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Quote to note

The Road To Wisdom

The road to wisdom? — Well,
it's plain
and simple to express:
Err
and err
and err again
but less
and less
and less.

— Piet Hein

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Pharmacogenomics: promise, prospects, and potential problems

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Buzzwords are usually short and punchy, but for the last three or four years the biggest buzzword in the pharmaceutical industry has been the ungainly six syllable "pharmacogenomics." It first appeared in the Lexis/Nexis database in April 1997; in 2000 it appeared in over 1,000 articles. But though it may now roll trippingly off many tongues, few yet understand the promise it holds, the prospects for its success, or the challenges its success could bring.

The promise

People respond to drugs in different ways. Children should not take aspirin because it is associated with Reye's syndrome in them, though not in adults. For some people, acetaminophen works best against headaches; other people get better relief with aspirin or ibuprofen. Most people tolerate penicillin quite well; about one out of 10,000 patients who use it go into life-threatening anaphylactic shock.

Pharmacogenomics is based on the idea that genetic variations account for some of the differences in how people interact with drugs.[1,2] The genetic variations involved are often alleles of genes involved in drug metabolism. The Cytochrome p450 gene super-family provides good examples. Humans have more than 30 of these genes, many of which have common variations called polymorphisms.

Some polymorphisms lead to variations in metabolism. In some cases they speed drug metabolism, leading to undertreatment; in others, they inhibit drug breakdown, leading to the risk of overdoses. In still others, they completely prevent molecular transformations. For example, codeine is a molecule closely related to, but different from, morphine. As codeine, it has no pain relieving ability, but the body transforms it into morphine. At least, most bodies do. About 4 to 10 percent of Americans have a polymorphism in one Cytochrome p450 gene, CYP 2D6, that, among many other things, prevents the transformation of codeine into morphine. As a result, these patients get no relief from codeine. Polymorphisms in the Cytochrome p450 system affect the metabolism of such drugs as beta blockers, antidepressants and antipsychotics.

Other kinds of genetic variations can also affect drug efficacy and safety. Genetic variations in cancer cells can make them susceptible to, or resistant to, different kinds of treatments. Genetic variations in Mycobacterium tuberculosis can make it resistant to any or all anti-tuberculosis drugs; variations in the genome of the strain of HIV infecting a patient can affect the speed with which it develops an immunity to some drugs. A list of genetic variants that are presently known to affect drug therapy is available on the Internet.[3]

For patients, the promise of pharmacogenomics is that genetic variations relevant to them can be assessed before a

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treatment is prescribed. With that knowledge, doctors can choose therapies that are safer and more effective. For the pharmaceutical industry, pharmacogenomics holds the promise of reviving drugs that were shelved, before or after FDA approval, because they were only effective in some patients — or because they were deadly to some patients. For some biotechnology companies, pharmacogenomics could provide a market for their patented genetic tests, or for human genetic variations important to pharmacogenomics that they have patented.

The prospects

Pharmacogenomics has been hailed as the next great drug breakthrough for nearly five years. The completion of the sequencing of the human genome increased the argument for pharmacogenomics; genetically "individualized medicine" became a major claimed benefit for the Human Genome Project. But the fact that genetic variations influence drug response has been known for more than a decade and clinical applications of pharmacogenomics remain uncommon. A few cancer centers test whether patients have a normal form of thiopurine methyltransferase before providing certain chemotherapy for acute lymphocytic leukemia; those few patients who lack functional copies of the gene for this enzyme can die from normal chemotherapy doses. The drug Herceptin is approved for use against only those metastatic breast cancers that over-express the HER2 protein gene. At least one clinical laboratory offers commercial testing for alleles of one Cytochrome p450 gene, CYP 2D6, but this testing is not in common use.

Why so little progress? The barriers are not all scientific. Few doctors are trained in pharmacogenomics. Even a trained doctor must start with a genetic test of a patient, a tumor or a pathogen, but genetic diagnostics are new, not generally provided by pharmaceutical companies, and may not be covered by health plans. Pharmaceutical companies may worry that dividing patients more accurately into those who will and will not benefit from their drugs will reduce their markets. They may also worry that testing requirements and warning labels will not protect them from liability if a "wrong" patient takes a drug and dies.

The FDA's reaction to pharmacogenomics remains unclear. How much evidence, and what strength of evidence, will it require to approve drugs that either work for a small and identifiable part of the population or that harm a small and identifiable number? How will it regulate, if at all, the genetic tests essential to using pharmacogenomics? These questions of regulation, liability and, fundamentally, of business consequences may be at least as responsible for the slow movement of pharmacogenomics as scientific uncertainty.

Ironically, pharmacogenomics could be advanced by lawsuits claiming that advance genetic testing should have been done — at least one such suit is pending against Glaxo SmithKline for its Lyme disease vaccine. But the likelihood that tort or product liability suits will advance the *rational* use of new therapies seems, at best, speculative.

The potential problems

In addition to commercial, legal and regulatory problems, pharmacogenomics raises at least four ethical concerns: treatment choices, privacy, "orphan" genotypes and race.

Consider this plausible scenario. A patient has been diagnosed with a fatal cancer. A new (and very expensive) drug has been approved that successfully treats some patients with that type of cancer. But the health plan's doctor says that the patient doesn't qualify for the treatment because her cancer is not the type responsive to this treatment. For her, there is no treatment other than palliation and no prognosis other than a rapid death. She refuses to go quietly and demands the new drug. The health plan balks. Should she get it?

This story is a dramatized version of a controversy over Herceptin. The FDA-approved labeling says, "Herceptin should only be used in patients whose tumors have HER2 protein overexpression." But desperate patients with metastatic breast cancer have been asking for "off-label" use of Herceptin. That's legal, but health plans paying the more than $3,000 per week for the drug do not always consider it appropriate. Herceptin is not a miracle drug for most users, but for those who over-express HER2, it does, on average, extend the length of life and improve its quality.

Dramatic stories make hard cases. In fact, doctors regularly (perhaps not regularly enough) refuse to prescribe treatments for patients that won't help them and health plans regularly refuse to pay for such treatments. Pharmacogenomics just seems different because we know this same drug will help some people with the same disease.

If the science behind a refusal to prescribe is good, the denial raises no ethical issues. But how "good" must the science be and what probabilities must it project? Should a patient with a 30 percent chance of benefiting receive the drug? Ten percent? One-tenth of a percent? How much evidence must support those probabilities? Refusing to pay for (or to prescribe) ineffective or unsafe drugs is simple in principle; the application is hard. Pharmacogenomics will make it harder.

For these treatment dilemmas to arise, physicians (and insurers) will have to gather information about many individuals' genomes. Genetic information is already sensitive. "Genetic privacy" statutes have been introduced in Congress and have passed in several states. Expanding the amount of individual genetic data collected will expand concerns about the privacy of that data. On the other hand, these concerns may already be exaggerated. That information is "genetic" does not, in itself, make it any more, or less, sensitive than any other medical data. The genetic data necessary for pharmacogenomics seems likely to have much less sensitive implications than genetic information that, for example, predicts a high likelihood of a dread disease.

Another new term,"orphan genotypes," provides a third concern. Assume a new drug is safe and effective for 99 percent of the population but, for the remaining 1 percent — who can be identified in advance by genetic testing — it is either ineffective or has terrible side effects. What incentive would companies then have to find a drug that would help all those in need? Would more people be helped by the approval of drugs limited to certain subpopulations than will be hurt by a diminution of incentives to find drugs for excluded subpopulations? One answer might be to avoid the question by creating incentives for companies to find drugs for the excluded groups. The term "orphan genotype" comes from "orphan diseases" — diseases with too

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Ask the ethicist:

Conflicting advance directives

Question: A 68-year-old woman was admitted for treatment of a large cardioembolic left hemispheric stroke in the setting of atrial fibrillation. Several years previously, she had named her husband her Durable Power of Attorney for Health Care (DPAHC). She had annotated this document to state that if she were ever permanently incapacitated and unable to communicate, she wished all treatments including artificial hydration and nutrition (AHN) to be discontinued. Basing their conclusion on MRI findings after two weeks, the neurologists informed the family that she would have permanent aphasia and right-sided paralysis. Her physicians offered placement of a feeding gastrostomy tube. When her husband learned that she would die without it, he consented to the surgery. Their two daughters were upset that their mother's expressed wishes were being ignored. The physicians then were uncertain whether they should respect the patient's previous written directive or the current directive of her DPAHC. How would you advise them?

Response: A DPAHC may make any treatment decision on behalf of an incapacitated patient that the patient could previously make. Neither a patient with capacity nor a legally appointed surrogate may demand a specific treatment, but both may refuse even life-sustaining treatment. The "living will" portion of a Health Care Proxy and annotations on a Durable Power of Attorney are written advance directives stating the patient's wishes. They are best regarded as the patient's advice to her legal surrogate and her professional caregivers. State proxy laws vary: a DPAHC who lacks knowledge of the patient's wishes may usually make a decision about AHN in the patient's "best interests." In New York State, however, a DPAHC ("Health Care Agent") who is not aware of a patient's wishes about AHN will not be able to make decisions about these measures. Institutional pressures may make it difficult to justify failure to place a feeding tube, but physicians must never act against what they consider to be the best interests of the patient. If the treating physician favors AHN and no proxy decision is available, a court must consent to surgery on the patient's behalf.

Two weeks after an embolic stroke, a prognosis of permanent loss of ability to communicate and permanent paralysis is difficult to make. Moreover, failure to regain the ability to take food by mouth is unusual after unilateral hemispheric insult. The physicians are obliged to indicate a reasonable range of possible outcomes, to be sure that the proxy's consent or refusal of treatment is "informed." They should explore the husband's understanding of the patient's advance directive in detail. Perhaps he believes she meant permanent, total inability to communicate or complete hemiplegia. Neither of those conditions is a likely outcome of an embolic stroke. He should also understand the handicap imposed by lesser degrees of dysphagia, dysphasia and hemiparesis. Because good ethics begins with good medicine, the patient or DPAHC must receive accurate medical information and must understand it. Otherwise, consent or refusal cannot be truly informed.

The efforts of the patient's attending physician or an ethics consultant should be directed at helping her husband to understand and accept his role: he is to decide as the patient would decide, not as he thinks best or in response to his anticipatory grief at losing his wife. If he accepts the physicians' prediction, he must also be helped to understand that his wife has chosen not to prolong her life under such circumstances. If he continues to insist on the feeding tube, it may be helpful to assure him that there is no legal or moral difference between refusing and withdrawing a treatment. He will be able to decide at a later date to discontinue the treatment if his wife does not become self-sufficient or recover her ability to communicate.

The patient created a written advance directive that her husband was obliged to follow. If in the years following the creation of this directive she had told her husband that she had changed her mind and would accept AHN, he could conform to her oral instruction. In practice, the DPAHC often fails to decide in accordance with the patient's expressed wishes. In this case, one or both daughters could seek to remove their father from his role as legal surrogate through court action. A physician responsible for the patient's care may also seek to have a legal guardian appointed to replace a DPAHC who appears to be acting against the patient's instructions. A court, however, is not likely to replace as DPAHC a spouse who is able to demonstrate his understanding of the situation the patient faces and the predicted consequences of various treatment decisions.

Physicians are not obligated to respect the wishes of family members who have not been appointed to be the patient's proxy, but they are understandably mindful of the rifts among family members that often follow on the death or incapacitation of a loved one, and may try to preserve family unity, reasoning that their patient would wish for that outcome. Family dynamics are complex, however; even the principals in a conflict may not fully understand them. It seems most prudent, therefore, to offer information and mediation, but not attempt to manage the disagreement or impose unwanted treatment. In this instance, the physicians merely offered the tube feeding, as they should. They did not try to force-feed their patient. This was a wise decision.

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Outcome: After several days, the daughters succeeded in persuading their father that a feeding tube should not be inserted. The patient died approximately a week later. □

Suggested Reading

[1] Bernat JL. *Ethical Issues in Neurology*, 2nd ed. Boston: Butterworth-Heinemann, 2002:79–104;157–81.

[2] Goldblatt D. A messy necessary end. Health care proxies deserve our support. *Neurology* 2001;56:148–52.

[3] Goldblatt D. Who's listening? Advance directives are not always directive. *The Neurologist* 2001;7:180–5.

The legal column:

The human chimera patent initiative

By Stuart A. Newman, PhD
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New York Medical College, Valhalla, NY

Listening to Congressional debate last July on H.R. 1644, the Human Cloning Prohibition Act of 2001,[1] many people were surprised to learn that the United States has no Federal laws prohibiting manipulation of human embryos chemically or genetically, or the bringing to term of any such embryo. This situation, which is out of line with that in Europe, Japan and a growing number of countries throughout the world, was on my mind in 1997 when, with the help of the social critic Jeremy Rifkin, president of the Foundation on Economic Trends in Washington, D.C., I decided to apply for a patent on embryos and animals containing human along with nonhuman cells — so-called "chimeras."

I had no intention of producing such creatures, nor does US patent law require that an actual prototype for an invention be supplied, only that feasibility be demonstrated, as well as novelty and utility. But ever since the 1980 Supreme Court decision in *Diamond v. Chakrabarty*,[2] it has been legal in the United States to obtain a patent on living organisms and their descendants. Moreover, Congress has drawn no line that would preclude a preterm human embryo, if appropriately modified, from being patented. Nor has it indicated how many human genes or cells an animal would have to contain before it could *not* be patented by virtue of the Constitutional protections pertaining to members of the human community. While a decision as to patentability by the US Patent and Trademark Office (PTO) would not control whether or not it would be legal to produce human-animal chimeras, or other types of biologically manipulated humans, we considered that applying for a chimera patent would raise these issues before the public and the legal system in a particularly dramatic fashion.

In the legal process that ultimately led to the *Chakrabarty* decision, an appeals court overruled the PTO's original rejection of the General Electric Corporation's application for a patent on oil-eating bacteria in an opinion that stated, absurdly, that bacteria are "more akin to inanimate chemical compositions … [than] to horses and honeybees and raspberries and roses." Within a few years, however, the *Chakrabarty* decision had served as a precedent for the issuing of patents on mice, pigs and cows, some containing introduced human genes, as well as on naturally occurring human bone-marrow cells.

As a research scientist in the field of embryonic development who has been concerned that the fruits of this work not be used to society's detriment, I acted on Rifkin's suggestion to invent something that was useful but also so disquieting that it would alert the public to the consequences of unrestricted technological development in this area. The proposed human-animal chimera, whose production would depend on techniques developed in the 1980s that led to the actual generation of "geeps" — animals that were part-goat and part-sheep[3,4] — could contain anything from a minuscule proportion to a majority of human cells. Like the geep, a human-chimp chimera would have recognizable resemblances to both originating species, perhaps stronger and hairier than a human, with mental qualities of both person and ape.

The proposed applications of this invention included the use of partly human embryos to test drugs and chemicals for toxicity, and the use of partly human animals as sources of tranplantable organs for human patients. It is clear from such examples that biotechnology is capable of producing items that, while legal and eminently useful, could nonetheless conflict with other cultural values, and would therefore be considered immoral and undesirable by many people.

Scientists can make such things, but would they? If so, would anyone market them and would physicians and the public accept their use? At the time our original filing was announced in early 1998, advocates of the patenting of organisms, including the scientist who patented the first mammal (the "Oncomouse," a research animal that developed cancer at 40 times the normal rate) criticized us for scaremongering. They accused us of presenting monstrous concoctions that no responsible scientist would contemplate producing or patenting. Since then, though, the Massachusetts biotechnology company, Advanced Cell Technology, has obtained a patent on a technique for creating cloned embryos produced from human cell nuclei and cow eggs. And the Geron Corporation of California, which holds licenses on patents for human embryo stem cells, has acquired the Scottish company that holds the patents on the cloning techniques that produced Dolly the sheep.

Indeed, the driving force behind the Congressional Human Cloning Prohibition Act, mentioned above, was concern about the desire of Geron and a number of university-based researchers, as well as patient advocate groups, to produce cloned human embryos to serve as sources of donor-matched human embryo stem cells. Such embryos would be both laboratory materials and potential children for anyone reckless enough to ignore the disastrous biological results of animal cloning experiments. The latter scenario has advocates in the scientific and medical communities, some of whom were afforded the prestigious forum of the National Academy of Sciences this past August. Because H.R. 1644 intended to block the possibility of full-term cloning by prohibiting the production of cloned embryos, it was supported by commentators across the political spectrum, including some prominent abortion rights advocates, and was passed with a bipartisan majority. (It is due to come before the Senate in early 2002). Among the scientific societies and their allies in Congress, however, this position was a minority one.

These developments suggest that, in the absence of binding restrictions — which would represent a societal agreement not to cross certain troubling lines

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Ethics and the humanities:

Wardlife: The Apprenticeship of a Young Writer as a Hospital Clerk

By Andrew Steinmetz
Vehicule Press, Montreal, Quebec, 1999

Review by John L. Wright, MD
Clinical Professor Emeritus
University of Washington, Seattle

It is not unusual that a young writer has a "daytime" job, but in Andrew Steinmetz's case his daytime job is what makes this, his first book, so valuable to healthcare professionals. Here's how he describes his role at a large metropolitan medical center: "I am a unit co-ordinator. A civilian among the troops. I sit with a dummy terminal beside a telephone with more keys than an accordion. I'm the one who relays messages, calls for reinforcements. A kind of in-house, on the scene dispatcher. … Someone who sits on the guard rail between sickness and health, whistles while he works, someone who knows as little magic as medicine and practices the authority of neither."

And it's from this perch, half in the intensive care unit (ICU), half in the emergency department (ED), that Steinmetz, with the perception and imagination of a good writer, of a poet, really, takes the time to write down, first as "finger exercises," the observations that so enrich this collection of "snapshots, still lifes, etudes."

On one level, I imagine Steinmetz as a young scientist penciling on graph paper — clean, factual, nonjudgmental — his findings. It's as if he's observing a colony of ants going about their daily routines unaware of mortality. In describing the ICU, he writes, "The nurses, residents, students, and staff doctors thrive on the spaciousness and overall newness of the place; it seems to have a placebo effect on everyone." Or again, "In come a surgery team on rounds. The chief resident leads the way, followed closely by his brood, a mix of junior residents and students hugging clipboards and nibbling Styrofoam cups. Patients rounds, these are imprinting rounds. A ragged bunch, their circadian rhythms hang on them like loose underwear. No surprise, the hours they keep are ridiculous. I wonder how their endogenous clocks are set?"

But Andrew Steinmetz is not detached. He shows us the full range of human behavior as it is played out, scene by scene in the ICU and ED, and he shows it in such a way that readers see beyond the common hierarchies to our common fate. He knows that we who walk these busy hallways, or lie in bed as patients, are aware of our mortality, however much we feign to disguise it. And it is this tension that he writes about, often using spinal-fluid-clear metaphors to maintain that strange balance between the humor and the pathos that is our life.

Of visitor P, whose wife is waiting for a liver transplant, a man he guesses is a smoker, age 45 to 50, he writes, "He wears that look of inadequacy to which men who live surrounded by a family of women commit themselves: doubtful, inadequate, a man who has worked a good while at a solitary trade, computers or engines, and now has been dropped — mid-stride — face to face with the uncertainties and vagaries of people." And later — Steinmetz often carries a single story over several intervening snapshots giving it depth — P is joined by D, both men's wives near death. At first they are strangers, "… now and then imposing an apologetic greeting, an embarrassed gesture." But after a few days they break decorum and start up a conversation. Now our ward clerk sees that, "They have given up on fair-play, on trying to make any sense of it, and turned: a friendship awoken with a single touch on the shoulder."

Concerning U, an elderly woman, whose husband is in to have a jejunostomy revised, Steinmetz observes, "… when she confers with the doctors she treats the occasion with a manner of grace and generosity of spirit." And when U thanks him with equal grace for the cup of tea he offers, Steinmetz concludes, "She could build a civil society all by herself." On the other hand, our ward clerk shivers when, in the ED, a young male prostitute is wheeled in, sadistically maimed, and he is moved to cry out, "Who did this? Why? Where is mercy? He [the patient] let in a chill from the outside, transported a little darkness into this bright clinical setting."

Although Steinmetz's job is only two-tenth time, he is not immune to the strain of medical center drama. Toward the end of the book, taking his 15 minutes break, he writes, "I check my watch, view the city from above. I'm seeking some perspective in a very literal way. … In the distance on bridges draped over the river, a chain of red lights signals the outbound traffic … commuters retreating to the suburbs, the South Shore and beyond, into the wilderness of population statistics ... of morbidity rates and demographic profiles. … I check my watch again and by some paralysis of will I cannot read the time." And later, when he goes off duty from the ED, he passes any number of patients waiting in wheelchairs and on gurneys wanting attention. He wonders where the orderlies are. He gets a blanket for one, but draws the line at a glass of water. And then, as if to relieve a flicker of guilt, he asks the reader, "You don't give money to every panhandler on every street corner do you? Of course not."

This neat and well-constructed book can be read in one uninterrupted evening, or, over several delightful, before-sleep reads. Andrew Steinmetz, by the writing of this book has done all healthcare professionals a kindness. He has given us a polished mirror, one that shows more than our faces. □

Dialogue:

The nature of morality: The category of bad acts

Three types of questions about the nature of morality can be distinguished: (a) philosophical, (b) psychological and (c) epidemiological. The philosophical question asks whether (and in what sense) "goodness" and "badness" are real or objective properties that particular actions possess in varying degrees. The psychological question asks, what are the mental states and processes associated with the human classification of events as good versus bad? The epidemiological question asks, what is the actual distribution of moral judgments across time (developmental time and historical time) and across space (for example, across cultures)? With such questions in mind, I develop a limited critique of Kagan's "The Nature of Morality" (*Lahey Clinic Medical Ethics Newsletter, Fall* 2001), while at the same time fully endorsing his central message that the study of moral psychology benefits greatly from the study of the emotions. Vice versa, I also suggest that an understanding of the cognitive side of moral judgment is a necessary precondition for a full understanding of the psychology of the emotions.

"Cognitivists" (Plato is perhaps the most famous) answer the philosophical question in the affirmative. They believe that any particular moral judgment, like scientific judgments, must thus be either true or false. They conclude, moral competence amounts to discovering the truth of the matter by means of either secular or theological modes of reasoning.

In contrast, philosophical "emotivists" (Hume is perhaps the most famous) argue that there really is no real property "out there" to be represented or described with such terms as "good" or "bad." According to the emotivists, moral judgments are neither true nor false. They are merely expressions of personal or collective choice. Judgments of "good" and "bad" just express likes and dislikes, positive and negative feeling states, tastes and aversions. What you should not do, say the emotivists, is ask whether likes, preferences or tastes are accurate estimations of what is truly "good" (or "bad"), because those moral terms are merely labels for our feelings.

Kagan suggests answers to the epidemiological and psychological questions. 1) The moral sense is unique to our species and universal across cultures and history. 2) Doing harm to others without reason is the only action considered immoral in all societies. 3) Moral judgments about particular actions do not converge over time or space. 4) In contemporary Western society a morality emphasizing autonomy (having the things you want, preference maximization) is superceding a morality emphasizing duties and obligations related to membership in social categories. 5) Adults experience their moral judgments both as "cognitive" judgments and "emotive" judgments; both reason and feeling play their part in moral psychology around the world. Nevertheless, Kagan believes, moral judgments are motivators of action primarily to the extent that they produce in human beings feelings of repugnance, guilt, indignation and shame; and he doubts the cognitive side of our moral nature is sufficient to motivate moral action.

He also tells this story about moral development. "Good/bad" categories, mostly devoid of meaning, are already (innately?) available to the neonate and then get "imposed on" experience and filled in with content. This happens once the child has the intellectual capacity to notice and remember connections between actions and their consequences, negative subjective states (uncertainty, feelings of tension, unpleasant emotions) and parental disapproval. With the exception of "arbitrary assault," Kagan seems to suggest that the connection between any action and its classification as "bad" is almost entirely mediated by parental reactions and the experience of negative feeling states. Here his fondness for emotivism seems most apparent.

My admiration for Kagan's research on morality and emotion is great and some of my own work[1,2,3] is strongly supportive of his observations about cross-cultural variability in moral judgments. In the places in India where I do research the category of "bad acts" includes a widow eating fish, a woman having a conversation with her husband's elder brother, and parents refusing to sleep in the same bed with their children.

I have also proposed that on a worldwide scale there is a "big three" of morality. There is an "ethics of autonomy" based on moral concepts such as harm, rights and justice, which is designed to protect individuals in pursuit of the gratification of their wants. There is an "ethics of community" based on moral concepts such as duty, hierarchy and interdependency, which is designed to help individuals achieve dignity by virtue of their role and position in a society. There is an "ethics of divinity" based on moral concepts such as natural order, sacred order, sanctity, sin and pollution, which is designed to maintain the integrity of the spiritual side of human nature. These ethics vary in their centrality and distribution both across and within groups.

I offer the following limited critique of Kagan's position: First, the prohibition on arbitrary assault is not the only "natural" or universal moral standard. There are many others, including the moral imperative to "treat like cases alike," to protect the vulnerable, to avoid incest, to reciprocate in social exchanges, to be grateful for gifts, to honor promises. I would add to the list many of the "virtues." Of course, as Kagan well knows, the rub with all such universal standards, including the norm against hurting others "without a reason," is that they are too abstract to determine moral decisions about particular cases. For example, even in cases of genocide or acts of "martyrdom" by terrorists, the killers typically believe they are acting in "self-defense" (that is, *with* reason) against some perceived threat to their group or way of life.

Secondly, a question arises. Is Kagan a soft cognitivist who believes, as I do, that human reason has limits and leaves room for fully rational and morally decent people to disagree in their moral judgments? Or is he an emotivist who believes that the experience of a negative feeling state is sufficient reason to classify almost anything as morally bad? One tenet of soft cognitivism is that normal human beings are intuitively philosophical cognitivists.

As Arthur Lovejoy has noted,[4] when someone says, "The conduct of Adolf Hitler was wicked," they "do not in fact conceive of themselves merely to be reporting on the state of their emotions." They mean to be saying something more than "I am very unpleasantly affected when I think of it." Any viable cultural system provides its members with "good reasons" for seeing this or that event in such a way that it can be locally experienced as a concrete instance of some abstract moral standard. This process of filling in with "good reasons" the gap between abstract universal moral standards and concrete local actions may involve many parochial concepts and beliefs, but it is very cognitive. I also suggest that one reason there is disagreement across cultures about which actions are good is because there are so many universal abstract moral standards (justice, loyalty, benevolence, duty, respect, liberty) that they are in conflict and cannot all be maximized simultaneously. A choice must be made about which "goods" take precedence. Hence one can be a soft cognitivist while granting that emotional experiences in childhood may play a big part in signaling which of the virtues is most important on the local cultural scene.

Thirdly, "Western society" is big enough to accommodate many different types of groups with many different types of ethics. Lene Jensen discovered that liberal and fundamentalist Protestants in the USA both endorse an ethics of community, despite Robert Bellah's concerns about excessive individualism.[5] The liberals also accept an ethics of autonomy while the fundamentalists don't. How these ethical ratios are playing themselves out is more complex than some of the critics of Western individualism and hedonism have suggested.

Finally, it seems to me that reason and feeling have never had symmetrical parts to play in moral psychology. Reason can justify our moral reactions (and if you are a fully rational person, motivate them as well) while feelings can only motivate behavior, but never justify it. Upon analysis, many emotions seem to contain within themselves a moral core. "Fear" is associated with issues of safety and harm and motivates us to eliminate the conditions that produce it. "Anger" and "indignation" are associated with issues of fairness, equity and just dessert and motivate us to eliminate injustice from the world. "Love" and "compassion" are associated with protection of the vulnerable and motivate us to take care of others. In each case, our emotional reactions can be justified by the good reasons (the "cognitive appraisal conditions," e.g., the threat to safety, the injustice, the vulnerability) that produced them. They can't be justified by simply pointing to the motivating feeling states (e.g., the heat or tension or uncertainty) that "drive" us to act. It would be quite insufficient to translate "I am angry at him" as only meaning "I have been unfairly treated by him." "I have been unfairly treated by him" is in the domain of reason. It is a proposition about a state of the world that can be judged true or false. If it is false, one should not be angry if one is a reasonable person. Yet, "anger" is more than its cognitive core. It is also the feeling state. And, of course, human societies have never been entirely populated by fully rational persons — those who are motivated to do all things only for good reasons. Which is why one suspects Kagan is right that without the feelings that go with guilt, shame, disgust, righteous indignation and the anticipation of stigma we would live in a less moral world. □

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University of Chicago

[1] Shweder RA, Mahapatra M, Miller JG. Kagan J, Lamb S eds. Culture and Moral Development. In *The Emergence of Morality in Young Children* Chicago: University of Chicago Press, 1987:1–83.

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Legal column *(Continued from Page 4)*

— the public could quickly accommodate itself to fabricated humans and near-humans, organisms that previously existed only in the realm of speculative fiction. With commercial interests continually touting the benefits of such "breakthroughs," the production of quasi-humans for research or therapy, using our technique or different ones, cannot be too far behind.

As it attempted with the Chakrabarty patent application, the PTO rejected our chimera patent in its initial reviews. Of course, the major difference between the *Chakrabarty* case and ours is that the PTO no longer opposes patents on organisms. Instead, it would like to draw a line between obviously troublesome inventions of the sort we propose and other life forms they have allowed to be patented, such as human bone-marrow cells and pigs containing human genes. Given the common evolutionary heritage and biological continuity of all organisms on Earth — we share more than 98 percent of our DNA sequence with chimpanzees, for example — this may be an impossible task. Ultimately, the patentability of part-human organisms may have to be resolved by the courts or Congress. But concealed within the patent issue is the deeper one of how far we as a society will go in permitting technology to blur the lines between human and non-human, person and artifact.[5,6] □

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Pharmacogenomics *(Continued from Page 2)*

few victims (and too small markets) to encourage research and development. But "orphan disease" led to the Orphan Disease Act, a successful effort to provide federal incentives to tackle these diseases. The extension of that Act to "orphan genotypes" may be wise.

The final issue raised by pharmacogenomics is only too familiar in the United States — race. Geneticists tell us race is meaningless in *Homo sapiens*, but physicians invariably identify patients by age, sex and race. Evidence already exists that members of different ethnic groups do, on average, react differently to different drugs. In the United States, for example, CYP 2D6 leaves about 7 percent of European-Americans unaffected by codeine, as compared to 1 to 3 percent among Asian-Americans or African-Americans. What will pharmacogenomics mean for the use of race in medicine and the meaning of race for the public?

It might help destroy the idea of genetic race. With pharmacogenomics, doctors would not treat patients with particular drugs according to race, but according to genotype. In many cases those genotypes will not be more or less common depending on race. And even when the frequencies are different, they will not be enormously different. If 93 percent of European-Americans can use one drug but 98 percent of African-Americans can, both genetic variations are found in both groups. Race, for any individual, will clearly be seen not to have a genetic definition, as people in both groups will share the same genes.

On the other hand, the path toward pharmacogenomics could reinforce outmoded public views of genes and race. Studies that show higher levels of genetically-based response to particular drugs by race could be read by the public to mean that races are genetically different, however the scientists may interpret them. Scientists — and journalists — will need to work to ensure that their results are not so misinterpreted. And scientists may well want to consider whether it is meaningful, or misleading, to label their research subjects by race.

Conclusion

Bioethical review, construed broadly, can be the life sciences' equivalent to an environmental impact statement, an advance assessment of the costs and risks of going down certain roads. The medical promise of pharmacogenomics seems clear and we should be able to handle the ethical issues raised by pharmacogenomics. Whether we will overcome other non-scientific barriers to individualized medicine remains to be seen. □

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Medical Ethics

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