

A Complex of Therapeutic and Preventive Measures of Urolithiasis in an Outpatient Setting

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Abstract: Article is dedicated to outpatient management of adults and children with urolithiasis. We have developed standards of equipment and recommendations of outpatient clinics managing urolithiasis based on our own long-term clinical experience analysis and international publications. Suggested protocol corresponds to basic aspects of diagnostic and treatment of patients with urolithiasis in outpatient conditions. Diagnostic and therapy procedures are divided into obligate and additional, used in children, young patients and in complicated patients. It was shown how important to determine conservative management individually according to detected risk factors, metabolic changes, physicochemical nature of calculi, co-morbidity and underwent surgical invasions of urinary tract in anamnesis of adults and children. Indications for phytotherapy, balneal and physiotherapeutic procedures were established. The necessity of multidisciplinary principal of urolithiasis management is shown. Long-term researches provided in Scientific Research Institute of Urology proved the necessity of standardized complex approach in investigation, outpatient surveillance and management of patients with urolithiasis in conditions of succession between outpatient and inpatient clinics, mutually responsible for management results. This measures may lead to statistically significant decrease of stone formation recurrence in more than 2.5-fold.

Keywords: urolithiasis, prevention, metaphylaxis, outpatient management, Urofronn.

In countries, including Uzbekistan, a tendency towards an increase in the incidence of urolithiasis is increasingly being noted. Urolithiasis is one of the forms of manifestation of metabolic diseases, which, according to scientists, will have a further upward trend due to significant changes in the nature and quality of people's nutrition, an increase in the number of adverse environmental and social factors that have both direct and indirect effects on the human body. . The relevance of the problem of urolithiasis is due to the fact that in 65-70% of cases the disease is diagnosed in people aged 20-55 years, i.e. during the most productive period of life. It is alarming that urolithiasis is increasingly being diagnosed in children, even in infancy. Despite the widespread introduction of new highly effective, non-invasive methods for the diagnosis and treatment of urolithiasis, the recurrence rate continues to be high up to 38.4% of cases. It is well known that no matter how effectively the operation to remove the stone is carried out, without the subsequent complex and individually selected metaphylaxis, the final result of the treatment will be unsatisfactory. In this regard, one of the most important areas in the organization of diagnosis, prevention and treatment of this disease, the creation of standard comprehensive protocols for managing patients at different stages of treatment, which should replace their

diverse set or complete absence in individual medical institutions, and in the first line at the clinics. A standardized integrated approach allows to unify the treatment of patients, develop a single agreed terminology with the involvement of endocrinologists, therapists, nutritionists, gastroenterologists, physiotherapists and doctors of other related specialties in the treatment and diagnostic process, who can prescribe additional treatment that affects the risk factors for stone formation, thereby reducing , the degree of relapse. The outpatient facility is the leading and most important, but, unfortunately, at the moment, the weakest link both in the diagnosis and in the conservative complex treatment of patients with urolithiasis, which often leads to the development of complications, and in some cases to organ-removing intervention, which has been proven in studies conducted at the RCEMC BF Urology

Table 1. Characteristics of the patients hospitalized with acute calculous obstructive pyelonephritis (259 patients).

Duration of illness from the onset of renal colic	Duration of fever (up to 38°C)
1 day = 72 (27,0%)	1 day = 51 (19,7%)
1-3 day = 138 (53,5%)	up to 3 day = 153 (59,1%)
3-5 and more = 48 (18,5%)	3-5 and more = 55 (21,2%)
	136 (52,5%) were self-medicating before calling an ambulance

It is the analysis and development of metaphylaxis of stone formation that this study is devoted to, its discussion and the result of the protocol for managing patients in an outpatient setting with urolithiasis.

The material and technical equipment of the clinic

Any medical institution (polyclinics, hospitals), regardless of its form of ownership, licensed for this type of medical care (treatment of urolithiasis in adults and children), must be equipped with equipment that allows diagnosing urolithiasis at the modern level. Treatment should be supplemented by a more detailed examination, determination of the composition of the stone, the state of metabolic disorders of the blood and urine, urine culture with the determination of antibiotic sensitivity, the study of hormonal levels, the identification of concomitant diseases predisposing to urolithiasis, etc. This will allow developing a conservative therapy for each individual patient aimed at metaphylaxis or stone formation prevention and rehabilitation. The following specialists should be consulted on the staff of an institution where assistance is provided to patients with urolithiasis: a urologist, a nephrologist, an endocrinologist, a therapist, a surgeon, a physiotherapist, as well as a pediatrician and a pediatric urologist-andrologist, if we are talking about a pediatric medical institution.

Examination of patients with urolithiasis

Anamnesis. Initially, as a rule, patients go to the clinic in case of renal colic (often accompanied by acute pyelonephritis), pain in the lumbar region, gross hematuria. Often, urolithiasis can be asymptomatic and detected during a random examination for another disease. After providing the patient with emergency care, getting rid of the stone, it is necessary to establish the causes (risk factors) that led to the disease, and conduct a comprehensive urological examination.

Adequate comprehensive therapeutic and diagnostic measures developed as a result of the examination will allow individual metaphylaxis to be carried out in each individual patient, which is especially important in children and young patients.

Risk factors for the formation of recurrent stones:

- onset at a young age (< 25 years);
- formation of more than 3 stones in 3 years;
- stones containing brushite;
- the only functioning kidney;
- drugs related to stone formation (drugs containing calcium, vitamin D, acetazolamides, high doses of ascorbic acid (> 4 g/day), sulfonamides, triamterene, indinavir);
- anomalies of the urinary system (spongy kidney, obstruction of the ureteropelvic segment, detached calyx, ureteral stricture, vesicoureteral reflux, horseshoe kidney, ureterocele);
- concomitant diseases contributing to stone formation (hyperparathyroidism, renal tubular acidosis, Crohn's disease, bowel surgery with resection of the small intestine, small bowel anastomosis, bone injuries with prolonged immobilization, malabsorptive conditions, sarcoidosis, cystine fibrosis, gout);
- features of the diet (low daily fluid intake, the predominance of products containing animal protein, increased consumption of salt);
- family history of the disease.

It is important that recently there has been a progressive increase in the incidence of urolithiasis among the child population of Uzbekistan. Studies conducted at the RCEMP BP Urology made it possible to identify risk factors for the development of urolithiasis in the pediatric age group.

Risk factors for stone formation in children:

- a history of risk factors for the development of urolithiasis, urological diseases, especially urolithiasis, accompanied by metabolic disorders of stone-forming substances in 68.5% of cases;
- the presence of anomalies of the urinary system in a child 21.2% of observations;
- family living in ecologically unfavorable conditions 88.5% of observations;
- the presence of bad habits in parents (smoking, alcohol consumption) 16.6% of observations;
- features of the course of pregnancy in the mother aggravated pregnancy against the background of toxicosis (82.7% of cases) and, in particular, preeclampsia (16.1% of cases), taking antiviral and antibacterial drugs (16.6% of cases).

Table 2. Daily urine collection methodology

1.	Urine collection is carried out in one container.	The container is measured in advance and marks are made on it: 0.5 l, 1 l, 1.5 l, 2 l, 2.5 l
2.	On the day of collecting daily urine, you must consume at least 2 liters of fluid.	It is necessary to take into account the consumed first courses, compotes, juices, etc.
3.	At the end of the collection of daily urine, shake it up, holding the container in your hands, and pour 100 g into a separate container.	
4.	Collect morning urine in a separate container	up to 100 ml
5.	Indicate the volume of urine collected during the day, the weight and height of the patient	
6.	At the end of the urine collection, venous blood is taken (on an empty stomach)	up to 20 ml

Laboratory, instrumental studies, as well as methods for visualizing stones. All patients with urolithiasis should systematically undergo the following examination (uncomplicated course of the disease):

- general clinical analysis of urine (1 time in 3 months and according to indications);
- biochemical blood test with the determination of the levels of creatinine, urea, potassium, sodium, calcium and uric acid (1 time in 3 months during the first year of observation, then 1 time in 6 months and according to indications);
- ultrasound examination of the kidneys, upper and lower third of the ureter, bladder (1 time in 3 months during the first year of observation, then 1 time in 6 months and according to indications);
- x-ray examination, panoramic picture of the abdomen, excretory urography (according to indications);
- urine culture with sensitivity to antibiotics, which is especially indicated for young patients, children and patients with calcium phosphate urolithiasis. Antibacterial therapy may be adequate only in conditions of restored passage of urine. The examination must be repeated after the course of therapy; in the absence of growth of microflora, antibiotic therapy should be stopped, a control analysis is prescribed (1 time in 3 months during the first year of observation, then 1 time in 6 months and according to indications);
- study of the chemical composition of the stone (stone passage, removal of stones during surgery);
- pH-metry of urine (1 time in 3 months during the first year of observation for 3-5 days). Keeping a diary of urine pH and correction of urine acidity is the most accessible and informative way to monitor the effectiveness and correction of ongoing metaphylaxis.

Patients with a long history of urolithiasis, recurrent stone formation, staghorn nephrolithiasis, young age, a single or only functioning kidney, bilateral stones need an additional examination to the main one described above, which is selected individually for each patient (complicated course of the disease) :

1. Biochemical study of blood and urine (analysis of metabolic disorders) with the determination of creatinine clearance, the level of calcium, phosphorus and uric acid in the blood and urine, the level of magnesium, chlorides, citrates and oxalates of urine, the daily volume of urine is taken into account (table 2).

This study must be performed twice before starting therapy.

The study of the level of stone-forming substances in the blood and urine, along with the study of the chemical composition of the stone, are the basis for effective metaphylaxis of stone formation. A control examination to determine the effectiveness of the prescribed treatment and adjust the dose of drugs should be carried out for the first year 1 time in 3-4 months, then 1 time in six months.

2. The study of liver enzymes (determination of the blood level of total bilirubin, its fractions, glucose levels, the level of total protein and its fractions).

3. Examination of peripheral blood serum for calcium (determination of the level of ionized Ca²⁺), and with its increase, a study of peripheral blood serum for the content of parathyroid hormone (once to clarify the diagnosis and according to indications).

4. X-ray examination (excretory urography or bolus computed tomography, antegrade and retrograde pyeloureterography, cystography according to indications)
5. Dynamic nephroscintigraphy. This study, along with determining the levels of nitrogenous wastes, allows us to assess the functional state of the kidneys and predetermine the further tactics of patient management (referring the patient for surgical treatment), which is of particular relevance in patients with staghorn urolithiasis (once a year and according to indications).
6. If hyperparathyroidism is suspected, topical diagnostics is indicated (ultrasound / computed tomography / magnetic resonance imaging of the neck and mediastinum / scintigraphy of the thyroid gland and parathyroid glands with Tc 99 m Sestamibi (Tc 99 m technetrit) (once to clarify the diagnosis and according to indications) .
7. Doppler ultrasonic examination of the kidneys (once to clarify the diagnosis and according to indications).

Table 3. The scope of follow-up examination of patients according to the type of health facility

type of medical facility	the scope of the survey
Polyclinic	pH-metry,
	Blood chemistry,
	General clinical analysis of urine,
	urine culture,
	Ultrasound examination of the organs of the urinary system, X-ray examination (survey and excretory urography)
Medical diagnostic centers, city, district and regional hospitals	Analysis of metabolic disorders (biochemical analysis of blood and urine),
	The chemical composition of the stone
	Computed tomography and magnetic resonance imaging
	Radionuclide study of the kidneys

It is important to note that it is also necessary to observe the hierarchy of medical institutions in accordance with their capabilities in the process of dynamic observation of the patient (Table 3).

Treatment of patients suffering from urolithiasis

To prescribe preventive treatment, the doctor should pay special attention to the patient's dietary habits, the nature and course of concomitant diseases, the features of the surgeries (and in some cases their complications) on the organs of the urinary system. If necessary, doctors of related specialties, surgeons, therapists (pediatricians), nutritionists, endocrinologists, nephrologists and physiotherapists, and a number of other specialists, should be involved in the treatment of patients, if necessary. All patients with urolithiasis should be taken under dispensary observation, which should last at least 5 years.

As a rule, in 80% of observations, already 1-2 months after the prescribed treatment, patients forget about medical recommendations, violate the diet and medication regimen. That is why all patients should be warned about the ineffectiveness of treatment in case of non-compliance or non-compliance with the recommended treatment and examination, taking full responsibility for possible complications.

Diet therapy and pharmacotherapy are used to correct the identified metabolic disorders in the blood and urine, litholysis, as well as the treatment of concomitant diseases involved in stone

formation. The appointment is made individually, depending on the chemical form of urolithiasis, the clinical course of the disease, concomitant diseases, and the age of the patient.

Fluid intake and diet. Patients are advised to exclude the consumption of highly salted, smoked, fried and canned foods. Daily fluid intake should be from 1.5 to 4.0 liters per day (depending on age, chemical form of urolithiasis, concomitant diseases) and distributed evenly throughout the day. In the diet, it is important to have a balanced intake of all food groups without visible priorities, to exclude foods with a high content of stone-forming substances, as well as drastically changing urine pH.

Medical treatment. The extensive experience accumulated at the RCEMP of the BF of Urology made it possible to develop schemes for the correction of metabolic disorders in uric acid, calcium oxalate and calcium phosphate forms of urolithiasis. The number of courses of treatment during the year is set individually under medical and laboratory control.

Correction of disorders of purine metabolism and pathogenetic pharmacotherapy for uric acid stones. Treatment regimens for hyperuricemia:

1. alkalization of urine pH, restriction of meat products, alcohol;
2. allopurinol inside 100 mg 4 r / day. 1 month or allopurinol / benzbromarone 120 mg orally (100 mg allopurinol + 20 mg benzbromarone) according to the instructions for the drug.

Treatment regimens for hyperuricuria: allopurinol 100 mg orally 4 times a day. 1 month or citric acid / potassium bicarbonate / sodium citrate according to the instructions for the drug, the dosage is selected individually 1 month. Litholysis schemes: Citric acid / potassium bicarbonate / sodium citrate according to the instructions for the drug, the dosage is selected individually for 1-3 months. The dosage of the citrate mixture is selected individually according to the schedule of urine pH fluctuations (morning, afternoon, evening).

For prevention, the average daily urine pH should be 6.8, for litholysis, pH = 7.2.

Correction of metabolic disorders of oxalic acid and calcium and pathogenetic pharmacotherapy for calcium oxalate and calcium phosphate stones. Treatment regimens for hyperoxaluria: Pyridoxine inside, 0.02 g 3 r / day. (adults) or 0.01 g 2 r / day. (children) 1 month or 5% solution in / m ml every other day, 15 injections and / or magnesium oxide inside after meals, 0.3 g 3 r / day. (adults) or 0.1 g 2 r / day. (children)

Hypercalcaemia treatment regimens: hydrochlorothiazide orally, 0.025 g 2 r / day. (women), 0.05 g r / day. (men) 1 month + potassium and magnesium asparaginate orally, 1 t r / day. 1 month or citric acid / potassium bicarbonate / sodium citrate dosage is selected individually to achieve the pH range of urine 6.2 6.4-1 month.

Treatment regimens for oxalate crystalluria: magnesium oxide inside after meals, 0.3 g 3 r / day. 1 month or etidronic acid 2% solution inside for 30 minutes. before meals, 15 ml r / day. 1 month or citric acid / potassium bicarbonate / sodium citrate dosage is selected individually to achieve the pH range of urine 6,26,4 1 month.

Treatment for calcium phosphate stones is only effective when the stone(s) are completely removed.

Drug treatment for cystine stones:

1. citric acid / potassium bicarbonate / sodium citrate (the dosage is selected individually according to the instructions for the drug to achieve a urine pH of more than 7.5 for 6 months under medical supervision and control of a general urine test at least 1 time per month;
2. penicillamine inside 250 mg
3. r / day. (adults), 10-50 mg/day. in 5 receptions (children) 6 months. (under strict monthly control of a clinical analysis of blood and urine) or ascorbic acid 3-5 g per day with cystine excretion less than 3-3.5 mmol / day for 6 months. under medical supervision and control of general urinalysis (at least 1 time per month).

In addition to specific citrate mixtures and medicines, patients, especially those who have undergone surgical interventions, should include drugs that improve microcirculation in the kidney (pentoxifylline orally at 100 mg 3 r / day for 1 month, dipyridamole orally at 25 mg 3 r / day, 1 months, tocopherol acetate inside at 100 IU / day, 1 month). The duration of treatment is set individually. These drugs can also be used with a decrease in the clearance of endogenous creatinine, an increase in the concentration of creatinine and / or urea in the blood serum.

In patients with urolithiasis, including in the children's age group, phytopreparations are widely used, which have a number of properties: they have a litholytic effect, improve metabolic processes, promote the excretion of metabolic products not only through the urinary system, but also through the gastrointestinal tract , and also contain antioxidants (urofronn, cystone, phytolysin, urolesan, etc.).

The use of Urofronn in clinical practice is convenient: it is available in 2 dosage forms of pills and drops for oral administration, which is especially important in children and allows it to be used to treat urolithiasis, chronic pyelonephritis in patients of all age groups. Urofronn is a drug containing extracts of centaury, lovage and rosemary. Urofront has a complex effect: diuretic, anti-inflammatory, antispasmodic, antioxidant and nephroprotective, reduces capillary permeability, potentiates the effects of antibiotics. Due to the antioxidant properties, the flavonoids in the composition of the drug help protect the kidneys from damage by free radicals. According to clinical data, Urofronn increases the excretion of uric acid and helps maintain the pH of urine in the range of 6.2-6.8, which is important in the treatment and prevention of urate urolithiasis. Apply the drug 2 tablets or 50 drops 3 times a day. For children, the dose of the drug depends on age: for infants, 10 drops 3 times a day, for preschool children, a single dose increases to 15 drops, and for school-age children, 25 drops or 1 tablet. Urofront can be used both in the active stage of the inflammatory process in combination with antibacterial agents, and as monotherapy as maintenance anti-relapse therapy in courses of 2-4 months. The high efficiency of the drug in complex lithokinetic therapy in patients with residual stones after extracorporeal lithotripsy has been shown. The greatest effectiveness of therapy is achieved only by the 3rd month of treatment with Urofron, which indicates the need to use this drug for at least 3 months continuously.

It is important to note that in the absence of acute pyelonephritis, phytotherapy can be prescribed for a long time. However, the activation of the inflammatory process in the urinary system, confirmed clinically, laboratory and instrumental methods, is an indication for a course of antibiotic therapy in accordance with the data of the antibiogram, which must be completed by a mandatory control study (control urine culture).

As a comparative analysis showed, correctly selected pharmacotherapy, regardless of the form of urolithiasis, is 88-98% (metabolic efficiency), clinical efficiency is 84-98% with uric acid, 74-96% with calcium-oxalate form of urolithiasis, 20-43% with phosphate stones. Litholysis of uric acid stones in the absence of urinary infection is effective in 84% of cases.

When prescribing a corrective drug therapy to a patient, it is necessary to monitor compliance with the doctor's prescriptions. If the patient refuses treatment, an appropriate entry must be made in the outpatient card.

Physiotherapy

In the era of widespread introduction of minimally invasive methods for removing stones from the urinary system, physiotherapy treatment has gained a second wind associated with a pronounced lithokinetic effect, especially after remote lithotripsy. The use of physical factors, both natural and preformed, in the treatment of patients with chronic calculous pyelonephritis makes it possible to enhance the positive effects of drug treatment. This makes it possible to influence locally and neurohumorally on the blood supply to the kidney, on the redox processes in it, the tone of the urinary tract, the immunological reactivity of the body and the functional state of the organs of the urinary system.

Spa treatment

Treatment at the resorts is possible at any time of the year. It is effective for kidney stones, the size and shape of which, as well as the condition of the upper urinary tract, allow us to hope for their independent discharge under the influence of the diuretic action of mineral waters. The use of similar bottled mineral waters does not replace a spa stay. An analysis of the long-term results of treatment of patients suffering from urolithiasis showed that compliance with the full scope of medical recommendations leads to a relapse only in 5.6% of cases, while unsystematic and incomplete metaphylaxis in 15.8% of cases (Figure 1).

The ineffectiveness of outpatient conservative therapy, leading to complications (the occurrence of attacks of pyelonephritis, obstructive complications, progressive decline in kidney function) is an indication for referring the patient for examination and treatment to the urological department of the hospital.

Figure 1. Stone recurrence in patients with KSD.

Conclusion

Thus, the main links in the metaphylaxis of stone formation and treatment at the outpatient stage should be aimed at correcting metabolic disorders of stone-forming substances in the blood and urine, sanitation of the urinary tract and normalization of the pH value of the urine, which must be started no earlier than 1 month after the surgical treatment (when the function of the renal parenchyma is restored). Treatment should be developed individually for each patient, depending on age, the chemical form of urolithiasis, the nature of concomitant diseases. Dispensary observation lasts at least 5 years. The systematic implementation of metaphylaxis, a clear and consistent continuity in the work of the clinic and the urological hospital leads to a decrease in the frequency of recurrence of stone formation by 2.8 times.

Literature

1. Лопаткин Н.А., Дзеранов Н.К. Пятнадцатилетний опыт применения ДЛТ в лечении МКБ // Материалы Пленума правления Российского общества урологов. М. 2003. С. 5-25.
2. Вороновицкий В.Д. Обоснование метода оперативного лечения нейромышечной дисплазии мочеточников у детей: дис. ... канд. мед. наук. М. 2001. 135с.
3. Кириллов В.И., Богданова Н.А. Нарушения уродинамики как патогенетический фактор хронических заболеваний почек у детей. // Российский вестник перинатологии и педиатрии. 2007. № 4. С. 42-49.

4. De Andrade A.S., de Silva A.M., Jalles L.M., Lopes M.F., de Brito T.N., de Pedrosa L.F. Relation between diet protein and calciuria in children and adolescents with nephrolithiasis // *Acta Cir Bras.* 2005. № 20. Suppl 1. P. 242-246.
5. Лопаткин Н.А., Трапезникова М.Ф., Дутов В.В., Дзеранов Н.К. Дистанционная ударно-волновая литотрипсия: прошлое, настоящее, будущее // *Урология.* 2007. №6. С. 3-13.
6. Дзеранов Н.К., Шадури В.Р. Тактика применения дистанционной литотрипсии при камнях мочеочника, осложненных острым пиелонефритом // *Всероссийская научно-практическая конференция «Современные принципы диагностики, профилактики и лечения инфекционно-воспалительных заболеваний почек, мочевыводящих путей и половых органов. 8-9 февраля 2007 г.»*. Тезисы докладов. Москва. 2007. С.47-48.
7. Дзеранов Н.К., Максимов В.А., Шадури В.Р. Выбор метода и сроков дренирования почки при обструктивном калькулезном пиелонефрите // *Сборник трудов Пленума Научного Общества Урологов Узбекистана.* Ташкент, 2008. С.41-43.
8. Guidelines 2007 edition. Guidelines on paediatric urology. P.42-50.
9. Черепанова Е.В. Фактор риска метаболических нарушений у детей с мочекаменной болезнью: дис. ... канд. мед. наук. М. 2008. 197с.
10. Аляев Ю.Г., Руденко В.И., Философова Е.В. Современные аспекты медикаментозного лечения больных мочекаменной болезнью // *Русский медицинский журнал.* 2004. Т. 12, № 8. С.534-540.
11. Козлова В.В. Клинико-этиопатогенетические особенности пиелонефрита у детей и пути повышения эффективности лечения: автореф. дис. .канд. мед. наук. Пермь. 2005. 25с.
12. Длин В.В., Шатохина О.В., Османов И.М., Юрьева Э.А. Эффективность Канефрона Н у детей с дисметаболической нефропатией с оксалатнокальциевой кристаллурией // *Вестник перинатальной фармакологии и нутрициологии.* 2008. Т. 5, № 4. С. 66-69.
13. Перепанова Т.С., Хазан П.Л. Растительный препарат Урофронн в лечении и профилактике инфекций мочевых путей // *Врачебное сословие.* 2005. № 4-5.С.1-4.
14. Амосов А.В. Растительный препарат Канефрон в урологической практике // *Врач.* 2000. № 6. С. 38-39.
15. Антибактериальная терапия // *Материалы цикла усовершенствования врачей.* Под редакцией проф. В.Н.Яковлева. Москва. 2002. 263с.
16. Большая Российская энциклопедия лекарственных средств. Т. 1-2. М. Ремедиум. 2001. 821 с.
17. Дзеранов Н.К., Бешлиев Д.А. Лечение мочекаменной болезни комплексная урологическая проблема // *Consilium medicum: приложение.* Урология. 2003. С.18-22.
18. Калинина С.М., Тиктинский О.Л., Александров В.П и соавт. Клиническая эффективность препарата Урофронн в лечении больных мочекаменной болезнью после оперативных вмешательств. Тезисы докладов VI Российского Национального Конгресса «Человек и лекарство». М. 1999. 298 с.