Special Section: International Voices

Conflict of Interest: A Japanese Perspective

AKIRA AKABAYASHI, BRIAN TAYLOR SLINGSBY, and
YOSHIYUKI TAKIMOTO

Conflict of Interest: A Newcomer to Japan's Biomedical Ethics

Until recently, many of Japan's medical and bioethical communities had ignored the issue of conflicts of interest (CIs). This is no longer the case. Discussion on the economic and ethical problems defined by CIs is now apparent in academic, political, and even industrial spheres. In June 2004, this debate was sparked by a scandal involving AnGes MG, Inc., a bioventure company set up by a faculty member at Osaka University Graduate School of Medicine. AnGes MG developed a gene therapy using the Hepatic Growth Factor for obstructive blood vessel disease. Japanese newspapers reported that "several physicians involved with clinical trials for AnGes obtained unlisted shares of stock. One physician allegedly received 32 million yen (U.S. $320,000) after AnGes MG went public on the 'Mothers' stock exchange" (a market for high-growth and emerging stocks).[1]

The AnGes MG scandal represents a great deal more than mere insider trading. It illustrates the changing tides among Japan's academic, governmental, and industrial sectors. As of April 2004, all national (public) universities became independent administrative institutions. This means that, although tax funds are still being directed toward universities, the procuring of funds has changed from one of distribution by bureaucrats to one where individual universities need to raise funds through business efforts. To better facilitate turning intellectual wealth into profitable ideas, the majority of universities have formed alliances with private companies. These partnerships have led to the development and success of university-based companies (e.g., bioventure). In fact, there exist several hundred university-based venture companies as of December 2004. This coincides with what Arnold Relman, the former *New England Journal of Medicine*'s editor, once called America's for-profit healthcare in the 1980s, "The New Medical–Industrial Complex."[2] Some 20 years later, Japan faces the potential for a similar medical–industrial complex and the CIs inherent to such a complex.

Japan's History of Conflict of Interest in Medical Practice and Clinical Research

Prior to the 1980s, medical providers (e.g., physicians) and industry (e.g., pharmaceutical companies) had a relatively congenial relationship. In October 1981, however, this relationship slightly changed when the Japan Pharma-

Cambridge Quarterly of Healthcare Ethics (2005), **14**, 277–280. Printed in the USA.

ceutical Manufacturers Association formed a cartel for reasons of solidarity: to contest drug price reductions proposed by medical institutions (e.g., hospitals, private practices) and to issue warnings to companies that violate cartel regulations. This cartel was soon accused by the Fair Trade Commission, a formal governmental regulating committee, of violating the Antimonopoly Act enacted in 1947.

In response to this, the Japan Pharmaceutical Manufacturers Association proposed a Medical Science and Pharmaceutical Fair Trade Agreement (FTA), which was approved by the Fair Trade Commission in January 1984. The FTA includes "restriction of offerings to medical facilities" and "fair trade criteria for alliances between academic academies." The FTA allowed authorities to fine pharmaceutical companies but did not allow them to fine individual physicians and/or researchers. Because of this, the FTA had little effect on the professional community.

It was not until the Parliament passed legislation that medical professionals began to be affected. During the late 1980s and the 1990s, several monetary scandals occurred involving politicians and officers of the Ministries. These included the "Recruit" insider-trading scandal in 1988 and the bribery case between the Aya-fukushi group and the Ministry of Health and Welfare (MHW) in 1996. These scandals ensued with the Parliament passing legislation in April 2000, "The National Public Official Moral Code."

According to this ethical code, civil servants are prohibited from receiving gifts from private parties (e.g., dinners, cash, quality goods). For medical providers, these parties most often consist of pharmaceutical companies. In Japan, physicians who work at a national-university hospital are employed as civil servants and are thereby bound by this piece of legislation: To accept a gift is a civil offense. This law, although not intended specifically for medical professionals, has had a significant impact on the custom of pharmaceutical companies giving gifts to physicians and/or researchers at national institutions.

The impact of this legislation has gone beyond national institutions. Because of the hierarchy of hospitals in Japan (e.g., university or national hospitals are most revered), giving gifts to medical professionals at other facilities—regardless of whether or not employees are civil servants—has gradually disappeared. This can be explained by understanding patterns of behavior within a somewhat hierarchical society. For example, a company that cannot present a gift to a renowned physician at a national-university hospital would no longer try to do the same for a physician at a less well-known hospital (this could be regarded as disrespecting the renowned physician).

Conflicts of interest in the context of ordinary *clinical practice* have never become a critical social issue in Japan. In fact, it was only by coincidence that this legislation solved many of the ethical problems inherent to this relationship. Recent scandals, however, have brought a great deal of attention to potential CIs in *clinical research* and the current lack of legislation and guidelines. The need for researchers to disclose all potential CIs in manuscripts submitted to international journals has also led to increased attention.[3]

The Ministry of Health, Labor and Welfare (formerly the MHW) in July 2003 issued Guidelines for Clinical Research in which CIs should be revealed to ethics committees and study participants. However, these guidelines have no legal binding power and, because of their ambiguity, often leave researchers confused about the concept itself.[4] To date, only six universities have estab-

lished rules for CIs in clinical research (data collected in June 2004). This dearth of discussion and regulation highlights a need to establish guidelines for potential CIs in the context of *clinical research*. Presently, the Association of Japanese Medical Colleges (AJMC) supported by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) is planning to draft CI guidelines just as the Association of American Medical Colleges has done.[5]

Conflict of Interest and the Process of Informed Consent

The process of informed consent has been proposed to be one possible solution to managing CIs in clinical research.[6] As clearly stated in the Declaration of Helsinki by the World Medical Association, researchers should describe their source of funding (e.g., a pharmaceutical company) in protocols, submitted manuscripts, and when receiving informed consent from study participants. We agree that this is effective in preventing CIs, at least in the case of an ethics committee review of a protocol.

However, mere disclosure of a CI may be insufficient and even harmful in Japan. Consider a physician who holds stock in a certain pharmaceutical company and this physician partakes in a clinical trial for a drug developed by the company. Would the physician feel a CI knowing that the stock price would rise if the drug were to become a success? Or let us suppose a renowned physician informs a patient of a potential CI when asking him or her to participate in a clinical trial. Would the patient really react to the disclosed CI? More than likely the patient would prioritize his or her trust in the physician over a disclosed CI. It is obvious that *mere informed consent cannot solve the problems of CI*.

Conflict of Interest as a Tool for Comparison

Many questions remain as to whether CIs are perceived and monitored differently among nations. In many ways, the meaning and perception of CIs differ in Japan—a society supported by fiduciary relationships—from those found in the United States—a society supported by contractual agreements. Social perception of CIs can thus reflect whether a society is biased toward fiduciary relationships or contractual agreements.

A similar example is the use of material transfer agreements (MTAs). Today, MTAs are mandatory for all international collaborative studies conducted in Japan. We suspect that few medical school deans actually read MTAs prior to signing them. Even though international collaborative studies necessitate MTAs, very few domestic studies *formally* require them. These observations intimate that Japanese researchers tend to prioritize fiduciary relationships over MTAs. Here we begin to see the consequence of disparities between Japan and other nations.

These apparent differences suggest that CI guidelines in Japan need to be specific to the culture, society, and healthcare system. Forthcoming guidelines for CIs in clinical research may not limit "the percentage of option stock or amount of money received from an industrial sponsor," but rather demand that physicians and researchers "stay within a range accepted by social norms." This wording leaves room for misinterpretation and, in so doing, poses the risk of deliberate misuse. How can Japan develop a set of guidelines that are

effective and have international accountability while still being suitable to Japanese social and cultural characteristics? This is a question that our professional community needs to answer immediately.

Conflicts beyond Economic Interests

Thus far, our discussion has focused primarily on conflicts of *monetary* interests, only one dimension of CIs. According to Morreim, a "conflict of interest can be found in any human endeavor; indeed, the clash between self-interest and altruism lies at the heart of morality. However, conflict of interests in healthcare are especially serious because of the patient's vulnerability."[7] Erde suggests that a CI is when "either motives that caregivers have *and/or* situations in which we could reasonably think caregivers' responsibilities to observe, judge, and act according to the moral requirements of their role are or will be compromised to an unacceptable degree."[8]

We agree that CIs go beyond economic incentives. Remaining aware of and addressing one's interests are fundamental components of patient care and biomedical research. As Spece et al. have pointed out, "To a large context, [CIs] are bound up with the questions: What does it mean to be a professional? What constitutes a proper physician–patient relationship?"[9] Staying aware of one's personal CIs as a clinician and/or researcher can help to develop a refined moral sense. Regardless of healthcare system or culture, physicians and researchers worldwide are tempted by their individual interests—be they monetary or not—and these temptations are often at the expense of patient welfare. Conflicts of interest are therefore a moral matter and, in so being, are universal.

Notes

1. Rinsho shikeni ni mikokaikabu (Prelisted shares go to physicians in charge of clinical trials). *Nihon Keizai Skimbun* (Nikkei) 2004, 12 June:11 (in Japanese).
2. Relman AS. The new medical-industrial complex. *New England Journal of Medicine* 1980;303(17): 963–70.
3. James A, Horton R, Collingridge D, McCornnell J, Butcher J. The Lancet's policy on conflicts of interest—2004. *Lancet* 2004;363:2–3.
4. Slingsby BT, Nagao N, Akabayashi A. Administrative legislation in Japan: Guidelines on scientific and ethical standards. *Cambridge Quarterly of Healthcare Ethics* 2004;13:245–53.
5. Association of American Medical Colleges (AAMC), Task Force on Financial Conflicts of Interest in Clinical Research. *Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interest in Human Subjects Research*. AAMC, 2001.
6. Lo B. Overview of conflicts of interest. In: *Resolving Ethical Dilemmas: A Guide for Clinicians*. Philadelphia: Lippincott Williams & Wilkins, 2000:231–5.
7. Morreim EH. Conflict of interest. In: Reich WT, ed. *Encyclopedia of Bioethics*, vol. 1, 3rd ed. New York: Macmillan, 2004:503–7, at 503.
8. Erde EL. Conflict of interest in medicine: A philosophical and ethical morphology. In: Spece RG, Shimm DS, Buchanan AE, eds. *Conflict of Interest in Clinical Practice and Research*. New York: Oxford University Press, 1996:12–41, at 33.
9. Spece RG, Shimm DS, Buchanan AE. Preface. In: Spece RG, Shimm DS, Buchanan AE, eds. *Conflict of Interest in Clinical Practice and Research*. New York: Oxford University Press, 1996:4–5, at ix.