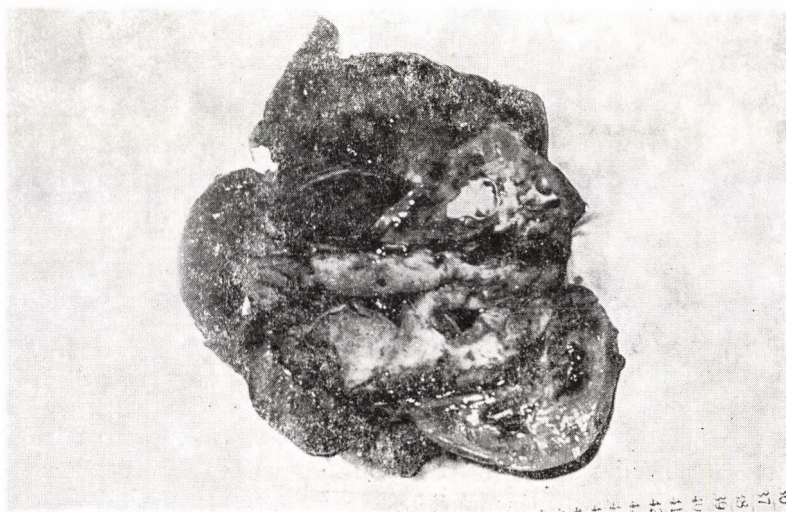


FIG. 5. Macroscopic picture of a left retroperitoneal tumour

Discussion

According to Frang's report [5] cysts occur fairly infrequently among retroperitoneal tumours. Kretschmer [cit. 5] found that each cystic retroperitoneal tumour derives from a fetal kidney element. This statement was supported by Maury's own case [cit. 5], where the wall of the cyst contained tubuli, glomeruli and ureter-like structures. Campbell [4] described a congenital cyst of mesonephrogenous origin having compressed the upper ureteral segment. In 1864 Virchow [cit. 7] found the majority of retroperitoneal tumours to be sarcomas.

Primary retroperitoneal tumours amount to 0.2% of all tumour cases [1, 2, 12, 13]. The number of cases published so far is estimated to be 3300. Gönczi et al. [7] in their study of 15-years' material found 24 primary retroperitoneal tumours. In the 10-years' patient material of the Mayo Clinic 46, in that of the Lahey Clinic under 30 years a total of 101, and at the Department of Surgery of Würzburg University a total of 41 cases were observed in the period between 1945 and 1970 [12]. Pákozdy [13] observed 11 cases of primary retroperitoneal tumours out of 18,868 operated patients between 1957 and 1967.

The reviewed cases also reveal that these tumours occur very rarely, their symptoms are not characteristic and they are difficult to diagnose. If the available diagnostic possibilities will not help promoting progress, surgical exploration is to be made as soon as possible.

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Primäre retroperitoneale Tumoren und Zysten

GY. BORS, L. POLYÁK und D. FRANG

In der Arbeit werden die sich auf die retroperitonealen Tumoren und Zysten beziehenden Kenntnisse — Ursprung, Aufteilung, diagnostische und differentialdiagnostische Möglichkeiten sowie therapeutische Lösungen — zusammengefaßt. Zum Abschluß werden drei eigene Fälle dargestellt.

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Anastomoses of the Colon Made by Inverting Sutures

B. KEMENES and P. VADÁSZ

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(Received 12 October, 1984)

The authors report on the advantages of inverting suture in the anastomoses of the colon. The comparative evaluation of the stapler gun technique and the sleeve technique is presented.

In recent years mostly Czerny's sutures, later anastomoses performed by the KC stapler, and lately, the sleeve anastomoses were performed at our Department in operations of the colon [14]. Our results corresponded not so much to the optimistic reports published after the first applications of these methods, but to the subsequent realistic analyses. Starting from the sleeve technique, attempts were made to proceed by considering the physiological characteristics. In anastomoses created by this technique, early and prolonged strictures may frequently develop [14]. This has produced some aversions to the otherwise easily and reliable constructible anastomoses. Development of stenoses was ascribed to the vulnerability of the serosa of the telescoped intestinal stump, and to the disorders in the blood supply of the relatively large portion of the invaginating intestinal wall.

The free surface of the serosa reacted with a strong inflammation on the exposure to the bacterial flora of the bowel contents and to the enzyme effects; the deficient blood supply resulted in necrobiotic processes. With our method we attempted to protect the serosa of the intestinal stump on the one hand, while, on the other, to create a better blood supply by decreasing the size of the invaginating portion. At the same time, there was a demand for a technique to be used in connection with end-to-end anastomoses involving the entire intestinal tract. Most of the stitches currently in use are perpendicular to the resection line, that is, they disregard the physiologically as well as anatomically important fact of the circular course of the functional end-artries supplying the gut. The suture presented by Halsted in 1887 had already reflected this view [7]. Taking into consideration the appropriate sizes and proportions, the 'U' stitches of a one-layer suture placed through the submucosa were found to fulfil all these purposes.

Importance of the 'Closed' Technique

The closed version of our method was constructed to eliminate the problems arising from an imperfect intestinal preparation and to prevent inoculation in operations of tumorous intestines (Figs 1 and 2). It cannot be expected that the mucosal surfaces become sterile even with the current up-to-date preparation of intestinal operations [10]. On the other hand, the lumen of the tumorous intestine, aborally, but also orally, from the tumour, contains a large number of detached inoculable tumour cells. Preliminary results of our investigations indicated that the number of tumour cells can be reduced, but cannot be eliminated on applying a 5-fluorouracil lavage [12]. Preparation by using a hyperosmotic solution increases the number of tumour cells in the ampulla. Following right hemicolectomy, relapses frequently occurred in telescoped stumps and anastomoses but recurrences were also found in the invaginated stump after Hartmann's operations [14].

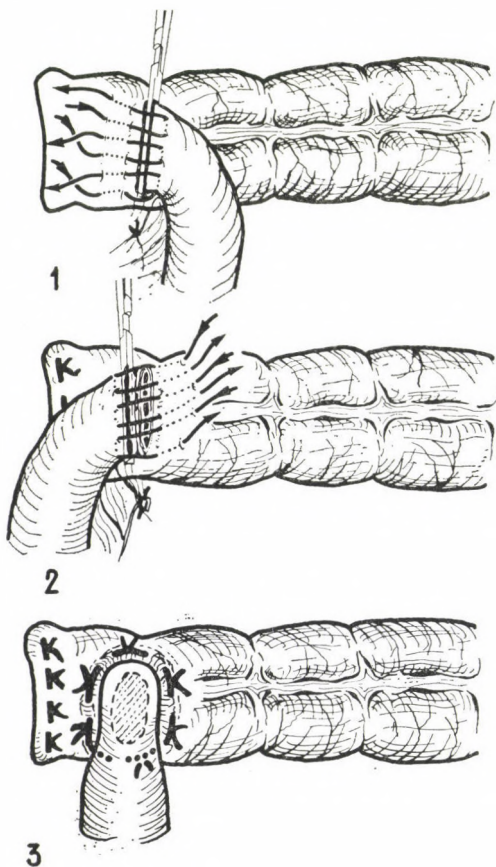


FIG. 1. Right end-to-side hemicolectomy with 'A' stitches

Both observations apply to surgical solutions where the surgeon can work at a distance from the tumour and he has less opportunity to violate the rule of 'no touch isolation' formulated by Turnbull. Undoubtedly, the detached tumour cells are present already at the start of the operation in the region of the suture line to be made. They will be implanted into the intestinal wall by the sutures or clips. This has been proved by the fact that when we switched over to the stapler gun technique the 10% anastomosis recurrences increased

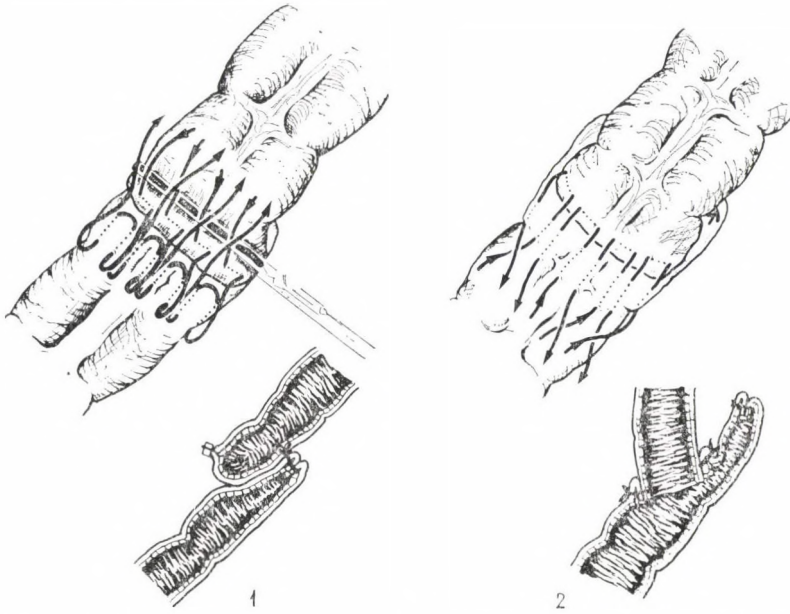


FIG. 2. End-to-side colocolostomy. Posterior wall with 'B' stitches, anterior wall with 'A' stitches. The anastomosis can also be placed on the tenia cutting it up longitudinally. In these cases only 'A' stitches are used

to 50%. We had to admit that we ourselves were responsible for moving tumour cells together with the intestinal mucus into the anastomosis; they were implanted by our clips into the intestinal wall. Only by administering cytostatic lavage did we succeed in decreasing the number of anastomosis recurrences to 25%. Simultaneously with switching over to the other technique, the number of septic complications also increased. For avoiding both mistakes, it is advisable to construct 'closed' anastomoses by inserting stitches not involving the intestinal lumen [2, 5, 9, 10, 13] (Fig. 3).

Colocolostomy does not differ from any other types of anastomoses involving other portions of the intestine. In case of colectostomy a minor alteration was employed.

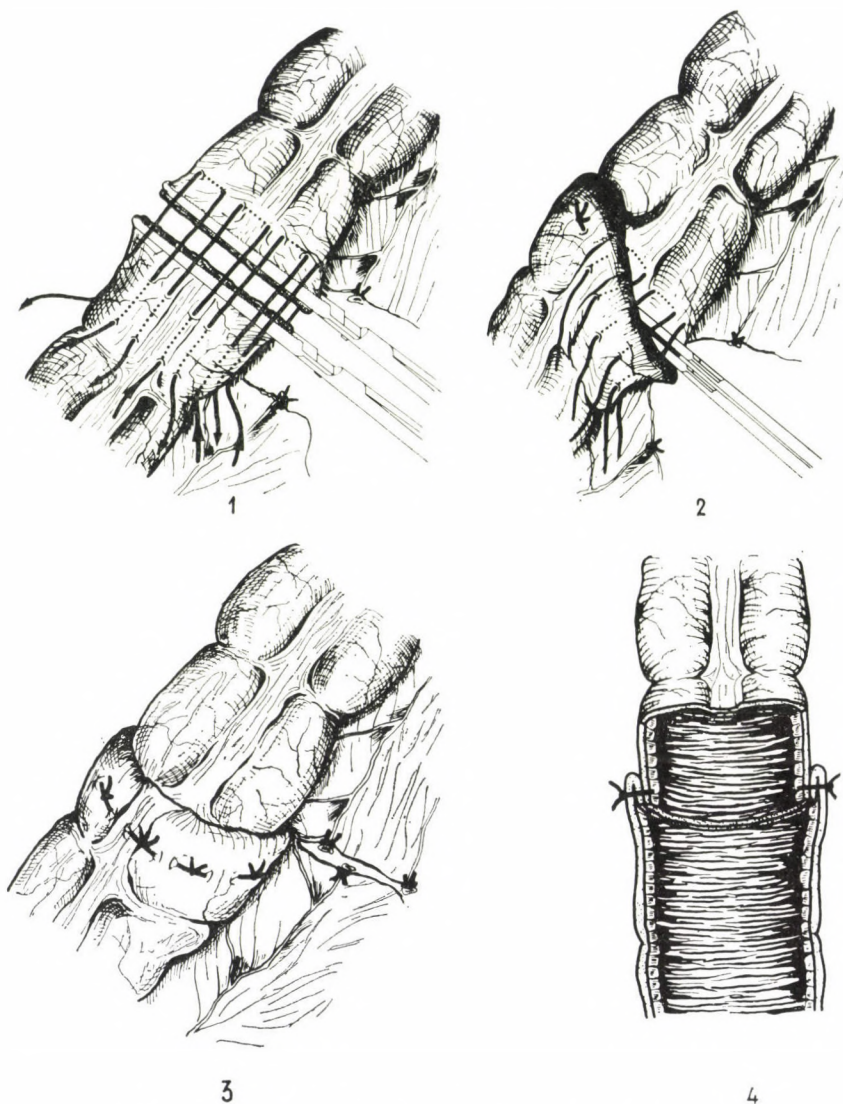


FIG. 3. End-to-end colocolostomy with 'A' stitches

Construction of Colorectostomy (Fig. 4)

The stitches remained unchanged, but we found a simpler way of placing them. It is difficult to insert stitches towards us in the sacral cavity, therefore, first they were placed into the colon stump parallel to the resection line, and later into the rectum. Then the threads were cut and the other strand of the 'U' stitch was inserted. The two proximal thread ends were promptly knotted,

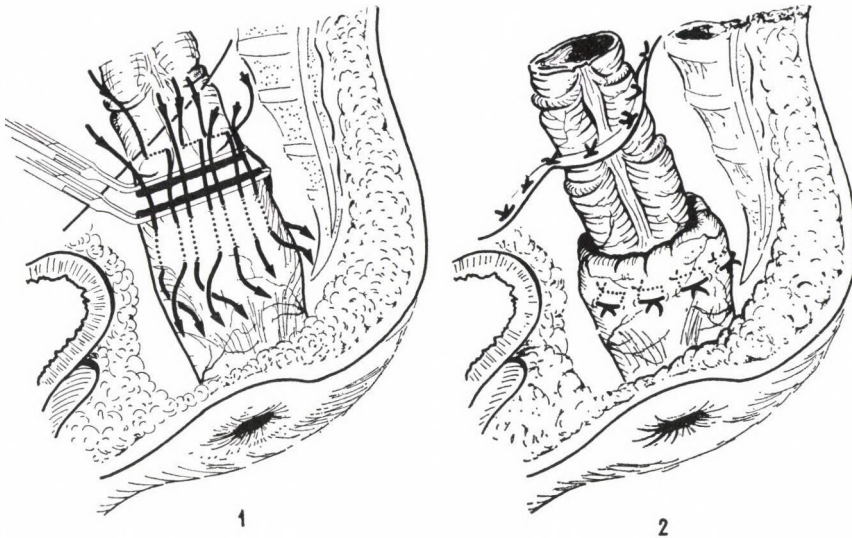


FIG. 4. Colorectostomy by two knots for each pair of threads with 'B' stitches

while the distal ones were knotted only after the invagination of the colonic stump. Thus the anastomosis is easy to construct by placing two knots for each pair of threads.

Preoperative and Postoperative Control

In colocolostomies after completing the anastomosis, dye was injected into the lumen and by pressing it into the anastomosis it was checked for hermetism. Four colocolic and 12 colorectal anastomoses were examined by the rectoscope 3 to 10 days after the operation. This kind of control examination was repeated in every three months.

Discussion

In the so-called 'closed' colonic anastomoses created by using inverting sutures, a minimal vascular damage is to be reckoned with, therefore there is only a small risk of suture insufficiency, of development of strictures as well as of inoculation as a result of stitches not involving the intestinal lumen, and of septic complications [1, 2, 3, 4, 6, 8, 10, 11, 13].

TABLE I

Method (without colostomy)	No. of operations	Suture insufficiency	Stercoral fistula	Suppuratio vuln.	Stricture	Anastomosis recurrence in one year	Mortality
Stapler gun	colocolostomy 12	1	1	4	0	2	1
	colorectostomy 28	3	5	11	2	8	3
Telescope technique	colocolostomy 4	0	0	0	1	0	0
	colorectostomy 4	0	0	1	3	0	1
Invaginated anastomoses	colocolostomy 9	0	0	0	0	0	1
	colorectostomy 13	0	0	0	0	0	0

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Anlegen von Kolonanastomosen mit einstülpender Naht

B. KEMENES und P. VADÁSZ

Nach Beschreibung des Anlegens der Dickdarmanastomose mit einstülpenden Nähten, werden die Vorteile der Methode erläutert; die Ergebnisse des Vergleichs des Verfahrens mit den bekannten, zur Anfertigung der Öffnungen gebräuchlichen Lösungen — Nahtpistole und Teleskop — zeigen anschauliche Tabellen.

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Б. КЕМЕНЕШ и П. ВАДАС

Авторы сообщают о сшитых инвагинирующими швами анастомозах толстой кишки, подчеркивая их достоинства, и демонстрируют на таблицах результаты сравнения таких анастомозов с соустьями, сделанными распространенными способами — телескопическим и с помощью сшивающего пистолета.

Oesophageal, Gastric and Small Bowel Anastomoses Made by the Sleeve Technique

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The authors report on their experiences in oesophageal, gastric and small bowel anastomoses made by inverting sutures. The technique of constructing the anastomoses is described with an emphasis on the necessity of considering the sizes and proportions. The advantages of the method are summarized and the operations performed so far are presented.

The surgery of the intestinal tract is based on the reliable construction of intestinal anastomoses. In the recent two decades great progress has been achieved to this end concerning surgical technique, tactics, suture material and surgical preparation. New methods attempted to correct the deficiencies of those believed to be perfect. These defects were reflected in the complication, the quality and quantity of which varied in accordance with the individual procedures used [1, 2, 3, 8, 9].

Requirements of constructing an ideal anastomosis are well known. Only tissues of an adequate blood supply can be sutured without tension and the stitches may only slightly disturb the blood supplies of the tissues. Identical tissues are to be united securing an early and adequate hermetism for the anastomosis. The stitches should not involve the intestinal lumen, the anastomosis should be constructed in a 'closed' form and it should not be followed by development of strictures. The above requirements necessarily arise from the physiological and pathophysiological properties of the intestinal tract, i.e. the defects are due to their injury [4, 5, 6, 8].

The various suturing techniques can be best assessed in the surgery of the oesophagus and the colon. In devising our procedure the solution of the problems arising in the latter two fields was aimed at.

Method

The 'A' stitches are used where the anastomosis to be created can be brought into the visual field, therefore knotting of the threads is easy to perform. First the distal intestine is sutured at a distance of 3×3 –5 mm, i.e.

9 to 15 mm apart from the resection line. The needle is inserted longitudinally through the submucosa and the stitch is terminated approaching the resection line at a distance of 3 to 5 mm. Then submucous stitches are inserted in the proximal stump parallel to the resection line at a distance of 3 to 5 mm from it. Stitches are repeatedly inserted into the aboral intestine parallel to the already inserted thread. About 6 to 9 stitches are placed circularly at a distance of 2 to 4 mm from each other. Knotting is performed gently, gradually with weak pulling. Vigorous pulling may induce plication resulting a fissure between the serosal surfaces. As a result of knotting, the proximal intestinal stump is telescoped into the distal one. The 6 to 10 mm end of the aboral intestine is inverted, becomes dilated and the oral stump may easily be slipped into it. The aboral stump complies with the oral one, and it becomes dilated right in the moment of knotting. The musculatures of the inverted and external intestinal walls exert their effects against each other. The two effects neutralize each other fixing the lumen in a position dilated to a medium degree.

The 'B' stitch is applied when the posterior surface of the stumps to be anastomosed is not within easy reach. In these cases, the intestinal stumps gripped by the instruments are unfolded, then the proximal intestine is stitched first placing both strands of the 'U' stitch to the distal intestine. The anastomosis will be constructed in a similar way than with the 'A' stitch but the knots will fall between the serosal surfaces. Consequently, threads requiring multiple knotting should not be used. Naturally, the anterior wall can also be sutured by 'B' stitches.

If the diameter of the proximal stump is smaller than that of the distal one, several stitches are placed for ensuring that the serous membranes should be apposed without folding despite the dilatation of the oral stump.

A 'closed' anastomosis can be created in the same way. After skeletization the remaining stump is grasped by Pean's forceps or by a tiny instrument with a strongly serrated jaw. The extent of skeletization does not exceed 6 to 10 mm from the resection line. The instruments are placed in a way that the mesenteric, serosa-free parts of the intestinal stump forming the weakest point of the intestinal wall should not contact each other in the anastomosis to be created. After performing the resection the tissues inbetween the jaws of the instruments are coagulated by touching the diathermic knife to the instruments. In this region bacteria are destroyed and also the possibility of capillary bleeding is excluded. The serosal membranes to be apposed are painted with iodine provoking thereby their fibrin-attaching mechanism and a bacteriostatic, cytostatic effect is achieved. The stitches are inserted, then the threads are knotted except for the pair of threads in the anterior corner. As a result of knotting, the proximal stump slips into the distal one together with the jaws of the instrument gripping the tissues. First the aboral, then the oral, instrument is removed. The still unknotted threads are knotted. The tissues joined

by coagulation are separated by embossing the wall from the direction of the oral intestine.

Attempts are generally made to create end-to-end and 'closed' anastomoses. The forceps facilitates our work making easy the insertion of stitches and the observance of proportions. If proportions are taken care of, the serosal surfaces will be precisely apposed, the interior surface of the anastomosis will completely be covered by the mucosa, and the submucous stitches uniting the intestinal stumps will half the ring forming the created anastomosis ensuring its mechanical stability.

The use of the forceps and the coagulation of the tissue will not worsen the properties of the anastomosis, since the narrow, crushed and coagulated tissue border does not play any role in the created anastomosis. These tissues will be sequestered in two weeks and will be replaced by mucosa. The intestinal stumps, however, are fixed by our instruments. In the 'closed' version, not even the needle holder touches the intestinal mucus.

Evaluation of the Operations Performed by Inversion

Although we have not specialized in oesophageal operations, we still often have to perform them when required by the surgical situation. In these instances our method is used for rapidly and safely performing our work by lifting the alpha-loop, creating three anastomoses, by making a blind closure of the afferent loop, by ligating the efferent loop under the jejuno-duodenostomy, and also by covering it with serosa. Marwedel's jejunostomy is also performed. On the seventh postoperative day passage examination is made using an absorbable contrast medium, then the patients are given tea and on the tenth day they may receive pulpy food (Figs 1, 2, and 3).

The invagination applied in gastric resections was initially aimed at practising the method, but the absence of the up to that time not infrequent gastric retention resulted in an exclusive use of this method in our gastric operations. It is to be noted that the resection line of the stomach is closed by the Soviet stapling device placing sutures in two layers, because in our opinion, in this way a reliable, but not thick, suture line is obtained. The lines of the stomach and the duodenum to be anastomosed should be fashioned to be equal because the compliance of the duodenum is limited. The anastomosis should provide enough space for the pulp of the thumb as opposed to anastomoses sutured in two layers. In this case neither stenosis due to anastomitis nor the dilatation of the anastomosis after termination of the necrobiotic processes can be expected. Necrobiotic processes occurring in the telescoped anastomosis are of a so small extension and size that the tissue of the anastomosis will be rebuilding fairly slowly.

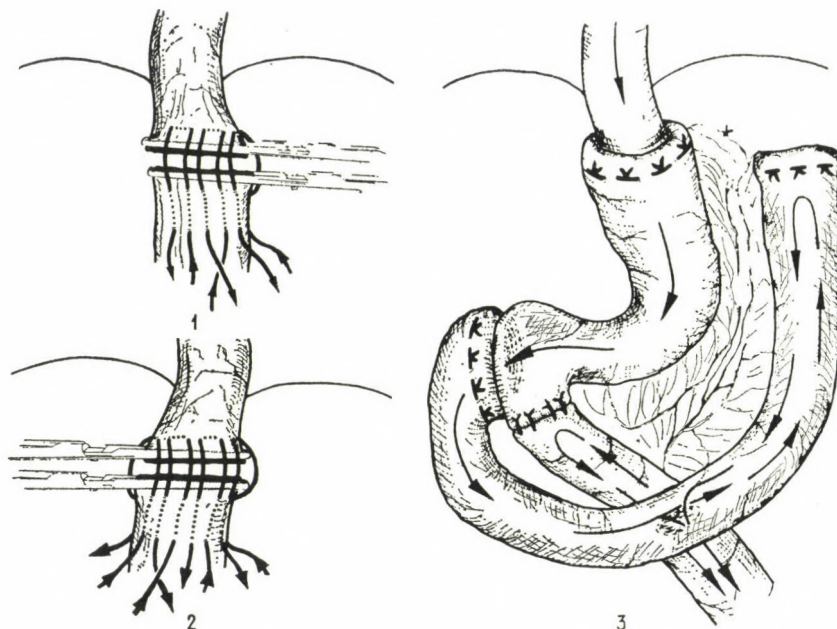


FIG. 1. Oesophagojejunostomy. 'A' stitches on the right and left side. State after gastrectomy

TABLE I

Summary of inverting sutures. In several cases multiple anastomoses were constructed. In 9 cases, passage disorder associated with carcinosis and ascites was remedied. Suture insufficiency was present in one case and this patient died within half a year. Ten additional patients died due to cachexia, pulmonary embolism, bilateral pneumonia and cardiorespiratory insufficiency. In the latter cases anastomoses covered by loose mucosa, oedema and macroscopic inflammatory reactions in an adhesion-free environment were found at autopsy

Type of operation	No. of operations	No. of sutures		Total	Suture insufficiency	Suppuration	Mortality	
		open	closed				in 2 weeks	later
Oesophagojejunoduodenostomy	9	18	18	36	1	0	1	1
Billroth I	41	4	37	41	0	1	0	2
Billroth II	5	4	6	10	0	0	0	0
Gastrojejunostomy	4	4	0	4	0	0	0	1
Gastrotomy	4	4	0	4	0	3	2	0
Duodenotomy	15	15	0	15	0	0	1	0
Jejunojunctionostomy	3	0	9	9	0	0	0	0
Jejunioileostomy	3	0	5	5	0	0	0	0
Ileocolostomy	1	1	0	1	0	0	0	1
Right hemicolectomy	14	0	20	20	0	0	1	0
Colocolostomy	9	6	6	12	0	0	1	0
Colorectostomy	13	0	13	13	0	0	0	0
Colotomy	4	4	0	4	0	1	0	0
Closure of colotomy	3	3	0	3	0	1	0	0
	138	63	114	177	1	6	6	5

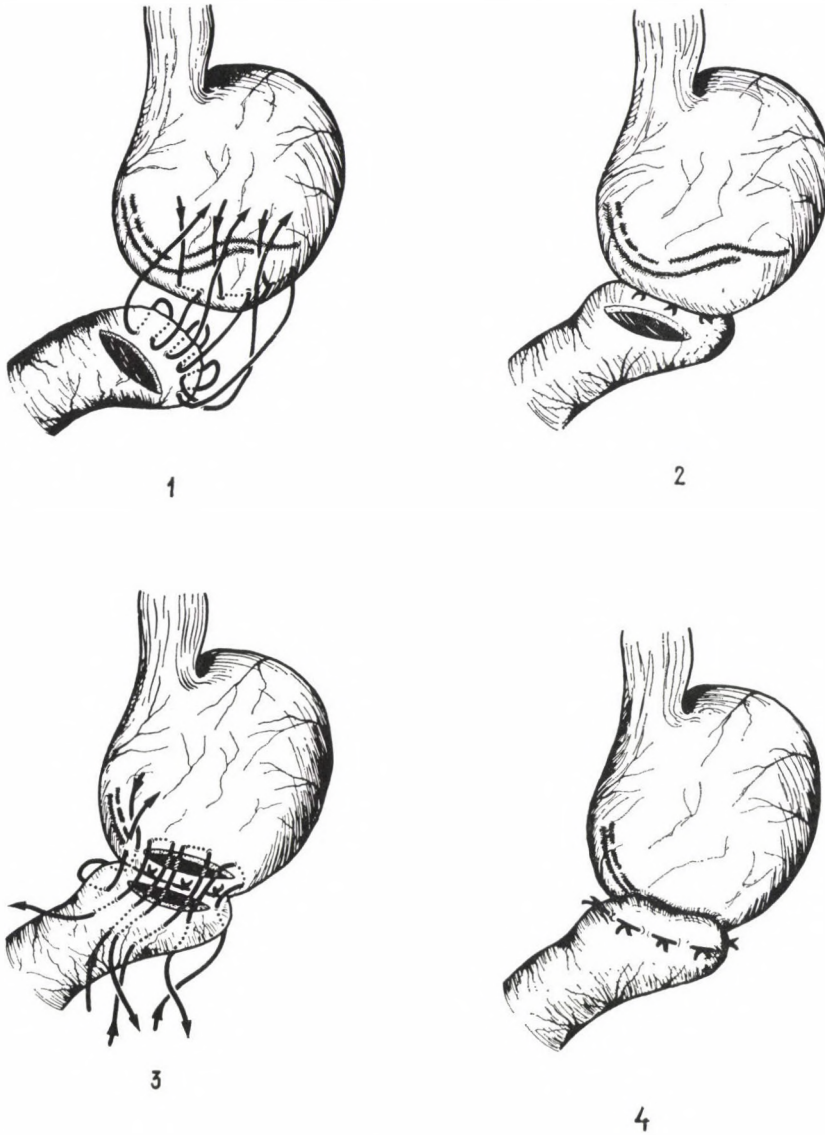


FIG. 2. Gastroduodenostomy. Posterior layer with 'B' stitches, anterior layer with 'A' stitches

It is a reliable method also in constructing gastrojejunostomy and side-to-side jejunostomy (Fig. 4), although the stitches are perpendicular to the course of the circular vessels in the vessel wall. Here, in the regions between the not too tightly knotted and relatively sparsely placed stitches the blood supply

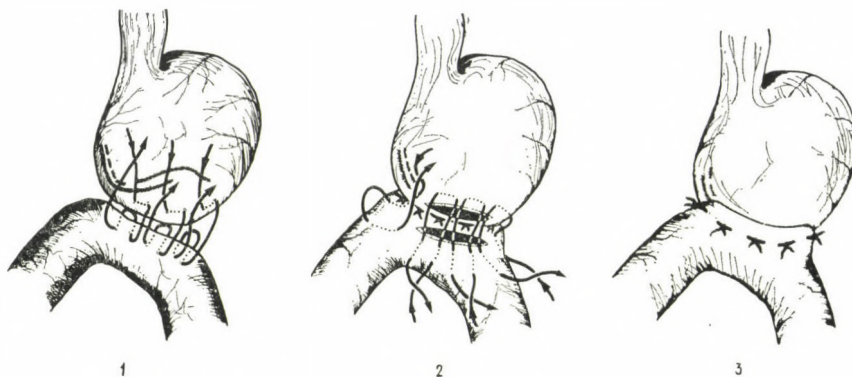


FIG. 3. Gastrojejunostomy. Posterior layer with 'B' stitches, anterior layer with 'A' stitches

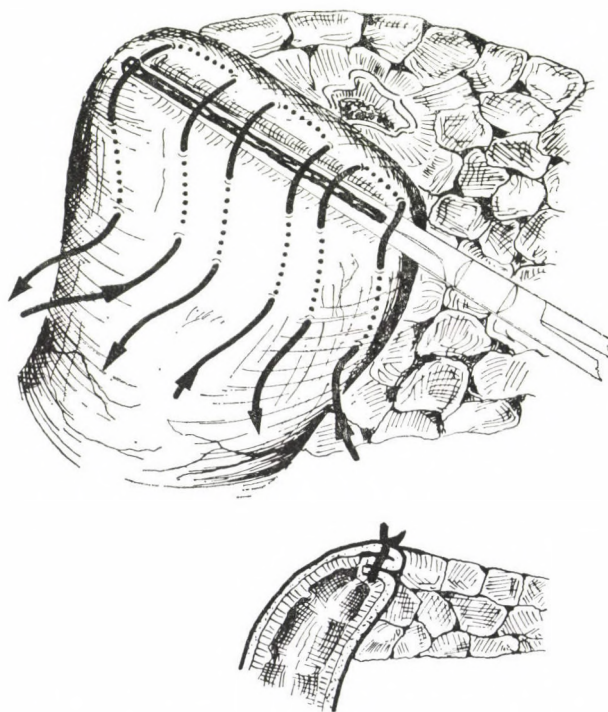


FIG. 4. End-to-end jejunostomy with 'A' stitches

of the tissue is not liable to become considerably damaged. This seems to be proved by the facts that no macroscopic necroses could be detected by gastrofiberscope in these cases, and that the rebuilding of the anastomosis is a very slow process. In side-to-side anastomoses Starlinger's coagulation is used.

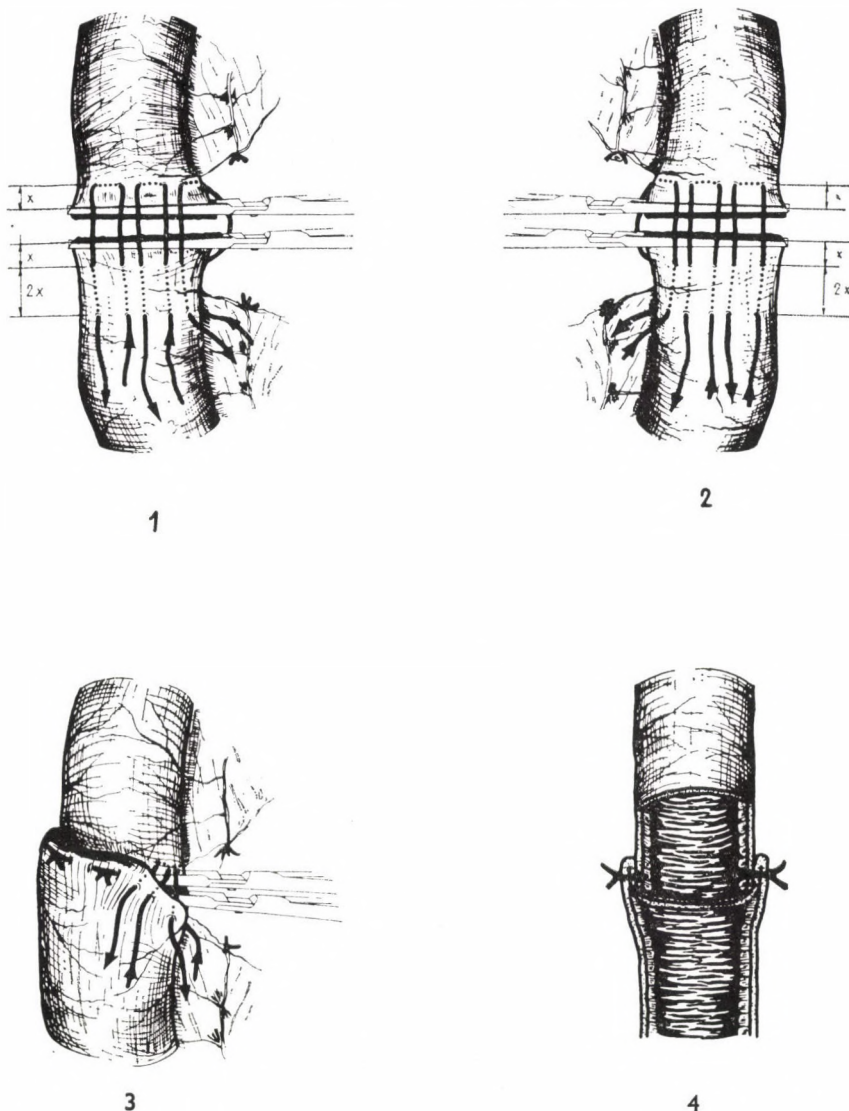


FIG. 5. Closure of duodenal stump. Small and large bowels can be closed in a similar manner

X-ray passage control examinations were made after gastric resections on the seventh postoperative day. Gastrofibroscopic controls on the fifth postoperative day were made only in 10 cases.

In small bowel operations our method may help in preventing the instruments from contacting the often strongly infected bowel contents. The

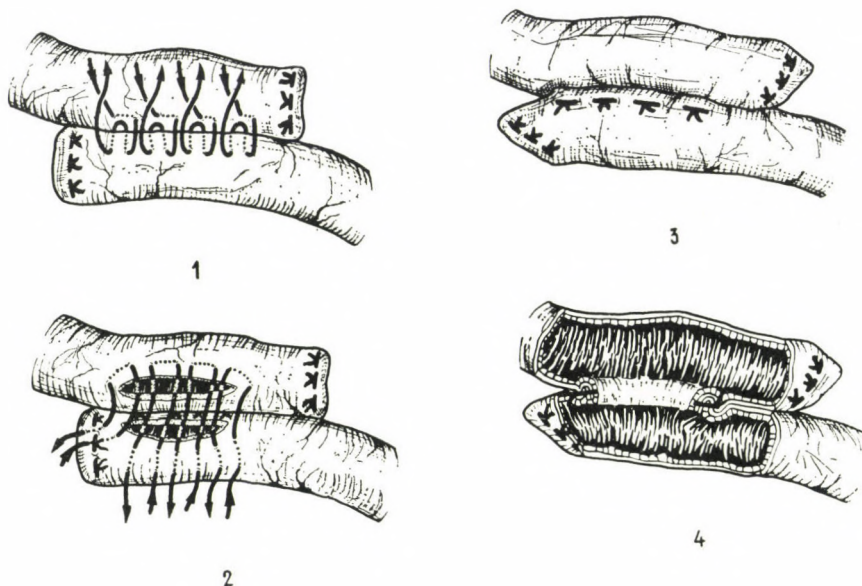


FIG. 6. Side-to-side jejunojejunostomy. Posterior wall with 'B' and anterior wall with 'A' stitches

10 to 15 cm portion of the distal bowel stump immediately becomes dilated as a result of the invagination, and the bowel contents is dumped through the anastomosis.

Discussion

The stitches inserted only minimally disturb the blood supply of the intestinal wall at the anastomosis. In end-to-end anastomoses they run parallel to the functional end arteries, in side-to-side anastomoses, the threads which are not pulled tight, producing only an apposition, allow vascularization. We attempt to create end-to-end anastomoses because the physiologically very important anatomical fact resulted by the circular course of end arteries can thus be best taken into consideration. Taking care of the vessels may reduce the number and extension of region becoming ischaemic, and thereby the possibility of suture insufficiencies and of development of strictures. It appears, that 'enforcing' the anastomosis created by the sleeve technique with an additional layer of stitches is distinctly harmful [5, 6, 7].

In most of the cases, the resection line can be selected in a way that skeletization be confined to the region up to the artery entering the intestinal wall. Skeletizing 6 to 10 mm of the bowel stumps will best ensure the blood

supply of the tissues of the anastomoses by vessels entering the border having developed after knotting.

The widely apposed serosal surfaces ensure an early and adequate hermetism. They are painted with iodine thereby provoking the fibrin-attaching mechanisms. There is also a possibility of using fibrin glue [6].

The anastomosis was constructed by applying a relatively small amount of threads not involving the intestinal lumen. As a result, no anastomitis, due to the drainage of the thread not even on applying traditional thread, should be reckoned with [1, 2, 8].

The strength of the anastomosis against stretching is also based on the two serosal surfaces being apposed in a ring-like manner and pressed together by the outwardly manifesting forces. In most anastomoses this force directly affects the fissure between the resection lines.

The tensile strength is determined by the stitches extensively involving the submucosa [1, 6, 8].

If the stitches are placed accurately, the diameter of the lumen undergoes permanent change but only of one of 15 to 20%.

Our method considers the following aspects: adequate blood supply of the tissues, apposition of equal tissues, in avoidance of the mucosa by stitches, diminished possibility of inflammatory reactions, and, at the same time, elimination of early and late strictures.

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Invaginierte Ösophagus- Magen- und Dünndarm-Anastomose

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Berichtet wird über die guten Erfahrungen mit den invaginiert genähten Ösophagus- Magen- und Dünndarmanastomosen. Nach Beschreibung der Technik des Anlegens der Anastomose, wobei die richtige Auswahl von Abmessungen und Proportionen von großer Bedeutung ist, werden die Vorteile der Methode zusammengefaßt und die durchgeführten Operationen in Tabellen geordnet dargestellt.

Подвернутые устья пищевода, желудка и тонкой кишки

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Авторы сообщают об удачном опыте, полученном ими при создании устьев пищевода, желудка и тонкой кишки, шитых подвернутым швом. Они описывают технику образования устья, подчеркивая необходимость придерживаться размеров и пропорций, обобщают достоинства этого метода и иллюстрируют с помощью таблицы произведенные ими до настоящего времени операции.

Partial Experimental Autotransplantation of the Spleen

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The authors performed autotransplantation of the spleen in 45 dogs. They found that, the pieces of the transplanted spleen underwent necrosis, but new malphigian bodies formed on their surface. These latter took over the sepsis-inhibiting function of the spleen. Thus the grafting of spleen can be useful and worth doing.

Spleen should be transplanted in thin slices since in case of a larger piece they may necrotize and give rise to abscesses.

In contrast to some earlier claims it is doubtful at present if splenectomy can be performed without more serious complications even in case of minor injury. This is especially true in childhood. This has already been reported earlier [1] when—in agreement with others [2, 4, 5, 6, 7, 10, 11, 13, 15, 16]—we suggested performing partial splenectomy. A special operative technique has also been designed to protect the patient from secondary haemorrhage or any other complications. There are cases, however, let alone splenectomies performed with haematological or any other therapeutic indication, when major spleen injury forces us, even in childhood, to perform a total splenectomy. This raises the question of the autotransplantation of the organ, since it is well known that in a state like that the defence of the organism against infection tends essentially to deteriorate and lethal sepsis may not infrequently occur [9]. This is so, to some extent, also in adults, though the defence mechanism of the organism is better in general as compared to children [2, 14].

Consequently, also we, like others [8, 14, 15], performed partial autotransplantation experiments in dogs. The difference was as compared to the earlier studies, that a fairly detailed histological follow-up of the fate of the spleen pieces re-implanted in various ways was made and this helped convincing us of the usefulness of the procedure. The importance of the question is also accentuated by the fact that, according to Cooper and Williamson [2], solely in the USA approximately 35,000 splenectomies are made per year and this figure can be estimated to be very high also on a world scale. In adults the spleen is an organ weighing about 150 g and it is better to re-implant as much

of it as possible with as much surface as possible. Preservation of spleen for autotransplantation [17] was attempted, in order to make this possible even if subsequently.

Experimental Method

The partial transplantation of autologous spleen was performed in 45 dogs. We wanted to see if the transplantation is worth performing only in case of complete splenectomy, and if so, what is the most effective way of the operation.

For this purpose, one-third of the spleens of 15 animals was resected and the removed part was re-implanted as a whole or with multiple incisions into the omentum. Twenty-five animals were splenectomized and transplantation into the omentum was made by implanting 2 times 3 cm large pieces of spleens in 10 cases, and spleen pieces of the same size cut by razor blades to 2 to 3 mm slices in 20 cases. In 5 cases spleen pieces cut into slices were implanted into the sheath of the rectus abdominis muscle, too. Embedding was made in paraffin, the histological section were stained with haematoxylin-chromotop.

Results and Discussion

As to the final result, there was no major difference in the further fate of spleen pieces obtained from the splenectomized animals or from those with only one-third of their spleen removed. Otherwise, in case of partial splenectomy autotransplantation of the resected piece is not required, the residual spleen is capable of fulfilling its original function. There was, however, a great difference where the spleen was transplanted not as a whole but cut into 2 to 3 mm pieces and these were covered independently of each other by the omentum. Thus their entire surface contacted the well-vascularized omentum. Transplantation into the sheath of the rectus abdominis muscle yielded also good results. This did, however, not yield better results than did the transplantation of the slices into the omentum which latter finally was found to be the simplest and most effective method. The site of transplantation was marked by black nylon thread to enable us to safely find it at autopsy.

The experimental animals were sacrificed at intervals ranging from one week to 6 months. The transplanted spleens and their environment were subjected to a detailed histological study yielding unexpected results.

In contrast with several authors, who had succeeded in proving by scintigraphy the survival even after half a year of the spleen pieces, we found that both the transplanted larger, as well as the smaller, spleen pieces underwent necrosis, and structures characteristic of the spleen tissue regenerated

exclusively on the surface of the transplants on the border of the vascularized autologous living tissue. This could have been demonstrated by scintigraphy.

Our results are supported by some micrographs selected from several histological pictures. The necrotized region is shown only in a few Figures since this is a negative phenomenon. The new malphigian bodies forming over the surface of the transplants as characteristic structures are, however, shown in several Figures in order to prove that the procedure is successful and is worth performing.

Histological Examination

Using a thin spleen slice, the interior of the transplant is replaced by the third week by scar tissue. Under the omental cover in the marginal region, a new lymphoreticular tissue and a malphigian body can be observed (Fig. 1).

Lymphoreticular tissue is visible in the marginal region of the thin spleen slice some weeks after transplantation. More inwardly in the necrosed part organized by connective tissue new vessels have entered into the vessels of the original spleen piece (Fig. 2).

Malphigian bodies have developed in the marginal regions of the connective tissue corpuscles corresponding to the thin transplanted spleen slice, by the end of the 8th week (Fig. 3).

Three months postoperatively the thin spleen slice is replaced by a scar tissue region with isolated malphigian bodies in which structures resembling germinal centres can be observed (Fig. 4).

Newly-formed isolated malphigian bodies can be found sporadically only in the omentum after 6 months in a thin spleen slice (Fig. 5).



FIG. 1

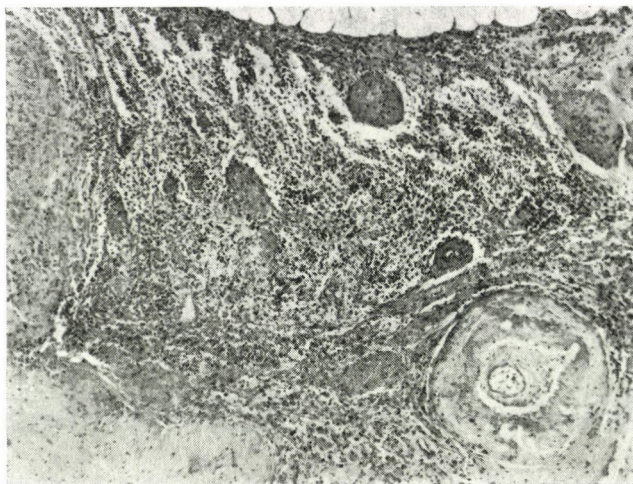


FIG. 2

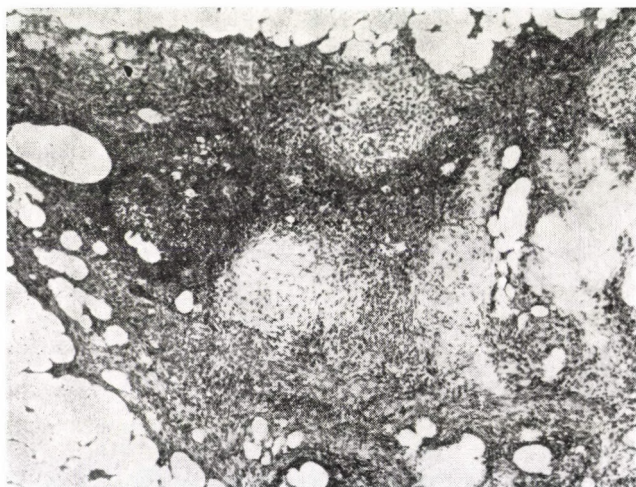


FIG. 3

By the end of the 3rd month, the interior of the 2 times 3 cm spleen piece shows scar shrinkage. In the marginal region, beneath the thick connective tissue capsule a newly formed lymphoreticular lining is present containing lymphocyte groups—malphigian body—around the small vessels (Fig. 6).

The interior of the implanted large spleen piece has undergone necrosis and a thick-walled abscess has developed by the end of the 4th week after operation. (This is the surgical risk of transplanting a larger piece of spleen.)

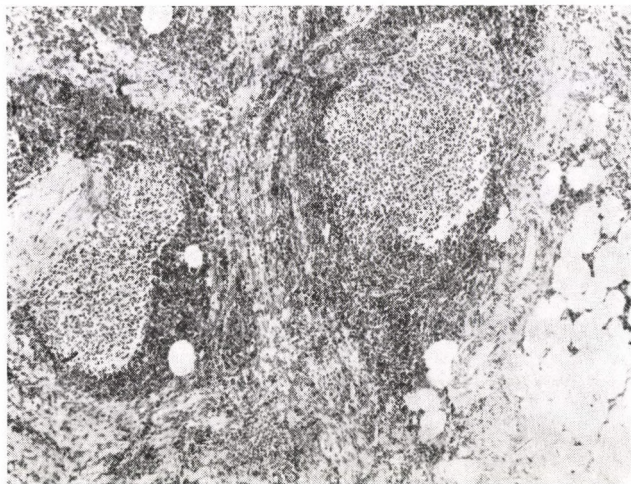


FIG. 4

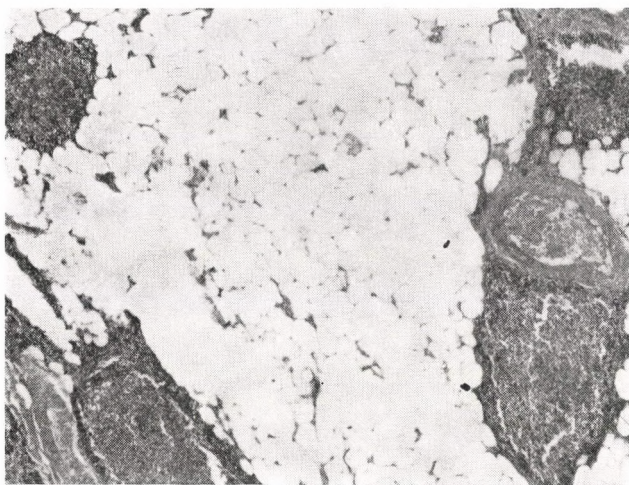


FIG. 5

A new lymphoreticular layer has formed in the connective tissular wall of the abscess where around the individual vessels lymphocyte aggregation—formation of malphigian body—is seen (Fig. 7).

Thick-walled abscess, the size of a nut, can be found containing a small amount of necrosed splenic residuum six months postoperatively, in a large piece of spleen. In the thick connective tissue capsule, mainly in the marginal areas and in the contacting omentum, newly-formed malphigian bodies are

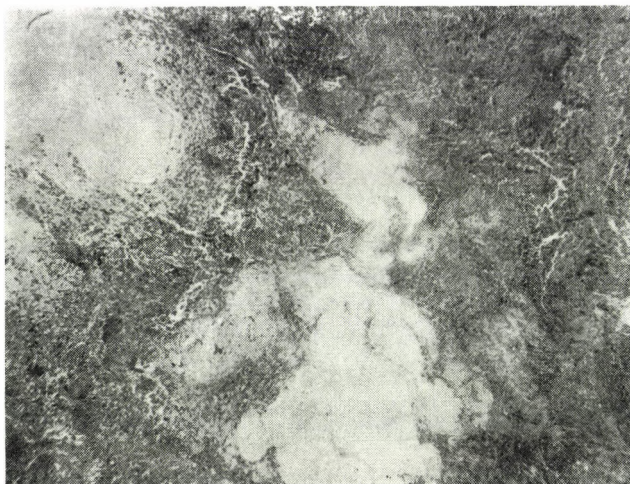


FIG. 6



FIG. 7

situated (Fig. 8). At a distance from the spleen piece, transplanted in between the muscle fascicles an isolated malphigian body has formed by the end of the 3rd month (Fig. 9).

Based on the results of these examinations, it is revealed that autotransplantation of the some millimeter thin spleen slices may yield the best result, while the necrosed middle portion of the thick spleen pieces may lead to formation of smaller or greater abscesses. The new malphigian bodies develop on the border of the transplant and the adjacent well-vascularized

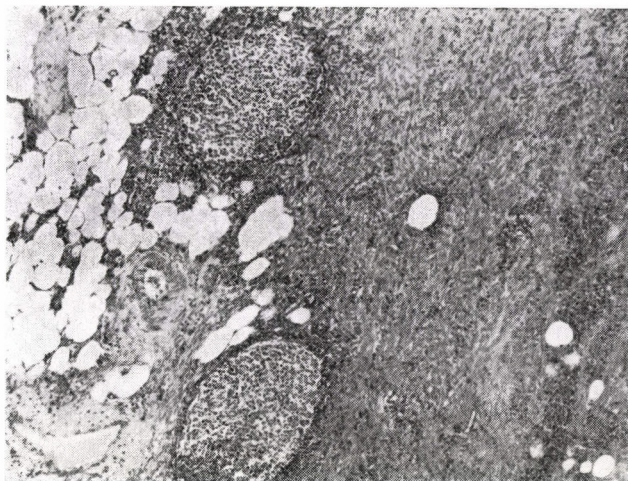


FIG. 8

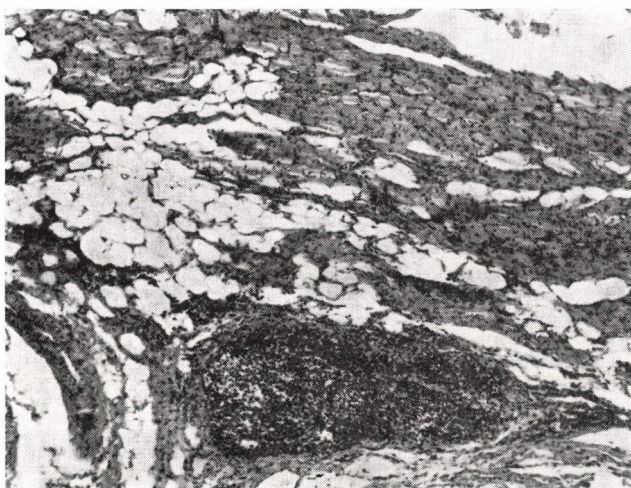


FIG. 9

tissues (omentum, rectus). The newly-formed malpighian bodies appear to be suitable for achieving our purpose, i.e. for fulfilling the immunological function of the spleen.

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Partielle, experimentelle, autologe Milztransplantation

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Die bei 45 Hunden durchgeführten autologen Milztransplantationen führten zur Feststellung, daß obwohl die transplantierten Milzabschnitte im wesentlichen nekrosieren, die sich auf ihrer Oberfläche gebildeten neuen Malphigi-Körper übernehmen aber die sepsishemmende Funktion der Milz, weshalb sich das Verfahren in diesem Sinne als wirksam und nützlich erwiesen hat. Es empfiehlt sich die Milz in dünne Schnitte geschnitten zu transplantieren, weil sich im Falle der Transplantation größerer Milzabschnitte aus dem sich nekrosierenden Milzgewebe unter Umständen ein Abszeß entwickelt, welcher sich öffnen und dadurch gefährlich werden kann.

Парциальная экспериментальная аутологичная трансплантация селезенки

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В экспериментах на 45 собаках авторы выполнили аутологичную трансплантацию селезенки у 45 собак, и установили, что хотя пересаженные кусочки селезенки в основном отмирают, на их поверхности образуются новые мальпигиевы клубочки, которые перенимают ту функцию селезенки, которая означает подавление сепсиса, поэтому с этой точки зрения описываемый способ является эффективным и полезным.

Целесообразно пересаживать селезенку, нарезав на тонкие ломтики, так как, в случае пересадки большого куска селезенки, из некротизирующейся селезеночной ткани может образоваться абсцесс, который при вскрытии представляет опасность.

Thermographic Study of Haemodynamic Changes Due to Arteriovenous Shunt

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The authors made thermographic studies on the haemodynamic changes due to arteriovenous shunt in animal experiments under different conditions. The effects due to acute and chronic fistulas in reaction-free and inflammatory environments were registered. Observations of diagnostic value were made on the haemodynamic changes due to arteriovenous shunt. These are of differential diagnostic importance also in human medical practice, therefore thermography is recommended to be used as new noninvasive diagnostic tools.

After Hunter [27] recognized in 1757 that the arteriovenous aneurysm is a direct communication between the artery and the vein, for more than one century, only clinicians were concerned with this pathological picture. Amussat [1] was the first in 1843 to create experimentally an arteriovenous fistula although this, too, happened to be by accident, since he wanted to create a simple aneurysm in horses but pseudocystic arteriovenous fistula developed.

The first truly conscious and scientific experiments were made by Vignolo [55] in 1902 who developed the method of lateral anastomosis between the artery and the vein. This has been used ever since by most of the researchers. In the course of his experiments he stated that in an acute case general blood pressure decreased in dogs by 10 mm Hg after creation of the fistula, with a simultaneous elevation of pressure in the neighbouring veins. He recognized the general characteristics of the arteriovenous fistula, i.e. (i) the oedema of tissues proximal to the fistula, (ii) venous pulsation, (iii) the bellows murmur, (iv) the vibrating thrill, (v) the possibility of the spontaneous healing of small (5 to 8 mm) fistulas and (vi) the thinning of the arterial wall leading to the fistula as a result of the disappearance of the elements of the media. Since he concentrated on studying only small fistulas, he failed to reveal some of the most interesting features of this change.

Franz [4] was the first in 1905 to describe the increase of temperature by 1.5 °C over the thigh surface of a 12-year-old boy due to a femoral arteriovenous fistula having persisted for 18 months, and a 3 cm increase in the length of the affected limb as compared to the contralateral side. Then he created experimentally small fistulas using lateral anastomosis. He proved

that the occlusion of the distal vein to the fistula does not prevent the continuous murmur and thrill. Ligation of the proximal vein, however, does completely eliminate both. He succeeded in showing the considerable immediate decrease in temperature after formation of the femoral fistula in the tissues proximal to the fistula which, gradually increasing, returns to normal temperature. After development of the collateral circulation, temperature increases in the tissues in the immediate vicinity of the fistula, while decreasing the temperature in the more distal tissues.

In 1920 Reid [38, 39, 40, 41] proved experimentally in dog's heart that long persisting arteriovenous fistulas may produce cardiomegaly. In one of his cases a carotid-jugular fistula having persisted for 33 months gave rise to cardiac hypertrophy and dilatation.

The initial studies on total blood volume were made by Holman [11, 12, 13, 14, 15, 16, 17] who carried out his investigations by using Hooper's method [26].

Starved dogs were administered 1 cm³ 1% Brilliant Vital Red Solution per 5 kg body weight into the jugular vein. Precisely after 4 minutes a blood sample was collected, centrifuged and the distribution of the dye was determined by comparing it to a standard solution. The examination showed a considerable increase in blood volume in experimental peripheral fistulas and experimental ventricular septal defects.

Lillehei [32] recorded, beside the blood volume determinations, also intracardial pressures. Schreiner [44] made isotope dilution tests using isotopes of a short half-life.

The physiological research of Epstein et al. [2, 3] Holman [19, 20, 21, 22, 23, 24, 25], Muenster et al. [35] and Sabiston et al. [42] were conducted, in addition to the haemodynamics, on the role and changes of the fluid-electrolyte metabolism.

The roentgenologic kymographic and angiographic studies were introduced into the experimental work by Holman [18] and by Hol and Ingebrigsten [10] for registering the haemodynamic effects of arteriovenous fistulas.

In Hungary, Solti et al. [50] carried out haemodynamic examinations studying the effects of congenital and acquired arteriovenous shunts.

With technical advancement the range of possibilities of research and therapy has widened by newer dye-dilution, isotopic and ultrasound diagnostic methods. The majority of methods known from the literature and from practice are invasive, they cannot be repeated and allow the recording of haemodynamic changes only of a small region. Our team intended to study the haemodynamic changes due to arteriovenous shunt in femoral fistulas produced in the hindlegs of dogs.

The experiments aimed at studying by a bloodless, noninvasive method the time, spatial (anatomical) haemodynamic changes due to shunt.

The method used in medical practice and developed by Selawry and Holland [45] and Tricoire [53, 54], i.e. liquid crystal thermography seemed to be a suitable method. In Hungary Göblyös et al. [6, 7, 8], Hargitai et al. [9] and Lelik et al. [30, 31] proved in their experimental work that the method can be used for monitoring changes in temperature due to inflammatory, vascular or tumorous diseases. Their procedure is, however, difficult to adapt for comparative examinations and for those of extensive regions. That is why our method of choice has become telethermography. In 1964 Winsor and Bendezu [56] already applied thermography for studying peripheral vascular diseases. Shalin [43] used thermography for localizing arteriovenous communications in the surgical treatment of varicose veins.

The new approach inherent in the noninvasive technique could become a useful diagnostic method to be applied by angiologists, radiologists and vascular surgeons [5, 28, 29, 33, 34, 46, 47, 48, 49, 51, 52, 57, 58, 59, 60].

Material and Method

The experiments were made in 14 mongrel dogs of both sexes weighing 13 to 15 kg. The animals were divided into two groups. (i) In 10 dogs a chronic, while (ii) in 4 animals an acute fistula was produced. Three dogs of the chronic group died of a septic complication. The examinations were made in this group after a postoperative period of 1 to 6 months.

Ten to 15 mm long lateral anastomoses were created in each case between the artery and the femoral vein which were sutured by 6/0 and 7/0 Prolene.

During clamping a 0.05 ml heparin solution per body weight was administered which was neutralized after release of the vessels and haemostasis by an adequate amount of protamine sulphate. The minimal blood loss was substituted by Rheomacrodex infusion injected via a saphenous cannula. The operations were made under pentobarbital anaesthesia with spontaneous respiration.

For our investigations the AGA 750 equipment of the Instrument and Measurement Technology Service of the Hungarian Academy of Sciences was applied which registers infra-red radiation on the wavelength range from 2 to 5.6 μm . The optics made of germanium converts these rays by a rotating prism of horizontal and vertical axis on an indium-antimonid (InSb) detector. The crystal cooled to -196°C by liquid nitrogen converts the infra-red rays into electric signals and transmits them to the monitor of the equipment based on the principle of a closed-chain TV. The warmest parts of the test target illuminate in a bright white colour, the colder range appears dark yellow-red-green, while the coldest parts are dark blue. The thermogram having been compared to the standard heat source, is evaluated quantitatively.

Evaluation is aided by a colour scale with a calibration of 10 colours appearing simultaneously with the thermogram which covers the range of 5 °C, i.e. each colour corresponds to 0.5 °C.

The experiments were made at a temperature of 22 to 25 °C in a draught-free environment. The body temperature of the animals was controlled and room temperature was kept at a constant level. The thermographic stand was placed at 120 cm from, while the camera at an angle of 75 to 80 degrees to the plane of the table.

The thermograms were taken from the image appearing on the colour TV monitor by using Forte-Color film.

The dogs were shaved from the inguinal region to the ankle then washed with alcohol.

In case of the chronically operated dogs no control thermograms were taken preoperatively, therefore in one dog a unilateral shunt was created and the nonoperated side was regarded as control.

In the acute experiments thermograms were made both before and after operation.

The thermographic studies were made under the conditions as follows.

1. After chronic shunt in a reaction-free environment.
2. After chronic shunt in an inflammatory environment.
3. After a unilateral chronic and an acute contralateral shunt.
4. Following an acute shunt.
5. Under the effect of cooling with a cold liquid on the side and on the contralateral side of the fistula after acute shunt.

The cold solution was 5 cm³ of physiological saline of a temperature of 12 °C. Thermograms were taken at 5-sec-intervals from the administration onwards.

Results

Proximal (Fig. 1A) and distal (Fig. 1B) thermograms of right chronic femoral arteriovenous fistulas of 4 months duration can be seen. Corresponding to the elevated blood flow in the shunt both thermograms show a warm area with increased blood flow in the right inguinal region. In Fig. 1B the leg is colder on the side of the shunt from the ankle downwards.

In the same dog, acute femoral fistula operation was done on the left side. Fig. 2A shows the acute control thermogram before, while Fig. 2B, after the operation.

Conclusion: Only the immediate environment of the anastomosis has become warm (increased blood flow is to be found only in the immediate vicinity of the fistula). Peripherally, a considerable cooling down and decreased

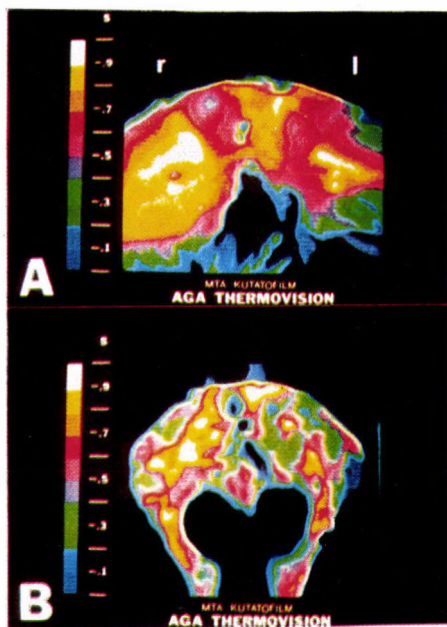


FIG. 1. Thermograms of a right chronic femoral arteriovenous fistula in dog after four months survival. A = distant view; B = close view; r = right side; l = left side

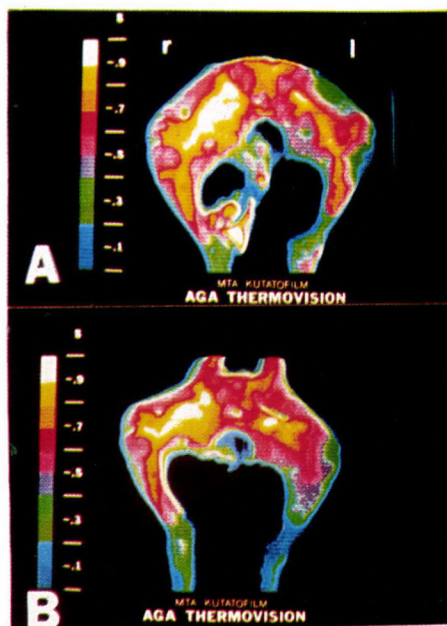


FIG. 2. Thermograms of a four-month-old right chronic femoral arteriovenous fistula (A) and of a left acute fistula in the same dog (B). r = right side; l = left side

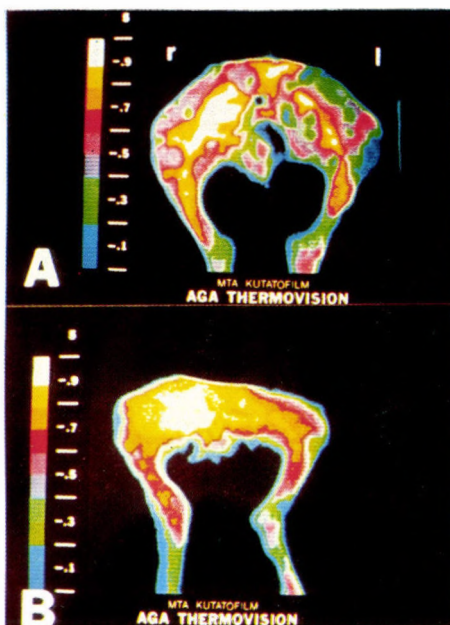


FIG. 3. Right chronic femoral fistula in an inflammation-free environment (A) and in an inflammatory environment (B). r = right side; l = left side

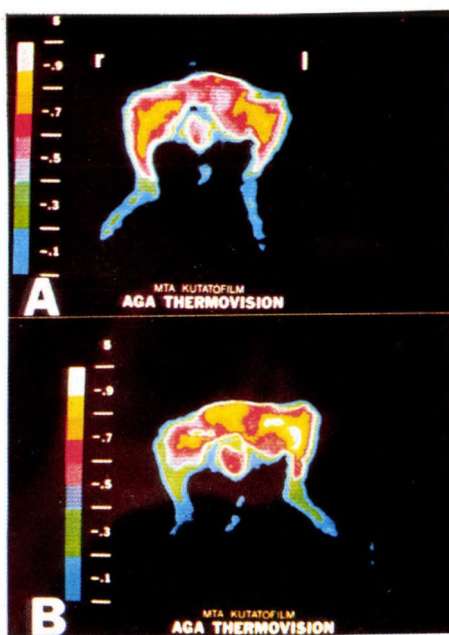


FIG. 4. Thermograms of a dog before (A) and after (B) a acute femoral arteriovenous shunt. r = right side; l = left side

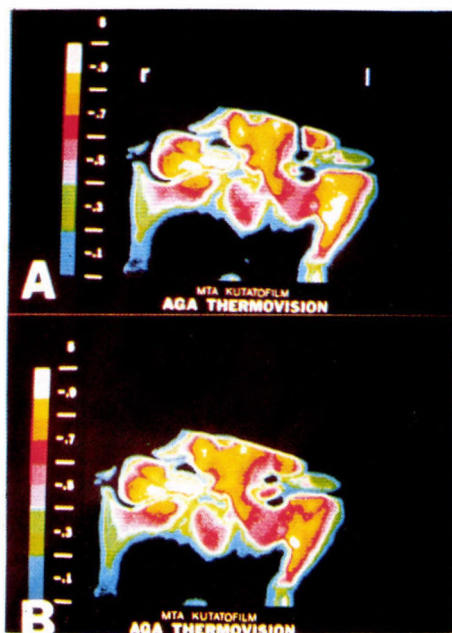


FIG. 5. Effect of cooling liquid injected into the left femoral artery in an extremity of intact blood flow. Thermogram A = control; B = after the injection of 5 ml liquid of 12 °C. r = right side; l = left side

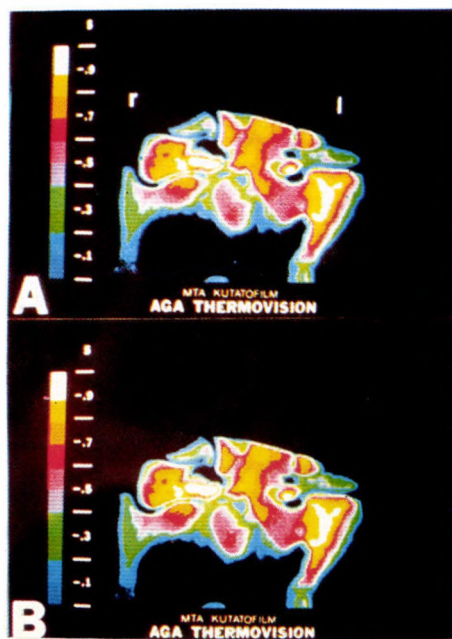


FIG. 6. Effect of cold liquid injected into right acute arteriovenous shunt in an operated extremity. A = control thermogram; B = thermogram after injection of 5 ml liquid of 12 °C. r = right side; l = left side

blood flow can be observed. Comparison of the operative region of a right chronic femoral fistula is shown in Fig. 3A in a reaction-free, while in Fig. 3B, in an inflammatory environment.

It can be established that: (i) in a reaction-free case the two inguinal regions can be well differentiated with an elevated blood flow on the side of the shunt. (ii) In an inflammatory environment the hyperaemia due to dermatitis may spread also to the nonoperated inguinal region. Consequently, the two regions do not differ from each other forming a confluent warm region.

However, the peripheral region on the side of the shunt is colder as compared to the contralateral side.

Thermography made during creation of an acute shunt:

Figure 4A shows a control thermogram made prior to operation. The two femoral regions are of the same temperature and of identical blood supply not counting the asymmetry due to the position. After an acute shunt (Fig. 4B) the inguinal region of the operated side cools down except for the shunt, the right lower extremity cannot be visualized in the thermogram. It can be ascribed to that the black region cools down to such an extent that it exceeds the lowest range of the thermogram. As a result of injecting 5 cm³ cold liquid of a temperature of 12 °C into the nonoperated femoral artery a moderate cooling down occurs distally to the site of injection (Fig. 5B) as opposed to the control thermogram (Fig. 5A).

A cold solution of identical amount and temperature injected into the femoral artery with an acute shunt does not cool down the periphery (Fig. 6A) and the central region is not cooled down either (Fig. 6B).

Discussion

In our acute experiments the immediate vicinity of the anastomosis showed only a moderate warming and elevation of blood flow following the opening of the fistula. At the same time, there was a considerable cooling down distally to the ankles. Similar observations were also made by Winsor et al. [58] in patients with Brescia Cimino shunt.

The warming up of the environment of the anastomosis takes some time. Within two to three months, collaterals develop, veins arterialize, hyperaemia occurs if the fistula is not obstructed.

In the chronic experiments without any exception hyperaemia exceeding the inguinal region could be observed. Warming up due to inflammatory skin infection can be well differentiated from an elevated blood flow in shunt, since (i) in the latter case hyperaemia correlates with the ramifications of the vascular tree, while in inflammation the affected region shows a confluent homogeneous shadow. (ii) Shunt flow as opposed to the inflammatory infiltra-

tion seriously impairs the blood flow of the distal portions of the extremities.

The cooling down and the reduced blood flow of the parts distal to the fistula are intensive both in the acute as well as in the chronic experiments.

That means that this pathological consequence of the fistulas most intensively appears right at the moment of fistula formation. In an acute case, as a result of the central drainage, an increased venous circulation, in the chronic case, due to the increased steal of blood via the gradually dilating vessels from the normal circulation into the fistula. This may prove that development of a secondary vasodilatation is not required for the appearance of the pathologic thermal effects of the shunt flow.

In our acute shunt operations, the cold solution injected into the femoral artery did not even cause a minimal cooling down in the distal regions of the extremities in the animals, while in an intact circulation the cooling effect of the solution was apparent.

The thermographic examinations helped determining (i) the size and (ii) the level of the region with a decreased blood flow, (iii) the proportion and (iv) the location of the hyperaemic region vs. the region with decreased blood flow.

The method enables us to make comparative studies and to wait until the disturbing phenomena subside (e.g. inflammation, injury).

In view of the above, thermography is recommended as a noninvasive tool in human medical practice.

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Thermographische Untersuchung der durch arteriovenösem Shunt verursachten hämodynamischen Veränderungen

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Die durch arteriovenösen Shunt bedingten hämodynamischen Änderungen wurden im Tierexperiment, unter verschiedenen Verhältnissen mittels Thermographie untersucht. Im Laufe der Registrierung der durch akute und chronische Fisteln verursachten Effekten in reaktionsfreier und entzündlicher Umgebung, bot sich die Möglichkeit zu diagnostischen Feststellungen im Zusammenhang mit den, dem arteriovenösen Shunt zufolge zustandegekommenen Durchblutungsänderungen. Da diesen Feststellungen auch in der klinischen Praxis eine differentialdiagnostische Bedeutung beizumessen ist, werden die beschriebenen Untersuchungen, als neue Mittel der non-invasiven Diagnostik zur weitläufigen Anwendung empfohlen.

Термографическое исследование гемодинамических изменений, вызванных артерио-венозным шунтом

ДЬ. АЧАДИ, Л. ПАПП, В. КЕКЕШИ, Б. ОШВАТ и Ш. ЮХАС-НАДЬ

В экспериментах на животных авторы изучали гемодинамические изменения, вызванные артерио-венозным шунтом, используя термографическую методику в различных условиях опыта. Регистрировались вызванные острой и хронической фистулами эффекты, при отсутствии реакции и в условиях воспаления. Авторы достигли результатов, имеющих диагностическую ценность, в связи с изменениями протекания крови, наступающими вследствие образования артерио-венозного шунта. Эти определения и в человеческой медицинской практике имеют дифференциально-диагностическое значение, поэтому авторы рекомендуют их для широкого использования в неинвазивной диагностике в качестве нового средства.

Combined Use of Bioplast and Tissue Adhesive in Experimental Nephrectomies in situ Renal Hypothermia

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In transvenous regional hypothermia wedge-shaped and flat lower pole resections were made in dogs. The cut surface of the kidney was covered by the combination of tissue adhesive and bioplast without sutures.

It was found that the polymerization time of the tissue adhesive almost doubled. The usual rigidity of the adhesive was more expressed than in normothermia and it was not influenced by re-heating. Recovery conditions were more favourable; a larger portion of the parenchyma could be preserved than with the traditional closure with needle and thread.

Attempts to preserve the organs or to save functioning renal parenchyma are very important goals of renal surgery.

In normothermia, both in clinical practice and in experiments the various tissue adhesive used for the renal parenchyma have proved to be effective [3].

Regional renal hypothermia provides substantial advantages in renal surgery. The kidney can be excluded from the circulation, i.e. longer and more complicated operation, too, can be performed under relatively favourable circumstances.

According to Markovic [4] and Wilhelm et al. [11], the theoretical basis of producing hypothermia through the venous circulation of the kidney—which appears to be a logical contradiction—is that the venous network of the kidney forms a homogeneous system, as opposed to the segmental arterial supply. Thus, if this network is opened, by nephrotomy, the outflow of the cooling fluid results in the required hypothermia. The experimental and clinical implications of this question have been dealt with in several of our studies [7, 8, 9, 10]. In a previous study the closure of nephrotomies by tissue adhesive performed in hypothermia has been compared to the closure using traditional sutures [7, 8]. The procedure by tissue adhesive was more useful since a larger portion of the renal parenchyma could be preserved than by the needle-thread technique. This systematic research has raised the question whether the large surfaces produced in resections with regional renal hypothermia could be closed by the above method in a way to preserve the largest volume of func-

tioning parenchyma. The question is made still more complicated by the fact that, during this study, the adhesive became more rigid in hypothermia than it usually was in normothermia and the rigidity of the adhesive did not even change when being re-heated. On several occasions [1, 2, 6], the oxidized cellulose preparation (Surgicel) was successfully combined with adhesive. Its reticular structure is more suitable for covering larger surfaces, although it was demonstrated experimentally that, being inserted in the renal parenchyma, it evokes a greater tissular response than, e.g. do bioplast preparations made of fibrin or collagen [1].

In spite of the problems indicated above the oxidized cellulose (Surgicel) used for the renal parenchyma seemed to be the best one to be combined with tissue adhesive.

Experimental Method

The experiments were made on 17 mongrel dogs of various of age, sex and weight.

After exposure of the left kidney and isolation of the hilus, the internal spermatic or the ovarian vein was dissected. A cannula which was then connected to the system of cooling fluid was fixed in the vessel. Prior to starting hypothermia, the renal artery and vein were compressed and a small nephrotomy was made at the lower pole simultaneously with starting the circulation of the hypothermic fluid, as shown in Fig. 1. After adequate decapsulation, the required wedge-shaped portion of the kidney was removed from the lower

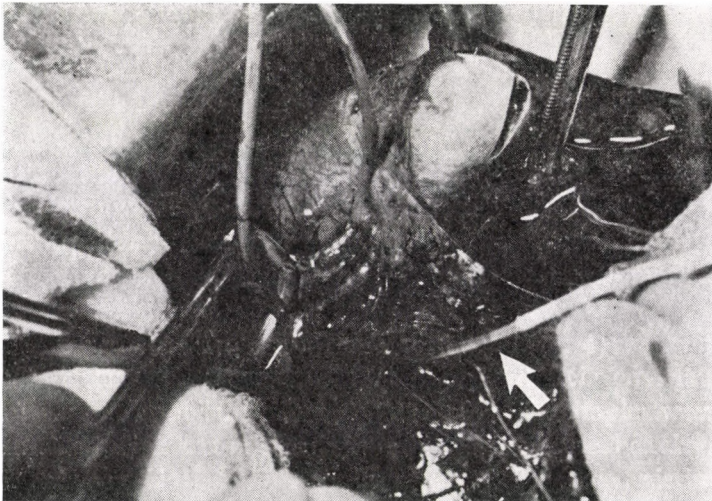


FIG. 1. The hypothermic fluid flows into the internal spermatic vein through a cannula fixed in it as indicated by the arrow

pole. The discharged hypothermic fluid did not disturb the operation. Temperature was measured at the corticomedullary border. The opened cavity system was closed by Dexon sutures. Subsequently, hypothermia was discontinued (after a cooling time of 25 to 90 minutes). The resection surfaces were dried, a minimal amount of Histoacryl blau (Braun, Melsungen) was put on the larger vessels and the surfaces were apposed using minimal compression. The subsequent step was the adhesion of the cut edges. This and the resulting state are shown in Fig. 2.

The cut edges were covered by the oxidized cellulose net with an overlap of 4 to 5 mm into each direction. On this surface 1 or 2 drops of adhesive were dropped which spread over the entire surface, keeping together and fixing the resected surfaces. This is demonstrated in Fig. 3. Figure 4 shows the state after decompression of the circulation. After performing a series of wedge-shaped resections polar resections were made at the lower pole in 7 cases. After closure of the cavity system Histoacryl blau was put on the transected vessels. The entire surface was covered by the oxidized cellulose net in a way to cover 4 to 5 mm of the renal capsule, too. Next to it, tissue adhesive was dropped on the surface of the net. The adhesive easily spread over the surface.

After decompression of the circulation, the oozing bleeding was minimized by the usual application of hot NaCl solution or by the insertion of a stitch (this latter was required in one case). The wound was closed layer by layer.

The sacrificed animals were dissected, the site of the operation was subjected to histological study.

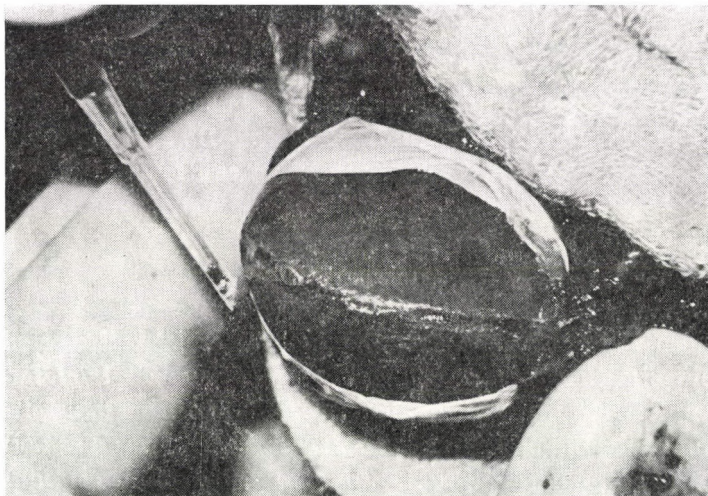


Fig. 2. State after apposition of the resected surfaces and adhesion of the edges

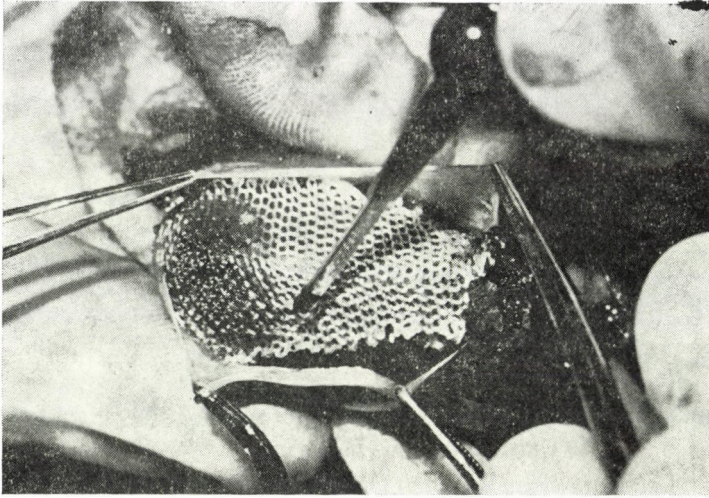


FIG. 3. Covering of the edges with an oxidized cellulose net before adhesion



FIG. 4. State after restoration of the circulation. The arrow points to the stump of the ligated internal spermatic vein

Evaluation of the Experiments, Discussion

In the 17 experiments no significant haemorrhages were observed after decompression of the hilus.

Complications due to the technical defects of transvenous perfusion cooling arose only in two cases. Cooling time ranged from 25 to 90 minutes

with a mean of 50 minutes. The temperature taken at the corticomedullary border was found to be 18 to 26 °C.

Problems concerning the technical performance of hypothermia and other observations were already discussed in previous studies [7, 8, 9, 10]. It was found that, as regards the behaviour of the tissue adhesive in hypothermia, polymerization time increased to the double or the double-and-a-half of that in normothermia. It should also be pointed out that the adhesive seemed to set on the surface, but its adherence to the parenchyma was still not perfect



FIG. 5. Detail of the experimental animal having survived for 60 days. The thickened capsule-like structure is well seen

because it could easily be lifted. This implies that at least three minutes should be waited for adhesion. The Surgical net adjusts well to the surface. The dropped adhesive spread easily over the surface. It was, however, much more rigid than it usually is in normothermia. On being re-heated, this rigidity did not change. Concerning the operative technique, this means that, if some safety stitches were to be inserted because of an oozing bleeding, this would be more difficult to perform.

After restoration of the circulation, the surfaces stuck to each other well, the Surgicel net combined with the adhesive secured the closure adequately. There was no opening of the renal wound. No animal was lost due to fatal bleeding.

The longest observation time was 240 days. On dissecting the animals, the surface of the kidney was shown macroscopically to be covered by smooth scar tissue at the site of the operation. Figure 5 shows a preparation deriving

from an experimental animal having survived for 60 days. The thickened capsule-like structure is clearly visible.

Figure 6 shows the histological section prepared from the operated kidney of the same animal. The red colour is the residue of the tissue adhesive showing a reticular structure by a special staining method [5]. According to the experiences made so far, the time of absorption of the tissue adhesive was somewhat modified as compared to that in normothermia. Additional studies are still needed to make more accurate observations.

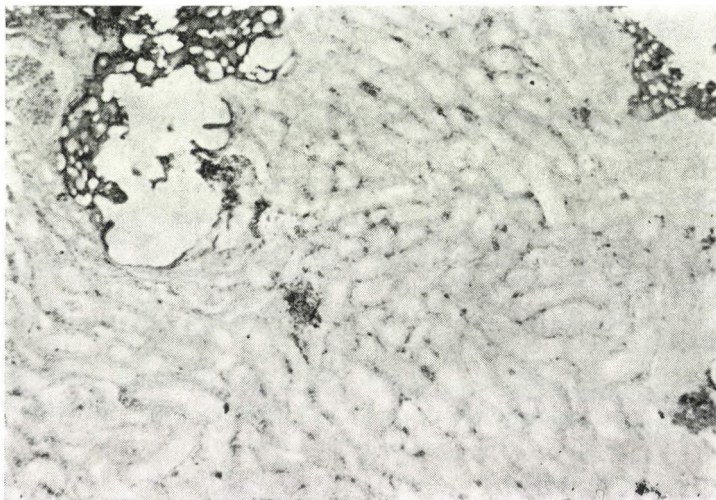


FIG. 6. Histological section of the kidney shown in Fig. 5, stained with the special Oil-Red-O technique ($\times 60$). The red reticular network is the residue of the tissue adhesive

It is also easy to cover the cut surfaces during polar resections. It has already been mentioned that a stitch had to be inserted in one case. This was not easy to perform due to the rigidity of the adhesive. As mentioned earlier, the polymerisate produced was, here too, more rigid. The results were in agreement with that described above, both macroscopically and microscopically. Naturally, scar tissue formation was also more expressed due to the larger amount of material. The scar of the lower pole appears to be as a white cap on the resected surface. Adhesions to adjacent organs (e.g. ureter) occurred in none of the cases.

The aim of our experiment was to establish whether these combined procedures could be used in regional renal hypothermia.

The results seem to prove that in suitable cases the above procedure can be fairly useful. It could be introduced into clinical practice, however, with due considerations.

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Kombinierte Anwendung von Bioplast und eines Gewebeklebers anlässlich von experimentellen Nierenresektionen bei in situ Nierenhypothermie

I. MIKÓ und I. FURKA

Bei durch die V. renalis zustandegebrachter regionaler Nierenhypothermie wurden bei Hunden keilförmige bzw. monoplanare Resektionen des unteren Pols durchgeführt. Die Wundfläche der Niere wurde — ohne Naht — mit einer aus Gewebekleber- und Bioplast-Material bestehenden Kombination bedeckt. Die Erfahrungen sprachen dafür, daß sich die Polymerisationszeit des Klebstoffes auf etwa das Doppelte erhöhte, die bei Normothermie übliche Steifheit des Klebstoffes ausgeprägter war und durch die Wiederwärmung nicht beeinflußt wurde. Auch die Heilungsbedingungen entwickelten sich vorteilhafter — es konnte mehr Nierenparenchym beibehalten werden, wie beim herkömmlichen Nadel-Faden-Verschluß.

Новый способ для заживления раневой поверхности почек

И. МИКО и И. ФУРКА

В экспериментах на собаках авторы произвели клиновидную или одноплоскостную резекцию нижнего полюса почки в условиях регионарной гипотермии почек, которую вызывали через венозный отдел. Раневую поверхность почек защищали комбинацией ткане-склеивающего материала и биопласта, без швов. Установили, что время полимеризации склеивающего вещества возросло вдвое; привычная в условиях нормотермии твердость клея была значительно более выраженной и на нее не оказывало влияния повторное нагревание. Условия заживления были более благоприятными: удавалось сохранить большее количество почечной паренхимы, чем при традиционном смыкании с помощью иглы и нити.

Prevention of Postoperative Thromboembolisms in General Surgery by the Combination of Heparin and Dihydroergotamine

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The effect and the degree of safety of administering a fixed combination of 5000 IU of heparin + 0.5 mg dihydroergotamine (HDHE s.c. per every 12 hours) as opposed to 5000 IU of heparin (LDH s.c. every 8 hours) was assessed in a prospective randomized study on 86 patients having undergone major abdominal operation. Postoperatively a deep vein thrombosis was detected by the radiofibrinogen test in 10% of the 40 patients of the HDHE group and in 13% of 46 of the LDH group. Four patients died. At autopsy neither fatal nor a contributing pulmonary embolism was found. 'Non-lethal' pulmonary embolism diagnosed by lung perfusion scintigraphy and by chest X-rays, developed in 2 patients treated with LDH and in one treated with HDHE. Two-thirds of the dose of heparin were identically effective in prevention of venous thromboembolisms than the whole dose if heparin was combined with DHE. The decrease of the heparin dose significantly reduced the number of wound haematomas and of suffusion due to injection.

Introduction

In reports on the causes of death and incapacity for work, thromboembolic complications associated with major operations, traumatological injuries and with various medical diseases have, in the recent 50 years, occupied a prominent place. According to some estimations, the number of cases of lethal pulmonary embolisms (pe) in the United States is 50,000 to 150,000 per year [1], while in the United Kingdom it approximates 20,000 [2]. In Hungary, yearly a total of 15,000 patients are hospitalized for some thromboembolic diseases, and 2000 patients die of pulmonary embolism [3]. A late complication of deep vein thrombosis (dvt) is chronic venous insufficiency which almost counts as an endemic disease in some countries.

In agreement with Kakkar et al. [4], several clinical studies proved that low-dose heparin (LDH) given subcutaneously, effectively reduces the frequency of postoperative thromboembolisms. The preventive effect of heparin was also investigated by us in a previous controlled randomized study made in 1979 on 80 general surgical and urological patients. Deep vein thrombosis was detected by the radiofibrinogen test in 35% of 37 controls and in 14% of 43

heparin-treated patients. The difference was significant (p 0.05) [5]. Objective clinical and pharmacokinetic studies have shown that 5000 IU of heparin given at every eight hours (i.e. three times daily) ('total' dose) ensures a more even and permanent plasma-level reducing the high frequency of thrombosis significantly more effectively than do the 12-hour, i.e. twice-daily treatments [6].

Heparin prophylaxis is, however, often associated with haemorrhagic complications. Although severe intra- and postoperative haemorrhages do only very rarely occur, minor suffusions at the site of injections and haematomas having developed in the surroundings of the surgical wound arise statistically significantly more often in heparinized patients than in the controls. During our own studies the local complications of heparin effect were assessed in a total of 537 surgical patients. Minor suffusions due to injection occurred in every fifth patient, while wound haematomas developed in every eighth one [5]. Undoubtedly, the risk incurred by low-dose heparin prophylaxis depends on the dose of heparin.

Dihydroergotamine (DHE) was shown to increase the speed of venous flow in the large veins of the lower extremities by constricting the capacitance vessels, while exerting only a negligible effect on the resistance vessels [7]. It was logical to postulate that better preventive results could be achieved by using the combination of heparin and DHE. The synergistic effect of these drugs can decrease to the minimum, or can eliminate altogether, the two, most important, factors in the pathogenesis of dvt, i.e. hypercoagulability and venostasis. It could also be concluded that the reduction of the daily dose of heparin could decrease the frequency of haemorrhagic complications, too. In fact, there is accumulating evidence to support the accuracy of this hypothesis [8, 9, 10].

All these considered, a randomized comparative clinical experiment was devised to test the effect of the heparin-DHE combination (given twice daily) in preventing postoperative thromboembolism, and the safety of administering this combination (three times daily) as compared to low-dose subcutaneous heparin. This paper presents the first data of the investigation series just being made.

Material and Method

Patients

Up to the present time, a total of 92, 40-year-old or older patients undergoing major abdominal operation have randomly been divided into two separate groups. Patients with recent myocardial infarction or rest angina were excluded. Patients undergoing operations of the goitre, of the lower extremities and left mastectomy were not studied either. Neither patients

receiving anticoagulant and thrombocyte-aggregation inhibiting drugs or dextran-type plasma volume extenders or those with a preoperative pathologic tendency to bleed were included. Thromboembolic risk factors were recorded for each patient. Six patients were excluded from the material because of neglect of the protocol and thus a total of 86 patients was examined.

In the *first (HDHE) group*, 40 patients received a fixed combination of 5000 IU of sodium heparin + 0.5 mg dihydroergotamine at 12 hour intervals.

In the *second (LDH) group*, 46 patients were given 5000 IU of sodium heparin at every eight hours.

The injections were made subcutaneously by the fine technique of Griffith and Boggs [11] into the anterior abdominal wall. The first injection was administered two hours preoperatively, then prophylaxis was continued for 7 postoperative days, or still longer, if the patient remained bed-ridden. The single-dose ampoules of the Sandoz AG were used.

Diagnosis of Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis was diagnosed, according to the method of Kakkar et al. [12], by the radiofibrinogen uptake test (RFUT). After blocking the thyroid with 150 mg potassium iodide, each patient was given i.v. 100 μ Ci 125 I-fibrinogen (Frederic Joliot Curie Institute, Budapest) before the operation or immediately after it. The labelled fibrinogen injection was repeated if radioactivity decreased before the 7th day. Scannings were daily made for 7 to 10 days in both legs by the Pitman 235 isotope localization monitor.

If RFUT was positive and the thrombosis was spreading proximally, for detection of pe, following injection of 2 to 4 mCi 99m Tc-macroaggregate albumin (Amersham, England), lung perfusion scintigraphy was performed by using an MB 9100 gamma camera (Gamma, Budapest). Besides, chest X-rays were also taken.

The patients died were autopsied in the course of which lethal pe was searched for.

Pre- and Postoperative Haemorrhage

Intraoperative loss of blood was assessed by the surgeon who stated whether excessive bleeding had occurred during surgery. Patients were daily monitored for haematoma formation in the region of surgical wounds and at the site of injections. The transfusion requirement, the haematocrit values measured preoperatively and on the sixth postoperative day, and the amount of blood collected daily in drainage sacs were recorded.

Statistics

For statistical analysis, the χ^2 -test and Student's two-sample test were used.

Results

Eighty-six patients, 35 males and 51 females, were examined. The groups could be well compared according to age, sex, body weight, blood group, the number of risk factors and to the type of operation. Table I shows the group data on the distribution of the various operations and frequency of the risk factors.

TABLE I
Group data

Total No. of patients	92	
Excluded patients	6 (3-3)	
	<i>HDHE group</i>	<i>LDH group</i>
Patients examined	40	46
Average age, yrs (extreme value)	62(41-85)	59(40-87)
Average weight (extreme value)	74(43-102)	72(45-98)
Operations		
stomach	4	6
gall bladder	20	28
colon/rectum	8	11
other major interventions	5	4
Patients with 2 risk factors	27	27
Patients with ≥ 3 risk factors	13	19

Frequency of dt and pe

Deep vein thrombosis developed in 4 of the 40 patients of the HDHE combination group (10%) and in 6 of the 46 patients of the LDH group (13%). The difference was statistically non-significant. Physical examination revealed symptoms suggestive of dvt in two of the 6 RFUT positive patients of the LDH group.

Four patients died (two in the HDHE and two in the LDH group): due to heart failure, peritonitis and carcinosis. All three were autopsied. At autopsy neither 'fatal' nor 'contributory' pulmonary emboli were found.

'Non-lethal' pulmonary embolism developed in two patients, both of them were treated by heparin alone. One case of pe was diagnosed also in the HDHE group. In this patient, however, pe developed on the 14th postoperative day, while administration of HDHE had previously been discontinued already on the 10th day, probably too early.

Table II summarizes the effect of prophylaxis on the frequency of postoperative thromboembolisms.

TABLE II
Incidence of thromboembolisms

	HDHE	LDH	p
No. of patients	40	46	
Deep vein thrombosis	4 (10%)	6 (13%)	NS
Died	2	2	
Autopsy ratio	100%	100%	
Lethal pulmonary embolism	—	—	
Contributory pulmonary embolism	—	—	
'Non-lethal' pulmonary embolism	1*	2	NS

* It developed on day 14, prophylaxis was stopped on day 10

Haemorrhagic Complications

Preoperative blood loss was under 500 ml and, in the opinion of the operating surgeon, excessive bleeding occurred in none of the cases. The difference between the two groups concerning the ratio of patients in need of transfusion, the amount of blood collected in the drainage sacs after the operation and concerning the postoperative decrease in haematocrit was not significant. Nevertheless, significantly more wound haematomas and suffusions due to injections were observed in the LDH group (Table III).

TABLE III
Haemorrhagic complications

	HDHE	LDH	p
No. of patients	40	46	
Patients requiring transfusion	7 (17.5%)	12 (26.1%)	NS
Amount of transfused blood, ml (mean \pm S.D.)	820 \pm 471	873 \pm 489	NS
Postoperative blood loss collected in drainage sacs, ml (mean \pm S.D.)	408 \pm 83	433 \pm 93	NS
Decrease in haematocrit, % (mean \pm S.D.)	5.8 \pm 0.6	5.2 \pm 0.5	NS
Suffusion due to injection	3	11	<0.05
Wound haematoma	1	7	<0.05

Discussion

In prevention of postoperative thromboembolic complications mechanical method and drug treatments are available. The mechanical method attempts to prevent stasis, while the individual drugs influence the changes in coagulation.

As far as the physical methods are concerned, stockings ensuring gradual compression, passive, intraoperative leg exercises performed by the use of Pedi Pulsor, intermittent pneumatic compression, electric leg-stimulation and intermittently pulsating stockings producing gradual compression may decrease the frequency of dvt. However, none of these methods has ever been proved to reduce the number of lethal pulmonary embolisms [13].

Among the drugs, the effect of low-dose heparin and dextran given subcutaneously is well founded [14, 15]. Studies evaluating the thrombocyte aggregation-inhibiting drugs, i.e. aspirin, dipyridamole, sulphinpyrazone, chloroquine, have not so far offered reliable evidence for the prophylactic effect of these drugs. Particularly, the proofs of its preventive effect against lethal pulmonary embolisms are lacking. There are, however, promising results but they are still to be verified [16].

Some promising approaches are being examined as, e.g. the ultra low-dose intravenous heparin [17], the semisynthetic heparin analogue [18] and the low-molecular-weight heparin [19].

The combination of heparin and dihydroergotamine is one of these new prophylactic possibilities. This combination exerts its effect on both factors inducing venous thrombogenesis: heparin stops the increased intraoperative coagulation tendency, while DHE increases the tone of veins thus preventing venous stasis. In the recent years, more than 20 randomized studies have documented by objective diagnostic methods the effectiveness of HDHE, particularly in traumatology after hip operations. During a multicentre trial in Switzerland involving 7413 orthopaedic patients, the prophylactic effects of lethal pulmonary embolisms of the HDHE combination and of dextran were compared. The two methods were equally effective. However, in the dextran group there were significantly more diffuse, intraoperative bleedings, wound haematomas and allergic reactions [20].

The latest investigations have revealed that DHE is not only an effective vasoconstrictor but also promotes the synthesis of prostaglandins which, in turn, favourably influence some thrombocyte functions [21]. It is also assumed that, due to the venoconstrictive effect of DHE, the release from the vessel wall of the plasminogen-activator is increased, thereby increasing the fibrinolytic activity, too [22].

In our prospective, randomized clinical study the effect of HDHE on general surgical patients was assessed. According to the results two-thirds of the heparin dose were equally effective in prevention of thromboembolisms than the whole dose, if the heparin was combined with DHE. At the same time, decrease of the heparin dose reduced significantly both the number of wound haematomas as well as that of suffusions due to injection.

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Vorbeugung der postoperativen Thromboembolien mit der Heparin-Dihydroergotamin-Kombination in der allgemeinen Chirurgie

T. SÁNDOR, E. LÁSZLÓ, F. MAGYARY, G. TURCSÁNYI, L. HETÉNYI und E. IZINGER

Der Arbeit liegen 86, eine große Bauchoperation überstandene Patienten zugrunde; im Laufe der bei ihnen durchgeführten prospektiven, randomisierten klinischen Versuchen wurden folgende Fragen geprüft: Wirkung und Verlässlichkeit der in fixer Kombination angewandten, aus 5000 I. E. Heparin + 0,5 mg Dihydroergotamin (HDHE, 12stündlich s. c.) bestehenden Medikation auf die Vorbeugung der postoperativen Thromboembolien — im Gegensatz zur Verabreichung von 5000 I. E. Heparin. Mit Hilfe des radiofibrinogenen Tests wurde bei 10% der 40 Patienten der HDHE-Gruppe und bei 13% der LDH-Gruppe postoperative Tiefvenenthrombose detektiert. 4 Patienten starben: Bei ihrer Sektion war weder ein fataler, noch ein konkomittierender Lungenembolus vorzufinden. Bei 2 der mit LDH und 1 der mit HDHE behandelten Patienten entwickelte sich mit Lungenperfusionsszintigraphie und Thorax-Röntgenaufnahme diagnostizierte, 'nicht tödliche' Lungenembolie. Zweidrittel der Heparindosis erwiesen sich zur Vorbeugung der Venenthromboembolien als ebenso wirksam, wie die klinisch empfohlene Volldosis, vorausgesetzt, daß Heparin in Kombination mit DHE verabreicht wurde. Durch die Herabsetzung der Heparindosis wurde die Zahl der Wundhämatome und der Injektionssuffusionen signifikant reduziert.

Предупреждение постоперативных тромбоэмболий в общей хирургии применением комбинации гепарин-дигидроэрготамин

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У 86 больных, перенесших большие операции в брюшной полости, в проспективных, рандомизированных клинических экспериментах мы оценивали: как влияет на профилактику послеоперационных тромбоэмболий и насколько безопасно применение комбинации точного количества (5000 ME) гепарина с 0,5 мг дигидроэрготамина (каждые 12 часов, подкожно) по сравнению с применением только 5000 ME гепарина. С помощью теста с радиоактивным фибриногеном мы обнаружили постоперативный тромбоз глубоких вен у 10% больных из 40 больных группы HDHE и у 13% больных из 46 в группе LDH. Умерли 4 больных. На вскрытии не обнаружили эмбола в легких, ни фатального, ни сопутствующего. «Не приводящая к смерти» легочная эмболия, диагностированная методом легочно-перфузионной сцинтиграфии и рентгенографией грудной клетки, возникла у двух больных из группы, леченной LDH, и один из группы, где больные получали комбинацию гепарина с дигидроэрготамином (HDHE). Две трети дозы гепарина были так же эффективны в профилактике венозных тромбозов, как и рекомендованная клинически целая доза, если его давали в комбинации с дигидроэрготамином (DHE). Уменьшение дозы гепарина достоверно снизило число раневых гематом и кровоподтеков после инъекций.

Patellar Chondropathy. II. Ultrastructure, Scanning Electron Microscopic Studies

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A scanning electron microscopic study of the chondropathy of the patellar articular surfaces following knee injury was made. The early signs of degeneration were evident in the superficial membrane. Here, the fibres running parallel with the surface then turning deep become irregularly arranged, i.e. the amount of matrix embedding the fibres was reduced and the uncovered fibres became fragmented causing degeneration of the superficial membrane.

During the progressive pathological process, as a result of the gradual deterioration of the interterritorial substance of the uncovered hyaline cartilage, spaces, fissures and deep pits were formed in the upper, then the lower, articular layers. The degeneration involved also the chondrons. With the disintegration of the chondrons the external and internal cell areolae disappear, the cell nests of chondrocytes are opened and the cells degenerate.

Finally, the irregular cellular and fibrous structures and their remnants as well as the elements of connective tissue proliferation initially associated with the degenerative process can be visualized ultrastructurally.

In a previous paper the pathology, clinical picture and the possibility of treatment of patellar chondropathy were studied [13]. The present report contains the results of the ultrastructural study of chondropathy.

Material and Method

The studies were made on small pieces of cartilage removed by surgery from a knee joint affected by arthrosis due to patellar chondropathy. On arthroscopic examinations preceding the operation as well as during surgery, changes corresponding to all the clinically definable stages of chondropathy could be found, i.e. the yellowish-brown discolouration, the oedematous loosening, and the lamellar-villous fragmentation of the cartilage, fissures of varying depths occasionally involving also the bone, and, in some cases, the circumscribed defect of the perichondrium spreading to the subchondrial bone [1, 2].

Surgical treatment consists in the abrasion of the degenerated articular surface with a sharp scalpel. Excision starts from the intact cartilage near the

border of the intact and pathological surfaces. In the regions, where after abrasion no chondral layer has actually been left, fine holes are drilled (of a diameter of 3.2 mm) in order to promote connective tissue proliferation [10].

The surgically removed cartilage pieces were fixed in 2.5% glutaraldehyde (pH 7.3) for one hour, then dehydrated in a graded series of ethanol. After drying at the critical point, the samples were covered by a coat of gold. Examination of the surface was made by a TESLA BS 300 scanning electron microscope [3].

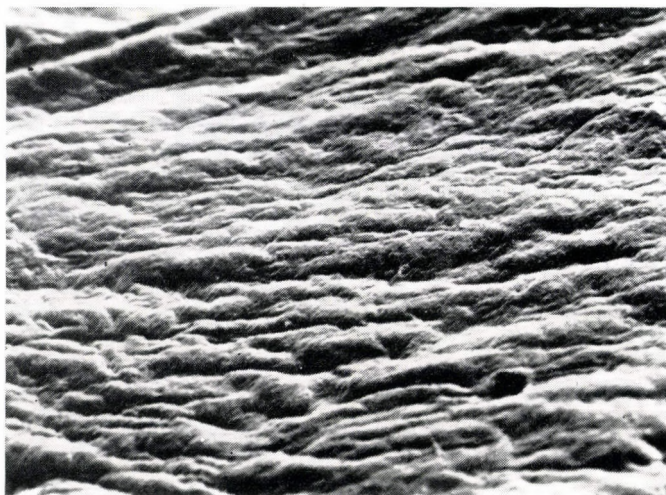
Observations

On the edge of the seemingly intact excised piece of cartilage the superficial membrane did not contain any cellular element. The parallelly running collagen fibres being the basic structural unit of the membrane, formed bundles. The individual bundles, while running longitudinally, passed round each other forming plexuses and the neighbouring plexuses were often replaced by the bundles composing them (Fig. 1).

The surface undulation of the superficial membrane could be observed throughout the thickness of the membrane (Fig. 2).

The virtual space between the membrane of the cartilage appearing to be intact microscopically and the chondral substance opened in some places, and the membrane was lifted (Fig. 3). The lifted and, as a consequence, stretched part of the membrane crinkled, cracked or was torn (Fig. 4).

Replacing the withdrawn superficial membrane, a layer of hyaline cartilage composed of regularly arranged chondrons appeared. These units within one layer were tightly pressed together, their touching surfaces became flattened as the peas in the pod (Fig. 5).





FIGS 1 and 2. The superficial membrane is composed of collagenous fibres running parallel with the surface and with each other ($\times 800$ and $\times 1280$)

In the progressive stage of chondropathy the severe involutonal and the regenerative tissular phenomena (e.g. formation of new fibres) showing no orientation occur simultaneously (Fig. 6).

On surfacing of the hyaline cartilage, the involution involves also the nests of chondrocytes near the cells, then also the cells degenerate (Figs 7 and 8).

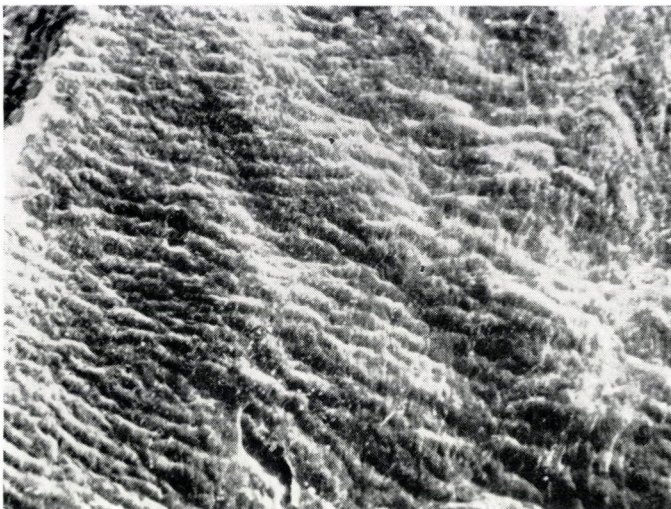


FIG. 3. The virtual space between the superficial membrane and the chondral substance opens in some places and the membrane is elevated ($\times 500$)



FIG. 4. The elevated and stretched part of the membrane becomes wrinkled, broken or torn ($\times 240$)

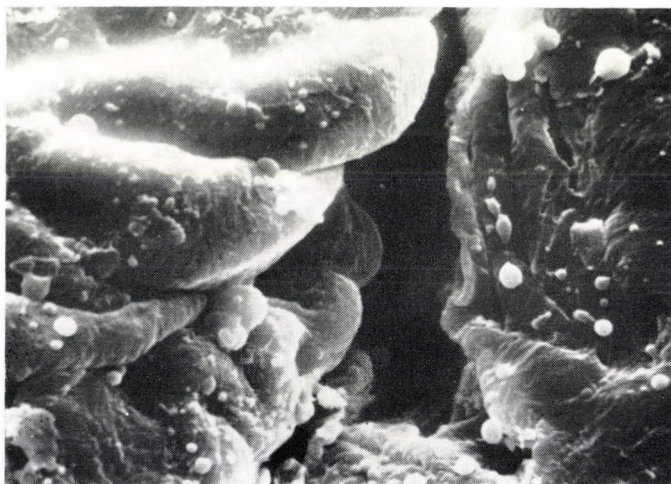


FIG. 5. In the place the membrane is becoming detached a regularly arranged chondral layer of hyaline cartilages appears ($\times 2400$)

As a result of degeneration of the chondral substance, a rough fragmented material is left over (Fig. 9), where the initial fine structure cannot be recognized.

The hyaline cartilage degenerated to the bone is occasionally replaced by a fibrous connective tissue intertwined with the degenerating and, in some places, re-forming chondral elements (Fig. 10).



FIG. 6. Beside the severe tissue involution, phenomena indicating regeneration, too, can be found (new fibre formation) but these show no orientation ($\times 840$)



FIGS 7 and 8. On surfacing of the hyaline cartilage, the involution involves also the cell nests of the chondrocytes, then also the released cells degenerate ($\times 2400$ and $\times 3200$)

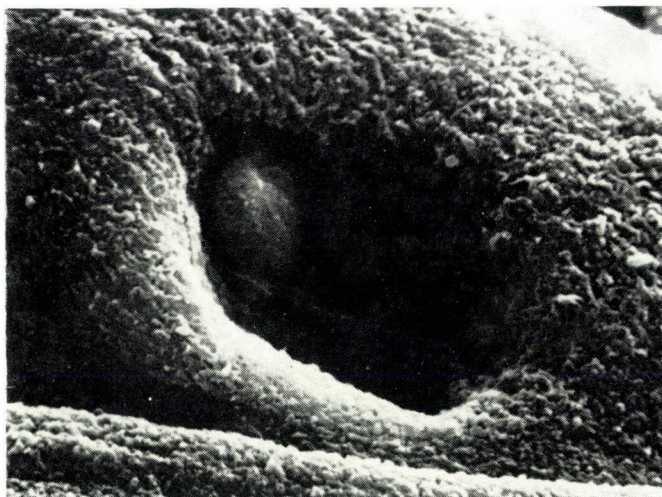


FIG. 8. See page 119

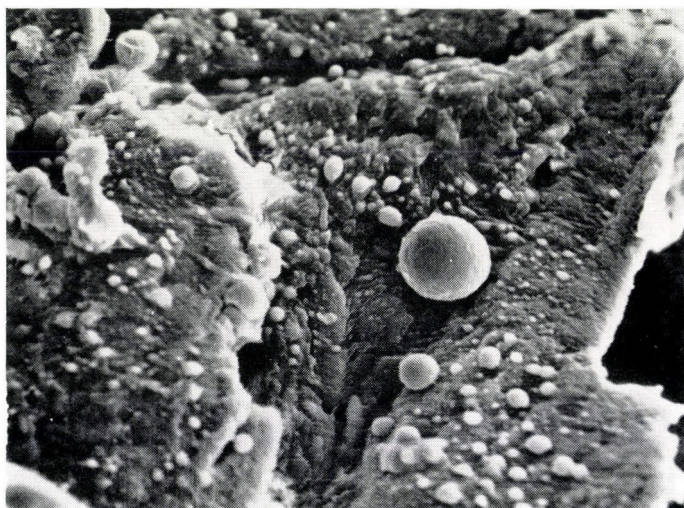


FIG. 9. As a result of the degeneration of the chondral substance, a debris is left over in which the initial fine structure cannot be recognized ($\times 660$)

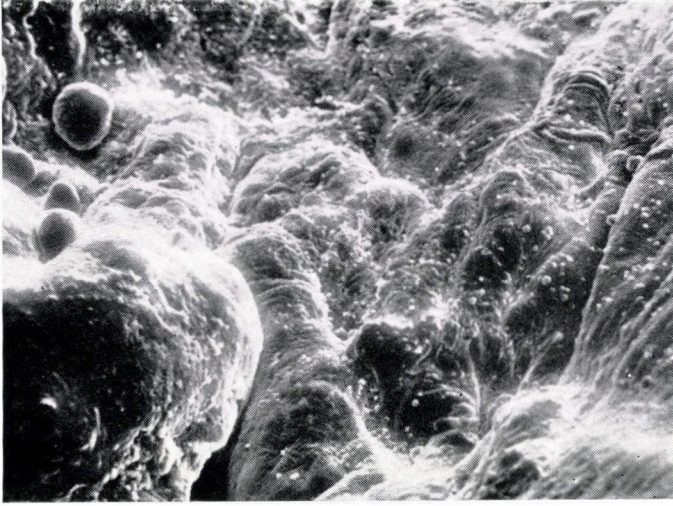


FIG. 10. The hyaline cartilage degenerated to the bone is replaced by a rough, fibrous connective tissue ($\times 220$)

Discussion

According to the view prevailing in the literature, the superficial membrane is composed of collagen fibres running parallel with the surface and also with each other [5, 7, 9]. This statement is too general and can be accepted only with some reservation because the network produced by the complicated intertwining of bundles composed of parallel collagen fibres dominated the secondary spatial structure (Fig. 11). As regards the function of the membrane, this network is more important than the simple parallel course within the

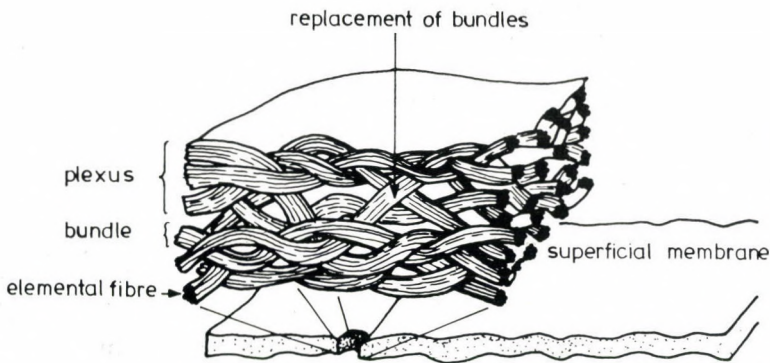


FIG. 11. While running longitudinally, the individual bundles form plexuses and the neighbouring plexuses are often replaced by the bundles composing them

bundle, since it provides the thin velamentous superficial membrane with a relatively great elastic tensile strength.

The possibility of tracing the described waves through the thickness of the superficial membrane shows that the undulation is caused by the structure of the chondral layer located directly underneath the membrane. It adheres to the regularly disturbed subsurface layer of chondrons as demonstrated schematically in Fig. 12.

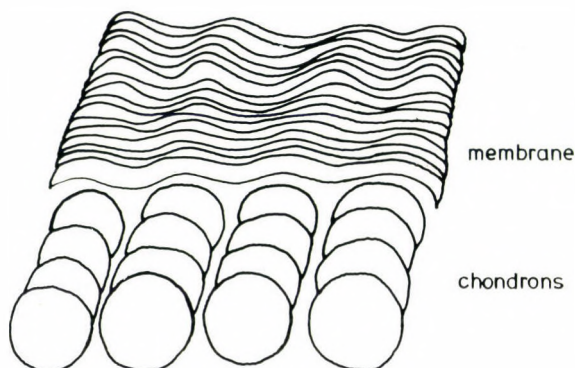


FIG. 12. The superficial membrane adheres closely to the chondral layer being nearest to the surface

It should be noted that the scanning electron microscopic pictures do not provide information on the thick solution of amorphous matrix surrounding the fibrous network of the superficial membrane. Partly by the capacity of liquids in evenly mediating pressure and partly by the adhesion and viscosity due to the molecular composition of the solution the matrix contributes to the elasticity of the superficial membrane, i.e. to its mechanical adaptability.

According to the generally accepted view, the adherence of the superficial membrane to the upper layers of chondrons is secured by the fibres turning deep from the membrane and by a gelatinous matrix [4, 11, 12]. The fixation of the membrane can be decisive at the beginning of the degenerative process of the cartilage. There is virtual space between of the membrane and the uppermost chondrons, which is flanked by structural elements adapting, in various ways and by different properties to mechanical strains. While the membrane corresponds in its entire thickness to a relatively homogeneous non-cellular tissue impregnated by an interfiber substance, beneath the membrane there are the groups of relatively independent chondrons. This fundamental structural difference is of primary importance in receiving and transmitting mechanical impulses when these cannot be conducted any longer by the continuous fluid space of the embedding matrix and the fibres protruding from the membrane into the chondral units.

The importance of defects in the adherence of the membrane is also revealed by the observation that detachment of the membrane from the chondrons and widening of the originally virtual space could be seen also beneath the surface which appeared to be intact microscopically. In the elevated region the stretched membrane becomes wrinkled and, as a result of the subsequent mechanical impulses, becomes injured. The microscopic lesion transforms into a surface defect on the stretched membrane and the weaker resistance will, in some places, be the starting point of the subsequent degenerative process. The observation, that the chondrons in one layer are pressed tightly together and, at the same time, the distance between the adjacent layers leaves sufficient space for the protruberance of the chondral surface to be maintained, may allow us to draw the conclusion that, different impulses act longitudinally and transversely and the chondrons are arranged along the line of the acting forces. A basically similar effect is assumed in the mechanical strains participating in building the architecture of the bone trabeculae.

The importance of mechanical impulses is analysed so much in detail, because the role of mechanical causes in the aetiology of chondropathy is the most emphasized in the literature among the endogenous as well as exogenous predisposing or stimulating factors [6, 8]. Of the endogenous ones, such are the anatomical variants (e.g. patellar dysplasia, parva, partia), pathologic patellar positions (e.g. lateralization, subluxation, habitual luxation, p. alta, dysplasia of the condyle of the femur), pathologic axial deformities (genu valgum-varum, rotatory position). Of the exogenous factors: direct chondral traumata (contusion, osteochondral pressure fracture) and posttraumatically impaired joint mechanics (joint fracture with step formation, axial and rotatory changes after fibular fracture, injury of the capsular ligament and of the meniscus, recurring patellar dislocation), and finally, the disproportion between the individual loading capacity and real loading (work, sports, obesity).

The common pathogenic factor in all the listed types of chondropathic processes is the incongruity between the surface and the acting forces.

In case if a sudden or gradual incongruity arises between the joint surface and the load, the initial structure undergoes reorganization. On the analogy of the restructuring processes of the bone trabeculae, the building of the tissue adapting to the new conditions will occur parallelly to the decomposition of old tissular elements in the biological process of change of the structure. If the possibilities of compensation of the structural change are exceeded by the extent of incongruity, involution becomes the basic biological phenomenon of the degenerative pathomechanism. The other conditions generally associated with the suddenly or chronically arising incongruities (e.g. changes in tissular diffusion on increase of joint pressure, tension due to oedema, enzyme release as a result of haemorrhage, direct tear, etc.) increase the dominance of chondral decomposition at the expense of rebuilding. Rebuilding cannot keep abreast

with the consequences of the pathologic conditions for the sole reason that, because with incongruity becoming permanent (that means that even the new situation will soon change), the control of tissue rebuilding will become dis-oriented.

The described mechanism is supported by histological observations stating that both lightmicroscopic and stereomicroscopic pictures reveal, in addition to severe tissue involution, also phenomena indicative of regeneration (e.g. new fibre formation), however, these regenerative rudiments show no kind of orientation.

In the studied cartilage pieces, involution predominated in each case. We saw that the normal ultrastructure is gradually replaced by the disorganization of the membrane structure, the deepening of the ripples, the loosening and roughening of bundles, and by the fragmentation of fibres and, as a consequence, by the elevation, wrinkling and injury of the membrane. The injuries of the membrane lead to the opening of the surface fissures, until finally the membrane disappears in regions of various size revealing the deeper layers and the outer areola of the chondrons.

Such surface injury may directly involve the chondrons of the hyaline cartilage where, at the beginning, the disorganization of the regular chondral layer, then the disappearance of the inner areolae lining the cell nests of the chondrocytes could be observed. The rough debris produced during the degeneration of the fibrous and cellular substance accumulates in an amount depending on the speed of production and elimination.

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Chondropathia Patellae. II. Ultrastruktur, Scanningelektronenmikroskopische Untersuchungen

I. SZILÁGYI, Z. DEMEL und T. SALACZ

Mit dem Scanning-Elektronenmikroskop wurde die ultrastrukturelle Untersuchung der sich nach Knieverletzungen auf der Gelenkfläche der Patella entwickelnden Chondropathie durchgeführt. Die Frühzeichen der Degeneration melden sich in der oberflächlichen Membran, wo sich die Anordnung der, der Oberfläche parallel verlaufenden und der der territorialen Gliederung entsprechend tiefwärts verlaufenden Fasern auflöst bzw. sich die Menge der die Fasern einbettenden Grundsubstanz verringert und die freigewordenen Fasern fragmentiert werden, was zur Zerstörung der oberflächlichen Membran führt.

Im Laufe der Progression des pathologischen Prozesses bilden sich wegen des graduellen Abbaus der interterritorealen Substanz des unbedeckten Hyalinknorpels zuerst in den oberen, sodann in den unteren Knorpelschichten Spalten, Rupturen bzw. tiefdringende grobe Risse und die Degeneration breitet sich auch auf die Chondroneinheiten aus. Mit der Desintegration der Chondrone verschwinden die äußeren und inneren Zellhöfe, die Zellneste der Chondrozyten öffnen sich und die Knorpelzellen gehen zugrunde.

Schließlich erscheinen auf dem ultrastrukturellen Bild irreguläre zellige und faserige Strukturelemente bzw. ihre Reste sowie die Elemente der den Degenerationsprozeß von Anfang an begleitenden reparative Bindegewebswucherung.

Chondropathia Patellae: II. Ультраструктура, исследования сканирующим микроскопом

И. СИЛАДИ, Ж. ДЭМЕЛ и Т. ШАЛАЦ

С помощью сканирующего микроскопа авторы выполнили ультраструктурное исследование хондропатии, возникающей на суставной поверхности надколенника, после повреждения колени. Ранние признаки дегенерации видны на суперфициальной мембране, где нарушается структура волокон, проходящих параллельно поверхности и, в соответствии с территориальным распределением, заворачивающих в глубину, или же количество основного вещества, в котором уложены волокна, уменьшается, и становящиеся свободными волокна фрагментируются, вследствие чего поверхностная мембрана погибает.

При прогрессировании процесса, из-за постепенного исчезновения интертерриториального вещества незащищенного гиалинового хряща, сначала в верхних, а затем и в нижних хрящевых слоях возникают трещины, цели, глубоко проникающие грубые провалы, и дегенерация распространяется и на хондровые единицы. С дезинтеграцией хондронов исчезают наружные и внутренние клеточные ареолы, клеточные гнезда хондроцитов удлиняются, хрящевые клетки погибают.

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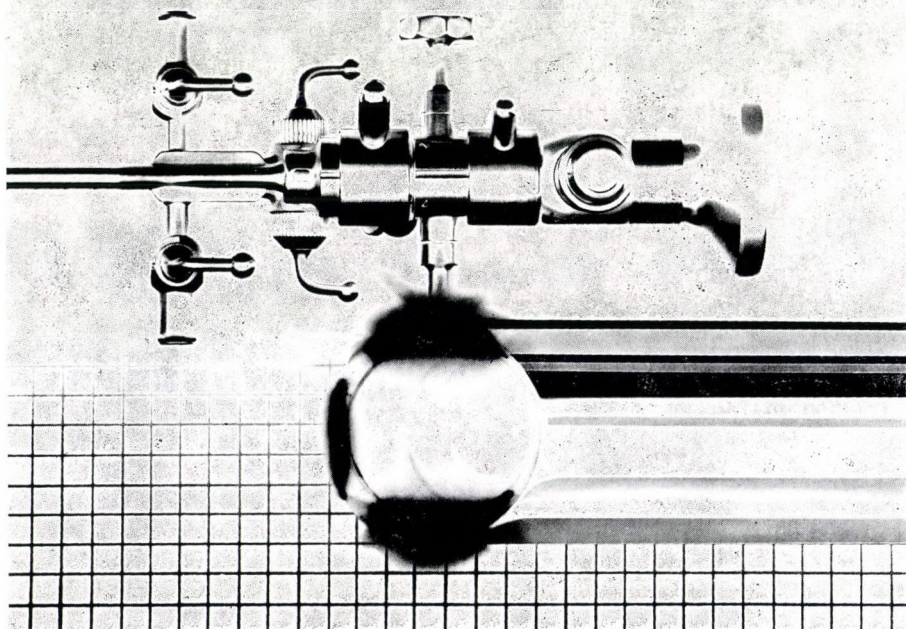
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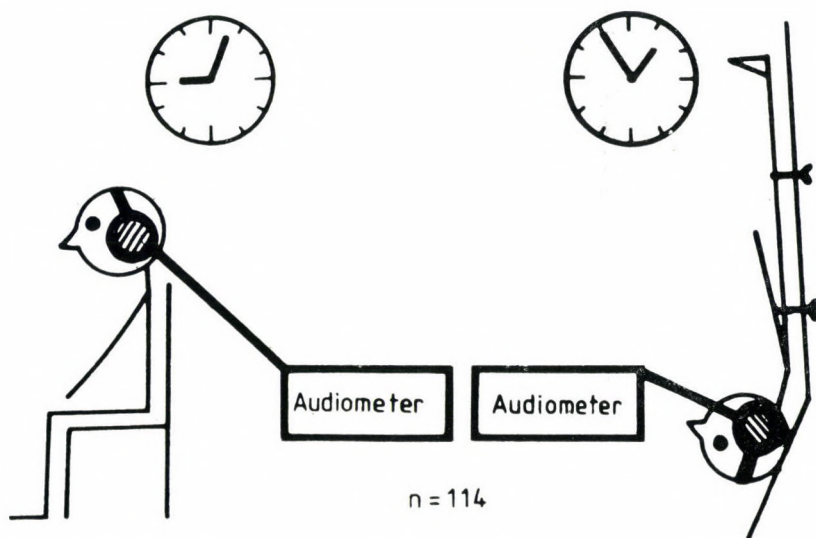


HEARING IMPAIRMENT AND THE LABYRINTHINE PERILYMPHATIC SYSTEM

by E. MIRISZLAI

In English. 1983. 134 pages, 77 figures, 15 tables. 14×21 cm. Hardcover \$9.50/DM 22.—
ISBN 963 05 3153 4

This book deals with the perilymphatic system, playing an important role in the clinical and experimental aspects of the inner ear, and the hearing impairments related to it. The physical and chemical characteristics of the fluids of the inner ear are reviewed and compared with those of the blood and the cerebrospinal fluid. The different views on the secretion of the inner ear and extracranial fluid spaces, are discussed. The factors leading to the changes in the pressure of the perilymphatic system and their effects upon hearing, both under experimental and clinical circumstances, are revealed in detail. Two new clinical entities, the perilymphatic fistula and round window membrane ruptures are surveyed. The clinical and experimental studies presented by the author contribute to a deeper understanding of conditions accompanied by the severe alteration of inner ear function, such as hearing impairment and vestibular function.



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SURGERY OF THE NEUROGENIC BLADDER

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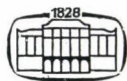
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Is Priming an Unripe Cervix with $\text{PGF}_{2\alpha}$ effective?*

H. WILKEN

University Women's Hospital, Rostock, GDR

(Received 6 February 1985)

A report is given about induction of labour in 1050 women using different methods to improve cervical condition before induction in 151 women. Administration of oestradiol intramuscularly had a better effect than the locally administered $\text{PGF}_{2\alpha}$.

Induction of labour in women with unripe cervix is still now a problem. We evaluated 1050 women with induction of labour. 681 (about two-thirds) of these were so-called terminated or programmed labours, 369 (about one-third) were indicated labours. The indications were postmaturity, pathological CTG, premature rupture of membranes, toxæmia, foetal growth retardation, etc.

Of these 151 had an unripe cervix (Bishop Score 0–4) and attempts were made to improve the cervical condition by priming. Several methods had already been proposed for cervical ripening (Table I).

Of these methods we used only two: 106 patients received oestradiol intramuscularly (4 times a day 5 mg oestradiol benzoate for 1–3 days). 45

TABLE I
Methods for cervical ripening before induction of labour

<i>Physical</i>	
balloon, vibration, electric stimulation laminaria, stripping of membranes	
<i>Drugs</i>	
Systemic:	oxytocin ('ripening infusion') oestradiol prostaglandins $\text{PGF}_{2\alpha}$, PGE_2
Local:	hyaluronidase relaxin oestradiol $\text{PGF}_{2\alpha}$ PGE_2

* Presented at the International Symposium on the Pregnant Uterus—a Commemoration of A. I. Csapó—16–18 October 1983, Hungary

TABLE II
Cervical condition and oxytocin requirement

Bishop score	Total	Oxytocin requirements		>10 IU
		—5 IU	6–10 IU	
0–4	114	80 (70.2%)	30 (26.3%)	4 (3.5%)
5–8	568	493 (86.9%)	69 (12.1%)	6 (1.0%)
9	301	292 (97.1%)	9 (2.9%)	
uncertain				

TABLE III
Cervical condition and labour outcome

Bishop score	Total	Caesarean section	Forceps	Vacuum extraction
0–4	150	13 (8.6%)	4 (2.6%)	7 (4.6%)
5–8	569	19 (3.3%)	40 (7.0%)	27 (4.7%)
9	306	4 (1.3%)	19 (6.2%)	13 (4.2%)

women received 4 mg PGF_{2x} intracervically in methylcellulose gel or by means of a cervical cap.

Table II shows the connection between cervical condition and oxytocin requirements. It is to be noted that patients with unripe cervix need more oxytocin.

The main disadvantage of labour induction in women with unripe cervix is the increased frequency of caesarean section because of delayed labour and the resulting hypoxia of the foetus (Table III).

In patients with unripe cervix the caesarean section rate is 2–3 times higher.

Results of Cervical Priming

Considering the Bishop scores before and after priming with both methods, the results are good (Table IV). About 80% showed a better score after priming than before.

Analysing the induction time, oxytocin requirements, and outcome of labour, the results in the primed women are, however, not so favourable. In Table V the induction times of all cases are compared with those of the primed women having a given Bishop-score before induction (after priming).

Prolonged labour occurs in primed women fairly infrequently (Table V). However, primed women need more oxytocin than do nonprimed (9.4% against 27.1%) (Table VI).

TABLE IV
Effect of priming

Types of priming	Total	Bishop score after priming		
		0-4	5-8	≥9
E ₂ i.m.	106	19 (17.9%)	65 (61.3%)	22 (20.7%)
1×PGF _{2α} intracervical	32	7 (21.8%)	21 (65.6%)	4 (12.5%)
2×PGF _{2α} intracervical	13	1	10 (76.6%)	2

TABLE V
Cervical condition and induction time

Bishop score	-12 h		13-18 h		>18 h	
	total	primed	total	primed	total	primed
0-4	134 (89.3%)	18 (66.6%)	15 (10.0%)	8 (29.5%)	1 (0.6%)	1 (3.3%)
5-8	531 (91.6%)	89 (92.6%)	27 (4.7%)	3 (3.1%)	7 (1.2%)	4 (4.2%)
9	304 (99.3%)	25 (89.3%)	1	2	1	1

TABLE VI
Oxytocin requirement in nonprimed and primed women

	Total	Oxytocin requirement	
		-5 IU	5 IU
Nonprimed	899	814	85 (9.4%)
Primed (several methods)	151	110	41 (27.1%)

As to labour outcome, the results are not so good either, because frequency of caesarean section is twice as high than in nonprimed cases (Table VII).

In conclusion, the cervical condition after artificial priming by oestradiol and by locally administered PGF_{2α} may not be so favourable than in naturally ripened cervixes. Unfortunately, the number of our primed cases with PGF_{2α} are not so high and we have not investigated the efficiency of other methods.

It is to be noted that administration of oestradiol intramuscularly in comparison with locally administered PGF_{2α} seems effective to some extent. Based on new observations on the changes in the myometrium, such as formation of gap junctions after administration of oestradiol, an explanation of the clinical effect of oestradiol might be possible.

TABLE VII
Labour outcome in nonprimed and primed women

	Total	Labour outcome		Vacuum extraction
		Caesarean section	Forceps	
Nonprimed	899	25 (3.6%)	52 (7.4%)	41 (5.8%)
Primed	151	11 (7.3%)	11 (7.3%)	8 (5.3%)

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2. René AMJ, Esteban-Altirriba J: Induction of labor a concept in change. J Perinat Med 11: 139-147, 1983

Hat sich PG_{2α} zur Vorerweiterung des Muttermundes als wirksam erwiesen?

H. WILKEN

Berichtet wird über die Geburtsinduktion von 1050 Frauen. In 151 Fällen kamen zur vorteilhaften Beeinflussung des Zustands des Gebärmutterhalses vor der Geburtsinduktion verschiedene Methoden zur Anwendung. Intramuskulär verabreichtes Östradiol erwies sich als wirksamer, als das lokal angewandte Prostaglandin (PGF_{2α}).

Эффективно ли раскрытие маточного зева с помощью применения простагландина F_{2α}?

Х. ВИЛКЕН

Автор сообщает о вызывании родов у 1050 женщин. Среди них в 151 случае применяли различные методы перед началом родов для благоприятного действия на состояние маточной шейки. Внутримышечное применение эстрадиола оказывало лучшее влияние, чем локально введенный PGF_{2α}.

Experiences with a new Priming Score for Estimation of Efficiency of PGF_{2α}-Gel for Cervical Maturation in First Trimester Induced Abortion*

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(Received 6 February, 1985)

A new priming score for estimation of the efficiency of a cervix priming with prostaglandins (PG) prior to first trimester induced abortion is presented. The score consists of five points: 1 = No effect or partial dilatation of the cervix, further mechanical dilatation is very difficult. 2 = Partial dilatation of the cervix, further mechanical dilatation is moderately difficult. 3 = Partial dilatation of the cervix, further mechanical dilatation is effortless. 4 = Cervix is open for pregnancy age, no further mechanical dilatation is required. 5 = Abortion.

A total of 340 primigravidae requiring a termination of first trimester pregnancy took part in a prospective study for testing the score. The cervix priming was performed by a single intracervical application of 2.5 mg PGF_{2α}-gel. Regarding the score, this regimen was found to be in 89.1% effective. In 8.5% a partial and in 2.4% no effect was recorded. Because the recommended score is related to the age of pregnancy, it is suitable for comparison of different prostaglandins and other methods for cervix priming prior to pregnancy termination.

Introduction

The use of prostaglandins (PG) to soften and dilate the cervix prior to termination of pregnancy may help in avoiding potential early and late complications like long-term sequelae from rapid mechanical dilatation especially in primigravidae. The most common methods of cervical softening prior to first trimester vacuum aspiration are: Intracervical application of a PG-gel [1, 6, 7, 19, 21], intravaginal administration of PG-suppositories [9, 10, 17, 18] or delivery systems containing PG [2, 8], and intracervical-intramural [20] or intramuscular PG-injection [4, 12, 15]. In the management PGF₂, PGE₂ and their derivatives are employed in various dosages. For estimating the efficiency of the various methods and dosages on cervical maturation, several scores have been developed or score-like systems are being used [1, 3, 5, 11, 12, 13, 15]. These scores are not comparable because they have no connection with

* Presented at the International Symposium on the Pregnant Uterus—a Commemoration of A. I. Csapó—October 16–18, 1983, Hungary

the age of pregnancy. The purpose of this study has been to present a score allowing a simple efficiency estimation of different prostaglandins and methods for cervix priming prior to termination of pregnancy.

Materials and Methods

A total of 340 primigravidae requiring a termination of first trimester pregnancy took part in a prospective study. The mean age of the women was 19 years, with a range from 14 to 41. 37.4% were 17 years old or younger. The length of gestation ranged between 6 and 14 weeks. All women gave written consent to the use of PG. Cervix priming was performed by a single intracervical application of 2.5 mg $\text{PGF}_{2\alpha}$ in 10 ml of a viscous gel (mucilago hydroxyaethylcellulosi). The women were instructed to rest 30 minutes following the PG-application. Vacuum aspiration was carried out 16 to 25 hours later under general anaesthesia. If the conceptus was expelled prior to the planned evacuation an earlier curettage was necessary. Special observation charts were used to record uterine contractions, pain, blood loss, blood pressure, pulse, temperature, and side-effects. In order to verify the effect of cervix priming the following scores were employed:

1 = No effect or partial dilatation of the cervix, further mechanical dilatation is very difficult

2 = Partial dilatation of the cervix, further mechanical dilatation is moderately difficult

3 = Partial dilatation of the cervix, further mechanical dilatation is effortless

4 = Cervix is open for pregnancy age, no further mechanical dilatation is required

5 = Abortion

Estimation: Score 1: without success

Score 2: partial success

Scores 3-5: success

Cervix is open for pregnancy age means that for the 6th to the 10th week of pregnancy the dilatation in millimetres is equal to the week of pregnancy. In the 11th and 12th week the dilatation in millimetres is equal to the week of pregnancy plus one millimetre.

Results

The results are summarized in Table I. The single priming dose of 2.5 mg $\text{PGF}_{2\alpha}$ -gel was found to be in 89.1% effective. In 8.5% a partial success was recorded. In contrast, 2.4% of the women failed to show any real effect.

The adverse reactions consisted of 26.6% nausea or vomiting. In 10.5% a short increase of systolic blood pressure was recorded requiring no treatment. Other slight side-effects were less than 1%. Serious adverse reactions to PG were not experienced. In addition, there was a clear correlation between the number of side-effects and the increase of the success rate noticed by the priming score (Fig. 1).

The early complication rate within 14 days was 8.2%. It consisted of 4.1% adnexitis and/or endometritis. In 2.6% temperatures above 37.5°C

TABLE I

The success rate of a cervix priming with $\text{PGF}_{2\alpha}$ -gel prior to vacuum aspiration for termination of pregnancy in the first trimester in regard to the priming score

Score	Primigravidae		Estimation
	total	per cent	
1	8	2.4	without success
2	29	8.5	partial success
3	115	33.8	success
4	73	21.5	(89.1 %)
5	115	33.8	
1-5	340	100.0	

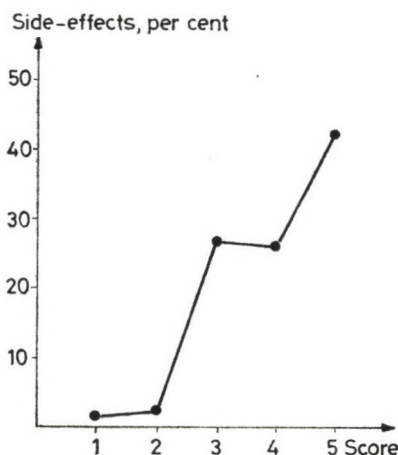


FIG. 1. Correlation between the number of side-effects and the increase of the success rate indicated by the priming score

without pelvic inflammation were observed. In 1.5% we recorded haemorrhages without retained placental tissue. The complication rate increased with the gestational age and was the highest if the priming score was 4. No cervical lesions could be observed and no perforation of the uterus occurred at operation.

Discussion

PG administration is employed to achieve cervical softening and dilatation prior to vacuum aspiration for termination of pregnancy. The research on the use of various PG-derivatives administered by different routes is in progress. To verify the effect of priming methods several scores have been developed [1, 3, 5, 11, 12, 13, 15]. These scores are not suitable for comparing the success rate of the different methods and PG because they do not take in consideration the age of pregnancy. For instance, a cervix dilatation of 10 millimetres is not required by a gestation age of 8 weeks but it is not sufficient for an age of 12 weeks. The recommended score eliminates this disadvantage and allows the comparison of different treatment schedules. In addition, we can get information on the side-effects and complication rates.

As expected on the basis of simultaneous systemic PG effect, a relationship was found between the extent of side-effects and the increasing priming score. Similar results were recorded by Seifert and Haßler [16] who established a correlation between clinical success and venous blood levels of $\text{PGF}_{2\alpha}$ after cervix priming.

The present results suggest that a locally applied dose of 2.5 mg $\text{PGF}_{2\alpha}$ can be useful to ripen the cervix in young primigravidae in order to avoid complications in subsequent pregnancies, although long-term follow-up would be needed to establish this.

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Erfahrungen mit der Anwendung eines neuen »priming score«-s zur Messung der Effektivität des zwecks Muttermunderweiterung verabreichten PG F_{2α}-Gels bei künstlichem Abort im ersten Trimester

G. GÖRETZLEHNER, G. KÖHLER, A. SCHUCHART und S. NIKSCHICK

Berichtet wird über die Erfahrungen mit einem neuen »priming score« zur Beurteilung der vor den künstlichen Aborten des ersten Trimester durchgeführten Muttermund-Vorerweiterung (»priming«). Der Score hat 5 Stufen: 1. Der Muttermund hat sich überhaupt nicht erweitert, die weitere mechanische Erweiterung ist schwierig. 2. Partielle Muttermunderweiterung, die weitere mechanische Erweiterung ist mittelmäßig schwierig. 3. Partielle Muttermunderweiterung, weitere Erweiterung kann ohne Widerstand durch-

geführt werden. 4. Der Muttermund ist genügend erweitert, weitere Erweiterungsmaßnahmen sind überflüssig. 5. Der Abort ist abgeklungen.

In die prospektive Studie der Scoreuntersuchung wurden 340 sich im ersten Trimester ihrer Gravidität befindliche, sich zur Schwangerschaftsunterbrechung gemeldete Primigraviden einbezogen. Zur Zervixvorerweiterung fand eine einmalige, intrazervikal verabreichte 2,5 mg PGF_{2α}-Gelinjektion eine Anwendung. Nach dem Score erwies sich diese Verabreichungsweise in 89,1% der Fälle als wirksam. Partielle Wirkung war in 8,5% und Wirkungslosigkeit in 2,4% der Fälle zu verzeichnen. Da das empfohlene Punktsystem auch das Schwangerschaftsalter berücksichtigt, scheint es sich auch zum Vergleich mit verschiedenen Prostaglandinen und sonstigen Vorerweiterungsverfahren zu eignen.

Опыт применения одного нового «*priming score*» для изменения эффективности PGF_{2α}, вводимого с целью ускорения созревания маточного зева, при искусственных выкидышах в первом триместре

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Авторы сообщают об опыте применения нового «*priming score*» для оценки предварительного расширения («*primings*») маточного зева, производимого в первом триместре перед искусственным выкидышем. Score имеет пять степеней: 1. Маточный зев совершенно не раскрыт, дальнейшее механическое его расширение трудно. 2. Частичное расширение маточного зева, дальнейшее механическое расширение является умеренно тяжелым. 3. Частичное раскрытие маточного зева, дальнейшее расширение производится без сопротивления. 4. Маточный зев достаточно раскрыт, в дальнейшем расширении нет нужды. 5. Аборт закончился.

340 первобеременных, явившихся на прерывание беременности в первом триместре, приняли участие в ожидаемом изучении score-исследования. Предварительное расширение шейки матки производили однократным, интрацервикальным введением 2,5 мг геля PGF_{2α}. По score этот метод применения был эффективным в 89,1% случаев. Частичное действие отмечали в 8,5%, его отсутствие — в 2,4%. Поскольку предлагаемая система очков принимает во внимание также и срок беременности, он кажется пригодным для сравнения простагландинов и других расширяющих средств.

Vaginal PGE₂ and intraamniotic PGF_{2α} for the Termination of Second Trimester Pregnancy*

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From September 1982 through June 1983 a study was carried out to examine the role of combinations of intraamniotic instillation of 20 mg PGE₂ (E) and 20 mg vaginal PGF₂ (F) for the termination of second trimester pregnancies. The statistical endpoints used were the P₅₀ abortion time, the 24 hr abortion rate, and the failure rate as defined as no abortion in 48 h. There were 5 study groups as described below:

	(n)	0 h	3 h	6 h
FF	(17)	2F	—	—
EEF	(100)	E	E	F
EFE	(25)	E	F	E
EF	(23)	E	F	—
FEE	(20)	F	E	E

The groups were comparable in terms of age, parity and of gestational age averaging 18 ± 1.3 weeks (SD). The results were:

	P ₅₀ h	24 h abortion rate, %	Failure rate, %
FF	18.5	83	12
EEF	10.5	88	10
EFE	11.8	88	8
EF	14.5	70	30
FEE	12	65	10

* $p < 0.05$

Based upon these results and previous data, the authors postulate that PGE₂ is the better agent for uterine conversion and that PGF_{2α} acts primarily as an oxytocic agent.

Prostaglandins (PGs) are the essential mediators of parturition [2]. Pharmacologic dosages of these agents are required to terminate midtrimester pregnancies. These megadose approaches lead to the familiar bothersome side-effects of nausea, vomiting, diarrhoea, hyperthermia, hypotension, hypertension, excessive uterine stimulation and retained placentae.

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There is biochemical and pharmacologic evidence suggesting that parturition is modulated by several PGs [3-8]. This study represents an attempt to evaluate the roles of exogenous combinations of PGE₂ and PGF_{2α} in the termination of second trimester pregnancies.

Materials and Methods

Women seeking second trimester abortion were assigned to one of five treatment methods. Patients were all cared for in the Gyn-Day Hospital of the Bronx Municipal Hospital Center.

TABLE I
Methods

<i>Drugs</i>	<i>Hours</i>		
	<i>Hrs. 0</i>	<i>3</i>	<i>6</i>
2F	F	F	—
EEF	E	E	F
EFE	E	F	E
EF	E	F	—
FEE	F	E	E

F = 20 mg PGF_{2α}, intraamniotic

E = 20 mg PGE₂, intravaginal

All women received standard workups which included a medical history, physical examination, birth control and abortion counselling, laboratory workup and a pregnancy sonogram. Women were randomly assigned treatment methods until achieving study groups, numbers of 20-25. The study was carried out from September 1981 through June 1983.

The standard second trimester abortion method used in our unit was PGF_{2α} 40 mg intraamniotic followed by intravenous oxytocin at 20-30 mU/min approximately 12 hrs after the amniotinfusion.

For the purpose of this study the standard method was compared to four others in which only 20 mg PGF_{2α} was given in association with a 20 mg vaginal suppository of PGE₂. There were 5 study groups with treatment schedules as outlined in Table I.

Most women receiving PGE₂ were given Lomotil and an antiemetic as prophylaxis against gastrointestinal side effects.

Results

The groups were comparable in terms of age and parity. For gestational age, the parity of the FF group was slightly higher than the rest (Table II). Statistical endpoints utilized were the P₅₀ cumulative abortion time, the 24 h cumulative abortion time, and failure rate as defined as no abortion in 48 h (Table III).

As noted in Table IV, the lowest P₅₀ value was obtained in the EEF group, and there was significance between this group and the FF group.

The 24 h abortion rates were lowest in the EF and the FEE group. The EF group also had the highest failure rate, indicating that the total dosage was simply inadequate.

A review of our records revealed multiple omissions in the recording of side effects, hence we cannot accurately report on whether the incidence was changed with these regimens.

TABLE II
Study groups

Method	n	Age	Parity	Gest. Age
FF	50	20.7 ± 1.6	2.1 ± 1.3	16.8 ± 0.32
EEF	100	22.2 ± 0.64	1.2 ± 0.12	17.8 ± 0.2
EFE	25	22 ± 5	1.2 ± 1.2	18 ± 1
EF	23	22.5 ± 6	1.3 ± 1.5	17.6 ± 1.3

TABLE III
Hypotheses RE: endpoints

P ₅₀	= index of uterine conversion
24 h abortion rate	= conversion and parturition
Failure rate	= nonconversion

TABLE IV
Results

	P _{50h}	24 h ab. rate %	Failure rate %
FF	18.5	83	12
EEF	10.5	88	3*
EFE	11.8	88*	8*
EF	14.5	70	30*
FEE	12	65*	10

* p < 0.05

Discussion

The hypothesis of this study was that combinations of PGE₂ and PGF_{2α} would be as effective or more effective than either agent alone. In previous studies it was established that the 40 mg PGF_{2α} intraamniotic should abort approximately 95% of women. For PGE₂ vaginal suppositories it was determined that 100 mg given over a period of 10 h followed by an oxytocin infusion would also be an effective approach.

In this study the PGE₂-PGF_{2α} hypothesis was evaluated using 1/2 the standard dosage of PGF_{2α} and 40% of the usual PGE₂ dosage. These 2 agents were given in 4 different combinations and compared vs. the standard PGF_{2α} technique.

The endpoints chosen were based upon the Csapó concept of uterine conversion. Csapó's theory states that the pregnant uterus is an inhibited organ which must be converted into a reactive one before parturition occurs [7]. Thus we have chosen the P₅₀ endpoint as the index of uterine conversion, the 24 h abortion rate as a measure of conversion plus parturition, and the failure rate as an index of nonconversion.

It was demonstrated that uterine conversion was slowest when PGF_{2α} was used alone. Statistical significance was demonstrated when PGF_{2α} was compared to EEF. All other methods using PGE₂ had lesser P₅₀ values than the PGF_{2α} group, but did not reach statistical differences in the relatively small numbers used in this study.

The poorest uterine conversion was seen when FF was used alone. Since the 24 h abortion rate was satisfactory in this group, it can be suspected that PGF_{2α} exerts its effect purely through its oxytocic action.

Failure rates were comparable in all groups except the EF protocol. In this group the dosage was simply inadequate.

The results of this study are in concert with several studies in which these 2 PGs have been compared from a biochemical and pharmacologic standpoint.

MacDonald and associates have demonstrated that the amnion produces PGE₂ only, whereas the chorion and decidua produces PGE₂ and PGF_{2α} [5]. From these data they have postulated that the foetus initiates labour by first secreting PGE which then somehow stimulates decidual and myometrial arousal.

Keirse et al. measured amniotic fluid PGs during labour and demonstrated that during the latent phase of labour there is a serial rise in both PGE₂ and PGF_{2α} [3, 4]. At about 4–5 cm dilatation, the concentration of PGE₂ no longer increased, but there was a steady rise in PGF_{2α}.

In an in vitro study using the Csapó electric field stimulation technique it was demonstrated on rabbit myometrium that PGF_{2α} had 1000 times the oxytocic activity of PGE₂. [7]

Finally, from pharmacologic studies using human second trimester abortion models, it has been shown that vaginal PGE₂ produces a uterine contraction pattern which is comparable to normal labour [6, 8]. In contrast PGF_{2α} produces a markedly abnormal pattern characterized by an elevated resting pressure with superimposed high active pressures. Despite this extraordinary myometrial activity, whether abortion will result is unpredictable from study of uterine pressure parameters.

It would appear then that there is suggestive evidence that combinations of PGE₂ and PGF_{2α} may be useful for the termination of pregnancies. By using both PGs in sequence, a more physiologic and dependable labour ensues, and the total dosage of drug is less than when either agent is used alone.

Conclusions

Methods in which PGE₂ were used first showed uniformly good P₅₀ values.

Intraamniotic PGF_{2α} had the slowest P₅₀ time; and in half dosage the lowest 24 h abortion rate.

Therefore it would suggest that PGE is more effective for uterine conversion, and the PGF serves primarily as an oxytocic agent.

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Anwendung von vaginalem PGE₂ und intraamnialem PGF_{2α} zur Unterbrechung von Schwangerschaften

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Zwischen 9.1982 und 6.1983 wurde die Wirkung des intraamnial verabreichten 20 mg PGE₂ (E) und des vaginal verabreichten 20 mg PGF_{2α} (F) bei der Unterbrechung von Schwangerschaften im zweiten Trimester verglichen; die Medikamente wurden in ver-

schiedenen Kombinationen dargereicht. Verwendet wurden folgende statistischen Endpunkte: P₅₀ = Abortzeit, 24 stündige Abortrate und Fehlerrate (Prozent der Frauen, die innerhalb von 48 Stunden nicht abortierten). Anhand der Kombinierung der beiden Präparate und der drei Verabreichungszeitpunkte wurden fünf Gruppen gebildet:

n	0 Stunde	3 Stunden	6 Stunden
FF (17)	2F	—	—
EEF (100)	E	E	F
EFE (25)	E	F	E
EF (23)	E	F	—
FEE (20)	F	E	E

Was Lebensalter, Parität und Schwangerschaftsalter [$18 \pm 1,3$ (S.D.) Wochen] anbelangt, waren die einzelnen Gruppen einander ähnlich.

Ergebnisse:

P ₅₀ Stunden	24 St. Abortrate %	Fehlerrate %
FF 18,5	83	12
EEF 10,5	88	10
EFE 11,8	88	8
EF 14,5	70	30
FEE 12	65	10

* $p < 0,05$

Aufgrund der angeführten Ergebnisse und der früheren Erfahrungen wird angenommen, daß sich PGE₂ zur Herbeiführung der Uteruskonversion besser eignet und daß PGF_{2α} primär als ein Oxytozikum wirkt.

Опыты с применением нового «priming score» созреваля шейки матки дали PG F2 alfa — измерения эффективности гели — при искусственном аборте в первые три месяца беременности

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С сентября 1982 г. по июнь 1983 г. проводили изучение роли комбинаций интраамниотического влияния 20 мг PGE₂ (E) и 20 мг влагалищного PGF₂ (F), для окончания второго триместра беременности. Статистически обрабатывались следующие показатели: время аборта P₅₀, выкидыш в течение 24 час, и неудача (отсутствие аборта в течение 48 час). Имелось 5 групп, как это описано ниже:

(n)	0 час	3 час	6 час
FF (17)	2 F	—	—
EEF (100)	E	E	F
EFE (25)	E	F	E
EF (23)	E	F	—
FEE (20)	F	E	E

Группы сравнивались по признаку возраста, способности к деторождению и гестационному сроку, равному в среднем $18 \pm 1,3$ нед (S. D.).

Были получены средующие результаты:

P ₅₀ час	Скорость аборта 24 ч, в %	Неудача, *
FF 18,5*	85	12
EEF 10,5*	88	10
EFE 11,8	88	8*
EF 14,5	70	30*
FEE 12	65*	10

* $p < .05$

Основываясь на результаты этих исследований и предыдущих данных, авторы предлагают, что PGE₂ является более хорошим средством для конверсии матки и что PGF_{2α} действует первично как окситоциновый агент.

Elective Induction of Labour in the Obstetrical Practice*

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Maternal and foetal results of 2020 elective inductions of labour are presented, compared with those of 2750 pregnancies in which labour was not induced during the 40th week of gestation, awaiting for its spontaneous onset.

The morbidity, mortality, and the frequency of obstetric operations during labour were compared. In all the parameters compared, there were better results in the electively induced group. The author attributed this difference to the establishment of careful selection criteria for elective induction. These criteria are: reliable estimate of gestational age, mature foetus over 3000 g of body weight, ripe cervix, proven myometrial sensitivity to oxytocin. Following these rules, the elective induction of labour can be a valuable and safe method of prevention of maternal and foetal complications.

Placental function may begin to deteriorate in pregnancies which last longer than the modal length of gestation [2, 3, 5, 6, 7]. The prevalence of meconium-stained liquor is 1.9 per cent at the beginning of the 40th week of gestation but 12.1 per cent and 33.4 per cent in the 41st and 42nd weeks, respectively. Perinatal mortality also increases during this period. On theoretical grounds therefore, there are arguments for seeking to effect delivery before this apparent deterioration in placental function begins to compromise the foetus. These considerations have prompted proposals that labour should be induced electively at term [4, 6, 8].

Some have proposed a wide use of elective induction at term [4]. In our own practice we have required that cases fulfil certain strict criteria before we have resorted to planned induction because we are aware that induction itself is associated with certain hazards. Whatever the degree of selection prior to planned induction of labour at term, a policy can only be justified if it is shown to be preferable to awaiting the onset of spontaneous labour.

Deliveries only with aphalic presentation after the 39th week were examined. Two groups were formed.

Group 1: Elective induction was done (2020 patients)

Group 2: We were waiting for spontaneous onset (2750 patients)

* Presented at the International Symposium on the Pregnant Uterus—a Commemoration of A. I. Csapó—16–18 October 1983.

Two kinds of outcome might happen to the latter group:

- a. delivery began spontaneously;
- b. because of placental insufficiency (amnioscopy or step test being found positive labour had to be induced (11.5%).

Cases had to meet the following criteria to be considered for elective induction at term:

1. *Reliable estimate of gestational maturity.* This implied a regular menstrual cycle, certainly concerning both the date of the last menstrual period and the date of quickening. This information had to be consistent with that derived from antenatal examinations.

2. *Foetal size.* The ultrasound measurement of foetal biparietal diameter had to exceed 92 mm. It was considered for excluding cases where the foetus weighed less than 3000 g.

3. *Foetal presentation.* Induction was only performed if the presentation was cephalic. In multiparae the head had to be at the pelvic inlet, in primiparae, within the inlet.

4. *Cervical maturity.* The cervix had to be mature judged by the following criteria:

Mature: fully or nearly fully effaced, with a centrally placed aperture admitting a finger.

Moderately mature: partially effaced, with the aperture admitting a finger; or a well-dilated (5 cm) but poorly effaced multiparous cervix.

5. *Uterine sensitivity to oxytocin.* The uterus had to be demonstrably sensitive to the intravenous administration of 0.01 U oxytocin/min within 10 minutes (Fig. 1).

6. *Other factors.* Certain foetal or maternal conditions contraindicated elective induction of labour. These included serious general maternal illness, toxæmia, placenta or vasa praevia, and previous uterine surgery.

On the basis of the above criteria, patients for possible elective induction at term were selected at 40th weeks of gestation. The plan was discussed with the pregnant woman and a day of delivery was chosen (usually one of the three days leading up to and including term). If the result of the oxytocin challenge test was satisfactory on the morning of the proposed day, we proceeded to induce labour. Slight digital dilation of the cervix and sweeping the membranes preceded amniotomy. If strong regular contractions did not commence within an hour after amniotomy, 1 or 2 mU of oxytocin/min was infused and the dose increased every ten minutes until adequate contractions began. The Cardiff infusion system or other type of pump was used in most cases.

During the past 10 years 2020 deliveries have been managed by this selective planned induction of labour.

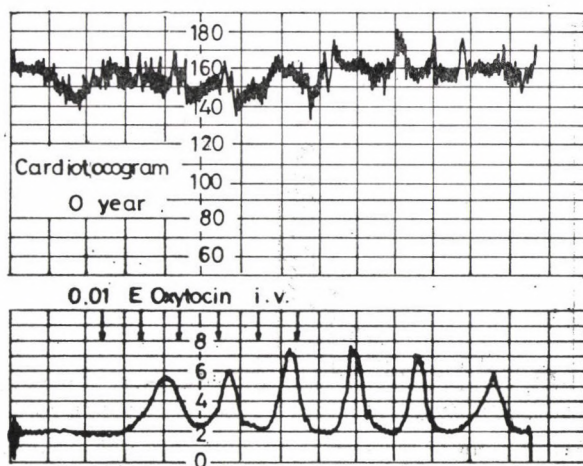


FIG. 1. Uterine sensitivity to oxytocin. The myometrium responds to the intravenous administration of 0.01 U oxytocin/min

The control group consisted of uncomplicated pregnancies ending in spontaneous cephalic delivery after the 40th week, or deliveries induced post term because of abnormal findings during regular amnioscopy or the step test. 2750 such controls were delivered during this period and 11.5 per cent of these followed induced labour. 38.0 per cent of the control group were primigravidae compared with 10.4 of the electively induced cases.

The method of inducing labour was the same as that used for the elective induction group. Foetal monitoring during labour was used in both groups with cardiotocography, and foetal scalp blood sampling.

Results

In the elective group 81.5 per cent of deliveries were induced within three days of term. Figure 2 compares the distribution of gestational ages of these patients with that of 1000 randomly sampled controls.

Adequate spontaneous uterine activity followed amniotomy in 16.0 per cent in the electively induced group. Among the remainder, only 15 cases did not respond satisfactorily to oxytocin infusion. In 12 of these (0.59 per cent) the progress of labour was unsatisfactory but delivery was achieved within 12 hours. In the remaining 3 cases (0.15 per cent) oxytocin was readministered successfully after a night's rest following the day of induction.

Excluding the 20 patients delivered by caesarean section, the mean duration of the 1st stage of labour in the elective induction group was 4 hour 35 min, while that of the 2nd stage was 26 min.

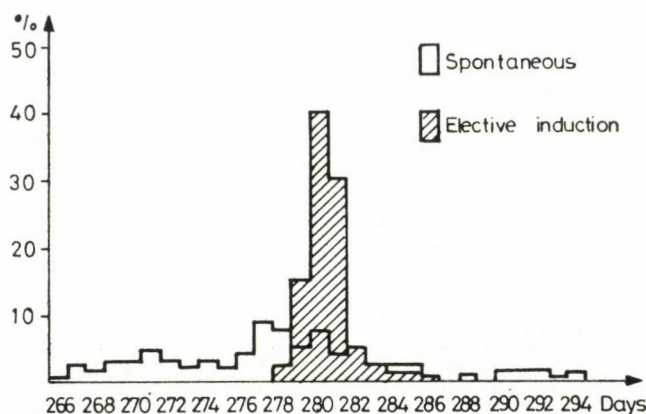


FIG. 2. Distribution of time of delivery in spontaneous and electively induced labour

The incidence of foetal heart rate (FHR) changes of hypoxic origin—late deceleration, persistent brady-, or tachycardia—during both the first and second stages of labour in the electively induced group was about half of that among controls.

Scalp blood was examined in 553 deliveries of the electively induced group (35.2 per cent) in different periods of the first stage of labour and on 783 occasions in total. These assessments of foetal acid-base status were sometimes prompted by abnormal FHR patterns, but also included cases in which data collection was the main objective. The analysis of these biochemical data suggests that the electively induced group had favourable figures by comparison with those of normal labour frequently quoted in the literature.

The frequency of caesarean section was considerably lower in the electively induced group than among controls (Table I). Caesarean section was performed in 20 (1.00 per cent) of the 2020 patients in the electively induced group. Four of these were indicated by cord prolapse, one by cord presentation and a sixth by haemorrhage resulting from disruption of a low-lying placenta on sweeping the membranes prior to amniotomy. The other 14 caesarean sections were performed for various reasons at later stages of labour.

Instrumental delivery (vacuum extraction) was also somewhat less frequent among cases than controls (Table I).

TABLE I

Operative delivery rate in the electively induced and the control group

	Elective induction (2020)	Controls (2750)
Caesarean section	20 (1.00%)	185 (6.72%)
Vacuum extraction	15 (0.74%)	26 (0.94%)

TABLE II

Apgar score, perinatal morbidity and mortality in the electively induced and the control group

		Elective induction	Control
Apgar score	<8	3.7%	17.6%
Morbidity		3.4%	7.0%
Mortality	N°1	0.5‰	N°6 1.7‰

 $n = 1; n = 6$

Foetal distress was the sole indication for instrumental delivery among the 15 cases of elective induction where it was used.

Perinatal morbidity and mortality. Table II demonstrates the lower neonatal morbidity and mortality rates in the electively induced group compared with the controls. The one-minute Apgar score was less than 8 in only 3.7 per cent of the cases compared with 17.6 per cent of the controls. Neonatal morbidity rates during the first six days (respiratory and circulatory complications, jaundice, pyrexia, weight loss and conjunctivitis) were 3.4 and 7.0 per cent in the cases and controls, respectively.

Perinatal mortality was low in both groups, but lower among the elective induction cases. In fact there was only one perinatal death among the electively induced cases. The infant concerned was mature (3800 g) and born in good condition after a 2-hour labour. On the second day of life pneumonia was diagnosed (later confirmed at autopsy) but the infant died on the 5th day in spite of therapy). In the control group there were 6 neonatal deaths, 3 low birth weight and 3 mature infants (among the latter one pneumonia, one brain injury and one congenital malformation were found).

Discussion

Reaching the term we had to make the choice of inducing labour or waiting. In the course of waiting, however, in some cases we may be compelled to induce the labour. That is why we consider the comparison of the two groups reasonable, admitting that the results of the latter subgroup cannot be anything but worse. In this group operative frequency, perinatal morbidity and mortality were higher than among the electively induced cases. The members of this group got into this situation just as a result of waiting. This is why we consider our policy justified.

Nevertheless, the selection criteria should be strict in order to avoid complications.

If the cases are selected according to the above criteria, complications are rare. Hypoxic FHR changes are unusual and foetal acid-base status during labour seems to be better than one might expect. This may be explained by a more satisfactory exchange capacity of the placenta coupled with a shorter duration of labour. As a consequence the oxygenation of the foetus does not deteriorate despite the stress effect of contractions.

We also feel that it is the careful selection of cases that has resulted in the presented exceptionally low total operative delivery rate of 1.6 per cent.

No perinatal deaths occurred, which could be attributed to our policy of selective planned induction of labour. This may have been partly due to the increased proportion of entire labour brought under control of continuous monitoring.

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Elektive Geburtsinduktion in der geburtshilflichen Praxis

L. G. LAMPÉ

Die mütterlichen und fötalen Ergebnisse von 2020 elektiv induzierten Entbindungen werden analysiert und mit 2750 Entbindungen verglichen, die in der 40. Schwangerschaftswoche, auf einen spontanen Beginn der Geburt wartend, nicht induziert wurden.

Verglichen wurden die Morbidität, Mortalität und die Frequenz der Entbindung beendenden Operationen. In Hinblick auf sämtliche untersuchten Parameter waren die Ergebnisse der elektiv induzierten Entbindungen besser. Dieser Unterschied ist den sorgfältig festgelegten Bedingungen der elektiven Induktion — zuverlässliche Ausrechnung der Gestationsalters, reife Frucht über 3000 g (mittels Ultraschall gemessen), reife Zervix und nachgewiesene Oxytozinempfindlichkeit des Myometriums — zu verdanken. Die Erfahrungen sprechen dafür, daß die elektive Entbindungsinduktion — falls die angeführten Bedingungen strengstens eingehalten werden — eine wertvolle und verlässliche Methode zur Vorbeugung der mütterlichen und fötalen Komplikationen darstellt.

Элективное вызывание родов в акушерской практике

Л. Г. ЛАМПЕ

Автор анализирует результаты, относящиеся к матери и плоду, 2020 элективно вызванных родов, и сравнивает их с результатами 2750 родов, которые не вызывали на 40-й неделе беременности, ожидая спонтанного начала.

Он сравнивает заболеваемость, летальность и частоту завершающих роды операций. Результаты элективно вызванных родов — в отношении всех сравниваемых параметров — были лучше. Эту разницу автор приписывает тщательно установленным условиям элективной индукции. Эти условия следующие: надежное вычисление гестационного возраста, зрелый плод массой свыше 3000 г (ультразвуковое измерение), зрелая шейка матки, проверенная чувствительность миометрия к окситоцину. При соблюдении этих правил, элективное вызывание родов может быть ценным и надежным методом для предупреждения осложнений со стороны матери и плода.

Termination of Normal and Pathological Pregnancy with Sulprostone*

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262 patients with normal pregnancy in the first and second trimester and 55 patients with pathological pregnancy (missed abortion, intrauterine death of the foetus, molar pregnancy) were successfully treated with the PGE₂ analogue Sulprostone (Schering A. G.). The drug was administered intramuscularly in the first trimester of normal and pathological pregnancy and by constant intravenous drop infusion for induction of abortion in the second and third trimesters of pregnancy. In case of 38 patients Sulprostone was injected intramural-cervically for cervical dilatation. The efficacy was high and the incidence of side-effects was low and more acceptable in all groups compared with that after natural prostaglandins. On the basis of the results presented, the authors recommend for pregnancy termination with Sulprostone the intramuscular route in the first trimester of normal and pathological pregnancy and intravenous infusion in the second and third trimesters.

Introduction

Surgical methods for normal and pathological pregnancy termination are connected with complications and long-term consequences. A noninvasive technique of abortion should reduce complications and later consequences such as cervical incompetence. In previous studies it has been shown that Sulprostone (16-phenoxy- ω -17,18,19,20-tetranor-PGE₂ methyl sulphonylamide) is effective in the termination of normal and disturbed pregnancy in all stages of gestation [3, 4]. It also causes a low incidence of side effects when compared to other prostaglandins. The present study was designed to evaluate the safety, effectiveness and acceptability of this drug to induce abortion in the first and second trimesters of normal and pathological pregnancy as well as to dilate the cervix prior to surgical artificial abortion.

Materials and Methods

The study comprised 317 women with ages ranging from 16 to 38 years, admitted to the Institute of Obstetrics and Gynaecology of the Medical Academy of Poznań because of: artificial abortion ($n = 252$), missed abortion

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($n = 23$), intrauterine death of the foetus ($n = 19$), molar pregnancy ($n = 5$) and the therapeutic abortion in the second trimester ($n = 10$). All patients were volunteers and had given their consent to administration of Sulprostone.

Among patients admitted due to artificial abortion, duration of amenorrhoea ranged from 6 to 12 weeks. The patients were divided into 3 groups. To patients in the first group ($n = 23$) Sulprostone was given 2–3 times 500 μg intramuscularly at 3–6 hour-intervals to induce abortion. The curettage was performed after abortion or within 24 hours when abortion did not occur. Success rate was evaluated according to the abortion score of Csapó [1]. In the second group ($n = 191$) Sulprostone was used for pharmacological cervix dilatation prior to curettage. In case of 38 patients 25 μg of the drug was administered intramural-cervically 12 hours before surgical evacuation of cavum uteri. In 191 pregnancies Sulprostone was administered intramuscularly with one dose of 500 μg also 12 hours prior to curettage.

In the group of missed abortion ($n = 23$) 1–3 doses of 500 μg were injected intramuscularly. In case of 10 patients admitted for therapeutical abortion in the second trimester group of intrauterine foetal death total dose of 1000–1500 μg of Sulprostone was infused for over 12 hours.

Results

The results obtained for all groups are reported in Tables I–V. In the Tables all side effects provoked by the administration of Sulprostone have also been enumerated.

TABLE I

Induction of abortion in the first trimester of pregnancy (2–3 times of 500 μg i.m.)

No. of patients	Nulliparae	Multiparae
23	13 (100%)	10 (100%)
Success rate ($\text{ABS} \geq 60$)	10 (76.9%)	10 (100%)
Instillation abortion time (IAT)	10.6 h	8.0 h
	No. of patients ($n = 23$)	per cent (100)
Side-effects		
nausea and vomiting	4	17.4
diarrhoea	2	8.7
shivering of legs and hands	2	8.7
blood loss ≥ 500 ml	1	4.3
Concomitant medication	12	52.2

The incidence of gastrointestinal side-effects in all groups was quite limited and clinically acceptable. In the case of induced uterine pains the analgesics (Dolantin) were offered on as-needed basis. Systemic side-effects requiring discontinuation of the therapy with Sulprostone were not observed.

TABLE II

Pre-evacuation cervix dilatation with 500 µg Sulprostone i.m.

No. of patients	Nulliparae	Multiparae
191	96 (100%)	92 (100%)
Success rate (dilatation equal to H8 or more)	81 (84.3%)	90 (97.8%)
	No. of patients (n = 191)	per cent (100)
Side-effects		
vomiting	21	11.0
diarrhoea	3	1.6
dyspnoea	3	1.6
shivering of legs and hands	3	1.6
decrease of blood pressure ≥ 20 mm Hg	3	1.6
blood loss ≥ 500 ml	1	0.5
Concomitant medication		
analgesics	30	15.7
sedatives	2	1.0
antiemetics	2	1.0
blood transfusion	1	0.5

TABLE III

Pre-evacuation cervix dilatation (25 µg intramural-cervical)

No. of patients	Nulliparae	Multiparae
38	5 (100%)	33 (100%)
Success rate (dilatation equal to H8 or more)	3 (60%)	26 (78.8%)
	No. of patients (n = 38)	per cent (100)
Side-effects		
nausea and vomiting	5	13.1
diarrhoea	1	2.6
dyspnoea	2	5.3
Concomitant medication	22	57.9

TABLE IV
Termination of missed abortion

	No. of patients (n = 23)	per cent (100)
Success rate (ABS \geq 60)	20	90.1
Side-effects		
nausea and vomiting	2	8.6
shivering of legs and hands	1	4.3
Concomitant medication	11	47.8

TABLE V
Management of the intrauterine foetal death (2nd and 3rd trimesters)

	No. of patients (n = 19)	per cent (100)
Success rate (ABS \geq 60)	19	100
Side-effects		
nausea and vomiting	2	10.5
bleeding more than 500 ml	2	10.5
shivering of legs and hands	1	5.2
Concomitant medication	14	73.6

The successful termination of molar pregnancy was performed in case of 5 patients with no serious side-effects and complications. We have also induced abortion in 5 pregnancies with uterus duplex, three of them were admitted to our institute after failed termination by curettage. Three patients after Manchester operation were also treated with success ($3 \times 500 \mu\text{g}$ at intervals of 4–6 hours).

Discussion

Application of Sulprostone for the termination of pregnancy in the second trimester has become the method of choice in our clinic due to the low percentage of side effects and effectiveness. Similarly, application of this drug to terminate pathological pregnancy (missed abortion, molar pregnancy, intrauterine foetal death) is far safer for patients than are surgical methods.

However, the interruption of normal pregnancy by induced abortion with prostaglandins is a controversial question. Several authors suggest that dilatation and suction are the methods of choice. Induction of abortion with

prostaglandins forces the patient to participate in all events for several hours which may have negative psychological influence. Presented results suggest the possibility of performing induced abortion by repeated intramuscular administration of 500 μ g Sulprostone. Although curettage after performed abortion is considered to be compulsory, it seems that the cervical dilatation with one injection of Sulprostone 12 hours prior to curettage is similarly effective. After cervical dilatation the curettage was simple, the bleeding weak. We have not observed any complications after pharmacological dilatation. Patients reporting in our institute are in the 9th week of pregnancy or more advanced. For that reason, for us dilatation and suction are no alternatives to dilatation and curettage. It seems that the more common use of Sulprostone for cervical dilatation before surgical termination of pregnancy (especially for nulliparae) will allow to diminish cervical incompetence in further pregnancies. A decrease in the frequency of complications in the subsequent pregnancies after interruption of pregnancy with prostaglandins has already been reported [2].

We have discontinued intramural-cervical application of Sulprostone. Several patients did not accept this way of drug application. The incidence of side-effects was high despite the fact that the total dose of prostaglandin was small. We have also registered strong uterine pains during the injection. This has forced us to apply analgesics in 60% of patients. Our results do not confirm the data of Wiechel [5].

On the basis of our results, the intramuscular administration seems to be preferable in the first trimester for cervical dilatation and other indications in this period of pregnancy as well. The intravenous administration with the above-mentioned dose schedule should be favoured in the second and third trimesters for all indications.

The specific uterotropic action of Sulprostone appears to be established after the comparison of the different routes of administrations and the incidence of side-effects.

One should inform the patient about the action of the drug before applying it. This simplifies, to a great extent, further cooperation of the patient and physician.

Acknowledgements

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Unterbrechung der normalen und pathologischen Schwangerschaft mit Sulprostone

Z. FISCHER, K. CHWALISZ und W. MICHAŁKIEWICZ

Das dem PGE_2 analoge Sulprostone (Schering A. G.) fand zur Behandlung von 262 normalen und 55 pathologischen (missed ab., intrauteriner Fruchttod, Molarschwangerschaft) eine erfolgreiche Anwendung. Bei normalen und pathologischen Schwangerschaften wurde das Präparat im ersten Trimester i. m. verabreicht, im zweiten und dritten Trimester dagegen in kontinuierlicher intravenöser Tropfinfusion. 38 Patientinnen wurde Sulprostone zwecks Muttermunderweiterung in den Muttermund und in die Gebärmutterwand injiziert. Die Effektivität des Präparats war befriedigend und der Anteil der Nebenwirkungen, die sämtliche Patientinnen besser tolerierten als die durch die natürlichen Prostaglandine verursachten, niedrig.

Anhand der ermittelten Ergebnisse scheint die Anwendung von Sulprostone — im ersten Trimester intramuskulär, im zweiten und dritten in intravenöser Infusion — empfehlenswert zu sein.

Прерывание нормальной и патологической беременности сульпростоном

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Авторы с успехом применяли аналог PGE_2 сульпростон (*Schering A. G.*) при 262 нормальных и 55 патологических (несостоявшийся аборт, внутриматочная гибель плода, беременность с заносом) беременностей. Препарат вводили внутримышечно в первом триместре нормальной и патологической беременности, и в виде внутривенной капельной инфузии во втором и третьем триместрах. С целью расширения маточного зева 38 больным сульпростон ввели в маточный зев и в стенку матки. Эффективность этого препарата хорошая, пропорция побочных действий была низкой, и для всех больных, по сравнению с побочными действиями при использовании простагландинов, более приемлемы побочные эффекты сульпростона.

На основании результатов, изложенных в статье, авторы рекомендуют интрамускулярное введение сульпростона в первом триместре, а во втором и третьем триместрах — внутривенную инфузию препарата.

Buccal and Oral Drugs: Induction of Labour*

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A total number of 154 pregnant patients were treated with one of 3 buccal/oral preparations (Pitocin®, Sandopart® buccal tablets of 200 and 50 IU of oxytocin, resp., and Prostin® oral tablet of 0.5 mg PGE₂) in order to induce labour. Standardization of the cases was done on the basis of Bishop score, parity, success of induction and dose schedules. Gestational ages varied from 37 to 42 weeks. The criterion of successful induction was establishment of labour with at least 5 cm cervical dilatation by 12 hours. All the three drugs gave equally good results and comparable that of oxytocin drip. Vaginal delivery rates were for Pitocin®, Sandopart®, and Prostin® 94.4, 96.7 and 91.9 per cent, respectively. In none of the cases were in serious danger either mother or foetus, therefore oral and buccal drugs are recommended for induction of labour; wherever favourable cervical maturity is established, with remarkable convenience to the patients.

Induction of labour is performed more frequently than ever before in order to improve perinatal outcome in complicated or high-risk pregnancies. Elective induction or programmed labour is being practised at several places almost routinely, or is being employed not so uncommonly by others [4].

The incidence of induction of labour varies from the very low figure of 2 per cent to nearly 25 per cent of all deliveries depending on the awareness, enthusiasm, and philosophical attitudes towards the procedure.

Intravenous oxytocin drip for induction of labour is a well-established and standard method since the days of Theobald [5]; it was subsequently put on firmer footing by Friedman and Turnbull by introduction of the titration method by intravenous infusion pump. This method suffers from the disadvantages of a continuous intravenous infusion, and it is often distasteful to, and imposes psychological strain on, the patient.

The convenience and comfort of buccal and oral administration of drugs for induction of labour is its singlemost superior point. It needs then to be seen if these easier methods can give the same other advantages of intravenous route. Claypool et al. [2] showed that buccal Pitocin® for elective induction of labour is effective, safe, simple and convenient. Several articles, summaries of which have been published in Bibliographia [1] indicated that Sandopart® is safe

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and effective when administered by buccal route. Elder [3] has demonstrated that oral PGE₂ is safe with favourable cervix especially in multiparous patients, and there is no need to monitor with electronic equipment.

It was therefore proposed to conduct a trial of induction of labour with the buccal and oral drugs. Buccal Pitocin® tablets of Parke Davis—200 units each, buccal Sandopart® tablets of Sandoz—50 units each, and, oral Prostin® tablets of Upjohn—0.5 mg each, were employed to test their usefulness in clinical application, and to note if these drugs were comparable to oxytocin in their effectiveness.

Material and Methods

The study was conducted in a private patients practice. The drugs were not assigned in randomized trial but were administered according to their availability from time to time. Standardization of cases was done on the basis of Bishop score, parity, criterion of successful induction and dose schedules. The gestational maturity had varied from 37 to 42 weeks, very few cases falling in the outer zones; the Bishop scores were from VI to XII, majority being from VIII to X; the cervical status (Mehta) was from VI to IX type, type VIII being the most common. The criterion of successful induction of labour was the establishment of labour with at least 5 cm dilatation of cervix by 12 hours of onset of induction procedure.

Artificial rupture of membranes was performed prior to administration of drugs in large majority of cases; in few it was done soon after painful uterine activity was appreciated. The buccal drugs were kept in the mouth between the upper gum and cheek in the region of molar teeth, and allowed to dissolve. The oral drug was swallowed like any other tablet.

The drug schedule were as follows:

Buccal Pitocin®

Each dose given ½ hourly

½ tablet — 100 U — 2 doses	2 tablets — 400 U — 3 doses
1 tablet — 200 U — 3 doses	2½ tablets — 500 U — 3 doses
1½ tablets — 300 U — 3 doses	
MAXIMUM — 4400 U	— 22 tablets

Buccal Sandopart®

Each dose given ½ hourly, of

1 tablet — 50 U — total of 10 tablets or 500 U

All doses complete in 4½ hours.

Oral Prostin®

0 h — 0.5 mg — 1 tab.
 ½ h — 0.5 mg — 1 tab.
 1½ h — 1.0 mg — 2 tab.
 2½ h — 1.0 mg — 2 tab.
 4½ h — 1.5 mg — 3 tab.
 6½ h — 1.5 mg — 3 tab. — total of 6 mg or 12 tablets.

No drug was administered to any patient after 7 cm dilatation of cervix.

Results

Number of cases. Buccal Pitocin® was given to 42, buccal Sandopart® to 32, and oral Prostin® to 80 patients.

Successful inductions. Table I indicates the number of successful inductions. Table II shows success rates by parity. All the three drugs gave equally good results and comparable to that of oxytocin.

TABLE I

Showing the number of successful inductions by drug employed

Drug	Total No.	Success	
		No.	%
Buccal Pitocin®	42	36	85.7
Buccal Sandopart®	32	30	93.8
Oral Prostin (PGE ₂)®	80	74	92.5

TABLE II

Showing success rates by parity

Parity 0	Total No.	Success	
		No.	%
Buccal Pitocin®	20	16	80.0
Buccal Sandopart®	17	15	88.2
Oral Prostin®	47	43	91.5

Parity I and more	Total No.	Success	
		No.	%
Buccal Pitocin®	22	20	90.9
Buccal Sandopart®	15	15	100.0
Oral Prostin®	33	31	93.9

TABLE III

Showing the modes of delivery in successfully induced cases

Drug	Total No.	Normal delivery		Forceps		C. section	
		No.	%	No.	%	No.	%
Buccal Pitocin®	36	30	83.3	4	11.1	2	5.5
Buccal Sandopart®	30	26	86.7	3	10.0	1	3.3
Oral Prostin®	74	62	83.8	6	8.1	6	8.1

TABLE IV

Showing the outcome in failed cases

Drug	Total No.	i.v. Oxytocin drip		C. Section
		Normal delivery	Forceps	
Buccal Pitocin®	6	2	1	3
Buccal Sandopart®	2	—	1	1
Oral Prostin®	6	—	—	6

TABLE V

Showing the average induction-delivery time in successfully induced and spontaneous vaginal delivery cases only, by parity

Drug	Parity 0	Parity I and more
	Mean In -D time	Mean In -D. time
Buccal Pitocin®	8 h 19 min	6 h 14 min
Buccal Sandopart®	6 h 34 min	6 h 10 min
Oral Prostin®	8 h 13 min	6 h 08 min

Mode of delivery. Table III depicts the modes of delivery in successfully induced cases only. A high order of normal deliveries was achieved in each group and the rates of total vaginal deliveries were 94.4 per cent with Pitocin® 96.7 per cent with Sandopart®, and 91.9 per cent with Prostin®. Table IV shows the modes of delivery amongst the failed cases. Ten out of the 14 cases had caesarean section deliveries.

Average induction-delivery time. The mean induction-delivery time amongst the successfully induced cases is shown by parity groups in Table V. In the multiparae, all methods had similar outcome. In the nulliparae, Sandopart® gave better result, while Pitocin® and Prostin® were comparable. Multiparous women always delivered in lesser time than the nulliparous ones.

Average doses employed. Table VI gives the mean doses employed for each of the drugs by parity. There was minimum difference of doses used for nulliparae

TABLE VI

Showing average dose of drug used in successful spontaneous vaginal deliveries

Drugs	Parity 0	Parity I and more
Buccal Pitocin®	3225 U (17 tab.)	2100 U (11 tab.)
Buccal Sandopart®	363 U (8 tab.)	303 U (7 tab.)
Oral Prostin®	3.3 mg (7 tab.)	2.1 mg (5 tab.)

TABLE VII

Showing success rates by indications for induction and method used

Indication	Buccal Pitocin®		Buccal Sandopart®		Oral Prostin®	
	T. No.	S. %	T. No.	S. %	T. No.	S. %
Elective—no uterine activity	16	87.5	16	100.0	29	100.0
Elective—uterine activity	10	90.0	4	75.0	20	100.0
Premature rupture of membranes	7	71.4	6	100.0	13	92.3
Postdatism	7	100.0	3	66.7	16	68.8
Others	2	90.0	3	100.0	2	100.0

and multiparae with Sandopart®. The nulliparous women always needed higher doses with any drug. Since the selection criteria and mean induction-delivery time are very similar in the multiparae with each of the regimes, it may be said that 11 tablets of Pitocin® are equivalent to 7 of Sandopart® and 5 of Prostin®, or approximately, 2100 U of Pitocin® will have the same effect as 300 U of Sandopart® or 2 mg of Prostin®.

Indications for induction. Table VII shows the success rates of the three methods by indications for induction of labour. That the three methods are effective in every indication is clearly shown. The number of cases in some indication groups is small, and the results, therefore, cannot reflect if any single drug gives preferential advantage over the others for induction of labour.

Side-effects and complications. The following side-effects and complications were looked for.

1. Hypertonicity of uterus
2. Bizarre uterine activity
3. Postpartum haemorrhage
4. Foetal distress
5. Low Apgar score

6. Icterus in newborn
7. Subconjunctival haemorrhage in newborn
8. Nausea, vomiting, or diarrhoea in patients

No case had foetal heart rate or uterine activity monitored by modern machines. Close conventional clinical observations were employed throughout labour and delivery.

Though hypertonicity was noted in few cases, it was generally temporary. In none was it serious enough to cause anxiety to mother of foetus. In no case was it necessary to ask the patient to spit out a buccal tablet or was it thought that the oral Prostin® was given excessively.

Bizarre uterine activity particularly related to frequency, intensity, sustenance and rhythm were noted. These were seen in some cases and few cases which failed to respond were due to abnormal uterine response. They were present with each of the drugs. By and large, the uterine activity was very satisfactory as clinically observed.

Immediate postpartum haemorrhage (250–500 ml) was noted in 12 cases, i.e. 7.8 per cent of the total. It was no more seen with any particular drug. Blood transfusion was not necessary in any study case.

Foetal distress was not detected in any case and Apgar scores in all cases, successful or failed, were 8 or more.

Icterus or subconjunctival haemorrhage in newborns was no different in the study patients than the overall delivered cases in the total practice.

Nausea, vomiting or diarrhoea were minimum with any of the drug regime. There was no increase in these with Prostin®.

Conclusions

The buccal and oral drugs administered and the regimes employed in this study for induction of labour were effective and safe. The three methods were comparable amongst themselves and were equally valuable as the intravenous oxytocin infusion method for induction of labour, with favourable cervical status and score.

The three methods were useful in all parity groups and for every type of indication.

All the three methods gave free movement and comfort to patients, and psychologically they were more relaxed compared with patients on oxytocin drips. The oral route was liked by patients more than the buccal.

No untoward side-effect or complication had occurred.

The buccal and oral drugs are therefore recommended for induction of labour, and the methods can be added as complementary list to the conventional methods of induction of labour with safety and satisfaction.

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Entbindungsinduktion mit oralen und bukkalen Medikamenten

A. C. МЕНТА

154 Schwangere wurden mit Pitocin®, Sandopart® und Prostin®, mit einem der bukkalen/oralen Präparaten zwecks Induzierung der Entbindung behandelt. Die ersten beiden Medikamente enthalten 200 bzw. 50 IU Oxytozin und das letzterwähnte 0,5 mg PGE₂. Die Standardisierung der Schwangeren erfolgte dem Bishop-score, der Zahl der Entbindungen, dem Erfolg der Geburtsindikation sowie dem Typ der Dosierung gemäß. Das Schwangerschaftsalter der Frauen lag zwischen 37 und 42 Wochen. Als Kriterium der erfolgreichen Induktion galt die Progression der Entbindung innerhalb der vom Anfang gerechneten 12 Stunden bis zu einer Muttermundweite von 5 cm. Alle drei der angewandten Präparate ergaben das gleiche gute, der Oxytozininfusion ähnliche Ergebnis. Der prozentuale Anteil der vaginalen Entbindungen betrug im Falle von Pitocin®, Sandopart® und Prostin® 94,4, 96,7 und 91,9%. Da es in keinem Fall zur Gefährdung der Mutter bzw. der Frucht kam, werden die oralen und bukkalen Präparate im Falle eines vorteilhaften Muttermundstatus zur Induktion der Entbindung als geeignet gehalten.

Вызывание родов оральными и буккальными лекарствами

A. Ц. МЕНТА

В общей сложности автор применил у 154 беременных женщин один из буккальных или оральных препаратов (питоцин®, сандопарт® и простино®) с целью вызывания родов. Первые два препарата содержат 200 или 50 ИЕ окситоцина, последний 0,5 мг PGE₂. Стандартизация беременных женщин производилась по шкале Бишопа, на основании числа родов, успешности вызывания родов и по типу дозирования препаратов. Сроки беременности колебались от 37 до 42 недель. Критерием успешной индукции было прогрессирование родов в течение 12 часов, начиная от их начала, до открытия маточного зева на 5 см. Все три примененных препарата дали одинаково хороший результат, похожий на эффект от инфузии окситоцина. Процентное соотношение влагалищных родов в случае применения питоцина®, сандопарта® и простино® составляло соответственно 94,4%, 96,7% и 91,9%. Ни в одном случае ни мать, ни плод не попали в опасное положение, поэтому автор считает оральные и буккальные препараты пригодными для вызывания родов в том случае, когда статус маточного зева является положительным, в интересах хорошего общего самочувствия роженицы.

Sulprostone in the Control of Postpartum Haemorrhage*

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A PGE₂ analogue, Sulprostone was administered to control the postpartum haemorrhage, immediately after the baby was born, to 74 healthy patients, who had normal pregnancy and delivery. Divided into three groups they received 50 or 100 µg intravenously, or 200 µg intramuscularly. The results were compared with those of a group of 54 patients, which received 0.2 mg methylergometrine i.m. and 5 IU oxytocin i.v. respectively.

The blood loss was measured during the third stage of labour and during two hours thereafter. The pilot dose of 50 µg was not effective enough. The blood loss in the group of 100 µg i.v. was 386 ± 175 ml, in the group of 200 µg i.m. 325 ± 197 ml, and in the methylergometrine–oxytocin group 302 ± 202 ml. Sulprostone 200 µg i.m. seems to be effective treatment to control the postpartum haemorrhage.

Only four patients had mild side-effects after Sulprostone administration.

Introduction

Sulprostone (Schering A. G.), the PGE₂ analogue, 16-phenoxy- ω -17,18,19,20-tetranor-PGE₂-, methyl sulphonylamide, has widely been used to induce midtrimester abortions [6]. There are other indications as menstrual induction [2] and induction of labour after foetal death and in hydatidiform mole [3]. Sulprostone is highly effective in both intravenous and intramuscular administration [4]. The advantage of this compound is the low frequency of gastrointestinal side-effects in comparison with PGF analogues [1, 4].

In this study we examined the effect of Sulprostone i.v. and i.m. on the prevention of the haemorrhage during the third stage of labour and two hours after the expulsion of the placenta by comparing it with the treatment of 0.2 mg methylergometrine i.m. and oxytocin IU i.v.

Material and Methods

Altogether 74 healthy patients received Sulprostone immediately after the baby was born. All patients had normal pregnancy and delivery. These patients were divided into three groups:

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- Group A: As a pilot test Sulprostone, 50 μg was administered intravenously.
- Group B: 100 μg Sulprostone was injected intravenously to 54 patients.
- Group C: In this group 10 patients received 200 μg Sulprostone intramuscularly.

In the fourth group, D, 54 patients received 0.2 mg methylergometrine (Myomergin, Leiras) i.m. and 5 IU oxytocin (Partolact, Star) i.v., which is our usual treatment.

The blood loss was measured for the time between childbirth and the expulsion of the placenta, and during two hours thereafter. Only the uterine bleeding was measured. If bleeding other than uterine was severe, the case was excluded from the study. Any blood loss from the episiotomy was reduced by compression.

The bed-pan was changed after the baby was born. After the expulsion of the placenta the bed-pan was changed again and all blood was collected during the subsequent two hours using a plastic bag.

Results

The age and the parity were similar in each group respectively, as well as the duration of the third stage and the total time of the labour (Table I). Table II shows the blood loss in each group. Sulprostone 50 μg was a pilot test. The dose was not enough. When 10 patients were treated, we increased the dose to 100 μg i.v. and 200 μg i.m. The blood loss was least before the expulsion of the placenta in the group D (Myomergin + Partolact), whereas the blood loss during the two hours after the placenta expulsion was least in the intramuscular Sulprostone group (Group C). Comparing the total blood loss, it was similar

TABLE I
The duration of labour

Sulprostone	Dose	No. of patients	Gravida	Para	Duration of labour					
					Phase I		Phase II	Phase III	Total	
					h	min	min	min	h	min
A. Intravenous	50 μg	10	1.9	1.9	6	36	9.1	7.2	6	52
B. Intravenous	100 μg	54	2.0	1.9	6	16	7.2	6.8	6	30
C. Intramuscular	200 μg	10	2.1	1.7	8	03	8.6	6.9	8	19
D. Methylergometrine-Oxytocin	0.2 mg i.m. 5 IU i.v.	54	1.9	1.8	6	32	8.5	7.2	6	48

in the group C and D (325 ± 197 and 302 ± 202 ml). It was not significantly different between group B and D. Only 4 patients had side-effects: shivering in one case in group A and B, and in two cases in group C.

TABLE II

Blood loss

	Sulprostone	No.	Before placenta expulsion	In 2 hours after placenta expulsion	Total
A	50 μ g i.v.	10	198 ± 164	222 ± 170	420 ± 241
B	100 μ g i.v.	54	224 ± 134	162 ± 127	386 ± 175
C	200 μ g i.m.	10	187 ± 168	138 ± 71	325 ± 197
D	Methyletergometr. 0.2 mg i.m. Oxytocin 5 IU i.v.	54	135 ± 109	167 ± 164	302 ± 202

Discussion

Sulprostone has less systemic side-effects than PGF prostaglandins. Because of the stability of the compound, it is possible to use it intravenously or intramuscularly [4]. In the present study the pilot dose of 50 μ g was not effective enough. The total blood loss was 420 ± 241 ml compared with 302 ± 202 ml of the methyletergometrine-oxytocin group. The blood loss was least during the third stage of labour in the methyletergometrine-oxytocin group, 135 ± 109 ml. During two hours after the placental expulsion, the bleeding was least in the group receiving 200 μ g Sulprostone i.m. This and the total bleeding show that the administration of 200 μ g Sulprostone i.m. immediately after the baby is born, is an effective treatment in the control of postpartum haemorrhage.

Four patients in the Sulprostone group had mild side-effects. The dose of this compound was smaller than used for abortion inductions. This most probably explains the low frequency of the side-effects.

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Sulprostone bei der Behandlung der postpartalen Blutungen

V. I. LAAJOKI und A. I. KIVIKOSKI

Zwecks Minderung des postpartalen Blutverlustes erhielten 74 gesunde Frauen, die ihre Kinder nach ungestörter Schwangerschaft komplikationsfrei auf die Welt brachten, unmittelbar nachdem das Neugeborene das Licht der Welt erblickte Sulprostone, ein dem PGE₂ analoges Präparat.

Es wurden drei Studiengruppen gebildet, je nachdem ob die Frauen 50 oder 100 µg intravenös erhielten oder aber 200 µg intramuskulär. Die Kontrollgruppe bestand aus 54 Patientinnen, denen 0,2 mg Methylergometrin intramuskulär oder 5 IU Oxytozin intravenös verabreicht wurden.

Der Blutverlust wurde in der dritten Phase der Entbindung und im Laufe der ersten 2 postpartalen Stunden gemessen. Die Probadosis von 50 µg erwies sich als unzureichend. In der Gruppe mit 100 µg i.v. betrug der Blutverlust 386 ± 175 ml, in der mit 200 µg i.m. 325 ± 197 ml und in der Methylergometrin + Oxytozin-Gruppe 325 ± 202 ml. Die Sulprostonebehandlung hat sich zur Herabsetzung der postpartalen Gebärmutterblutung als geeignet erwiesen. Während der Sulprostonetherapie haben sich milde Nebenwirkungen nur in 4 Fällen gemeldet.

Сульпростон в лечении послеродовых кровотечений

В. И. ЛААЙОКИ и А. И. КИВИКОСКИ

Аналог PGE₂, сульпростон (*Sulprostone*) давали 74 здоровым женщинам, которые после нормальной беременности без осложнений родили детей. Введение препарата преследовало цель уменьшить послеродовую потерю крови, при этом сульпростон давали сразу после появления на свет новорожденного.

Были созданы три исследуемые группы, в которых роженицы получали 50 или 100 мкг препарата внутривенно, или 200 мкг внутримышечно. Результаты лечения сравнивали с результатами, полученными в группе, состоящей из 54 пациентов, которым вводили 0,2 мг метизргометрина внутримышечно или 5 ИЕ окситоцина внутривенно.

Потерю крови измеряли в третьей стадии родов и на протяжении двух часов после родов. Пробная доза в 50 мкг не давала удовлетворительного результата. В группе, где вводили 100 мкг внутривенно, потеря крови составляла 386 ± 175 мл, в группе с внутримышечным введением 200 мкг потеря крови составляла 325 ± 197 мл, в группе, где роженицам вводили метилэргометрин + окситоцин, потеря крови была 325 ± 202 мл. 200 мкг внутримышечно введенного сульпростона кажется эффективным средством для уменьшения послеродового маточного кровотечения. Только у 4 пациентов наблюдались слабые побочные явления после введения сульпростона.

Surgical Management of Complaints Due to Independent Bone Fragments in Osgood–Schlatter Disease (Apophysitis of the Tuberosity of the Tibia)

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The surgical treatment of complaints due to independent bone parts in Osgood–Schlatter disease is described. Operations inducing the removal of the independent bone piece, the abrasion of the exostosis and the excision of inflamed connective tissue in their environment, were performed in 21 cases. By the intervention all patients could be relieved from their complaints. The pains are supposed to be due to inflammation caused by irritation on the surrounding region.

Introduction

The aetiology, course and treatment of the Osgood–Schlatter disease is well known from the literature. The disease usually develops in puberty causing pains and swelling around the tuberosity of the tibia. X-ray shows the ossification disorder of the tuberosity of the tibia and fragmentation of the apophysis. In these cases, the patient is forbidden to overstrain the quadriceps muscle and this will in general suffice for termination of the complaints. In other cases, a more serious rest (e.g. plaster cast) is required.

Aseptic necrosis of the tuberosity of the tibia can be supposed to be cured when the apophysis displays a homogeneous structure and the patient's complaints have disappeared. It is generally found that the disease spontaneously heals by the end of puberty up to completion of ossification. Rarely though it may occur that complaints reappear several times, moreover there were patients whose complaints reappeared within a couple of years following puberty.

Patients

This unusual course of Osgood–Schlatter disease was observed in 21 cases at the Department of Orthopaedics, Semmelweis University Medical School, Budapest between 1976 and 1984. Five of the patients at the age of 14–16

and in the other 16 still later (18–32 years) recurrent pains of the tuberosity of the tibia arose. Based on their histories, the clinical symptoms, the course of their disease as well as on X-ray findings, their disease was diagnosed as aseptic necrosis of the tuberosity of the tibia. The X-ray finding differed from that in the Osgood-Schlatter disease in that ventrally to the tuberosity of the tibia,

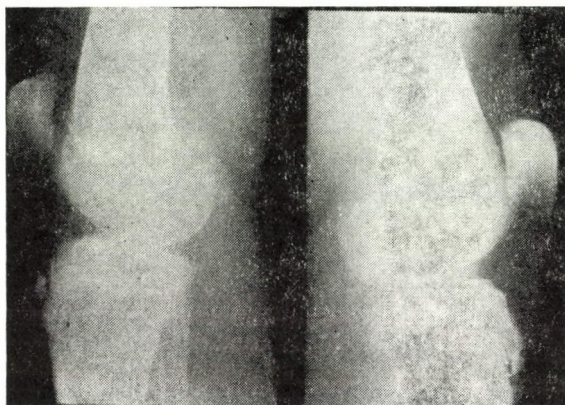


FIG. 1. Comparative lateral view X-ray of the knee. Ventrally to the inhomogeneous right tuberosity of the tibia, there is an about pea-sized separate bone



FIG. 2. Higher power later view X-ray of the left knee. The tuberosity of the tibia is inhomogeneous. Ventrally and proximally to it a sharp-edged, independent bone can be seen

an independent small bone or a structure simulating a prominent exostosis could be noted (Figs 1-3).

The Osgood-Schlatter disease occurs in a ratio of 3 to 1 in boys and girls [5]. In the described group, this ratio has shifted toward the boys (20 boys, one girl).



FIG. 3. Higher power lateral view roentgenogram of the left knee. Before the inhomogeneous tuberosity of the tibia a bean-sized independent bone with a thorn-like protuberance over it is present

As it was assumed that irritation was due to a separate bone fragment or a thorn-like exostosis giving rise to recurrent pains, and this detached bone fragment had already been completely separated and its attachment to the tibia was found to be improbable, the surgical removal of the separate bone fragment, i.e. resection of the thorn-like bone was decided upon. During the operations, the separate bone fragment was found between the patellar ligament proper and the tibia in 12 and within the substance of the patellar ligament proper in 6 cases. In three cases, the thorn-like exostosis was observed at the insertion of the ligament.

Histological study of the removed bones disclosed them to be composed mainly of necrotic bone tissue (Fig. 4), however, sporadically with signs of regeneration and osteoid (Fig. 5), resp. The surface of the separate bone fragment was covered by a fibrous, in some places degenerated, hyaline cartilage (Fig. 6). The synovial membrane surrounding showed signs of inflammation (Fig. 7).

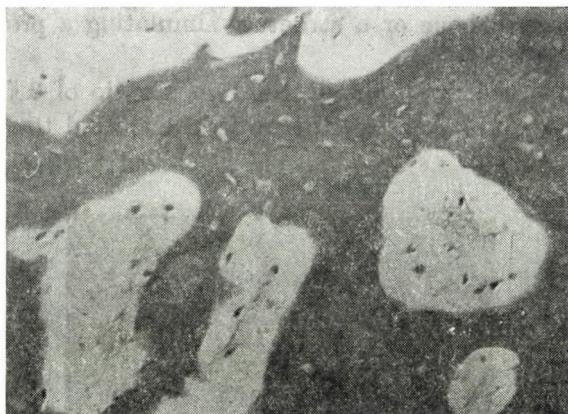


FIG. 4. Synovial membrane with signs of chronic inflammation from the environment of the separate bone fragment, $\times 40$, H & E staining

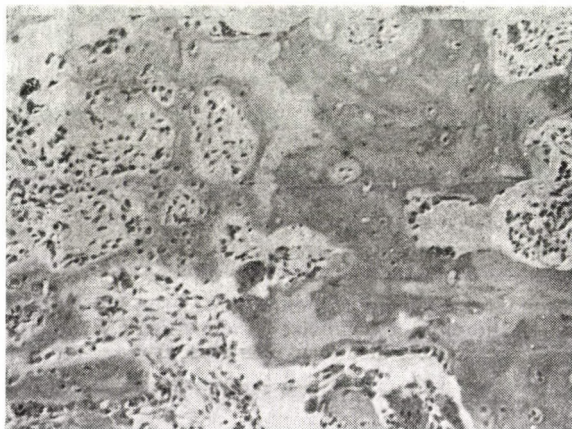


FIG. 5

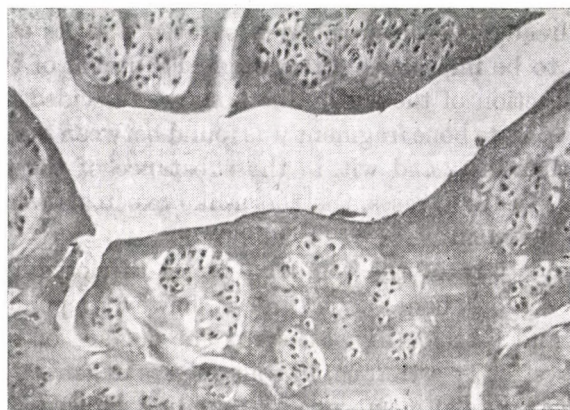


FIG. 6



FIG. 7

Following operation, pain disappeared in all of our cases and movement of the knee returned soon. Control examinations performed later, on an average after one year, showed the patients to be complaint-free. Swelling and inhibition of movement have not developed. In the majority of cases, a bulkier appearance of the tuberosity of the tibia could still be observed but it caused no complaints.

Case Reports

Case 1. P. Zs., a 15-year-old boy had noticed a small intumescence below his knee two years before examination. On overexertion, mainly when climbing stairs, he felt pain over this area. On examination both knees were found to move freely. The tuberosity of the tibia on both knees projected outward better than usual, on the right side the protrusion was sensitive to pressure.

A bilateral comparative X-ray study of the knees was made. Ventrally to the tuberosity of the tibia, the right lateral view (Fig. 1) showed an about pea-sized, detached bone fragment.

Operation revealed an about pea-sized, separate bone between the proper patellar ligament and the anterior surface of the tibia, surrounded by a richly vascularized bursa. The bone piece and the surrounding bursa were removed.

Case 2. N. A., a 20-year-old male patient had noticed 4-5 years earlier, a sensitive, bony protuberance on the anterior surface of his left tibia corresponding to the tuberosity of the tibia, which on exertion, mostly while squatting, was painful. For three years, his complaints were increasing. On examination, both sides were found to move freely. The left tuberosity of the tibia protruded more than on the contralateral side, on pressure it was painful and an about hazel-nut-sized, mobile, bony structure was palpable.

A bilateral comparative knee X-ray was made. The lateral view picture revealed, ventrally and proximally to the left tuberosity of the tibia an inhomogeneous, detached bony structure, about the size of a plum stone and of sharp edges.

Operation: The about plum-stone-sized bony structure harboured in the substance of the patellar ligament was enucleated and removed.

Case 3. F. J., a boy, aged 19 years, had been feeling pain in his left knee prior to his admission, without any particular precedents. The pain increased on overexertion. The examination revealed both knees to move freely without pain. On the left side, the tuberosity of the tibia was sensitive to pressure.

Bilateral comparative X-ray of the knees was made. The lateral view roentgenogram of the left knee disclosed ventrally to the inhomogeneous tuberosity of the tibia, an about bean-sized, separate round bony structure with a thorn-like protuberance over it.

Operation: The about bean-sized, separate bone underneath the insertion of the patellar ligament proper was removed, then the uneven surface of the thorn-like protuberance of the bone surface was abraded. The bursa showing signs of inflammation adjacent to the exostosis was excised (Fig. 4).

Discussion

1. In the literature known by us only Mital et al. [5] have reported on 14 similar operated cases. They attribute the development of the change to trauma due to traction. According to them, the detached bone fragments correspond to the non-fused pieces of a necrotized apophysis. This is indicated by the histological changes, i.e. the bone trabeculae containing empty, necrosed lacunae.

2. In some cases, the separate bone pieces had already been observed during the course of the disease or during puberty. In other instances, the patients reported with their complaints already after termination of the ossification process. X-ray studies performed in such cases, also here, revealed the independent bonlets and exostosis indicative of the Osgood-Schlatter disease.

3. Around the detached bones or exostoses, an inflammatory connective tissue reaction was seen. It is justified to suppose that the pains are due to this inflammatory reaction.

4. Analysing our cases and comparing them with those in which Osgood-Schlatter disease was not associated with the described changes and so they did not need to be operated, no factor was found accounting for the observed phenomena.

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Chirurgische Lösung der durch alleinstehende Knochenabschnitte verursachten Beschwerden bei Osgood-Schlatterscher Krankheit (Apophysitis tuberositatis tibiae)

I. CSER und GY. LÉNÁRT

Beschrieben wird die chirurgische Behandlung der durch alleinstehende Knochenabschnitte verursachten Beschwerden bei Osgood-Schlatterscher Krankheit. Die in 21 Fällen durchgeführte Operation bestand aus der Entfernung des alleinstehenden Knochenabschnitts, dem Abmeißeln der Exostose und der Exzision des in der Umgebung befindlichen entzündlichen Bindegewebes. Mit dem Eingriff konnte in sämtlichen Fällen Beschwerdefreiheit erzielt werden. Für die Schmerzen war die irritationsbedingte Entzündung der Umgebung verantwortlich.

Хирургическое разрешение жалоб, вызванных отдельными костными частями, при болезни Осгуда-Шлаттера

И. ЧЕР и ДЬ. ЛЕНАРТ

Авторы описывают оперативное лечение жалоб при болезни Осгуда-Шлаттера, вызванных отдельными костными частями. Операция была произведена в 21 случае, она состояла из удаления разрозненных кусочков кости, иссечения экзостозов, или вырезания воспаленной соединительной ткани, находящейся в области костных наростов. Благодаря хирургическому вмешательству, во всех случаях удалось добиться отсутствия жалоб. Причину болей авторы видят в воспалении, возникающем в ответ на раздражение окружающих тканей.

The Effect of Fetectomy on Prostaglandin Receptors of the Rat Myometrium

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It has been postulated that intrauterine volume plays a role in the timing of parturition. In previous studies we found that the onset of parturition in the rat was associated with significant increases in the concentration of receptors for $\text{PGF}_{2\alpha}$ in the myometrium. To determine the effect of intrauterine volume on the concentrations of this myometrial receptor, we compared receptor levels in pregnant and fetectomized horns from unilaterally fetectomized pregnant rats near the time of parturition ($n = 3$). Myometria from pregnant horns contained substantially greater concentration of protein than did those from the contralateral fetectomized horns. The amounts of receptors per horn for $\text{PGF}_{2\alpha}$ were about 3 times greater in myometria from pregnant horns than in those from fetectomized horns. However, near term the concentration of receptors per protein contents was the same in pregnant and fetectomized horns. These results suggest that uterine stretch causes hyperplasia and hypertrophy of the myometrium being indicative of more protein per pregnant than fetectomized horns. However, the rise in the concentration of receptors for $\text{PGF}_{2\alpha}$ about the time of labour appears to be induced by hormonal and not by physical factors.

Despite intensive investigations, the initiation of labour is unclear. In the rat, the evidence that prostaglandins are involved in the onset of labour and parturition includes the following:

1. Parturition is induced prematurely by the administration of PGs [5].
2. Inhibitors of PG synthesis administered late in pregnancy delay prolonged parturition [1, 9, 22].
3. Uterine venous levels of PGs of the E and F series increase before parturition [16, 2].
4. Increasing quantities of prostaglandins are found in the amniotic fluid near term, and uterine production of F prostaglandins increases markedly before delivery [6, 13].

However, the identity and the mode [3] of action of the PGs involved in parturition are at present uncertain. According to our own and others' studies on the isometric contractile activity of the myometrium [12], the sensitivity of the rat uterus to $\text{PGF}_{2\alpha}$ during pregnancy is maximal near term. We have postulated that the change in sensitivity is, at least in part, determined by changes in the concentration of the myometrial $\text{PGF}_{2\alpha}$ receptors. The con-

centration of $\text{PGF}_{2\alpha}$ receptors, in turn, appears to be regulated by steroid hormones [17]. It is possible, however, that nonhormonal factors may also contribute to the increase of uterine sensitivity to $\text{PGF}_{2\alpha}$. For example, Csapó and Lloyd-Jacob have postulated that intrauterine volume plays a role in the timing of parturition [7].

It was found that in response to a given concentration of oxytocin (OT), the pregnant horn of unilaterally pregnant rabbits contracted with greater force and frequency than the nonpregnant horn. These findings suggest that the distension of the uterus by the fetuses near term may contribute to an increase in myometrial sensitivity to OT [14, 19].

Alternatively, because uterine stretch causes an increase in myometrial actomyosin concentration [11, 12], the increased response of the pregnant horn to OT and PGs may be the result of an enlarged contractile apparatus. To determine the effect of the intrauterine volume on the sensitivity of the rat myometrium to $\text{PGF}_{2\alpha}$, we compared the concentration of $\text{PGF}_{2\alpha}$ receptors in pregnant and fetectomized uterine horns, in unilaterally fetectomized pregnant rats near term. Our findings indicate that the development of the fetus and the endocrine changes of pregnancy cause myometrial cell hyperplasia and hypertrophy but not the marked rise in the concentration of $\text{PGF}_{2\alpha}$ receptors.

Methods

Exact time pregnant rat was purchased (Sprague-Dawley). Labour usually occurred between the evening of day 21 and the afternoon of day 22. The rats were anaesthetized with Ketamine 90 mg/kg and Rompun 10 mg/kg i.m. for 30–60 min on day 17 of pregnancy, and removing the pups unilaterally from one of the two horns, the horns were sutured. The two fetectomized and pregnant horns were removed on day 21 of pregnancy, divided, cut longitudinally and freed of the fetuses and the placentae. Each horn was weighed, and its protein content measured.

Membrane Preparation

After removing the pups the uteri were placed in ice cold buffer of the following composition: 0.25 M saccharose, 10 mM TRIS-HCl pH 7.4, 1 mM mercaptoethanol, 1 mM EDTA and 10 $\mu\text{g}/\text{ml}$ indomethacin. The myometria were separated from fatty, connective tissue and decidua. The separated myometria were finely minced with scissors, and homogenized in a Polytron PCU-2 homogenizer at a setting of 5–6 using two 15-sec bursts. The resulted homogenate was filtered through 4 layers of cheesecloth, and homogenized in a Dounce homogenizer with five strokes. The so obtained homogenate was centri-

fuged at 1000 *g* for 10 minutes. The supernatant was further centrifuged at 10 000 *g* for 10 minutes. The pellet was discarded and the supernatant was further centrifuged at 100 000 *g* for 60 minutes. The supernatant was discarded and the pellet (microsomal fraction) was resuspended in 0.025 M TRIS-HCl pH 7.4, containing 1 mM CaCl₂ in a Dounce homogenizer with pestle A by 5 strokes, and used for radioligand-binding assay immediately, because there was a loss in the binding during the freezing procedure. The purification of 5'-nucleotidase in this fraction was about 3–4 fold ($\mu\text{mol P}_i$ released from 5' AMP/min/mg protein). The protein concentration was determined as described by Bradford with bovine serum albumin as standard.

Binding Assay

An appropriate amount of the ($\text{H}^3/\text{PGF}_{2\alpha}$) spec. act. 150–180 Ci/mmol) in ethanol was pipetted into a disposable glass test tube. The ethanol was evaporated under a stream of air. The typical binding reaction was carried out in a total volume of 0.2 ml, 0.01 M TRIS-HCl pH 7.4 containing (H^3) $\text{PGF}_{2\alpha}$ in an adequate amount, CaCl₂ 1.0 mM and the partially purified membrane fraction of 100–200 μg protein. Binding was a linear function of the final protein concentration up to 1.5 mg/ml. Samples were incubated at 37 °C for 60 min under continuous shaking. The binding reaction was terminated by adding 1 ml of ice-cold 0.025 M TRIS-HCl pH 7.4, put in ice bath and immediately filtering the samples over Millipore filters (0.45 μm) under vacuum. Each test tube was washed twice with 2 ml TRIS-HCl pH 7.4 and the filters were washed with 10 ml of the same buffer at 0 °C. The filters were dried then counted over a 10-min period with a scintillation cocktail in a Beckmann LS-7000 Scintillation counter, with an error of 2%, and 50% accuracy. Specific binding was defined as the difference between binding in the absence and the presence of an excess of unlabelled $\text{PGF}_{2\alpha}$. In our experiments, nonspecific binding was the same as in blanks which contained everything except the membrane fraction. The absolute value of specific binding was calculated from the specific radioactivity of the $\text{PGF}_{2\alpha}$, the radioactivity bound, and the amount of protein used.

The affinity and capacity of the membrane for $\text{PGF}_{2\alpha}$ was estimated by the Scatchard plot, with linear regression analysis. In this case final concentration of $\text{PGF}_{2\alpha}$ in the incubation medium ranged from 0.25 pmol to 25 pmol, obtained by appropriate mixtures of labelled and unlabelled hormone. The unlabelled $\text{PGF}_{2\alpha}$ concentration was 5×10^{-5} M. The free hormone concentration was calculated from the difference between the total amount and the amount bound.

The statistical difference between the means was estimated by Student's *t* test.

Results

Figure 1 demonstrates the wet weight and the protein contents of the pregnant and fetectomized horns of rats. The figure shows that the wet weight and the protein content of the partially purified membrane fraction of the pregnant horn were about 3 times greater than that of the fetectomized horn. The fetectomized horns get involuted after fetectomy.

The binding of $\text{PGF}_{2\alpha}$ plotted by Scatchard is shown in Fig. 2. The Scatchard analysis of $\text{PGF}_{2\alpha}$ binding by myometrial membranes from pregnant and fetectomized horns on day 21 shows that the concentration of receptor sites and the affinity of receptors for $\text{PGF}_{2\alpha}$ did not differ from each other. As in our earlier studies, we found two independent binding sites in the partially purified membrane fraction of rat myometrium. There was no difference in the capacity of the high- and low-affinity binding sites. It was 96 and 94 and 305 and 312 fmol/mg protein, respectively, between the two horns. The apparent affinity of receptor sites for $\text{PGF}_{2\alpha}$ was 1.8×10^{-9} M and 2.1×10^{-8} M in the pregnant horn and 1.5×10^{-9} and 2.0×10^{-8} M in the fetectomized horn. The two curvilinear plots were almost identical. A Hill analysis of binding experiments yielded no cooperativity between binding sites.

The total amount of receptors for $\text{PGF}_{2\alpha}$ per horn and per mg protein is shown in Fig. 3. When the amount of receptors was expressed per mg protein, there was no difference between pregnant and fetectomized horn (B). When the amount of $\text{PGF}_{2\alpha}$ receptors was expressed per horn, the concentration of receptors was 3 times higher in the pregnant than in the fetectomized horn ($p < 0.01$). (A). This increase seems to be more apparent than real, while the concentration of receptors per mg protein was the same.

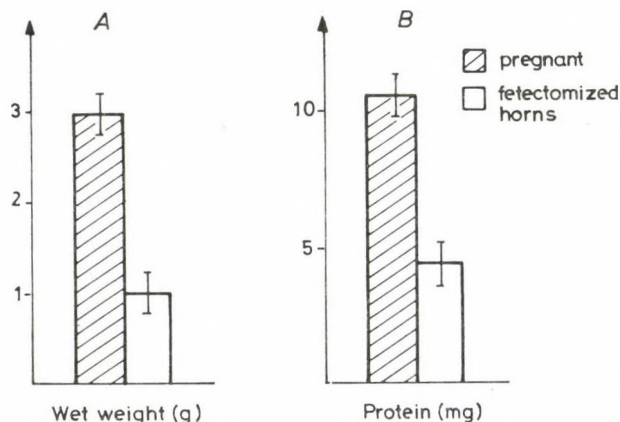


FIG. 1. Comparison of the wet weight (A) and the protein content in 100 000 g particulate fractions (B) of the myometrium from pregnant and fetectomized horns of rats near parturition. Data from three different experiments \pm S.E.M. Each value is the mean of 5 replicates

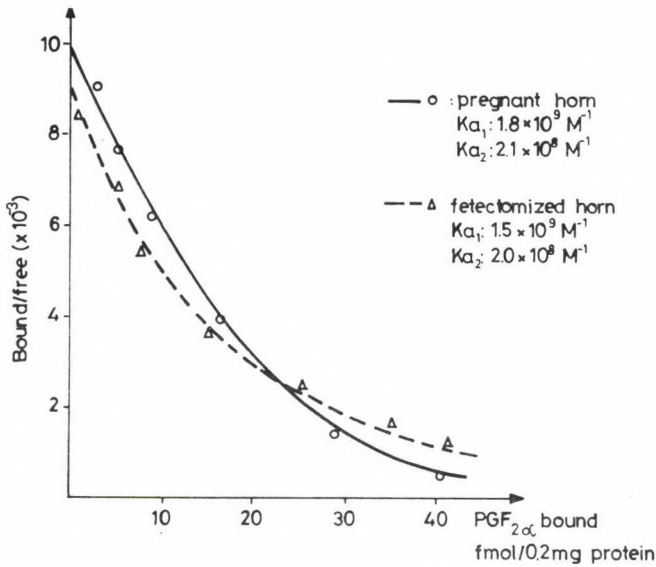


FIG. 2. Scatchard plots of $\text{PGF}_{2\alpha}$ at 21 days of pregnancy from the pregnant and fetectomized horns of rats $\text{PGF}_{2\alpha}$ binding in the pregnant and fetectomized horns. Three different experiments

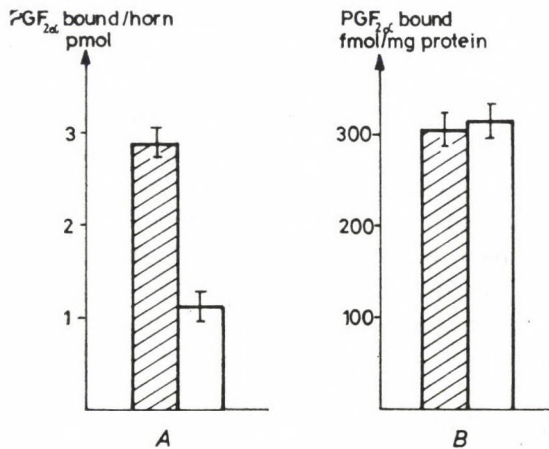


FIG. 3. Comparison between pregnant and fetectomized uterine horns with respect to amount per horn of $\text{PGF}_{2\alpha}$ receptors (A) and with that of $\text{PGF}_{2\alpha}$ receptors per mg protein (B). Three different experiments \pm S.E.M.

Discussion

The distension of the uterus contributes to the growth of the myometrium [18, 20]. The myometrial growth is characterized by hyperplasia and hypertrophy of the myometrium caused by oestrogen action and uterine stretch [12, 18]. Other studies on unilaterally pregnant rats demonstrated that stretch contributes to increases in both DNA and protein per uterus [3]. Our findings, which compare pregnant and fetectomized uterine horns near term, show that stretch contributes to increasing the protein per uterus. It might be postulated that the increased sensitivity to PGs of the uterus at term is the result of an appreciable increase in cell number and size during pregnancy, along with the expansion of the contractile apparatus. However, in the light of our findings that the increased sensitivity of the rat myometrium on the day of parturition corresponds in part to an increase in PG receptors, and the concentration of $\text{PGF}_{2\alpha}$ receptors was the same in the pregnant and the fetectomized horns of pregnant rats, we can conclude that the sensitivity of the uterus to $\text{PGF}_{2\alpha}$ is not regulated by stretch. However, the development of the contractile apparatus due to stretch would appear to be important in the development of the contractile force in response to PG. A similar result was found in unilaterally pregnant rats in the concentration of OT receptors were not regulated by stretch [3]. The pregnant horns of unilaterally pregnant rabbits elicited a much greater response to OT than did the nonpregnant horns [14] and near term the spontaneous contractions of the pregnant horns were more frequent than those of the nonpregnant horns [19].

As in the case of OT receptors, when expressed per cell [3], the concentration of oestrogen in both the nuclear and cytosol fractions of the myometrium were almost identical in pregnant and nonpregnant horns. These findings suggest that stretch does not contribute to the effect of circulating hormones on the concentration of oestrogen receptors.

Distension has been shown to improve impulse conduction in smooth muscle [11], and to increase the frequency at which trains of impulses are generated [8]. The most important determinants of the electrical activity and contractions of the circular muscle in the pregnant rat uterus are the uterine volume and the ovarian hormones. The fetoplacental unit is of lesser significance. There was a gradual decline in the resting potential of the pregnant as compared to the nonpregnant myometrium of unilaterally pregnant rats. In the absence of chronic stretch or adequate levels of circulating oestrogen, the membrane potential of the circular muscle of the uterus does not decline at term [15]. This, and other changes in the action potential were similar to those reported for indomethacin and aspirin [4].

In summary, chronic stretch causes hypertrophy and hyperplasia of the myometrium and a gradual decline in the resting potential. There is no change

in the concentration of PG receptors per mg protein, similarly to the OT and E receptors. In the regulation of PGF_{2α} receptors the most important factors seem to be the ovarian steroids, rather than physical factors, but little is known about the mechanism of the regulation in the pregnant myometrium near term. This constitutes a challenge to continue our investigations.

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Über die Wirkung der Fetektomie auf die Prostaglandin Rezeptoren im Myometrium der Ratte

F. LINTNER, F. HERTELENDY und B. ZSOLNAY

Aufgrund von Literaturdaten nehmen mehrere Autoren an, daß der Zeitpunkt des Geburtsbeginns auch vom intrauterinen Volumen abhängig ist. Frühere Studien haben es nachgewiesen, daß bei der Ratte beim Geburtsbeginn die Konzentration der PGF_{2 α} -Rezeptoren im Myometrium signifikant erhöht war. Im Interesse der Untersuchung der Wirkung des intrauterinen Volumens auf die myometrialen PGF_{2 α} -Rezeptoren, wurden während der Entbindung bei unilateral fetektomierten trächtigen Ratten die PGF_{2 α} -Rezeptorkonzentration der trächtigen und fetektomierten Tuben verglichen. Die PGF_{2 α} -Rezeptorkonzentration/Tube lag in der trächtigen Tube 3mal höher als in der fetektomierten Tube. Die Rezeptorkonzentration/mg Eiweiß erwiesen sich dagegen in der trächtigen und in der fetektomierten Tube als identisch. Die Ergebnisse sprechen dafür, daß durch die Spannung der Muskulatur der Gebärmutter Hypertrophie und Hyperplasie des Myometriums herbeigeführt werden, wofür der größere Eiweißgehalt der trächtigen Tube einen Beweis liefert. Die Erhöhung der PGF_{2 α} -Rezeptorkonzentration steht während der Geburt unter der Regelung hormonaler Faktoren, einem Prozeß, in dem das intrauterine Volumen keine Rolle spielt.

Влияние фетэктомии на простагландиновые рецепторы в миометрии крысы

Ф. ЛИНТНЕР, Ф. ХЕРТЕЛЕНДИ, и Б. ЖОЛНАИ

На основании литературных данных многие исследователи предполагают, что внутриматочный объем играет роль в начале родов. Согласно нашим предыдущим исследованиям, в начале родов у крыс концентрация PGF_{2 α} рецепторов в миометрии достоверно повысилась. Целью наших исследований было изучение влияния внутриматочного объема на PGF_{2 α} рецепторы в миометрии, поэтому мы сравнивали во время родов концентрацию PGF_{2 α} рецепторов в беременных и фетэктомизированных рогах матки у односторонне фетэктомизированных крыс. Содержание белка в беременном роге матки было значительно выше, чем в фетэктомизированном роге. Отношение концентрация PGF_{2 α} рецептор/рог в беременном роге было в три раза больше, чем в фетэктомизированном роге. В то же время концентрация рецепторов/мг белка была одинаковой как в фетэктомизированном, так и в беременном рогах. Результаты подтверждают, что напряжение мускулатуры матки вызывает гипертрофию и гиперплазию миометрия, что доказывается большим содержанием белка в беременном роге. Увеличение концентрации PGF_{2 α} рецепторов во время родов регулируется в первую очередь гормональными факторами, и внутриматочный объем в этом процессе роли не играет.

Axial and Random Skin Flaps

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Skin replacement by using pedicle flaps has undergone a change in attitudes during the recent 20 years. The most important results have been collected on the basis of literary data which, in our opinion, served as bases for the changes most decisively influencing flap grafting.

1. A better understanding of the structure and blood supply of the skin and of the subcutaneous tissues led to the discovery and extensive use of regional pedicle grafts.

2. By differentiating between axial and random flaps, various types of flaps with different biological behaviours could be classified.

3. In possession of our current knowledge the method using surgical tube flap is considered to be outdated not playing any more a role in circular reconstruction [3,36].

4. The axial skin flap does not need delay procedures, since on transferring the flap its blood supply remains unchanged. Only the transplanted random flap should be delayed or if it is larger than usual, an independent random flap should be used.

5. Reduction of the pedicle of the axial skin flap has led to the discovery of the island flap, which can also be applied for regional, but—by using the microvascular method—also for distant replacement.

6. The conception of musculocutaneous skin flaps has been based on these experimental and clinical results.

Skin repair using skin flaps is the oldest goal and most ancient method of reconstructive surgery. A nose reconstruction by using a forehead flap can already be found in *Sushruta Samhita* written around 600 B. C. [20]. A similar replacement was made by Tagliacozzi in 1597 who used a brachial skin flap [37]. A systematic literature deriving from reliable sources and coming up to scientific standards has become available only in the last two centuries. In addition to grafting of island-like and pedicled flaps, a large number of flap grafting techniques have become known [8, 42]. The basic rule, according to which, the length of the flap cannot exceed its width, i.e. it cannot be longer than its double not even in the region with the best blood supply (ratios of 1 : 1 and 2 : 1), has been based on long practice.

For increasing the length of the flap and for avoiding the frequently occurring necrosis, two new methods were developed. In 1916–1917 a plastic procedure using a tubed pedicle flap has been introduced by three surgeons (Filatov, Ganzer and Gillies) [11, 39] independently of each other. The other

method is to apply delay transfer flap which meant a circular incision raising the flap from its bed two to three weeks prior to the planned reconstruction practically forcing the pedicle flap to develop further collateral circulation [9, 12, 30].

The medially pedicled deltopectoral skin flap of Bahamyan reported in 1965 [3] has proved to be revolutionary in plastic surgery. A skin flap with a good blood supply grafted over the intercostal perforating branches of the internal thoracic artery, has seemingly violated the infallibility of the length-width ratio. A better understanding of the blood supply of the skin and the subcutaneous tissues has led to a change in attitudes in plastic surgery as a result of which skin repair by grafting skin flaps has become safer and more successful, opening up new vistas in the extensive application of regional pedicle flaps.

Anatomy

The skin is supplied by blood via two routes.

1. The musculocutaneous perforating branches run perpendicularly from the muscles below them to the skin forming a rich network in the subcutaneous layer [29], while a less abundant one in the subdermal layer [26], ending in the subpapillary plexus [10, 28].

2. The direct cutaneous arteries are branches of the segmental arteries running directly to the skin and providing the blood supply of the body ensuring the independent vascular supply of a skin region [25, 28, 29].

Skin flaps were studied by McGregor and Morgan [24] according to the quality of their blood supply, differentiating between axial and random flaps.

Random skin flap is a flap which can be cut from any body surface, with no independent arterio-venous system fed by the poor subcutaneous and subdermal network eventually present in the pedicle flap (Fig. 1a, b).

Axial (or arterial) skin flap is a type of flap possessing an independent arteriovenous system. The skin region corresponds to the vascular region of one, or more, direct cutaneous arteries (Fig. 2a, b).

Random Skin Flaps

The full-thickness flap consists of the skin and the subcutaneous adipose tissue. It is separated from the muscle by a thin fascial sheet. When the skin flap is raised in the plane of the fascia, the musculocutaneous perforating branches are transected and thus the minor vessels of the subcutaneous and subdermal plexus, which are being randomly present in the pedicle of the

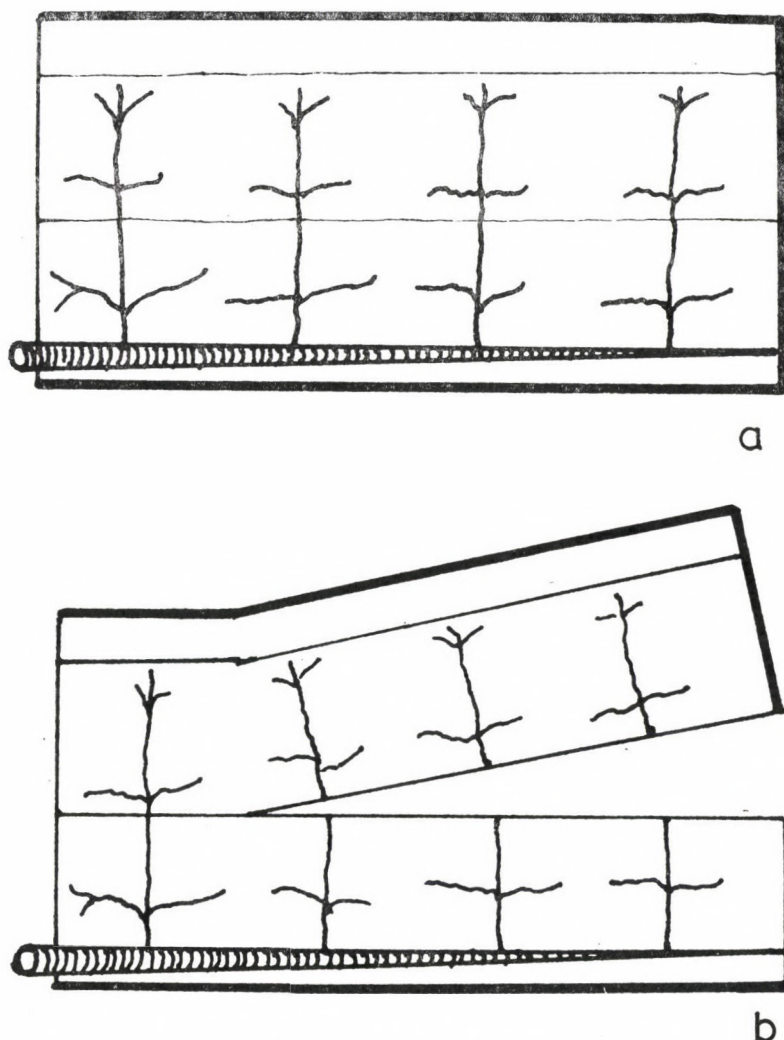


FIG. 1a. In the randomly vascularized region, the blood supply of the skin, fat and muscle are provided by the branches of the nutrient artery. b. A random skin flap

flap, will subsequently provide the blood supply. The capacity of the subcutaneous and subdermal plexus is, however, limited and the horizontal anastomotic system is poor. This accounts for the fact that the length-width ratio of the skin flap is 1 to 1, not exceeding the ratio of 2 to 1 not even in the region with the best blood supply (e.g. face), due to a risk of skin flap necrosis. In vain do we increase the width of the flap pedicle, the surface (the volume) and the oxygen demand of the skin flap will increase quadratically with its

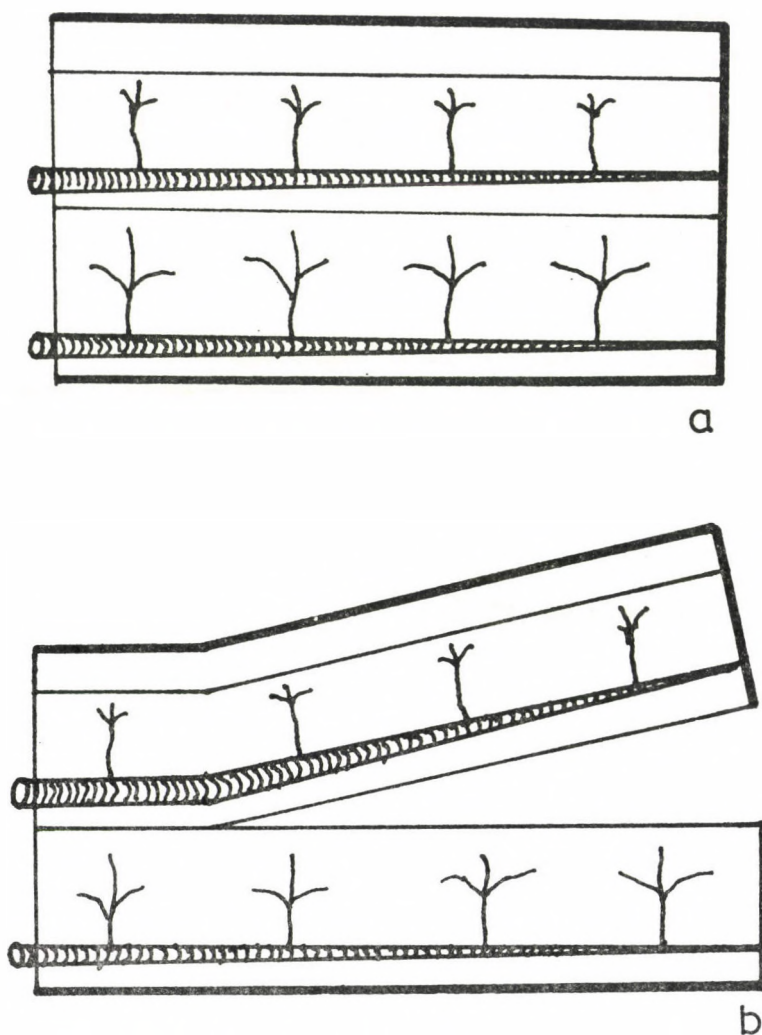


FIG. 2a. In the region of axial vascularization, blood supply of the skin and muscle is ensured by a separate artery. b. An axial skin flap

length. The amount of blood flowing through a given diameter depends on the diameter of the vessel, on blood pressure and on peripheral resistance, which is biologically inconceivable. The conclusion to be drawn is that the length of random skin flaps should not be further increased, therefore, considering their other drawbacks (i.e. cicatrization, shrinkage, secondary defect of the donor site) that are to be used only after due consideration, with a narrow range of indication [5, 14, 18].

Axial Skin Flaps

In the blood supply of the human body segmentation having been preserved during phylogenesis is notable, that means that the artery, vein and the nerve run together in the symmetrical truncal segments, however, with a similar arrangement also in the extremities [10]. The peripheral artery forms branches to the skin at definite places (direct cutaneous artery) which independently supply with blood the circumscribed skin region. The arteries usually have two accompanying veins (*venae comitantes*). As venous circulation fully corresponds to the arterial circulation it will not be discussed here in detail. The direct cutaneous artery in the subcutaneous region runs parallel with it forming a subcutaneous network, ending finally in the subpapillary plexus.

The conception that each skin artery supplies a given region of the skin, has been put forward not earlier than in 1889 by Manchot [19]. Milton [25] pointed out the importance of the direct cutaneous arteries, verifying by his experiments that, by preserving the nourishing vessel, a long flap with a thin

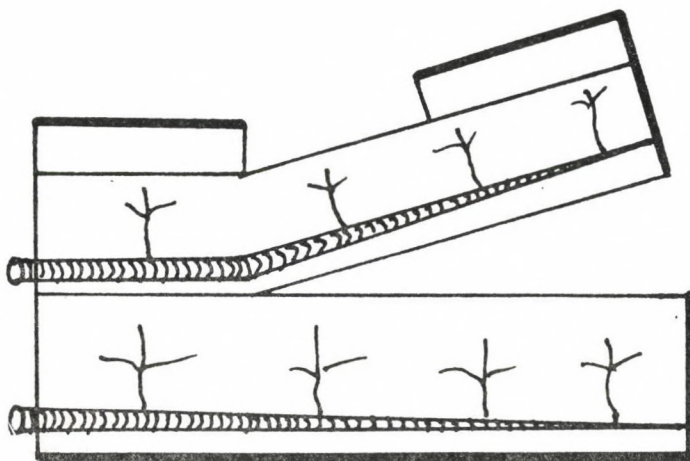


FIG. 3. An island skin flap

pedicle can be cut out for which the traditional length-width ratio is not valid. Moreover, he reduced the pedicle flap entirely to the vascular bundle, practically preparing an island flap (Fig. 3). Recognizing the significance of the axial blood supply of the skin flap, Smith [34] laid down the anatomical bases of the groin flap creating thereby the conditions of its clinical application [23].

Based on these experimental results and the clinical practice, were the axial and random pattern flaps named by McGregor and Morgan [24].

Clinical Use of Axial Skin Flaps

Parallel to the experiments mentioned above, several types of axial skin flaps had already been used in clinical practice: a frontal pedicle flap [21], a deltopectoral flap [3], a groin flap [23], a hypogastric flap [32], an acromio-pectoral flap [7, 33] as well as more island flap [4].

The anatomically supposed border of the axial skin flap was strikingly different from the length of the clinically applied skin flap. Peculiarly enough, the skin flaps far exceeding the anatomical border of axial blood supply proved to be of a favourable blood supply and viability. For illustration, it should be mentioned that the deltopectoral skin flap is supplied with blood from three directions (Fig. 4). On elevating the flap, the perforating arteries of the internal thoracic artery remain intact, thus blood supply is axial only in the TI region of the figure. The thoracoacromial artery and the musculocutaneous perforating branches of the deltoid muscle are transected and so the TA and MC regions form a random skin flap connected with the region of axial blood supply. It is known from practice that a skin flap of such size and extension can be safely used without delay [22]. This was explained by McGregor's clinical measurements [24] and by Smith's [35] animal experiments. Their results and conclusions are summarized as follows:

1. The adjacent regions of independent blood supply are in a dynamic pressure equilibrium with each other. There is no rigid 'watershed' not even in the median line of the body as it had been supposed earlier. If the nutrient artery of one of the regions is compressed, the blood supply of the adjacent

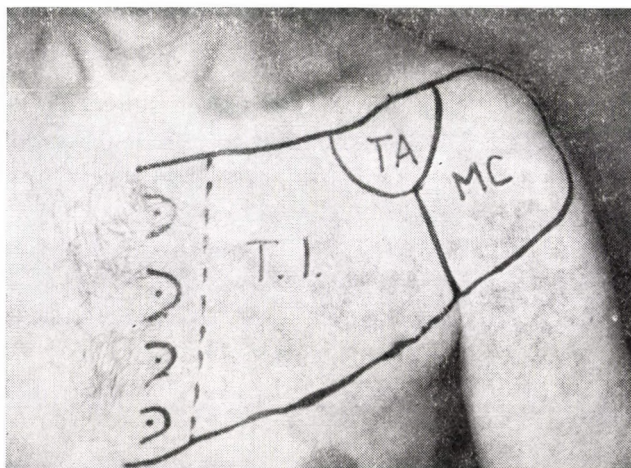


FIG. 4. Blood supply of a deltopectoral skin flap. TI = perforating branches coming from the internal thoracic artery; TA = thoracoacromial artery. MC = musculocutaneous perforating branches coming from the deltoid muscle

region will involve also this region. This is the case when the length of the flap goes beyond its own vascular region: the collaterals of the border region are opened and the region of the blood supply is extended.

2. The end of the axial skin flaps is randomly vascularized. At the anatomical border of the axial skin flap (at the point where the axial arteriovenous system is still recognizable), blood supply is perfect, being unchanged even on lifting of the skin flap and thus being still capable of supplying with blood a connected random skin flap of a smaller surface, essentially increasing thereby the length of the flap. This explains why the deltopectoral skin flap can be extended without delay to the deltopectoral sulcus and the temporal pedicle flap to the contralateral side.

3. The pedicle of the axial skin flap can be reduced to a vascular pedicle without changing its blood supply. Thus it practically becomes an island flap which is not only regional but can be used for distant grafting with microvascular anastomosis [15, 27, 38].

The most critical point of the axial skin flap is its random end portion, its necrosis may jeopardize the result of the entire reconstruction. Obviously, the subsequent investigations have attempted at clarifying the adequate flap length which can be grafted, without the risk of necrosis, and also how the viability (blood flow) of the skin flap can be increased.

Already Filatov [11] observed that, being transected, the end portion of the skin flap does not bleed and blood appears only with a delay of a couple of minutes. It is a well-known phenomenon that the blood flow of the skin flap is the worst in the first 24 hours, with an improving blood supply later on. So the first 24 hours are critical concerning skin flap necrosis; flaps surviving this period are unlikely to necrose. Aarts [1], Sasaki and Pang [31] as well as Reinisch [30] attribute the decreased blood flow to the postoperative peripheral vasoconstriction and to the altered redistribution. Reinisch performed peripheral sympathectomy (regional intravascular sympathetic blockade) by drug (6-hydroxydopamine) and by electrical stimulation and observed an increase in the flap length of the surviving part. He attributed his result to the fact that, due to vasoconstriction, blood circulates before the minor nutrient vessels through an arteriovenous shunt. However, Kerrigan [16] has challenged this hypothesis because of his claim that only 10% of the overall amount of blood passes through the arteriovenous shunt and so it can play no decisive role in the low perfusion of the nutrient vessels. Wray and Young, too, refuted the effect of fashionable drugs increasing flap survival (i.e. of isoxuprine hydrochloride, propranolol, heparin).

Several researchers repeatedly stress the role of harmful mechanical factors in skin flap survival. Wexler [40] has confirmed by his experiments how sensitive skin flaps are to wound tension, twisting or kinking. This has

been proved also by Larrate [17]. According to his observation, by overstretching, the length of the viable skin flap, is reduced. Aryan [2] has drawn attention to the reduced resistance of random skin flaps to infection. The fact that skin flaps are highly sensitive to mechanical effects is well known. It is therefore, of paramount importance that only tension-free, well-vascularized flaps should be used for replacement.

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Axiale und Random-Hautlappen

L. BORBÉLY und Á. KOVÁCS

Die sich auf den Lappen-Hautersatz beziehenden Anschauungen haben sich in den letzten zwanzig Jahren wesentlich geändert. Die wichtigsten Ergebnisse, die die Grundlage der die Lappenplastik entscheidend beeinflussenden Änderungen bildeten, waren im Spiegel der Literatur wie folgt:

1. Die Entdeckung und weitläufige Verbreitung der regionalen gestielten Lappen ermöglichte die ausführlichere Klärung der Struktur und Blutversorgung der Haut und der subkutanen Gewebe.

2. Die Differenzierung der axialen und Randomlappen ermöglichte die Klassifizierung der sich biologisch unterschiedlich verhaltenden Lappentypen.

3. Im Besitz unserer heutigen Kenntnisse wird die Methode des übertragenen Zylinderlappens als veraltet betrachtet, d. h., daß sie in der zirkulären Rekonstruktion bereits keine Rolle spielt [3, 36].

4. Der axiale Hautlappen beansprucht keine Verzögerung, da ja die Blutversorgung beim Hochheben des Lappens unverändert bleibt. Eine Verzögerung ist nur im Falle eines angelegten Random-Lappens nötig, oder wenn größere, selbständige Random-Lappen angewendet werden.

5. Die Reduktion des Stiels des axialen Lappens führte zur Entdeckung des Insellappens, welcher sich zur regionalen, aber mit der mikrovaskulären Methode auch zum Fernersatz eignet.

6. Die angeführten experimentellen und klinischen Ergebnisse bildeten die Grundlage der Konzeption der muskulokutanen Lappen. —

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Comparison of the Postoperative Changes in the Humoral and Cellular Immune Activity in Septic and Non-septic Colorectal Cancer Patients

A. NAGY,¹ ILDIKÓ PETRI,² GY. BARADNAY,¹ MÁRIA RASZTIK,¹ ENIKŐ MOZGA,¹

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(Received 10 May 1985)

The effect of sepsis on the host resistance of 34 colorectal cancer patients with normal preoperative immune reactivity was studied. A significant change ($p < 0.01$) was found in the IgG level of the septic patients ($n = 13$) when comparing their values with those of the non-septic patients ($n = 21$), on the third and 7th days postoperatively. There was no appreciable change in the IgA and IgM levels.

The E rosette formation and the blast transformation values of the patients showed a marked decrease on the 7th day postoperatively. In the non-septic patients the normal initial values reappeared on the 10th postoperative day, while in the septic cases they significantly decreased as compared to both their own values and to those of the non-septic patients assessed during the same period ($p < 0.05$).

The possible factors serving for the prevention of decrease in the resistance of the host organism, are discussed.

Postoperative clinical and experimental evidence has been provided for the correlation between impaired immune defense and the incidence of postoperative complications [4, 9, 14, 16, 20]. It was also observed that anaesthesia, intraoperative loss of blood, some drugs and several other factors may produce a transitional deterioration in postoperative immune activity [8, 10, 12, 21, 22, 23]. Sepsis impairs the cellular metabolism as a result of its catabolic and direct toxic effects. Obviously, this statement applies also to the immunocytes [2, 11, 13, 17, 18]. Although immunological changes due to sepsis are well established the degree of these disturbances and the quality of the various types of immunocytes participating in the process is still controversial [3, 5]. The correlation between the preoperatively measured immune activity of the septic patients and the forms and degree of the disturbances of postoperative immune defense, has not been clarified.

The present study aims at providing data on the postoperative changes in the humoral and cellular immune defense of septic and non-septic colorectal carcinoma patients and of those with a normal preoperative immune status.

Material and Method

Investigations were made in 55 colorectal carcinoma patients operated between 1st September 1983 and 31st March 1984, at the 1st Department of Surgery of Szeged University Medical School. For characterizing the humoral immune defense, the plasma IgG, IgA and IgM levels were determined by electrophoresis. For assessing T lymphocyte function, blast transformation ability stimulated by phytohaemagglutinin and Pokeweed mitogen, respectively, as well as spontaneous and active rosette formation were studied [1, 15, 19]. The preoperative values of colorectal carcinoma patients were compared to those of 50 normal controls, according to the tests described above [15]. Twenty-one patients who proved to be hypoergic in their preoperative immune activity, they were excluded from the subsequent examinations. Blood samples were obtained in 34 patients with normal immune defense on the third, 7th and 10th postoperative days.

The patients were divided into septic and non-septic groups on the basis of the parameters listed below:

1. Physical and radiological signs indicative of peritonitis, and a finding suggesting peritonitis during reoperation.
2. High temperatures (over 38 °C after three successive days).
3. A leukocyte count over 1000 g/l on more than three occasions, at two-day intervals, or one below 4000 g/l associated with changes in liver and kidney functions.
4. Positive haemoculture on at least two occasions within three days.
5. Wound infection with general septic effects.
6. Documented intra-abdominal abscesses.
7. Documented extra-abdominal septic process.

At least four of the seven parameters had to be positive to classify patient into the septic group. Using this procedure, 21 patients were grouped as non-septic and 13 patients as septic.

The two groups were compared according to age and sex distribution, types of operation and to some other factors affecting the immune defense (i.e. stage of tumour, amount of intra-operative blood loss, duration of operation, administration of drugs affecting the immune system, immunosuppressive treatment.)

For the statistical analysis of data, the Wilcoxon rank sum test was applied ($p < 0.05$).

Results

Figure 1 summarizes the changes in postoperative IgG, IgA and IgM plasma levels of septic and non-septic colorectal cancer patients. In the septic group a significant change in the IgG level was observed on the third and 7th postoperative days as compared to the preoperative average values ($p < 0.01$). By the 10th day, however, the plasma IgG level returned to the normal. Similar changes were measured also in the non-septic patients, but they were not significant as compared to either the preoperative values or to the values of septic patients observed during the same period. No estimable change was noted in the postoperative IgA and IgM values, either in the septic or in the non-septic groups.

In Fig. 2, the active and spontaneous ability for rosette formation of the lymphocytes of the non-septic and septic patients were compared. The active rosette-formation did not change in the postoperative period.

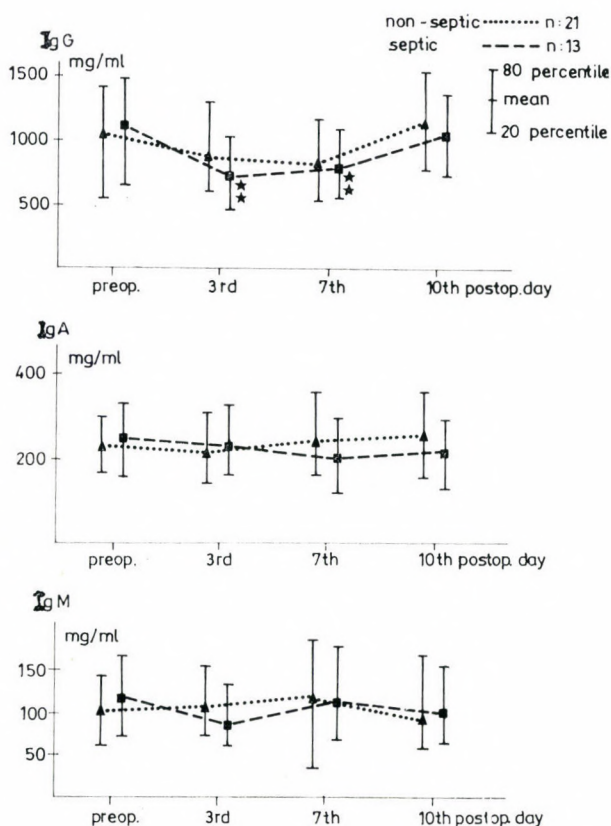


FIG. 1

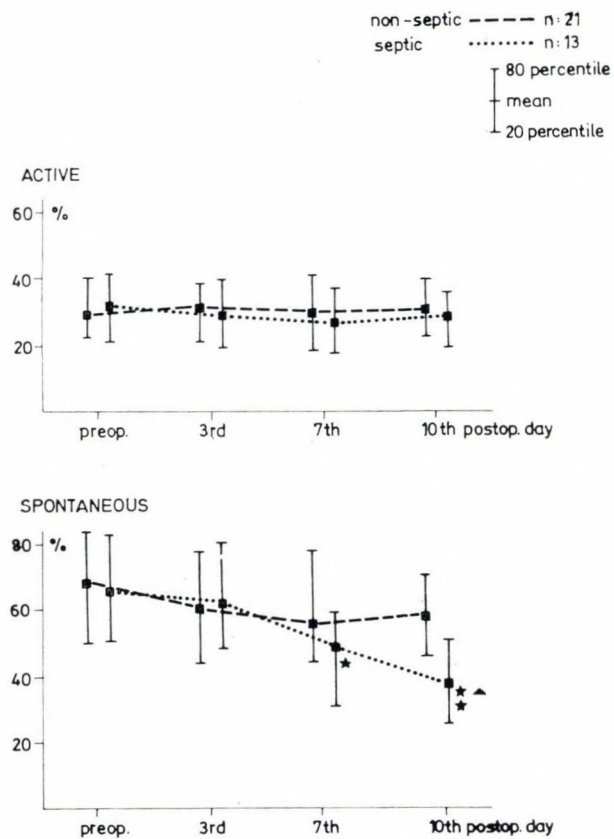


FIG. 2

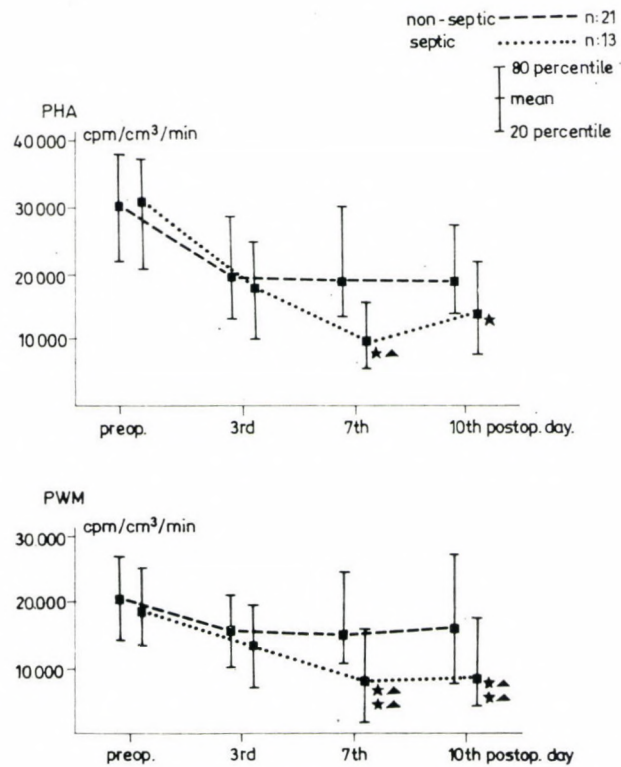


FIG. 3

The spontaneous rosette formation showed a decreasing tendency in both groups up to the 7th postoperative day. On the 10th postoperative day the values of the non-septic patients returned to the level measured preoperatively. On the contrary, in the septic group the decreasing tendency continued also on the 10th postoperative day, the results being significantly lower than the values measured either preoperatively or in the septic patients in the same period ($p < 0.01$).

The change in the blast transformation capacity of lymphocytes of the septic cases (Fig. 3) was very similar to that in non-septic cases with the difference that the immune defense had been significantly weaker, not on the 10th, but already on the 7th postoperative days than the values measured in the same period either preoperatively or in the non-septic cases.

Discussion

Continuous efforts are made to reduce the incidence of postoperative septic complications as much as possible. With the uncontrolled application of antibiotics having proved harmful, surgeons have become concerned, beside minimizing the hazards antibiotic therapies, with the changes in immune activity following surgical intervention [10, 14, 15, 19].

The titre of natural antibodies against various bacteria, the strength of complement functions and the chemotactic activity as well as the phagocytosis of leucocytes and monocytes were shown to play an important role in protection against infections [2, 3, 5, 11, 13]. Despite the intensive research work going on in this field, there are controversies as to the character and magnitude of postoperative changes in the immune defense process. The differences in the data published by various authors can be attributed mostly to methodological difficulties. Under clinical circumstances it is difficult to follow even the most important parameters by using time- and energy consuming techniques. Moreover, the studied groups of patients are often heterogeneous.

In the present study the postoperative changes in plasma immunoglobulins, active and spontaneous rosette formation and the blast transformation ability of lymphocytes were examined in non-septic and septic colorectal cancer patients. Special attention was paid to the homogeneity of the compared population of patients. It was shown that, in our patients, the plasma IgG level significantly decreased on the third postoperative day, then returned to the preoperative value. No significant difference in the decrease between the two groups was found neither in the plasma IgA nor in IgM levels in the postoperative period.

These results indicate that there is no significant difference in the B lymphocyte function of postoperatively non-septic and septic colorectal patients.

No difference appeared in the parameters characterizing the T lymphocyte function of the non-septic patients either. At the same time, a significant change was noted in the cellular immune activity of the septic cases on the 7th and 10th postoperative days as compared to the values measured preoperatively and to those in the non-septic patients during the same period.

Grzelah et al. [8] observed that, after gynaecological operations the number of B lymphocytes was reduced on the third postoperative day, which was followed by a rapid normalization. Also the number of both T lymphocyte populations decreased, but this occurred subsequently and was more permanent. The studies were made by using monoclonal antibodies. Using our own procedure, this phenomenon was apparent only in septic patients. This difference, as compared to non-septic cases, may serve as a circumstantial evidence for considerable changes occurring in T lymphocyte activity of non-septic and septic cases. If considering that preoperative immune activity and septic complications are also closely correlated [9, 14], a double immunosuppressive effect is to be reckoned with in patients becoming septic in the postoperative period.

Due to the causes listed above, it would be particularly important to reveal the possibilities of preventing the decrease in postoperative immune reactivity due to preoperative immunostimulation and sepsis. Although several encouraging results were achieved by parenteral hyperalimentation [7], vaccination [15], levamisole treatment [14] and by experiments on administering some peptides [6], the problem of preserving the immune stability of the patients cannot be regarded as solved.

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Gegenüberstellung der postoperativen Veränderungen der humoralen und zellulären Immunaktivität bei Patienten mit septischem und nicht septischem kolorektalem Krebs

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Bei 34, über normale Immunreaktivität verfügenden, an Kolontumor leidenden Patienten wurde präoperativ die Wirkung der Sepsis vom Standpunkt der Wirtresistenz untersucht. Die Gestaltung des IgG-Spiegels der septischen Patienten (n: 13) zeigte am 3. und 7. postoperativen Tag, im Vergleich mit den Werten der nicht septischen Patienten (n: 21) eine signifikante Abnahme ($p < 0,01$). Die IgA- und IgM-Spiegel zeigten keine bewertbaren Änderungen.

Die E-Rosettenbildungs- und Blasttransformationswerte der Patienten nahmen im Laufe der ersten 7 postoperativen Tage stark ab. Bei den nicht septischen Patienten kehren die Werte am 10. postoperativen Tag auf das normale Ausgangsniveau zurück, bei den septischen Patienten kann dagegen sowohl im Vergleich zu ihren eigenen Ausgangswerten ($p < 0,01$) als auch zu den in denselben Zeitpunkten bestimmten Werten der nicht septischen Patienten ($p < 0,05$) eine signifikante Verringerung nachgewiesen werden.

Im Zusammenhang mit den septischen Fällen finden jene möglichen Ursachen die zur Abwehr der Verringerung der Resistenz des Wirtsorganismus dienen, eine ausführliche Besprechung.

Сравнение постоперативных изменений в гуморальной и клеточной иммунологической активности у пациентов с септическим и не-септическим коло-ректальным раком

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У 34 больных с опухолью толстой кишки, имеющих нормальную иммунологическую реактивность, авторы исследовали перед операцией влияние сепсиса с точки зрения резистентности хозяина. Было показано, что уровень IgG у септических больных ($n = 13$) на 3-й и 7-й дни после операции достоверно ниже ($p < 0,01$), чем значения у не-септических больных ($n = 21$). В формировании уровней IgA и IgM заметного изменения не наблюдали.

Реакция Е-розеткообразования и значения бластной трансформации у больных в первые 7 дней после операции сильно уменьшаются. У не-септических больных на 10 постоперативный день восстанавливается нормальное исходное значение, тогда как у септических больных достоверное уменьшение наблюдается как по сравнению с собственными исходными значениями ($p < 0,01$), так и по сравнению с значениями у несептических больных, определенными в тот же период ($p < 0,05$).

Авторы обсуждают те возможные причины, которые предотвращают уменьшение сопротивляемости организма у больных с сепсисом.

Haemodynamic and Thermographic Signs of Intramyocardial Venous Outflow Redistribution Induced by Coronary Sinus Occlusion in the Canine Heart

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Short occlusions of the coronary sinus (CS) were performed in open chest dogs in order to study the clinico-physiologic aspects of changes induced by this manoeuvre both in intracoronary pressure distribution and myocardial blood supply. It was found that when mean CS blood flow (EM flowmeter) was plotted against mean CS pressure during the gradual blockade of the CS outflow, a perfectly linear relation could be established between these variables beyond the physiologic CS pressure range (>10 mmHg). Inotropic stimulation (adrenaline administration), without affecting its basic characteristics, shifted this line to higher pressure-flow ranges. On occluding the sinus, intracoronary arterial pressure distal to the ligated LAD branch also increases, but to a lesser degree than CS outflow pressure; within the ischaemic zone this results in a complete reversal of the arteriovenous pressure gradient during a considerable part of the cardiac cycle. Blood supply to the non-ischaemic heart was estimated with the aid of the computerized thermographic method developed by the authors. It was demonstrated that cardiac heat emission reflecting changes in subepicardial blood flow is singularly little affected by CS occlusion. From all these findings it is evident that occlusion of the CS involves a drastic coronary outflow redistribution but not a drastic inflow reduction in the heart. The results were interpreted in terms of newly developed cardiosurgical procedures aimed at to preserve myocardial viability, and it was concluded that the occurrence of adverse coronary actions offsetting the potential benefits of these procedures is of very low probability.

The invention of new and ingenious methods [11, 12] for protecting the jeopardized myocardium via the coronary sinus has created renewed interest [12] in perpetuation of Claude Beck's classic efforts aimed at providing a *permanent* extra amount of blood flow to the heart muscle through the sinus [2]. The transformation of Beck's original idea into more securely circumscribed goals (e.g. *intermittent* occlusion of the sinus for a limited period of time) has rendered the actions exerted by these procedures on myocardial blood supply a principal concern of investigations [12]. There have been special concerns that sinus occlusions might have an adverse coronary effect within the normal cardiac zone. The object of this study was, therefore, to provide a description of some selected consequences of coronary sinus occlusion which may help to interpret, in terms of myocardial blood supply, the ensuing local haemodynamic pattern of the coronary bed. Preliminary accounts of these results have already been presented [6, 10].

Material and methods

A total of twenty-one open chest dogs were studied under chloralose ($100 \text{ mg} \cdot \text{kg}^{-1}$) or pentobarbital sodium ($30\text{--}35 \text{ mg} \cdot \text{kg}^{-1}$) anaesthesia, successful experimental measurements being made in seventeen dogs ($18\text{--}26 \text{ kg}$ body weight). The heart was exposed by a transsternal dissection in the fourth intercostal space. Respiration was maintained with room air from a RO-5 respirator through an endotracheal tube. Intravascular pressures in the abdominal aorta and the greater cardiac vein, referred to coronary sinus level, were measured by Statham gauges (P 23 Db) and recorded on a four-channel Hellige multiscrptor. In four animals the outflow from the coronary sinus was also registered with the aid of an electromagnetic flowmeter (Carolina Electronics, Model 601 D) by using an extracorporeal flow probe fitted around a large-bore ($>5 \text{ mm}$) closed artificial circuit between the sinus and the cannulated central stump of a femoral vein. In another five dogs peripheral coronary pressure (PCP) in the ligated left anterior descending branch of the left coronary artery was measured through an indwelling needle inserted immediately distal to the occluding snare. The coronary sinus was occluded abruptly with a snare occluder placed around its terminal part, except in experiments where flow measurements were made; in the latter cases it was blocked in a step-by-step manner by using a screw clamp on the outflow circuit. Drugs were dissolved in PS and administered, in most experiments, by continuous infusion for $3\text{--}6 \text{ min}$ (to obtain steady state responses) through a catheter introduced into the left auricle. The dose range for adrenaline was $0.5\text{--}2.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, while the dose of adenosine was $60 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. In two experiments noradrenaline ($0.25\text{--}1.0 \mu\text{g} \cdot \text{kg}^{-1}$) and isoproterenol ($0.2 \mu\text{g} \cdot \text{kg}^{-1}$) were administered intravenously in bolus injections. The animals were given heparin ($500 \text{ IU} \cdot \text{kg}^{-1}$). In an experimental series computer-assisted teletermography of the heart was performed according to the technique developed by us in collaboration with the Institute for Coordination of Computer Technique (Budapest) and fully described elsewhere [14, 16]. Briefly, the thermographic cardiac images on the photographic colour prints were displayed by a colour display processor, they were resolved into a great number of data points, the signals were converted from analogue to digital, and appropriate coordinate values were ordered to each point by a special computer program. Thereafter, the total extension of every given set of data points (number of points) belonging to a particular temperature (colour) range was computed and the distribution of these areas was described in histograms. From the size of areas and their calibrated temperature ranges the mean temperature ($^{\circ}\text{C}$) of the whole visible cardiac surface could be determined. The inferences drawn in this paper were based on a total of several million data points ("thermographic samples"), and the order of magnitude characterizing an

individual cardiac image was roughly equivalent to $0.5 \cdot 10^5$ samples. The thermograms were taken at room temperature (24–26 °C). The sensitivity of the thermovision equipment (AGA 750) was adjusted to cover a 5 °C temperature range in all experiments.

Statistically evaluated numerical data are given as mean \pm S.E.M. The significance of results was calculated by using Student's *t*-test for paired data.

Results

Coronary sinus pressure-flow relationship

The dependence of the sinus outflow upon the artificially augmented coronary sinus pressure was studied under pentobarbital narcosis when the systemic haemodynamic effects of this procedure are reportedly absent or slight [7, 8, 21], and recorded for periods of gradual outflow hindrance lasting between 2–3 minutes. During a step-by-step occlusion of the outflow tube the values of mean flow and pressure in the coronary sinus were found to be inversely and linearly related over a sinus pressure of 7–8 mmHg (Fig. 1). Accord-

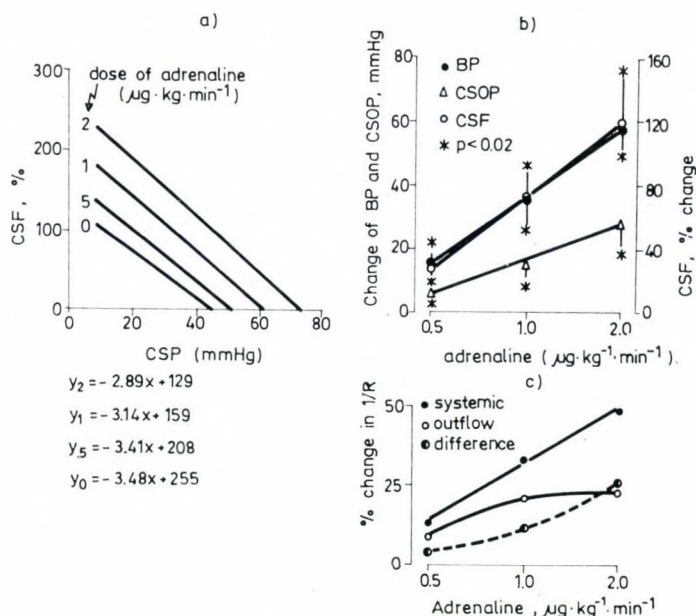


FIG. 1. Adrenaline-induced changes of pressure-flow relation in the coronary sinus. Mean values of four experiments. *a*: Decrease of flow caused by pressure increase in the sinus. Below: equations for linear regressions. *b*: Dose-dependent changes of haemodynamic variables. *c*: Dose-dependent changes in vascular conductance ($1/\text{resistance}$). Abbreviations: BP, mean blood pressure; CSF, coronary sinus flow; SCP, coronary sinus pressure; SCOP, coronary sinus occlusion pressure; R, resistance

ingly, the data obtained were normalized for blood flow determined at 10 mmHg outflow pressure; this level, as recorded in the control state, was regarded the 100% value of outflow. The relation of the decreasing flow to the increasing pressure was very strict in all experiments: both before and after adrenaline the individual lines drawn from least-square regressions for the data points had correlation coefficients between 0.95 and 0.99. The average values of all data are given in Fig. 1. It will be seen that adrenaline, without considerably affecting their slopes, forced the lines to make a parallel shift to the right (a). Although the regression coefficients (i.e. the slopes of the lines) also exhibited a slight increase, this change was not significant statistically (>0.05). However, the shift to the right of the intercept on the pressure axis (i.e. the coronary sinus occlusion pressure, CSOP) which, similar to the increments in mean arterial blood pressure and resting coronary sinus outflow, proved to be dose-dependent, was highly significant statistically at every dose (b). A nearly linear and an exponential increase of the reciprocal values in the virtual systemic (inflow) resistance (% outflow/% blood pressure) and in the virtual outflow resistance (% outflow/% (CSOP-10)), respectively were also established (c).

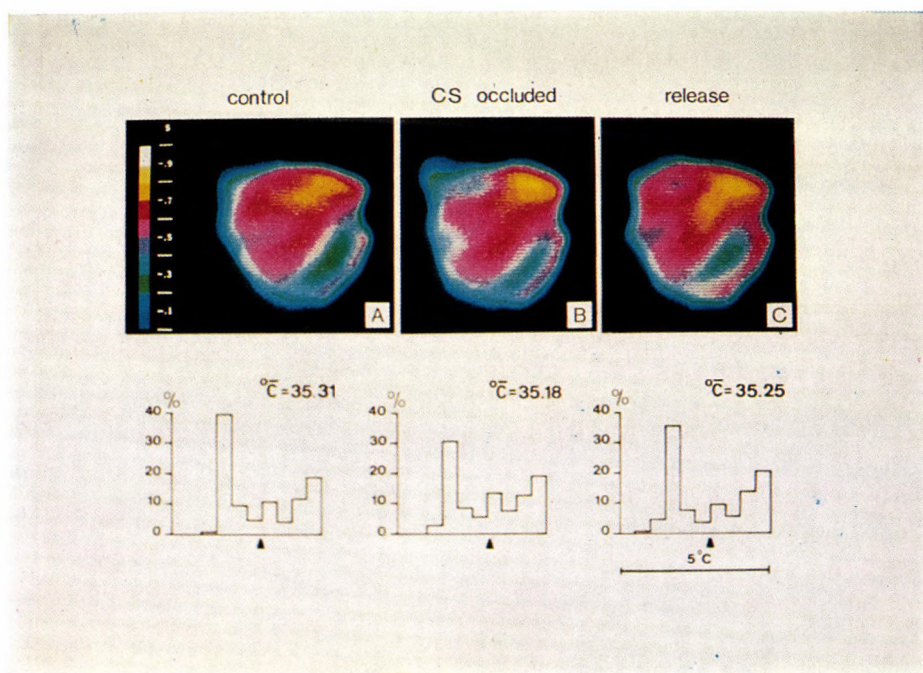


FIG. 2. Sinus occlusion elicits very slight modification in the cardiac thermograms. Above: original thermograms (on the left-side calibration each colour-shade corresponds to a temperature range of 0.5 °C. From above downwards: cooling). Below: computerized histograms of the cardiac images (each column = 0.5 °C range). ▲ = mean temperature (°C). The shift to right of the mean corresponds to cooling

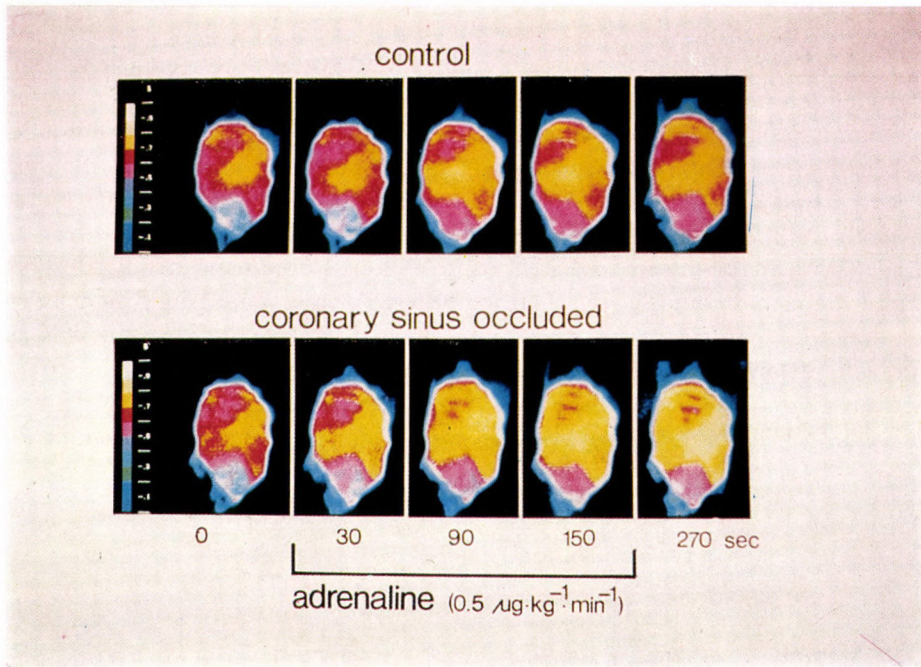


FIG. 3. Thermographic signs of adrenaline-induced coronary vasodilation. Original thermograms taken before (above) and after (below) sinus occlusion

Thermographic estimation of myocardial blood flow

In order to obtain steady state responses the coronary sinus was occluded for at least 2 min in every experiment. Typical patterns of epicardial temperature distribution are demonstrated in Figs 2 and 3. Both the original thermographic records and the computer-evaluated quantitative measurements (Fig. 2 below and Fig. 4) show that the abrupt and complete occlusion of the coronary sinus did not affect considerably the flow-dependent heat emission from the cardiac surface. Similar results were obtained both in chloralose and in pentobarbital narcosis. Coronary sinus occlusion produced only a 0.02 ± 0.03 °C cooling in 12 trials performed in five experiments. Since transmural shifts in coronary blood flow (if any) were not known, coronary sinus occlusion-induced alterations in epicardial temperature are best compared to a parallel series of former experiments where computer-evaluated subepicardial thermal changes were plotted against directly measured blood flow changes in the LAD artery [14]. As can be seen in Fig. 5, in spite of the variability of individual responses, the average probable fall in myocardial blood supply is less than 20% of the control value. (The close fitting of the mean \pm S.E.M. into the

regression line used for this estimation suggests that the individual responses are evenly distributed.)

Moreover, thermographically determined vasodilator capacity of the coronary arteries, as induced either by beta-adrenergic stimulation or hypoxia, was maintained during the periods of coronary sinus occlusion. It follows from the first series of experiments that, by administering higher catecholamine doses ($>1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) the behavior of the resting inflow and outflow vascular conductance is dissimilar in the coronary bed (Fig. 1c). This fact may be related to an intramural redistribution of blood flow during strong adrenergic stimulation, undetectable by thermography. At the same time, higher doses of adrenaline induce a more than 50% flow increase (Fig. 1b); in this case the calibration of thermographic flow measurements against the directly measured flow becomes curvilinear ("saturation part of the curve", Papp et al., to be published). Accordingly, to test vasodilator capacity, an adrenaline dose

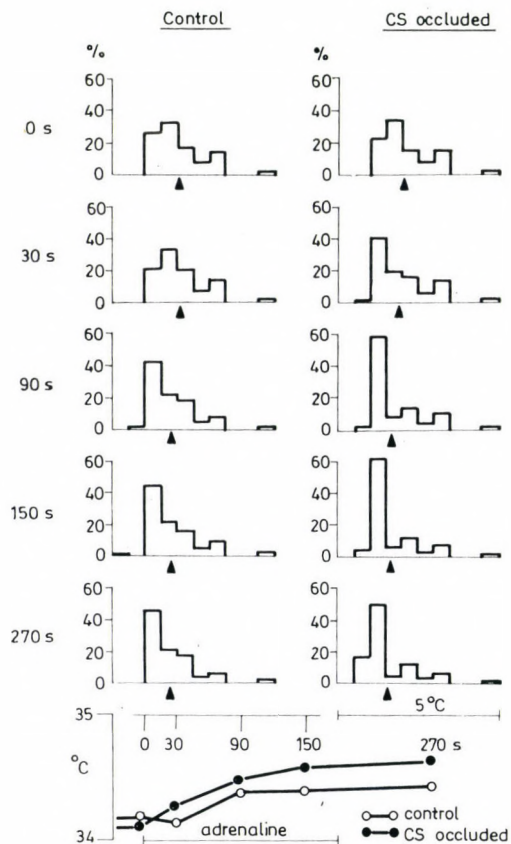


FIG. 4. Above: histograms describing the computerized evaluation of thermograms shown in Fig. 3. Signs as in Fig. 2. Below: diagram of changes in mean temperature

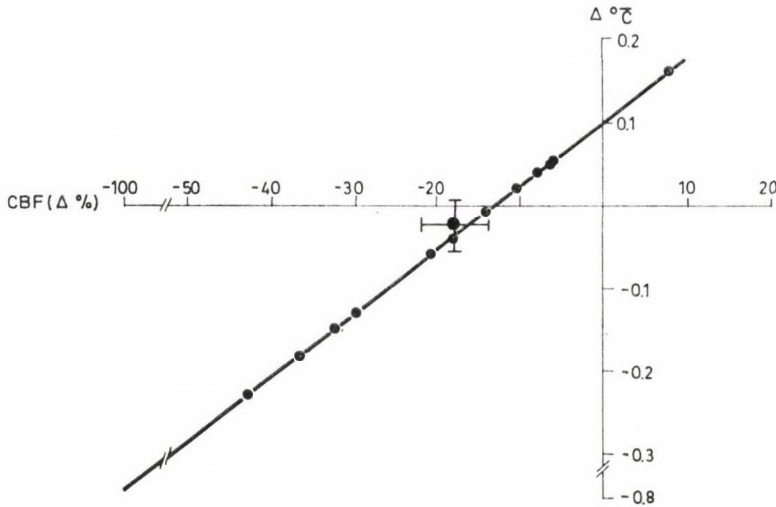


FIG. 5. Sinus occlusion-induced thermographic changes plotted against coronary blood flow (CBF). The regression used for evaluation was obtained in former studies [14]. Large symbol: mean \pm S.E.M. For further explanation see text

of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was selected. It was found that coronary sinus occlusion may delay, but it can scarcely attenuate catecholamine-induced coronary vasodilation. Occasionally, with blocked coronary sinus flow the response could be even greater (Figs 3 and 4). On the average, there was no significant difference between peak responses of the epicardial warming (0.57 ± 0.18 vs. $0.51 \pm 0.07 \Delta^\circ\text{C}$, $n = 3$, $p > 0.7$). Similar observations were made in two animals by testing hypoxic (reactive hyperemic) vasodilator capacity by occluding the LAD artery for 1 min or by infusing the tentative mediator of this autoregulatory response (adenosine) for 3 min in a submaximal dose ($60 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Redistribution of intravascular pressure gradients within the ischaemic zone

In five animals under pentobarbital the arterial pressure within the acutely occluded LAD coronary branch (peripheral coronary pressure, PCP) was recorded during the occlusion of the sinus. A typical tracing is shown in Fig. 6, while the statistical evaluation of the results is presented in Fig. 7. Occlusion of the sinus elicited a moderate abrupt increase in PCP. However, this response was less than the increase of coronary sinus pressure. Consequently, the positive pressure gradients existing between the control levels of peripheral coronary pressure and coronary sinus pressure get reversed (systolic and mean pressures) or practically abolished (diastolic pressure).

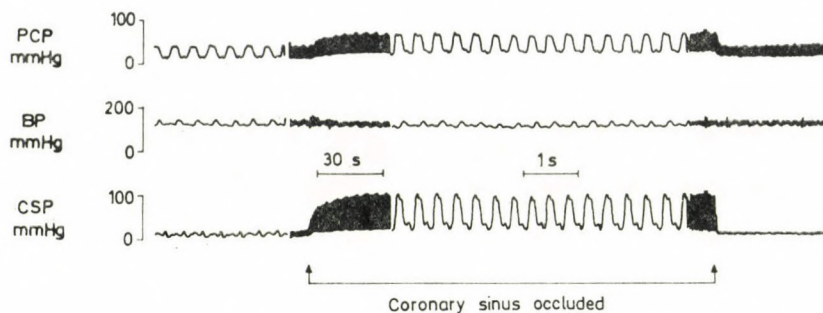


FIG. 6. Haemodynamics of sinus occlusion in regional myocardial ischaemia (LAD artery was occluded 30 min prior to the measurement). From above downwards: peripheral coronary pressure (PCP), arterial blood pressure (BP), coronary sinus pressure (CSP)

In two other preparations the response of peripheral coronary pressure to catecholamine administration was examined. It was found that on occluding the sinus, beside the coronary sinus pressure the former variable also exhibited a potentiated increase (Fig. 8). Because this phenomenon can be induced by

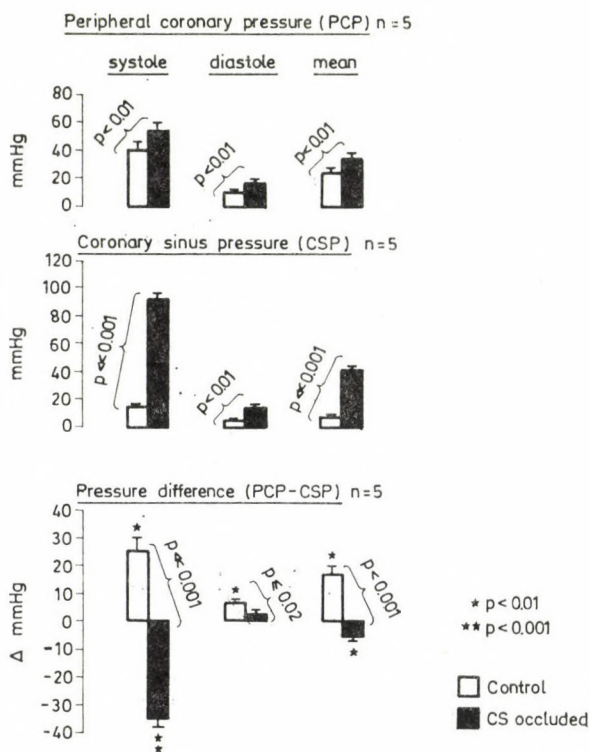


FIG. 7. Statistical evaluation of local haemodynamic effects induced by sinus occlusion in the ischaemic heart. For explanation see text

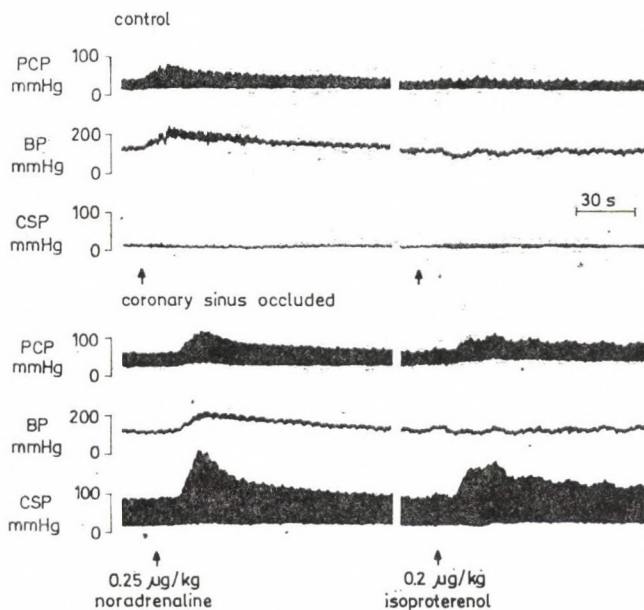


FIG. 8. Effects of catecholamines on local coronary ischaemic haemodynamics before (upper panels) and after (lower panels) coronary sinus occlusion. Signs as in Fig. 6

both the predominantly alpha-stimulant noradrenaline and the pure beta-stimulant isoproterenol, it seems to be independent of concomitant changes in arterial blood pressure.

Discussion

A major finding of this study has been the new experimental proof of a reasonably well preserved blood supply to the normal (non-ischaemic) myocardial tissue during occlusion of the coronary sinus. There is an increasing evidence, both in surgery and in experimental cardiology, in favour of effective myocardial protection via new and sophisticated "retrograde" procedures that involve the access to the endangered myocardium through the sinus [11, 12, 20]. Although a protective means of such type inevitably leads to some degree of a temporary blockade in the sinus outflow, in the light of the present findings the possibility of a considerable coronary arterial flow reduction offsetting the benefits of these techniques seems very slight. It has been a theoretical as well as a practical concern of several authors that coronary sinus occlusion reduces immediately the arterial inflow in the left heart [3, 5, 12, 13]. However, our capability to interpret the functional significance of these flow alterations, similar to many an analogous flow pattern, has been limited in the past by the lack of reliable information on the simultaneous changes in myocardial blood

supply at the tissue level. Precisely for these reasons we have developed recently a new computer-assisted method for the quantitative evaluation of the colour cardiac thermograms [14, 15, 16], which reflect correctly, on the cardiac surface, the balance between tissue blood supply and myocardial heat generation. With the availability of the results of our recent efforts directed to find mathematical correlation between the flow-dependent heat transfer characteristics of the myocardium and epicardial thermal images on one hand, and between directly measured flow and computerized thermograms on the other, the quantification of thermograms in terms of blood supply now seems possible [14, 15]. Mean subepicardial temperature proved to be directly related to the rate of flow through this layer [14, 17].

The present findings indicate that on occluding the coronary sinus thermographically determined mean temperature on the cardiac surface is more likely to remain unchanged than to fall. More importantly, the great majority of responses was within 0.15°C , i.e. well within the range of the compensatory collateral response observed in regional left ventricular ischaemia [16]. To facilitate comparison each individual thermal response obtained in this study was plotted against the relevant estimated flow value (see Fig. 5) as it was established in former experiments [14]. Since the line of regression of this relation has a positive intercept on the ordinate, there is perhaps a further refinement in the interpretation which should be noted: this concerns the methodological problems of thermographic flow calibration.

The above calibration may underestimate coronary blood flow if, under the influence of a sudden flow restriction, the unchanged level of myocardial energy utilization shifts the thermodynamic balance in the subepicardial layer to a warmer range: thus, the high ordinate intercept may imply some virtual "hot spots" [19] on the surface. However, the above calibration will overestimate blood flow if the contribution of collaterals is different in the two experimental series. Nevertheless, we believe that the $18.2 \pm 4.3\%$ average fall in flow (Fig. 5) is a pessimistic estimation of the real response.

At the same time, in the intact organism any decrease in the oxygen supply to the heart muscle can be effectively counterbalanced by a reflexly induced simultaneous decrease in the myocardial oxygen requirement [6, 7, 13, 21] occurring on stimulation of venous coronary receptors (not examined in this study). A potentially deleterious change of coronary adaptation was also refuted by the intactness of the autoregulatory capacity (Figs 3 and 4): it was shown formerly that even a slight exhaustion of autoregulatory reserve severely restricts the propensity of the coronary vessels for further vasodilation [9]. This was clearly not the case in these experiments.

The close *linear* dependence of coronary sinus flow upon the relevant venous outflow pressure, and, the unequivocal maintenance of this relation even under the conditions of an excessive adrenergic stimulation (Fig. 1)

provides a strong haemodynamic argument for the correctness of the above interpretation. These measurements essentially confirm and extend the results obtained in former excellent studies [1, 4, 5, 18, 22] concerning the partition and dynamics of coronary venous flow. The present results indicate that the mechanical hindrance, established in the experimental setup, was the chief determinant of the changing outflow resistance and imply an abundant network of venous channels which are collateral to the tributaries of the coronary sinus. The connection of this draining system with the collaterals on the arterial side is evident from the fact that peripheral coronary pressure which represent the intravascular driving force in the arterial collateral network was found to increase after the occlusion of the coronary sinus. Since this response was synchronous with the apparent reversal of arteriovenous pressure gradient within the ischaemic zone, it could mean an augmented arterial and/or reversed venous collateral supply to the capillary bed of the latter region and may contribute to the beneficial effects of coronary sinus occlusion in regional disturbances of cardiac blood supply. Since ischaemic events in the heart are often associated with increased sympathetic drive which, especially in an excessive form in itself may be detrimental for the jeopardized cardiac cells, we believe that the effect of sinus occlusion on this response is of particular importance. From the haemodynamic point of view, the demonstration of dose-dependently shifted but phenomenologically unchanged pressure-flow relations in the sinus after catecholamine administration permits to validate the therapeutic implications of sinus occlusion for the heart muscle subjected to strong sympathetic influences *and* ischaemia. The direct thermographic consequences of these reactions remain to be determined in further studies.

Acknowledgement

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Hämodynamische und thermographische Zeichen der durch Sinus coronarius-Okklusion ausgelösten Venenfluß-Redistribution am Hundeherz

VIOLETTA KÉKESI, L. PAPP und S. JUHÁSZ-NAGY

Untersucht wurden die klinikophysiologischen Beziehungen der durch kurzfristige Sinus coronarius-Okklusionen ausgelösten Änderungen der intrakoronaren Druckverteilung und der myokardialen Blutversorgung bei Hunden mit offenem Brustkorb. Es wurde festgestellt, daß im Laufe der graduellen Blockade des Sinus coronarius-Abflusses zwischen der Sinus coronarius-Mitteldurchblutung (EM-Durchflußmesser) und dem Sinus coronarius-Mitteldruck über dem physiologischen Druckbereich (>10 mmHg) eine vollkommen lineare Korrelation besteht. Durch inotrope Stimulation (Adrenalingabe) wird diese lineare Korrelation in ein höheres Druck-Strömungsbereich verschoben, ohne daß sich ihr grundlegendes Charakteristikum ändern würde. Unter Wirkung der Sinusokklusion erhöht sich auch der vom unterbundenen LAD-Koronarast distal meßbare arterielle Intrakoronardruck, aber in geringerem Maße als der Druck des Sinus coronarius. Dies hat auf dem ischämischen Gebiet während einem beträchtlichen Abschnitt des Herzzyklus die Umkehr der arteriovenösen Druckdifferenz zur Folge. Die Blutversorgung des intakten, nicht ischämischen Herzens wurde mit dem im Institut entwickelten rechnergestützten thermographischen Verfahren untersucht, wobei es nachzuweisen war, daß die der subepikardialen Durchblutung gut folgende myokardiale Wärmeabgabe durch die Sinus coronarius-

Okklusion in nur überraschend geringem Maße beeinflusst wird. Aus den angeführten Ergebnissen geht hervor, daß die Sinus coronarius-Okklusion die beträchtliche Redistribution der venösen Koronardurchblutung zur Folge hat, während die arterielle Einströmung nicht wesentlich herabgesetzt wird. Die Ergebnisse wurden vom Standpunkt der im Interesse der Bewahrung der Lebensfähigkeit des Myokards neuestens entwickelten herzchirurgischen Methoden gedeutet, woraus sich die Folgerung ergab, daß der Auftritt unvorteilhafter Koronarwirkungen, die die potentiell günstige Wirkung der obigen Eingriffe ausgleichen würden — äußerst unwahrscheinlich ist.

Гемодинамические и термографические признаки перераспределения интрамиокардиального венозного оттока, вызванного окклюзией коронарного синуса сердца собаки

В. КЕКЕШИ, Л. ПАП и. Ш. ЮХАС-НАДЬ

В экспериментах на собаках с открытой грудной клеткой авторы изучали внутри-коронарное распределение давления и изменения миокардиального кровоснабжения в клинико-физиологическом аспекте, вызванные кратковременными окклюзиями коронарного синуса (SC). Они установили, что, в ходе ступенчатой блокады SC оттока, между средним кровотоком коронарного синуса (измеритель кровотока ЕМ) и средним давлением в синусе наблюдается идеальная линейная зависимость над областью физиологических значений давления (>10 мм рт. ст.). Инотропная стимуляция (введение адреналина) вышеупомянутую линейную зависимость смещает в область более высоких давления и кровотока, не изменяя ее основную характеристику. Интракоронарное артериальное давление, измеряемое дистальнее перевязанной LAD коронарной ветви, тоже повышается, но в меньшей степени, чем давление в коронарном синусе. В результате на ишемическом участке происходит поворот разницы артерио-венозного давления в течение значительной части сердечного цикла. Кровоснабжение интактного, не-ишемического сердца авторы изучали модифицированным ими компьютерным термографическим методом. Показали, что миокардиальную теплоотдачу, хорошо отражающую субэпикардиальные изменения кровотока, окклюзия коронарного синуса изменяет в чрезвычайно малой степени. Как показывают полученные результаты, окклюзия SC вызывает значительное перераспределение венозного коронарного кровотока, в то же время существенно не уменьшая артериальный приток. Полученные результаты авторы интерпретируют с точки зрения недавно развитых методов сердечной хирургии, направленных на сохранение жизненной способности сердечной мышцы, и приходят к выводу, что очень маловероятно появление таких неблагоприятных коронарных действий, которые уравнивали бы потенциально благотворные влияния вышеописанных вмешательств.

Date on Renal Hypothermia by the Venous Passage

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The temperature values obtained in renal hypothermia through the venous circulation were biometrically analysed. It was found that there could be even about 4 °C temperature differences between the lower and upper poles of the kidney, always as large as 4 °C could be elicited in the first five minutes of hypothermia, the lower pole being colder. Similar but smaller differences were observed in ten minutes' hypothermia.

Several studies have already been presented on the clinical and experimental implications of renal hypothermia. These works revealed that an adequate degree of hypothermia can be achieved both *in situ* as well as extracorporeally. The technique of this method was elaborated and modified [2, 3, 4, 5]. The rate of temperature decrease in the function of time was also studied [6].

On first inspection it seems to be illogical to perfuse the cooling fluid against the circulation.

Marekovic [1] and Wilhelm [7, 8] showed that the renal veins form an anastomotic system as compared to the arteries which are arranged segmentally. If the venous system is drained, e.g. by nephrotomy, the cooling fluid flows out producing the adequate degree of hypothermia either *in situ* or extracorporeally.

The simplest way of drainage is radial nephrotomy. The degree of hypothermia was measured at the corticomedullary border in these experiments. Initially, temperature was measured only at the lower pole of the kidney. Subsequently, nephrotomies were also made at the upper pole and temperature was recorded. These experiments were conducted in dogs.

It was noted that the 5-minute cooling temperature values fairly differed between the two poles, the greatest difference being 10 °C.

Since there was no explanation for the significant temperature differences and no similar data could be found in the literature, a series of experiments were performed in dogs.

Method

Through a cannula inserted into the renal vein a total of 19 dog kidneys were perfused and cooled with 4 to 6 °C magnesium sulphate-free Collins₄ cooling fluid extracorporeally at room temperature (21.5 to 23.5 °C).

Radial nephrotomies were performed at the following locations:

Group I: lower pole

Group II: lower pole + mid-portion of the kidney

Group III: lower pole + mid-portion + upper pole

Group IV: lower pole

Group V: upper pole + mid-portion.

Temperatures were synchronously recorded in each group at the lower pole (A), in the mid-portion (B) and at the upper pole (C) at the 5th and 10th minutes from the beginning of perfusion and, in 8 cases, also at the 15th minute.

Then the differences in each case and their averages, respectively, between the upper pole and the mid-portion (C-B) and the mid-portion and the lower pole (B-A), respectively were defined.

Regarding that all conclusions based on the differences can be accepted after mathematical-statistical analysis only, the confidence interval of the average differences in temperature was calculated and, since it did not reach zero, the averages of temperature differences were, in each case, significantly higher than zero ($p < 5\%$).

Evaluation of the experiment is presented by an example below.

In 19 kidneys, the temperature differences between the mid-portion and the lower pole (B-A) were as follows.

1. 0	7. 3.0	13. 1.0
2. 0	8. 2.0	14. 4.0
3. 0.2	9. 4.4	15. 4.0
4. 5.5	10. 3.0	16. 1.0
5. 3.0	11. 4.0	17. 2.0
6. 1.0	12. 1.0	18. 3.0
		19. 1.0

The average of the temperature differences was $\bar{x} = 2.24$ °C, the scatter of the average being $S_{\bar{x}} = 0.40$.

In case of small samples of $n < 100$ elements, the \bar{x} average of the population of normal scatter falls into the $[\bar{x} \pm t_{(n-1)}; p, S_{\bar{x}}]$, the so-called confidence interval, since the random variable of the Student t scatter (t), according to definition, is greater than $[\pm t_{(n-1)}; 5\%]$ only with a probability of less than 5%.

In our example:

$$\bar{x} \pm t_{(18)}; 5\% \cdot S_{\bar{x}} = 2.14 \pm 0.78^{\circ}\text{C}.$$

Consequently, the zero falls fairly beyond the $[1.36; 2.92]^{\circ}\text{C}$ confidence interval and so, after 5 minutes of hypothermia, the average difference in temperature between the mid-portion of the kidney and the lower pole differs significantly from zero ($p < 5\%$).

Results

In the 5th minute of venous renal hypothermia connected with nephrotomy, the average temperature difference between the mid-portion of the kidney and the lower pole (B-A), i.e. the confidence interval is

$$\text{B-A} : \bar{x} = 2.14 \pm 0.78^{\circ}\text{C} \quad p < 5\%.$$

Between the upper pole and the mid-portion it is

$$\text{C-B} : \bar{x} = 1.75 \pm 10.5^{\circ}\text{C} \quad p < 5\%.$$

The average difference between the upper and lower poles of the kidney is

$$\text{C-A} : \bar{x} = 3.89 \pm 1.44^{\circ}\text{C} \quad p < 5\%.$$

Similar analysis was made of the values recorded after a 10-minute hypothermia. The average temperature difference and the confidence interval between the individual renal portions were as follows.

$$\text{B-A} : 0.96 \pm 0.59^{\circ}\text{C} \quad p < 5\%$$

$$\text{C-B} : 1.52 \pm 0.86^{\circ}\text{C} \quad p < 5\%$$

$$\text{C-A} : 2.48 \pm 1.01^{\circ}\text{C} \quad p < 5\%.$$

After 15 minutes of hypothermia, the differences were, more or less, smoothed out but in 8 cases temperatures were still measured with the following results.

$$\text{B-A} : 1.0 \pm 0.89^{\circ}\text{C} \quad p 5\%$$

$$\text{C-B} : 1.0 \pm 0.99^{\circ}\text{C} \quad p 5\%$$

$$\text{C-A} : 2.0 \pm 0.46^{\circ}\text{C} \quad p 5\%.$$

Discussion

The analysis has disclosed that in the first 5 minutes of hypothermia through the venous passage the average temperature difference between the lower and upper poles of the kidney is almost 4°C ; always the lower pole being the cooler.

The average difference between the lower pole and the mid-portion of the kidney is 2.15 °C also with the lower pole being the colder.

After 10 minutes of hypothermia, the average values already decrease to their half, i.e. the difference between the upper and lower poles is 2.5, while that between the mid-portion and the lower pole only 1 °C.

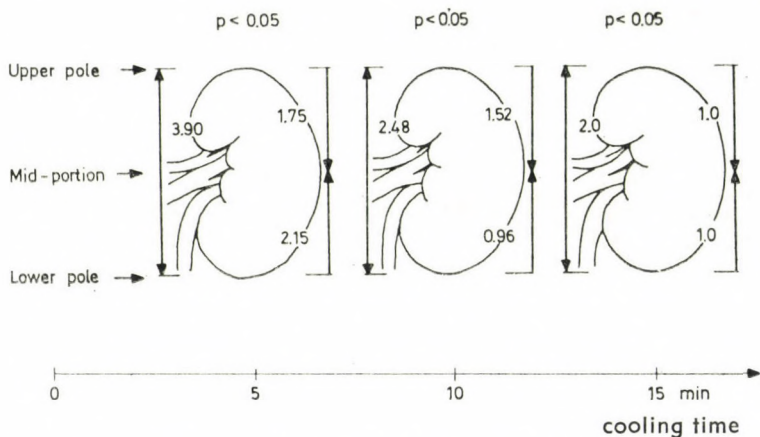


FIG. 1. Average temperature differences between the individual kidney portions in hypothermia through the venous passage

After 15 minutes, the fluctuation is around 1 °C. It is true that calculations were made only in 8 animals, since after 15 minutes the values are almost smoothed out.

The values obtained are shown in Fig. 1, where the temperature differences can be well followed.

It can also be noted that the difference between the upper and lower pole is 4 °C in the first 5 minutes, while 2.5 °C after 10 minutes.

This means that the lower pole cools down first and this is equalized after 10 to 15 minutes. It should also be noted that similar data were obtained in 10 clinical cases, too. The explanation of the phenomenon is, presently, hypothetic, further investigations are still needed (corrosion preparations, comparative planimetric electron microscopic examination of the venous system). Its clinical importance is also to be analysed.

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Daten zur Hypothermie durch die Vena renalis

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Die anlässlich der durch die Vena renalis vorgenommene Hypothermie der Niere erhaltenen Temperaturwerte wurden biometrisch analysiert: In den ersten 5 Minuten der Hypothermie kann zwischen dem unteren und oberen Nierenpol sogar ein Temperaturunterschied von rund 4 °C vorliegen, wobei stets der untere Pol der kältere ist.

Dieser Unterschied war auch nach 10minütiger Hypothermie zu beobachten, obwohl die Temperaturdifferenz auf die Hälfte zurückfiel.

Данные к гипотермии почки, осуществляемой через венозную ножку

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Авторы анализировали биометрическим методом значения температуры, полученные в связи с охлаждением почки через венозную ножку, и обнаружили, что, в первые пять минут охлаждения, разница температур между нижним и верхним полюсами почки может достигать 4 °C, причем нижний полюс всегда холоднее. Эту разницу отмечали и после 10-минутного охлаждения — хотя разница между температурами уменьшилась наполовину.

Arteriovenous Shunt-Circulation in Lymphoedematous Limbs

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In lymphoedema of the extremities arteriovenous shunt circulation develops. Regulation of limb circulation was studied in 28 cases of (primary and secondary) lymphoedema by using the venous isotope dilution method and technetium-macroaggregate perfusion scintigraphy. As a result of lymphoedema, limb circulation (total limb circulation) increases, arteriovenous O₂ difference is low and the O₂ uptake of the tissues is normal. The development of arteriovenous (micro-, and macro-) shunts can be directly visualized by perfusion scintigraphy. In lymphoedema of the extremities the nutritive—capillary—blood supply of the tissues remains normal and therefore, no trophic disturbances develop. Lymphoedema is often associated with a fairly considerable arteriovenous shunt circulation and, in such cases, the cardiac output as well as cardiac performance are enhanced.

Limb oedema due to lymphostasis, is a specific and not infrequent disease. The insufficiency of the lymph circulation can develop both in the forms of congenital and acquired (primary and secondary) lymphoedema. The limb is characterized by an elastic and hard swelling. It is striking that in lymphoedema the venous blood—that of the femoral vein—is bright red. Results of our previous studies have already indicated that parallel with the lymphoedema, arteriovenous anastomoses develop on the affected limb [13, 14]. The present investigations aimed at studying the regulation of limb circulation and the characteristic features of arteriovenous shunt circulation in lymphoedema.

Patients and Methods

Limb circulation due to lymphoedema was studied in 28 patients. Of the 28 patients, 16 were females and 12 males, with an average age of 44.4 (18 to 61) years.

Primary lymphoedema (mostly lymphoedema praecox) was found in 11 cases, while 17 patients had secondary lymphoedema. Of the 28 patients 16 were affected by unilateral lymphoedema, involving only one limb.

Blood flow of the extremity was measured by the venous isotope-dilution method by administration of ¹³¹I albumin [12]. The method enables the exact

determination of the total blood flow perfusing through the limb. The normal value of the limb blood flow, according to several hundred measurements, was 350 ± 50 ml/min [15]. Cardiac output was assessed according to the dye-

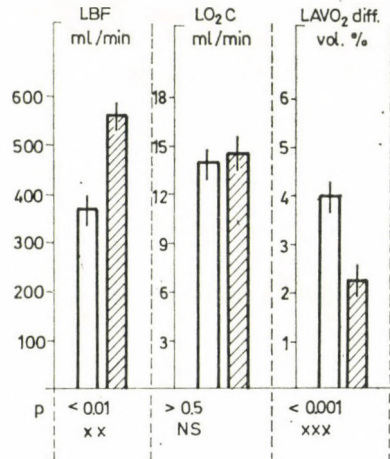


FIG. 1. Change in limb blood flow, O₂ uptake and arteriovenous O₂ difference in lymphoedema. LBF = total limb blood flow; LO₂C = O₂ uptake of limb tissues; LAVO₂ diff. = limb arteriovenous O₂ difference; Empty columns = values obtained in intact limbs. Cross-hatched columns = values obtained in lymphoedematous limb; *p* = value of statistical significance; x = significant changes: <0.05; xx = strongly significant changes: <0.01; xxx = very strongly significant changes: <0.001; NS = non-significant change

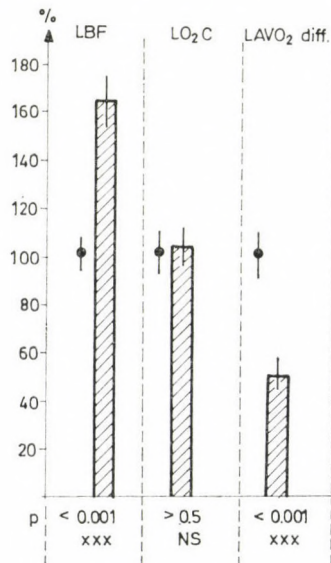


FIG. 2. Regulation of limb circulation in lymphoedema. The values obtained in lymphoedema of the extremities (limb blood flow, limb O₂ uptake, limb arteriovenous O₂ difference) were expressed in the percentage of normal values. The normal, average, values were taken as 100 (for abbreviations see Fig. 1)

dilution principle. The O_2 content of the arterial and venous blood of the limb was determined from the blood obtained by puncture of the femoral artery and vein. The O_2 uptake (consumption) of the tissues was calculated from the ratio of the blood flow and the arteriovenous O_2 difference. Perfusion scintigraphy

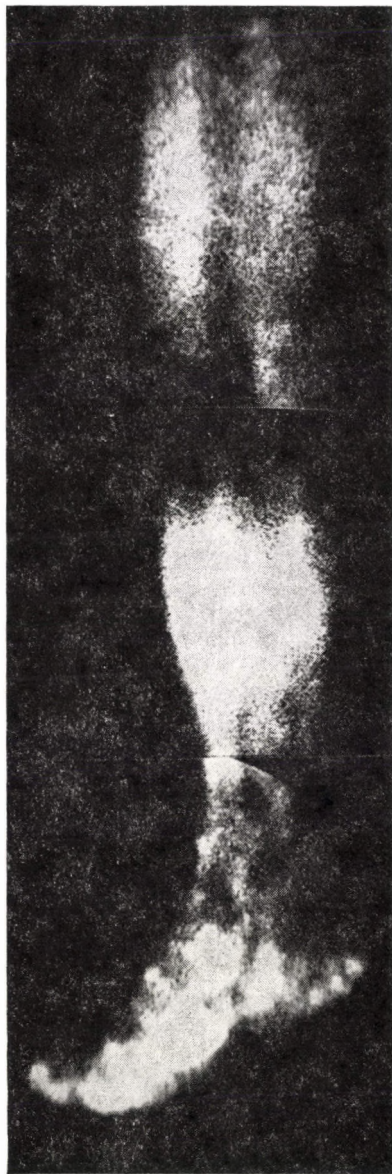


FIG. 3. Multiple arteriovenous shunts associated with unilateral—secondary—lymphoedema in the thigh, lower leg and foot. Perfusion scintiscan: In the regions of the thigh, knee, lower leg, ankle and the foot, there are spotty regions with no isotope accumulation (black areas) corresponding to the vascular regions with shunt

of the limb was used for visualizing arteriovenous shunts. Technetium serum albumin macroaggregate ($^{99}\text{Tc}^{\text{m}}$ -HSA MAA) was applied as tracer [14].

The results were analysed by Student's one- and two-sample *t*-tests.

Results

According to the flow studies of 10 unilateral lymphoedemas of the limb, the total blood flow in the lymphoedematous limb was high. The O_2 uptake of the limb tissues was normal and the arteriovenous O_2 difference in the limb was low. In the other intact limb, blood flow and the arteriovenous O_2 dif-



FIG. 4. Extensive arteriovenous shunts in the regions of the leg and foot in lymphoedema. Perfusion scintigraphy shows no isotope accumulation corresponding to the arteriovenous communications (black areas in the regions of the lower leg, ankle, dorsum and the sole)

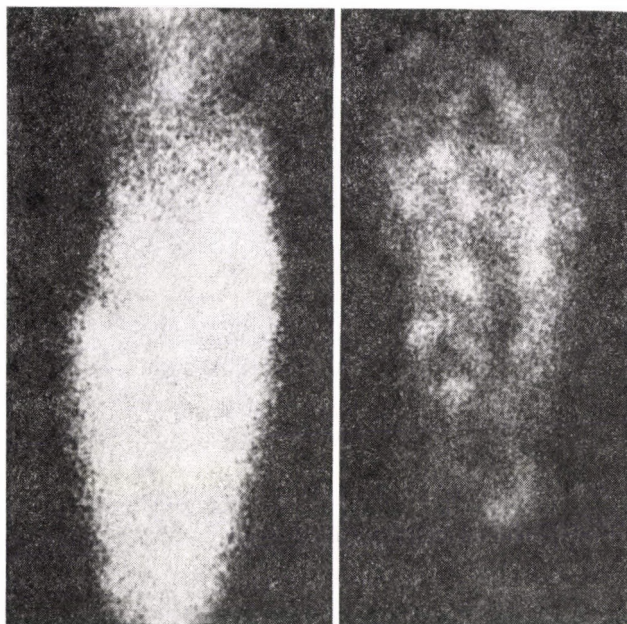


FIG. 5. Multiple arteriovenous shunts in a lymphoedematous limb. Perfusion scintigraphy from the regions of the healthy and lymphoedematous leg (unilateral lymphoedema). On the left, the scintiscan of the intact limb—leg—normal isotope accumulation (even isotope uptake) can be seen. The scintiscan of the lymphoedematous limb, on the right shows several black spotty areas (lack of isotope accumulation) corresponding to several arteriovenous shunts

ference of healthy circulation were normal. (According to studies made in 100 individuals, the normal values of limb blood circulation were as follows: blood flow = 360 ± 50 ml/min, O_2 uptake = 14.0 ± 0.5 ml/min, arteriovenous O_2 difference = 4.0 ± 0.5 vol%.)

Results of our studies are graphically shown in Fig. 1.

Further studies, made in 10 patients, with bilateral lymphoedema, the blood flow in the lymphoedematous limb was essentially higher than the normal value, the O_2 consumption of the limb tissues was normal, while the arteriovenous O_2 uptake was pathologically low. Results are demonstrated in Fig. 2, the values measured in the lymphoedematous limb being expressed in the percentage of the corresponding normal limb blood flow values. As controls the limb blood flow data of 35 individuals of similar age group, but not affected by vascular disease were used.

The regions of arteriovenous shunts were revealed by perfusion scintigraphy in 8 patients. Multiple arteriovenous shunts appearing in spotty areas could be demonstrated. Due to the arteriovenous shunts, part of the macro-aggregate-albumin injected into the femoral artery entered directly the venous circulation, and from here, it was transported to the lung capillaries. The simul-

taneously performed lung scintigraphy (similar to the routine scintigraphic picture) revealed isotope accumulation in the region of the lungs. Consequently no isotope accumulation occurred at the region of the arteriovenous shunts (no isotope entered these capillary regions). The empty-non-filling regions well indicate the vascular regions with arteriovenous communication. Figures 3 to 5 show characteristic scintiscans of lymphoedemas.

Discussion

As a result of lymphoedema, limb circulation shows considerable changes. It has long been known that, due to a chronic insufficiency of the lymph circulation, lymphovenous anastomoses can open. Such lymphovenous shunt-circulation does, however, infrequently occur in lymphoedema of the limb. In case if it develops, lymph flow through the lymphovenous communications directly into the venous circulation is insignificantly low [7, 11]. Studying limb blood flow, several authors found it to be normal or decreased [1, 10]. It is actually only the nutritive—capillary—limb blood flow which is normal in lymphoedema, the total limb blood flow being high. Esterley and Wood [2] found the arteriovenous O_2 difference of the limb to be low in congenital lymphoedema. Their observations were confirmed by our studies: in lymphoedema the blood of the femoral vein is relatively rich in O_2 (its O_2 content is higher), while the limb arteriovenous O_2 difference is low. This is suggestive, in itself, of arteriovenous shunt-circulation. Jacobson [4] observed high limb blood flow in the lymphoedema of the upper extremities following radical mastectomy. Our previous investigations showed [12] that, as a result of lymphoedema, limb blood flow increases and the arteriovenous O_2 difference is low. Because of the arteriovenous shunt-circulation, the cardiac output of such patients is, usually, higher than normal [12]. It is worth noting that, in animal experiments producing artificial lymphoedema, arteriovenous shunt pathways were shown using the India ink-gelatin injection method and the polyvinylchloride injection technique. It was found that in lymphoedema of the limb the nutritive—capillary—blood flow was normal [14].

Data of our present studies have proved that, due to lymphoedema, limb circulation considerably changes in the affected limb and multiple arteriovenous shunt-circulation develop. The total limb blood flow significantly increased, peripheral vascular resistance was low and the limb arteriovenous O_2 difference was amazingly small. The O_2 supply (O_2 uptake) of the tissues was normal (the nutritive—capillary—limb blood flow, too, remains normal). It should also be noted that, based only on clinical symptoms, several authors assumed the development of significant arteriovenous—short circuit—pathways in the lymphoedema of extremities [5, 6]. As shown by our perfusion scintigraphic

studies, due to lymphoedema, multiple spotty areas of arteriovenous shunts appear primarily under the knee.

The amount of blood circulating through the shunt pathways was, according to our measurements, on an average of 200 to 500 ml/s (calculated for one of the lower extremities). In case of unilateral lymphoedema, the limb blood flow of the healthy, contralateral limb is of normal size. In extensive arteriovenous shunts and in bilateral lymphoedema, due to arteriovenous shunt-circulation, cardiac output is enhanced, and the load of the heart also increases [13]. Concerning the mechanism of the development of arteriovenous shunt-circulation, the change in capillary circulation due to lymphoedema, the compression of the individual capillary pathways due to oedema and the aetiological role of local hypoxia can be supposed to be responsible [14]. It is noteworthy that in the lower extremities, arteriovenous shunts can develop due to permanently impeded venous circulation [3, 9, 18] as well as to obliterative peripheral arterial disease (8, 17).

In addition to the theoretical and haemodynamic specificities of the changes in limb circulation following lymphoedema, they also have several important clinical implications. Arteriovenous shunt-circulation arising in lymphoedema may impose an additional load on the heart and may thus lead to chronic cardiomegaly. In lymphoedema total limb blood flow markedly increases due to shunts but the nutritive blood, i.e. O_2 , supply of the tissues remains normal. This accounts for the fact that in lymphoedema, in contrast to venous thrombosis and peripheral arterial occlusion, despite the oedema, no tissue impairment and trophic disturbances of the limb occur. Finally, based on our experiments and clinical studies, it seems that the developing arteriovenous shunt-circulation is partially reversible and it may recede—mainly in lymphoedema of not long standing—as lymph stasis disappears. That is why attempts have to be made, in lymphoedema, to decrease lymph stasis as soon as possible (surgical correction, medication, exercise-massage). In a pre-vailing lymphoedema, attempts to ligate arteriovenous shunts are futile.

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Arteriovenöse Shuntzirkulation beim Lymphödem der Extremitäten

F. SOLTÍ, M. ISKUM, CS. BÁNOS und F. SALAMON

Beim Lymphödem der Extremitäten kommt arteriovenöse Shuntzirkulation zustande. In 28 Fällen mit einem Lymphödem der Extremitäten (primäres und sekundäres Lymphödem) wurden mit venöser Isotopen-Dilutionsmethodik und Isotopenszintigraphie der Extremitäten mit Technetium-Makroaggregat die Regelung des Extremitätenkreislaufes analysiert. Unter Wirkung des Lymphödems steigt die Extremitätendurchblutung (die totale Extremitätendurchblutung) an, die arteriovenöse O₂-Differenz der Extremitäten liegt niedrig, während die O₂-Aufnahme der Extremitätengewebe normal ist. Die Entwicklung der arteriovenösen Shunts (Mikro- und Makroshunts) kann mit Isotopenszintigraphie der Extremitäten direkt dargestellt werden. Da bei Lymphödem der Extremitäten die nutritive — kapilläre — Blutversorgung der Gewebe normal bleibt, treten keine trophischen Störungen auf. Zum Lymphödem der Extremitäten gesellt sich nicht selten ein ausgiebiger arteriovenöser Shuntkreislauf, womit parallel sich auch das Minutenvolumen und die Herzarbeit steigern.

Артерио-венозное шунт-кровообращение при лимфоотёке конечностей

Ф. ШОЛТИ, М. ИШКУМ, Ч. БАНОШ и Ф. ШАЛАМОН

При лимфоотёке конечности возникает артериовенозное шунт-кровообращение. Авторы в 28 случаях лимфоотек конечностей (первичный и вторичный лимфоотек) изучали регуляцию кровообращения в конечностях, пользуясь методикой венозной изотопной дилуции и методом сцинтиграфии конечности с макроагрегатом изотопа технеция. Под воздействием лимфоотек кровотоков в конечности (тотальный кровоток) возрастает, артерио-венозная O_2 -разница низкая, потребление же кислорода тканями конечности нормальное. Образование артерио-венозных шунтов (микро- и макрошунтов) можно непосредственно изобразить методом изотопной сцинтиграфии. При лимфоотек конечностей нутритивное — капиллярное — кровоснабжение тканей остается нормальным, благодаря чему трофические нарушения не развиваются. Лимфоотек конечностей нередко сопровождается довольно большим артерио-венозным шунтовым кровообращением, и в таких случаях минутный объем сердца и работа сердца повышаются.

Palliative Surgical Treatment of Inoperable Oesophageal and Cardia Tumours with Prosthesis

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During a 12-year period, 112 palliative surgical intubations were performed for nutritional inability due to tumours causing oesophageal stricture, tumours of the cardia and of the stomach unmanageable by anastomosis, and to that of the gastric stump. Surgical complications and mortality can be considerably reduced by careful preparation and practice. Palliative intubation is suitable for making the patient's normal nutrition possible and the rest of his or her life more endurable. The intervention is recommended to replace the bypass anastomosis incurring a great risk and gastrostomy producing several objective and psychic complaints.

With the advance of anaesthesiology, and the spreading of operations in the thoracic cavity, oesophageal surgery has made an amazing progress. Resection and substitution can be solved technically. A problem is still posed by the high ratio of patients with oesophageal tumours recognized in the inoperable stage, which, according to the statistics of Grewe [1, 12], fluctuates between 44 and 93%. According to Ong [29], resectability is less than 50%. For the nutrition of patients being unable to swallow, the creation of gastric fistula has been extensively used instead of the bypass anastomosis requiring a larger operation and subjecting the patient to a greater strain. To eliminate tumorous stricture, several attempts have been made [1, 2, 3, 4, 5, 6, 9, 12, 13, 20, 21, 23, 25, 34, 35] and various prostheses have been used. The advantage of prostheses can be evaluated only by someone who had the possibility to make gastrostomies and to compare the fate of these patients with that of the intubated ones. With a prosthesis the peroral nutrition of the patient is possible, he or she can feel the taste of the food and is not in need of using an aid (bladder syringe), thereby not becoming a social misfit.

Insertion of the prosthesis is made by two basic methods, by the endoscopic (EI) and surgical intubation (SI). At our department, the latter is performed and the obtained experiences are being reviewed.

Of the prostheses used by us the Celestin tube was found to be the most suitable for malignant strictures and this is currently in use as well.

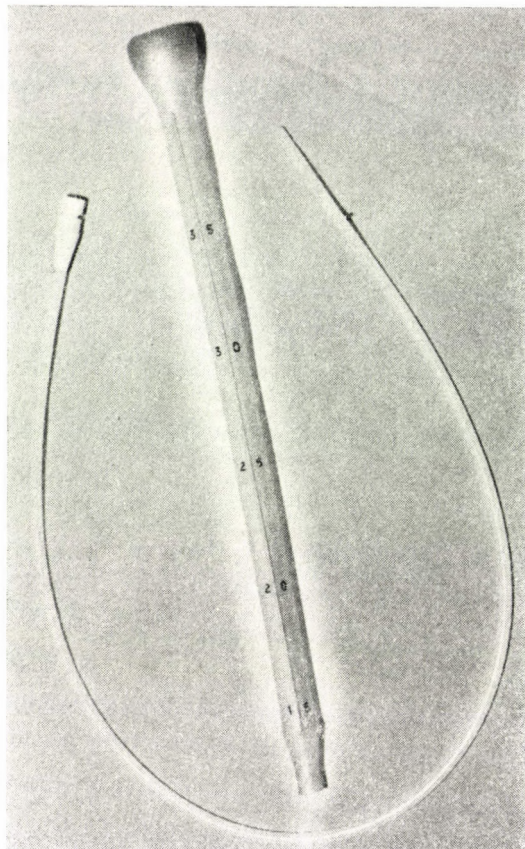


FIG. 1. Celestin tube and guide

The Celestin tube* provided with a cm calibration is 28.5 cm long, its upper end is calyx shaped. Its diameter is 15 to 13 mm, and it is made of latex reinforced by a flexible nylon spiral. Into the tube a dense fibre for X-ray examination has been built in. The accessory part of the tube is a guide made of synthetic material. Both are available sterile and packed in foil (Fig. 1).

Intubation was made in the strictures causing nutritional inability as seen below:

1. Inoperable oesophageal tumour (in cases of tumours harboured in the upper third of the oesophagus where the rim of the tube disappears in the lumen of the oesophagus, otherwise it would cause a respiratory obstacle).
2. Oesophagotracheobronchial fistula.
3. Inoperable cardia tumour.

* AMBLELETIN LTD, P.O. Box 1, Tetbury, Glos., GL 8 STL, England

4. Inoperable stenosing gastric or gastric stump tumour if GEA cannot be performed.

5. In some cases of benign strictures.

If is technically easy to insert the tube, it can be performed at any institute. It is still advisable to perform at a department where radical oesophageal operation can also be made, because inoperability can, not once, be decided only intraoperatively. In case of a doubtful operability, thoracotomy and after explorative laparotomy are performed corresponding to the localization of the tumour. In cases of cardia tumour and in those found to be inoperable on physical examination, only laparotomy was performed. The guide attached to the tube is introduced into the stomach by the anaesthesiologist or the physician controlling the endoscopy. In case it fails, a laryngological bougie is applied and being attached to it, the tube is introduced. It occurred that a thin Boas tube could be more easily introduced as a guide incurring

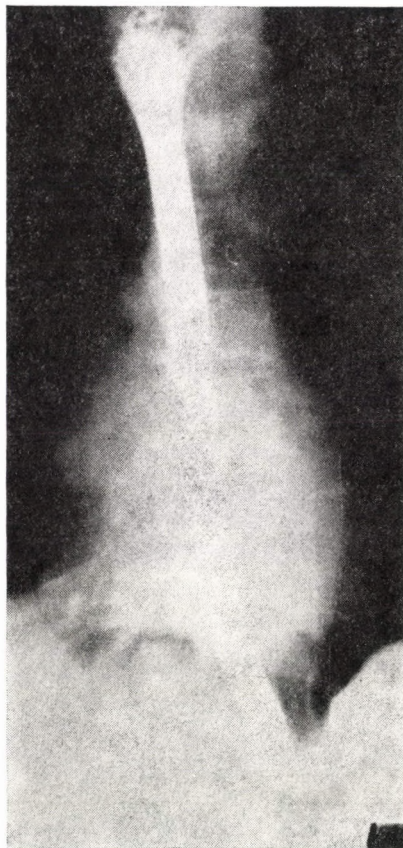


FIG. 2. Celestin tube introduced due to inoperable tumour at the border of the upper and mid-portions of the oesophagus

a smaller risk of perforation. If these attempts happen to be unsuccessful, the stomach is opened and introduction of the guide, with the tube being attached, can be attempted from the side of the cardia, after it has been pulled through the tumourous territory and the mouth. The tube should be positioned so that its funnel-like end be elastically fixed to the tumour with its rim on the intact oesophageal portion above the tumour. This is of primary importance also in fixing the tube, therefore without endoscopic control blind introduction is not recommended. Then the distal part of the tube is shortened to fit its place, paying attention to that its end should not touch the gastric wall thereby producing decubitus. Two threads are tied to the gastric portion of the tube pulling them out through the gastric wall and covering them with serosa. This fixation, if the threads are not tightly knotted, will not cut through and will ensure the fixing in place of the tube for a long time (Fig. 2). For preventing regurgitation of the gastric content, a thumb-stall with a cut end is fixed, in several cases. This was found not to be specially advantageous, however. Regurgitation or vomiting could be prevented even without it if the patients were lying with their heads in a higher position during sleep. If a patient with the Celestin tube threw up, the tube became clogged. The obstruction was caused by neglecting lating prescriptions (chewing of the food thoroughly, keeping a pulpy-liquid diet, fluid consumption during meals) and mostly by the swallowing of pieces of meat. With one exception, these could be removed endoscopically and the tube could be cleaned. Postoperative treatment does, otherwise, not differ from that of patients operated by opening of the stomach.

Patient Material, Results

In the period between 1972 and 1983, a total of 112 intubations were performed in 104 patients at our department. Of them 86 were males and 18 females, with an age range of 38 to 85 and with an average age of 63 (Table I and II). Intubation for nutritional inability was made, in 56 cases, because of inoperable tumour of the oesophagus associated, in 4 cases, with oesophageal fistula. Intubation was performed in 40 cases because of the tumorous stricture of the cardia region, in 4 cases of that of the stomach, gastric stump and of the anastomosis, respectively. Four patients were intubated due to benign strictures (Table IV).

TABLE I
Sex distribution of the patients

Year	No. of patients	Male	Female	No. of intubations
1972–1983	104	86	18	112

TABLE II
Age distribution of the patients

No. of patients	Age in 10-year periods					
	31—40	41—50	51—60	61—70	71—80	over 81
104	2	6	28	37	30	1

TABLE III
Indications of insertion of prosthesis

Inoperable oesophageal fistula with oesophagotracheobronchial fistula	52 4
Inoperable cardia tumour	40
Inoperable tumour of the stomach unmanageable by anastomosis, tumours of the gastric stump and of the anastomosis	4
Benign oesophageal stricture	4
Total	104

*

TABLE IV
Site of tumorous or benign stricture

Localization		No. of patients
Oesophagus	upper segment	8
	mid segment	24
	lower segment	28
Cardia region		40
Stomach, gastric stump anastomosis		4
Total		104

For bridging of inoperable tumours and of those constricting stomach unmanageable by anastomosis, of gastric stump or anastomosis, instead of oesophagojejunostomy exposing the patient to a greater strain, or of jejunostomy putting him or her to great inconvenience, the Celestin tube was introduced in 1979 at our department and has been used so far. Two to three lateral openings are made in the gastric portion of the tube, with its funnel-like end resting on the cardia. Its end led into the duodenum, or the efferent loop is fixed to the intestinal wall (Fig. 3). (These cases are dealt with in details in other reports.)

Because of benign stricture, Celestin tube was introduced in 4 cases.



FIG. 3. Use of the Celestin tube for bridging an inoperable gastric tumour unmanageable by anastomosis with the duodenum

The oesophageal strictures, due to reflux oesophagitis of the male patients H. P. (aged 70) and Z. I. (aged 75) were unsuccessfully dilated. Their general state did not make the radical thoracoabdominal operation possible, therefore they were intubated.

The oesophageal stricture of S. Gy., a female patient, aged 74, was diagnosed by endoscopy to be malignant. Her general state contraindicated radical operation, consequently intubation was performed. She died due to myocardial infarction three days after the operation. At autopsy, no tumour was found in the oesophagus, the morphological picture offered no proofs on the origin of the stricture. The portal lymph nodes were metastasized by anaplastic carcinoma but with no primary tumour.

F. S., a male patient, aged 54, had a history of oesophageal stricture after swallowing caustic soda in his childhood. The stricture had been dilated

several times. In another institute he was operated two years ago for malignant goitre. Due to paresis of the recurrent laryngeal nerve, tracheostomy was performed. At the department of laryngology, on additional dilation of his oesophageal stricture, his oesophagus was perforated which was treated conservatively at our department. On the third day after perforation an operation had to be performed due to massive gastrointestinal haemorrhage. Bleeding arose in a duodenal ulcer, of a diameter of 2 cm, penetrating into the pancreas. Billroth II resection was performed and the stricture of the oesophagus was bridged by the Celestin tube. After operation empyema developed in the right thoracic cavity which healed as a result of drainage and suction. Presently his nutrition is undisturbed.

EI and SI can be associated with various complications, using the endoscopic procedure, though only slighter infectious complications may occur. As a result of using mostly rigid tools, and of dilations, perforations are more frequent [3, 10]. Dislocation, dislodgement of the usually more slender tubes being unfixed more often occur, and reintubation is not without complications either [1, 2]. The mortality rate of EI has been reported to be 0.6 to 25% [1, 2, 4, 10, 16, 23, 28].

According to literary data [2, 14, 19, 23, 26, 38], complications of different degrees of severity associated with SI occur in 20 to 60%. In our cases, there were no significant differences in the number and quality of complications developing after 104 intubations and 8 reintubations. So these are discussed together based on 112 operations. The first and second half of our operations (56 operations each) are evaluated also separately, because, according to our experiences, the number and severity of complications (Table V), and the mortality (Table VIII) have considerably decreased in the second group.

Intraoperative perforation occurred in two cases. In both of them, the oesophageal-cardia tumour was perforated by the guide in the direction of the abdominal cavity. After being sutured and covered by the omentum, both of them healed without complications. Of the three cases of thoracic empyema two could have been the consequence of the perforated tumour located in the thoracic portion of the oesophagus which escaped detection during the operation. In the third case, mentioned earlier (F. S. 54, male) empyema was the result of perforation occurring during dilation of the oesophagus three days earlier. Perforation caused by the tube occurred in one case. The patient did not consent to the removal of the tube that had slipped into the stomach. He consumed liquid and pulpy food. Three months after dislocation of the tube, the patient was hospitalized in the terminal stage, and died. At autopsy, the tube was found in a fixed position in the newly developed, gastrocolic fistula. In our second case, perforation was not caused by the tube. The 66-year-old patient had a history of Billroth II resection, due to duodenal ulcer having developed 13 years ago, of vascular stenosis for 10 years, ileofemoral

TABLE V
Postoperative complications

Complication			After the 1st 56 operations	After the 2nd 56 operations	Total
Pneumonia			14 (25%)	8 (14.3%)	22 (19.6%)
Pulmonary embolism			3	1	4
Thoracic empyema			2	1	3
Circulatory failure			1	2	3
Infarction			—	1	1
Hepatic failure (cirrhosis)			1	—	—
Intra-operative perforation			2	—	2
Post-operative perforation			1	—	—
Haemorrhage			2	—	2
Disruption of the abdominal wall			2	—	2
Suture insufficiency of the stomach			4	2	6
Infection	in the abd. cavity	diffuse	3	—	3
		circum- scribed	2 (8.9%)	2 (3.5%)	4 (6.2%)
	in the abd. wall		20 (35.7%)	12 (21.4%)	32 (28.5%)
Tube	dislocation clogging		7 (12.5%)	1 (1.7%)	8 (7.1%)
			—	1	1

The individual complications occurred in association with each other.

bypass for two years, of swallowing complaint for 4 months and of vomiting and loss of weight. There was a constrictive tumour on the oesophagus starting at a distance of 37 cm from the dentition, involving the cardia. Ultrasonography was suggestive of metastasis of the liver. A prosthesis was inserted. The patient died due to cardiopulmonary insufficiency eight days postoperatively. At autopsy, adjacent to the tumour, an infracardially perforated callous peptic ulcer was revealed communicating with an encapsulated abscess, of a diameter of 3 cm, attached to its environment. This could have been present at the time of the operation, but no adhesiotomy around the tumour was performed, the ulcer and the abscess were not diagnosed, it was thought to be a tumorous change. The immediate cause of death was confluent bronchopneumonia.

Excessive bleeding requiring transfusion occurred in two cases.

The pulmonary complication usually of aged patients with difficulty in swallowing is frequent even after thorough preparation. In our cases a total of 22 (19.6%) patients was affected in 14 cases (25%) after the first 56 operations, while in 8 cases (14%) following the second series of 56 operations after a more adequate preparation.

In two cases, the abdominal wall disrupted. Suture insufficiency of the stomach occurred in 6 cases, in 2 of them with diffuse, in 4 with circumscribed, consequential peritonitis, one case of subdiaphragmatic abscess, and three cases of suppuration localized to the upper part of the abdominal cavity, were encountered. Suppuration of the abdominal wall occurred in 32 case. These were not too serious but, nevertheless, prolonged the time of nursing. The number of these infectious complications, of both the more severe one of the abdominal cavity as well as of the milder suppuration of the abdominal wall decreased significantly in the second group of our operations. This can be less attributed to routine than to the presurgical preparations recently made. In the emaciated organism the gastric content often of anacid mixed bacterial flora may easily cause infection on opening of the stomach or at fixing of the tube even with careful isolation. In prevention patients capable of drinking fluid are given hydrochloride pepsin, 3×2 tablets of pulverized Klion* (500 mg metronidazole) for three days prior to the operation, 1.5 g Neomycin on the day before the operation and 80 mg Gentamycin right before the operation.

Among the other complications, circulatory failure occurred in two cases, myocardial infarction in one, pulmonary embolism in four and hepatic failure in a cirrhotic patient in one case.

As later complications, of the tubes inserted in the first half of the operations 6 dislocated because of tumour. After two years one tube introduced due to benign stricture, six toward the stomach and two toward the pharynx.

TABLE VI
Reoperations

Indication	Operation	After 1st 56	After 2nd 56	Total
	Early			
Disruption of the abdominal wall	resuturing	2	—	2
Suture insufficiency,	exposure,	5	1	6
infection of the abdominal cavity	drainage			
Thoracic empyema	suction, lavage	2	1	3
	drainage			
	Late			
Dislocation of tube	removal,	6	1	
Clogging of tube	reintubation	—	1	8
Paresis of recurrent nerve	tracheotomy	1	—	1
Total		16	4	20

* Chemical Works of Gedeon Richter, Budapest

TABLE VII
Mortality rates of surgical intubation

Author	No. of cases	Mortality rate, %
Gallagher et al.	9	11
Duvoisin et al.	95	14
Johnson et al.	11	18
Angorn	90	20
Das and John	60	20
Kohaus et al.	22	20
Häring et al.	59	23.7
Nüllen et al.	52	27
Amman and Collis	17	30
Saunders	105	30

The dislodged tubes were removed and replaced by another one. One patient did not consent to the removal of a tube having slipped into the stomach. One tube had to be exchanged for a new one due to clogging.

After operation and resuturing due to disruption, early reoperations were performed in two cases, exploration and drainage due to empyema in three cases. Late reoperation, removal of the dislocated tube and reintubation were made in 7 cases. One patient's tube was clogged by his drugs taken in tablets. It could not be cleaned, and had to be removed and replaced by a new one. Because of paresis of the recurrent nerve due to tumour propagation, tracheostomy was made in one case (Table VI).

According to the literary data, the operative mortality of SI [1, 2, 7, 8, 9, 19, 20, 27, 33] is 11 to 30% (Table VII). The most frequent cause of death is the infectious complication. In our cases a total of 25 (22.3%) patients died, of them 10 died due to infection (16.1%) and 6 (5.2%), as a result of other complications. After the first series of 56 operations 19 (33.9%), while after the second one of 56 operations 6 (10.7%) patients died. The 26.7% mortality rate (15 patients) of the first group due to pulmonary, thoracic and abdominal infections decreased, in the second group to one of 7.1% (4 patients) with a more thoroughgoing respiratory and with the above-mentioned surgical preparation applied in the majority of patients (Table VIII).

The average nursing time of the patients was 29 days. In complication-free cases, they were dismissed from hospital on the 8th to 10th day. Nineteen per cent of the patients died within 3, while 43% within 6 months. The longest survival time in malignant stricture was 18 months. During this time the swallowing ability of the patients was good in 91%, satisfactory in 7% and bad in 2%, these latter could only take fluid. In some cases the obstruction due to inadequate food could be eliminated by endoscopic removal or cleaning. The tube had to be removed and replaced by a new one for this reason only in one case.

Discussion

In case of advanced inoperable stricture of the oesophagus and in cardia carcinoma parenteral feeding, bypass anastomosis, gastric fistula and intubation can be explored for nutrition. Parenteral feeding cannot be sustained for a long time and it can be considered only in patients of the most severe condition. The mortality rate of bypass anastomosis that exposes the patient to a great strain is 60% and often the result is unsatisfactory [32, 37]. Beside the fact that nutrition has objective and psychic implications, the gastric fistula does not solve saliva aspiration, dysphagia and the inability to swallow. In the rest of the patients' life, insertion of a prosthesis seems to be a less risky and the most suitable solution ensuring the possibility of normal nutrition. Since the introduction of the procedure both the tubes and methods of insertion, that is EI and SI with opening the stomach have been considerably modified.

The various complications due to EI occurred in 26%, with a mortality rate of 0.6 to 25% [1, 2, 4, 10, 16, 23, 28]. As a result of intubation and of dilation perforation was more frequent [3, 10], mainly in the lower segment, therefore this technique is primarily used in tumours of the upper and middle parts of the oesophagus [1, 2, 8, 10, 33]. Bueß et al. [4] performed, however, the endoscopic introduction of the Celestin tube under X-ray guidance, with a mortality rate of 33.2% in the proximal part, and with one of 5.5% in the distal part in case of cardia tumours. The usually thin, unfixed tube introduced endoscopically is dislodged more easily (6 to 22%), reintubation is to be performed more often. On the other hand, it is not associated with wound infections which occur in 20 to 66% as a consequence of laparotomy and of opening

TABLE VIII
Mortality rates, causes of death

Causes of death	Died after the 1st 56 operations	Died after the 2nd 56 operations	Total
Suture insufficiency peritonitis	8 (14.2%)	1 (0.9%)	9 (8%)
Subphrenic abscess	1	—	—
Thoracic empyema	1	1	2
Pneumonia	5 (8.9%)	2 (3.5%)	7 (12.5%)
Pulmonary embolism	1	—	1
Circulatory failure	2	1	3
Myocardial infarction	—	1	1
Hepatic failure (cirrhosis)	1	—	1
Total	19 (33.9%)	6 (10.7%)	25 (22.3%)

of the stomach [4, 15, 19, 27, 31, 33]. Both procedures are often associated with bronchopneumonia. In the complication-free cases of EI only little, i.e. 2 to 3 days, of nursing are required.

The 112 SI of our patients were made in 90% by the Celestin tube. In tumorous cases favourable results were obtained. In our cases, there occurred no oesophagus deviation, and compression due to inoperable pulmonary tumour, the straightening and bridging of which are recommended by Kotsis et al. [21, 22] in their modified surgical intubation to be performed by a tygon tube of a more rigid wall. The cracking, compression and the damage of the wall of the flexible Celestin tube and the resulting nutritioinal disorder and perforation [25, 30, 34] did not occur in our tumorous cases during their survival. The only perforation in a patient who did not consent to removal of his tube having slipped into the stomach 5 months after introduction was caused by an intact tube having become fixed in the gastrocolic fistula as revealed by autopsy 3 months later. Z. I., a 75-year-old male patient, whose intubation had been performed because of benign stricture due to reflux oesophagitis, could excellently take food for two years, and had no complaints suggestive of reflux. His difficulty in swallowing started two to three months before his re-admission. On examination, the Celestin tube was found to have slipped

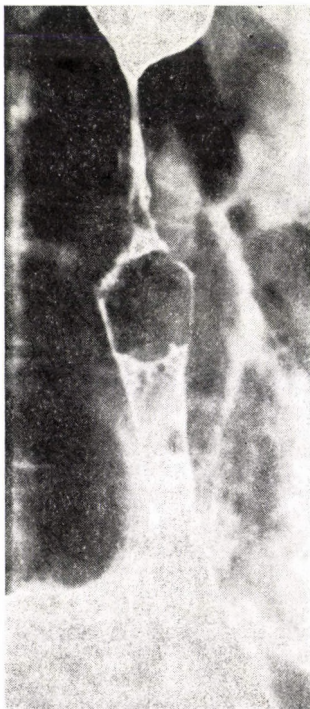


FIG. 4. Celestin tube having slipped into the benign stricture 27 months after intubation

down into the stricture (Fig. 4), it was removed and replaced by another one. The latex wall of the removed tube was damaged in some places, the nylon spirals were lying free. In our tumorous cases, the longest survival time was 18 months, during this period no destruction of the tubular wall was observed. In case of a survival time expected to be longer, so, first of all, in intubation performed exceptionally in benign stricture, a tube with a more resistant wall seems to be more suitable.

The general state of mostly aged, tumorous patients having been unable, for a longer time, to adequately eat and with a difficulty to swallow predisposes to various complications. The most frequent complications of SI are bronchopneumonia and wound infection. The operation mortality is 14 to 30% [1, 2, 4, 7, 8, 9, 15, 19, 20, 27, 31, 33]. The complications and the mortality rate can be significantly reduced by a careful preparation. This is shown by our patient material, where, with a more intensive general preparation (fluid, electrolyte, protein deficiency, etc.) and with techniques preventing primarily wound and respiratory infections, the number and incidence rate of bronchopneumonias decreased from 25% to 19.6% in the second half of the operations. During the same period infections of the abdominal cavity decreased from 8.9% to 3.5%, the suppuration of the abdominal wall from 35.7% to 28.5% and the mortality rate from 33.9% to 10.7%. Experience and practice helped in achieving more favourable results as shown by the reduced number of dislodged tubes being 7 in the first half, while only one in the second half of the operations.

The guide for intubation could, in each case, be passed through the tumour. If it was not possible orally then from the direction of the stomach. Failure with SI infrequently occurs [2]. The tube was, in each case, passed through the cardia and its function was blocked. Some authors [21] consider it more favourable—because of a possible reflux—to insert the tube, in case of a tumour harboured in the upper oesophageal segment, only into the oesophagus and to preserve the function of the cardia. In our cases reflux causing complaints was not observed, however, with an adequately long portion in an adequate state of the distal part of the tube in the stomach being fixed, it will remain in place for a longer time, it will not be dislodged, its end will not injure or perforate the gastric wall. During control period 91% of the patients could take normal, 7% pulpy and 2% liquid food.

According to the literature, there are more complications and a higher mortality rate after SI than following EI, although varying between wide limits. The advantage of SI is that it can be performed in almost every case with fewer perforations during intubation, the fixed tube becomes much less dislodged, remains in place for a longer time and ensures better nutrition. The marked differences in the results arise not only from the patient material but from experiences, practice and, last but not least, from preparation. In

view of this, the surgical complications, the mortality rate can be reduced, but not avoided. This means a compromise with the disease, but it does not contraindicate the operation in order to ensure the normal nutrition of these patients and to make the rest of their life more endurable.

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Palliative chirurgische Behandlung inoperabler Ösophagus-Kardia-Tumoren mit Endoprothese

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Im Verlauf von 12 Jahren wurden wegen durch inoperable, stenosierende Ösophagus-, Kardia-, zur Anastomose ungeeigneten Magen- und Magenstumpftumoren verursachter Ernährungsunfähigkeit 112 palliative chirurgische Intubationen durchgeführt. Durch sorgfältiger Vorbereitung und chirurgischer Gewandtheit kann die Zahl der postoperativen Komplikationen bzw. der Mortalitätsrate wesentlich herabgesetzt werden. Die palliative Intubation ermöglichte die normale Ernährung der Patienten und half ihnen ihr Leid etwas leichter zu ertragen. Anhand der vorteilhaften Erfahrungen wird die Anwendung des chirurgischen Verfahrens anstatt der mit großem Risiko verbundenen umgenenden Anastomosen und der zahlreiche objektive und psychische Beschwerden verursachenden Magenfistel empfohlen.

Паллиативное хирургическое лечение эндопротезом неоперабельных опухолей кардии пищевода

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Авторы за 12 лет произвели 112 паллиативных хирургических интубаций, так как больные не могли питаться вследствие наличия у них неоперабельных, сужающих пищевод и кардию, непригодных для анастомоза опухолей желудка и культи желудка. Операционные осложнения и летальность удалось значительно снизить тщательной подготовкой к операции, приобретением практики. Паллиативная интубация пригодна для того, чтобы, обеспечив таким больным возможность нормально питаться, сделать терпимыми оставшиеся годы жизни. Основываясь на благоприятных результатах применения этого метода, авторы рекомендуют его вместо операции анастомоза, которая сопровождается большим риском, и фистулы желудка, вызывающей психические жалобы.

Restoration of Skin Defects with Fibrin Glue

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After experiments with absorbable bioplasts for substitution of skin defects, this time the absorbable fibrin glue named Tissucol was used by the authors. The experiments on 22 dogs unanimously proved that, beneath the layer of tissue adhesive, scarring occurred free of inflammation as compared to the controls where inflammatory phenomena were not excluded. The procedure has been found good and useful in high-degree burns and injuries up to their final management.

Introduction

In skin defects occurring after serious burns or other traumata, the most urgent life saving task is to substitute the arising skin defects. For this purpose earlier various absorbable synthetic materials, bioplasts, were used with the thought in mind that final, permanent skin substitution can be expected exclusively by using autologous skin graft or that gained from monozygotic twins [1, 2, 3, 4, 5, 6]. The bioplasts used for this purpose were gelatinous fibrin [3, 4, 5] or absorbable synthetic materials made of cellulose. Their mutual properties were elasticity and plasticity, but they were not liquid and could, as a result, not perfectly and promptly adjust to the wound surface only after becoming wet.

Method

Attempts were made to find a material which immediately adjusted perfectly to the wound surface, moreover it even stuck to it. The fibrin glue Tissucol® (Immunol AG, Wien), being an absorbable tissue adhesive proved to be adequate for this purpose.

Despite that the directions for use of Tissucol can be found enclosed to the preparate, a brief survey is given here. Basically it is a material made of two components, a part of which is in a lyophilized state, being composed of 75 to 115 mg of protein capable of sticking. Out of this fibrinogen is 70 to 110 mg, plasmafibrinectin (CIG) is 2 to 9 mg, factor XIII is 10 to 50 U, plasminogen is 20 to 80 µg, aprotinin solution (bovine) a is 3000 IU/ml, lyophilized

thrombin 4 IU, thrombin 500, lyophilized (bovine) 500 IU and calcium chloride solution is 40 mmol CaCl_2 /l. Enclosed one may find a double syringe provided with a DUPLOJECT ending together with needles. The material should be stored at $+2$ and $+8^\circ\text{C}$ when used should be warmed in a water bath to 37°C . Although the fibrin film earlier used by us has proved suitable for this purpose, Tissucol is more adaptable for substituting skin defects, because it is used in liquefied form, thus closing the wound hermetically. It sticks to the wound and the thickness of the layer can be regulated according to the user's intentions. Otherwise, the problem of skin substitution is, also currently, a matter of great concern, proved by the large number of publications, reports and monographs on the subject [7, 8, 9, 10, 11].

In our experimental studies 22 mongrel dogs of both sexes were used with simultaneous control of each experiment, to be able to judge them objectively. The back of the dogs under sodium hexobarbital anaesthesia was shaved and the skin was removed in its entire thickness over two 4×4 cm surfaces. The skin was untouched at a distance of 5 cm between the two 4×4 skin defects. The cranial skin defects of three simultaneously operated animals were covered with the fibrin glue, while the caudal skin defects were covered with a gauze swab smeared with simple sterile boric acid ointment. After setting of the fibrin glue, the region smeared with the glue was covered in the same ointment. With maximal sterility, the animals were bandaged in a way that they were unable to discord or rub off the bandages. They were observed for a certain period and a new bandage was applied if it became necessary due to observation or to any other causes.

Results

The animals tolerated the operation well, they did not become too restless even after awakening. Suppuration did not occur at the site of the skin defect covered with fibrin, while it did, however, in most of the cases when vaseline was used. The dogs, were fed a mixed diet, their fluid consumption was not limited and they were sacrificed after two to five weeks. On the sixth week the skin defect of animals treated with fibrin glue disappeared and the animals killed subsequently on the 8th day could not be evaluated histologically.

Each experimental animal was examined histologically. The 22 animals were sacrificed according to the following grouping and dates.

Sacrificed on the 10th day	2 animals
Sacrificed by the 2nd week	4 animals
Sacrificed after 2.5 weeks	2 animals
Sacrificed after 3 weeks	4 animals

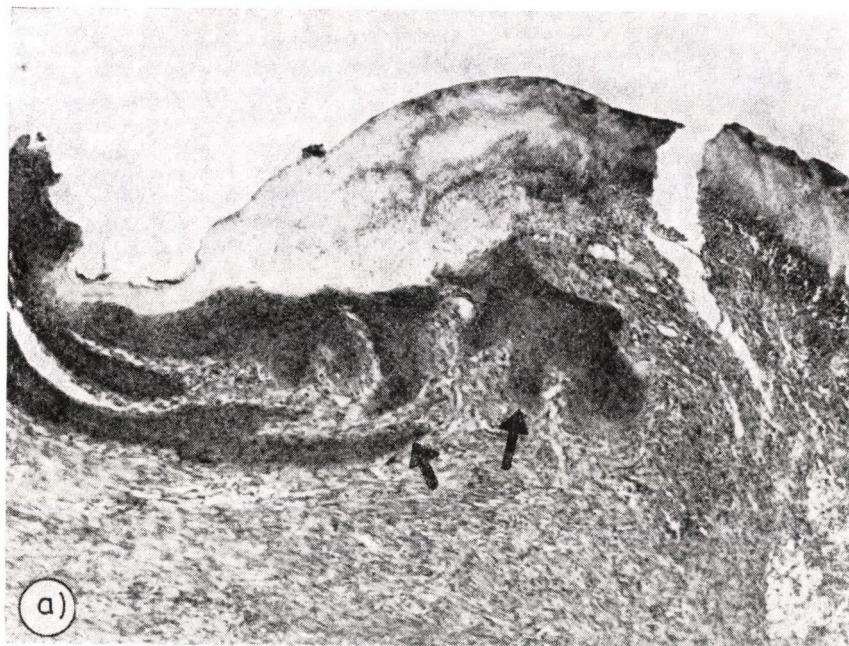


FIG. 1a. Two-week state



FIG. 1b. Control after two weeks, $\times 20$

Sacrificed by the 4th week	4 animals
Sacrificed by the 5th week	4 animals
Sacrificed by the 8th week	2 animals

Since, the glue exceeded in a 3 mm strip the site of the skin defect, the closure of the wound could be considered to be adequate and it ensured a complete protection. The same, however, could not be said, in case of the bandage impregnated with boric acid ointment, when the exogenous infection produced a purulent wound, although during dressing of the wound, sterility was maintained.

The results of the investigations were illustrated by photographs prepared from the histological sections. The figures were designated as *a* or *b*, *a* standing for fibrin-treated and *b* for non-fibrin-treated skin defects. Sections were stained with haematoxylin-eosin.



FIG. 2a. 2.5-week state

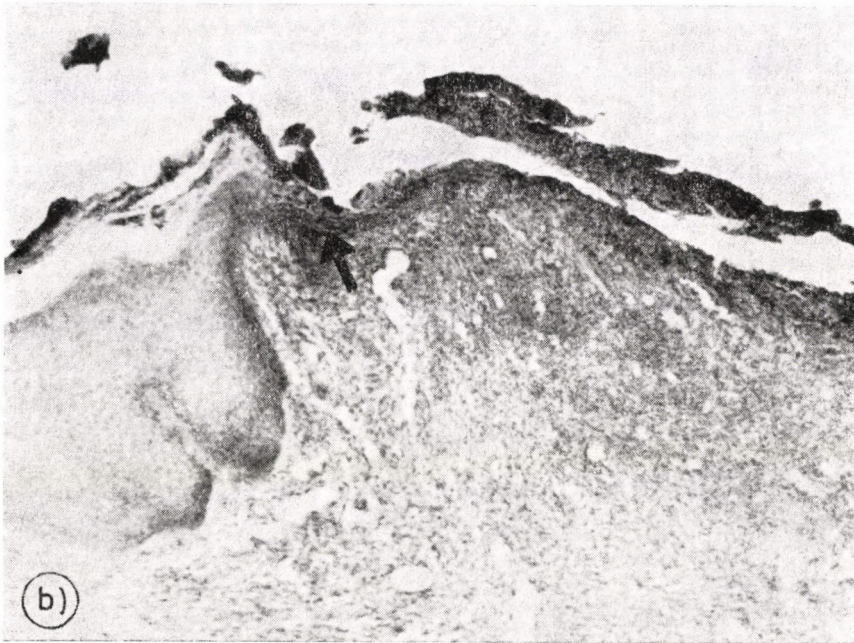
FIG. 2b. Control after 2.5 weeks, $\times 20$

Figure 1a shows the two-week stage. On the surface the scab is composed of a thick necrotized layer, containing also fibrin. This layer is sharply demarcated by the intact connective tissue underneath it. Beneath the fibrin, the epithelization has started. The epithelium is indicated in each figure by arrows.

Figure 1b: Control after two weeks. At the edge of the wound surface there is a weak epithelization. Subepithalially and involving the entire wound surface, an expressed inflammatory infiltration can be found with scar tissue formation underneath.

Figure 2a: At the stage after two-and-a-half weeks, there is an advanced epithelization over the surface. The wound surface is covered by a thick scab with a thickly infiltrated fibrin layer beneath it. Underneath there is an inflammation-free scar tissue. The fibrin layer practically protects the deeper layers from the inflammatory reaction. At the border between the fibrin and the connective tissue, the epithelization is clearly observable.

Figure 2b: Control after two-and-a-half weeks. On the surface there is a scab composed of a thin necrotic tissue. The epithelium has crept over the marginal portion, but the whole region is deeply infiltrated by inflammation.

Figure 3a: Three-week material. There is a scab formed of necrotized tissue, with a fibrin layer covering the wound surface underneath. Beneath the fibrin there is mostly epithelium with papillation, in some places. The connective tissue under the epithelium is free of inflammation.

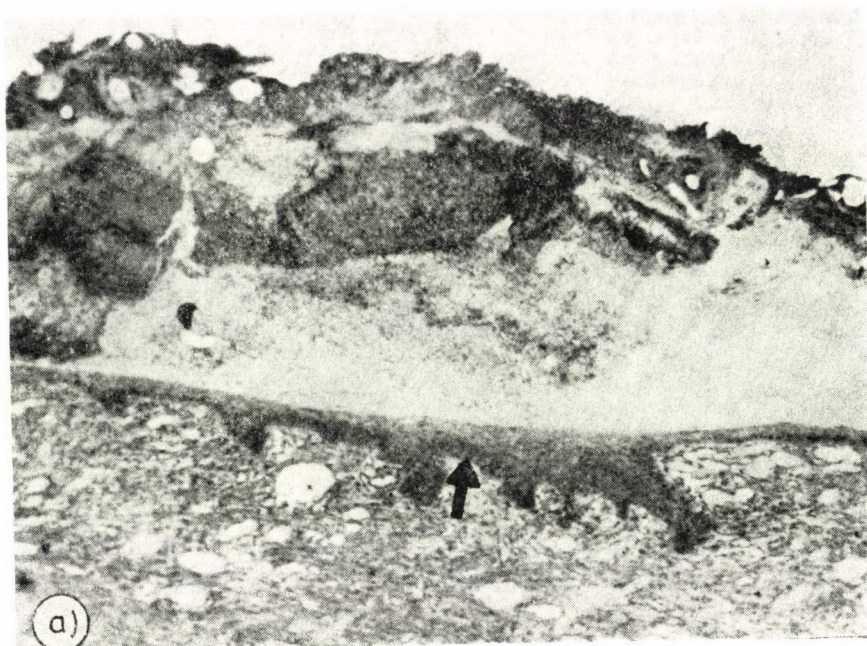


FIG. 3a. Three-week material

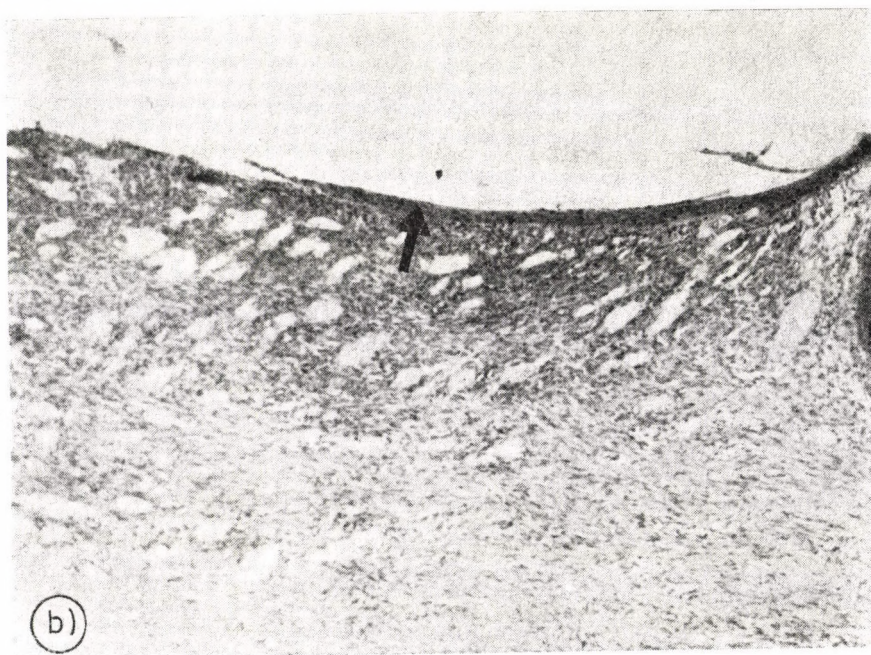


FIG. 3b. Control after 3 weeks, $\times 20$

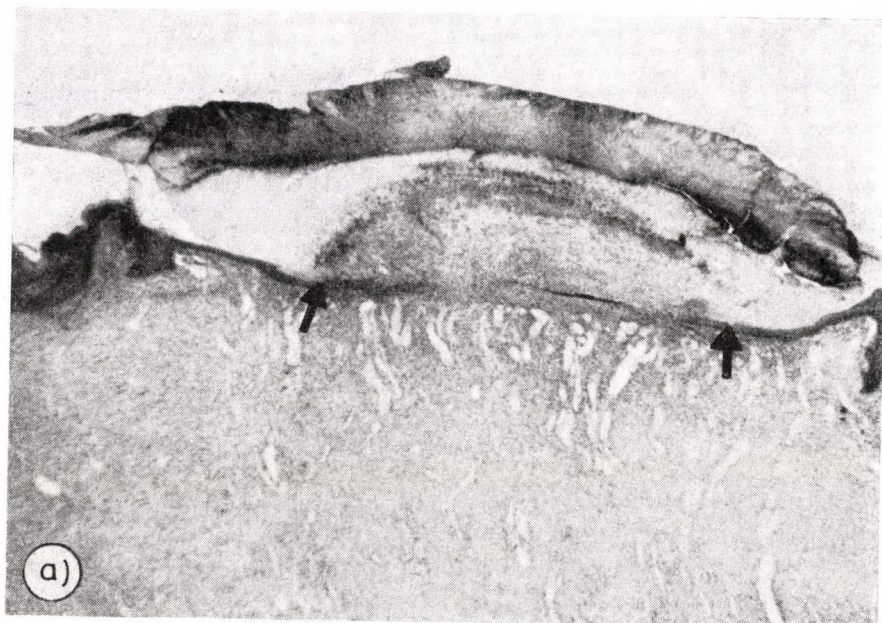


FIG. 4a. Four-week material



FIG. 4b. Control after 4 weeks, $\times 8$



FIG. 5a. Five-week state

FIG. 5b. Control after 5 weeks, $\times 8$

Figure 3b: Three-week control. A large portion of the surface has epithelized. In the mid-region with missing epithelium, but also subepithelially, an inflammatory, strongly infiltrated connective tissue is present.

Figure 4a: Four-week material. Above the light fibrin layer there is a thick layer of scab. Underneath the fibrin epithelium has crept over the inflammation-free connective tissue covering almost the entire wound surface.

Figure 4b: Control after 4 weeks: On the surface a scab composed of necrotized tissue and necrotized leucocytes can be seen with the epithelium creeping underneath it laterally. Under the scab the connective tissue is still infiltrated by inflammation.

Figure 5a: Stage at five weeks. The surface has completely healed covered by a relatively thick papillated epithelium showing keratinization. The accessory components of the skin, i.e. the hair follicle, the sebaceous and sweat glands, are missing.

Figure 5b: Five-week control: A thinner skin of more compact structure has formed then in the cases treated with fibrin. Its surface is covered by a thin, homogeneous epithelium. The accessory components of the skin are here, too, absent.

Discussion

It appears that, in comparison to earlier experiments with bioplasts, which were considered to be successful, the fibrin glue provides a better closure of the wound, producing a better, inflammation-free epithelization than the control and than the earlier experiments along this line.

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Bedeckung von Hautdefekten mit Fibrinkleber

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Nach den früheren mit resorbierenden Bioplasten durchgeführten Hautersatzversuchen, kam diesmal der sich resorbierende Fibrinkleber Tissucol zur Anwendung. Die bei 22 Hunden durchgeführten Experimente haben es eindeutig bewiesen, daß die Epithelisation entzündungsfrei verläuft, im Gegensatz zu den Kontrolltieren, wo entzündliche Erscheinungen nicht auszuschließen waren. Die Methode hat sich bei schweren Verbrennungen bzw. Verletzungen bis zur definitiven Versorgung als vorteilhaft und nützlich erwiesen.

Закрытие дефектов кожи фибриновым клеем

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Авторы — после выполненных ранее экспериментов с закрытием кожных дефектов рассасывающимися биопластами — в данном случае пользовались рассасывающимся фибриновым клеем тиссуколом (*Tissucol*). Эксперименты, проведенные на 22 собаках, однозначно показали, что эпителизация под слоем тканевого клея происходит без воспаления, в противоположность контролю, где иногда наблюдались воспалительные явления. Авторы считают, что данный способ может быть полезным и эффективным до применения окончательного лечения при тяжелых ожогах и травмах.

Inosine Increases Anoxic Tolerance and Postischaemic Restitution of the Heart: Experimental Studies on Possible Mechanism(s) of Action

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Various experimental models were utilized to determine the *in vivo* cardiac actions underlying the presumptive therapeutic benefit of the naturally occurring adenine nucleoside, inosine. 1. In pentobarbital-anaesthetized dogs coronary vasodilator responses to arterial hypoxia were augmented and postanoxic depression of cardiac contractile force was prevented by i.v. infusion of inosine ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). 2. Thermographic observations demonstrated in the *in situ* dog heart a significant inosine-induced epicardial warming (coronary flow increase) which was resistant to P_1 -purinergic blockade (aminophylline). 3. Following total cardiopulmonary bypass and cardioplegic cardiac arrest of 90 min duration in the dog, inosine administration ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) evoked a lasting increase in myocardial contractile force and cardiac output. 4. In Langendorff perfused guinea pig hearts subjected to normothermic ischaemia of 1 hour duration and treated with inosine ($0.05 \text{ mg} \cdot \text{min}^{-1}$), the release of cytoplasmatic enzymes (CK-MB, α -HBDH) and myoglobin was significantly less than in untreated ischaemic controls. In the two latter series of experiments (3 and 4) the inosine action was contrasted by the deleterious effect of catecholamines (noradrenaline and isoproterenol) administered in moderate or small doses, respectively. It was concluded that inosine has cardioprotective actions partly related to and partly independent of its influence on coronary blood supply, suggesting that administration of the nucleoside may be useful in various surgical attempts directed to myocardial salvage.

The depression of ventricular force after cardiopulmonary bypass is a common feature of cardiac activity in patients subjected to major surgical interventions [18]. Treatment with catecholamines, such as isoproterenol, noradrenaline or dopamine, has not satisfied the therapeutic demands in alleviating this symptom. Because of their pharmacologic properties, the catecholamines after a transitory stimulation may worsen the metabolic state of the heart by an undue increase of the myocardial oxygen requirement. As a result of the subsequent cardiac exhaustion the excessive postoperative treatment with catecholamines can be the dominant factor of surgical mortality in critically ill patients after major operations on the heart [6]. This fact is sufficient to justify an inquiry into the use of new cardiostimulatory agents which do not affect adversely myocardial metabolism. In continuation of our former results [2, 8, 14, 16], the present paper attempts to examine some potential

cardiosurgical aspects involved in the circulatory effects of the naturally occurring cardiotonic nucleoside, inosine. Special attention was focused on the short-term and long-term anoxic tolerance of the heart muscle. Preliminary results have already been presented [9].

Methods

Experiments on the hypoxic adaptability of the in situ heart were made using six open chest dogs [13–19 kg b.w.] anaesthetized with pentobarbital sodium, 30–35 mg · kg⁻¹ given intravenously. The animals were instrumented conventionally to measure arterial blood pressure (Statham gauge, P 23 Db), blood flow of the left anterior descending (LAD) coronary artery (Statham SP 2201 EM flowmeter), and left ventricular contractile force (strain gauge arch). After completing surgery, the cardiac force was weakened, in order to reduce contractility by at least 25–30 per cent of the control by administering an extra dose (150–200 mg) of pentobarbital in i.v. bolus. Thereafter, adaptability was tested using the standardized method of our laboratory [7], by asphyxiating the animals for a period of 60 sec; this procedure causes arterial pO₂ to diminish by more than 50–55 mm Hg. Each animal served its own control; inosine (5 mg · kg⁻¹ · min⁻¹ for 5 min) was administered intravenously after determining repeatedly the standard response, and the asphyxic test was renewed at the termination of the infusion period.

Experiments with thermography were conducted in open chest dogs with the aid of an AGA 750 Thermovision equipment. Technical details of the methodology have been fully described elsewhere [15]. The test-drugs were given intracoronarily through an indwelling needle introduced into the LAD artery.

In experiments simulating the conditions of cardiac surgery the routine procedure of total cardiopulmonary bypass was utilized. The animals (seven dogs, 21–35 kg b.w.) were narcotized with pentobarbital (30 mg · kg⁻¹) and instrumented with a flow probe (Statham SP 2201) fitted around the ascending aorta and a strain gauge sutured to the left ventricle in order to determine cardiac output and myocardial contractile force, respectively. Arterial blood pressure was measured in the left carotid with a Statham gauge (P 23 Db). After cannulation of the v.v. cavae the basal (preoperative) levels of the cardiovascular variables were registered. Thereafter, cardiac activity was arrested by injecting 200 ml of cold (4 °C) Bretschneider's solution into the aortic root proximal to the simultaneously cross-clamped ascending aorta. Cardiopulmonary bypass was maintained at 28 °C with the aid of a roller pump (Pemco) and a disposable oxygenator (Bentley BOS-5). Following a global myocardial flow stop of 90 min duration, the animals were rewarmed and, by waning from

the heart-lung machine, the normal circulation was reestablished according to the conventional practice of cardiac surgery. The caval cannulas, however, were left in place. After an appropriate period allowed for haemodynamic stabilization, the preparations were given first catecholamines (adrenaline or noradrenaline, $1 \mu\text{g} \cdot \text{kg}^{-1}$), thereafter inosine ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ i.v., for 5 min). Changes in cardiovascular variables were evaluated only after the primary, short-lived immediate pharmacologic actions had disappeared.

For studying metabolic actions of inosine isolated hearts of young guinea pigs of both sexes (300–400 g b.w.) were perfused at 37°C according to the Langendorff technique at a 70 cm H_2O pressure head as described formerly in detail [19]. Briefly, after a 30 min stabilization period, the perfusion (Krebs–Henseleit solution gassed with $\text{O}_2 : \text{CO}_2 = 95\% : 5\%$) was discontinued for 60 min, but the preparations were kept warm [37°C]. After this inflow-stop reperfusion was continued for 30 min; from the aliquots of per-

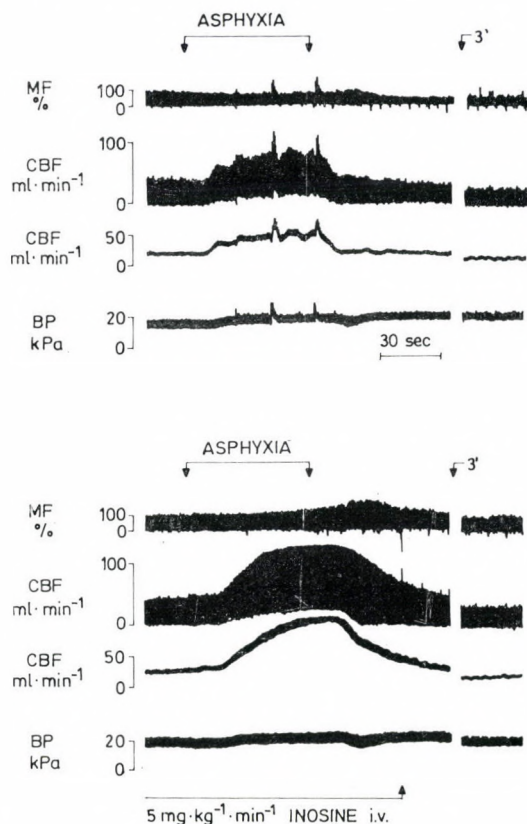


FIG. 1. Inosine potentiates asphyxia-induced coronary vasodilation and prevents cardio-pression in the dog. Upper panel: control, lower panel: inosine-treated. From above downwards the tracings are: myocardial force (MF, left ventricular), coronary blood flow (CBF, LAD artery), arterial blood pressure (BP, 1 kPa \cong 7.5 mm Hg)

fusate, by using Boehringer monotests, activities of cardiospecific isoenzymes of creatine kinase and lactate dehydrogenase (CK-MB and α -HBDH) were determined. Myoglobin was measured spectrophotometrically as described formerly [19]. Intracellular constituents were standardized for units of time (min) and heart weight (g). Control preparations did not receive any treatment; the experimental groups were infused either with inosine ($0.05 \text{ mg} \cdot \text{min}^{-1}$) or isuprel ($0.002 \mu\text{g} \cdot \text{min}^{-1}$), respectively, before and after the periods of global ischaemia for 30 min each.

Statistical evaluation was performed with Student's *t*-test for paired and unpaired data.

Results

Asphyx tolerance: dog heart. Figure 1 illustrates the typical response of the pharmacologically depressed heart to the standardized asphyxic test: a slight increase of blood pressure was associated with a considerable coronary vasodilation, while the manoeuvre elicited a decrease rather than an increase of the left ventricular contractile force. After 3 min, myocardial contractility was still depressed. The test was repeated after infusion of inosine for 5 min: a nucleoside-induced potentiated coronary response and an improved cardiac contractility should be noted, together with the absence of arrhythmias at this stage. A similar, albeit somewhat less pronounced pattern was obtained

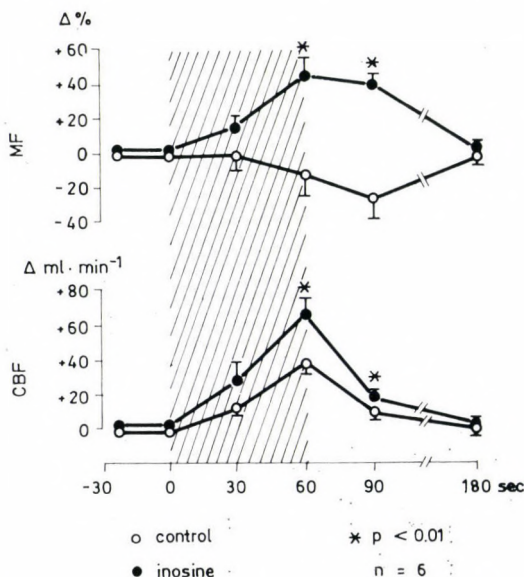


FIG. 2. Statistically evaluated responses to asphyxia (cross-hatched area) in the canine heart. Average values \pm S.E.M. of 6 experiments

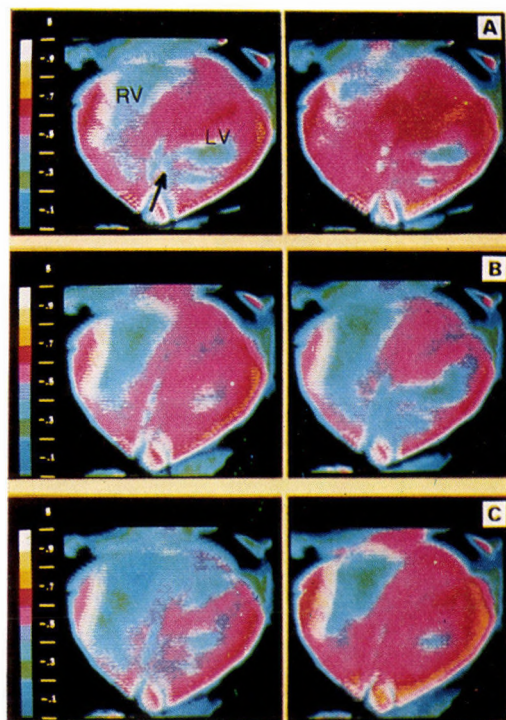


FIG. 3. Adenosine-blockade with aminophylline ($6 \text{ mg} \cdot \text{kg}^{-1} \text{ i.v.}$) does not prevent inosine-induced coronary vasodilation. Original thermographic images of the dog heart. Left row: control panels. (Calibration on the left: each colour = 0.5°C range; from above downwards: cooling.) *A* $40 \mu\text{g} \cdot \text{min}^{-1}$ adenosine infused into the LAD artery (arrow) elicits warming (vasodilation). *B* The same dose of adenosine after aminophylline: only the slight cooling effect of the ventricle is seen. *C* Inosine ($4 \text{ mg} \cdot \text{min}^{-1}$) still elicits vasodilation.

Abbreviations: *LV*: left ventricle *RV*: right ventricle

in a total of six experiments (Fig. 2). The difference between control responses and those influenced by inosine was highly significant statistically at the critical phases.

Visualization of inosine effect. Supplementary experiments (two dogs) with thermography confirmed that the key factor of the inosine-induced adaptive modulation: the coronary response to inosine was resistant (in contrast with the analogous vascular response elicited by the closely related nucleoside, adenosine) to the specific blocking agent of the purinergic P_1 receptors, aminophylline (Fig. 3). This fact may indicate a stabilized action and/or presence of adenosine in the vascular wall where the latter nucleoside is thought to act as a tissue-transmitter for anoxic coronary vasodilation. The results are validated by utilizing a submaximal dose of adenosine ($40 \mu\text{g} \cdot \text{min}^{-1}$) and a suprathreshold dose of inosine ($4 \text{ mg} \cdot \text{min}^{-1}$) to demonstrate this relation (Fig. 3).

TABLE I

Lasting circulatory changes after administering inotropes to dogs subjected to cardioplegic arrest⁺

	Catecholamines (n = 6)**		Inosine (n = 5)***		Difference between changes (unpaired <i>t</i> -test)
	control	change	control	change	
Mean blood pressure (kPa)	10.2 ± 0.8	-1.6 ± 0.5	8.1 ± 0.5	+0.6 ± 0.3	<0.02
<i>p</i> (paired <i>t</i> -test)		<0.05		N.S.	
Cardiac output (ml · min ⁻¹ · kg ⁻¹)	61.7 ± 7.9	-16.1 ± 4.8	48.0 ± 6.6	+11.3 ± 3.5	<0.01
<i>p</i> (paired <i>t</i> -test)		<0.05		<0.05	
Left ventricular force* (per cent)	100 ± 0	-40.6 ± 11.4	100 ± 0	+29.4 ± 9.5	<0.01
<i>p</i> (paired <i>t</i> -test)		<0.02		<0.05	

* Mean values ± S.E.M.

** Noradrenaline or adrenaline (1 µg · kg⁻¹ iv.), pooled data

*** 5 mg · kg⁻¹ · min⁻¹ for 5 min, i.v.

+ Control: pre-drug value

N.S. = non = significance

Cardiopulmonary bypass. Myocardial ischaemia, even with cardioplegic protection, reduced ventricular contractile force by 35 ± 7.6 per cent ($p < 0.01$) as compared to the control level measured before the bypass. Since in former experiments [8, 16] inosine was shown to influence persistently the actions of catecholamines on the cardiovascular system, postischaemic bypass preparations were treated with these drugs in the order indicated in *Methods*. The results are summarized in Table I. The sustained action of inosine is contrasted with the secondary cardiopression evoked by catecholamine administration. (For comparison medium doses of the latter drugs were chosen, and the use of isoproterenol, having a very pronounced tachycardiac effect, not comparable to the effects induced by any of the former agents, was avoided intentionally.) Nevertheless, the introductory response in heart rate ($+2 \pm 2$ vs $+19 \pm 6$ beats · min⁻¹) was found to be always less following inosine treatment than immediately after the injection of catecholamines.

Isolated hearts. The Langendorff-perfused guinea pig heart subjected to the global ischaemic stress of the 'surgical type' released a considerable amount of its intracellular constituents (Table II), while in the preischaemic period no release was measurable. Since the degree of this release can be regarded characteristic of the ischaemic damage, the degree of a protective action is also indicated by the inhibition of the release. In the inosine-treated group such type of influence was clearly evident. In these series of experiments the action of inosine was compared to that of the most 'malignant' cardiostimula-

TABLE II

Release of enzymes and myoglobin from the guinea pigs heart after 60 min ischemia**

	Reperfusion, 1 min		
	Control	Inosine ^a	Isuprel ^b
CK - MB ($10^{-2}\text{U} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	1.23 ± 0.15	0.52 ± 0.14	2.85 ± 0.32
	$\begin{array}{c} \text{Control} \text{ --- } < 0.01^c \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \end{array}$		
α -HBDH ($10^{-3}\text{U} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	3.50 ± 0.53	0.28 ± 0.09	17.45 ± 2.09
	$\begin{array}{c} \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \end{array}$		
Myoglobin ($\text{mg} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	9.45 ± 3.32	0.62 ± 0.18	25.95 ± 3.62
	$\begin{array}{c} \text{Control} \text{ --- } < 0.05 \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.01 \text{ --- } \text{Isuprel} \end{array}$		
	Reperfusion, 30 min		
	Control	Inosine ^a	Isuprel ^b
CK - MB ($10^{-2}\text{U} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	1.76 ± 0.44	0.39 ± 0.12	3.38 ± 0.43
	$\begin{array}{c} \text{Control} \text{ --- } < 0.01 \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.05 \text{ --- } \text{Isuprel} \end{array}$		
α -HBDH ($10^{-3}\text{U} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	4.95 ± 0.99	0.98 ± 0.25	24.03 ± 2.91
	$\begin{array}{c} \text{Control} \text{ --- } < 0.01 \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \end{array}$		
Myoglobin ($\text{mg} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)	7.23 ± 1.48	1.18 ± 0.27	26.63 ± 3.50
	$\begin{array}{c} \text{Control} \text{ --- } < 0.01 \text{ --- } \text{Inosine} \\ \text{Control} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \\ \text{Inosine} \text{ --- } < 0.001 \text{ --- } \text{Isuprel} \end{array}$		

** Mean values \pm S.E.M. of 8-8 isolated heart^a 0.05 mg \cdot min⁻¹^b 0.002 μ g \cdot min⁻¹^c *p* values according to the two-tailed Student's *t* test for unpaired data

tor inotrope, isoproterenol which, according to expectations, considerably potentiated both enzyme and myoglobin losses from the myocardium. The effects exerted by these agents were highly different statistically of each other and of results obtained in the control ischaemic group, respectively.

Discussion

The present results suggest that the administration of inosine is effective in ameliorating some haemodynamic and biochemical signs of a hypoxic or an ischaemic stress on the cardiac muscle. In general, the nucleoside seems to be beneficial in depressed contractile states of heart preparations subjected to both a short and a prolonged metabolic loads. It is unknown why the reduced inotropism and/or pumping activity were affected favourably by inosine administration. There are at least three possibilities (*a*) the inosine-induced coronary flow increase may have abolished some (unknown) restriction of vascular adaptation during the anoxic stress; (*b*) the direct cardiostimulation exerted by inosine, possessing an inotropic action of its own, may have been sufficient enough for the desired compensatory effect and (*c*) the advantageous action may have been due, via a secondary effect, to biochemical mechanisms, probably those connected with the adenine nucleotide resynthesis—an especially weak point in the chain of the respective biochemical events. All these possibilities can be substantiated by well-established experimental facts. (For reference see the comprehensive reviews 1, 14.)

a. Since the metabolic autoregulatory response was considerably augmented by inosine during the asphyxic stress employed in this study, it seems likely that the nucleoside exerts an influence on the adaptive reserve of the coronary bed, and that, in turn, seems to be related to its own vasodilator action. Further corroboration comes from the fact that blocking exogenous adenosine (which is believed to be the endogenously released transmitter in the mechanism of coronary adaptation) did not prevent inosine to elicit its direct coronary vascular effect. Similar observations were made on isolated coronary strips [4]. It can be assumed therefore that the potentiated asphyxic adaptation during inosine administration was similar to, or identical with, that reported by Kékesi [10] and Kékesi et al. [11, 12, 13] who were able to restore the responsiveness of partially blocked adenosine receptors with inosine treatment. According to the theory of hers and her co-workers [10, 13], inosine is an important physiologic modulator ensuring the stability of coronary adenosine receptors.

b. The present experiments confirm earlier observations which established a positive inotropic inosine action on the normal [5, 8] and the ischaemic heart, as well [2, 17, 20, 21]. This effect was easily distinguishable from that caused by the stimulation of the cardiac adrenergic receptors that affect adversely myocardial metabolic economy [6, 14, 22]. In the present study the sharp contrast between these two types of cardiostimulation was demonstrated by the experimental series simulating the conditions of open heart surgery. Papp et al. [14] disclosed formerly and identical relation between these two types of agents by using the *in situ* canine heart preparation.

c. The unique combinations of cardiostimulatory and cardioprotective effects in the action of the nucleoside [1, 14] were also highlighted by the present observations on isolated hearts. Since these results cannot be explained satisfactorily by influences on myocardial blood supply which was arrested completely during the critical part of the cardiac damage, our experiments suggest a non-vascular component in the beneficial action, too.

It is known that a progressive loss of the cardiac adenine nucleotides occurs during a prolonged period of ischaemia. This depletion was found to be accentuated paradoxically by repeated administration of cardioplegic solutions [3]. The metabolic effect of inosine is suggestive of a direct or indirect utilization of this nucleoside in the salvage pathways leading to the replenishment of depleted myocardial nucleotide pools. The latter biochemical process is less time-consuming and less costly from the energetic point of view than the *de novo* synthesis of these chemical structures [3, 23].

Another possibility has been raised by Smiseth and Mjös [17] whose important work demonstrated an inosine-induced shift in myocardial substrate utilization probably resulting from a direct general antilipolytic effect of the nucleoside which, due to the consecutively decreased myocardial consumption of free fatty acids, may contribute to the favourable action. Increased cardiac utilization of free fatty acids is known to aggravate the ischaemic injury and vice versa, while a relative increase in utilization of carbohydrates can be considered advantageous for ischaemic tolerance.

In general, the results of this study strongly support the possibility that inosine is able to favourably modify the ischaemic tolerance of the cardiac muscle, thus suggesting a potential therapeutic benefit in heart surgery by using this agent.

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Durch Inosin werden die anoxische Toleranz und die postischämische Restitution des Herzens gesteigert: Experimentelle Untersuchung des hypothetischen Wirkungsmechanismus oder der Wirkungsmechanismen

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Zwecks Klärung der im Hintergrund der hypothetischen therapeutischen Nützlichkeit des im Organismus vorkommenden Adenin-Nukleosid — Inosin — stehenden *in vivo* kardialen Effekte wurden mehrere Versuchsmodelle angewandt: 1. Bei mit Pentobarbital narkotisierten Hunden wurden durch intravenöse Inosininfusion ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) die durch arterielle Hypoxie bedingte Koronarienerweiterung gesteigert und die Entwicklung der postanoxischen Depression der ventrikulären Kontraktionskraft gehemmt. 2. Die an Hundeherzen *in situ* stattgefundenen Beobachtungen bestätigten die mit Inosin auslösbare bedeutende epikardiale Erwärmung (Steigerung der Koronariendurchblutung), die sich gegenüber dem P_1 -purinerg-blockierenden Aminophyllin als resistent erwies. 3. Durch die Verabreichung von Inosin ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) nach bei Hunden durchgeführtem totalem kardiopulmonalem Bypass und 90minütigem kardioplegischem Herzstillstand wurden der Daueranstieg der Kontraktionskraft und des Minutenvolumens des Herzens ausgelöst. 4. Durch Inosinbehandlung ($0,05 \text{ mg} \cdot \text{min}^{-1}$) nach an perfundiertem Meerschweinchenherz mit der Langendorff-Technik herbeigeführter Istündiger normothermischer Ischämie wurde die Freisetzung der zytoplasmatischen Enzyme (CK-MB, Alpha-HBDH) und des Myoglobins im Vergleich zur Kontrolle signifikant verringert. In den beiden letzterwähnten Versuchsserien (3. und 4.) wurde durch die, als Kontrast des Inosins angewandten Katecholamine (Noradrenalin und Isoproterenol) bereits in mittelgroßen und kleinen Dosen eine herzscheidende Wirkung ausgelöst. Daraus wurde gefolgert, daß Inosin — teils sich der die Blutversorgung der Koronarien betreffende Wirkung anschließend, teils unabhängig davon — über eine kardioprotektive Wirkung verfügt, d.h., daß sich der Einsatz dieses Nukleosids im Laufe der verschiedenen, im Interesse der Bewahrung der Intaktheit des Myokards durchgeführten chirurgischen Eingriffe als nützlich erweist.

Инозин повышает толерантность к аноксии и постисхемическую реституцию сердца: экспериментальное изучение предполагаемого механизма (-ов)

З. САБО, И. ЛЕНДЬЕЛ, Л. ПАПП и Ш. ЮХАС-НАДЬ

Авторы применяли разные экспериментальные модели, чтобы обрисовать встречающийся в организме аденин-нуклеозид: находящиеся на заднем плане предполагаемой терапевтической полезности инозина кардиальные эффекты *in vivo*. 1. Внутривенное введение ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) инозина собакам, находящимся под барбиталовым наркозом, увеличивало коронарную дилатацию, наступающую в ответ на артериальную гипоксию, и задерживало развитие postanоксической депрессии сократительной силы желудочков. 2. Термографические наблюдения, проведенные на сердце собаки *in situ*, подтвердили, что инозином можно вызвать значительное нагревание эпикарда (усиление коронарного кровотока), которое оказалось резистентным по отношению к P_1 -пуринергическому блоктору аминофиллину. 3. Применение инозина ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) после полного кardiопульмонального *bypass* и кardiopleгической остановки сердца продолжительностью 90 мин в опытах на собаках вызывало стойкое усиление сократительной силы сердца и повышение минутного объема. 4. Введение инозина ($0,05 \text{ mg} \cdot \text{min}^{-1}$) в перфузируемое техникой Лангендорфа сердце морской свинки, после продолжительной (1 час) нормотермической ишемии, достоверно уменьшало высвобождение цитоплазматических энзимов (CK-MB, α -HBDH) и миоглобина по сравнению с контролем (без инозина). Примененные в двух последних экспериментальных сериях — в качестве контраста действия инозина — катехоламины (норадреналин и изопроterenол) уже в средних и малых дозах оказывали повреждающее действие на сердце. Авторы делают вывод, что инозин — отчасти в связи с действием, оказываемым на коронарное кровоснабжение, отчасти независимо от него, — обладает кardiопротективным эффектом, и это означает, что применение нуклеозида может быть полезным при различных хирургических вмешательствах, направленных на сохранение целостности миокарда.

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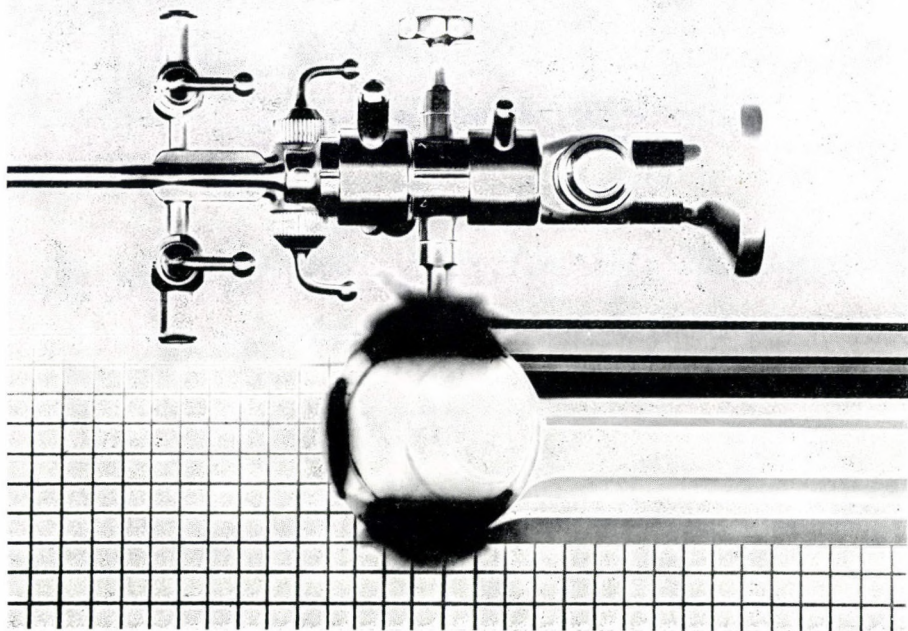
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