# THE SENSITIVITY OF TUSSIPHONOGRAPHY FOR ASSESSING THE EFFECTIVENESS OF TREATMENT

KORPAS J, SALAT D, SADLONOVA J, VRABEC M, KUDLICKA J

# VHODNOSŤ POUŽITIA TUSIFONOGRAFIE NA POSÚDENIE ÚČINNOSTI LIEČBY

#### Abstract

Korpas J, Salat D, Sadlonova J, Vrabec M, Kudlicka J: The sensitivity of tussiphonography for assessing the effectiveness of treatment Bratisl Lek Listy 2000; 101 (2): 71–77

Our previous studies have demonstrated that tussiphonogram is suitable not only for the detection of pathological condition in the respiratory tract but also for treatment effectiveness assessment. The purpose of this study was to evaluate the possibilities of tussiphonography in detection of already little pathological changes in the airways and lungs. Therefore the changes of voluntary cough sound indexes were compared with pulmonary function tests in selected group of asthmatics before and after a pulsatile electromagnetic therapy in which the effect of therapy on pulmonary function tests was minimal. After magnetotherapy in 18 patients with increased expiratory forced lung capacity by 7.3 % and increased peak inspiratory flow by 31.7 % in average the voluntary cough sound intensity decreased by 37.8 %, the sound duration shortened by 11 % and the sound pattern showed the tendency to normalization. The improvement of mentioned cough indexes was absent in 17 patients who were treated by magnetotherapy too, but at the same time suffered from respiratory viral infection and in 22 patients treated only with climatotherapy and antiasthmatics. Changes of flowvolume loops in patients were not in the close relation to other followed indices. The correlation analysis showed a functional connection in relative differences of cough sound indices and some pulmonary function tests. The results confirmed the suitability of tussiphonography to indicate even mild pathological changes in respiratory tract. (Fig. 4, Ref. 21.)

*Key words: tus*siphonography, sensitivity of tussiphonography, assessment of treatment, bronchial asthma.

Our previous studies have demonstrated that tussiphonogram (record of the acoustic cough sound pressure) is suitable for the detection of pathological conditions in the respiratory tract, the

#### Abstrakt

Korpáš, J., Salát, D., Sadloňová, J., Vrabec, M., Kudlička, J.: Vhodnosť použitia tusifonografie pre zistenie účinnosti liečby Bratisl. lek. Listy, 101, 2000, č. 2, s. 71–77

V našich predchádzajúcich štúdiách sme zistili, že zmeny tusifonogramu môžu nielen detegovať patologický stav dýchacích ciest, ale aj dokumentovať účinnosť liečby. Cieľom štúdia bolo zistiť, či je tusifonografia dostatočne citlivou metódou pre zistenie už aj malých patologických zmien v dýchacích cestách a v pľúcach. Za týmto účelom sme porovnali zmeny ukazovateľov vôľového kašľa s pľúcnými funkčnými testmi vo vybranej skupine astmatikov, ktorých sme liečili pulzným magnetickým poľom a účinnosť použitej terapie sa prejavila u nich iba minimálnym zlepšením niektorých ukazovateľov pľúcnych funkčných testov.

Po magnetoterapii u 18 pacientov so zvýšením úsilnej exspiračnej vitálnej kapacity o 7,3 % a zvýšením maximálnej výdychovej rýchlosti o 31,7 % v priemere, intenzita zvuku vôľového kašľa sa znížila o 37,8 %, trvanie jeho zvuku sa skrátilo o 11 % a charakter zvuku mal tendenciu k normalizácii. Zlepšenie týchto ukazovateľov zvuku voluntárneho kašľa chýbalo u 17 pacientov, ktorí boli liečení ako predchádzajúca skupina, ale súčasne mali respiračnú vírusovú infekciu, a 22 pacientov, ktorí boli liečení len klimaticky a antiastmatikami. Zmeny slučky prietok objem nezáviseli od ostatných sledovaných zmien. Korelačná analýza ukázala funkčný vzťah v relatívnych rozdieloch medzi ukazovateľmi zvuku vôľového kašľa a niektorými ukazovateľmi funkčných testov pľúc. Poznatky svedčia o vhodnosti použitia tusifonografie na zistenie už aj malých patologických zmien v dýchacom trakte. (*Obr. 4, lit. 21.*)

Kľúčové slová: tusifonografia, senzitivita tusifonografie, účinnosť liečby, bronchiálna astma.

cough sound character (acute, chronic), for the rough localisation of a process (larynx, trachea, bronchi), the tendency of its development and also the effectiveness of the treatment. It was obser-

Department of Pathophysiology, Jessenius Medical School Martin. patf@dean4.jfmed.uniba.sk

Sanatorium Helios, Štrbské Pleso, 1st Internal Clinic, Jessenius Medical School, Martin, Slovak Academy of Sciences, Martin

Address for correspondence: J. Korpas, MD, DSc, Dpt of Pathophysiology, Jessenius Medical School, P.O. Box 34, SK-037 53 Martin, Slovakia. Phone: +421.842.4238 213, Fax: +421.842.4134 807

Ústav patofyziológie Jeseniovej lekárskej fakulty Univerzity Komenského v Martine, Sanatórium Helios na Štrbskom Plese, 1. interná klinika Jeseniovej lekárskej fakulty Univerzity Komenského v Martine, Slovenská akadémia vied v Martine

Adresa: Prof. MUDr. J. Korpáš, DrSc., Ústav patofyziológie JLF UK, P.O. Box 34, 037 53 Martin.

ved that the pathological cough sound record changes improved or were abolished after improvement of the clinical status due to effective treatment in patients suffering from acute or chronic inflammation of the airways (Sadloňová et al., 1992; Korpáš et al., 1992, 1996; Korpáš and Honda 1996). The question of tussiphonography sensitivity for expression small pathological changes in the airways remains open. In an effort to ascertain the sensitivity of tussiphonography the changes of voluntary cough sound indices were compared with pulmonary function tests in a group of asthmatics before and after pulsatile electromagnetic therapy in which the influence of therapy on pulmonary function tests was minimal. It will be interesting to evaluate the usefilness of cough sound indices for the detection of these moderate functional changes.

# Material and methods

#### Subjects

Fifty seven patients in the Sanatorium Helios-Štrbské Pleso participated in this study. All patients had previously been diagnosed as having bronchial asthma on the basis of clinical criteria (American Thoracic Society standards 1987, National Heart, Lung and Blood Institute, international consensus 1992). The patients were on a stable therapeutic regimen for their asthma for the 4 weeks prior to study entry ordered by health dispensation centres. For the study were selected patients with approximately equal degree of asthma and therapy (all had been on corticoids with individual differences in bronchodilatators). This basic therapy could not been omitted according to the decision of the Ethical committee.

The study was conducted during two periods. The 1st group in September consisted of 18 patients, 11 females and 7 males, age of  $49\pm2.7$  (mean $\pm$ SE) yrs. They were treated with antiasthmatic drugs, climatotherapy and magnetotherapy.

The 2nd group was examined in December and consisted of 17 patients, 11 females and 6 males, age  $46\pm3,3$  (mean $\pm$ SE) yrs. The patients of this group had gradually shown clinical symptoms of respiratory viral infection during application of magnetotherapy, pronounced at the end of treatment. Was not interrupted our the examination the changes of cough indices and pulmonary function tests were further observed. These patients were evaluated separately in this group.

Patients of the 2nd group were treated likewise by antiasthamatics, climatotherapy and magnetotherapy as patients of the 1st group.

A 3rd group cosisted of 22 patients, 12 females and 10 males, age  $44,9\pm2,9$  (mean $\pm$ SE) yrs. The patients of this control group were treated only with antiasthmatic drugs and climatotherapy.

None of the patients of the 1st and the 3rd group had symptoms or signs of chest infection.

The study was approved by the Ethics Committee of the Sanatorium Helios and informed consent was obtained from all subjects after the purpose of the test had been explained.

#### Cough sound

The sound of voluntary cough was recorded by microphone on a tape recorder and processed computer with the help of. The method assessed the cough sound intensity, duration and pattern has been described before (Sadloňová et al., 1992; Korpáš et al., 1992, 1996; Korpáš and Honda, 1996). The sound pattern, except of individual records, was expressed by a histographic curve (Vrabec et al., 1993; Vrabec and Korpáš, 1990), which illustrates the sound amplitudes according to their frequencies.

## Magnetotherapy

A pulsatile electromagnetic field has been applied by equipment MTU 500H (Therapy System, Brno, Czech Republic) two times daily for 20 minutes with a magnetic induction 3 m T and frequency 4,5 Hz, for 5 days, as recommended by the manufacturer (Biotrop parameters for MTU 500H).

#### Pulmonary function tests

Measurements were performed using a Spirometer 100 Handi (ZAN, Germany) in accordance with standardized guidelines (10). Expiratory forced vital capacity (FVCex), inspiratory vital capacity (IVC), expiratory reserve volume (ERV), inspiratory reserve volume (IRV), forced expiratory volume in 1 s (FEV1), percentage of FEV1/FVCex, maximal expiratory flow at 75 %, 50 % and 25 % (MEF75, MEF50, MEF25), peak expiratory flow (PEF) and peak inspiratory flow (PIF) were measured before and after magnetotherapy. Spirometric performance in patients of the 3rd group was recorded in the same time span as in the patients of the 1st and 2nd groups.

The examination of the pulmonary function tests was completed by evaluation of flow-volume loops.

#### Statistical analysis

The one-way analysis of variance was used to analyse the effect of the therapy mode on absolute and relative (%) differences of cough sound and pulmonary parameters. Normality of the tested samples was verified by the Kolmogorov-Smirnov goodness-of-fit test. The homogeneity of the variance was verified by the Bartlett's test. A p-value of 0,05 or less was taken as indicating statistical significance.

Correlation analysis was used for the estimation of a relationship between both, cough sound indexes and pulmonary function test parameters and also for correlation of these parameters expressed as relative (%) differences before and after electromagnetic therapy.

Linear regression analysis was used to express the relationship between statistically dependent variables.

## Results

After pulsatile electromagnetic therapy in patients of the 1st group the cough sound intensity decreased significantly by 37,8 % (p=0,009). The cough sound duration likewise significantly decreased by 11 % (p=0,03) (Fig. 1).

The sound pattern was improved in 14 patients of this group. Three representative examples of sound records are show in Fig. 2. Similar improvement was observed also in others. In remaining 4 patients the finding were unchanged. Quantitative changes of cough sound pattern in average in the first group are shown by the sound histogram in Fig. 3. The differences between the histographic curve before and after electromagnetic therapy are statistically significant from the 6-16 AU of amplitude (p<0.05).

The cough sound intensity and duration changes were not significantly different in average in patients of the 2nd and 3rd group



Fig. 1. Comparison of cough sound intensity and sound duration in patients suffering from asthma (1st group), asthma and virosis (2nd group) before (grey bars) and after (black bars) magnetotherapy and in asthmatics (3rd group) before (grey bars) and after (black bars) treatment only by antiasthmatic drugs.

Obr. 1. Porovnanie intenzity zvuku vôľového kašľa a trvania zvuku vôľového kašľa u pacientov s astmou (skupina 1), astmou a virózou (skupina 2) pred (šedé stĺpce) a po (čierne stĺpce) magnetoterapii a u astmatikov (skupina 3) pred (šedé stĺpce) a po (čierne stĺpce) liečbe len antihistaminikami.

(Fig. 1). The sound pattern in the 2nd group mildly improved only in 3 patients and in the 3rd group in 4 patients. In others the sound pattern did not change or it deteriorated. Similarly, significant histographic changes in these groups were not found.

The pulmonary function tests showed statistically significant changes in patients of the 1st group only in FVCex and PIF. The value of FVCex before the therapy was 2,75 l which increased to 2,95 l (+7,3 %). PIF increased in average from 2,52 l.s<sup>-1</sup> to 3,32 l.s<sup>-1</sup> (+31,7 %) after magnetotherapy. The other values did not change significantly.

In the 2nd group the PEF values significantly increased in average from  $4,34 \text{ l.s}^{-1}$  to  $4,99 \text{ l.s}^{-1}$  (+14,7 %).

Examination of the flow-volume loops showed typical patterns for asthma. They improved after electromagnetotherapy in patients of the 1st group by 44 % (8 of 19 patients) and in the 2nd group by 47 % (8 of 17 patients). In the 3rd group the improvement was present only in 32 % (7 of 22) patients. These differences are statistically not significant. In other patients the loops deteriorated or did not show improvement.

We did not find significant correlation between absolute cough sound indices and pulmonary function test parameters. But the correlation of the relative differences (in %) of cough sound intensity and FVC and cough sound duration and ERV before and after magnetotherapy in the 1st group showed statistically significant relations. Similarly positive was the correlation of the differences in cough sound duration and values of FVC, IVC and FEV1 in the 2nd group. In the 3rd group we did not find statistically significant correlations.



PAC. 07

PAC. 08





Fig. 2. The normal (double sound and single sound) cough sound records in comparison with examples of pathological cough sound pattern in 3 patients suffering from bronchial asthma before (B) and after (A) magnetotehrapy. Obr. 2. Záznamy normálnych ukazovateľov zvuku vôľového kašľa (dvojitý a jednoduchý zvuk) v porovnaní s obrazom patologických ukazovateľov vôľového kašľa u 3 pacientov s bronchiálnou astmou pred (B) a po (A) magnetoterapii.

The corresponding scatter plots with regression lines show the real situation if we divide each diagram into quarters along the zero axis (Fig. 4). Total improvement (the number of patients in the right quarter below in both indices, the right quarter above and the left quarter bellow in one index) was present in majority of patients (in range of 71—94 %). In the upper left quarter are the number of patients deteriorated in both indices who are in minority of cases.

## Discussion

The improvement or normalisation of the pathological cough sound records related to the efficiency of clinical treatment has been described before (Sadloňová et al., 1992; Korpáš et al., 1992, 1996; Korpáš and Honda, 1996). The aim of this study was to assess the suitability of tussiphonography for detection of not only severe pathological changes in the respiratory tract, but mild ones,



Fig. 3. Tract from the histogram representing the statistically significant frequncy distribution of cough sound amplitudes in patients of the 1st group suffering from asthma before (B curve) and after (A curve; both with 95 % indication of the confidence intervals) magnetotherapy. Obr. 3. Histogram znázorňujúci štatisticky signifikantnú frekvenčnú distribúciu amplitúd zvuku vôľového kašľa u pacientov v skupine 1 s diagnózou asthma bronchiale pred (krivka B) a po (krivka A) (obe s 95 % indikáciou intervalu spoľahlivosti) magnetoterapii.

too. Mild changes in the airways were determined with the help of pulmonary function tests. It is well known from the literature that the pulmonary function tests have an important role in routine clinical evaluation of pulmonary disorders. They give quantitative data so that the progress of a lung disease as well as its response to treatment may be followed (Wilson, 1992; Cochrane, 1990; Stark, 1990). The pulmonary function tests are normally used in the basic assessment of bronchial asthma severity, progression and prognosis as well as diagnosis (Krištufek et al., 1982; Mayer and Redhammer, 1982; Mayer, 1989; Hovard, 1990). The patients were asthmatics approximately of the same degree. They were selected from a large group of patients treated by pulsatile electromagnetic field on the basis of the modest effect on pulmonary function tests.

In patients of the 1st group statistically significant changes were not recorded beside of the increased FVCex by 7 % and increased PIF by 32 %. In the 2nd group only PEF increased by 15 %. Mild improvement was not surprising because in mild asthma or asthma in remission e.g. the FEV1 and FVC are sometimes both within the predicted normal range for the individual age and height (Stark, 1990). On the contrary it was positive from the view-point of our aim. The improvements, though mild, were ascribed to the bronchodilatation effect of magnetotherapy but without detailed analysis because the effect of pulsatile electromagnetic field application on bronchial asthma was not the object of this study. Some diversity in changes (e.g. PEF and PIF) of pulmonary function tests are known from other studies for instance the relationship between PEF and FEV1 is poor and it is not possible to predict FEV1 from PEF and vice versa (Nolan and White, 1999).

No significant changes of the pulmonary function test values in patients of the 3rd group were found.

Repetition of histamine or metacholine provocation test performed in health dispensation centres, where it was positive, was omitted in sanatorium because of the possible hazards of increasing airflow obstruction (Stark, 1990). The tussiphonographic changes before the electromagnetotherapy were in agreement with our previous findings (Sadloňová et al., 1992; Korpáš et al., 1996) and they were in consensus with function tests. After the magnetotherapy (five days therapy only) they singnificantly testified the improvement of cough indexes in the 1st group despite of modest effect on pulmonary function tests. The cough sound intensity decreased by 38 % and the cough sound duration shortened by 11 %. The sound pattern and the histographic curve showed tendency for normalisation (creation of double sounds) and decreasing of the middle part of the histogram. These changes of histographic curve in pathological conditions were described before (Korpáš et al., 1996; Vrabec et al., 1993; Vrabec and Korpáš, 1990). The changes of the cough sound intensity, sound duration and pattern indexes confirm that tussiphonography is a good indicator of even mild pathological changes.

The respiratory viral infection in patients of the 2nd group was apparent and manifested by fever, weakness, anorexia, cough, expectoration etc. We suppose that the higher quantity of mucus by irritation of receptors in the mucus membrane during viral inflammation of the airways masked the favourable effect of magnetotherapy. The importance of the presence of mucus in the airways for pathological cough creation was described before (Korpáš et al., 1987, 1993, 1996). It is interesting that the increased PEF, which was observed in this group, was not manifest in the cough sound. The phenomenon of increased PEF could be explained by higher irritability of the airways.

In the 3rd group the patients were treated only by antiasthmatics and climatotherapy. This therapy was sufficient to keep a stable moderate status of patients but it was not sufficient for an improvement of asthma estimated by pulmonary function tests. Therefore the improvement of cough sound indexes was absent.

The changes of cough indices in patients of the 1st group with bronchial asthma i.e. pathological pattern, increased intensity and prolonged sound duration are in agreement with our previous findings (Sadloňová et al., 1992; Korpáš et al., 1992, 1996; Korpáš and Honda, 1996).

The changes of flow-volume loops were not in close consensus with other followed indices. It is well known from the literature that examination of the flow-volume loop may be useful in diagnosis but it has not been shown to be of value in assessing the subsequent course or response to treatment (Stark, 1990).

The correlation analysis showed a functional association in relative differences of cough sound indexes and pulmonary function test parameters only in patients of the 1st and the 2nd group. These results may be caused by effective magnetotherapy not evaluated in this study was mentioned before. The fact of significant correlation of cough sound indexes and some parameters of pulmonary function tests in patients of the 2nd group confirmed the association between the mentioned values.

Tussiphonography is a very sensitive, non-invasive, auxiliary examination method for estimation of pathological conditions in the airways and lungs. It is suitable for achievement of first and quick information in the time when other methods of examination do not allow the establishment of a correct diagnosis. In addition the tussiphonogram may be of value in prognosis because its changes may indicate the effectiveness of therapy and the progress of disease (Widdicombe, 1987). The combination of tussiphonogram and the pulmonary function tests give more information about the



Fig. 4. The scatter plots with the regression lines of the statistically dependent pairs both, sound indexes and pulmonary parameters and with Pearson's correlation coefficients R, P values and regression line equations; CSI — cough sound intensity, CSD — cough sound duration, FVC — forced vital capacity, IVC — inspiratory vital capacity, ERV — expiratory reserve volume, FEV1 — forced expiratory volume in 1 s. Points in the right quarter below show improvement in both parameters, and those in the right quarter above and left quarter below show improvement in one parameter. Points in the upper left quarter show deterioration in both parameters.

Obr. 4. Rozptylový diagram s regresnými krivkami štatisticky závislých dvojíc indexov zvuku vôľového kašľa a plúcnych parametrov a s Pearsonovým korelačným koeficientom R, hodnotami P a rovnicami regresných kriviek; CSI — intenzita zvuku vôľového kašľa, CSD — trvanie zvuku vôľového kašľa, FVC — úsilná dychová kapacita, IVC — inspiračná vitálna kapacita, ERV — exspiračný rezervný objem, FEV1 sekundový exspiračný rezervný objem. Body v pravej štrbine dole ukazujú zlepšenie oboch parametrov, body v hornej pravej štvrtine a ľavej dolnej štvrtine ukazujú zlepšenie v 1 parametri. Body v hornej ľavej štvrtine ukazujú zhoršenie v oboch parametroch.

pathological situation in the airways than either of them alone. The differences in obtained results between tussiphonography and function tests can be explained in methodical disparity, on the one hand the registration of the acoustic sound pressure, on the other hand registration of volume and flow, despite of common denominators which are the volume and velocity of flow, diameter of the airways etc. The only problem of a widespread use of tussiphonography in clinical practice is that we are lacking standardised apparatus for cough sound registration and evaluation commercialisation.

#### References

**1. American Thoracic Society.** Standards for diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Amer Rev Resp Dis 1987; 136: 225–244.

**2. Biotrop Parameters** for MTU 500 H, Therapy systems, 615 00 Brno, Nopova 33. Czech Republic.

**3. Cochrane GM:** Asthma. Pathophysiology. Pp. 609—619. In: Brewis RAL, Gibson GJ, Geddes DM (Eds): Respiratory Medicine. London—Philadelphia—Toronto—Sydney—Tokyo, Bailliere Tindall 1990, 1559 p.

**4. Howard P:** Chronic obstructive pulmonary disease. Clinical features and management. Pp. 520—534. In: Brewis RAL, Gibson GJ, Geddes DM (Eds): Respiratory Medicine. London—Philadelphia—Toronto—Sydney—Tokyo, Bailliere Tindal 1990, 1559 p.

5. Korpáš J, Sadloňová J, Salát D, Masárová E: The origin of cough sounds. Clin Resp Physiol, 1987; 10: Suppl. 23: 47–50.

**6. Korpáš J, Sadloňová J, Salát D, Debreczeni LA**: Tussiphonography: A new tool for diagnosis of airways inflammation. Pp. 252—257. In: Salát D et al (Eds): Proceedings of 1st High Tatras International Health Symposium. New York, Bratislava, Tatranská Polianka, Sympos 1992, 306 p.

7. Korpáš J, Widdicombe JG, Vrabec M: Influence of simulated mucus on cough sounds in cats. Res Med 1993; 87: 49—54.

**8. Korpáš J, Sadloňová J, Vrabec M**: Analysis of the cough sound: an Overview. Pulmon Pharmacol 1996; 9: 261—268.

**9. Korpáš J, Honda Y**: Aspects of airway defence mechanisms. Pathophysiology 1996; 3: 81—86.

**10. Krištufek et al**: Funkcia dýchania v laboratornej a klinickej praxi. Martin, Osveta 1982, 296 p.

**11. Mayer M, Redhammer R**: Funkčné testy pľúc v praxi. Martin, Osveta 1982, 468 p.

**12. Mayer M**: Choroby dýchacích orgánov. Pp. 273—329. In: Dieška D et al (Eds): Vnútorné lekárstvo 3. Martin, Osveta 1989, 480 p.

**13. National Heart.** Lung and Blood Institute, National Institute of Health, Bethesda, Maryland 20892. International consensus report on diagnosis and treatment of asthma. Europ Resp J 1992; 5: 601—641.

**14. Nolan D, White P**: FEV1 and PEF in COPD management. Thorax 1999; 54: 468—469.

**15.** Quanjer P.H, Tammeling G.J, Cotes J.E. et al: Lung volumes and forced ventilatory flows. Report working party standardisation of lung function tests. Europ Resp J 1993; 6: Suppl. 16: 5—40.

16. Sadloňová J, Korpáš J, Salát D, Vrabec M: Possibilities to observe pathological conditions of the airways on the basis of tussiphonography. Pp. 258—264. In: Salát D et al (Eds): Proceedings of 1st High Tatras International Health Symposium. New York—Bratislava—Tatranská Polianka, Sympos 1992, 306 p.

**17. Stark JE**: Asthma. Clinical features and investigation. Pp. 619—644. In: Brewis RAL, Gibson GJ, Geddes DM (Eds): Respiratory Medicine. London—Philadelphia—Toronto—Sydney—Tokyo, Bailliere Tindall, 1990, 1559 p.

**18. Vrabec M, Korpáš J**: Objectification of cough sound characteristics (in slovak). Bratisl Lek Listy 1990; 91: 634—636.

**19. Vrabec M, Novotná A, Korpáš J**: Computer analysis of cough sound pattern. Proceedings of the 2nd High Tatras International Healts. In: Salát D et al (Eds): New York—Bratislava—Tatranská Polianka, Sympos 1993, 350 p.

**20. Widdicombe J.G**: Symposium on the cough reflex — summary. Clin Resp Physiol 1987; 23: Suppl. 10: 73—74.

21. Wilson L.M: Diagnostic Procedures in Respiratory Disease. Pp. 530—
542. In: Price SA, Wilson LM (Eds): Pathophysiology. St. Louis—Baltimore—Boston—Chicago—Philadelphia—Sydney—Toronto, Mosby 1992, 1137 p.

Received December 16, 1998. Accepted January 21, 2000.