

T. G. Marshall

“THE SCIENCE OF SAFETY” — IS IT REALISTIC TO EXPECT MEDICINE TO CHANGE TO A SCIENCE-BASE FROM ITS EVIDENCE-BASE?

Introduction. A century ago, Max Planck’s autobiography described the pace of scientific change: “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it” [1]. Today, as Medical Science struggles to assimilate discoveries springing from the decoding of the Human Genome, two obvious questions arise — “how long will it take for this new Genomic Science to take hold in general medical practice?” and “will this be fast enough to keep pace with the epidemic proliferation of chronic disease?”

Rise in prevalence of chronic disease. By the year 2000, approximately 125 million Americans (45% of the population) had chronic conditions and 61 million (21% of the population) had multiple chronic conditions [2]. Among children, the rate of chronic health conditions increased from 12,8% in 1994 to 26,6% in 2006, particularly for asthma, obesity, and behavior and learning problems, according to results of a new prospective study published in the 2010 paper in *Journal of the American Medical Association* [3].

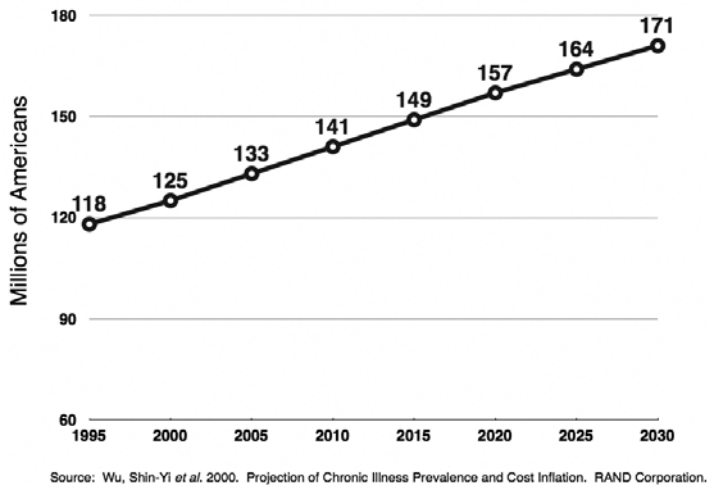


Fig.1. Projected increasing prevalence of chronic disease in the USA [4]

Shin-Yi Wu, *et al.*, performed a projection of chronic illness prevalence and cost inflation for the Rand corporation [4]. The results, shown in Figure 1, show a rise more rapid

Marshall Trevor Gordon — Professor, B.E., M.E., Ph.D., Director of the Autoimmunity Research Foundation, Thousand Oaks, California, USA; Adjunct Professor in the Faculty of Health Sciences at Murdoch University, Western Australia, Australian Union; e-mail: trevor.m@autoimmunityresearch.org

© T. G. Marshall, 2013

than the expected increase in population. Whether due to secondary factors, such as better diagnosis of chronic disease during this period, or to an increased disease incidence, the potential economic impact is undeniable.

A meta-analysis of studies published in *the British Medical Journal*, *Journal of the American Medical Association*, *The Lancet*, and *the New England Journal of Medicine* between 1966 and 2010, demonstrated that the median effect size in placebo controlled drug trials dropped steadily during that period, reflecting that the new pharmaceuticals being tested were becoming less and less effective [5]. Significantly, during the last decade, 2001 to 2010, the average effect size achieved in studies was just 1.0 to 1.5. Although this decline might well be due to issues other than reducing drug efficacy, it is hard to write off the observed decline as solely due to secondary effects.

Thus, while illness is rising quickly, drug effectiveness seems to be declining. Combined, the rate of decline in public health is clearly outstripping the pace of scientific progress postulated by Planck. It is clear that real breakthroughs are needed, and it is becoming essential to reduce the delay between scientific discovery and clinical therapeutics.

The Science of Safety. The previous United States (US) Food and Drug Administration (FDA) Commissioner, Andrew von Eschenbach, in 2007 described a “Science of Safety” which “combines an understanding of disease and its origins at the molecular level (including adverse events) with new methods of signal detection, data mining, and analysis” [6]. However, that concept did not gain much traction, leading his successor, Margaret Hamburg, to state that the FDA is “left relying on 20th century approaches for the review, approval and oversight of the treatments and cures of the 21st century” [7]. Nevertheless, Eschenbach’s “Science of Safety” does serve as a useful definition of the role that molecular science could be playing in clinical medicine [8].

We have proposed that a safe, widely used blood-pressure drug, olmesartan, could be retargeted to a different indication, Amyotrophic Lateral Sclerosis (ALS). The FDA has insisted that the testing and approval process starts with a requirement to repeat the animal safety and carcinogenicity testing already performed in the original indication, hypertension. From that point the drug has to again traverse Phase 1, Phase 2, Phase 3 (and perhaps even Phase 4) clinical trials before gaining approval in the new indication, a process which takes, on average, around 12 years. Until we can figure out how to satisfy the FDA animal studies requirement, our research is at a standstill, and ALS remains a deadly disease without an effective therapy.

Einstein reminds us that “Insanity is doing the same thing over and over and expecting a different result.” Andrew von Eschenbach’s “Science of Safety” would allow regulators to use a science-based understanding of how the drug actually works, thus accelerating widespread availability of the drug in its new indication.

What is especially interesting is that our many scientific papers explaining the Science of Safety relevant to this retargeting were not deemed to be relevant by FDA examiners [9–10], even our explanations of why the drug behaves differently in a Rat vitamin D nuclear receptor (VDR) to a Human VDR [11].

Science is a moving target, currently growing with particularly rapidity. In just the five years since this “Science of Safety” was proposed, the Human Microbiome Project (HMP) has sequenced the genomes of thousands of microbes which make up the Human Metagenome. This led to the recognition that Man is a Superorganism, its metabolism driven not only by the approximately 26,000 genes of the human genome but by millions of genes from

the organisms which comprise its Microbiome. However, the FDA has failed to anticipate the resulting paradigm shift. To date, their primary response has been to halt the promising research on fecal transplants. FDA seeks to better understand how such transplants could possibly be 92% effective when treating antibiotic-resistant *Clostridium difficile* infection in the intensive care unit [12–14].

This untimely ban on fecal transplant research nevertheless illustrates exactly what a science-base would offer to Medicine — the ability to embrace change. Physicians are still taught to apply the 19th century Postulates of Robert Koch when looking for infectious disease causation, postulates which are anachronistic in this age of the (meta)genome. Physicians are taught that the human body is a sterile compartment at the same time molecular biologists are unlocking its secrets at the level of individual genes.

Thus there will almost certainly need to be paradigm change accompanying any real medical breakthrough related to the Microbiome. Although the distance between Koch's Postulates and Metagenomics is huge, more than 100 years have elapsed during which these postulates have remained on a shaky foundation. A half-century ago it was recognized that *Mycobacterium leprae* could only be replicated in the armadillo, while *Mycobacterium tuberculosis* and *Salmonella typhi* can persist in a latent state, without causing disease. It would seem that the description of how multiple organisms could come together in a Microbiota to cause disease should be readily acceptable, given the passing of more than 100 years. Rather than banning a scientifically compelling procedure with a promising outcome and an impeccable safety record, regulators should focus on embracing the new Metagenomic science.

Andrew von Eschenbach now chairs the Manhattan Institute's "Project FDA," which continues to encourage the FDA to allow molecular science to take a larger role in drug approval. Writing about a similar case of regulatory over-reach to that of the fecal transplant, a halt in autologous stem cell transplants, he recently pointed out that the agency thought "it had only called a time-out until it could apply its regulatory process designed to analyze the therapy's effectiveness and potential risks." Yet that "time out" effectively signals "game over" for American companies developing new, vital technologies [15].

Lacking an up-to-date scientific understanding, our regulators have additionally been too quick to incorrectly label "innovation" as "quackery." A science-base brings understanding, and understanding allows us to move beyond fear of the unknown. An "understanding of disease and its origins at the molecular level" allows us to embrace the true complexity of the human body. The FDA whose science is "relying upon 20th century approaches" necessarily leads to rejection of "cures of the 21st century," because "until FDA reviewers can be confident of the benefits and risks of a new technology, their duty is "to stop it" and "stop it they will" [15].

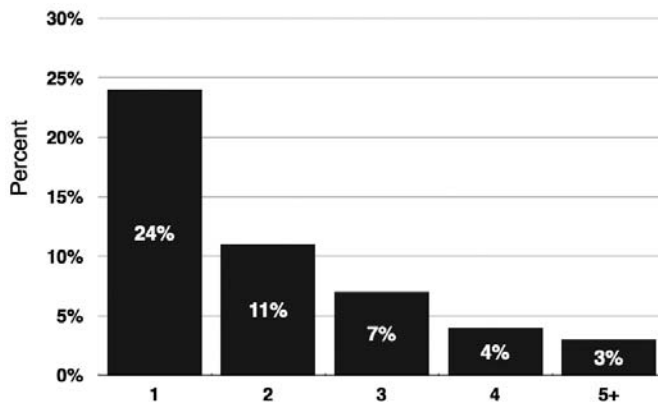
Standard of Care. Standard of Care arose as the legal concept of a general duty of care between individuals. But the need for measurement of this standard has caused it to evolve into a series of rules and regulations. In many countries a clinical "Standard of Care," from which a physician is essentially unable to deviate, is slowly being enshrined into law. Yet the standard of care for many chronic inflammatory diseases still relies upon two drugs more than half a century old, methotrexate and prednisone. There still is no cure for the majority of patients, just palliation of disease symptoms and an incessant fear of relapse.

Physicians who want to "try something new" with a patient run the risks of losing their licenses if they pursue their instinct, their training to "practice", and deviate from the stan-

dard of care. As Tonelli observed: “The epistemology of evidence-based medicine (EBM) categorizes expert opinion as the lowest form of medical evidence, superseded even by methodologically flawed clinical research” [16]. This presents a fundamental barrier to the adoption of complex scientific concepts, especially those representing a major paradigm change (such as discoveries surrounding the Human Microbiome).

Off-Label Prescribing. In the USA, as the FDA is responsible for certifying the efficacy of a drug for every specific indication, if a physician wishes to prescribe the drug for use in a different diagnosis then that is considered an “off-label” prescription. When the intent is the “practice of medicine” a physician may use a product for an indication not in the approved labeling. Should they do so, they have the “responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects” [17]. Off-label prescribing is quite prevalent in the USA, especially in those many diagnoses which are not well-served by approved medications.

The “practice of medicine” by primary care physicians. Physicians in general family practice are often looking at a significantly different population from that which was used by regulators to test safety and efficacy of the pharmacopoeia.



Source: Johns Hopkins University, Partnership for Solutions. 2001. Medical Expenditure Panel Survey.

Fig. 2. Number of chronic conditions suffered by Americans [18]

The US FDA has historically matched drugs to indications one by one. There has been little effort spent examining a drug’s behavior when comorbid conditions are present, and the cohorts selected for drug studies are almost invariably selected only if no comorbid diagnoses are present.

Yet the general family practice physician deals with a patient load where comorbidities are more common than not. Figure 2 shows that although 24% of the US population has one chronic diagnosis, a total of 25% are suffering from more than one comorbid condition [18].

Thus it is these physicians who are most likely to first observe interactions between the drugs they prescribe for the differing comorbidities, and also observe increased or reduced efficacy of drugs due to potential interactions. It would seem sensible to try and

harness the expertise they develop from their practice, yet the exact opposite seems to be happening. A regulatory environment has arisen where the average US physician lives in fear of regulatory authority, authority which more typically seems to dispense discipline than kudos.

Should a physician deviate from standard of care they run the risk of being disciplined by their Medical Boards, accused of unprofessional conduct, incompetence, or even gross negligence. Each US State has its own Board of Medicine, which is typically staffed by political appointees. Thus, there tends to be a disconnect between reports in the scientific literature, which is global in its reach, and the standard of care, which is administered by local peers.

Discipline of physicians who “think outside the box”. A decade ago we published a hypothesis in *Vestnik MKDTS (Kazan)* [19], outlining a mechanism by which persistent intracellular microbes could manipulate the human Interactome so as to cause a wide spectrum of chronic disease. We described early success in the idiopathic disease Sarcoidosis when retargeting a drug initially approved for hypertension, olmesartan medoxomil, by altering its dosing schedule. As the decade passed by, the science gelled, and we continued to publish papers describing that science in ever more detail. We received emails and phone calls from physicians all over the world seeking therapeutic options for patients who were generally too ill to respond to “standard of care.” Using an Internet website for coordination, a diverse group of physicians took the initiative to successfully prescribe olmesartan, off-label, in a wide variety of chronic conditions ranging from Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) [20] to Ankylosing Spondylitis [10].

The key to our intervention is its apparent stimulation of the human innate immune system, and its ability to thus counteract a major survival pathway by which the accumulating human microbiome ensures its own persistence. But immunostimulation is a diametrically different approach from the prednisone and methotrexate anti-inflammatories so often used in these diseases, and many of the biomarkers commonly used in clinical practice fail to be useful during immunostimulative therapy.

Worse, one of them, serum creatinine, sometimes indicates kidney failure when no kidney damage is actually present. Our drug appears to activate the VDR, which is known to down-regulate renin (see, for example, Figure 1 in Porsti [21]). Thus even though creatinine might seem elevated, the kidneys appear to escape harm most likely due, in part, to the suppression of renin. There have been a number of papers by other research groups detailing these issues [5, 21–23].

Yet there remain physicians who are not interested in reading scientific papers, and who prefer to insist that their colleagues, those trying to apply emerging technologies, adhere solely to the standard of care.

The first major complaint was laid with the “College of Physicians and Surgeons of British Columbia” against a Canadian colleague who was accused of “causing kidney damage” to a patient. After investigation, the College noted that the lab parameters demonstrated a risk of acute renal failure, but did not reflect actual renal injury. The College dismissed the complaint noting that:

“Literature supporting the elements of the protocol: the induction of autoimmune disease by vitamin D receptor dysfunction and the vitamin D metabolites being clinical markers in autoimmune disease and chronic disease, is also abundantly referenced, including in the two papers cited... from the prestigious *Annals of the New York Academy of Sciences*.”

Although Canada might have recognized the criteria enshrined in FDA's guidance for off-label prescribing, Washington State (just a few hundred miles away) was not willing to apply the same standards. An essentially identical complaint was laid against a physician in Washington State, who was only able to retain her license by promising never to use this new science again, and to have her prescribing activities supervised by a Preceptor. Additionally, the disciplinary order was made public, subjecting her to public and professional ridicule [24].

Worse, in Arizona, a practitioner was arrested and charged with "Criminal Child and Vulnerable Adult Abuse." She has lost her license, and is waiting to hear if she will go to jail. This on substantially the same accusation and evidential base as was dismissed in Canada. In this case the professional ridicule has included television news broadcasts showing her clinic being raided by police, and her arrest "mugshot" being freely available by Internet search.

Legislative Initiatives — "Emerging Medical care" in California. In 2005, the State of California noted that "Since the National Institute of Medicine has reported that it can take up to 17 years for a new best practice to reach the average physician and surgeon, it is prudent to give attention to new developments not only in general medical care but in the actual treatment of specific diseases, particularly those that are not yet broadly recognized in California" [25].

The subsequent amendment to California's "Business and Professions Code" enshrined that no physician could be accused of unprofessional conduct "solely on the basis that the treatment or advice he or she rendered to a patient is emerging care" [25]. Essentially, a patient must first be informed as to the standard of care for the diagnosed condition, and must give informed consent to the non-standard treatment.

There are additional due-diligence riders, including the necessity to undertake a competent medical examination and to document an indication for treatment. Following opposition from the Medical Oncology Association of Southern California, language was inserted to ensure that any therapy "does not cause a delay in, or discourage traditional diagnosis of, a condition of the patient." In practice, this additional language has not reduced the effectiveness of this legislation.

With just 300 words, the California legislature thus removed the fear of arrest, or professional ridicule, from physicians in California who, in the course of their medical practice, might wish to employ "Emerging Medical Care." Not only they have been freed to practice medicine to the very best of their ability, but patients have been empowered to become an active participant in their own therapy.

The Science of Safety is an essential precursor to medical progress. Another barrier to the successful development of innovative therapies is the over-reliance on animal models. Testing in mice remains the cornerstone of the drug approval process for many regulatory agencies, especially the FDA. While several decades ago, differences in the metabolism and immune response of mice and men may have been less apparent, molecular science is increasingly pointing out wide discrepancies between the genomes of the two species. Despite this, results from human and murine studies coexist in the literature without clear discrimination, making species-related differences increasingly difficult for doctors and researchers to assess. Thus, while the symptoms of an inflammatory condition can sometimes be re-created in a mouse model, the development of such symptoms may not actually result from the same molecular processes which drive such pathology in *Homo sapiens*.

While the murine immune response relies on a cascade of nitric oxide, the human innate immune response is governed in large part by nuclear receptors that have little homology in mice. For example, in *Homo sapiens*, the VDR controls key components of innate immunity including the beta-defensin and cathelicidin antimicrobial peptides, as well as the expression of TLR-2. However, the murine VDR does not even express cathelicidin [26]. Indeed, Gombart *et al.* have described an Alu-mediated divergence in steroid hormone nuclear receptor gene regulation between humans/primates and other mammals [27]. This divergence has remained under purifying selection for around 55–60 million years, and has placed the cathelicidin pathway under VDR control only in humans and closely related primates. Even so, cathelicidin is still regulated in primates differently than in man. This marks a great difference in the way the two species react to intracellular pathogens. It also means that many of the pathogenic components of the murine microbiome must have developed different survival mechanisms from those used by pathogens to populate the human microbiome. As an increasing number of inflammatory diseases are tied to alterations in microbiome composition, these differences make murine metabolites even more distant from those driving human disease.

Our molecular research confirms differences in the structure and function of murine VDR. We have shown that the medication olmesartan medoxomil binds into a different conformation in the murine VDR than it does when it binds into the human VDR [11]. This means that efforts to test the efficacy of olmesartan medoxomil in mice will almost certainly lead to faulty outcomes that cannot successfully be translated to humans. This species-specific variation was observed (and ignored) in the studies which were previously performed to enable FDA to evaluate carcinogenicity of the drug in its hypertensive indication. The FDA Prescribing Information summarizes [28]:

“Both olmesartan medoxomil and olmesartan tested negative in the in vitro Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung) and tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. Olmesartan medoxomil tested negative in vivo for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).”

Seok and 39 other authors recently published a seminal study [29]. This study compared the human immune response to the murine immune response during periods of significant inflammatory challenges. The team observed clear discrepancies between the immune related responses demonstrated by each species. Acute inflammatory stressors from different etiologies resulted in similar genomic responses among human subjects. However, the corresponding inflammatory responses in mice correlated very poorly. Indeed, in cases where inflammatory stress impacted the expression of human genes, murine models were close to “random chance” (50:50) in matching those of their human counterparts. This randomness is confounded by the inbred nature of the mouse model and the fact that human subjects and mouse models often have different temporal spans of recovery. Additionally, in the words of Seok *et al.*, “late events related to the clinical care of the patients (such as fluids, drugs, surgery, and life support) likely alter genomic responses that are not captured in murine models.”

Nevertheless, the US FDA will not allow studies in human subjects to move forward in the absence of murine data, leading to a catch-22 situation in which arguably the most innovative and significant new drugs simply cannot get out of the starting blocks.

Discussion. One of the problems facing today's FDA is that it considers its role to be "regulatory science" [7]. Yet, "regulatory science" is essentially an oxymoron, as regulations are fixed, immovable, unchangeable, whereas science is dynamic and constantly changing. Achieving the appropriate balance between these two elements is difficult. A philosophical discrepancy between reasoning of an experimental scientist (targeted on the truth revealed by intentional tests and mistakes) and clinical reasoning of a medical doctor (targeted on benefit for a patient and avoidance of any mistakes) is obvious and needs special harmonization during medical education, which was discussed elsewhere [30]. However, we have seen little recognition of this dichotomy amongst the FDA leaders we have interviewed. For at least the last five years it seems as though the regulatory focus has been strengthened, and the dynamic nature of science has been de-emphasized.

Yet this has occurred at the same time the pace of scientific change has quickened in research labs and clinics. Five years ago the Human Microbiome Project was just beginning. The subsequent understanding of the Microbiome, and the emerging field of Metagenomics, is turning molecular biology on its head. Our experience is that many individual physicians seem to recognize a responsibility to keep pace with this degree of scientific change. It is thus sensible to enlist skilled Physician Expertise into both drug evaluation and post-marketing observation.

In his article "Medical Innovation: How the U.S. Can Retain Its Lead," Andrew von Eschenbach has proposed that FDA could institute pilot programs to accelerate promising therapies by allowing them to be approved based on safety, with efficacy to be proven in later physician-based trials [8]. This would facilitate the ability of physicians to play a bigger role in helping assess the efficacy of emerging medical therapies.

Many physicians contact us about our research. However, more often than not, upon follow-up we find that the fear of being questioned about off-label prescribing has tempered their desire to help their patients. Many physicians do not have time to explain their detailed scientific rationale to, for example, a pharmacist who is questioning a prescription. They also worry that a formal complaint might be lodged. Physician expertise can therefore only be harnessed once a physician's fear of public ridicule and career destruction has been removed. However, even California's relatively modest legislative initiative has shown that it can overcome these barriers.

There is a concern that patient safety might be compromised if "renegade physicians" were to become more prevalent as restrictions on a physician's practice are relaxed. However, one only has to glance through consumer magazines, or surf the Internet, to find that there are already plenty of dubious offers being made to patients based on loopholes in the current regulatory regime. The benefits to society from harnessing physician expertise would seem to transcend such concerns.

It is clear that if the future economic burden of chronic disease is to be reduced, a balance has to be drawn between the quest for absolute safety and the need for real therapeutic breakthroughs. Without a renewed regulatory focus on science, it is difficult to see how any real breakthroughs are going to be achieved.

References

1. Kuhn T.S. The structure of scientific revolutions. Chicago: University of Chicago Press, 1962. 172 p.
2. Anderson G., Horvath J. The growing burden of chronic disease in America // Public health reports. 2004. May-Jun. Vol. 119(3). P.263–270. PubMed PMID: 15158105. Pubmed Central PMCID: 1497638.
3. Van Cleave J., Gortmaker S.L., Perrin J.M. Dynamics of obesity and chronic health conditions among children and youth // The Journal of the American Medical Association. 2010. Feb 17. Vol. 303(7). P.623–630. PubMed PMID: 20159870.
4. Wu S.Y., Green A. Projection of chronic illness prevalence and cost inflation. Santa Monica, CA: RAND Health, 2000.
5. Olsson M., Marcus S.C. Decline in placebo-controlled trial results suggests new directions for comparative effectiveness research // Health affairs. 2013. Jun. Vol. 32(6). P.1116–1125. PubMed PMID: 23733987.
6. FDA. gov. Overview of FDA Mission, Statement of Andrew C. von Eschenbach, M.D. Commissioner of Food and Drugs, before the House Committee on Oversight and Government Reform 2007 [accessed May 15, 2013]. Available from: <http://www.fda.gov/NewsEvents/Testimony/ucm154019.htm>.
7. FDA. gov. Remarks as Delivered of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, National Press Club Speaker Luncheon 2010 [accessed May 15, 2013]. Available from: <http://www.fda.gov/NewsEvents/Speeches/ucm229195.htm>.
8. von Eschenbach A.W. Medical Innovation: How the U.S. Can Retain Its Lead // Wall Street Journal. Feb 14, 2012 [accessed May 15, 2013]. Available from: <http://online.wsj.com/article/SB10001424052970203646004577215403399350874.html>.
9. Proal A.D., Albert P.J., Marshall T.G. The human microbiome and autoimmunity // Current opinion in rheumatology. 2013. Mar. Vol. 25(2). P.234–240. PubMed PMID: 23370376.
10. Proal A.D., Albert P.J., Blaney G.P. et al. Immunostimulation in the era of the metagenome // Cellular & molecular immunology. 2011. May. Vol. 8(3). P.213–225. PubMed PMID: 21278764.
11. Marshall T.G. Molecular static and dynamic analyses reveal flaw in murine model used by US FDA to detect drug carcinogenicity: Nature Precedings; 2007 [accessed May 15, 2013]. Available from: <http://precedings.nature.com/documents/52/version/1>.
12. Kassam Z., Hundal R., Marshall J.K., Lee C.H. Fecal transplant via retention enema for refractory or recurrent Clostridium difficile infection // Archives of internal medicine. 2012. Jan 23. Vol. 72(2). P.191–193. PubMed PMID: 22271132.
13. Flore K. Fecal Transplant: FDA Wants Regulation: MedPage Today; 2013 [accessed May 15, 2013]. Available from: <http://www.medpagetoday.com/InfectiousDisease/GeneralInfectiousDisease/39169>.
14. Petrochko C. More Evidence Fecal Transplant Clears C. diff: MedPage Today; 2013 [accessed May 15, 2013]. Available from: <http://www.medpagetoday.com/MeetingCoverage/DDW/39351>.
15. Manhattan Institute. Andrew von Eschenbach 2013 [accessed May 15, 2013]. Available from: <http://www.manhattan-institute.org/html/eschenbach.htm>.
16. Tonelli M.R. In defense of expert opinion // Academic medicine: Journal of the Association of American Medical Colleges. 1999. Nov. Vol. 74(11). P.1187–1192. PubMed PMID: 10587679.
17. FDA. gov. “Off-Label” and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices — Information Sheet 2011 [accessed May 15, 2013]. Available from: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>.
18. Partnership for Solutions National Program O, Partnership for Solutions JHU. Chronic conditions: making the case for ongoing care. 2004.
19. Маршалл Т. Г., Маршалл Ф. Е., Фенстер Б. Антибактериальная терапия вызывает ремиссию при саркоидозе // Вестн. МКДЦ (Казань). 2004. Т. 3, № 1. С. 123–129.
20. Proal A.D., Albert P.J., Marshall T.G., Blaney G.P., Lindseth I.A. Immunostimulation in the treatment for chronic fatigue syndrome/myalgic encephalomyelitis // Immunologic research. 2013. Apr 11. PubMed PMID: 23576059.
21. Porsti I.H. Expanding targets of vitamin D receptor activation: downregulation of several RAS components in the kidney // Kidney international. 2008. Dec. Vol. 74(11). P.1371–1373. PubMed PMID: 19008907.
22. Palmer B.F. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatinine and/or serum potassium concentration rises. Nephrology, dialysis, transplantation // The European Dialysis and Transplant Association — European Renal Association. 2003 Oct. Vol. 18(10). P.1973–1975. PubMed PMID: 13679467.
23. Ryan M.J., Tuttle K.R. Elevations in serum creatinine with RAAS blockade: why isn't it a sign of kidney injury? // Current opinion in nephrology and hypertension. 2008. Sep. Vol. 17(5). P.443–449. PubMed PMID: 18695383.

24. Dept of Health SoW. Stipulated findings of fact, conclusions of law, and agreed order, Case M2012–269. 2012.
25. Legislative Counsel SoC. ASSEMBLY COMMITTEE ON BUSINESS AND PROFESSIONS 2005 [accessed May 15, 2013]. Available from: <http://goo.gl/OfLEB>.
26. *Brahmachary M., Schonbach C., Yang L.* et al. Computational promoter analysis of mouse, rat and human antimicrobial peptide-coding genes // *BMC bioinformatics*. 2006;7 Suppl 5:S8. PubMed PMID: 17254313. Pubmed Central PMCID: 1764486.
27. *Gombart A. F., Saito T., Koeffler H. P.* Exaptation of an ancient Alu short interspersed element provides a highly conserved vitamin D-mediated innate immune response in humans and primates // *BMC genomics*. 2009. Vol. 10. P. 321. PubMed PMID: 19607716. Pubmed Central PMCID: 2716374.
28. *Daiichi S.* Benicar® (olmesartan medoxomil) tablets 2012 [accessed May 15, 2013]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021286s023lbl.pdf.
29. *Seok J., Warren H. S., Cuenca A. G.* et al. Genomic responses in mouse models poorly mimic human inflammatory diseases // *Proceedings of the National Academy of Sciences of the United States of America*. 2013. Feb 26. Vol. 110(9). P. 3507–3512. PubMed PMID: 23401516. Pubmed Central PMCID: 3587220.
30. *Зайчик А. Ш., Чурилов Л. П.* Врач, пациент и общество. Часть II. «Жрец — Страждущий»... «Учитель — Ученик» // *Медицина XXI век*. 2009. №1 (14). С. 91–96.

Статья поступила в редакцию 21 мая 2013 г.