UPDATE ON GENE THERAPY FOR INTIMAL HYPERPLASIA

REIS ED, SKLADANY M

NAJNOVŠIE POZNATKY O MOŽNOSTIACH GÉNOVEJ TERAPIE HYPERPLÁZIE INTÍMY

Abstract

Reis ED, Skladany M:
Update on gene therapy for intimal hyperplasia
Bratisl Lek Listy 1999; 100 (8): 417–421

Trauma to the vessel wall leads to smooth muscle cell (SMC) activation and eventual intimal hyperplasia. This process occurs in restenosis following balloon angioplasty, particularly with stent placement, occlusion of vascular bypasses, and arteriopathy of chronic allograft rejection. Genetic interventions affecting the cell cycle or early postinjury events have been successful in limiting SMC proliferation *in vitro and* in animal models. Gene therapy strategies have included the use of antisense oligonucleotides to block protein synthesis, transduced genes to cause cytotoxicity, and genetically engineered cells to decrease the response to injury. The clinical application of gene therapy in vascular diseases should follow the evolution of delivery systems that enable efficient local gene transfer to the arterial wall. *(Tab. 1, Fig. 1, Ref. 30.)*
Key words: gene therapy, intimal hyperplasia, vascular smooth muscle cell, restenosis.

Abstrakt

Reis E.D., Skladany M.:
Najnovšie poznatky o možnostiach génovej terapie hyperplázie intímy
Bratisl. lek. Listy, 100, 1999, č. 8, s. 417–421

Traumatické poškodenie cievnej steny vedie k aktivácii hladkých svalových buniek (HSB) a prípadnej hyperplázii intímy. Tento proces býva následok restenózy po balónikovej angioplastike, najmä v prípade umiestnenia stentu, upchatia cievnych bypassov a chronickej artériopatie srdcového allograftu. Genetické zásahy do bunkového cyklu alebo skorých procesov po poškodení dokázali úspešne obmedziť proliferáciu HSB in vitro a na zvieracích modeloch. Génová terapia zahrňovala využitie antitenzných oligonukleotidov pri blokovaní proteosyntézy, génovú transdukciu na vyvolanie cytotoxického efektu, a genetickým inžinierstvom vytvorené bunky na oslabenie odpovede na poškodenie. *(Tab. 1, obr. 1, lit. 30.)*
Kľúčové slová: génová terapia, hyperplázia intímy, cievna hladká svalová bunka, restenóza.

The term, gene therapy, is used generally in reference to any genetic manipulation intended to treat or prevent disease. The "appeal" of gene therapy has two main roots, one factual and one theoretical. Current laboratory techniques allow identification, cloning, and transfer of certain genes from one cell to another. The theory is that such technology could be applied efficiently in vivo with advantages over standard treatments. Gene therapy could be less toxic, less expensive, and more effective than conventional, long-term drug therapy, particularly in chronic diseases; however, to achieve these standards, a sufficient number of cells involved in the pathologic process must be modified genetically, which remains a challenge.

Gene therapy requires a gene, vector, and delivery system. Genes that have been isolated abound currently, their numbers growing rapidly along with progress in the Human Genome Project. Single or multiple genetic defects have been identified in a great number of diseases. The traditional categories of "genetic" and "acquired" disease are no longer clear-cut definitions. As the understanding of mechanisms of disease advances, the role of genes becomes more apparent. Deletions, mutations, and transpositions can lead to disease even when such molecular defects are acquired in adult life. A common example is radiation-induced malignancy-deoxyribonucleic acid (DNA) damage transmitted to cell progeny as mutations that lead to cancer.

Intimal hyperplasia (IH) is clearly acquired, but it may be affected by predisposing genetic factors such as hypercholesterolemia (Ross, 1993; Davies & Hagen, 1994). IH is characterized by proliferation of medial smooth muscle cells (SMC), and is prominent in restenosis following angioplasty (Popma et al., 1991), particularly with stenting (Johhnson et al., 1990). To a certain extent,

Department of Surgery, The Mount Sinai Medical Center, New York, NY, USA
Address for correspondence: E.D. Reis, MD, Ass. Professor, Dpt of Surgery, The Mount Sinai Medical Center, One Gustave L. Levy Place, Box #1259, New York, NY 10029-6574.
Phone: +1.212.241 2022, Fax: +1.212.987 9310, Internet: ernane.reis@smtplink.mssm.edu

Department of Surgery, The Mount Sinai Medical Center, New York, NY, USA
Adresa: E.D. Reis, MD, Ass. Professor, Dpt of Surgery, The Mount Sinai Medical Center, One Gustave L. Levy Place, Box #1259, New York, NY 10029-6574.

IH is present in all types of vascular reconstructions including prosthetic and autologous grafts (Clowes et al., 1994), and found in solid organ allografts, having a substantial role in chronic rejection (Häyry and Yilmaz, 1995). IH is a result of the vessel wall's response to injury. The initial insult may be of a physical, chemical, or immunologic nature. SMC are stimulated to proliferate, migrate from the media toward the intima, and produce extracellular matrix (Casscells, 1992). This process narrows eventually or occludes the vessel lumen completely, which often translates into clinical ischemia. Therefore, the control of IH would probably have important clinical applications.

Many conventional pharmacologic approaches have been tested to control IH; however, the modest success achieved in animal models could not be reproduced in clinical trials. Although trials are now beginning (Isner et al., 1996), a number of factors indicate gene therapy is a promising approach. First, because the current understanding of the mechanisms of IH allows specific therapeutic interventions to be designed. Second, animal models of IH are developed widely (Ferrel et al., 1992; Schwartz, 1994; Reis et al., 1998), and gene therapy has been successful in pre-clinical studies (von der Leyen et al., 1995; Rade et al., 1996). Third, as gene therapy is applied in other fields, particularly oncology, advances can be incorporated into vascular disease. Finally, a variety of catheters and biomaterials are available currently for safer and more effective local delivery of therapeutic agents to the vessel wall (Riessen & Isner, 1994).

In vascular diseases, the main candidates for gene therapy are those conditions where an "acute" insult leads to IH. Studies using drugs such as heparin suggest therapy is more effective when initiated at the time of injury (Clowes et al., 1994). Conceivably, the same applies to molecular therapies, because early intervention on intracellular signaling pathways is more likely to affect the cell cycle and have greater impact on the proliferative process (Isner et al., 1996).

In the following sections, the pathogenesis of IH is reviewed briefly, current strategies of molecular therapy are discussed, and future approaches are suggested with emphasis on translation into clinical practice.

Pathogenesis of intimal hyperplasia (IH)

The current understanding of the mechanisms of IH is based largely on animal studies of acute arterial injury. Trauma to any layer of the arterial wall induces SMC phenotypic transformation and activates a cascade of mediators (Fig. 1). Dedifferentiation increases the sensitivity of SMC to growth factors and cytokines, a process that begins hours after the insult and continues for several months. Activated vascular smooth muscle cells (VSMC) proliferate, migrate toward the vessel lumen, and synthesize extracellular matrix leading to neointimal formation. Therefore, in the injured vessel, two populations of VSMC are present: quiescent cells with contractile function; and proliferating, activated cells, with secretory function. Macrophages, T-cells, and platelets can be present in the neointima, and their products contribute to endothelial dysfunction and SMC disregulation (Davies and Hagen, 1994). In essence, the neointima is a composite of activated cells interacting in an attempt to heal the vessel after injury. Sometimes, this process is excessive and leads to luminal narrowing. The threshold for stenosis varies in different species and according to vessel characteristics (Schwartz, 1994; Isner et al., 1996). It also depends on the quality, intensity, and duration of the insult and other factors such as diabetes, hypercholesterolemia, and renal failure (Ross, 1993).

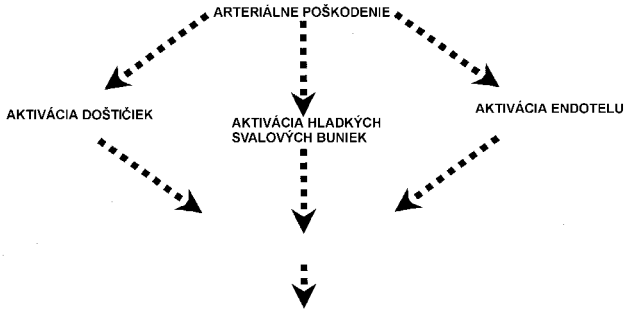

Fig. 1. Representation of the response to arterial injury.
Obr. 1. Schéma odpovede na arteriálne poškodenie.

Several mediators that influence the balance between normal healing and pathologic stenosis have been identified (Fig. 1). Platelets release platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-ß); PDGF induces SMC migration and TGF-ß is an important regulator of extracellular matrix production. The angiogenic agent, basic fibroblast-derived growth factor (bFDGF), stimulates endothelial cell mitogenesis. Nitric oxide (NO) appears to be an endogenous inhibitor of VSMC growth and migration, in addition to its role as an endothelium-derived vasodilator (Ignarro, 1993). Angiotensin II (Ang II) can activate various components of the tyrosine kinase signaling cascade, thus promoting cell growth. The transcription factor, E2F, coordinates the induction of cell cycle regulatory genes such as Cdc2, *c-myb*, and c-Myc (Gibbons and Dzau, 1996). Genes activated in VSMC, either *in vitro* by growth factors or *in vivo* by arterial injury (Taubman, 1993), are attractive targets for molecular therapies.

Gene therapy approaches

The term, gene therapy, is applied to all treatment involving genetic alteration of cells. In this context, a cell function is either modified by a change in the cell's genome or the influence of another genetically altered cell.

Genetic material can be introduced into cells by use of appropriate vectors. Although almost any type of cell can be manipulated genetically in culture, attempts of *in vivo* gene transfer are often hampered by low efficiency and inadequate specificity. Plasmids, liposomes, and viruses are vectors used commonly for *in vivo* gene transfer (Riessen and Isner, 1994). Plasmids are fragments of extra-chromosomique DNA susceptible to autonomous replication, which can be modified to make convenient vectors; however, they have limited efficiency *in vivo*. Liposome complexes are preparations of cationic lipid molecules that coat the negatively charged DNA allowing incorporation into cell membranes. Liposomes are degraded in the cytoplasm releasing plasmid DNA; however, these vectors also produce low rates of gene transfer *in vivo.*

Viral vector systems are more efficient for *in vivo* gene transfer. A number of viruses have been used successfully and different properties can be attributed to each species. Most frequently, retroviruses and adenoviruses are used. Retroviral vectors infect proliferating cells and integrate into the host's genome, permitting long-term expression of the transgene. An adenovirus-transferred gene is not integrated into the host's genome and gene expression is transient. In addition, adenoviruses infect quiescent cells, and their usefulness is limited by toxicity to tissues other than the target. Replication-defective viral vectors have been constructed to minimize the risk of random infection. In this case, a viral particle produced by a packaging cell line cannot replicate after it infects a host cell.

To confirm gene transfer, marker-genes are often used. The *Escherichia coli* beta-galactosidase (ß-gal) gene is an example. ß-gal catalyzes the formation of a product that stains blue with histochemical techniques, indicating expression of the transgene.

Indirect or cell-mediated gene transfer involves genetic modification of endothelial cells or SMC in culture and subsequent seeding of these cells into the vasculature. Endothelial cells transduced *in vitro* with a retroviral vector expressing the ß-gal gene have been introduced onto iliofemoral arteries of Yucatan minipigs using a double-balloon catheter after denudation of the endothelium. Examination of arterial segments 2 to 4 weeks later disclosed endothelial cells in the intima expressing ß-gal activity. Using the same model, SMC were implanted and ß-gal activity was demonstrated in the intima and media (Nabel et al., 1989; Nabel et al., 1990). Cultured rat SMC infected with a replication-defective retrovirus containing human genes have been seeded onto the surface of injured rat carotid artery and continued to express the introduced gene over a long period (Clowes et al., 1994). Human genes have been introduced into baboons using prosthetic vascular grafts seeded with retrovirally transduced SMC (Geary et al., 1994). Genetically engineered endothelial cells have been used to improve the surface of a metallic endovascular prosthesis in a sheep model (Flugelman, 1995).

Direct gene transfer into the vessel eliminates the need for prior cell transfection *in vitro* and is more likely to have clinical applications. In several animal models, expression of marker genes in the arterial wall has been achieved with pure DNA or a mixture of plasmid DNA with cationic liposomes. Delivery systems included intravenous injection, a hydrogel-coated angioplasty balloon, and other percutaneous devices (Riessen and Isner, 1994; Flugelman, 1995; Isner et al., 1996). Using the Yucatan minipig model, a retroviral vector and liposomes containing a marker gene were introduced into the arterial wall. Evidence of recombinant gene expression in the intima, media and adventitia was observed for up to five months (Nabel et al., 1989, 1990). A therapeutic approach was reported using the herpesvirus thymidine kinase (TK) gene delivered by an adenoviral vector into porcine arteries. Cells expressing the TK gene produce a cytotoxic drug when exposed to gancyclovir. In these studies, intimal hyperplasia decreased after a course of ganciclovir treatment (Ohno et al., 1994). An efficient Sendai virus/liposome technique was used to transfect NO synthase gene into the vessel wall after balloon injury in a rat model. Local generation of NO resulted in substantial inhibition of neointimal formation (von der Leyen et al., 1995).

Another strategy of gene therapy involves the use of *antisense oligonucleotides*-short segments of synthetic DNA that, after cellular uptake, can bind to messenger ribonucleic acid (mRNA), blocking its translation. They can be targeted specifically against mRNA encoding proteins essential for cell proliferation. Antisense oligonucleotides (AON) have been found to reduce neointimal formation after denudation of rat carotid and porcine coronary arteries (Riessen and Isner, 1994). In one experiment, antisense *c-myb* oligonucleotide was added to a gel solution and applied around injured rat carotid arteries. Results showed no detectable levels of *c-myb* mRNA and a significant reduction of intimal accumulation in treated animals (Simons et al., 1992). The proto-oncogene, *c-myb*, is involved in mitogen-induced proliferation of SMC. Recently, an AON against the cdk2 gene was shown to inhibit IH of transplant arteriopathy in a mouse heart transplant model (Suzuki et al., 1997). Table 1 summarizes gene therapy approaches for control of IH. Importantly, these approaches are primarily based on molecular events known to participate in the disease process.

Future research

Attempts of *in vivo* infection using adenovirus have been hampered by toxic effects and transient expression of these vectors. Adeno-associated viruses are attractive vectors to circumvent these problems because they have high transduction frequency, in-

Tab. 1. Pathobiologic mechanisms of intimal hyperplasia with potential for gene-based control (modified from Gibbons, 1996).

Process	Gene
Endothelial dysfunction	NO; VEGF; FGF
Thrombosis	Iib/IIIa receptor; tissue factor; t-PA
SMC activation	Gax; adhesion molecules
Cell growth	E2F decoys; pRB; p21, p27, p53
Cell migration	Integrins; PDGF; t-PA
Matrix production	MMPs; plasmin
Apoptosis	Bax

NO: nitric oxide, VEGF: vascular endothelial growth factor, FGF: fibroblast growth factor, t-PA: tissue plasminogen activator, pRB: retinoblastoma protein, PDGF: platelet-derived growth factor, MMPs: matrix metalloproteins.

Tab. 1. Patobiologické mechanizmy hyperplázie intimy s možnosťami genetickej kontroly (modifikované podľa Gibbonsa,1996).

Proces	Gény
Endotelová dysfunkcia	NO,VEGF,FGF
Trombóza	Iib/IIIa receptor, tkanivový faktor,t-PA
aktivácia HSB	Gax,adhezívne molekuly
Bunkový rast	E2F návnada,provokatér, pRB,p21,p27,p53
Bunková migrácia	Integríny,PDGF,t-PA
Tvorba matrixu	MMPs,plazmín
Apoptóza	Bax

NO: oxid dusnatý, VEGFG: cievny endotelový rastový faktor, FGF: fibroblastový rastový faktor, t-PA: tkanivový aktivátor plazminogénu, pRB: retinoblastómový proteín, PDGF: rastový faktor pochádzajúci z trombocytov, MMPs: metaloproteíny matrixu

tegrate into the genome, and are less immunogenic. Also, they have not been found to cause disease or tumor in humans. Tissue-specific endogenous promoters (e.g., actin promoter if the target cells are SMC) may further refine arterial gene transfer by allowing one to restrict gene expression to a certain cell type within the arterial segment at the site of transfection.

Gene transfer to a high percent of cells would most likely be required for effective genetic manipulation of IH. However, a lower transfection efficiency might be sufficient if a secreted gene product can exert a paracrine effect on neighboring cells. Such a ”stand-by” effect is observed with the “suicidal” TK gene. Other genes with similar properties may become available.

Concurrent with the growing interest in local delivery of pharmacologic agents, much attention during previous years has been given to site-specific gene therapy for vascular disorders, particularly restenosis and thrombosis. Local delivery of DNA, like local delivery of drugs, is expected to increase the efficacy and reduce systemic toxicity of recombinant gene products. In response to specific needs for gene delivery, catheters and prostheses are being improved rapidly and protocols for clinical trials are appearing in the literature (Isner et al., 1996).

Encapsulation of genetically modified cells has been used as a means to achieve *in-situ* gene therapy. This technology involves the use of synthetic membranes to protect packaging cell lines, allowing continuous delivery of their products (Lysaght and Aebischer, 1999). Studies using periarterial retroviral vector delivery suggest encapsulated xenogeneic cells survive and deliver viral vectors in perivascular tissues, with transduction into the arterial wall (Reis et al., 1996). Such strategy minimizes intra-luminal manipulations, avoiding additional vessel injury, ischemia, and thrombosis.

Among the genes with potential for use in clinical trials of vascular gene therapy are the tissue plasminogen activator (t-PA) (Flugelman, 1995) and hirudin (Rade et al., 1996) genes that modulate the clotting system, the vascular endothelial growth factor gene that enhances endothelial growth, and other genes that suppress VSMC proliferation (Li and Brooks, 1999). Protocols established previously can be followed for monitoring of patients and the efficacy of interventions because gene therapy can be delivered by the same methods used for drug therapy. Safety issues must be considered carefully in the preparation of clinical trials (Isner et al., 1996; Smith et al., 1996).

In summary, it is reasonable to attempt controlling IH by targeting proliferating medial SMC. The most effective approach may be to target components of the intracellular signaling cascades shared by many growth regulatory molecules, and commence therapy immediately after the triggering insult to the vessel wall. Variants of this strategy can be adapted to specific settings: for restenosis, gene delivery at the time of balloon injury, and through the same angioplasty catheter; for vascular bypass occlusion, genetic modification of vein grafts, or coating of prosthetic grafts with genetically engineered cells; and for transplant arteriosclerosis, pre-treatment of allografts.

Powerful molecular tools for control of IH have been developed in the laboratory. In clinical practice, devices for vascular interventions and biomaterial are becoming safer and more efficient. It is the combination of these advances that holds promise for the effective treatment of IH.

References

Casscells W: Migration of smooth muscle and endothelial cells: critical events in restenosis. Circulation 1992; 86: 723—729.

Clowes MM, Lynch CM, Miller AD, Miller DG, Osborne WRA, Clowes AW: Long-term biological response of injured rat carotid artery seeded with smooth muscle cells expressing retrovirally introduced human genes. J Clin Invest 1994; 93: 644—651.

Davies MG, Hagen PO: Pathobiology of intimal hyperplasia. Brit J Surg 1994; 81: 1254—1269.

Ferrell M, Fuster V, Chesebro JH: A dilemma for the 1990s. Choosing appropriate experimental animal model for the prevention of restenosis. Circulation 1992; 85: 1630—1631.

Flugelman MY: Inhibition of intravascular thrombosis and vascular smooth muscle cell proliferation by gene therapy. Thromb Haemost 1995; 74: 406—410.

Geary RL, Clowes AW, Lau S, Vergel S, Dale DC, Osborne WRA: Gene transfer in baboons using prosthetic vascular grafts seeded with retrovirally transduced smooth muscle cells: a model for local and systemic gene therapy. Hum Gene Ther 1994; 5: 1211—1216.

Gibbons GH, Dzau VJ: Molecular therapies for vascular diseases. Science 1996; 272: 689—693.

Häyry P, Yilmaz S: Role of growth factors in graft vessel disease. Transplant Proc 1995; 27 (3): 2066—2067.

Ignarro LJ: Nitric oxide-mediated vasorelaxation. Thromb Haemost 1993; 79 (1): 148—151.

Isner JM, Walsh K, Rosenfield K, Schainfeld R, Asahara T, Hogan K, Pieczek A: (Clinical Protocol) Arterial gene therapy for restenosis. Hum Gene Ther 1996; 7: 989—1011.

Johhnson DE, Hinohara T, Selmon MR, Braden LJ, Simpson JB: Primary peripheral arterial stenoses and restenoses excised by transluminal atherectomy: A histopathologic study. J Amer Coll Cardiol 1990; 15: 419—425.

Li J-M, Brooks G: Cell cycle regulatory molecules (cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors) and the cardiovascular system. Potential targets for therapy? Europ Heart J 1999; 20: 406—420.

Lysaght MJ, Aebischer P: Encapsulated cells as therapy. Sci Amer 1999; 280: 76—82.

Maillard L, Van Belle E, Smith RC, Le Roux A, Denefle P, Steg G, Barry JJ, Branellec D, Isner JM, Walsh K: Percutaneous delivery of the gax gene inhibits vessel stenosis in a rabbit model of balloon angioplasty. Cardiovasc Res 1997; 35: 536—546.

Nabel EG, Plautz G, Boyce FM, Stanley JC, Nabel GJ: Recombinant gene expression in vivo within endothelial cells of the arterial wall. Science 1989; 244: 1344—1346.

Nabel EG, Plautz G, Nabel GJ: Site-specific gene expression in vivo by direct gene transfer into the arterial wall. Science 1990; 249: 1285—1288.

Ohno T, Gordon D, San H, Pompili VJ, Imperiale MJ, Nabel GJ, Nabel EG: Gene therapy for vascular smooth muscle cell proliferation after arterial injury. Science 1994; 265: 781—784.

Popma J, Califf R, Topol E: Clinical trials of restenosis after PTCA. Circulation 1991; 84: 1426—1436.

Rade JJ, Schulick AH, Virmani R, Dichek DA: Local adenoviral-mediated expression of recombinant hirudin reduces neointima formation after arterial injury. Natl Med 1996; 2: 293—297.

Reis ED, Joseph J-M, Mosimann F, Breakefield XO, Aebischer P: Gene transfer into arterial neointima using periadventitial encapsulated retroviral packaging cell line (Abstr). 1996 Meeting on Gene Therapy; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, September 1996.

Reis ED, Roque M, Zhang WX, Fallon JT, Weinberg H, Badimon JJ, Taubman M: Neointimal hyperplasia after femoral artery transluminal injury in C57BL/6 and FVB mice. Surg Forum 1998; 49: 303—305.

Riessen R, Isner JM: Prospects for site-specific delivery of pharmacologic and molecular therapies. J Amer Coll Cardiol 1994; 23: 1234—1244.

Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362: 801—809.

Schwartz RS: Editorial. Neointima and arterial injury: dogs, rats, pigs and more. Lab Invest 1994; 71: 789—791.

Simons M, Edelman ER, DeKeyser J-L, Langer R, Rosenberg RD: Antisense c-*myb* oligonucleotides inhibit intimal arterial smooth muscle cell accumulation *in vivo*. Nature 1992; 359: 67—70.

Smith KT, Shepherd AJ, Boyd JE, Lees GM: Gene delivery systems for use in gene therapy: an overview of quality assurance and safety issues. Gene Ther 1996; 3: 190—200.

Suzuki J, Isobe M, Morishita R, Aoki M, Horie S, Okubo Y, Kaneda Y, Sawa Y, Matsuda H, Ogihara T, Sekiguchi M: Prevention of graft coronary arteriosclerosis by antisense cdk2 kinase oligonucleotide. Nature Med 1997; 3: 898—899.

Taubman MB: Gene induction in vessel wall injury. Thromb Haemost 1993; 79 (1): 180—183.

Ueda M, Becker AE, Tsukada T, Numano F, Fugimoto T: Fibro-cellular tissue response after percutaneous transluminal coronary angioplasty: an immunocytochemical analysis of the cellular composition. Circulation 1991; 83: 1327—1332.

von der Leyen HE, Gibbons GH, Morishita R, Lewis NP, Zhang L, Nakajima M, Kaneda Y, Cooke JP, Dzau VJ: Gene therapy inhibiting neointimal vascular lesion: in vivo transfer of endothelial cell nitric oxide synthase gene. Proc Natl Acad Sci USA 1995; 92 (4): 1137—1141.

Received May 28, 1999.
Accepted July 9, 1999.

PREDSTAVUJEME NOVÉ KNIHY

Moravec R.: Z chirurgovho zápisníka. Bratislava, Odkaz 1998, 99 strán.

V čase zrenia a dozrievania prichádza čas, keď sa mnohí vracajú k vlastnej práci a bilancujú počiny pohľadom späť a sprítomňujú mnohé vo viere, aby s ich pamäťou neodišlo do stratena obdobie ich žitia, názory *a p*ostoje k vlastnému osobnému prínosu. Do tohto rámca patrí aj knižka profesora Moravca, ktorú nazval *Z chirurgovho zápisníka*. Uverejňujeme slová, ktoré do úvodu napísal profesor Čižmárik.

Redakcia

Na úvod

Vždy ma priťahovali knihy, články, alebo aj monografické diela, ktoré rozprávali o živote a práci významných odborníkov z rozličných vedných odborov. Čítaval som ich pozorne a aj keď sa netýkali odboru, ktorému som sa upísal ja sám, z poznatkov, ktoré približovali, som sa poučil a niektoré som mohol aplikovať aj vo svojej práci. Takto som v živote spájal príjemné s užitočným.

Cena a význam takýchto diel veľmi stúpne, keď ich napíše významný odborník orientujúci sa väčšinou na poznatky, spomienky alebo udalosti, ktoré sám prežil. Tým sa dielo dostáva do polohy autentickej a nesprostredkovateľnej.

Takýmito spomienkami sú aj stránky, ktoré napísal významný vedecký pracovník v odbore chirurgie, lekár, vysokoškolský učiteľ, prof. MUDr. Rudolf Moravec, DrSc.

Počas mnohých rokov som mal možnosť z viacerých aspektov a strán sledovať jeho pôsobenie na Lekárskej fakulte Univerzity Komenského a na I. chirurgickej klinike Fakultnej nemocnice v Bratislave, teda na pracoviskách, na ktorých prešiel cestou vývoja vysokoškolského učiteľa a vedeckého pracovníka. Bola to cesta nie vždy ľahká, nie vždy priamočiara a ani nie vždy taká, aby sa dala presne naplánovať, či predpovedať. To potvrdzujú nasledovné stránky a udalosti, ktoré on sám opisuje.

Po prečítaní práce som si položil otázku, v čom sa toto spomienkové dielo odlišuje od iných analogických diel a čo sa mi na ňom najväčšmi páči?

Predovšetkým to, že je napísané s láskou k rodisku a jeho okoliu, k študentovi, pacientovi a najmä k chirurgovi. Ďalej si myslím, že je napísané tak, aby u každého vnímavého čitateľa vzbudzovalo úctu k povolaniu lekára a k profesii chirurga, čo je pre nás všetkých v tejto hektickej dobe veľmi potrebné. A nie v poslednom rade je to štýl, ktorým je dielo napísané. Keďže autora poznám dlhé roky, môžem povedať, že je to štýl pre neho typický a jemu vlastný.

Výsledkom úvah, spomienok a názorov prof. Moravca je akýsi trojdimenzionálny pohľad, v ktorom sa nachádza rodný kraj, ľudia a medicína. Na základe opisovaných faktov vychádza z toho autor ako dôverný znalec všetkých troch aspektov a rozmerov.

V slovenskej literatúre je doteraz pomerne málo spomienkových diel renomovaných odborníkov, ba zdá sa, že práve týmto ľuďom sa tento druh literatúry akosi nechce písať a vydávať. Je to na škodu veci, literatúry a v konečnom dôsledku aj slovenskej kultúry.

Spomienky prof. Moravca si zaslúžia, aby sme ich vrelo privítali, pretože zapĺňajú medzeru, ktorú v tejto oblasti evidujeme.

Možno predpokladať, že spomienky prof. MUDr. Rudolfa Moravca, DrSc., vyvolajú polemiku a výmenu názorov. Myslím si, že je to dobré. Autorovi zrejme išlo aj o to. Veď len takto postavený problém má svoj ďalší vývin a rozmery.

Ďakujem za možnosť vyjadriť sa k tomuto dielu a želám mu na ceste k čitateľovi veľa úspechov.

Bratislava, január 1998
Prof. RNDr. Jozef Čižmárik, CSc.