VITAMIN A AND BIRTH DEFECTS

Continuing Caution Is Needed

VITAMINS are essential to good health, yet the consumption of excessive amounts of some vitamins, particularly A and D, can lead to toxicity. In this issue of the *Journal*, Rothman et al.[1] add to a body of evidence suggesting that the consumption of too much vitamin A by pregnant women may cause birth defects. On the other hand, the Public Health Service recommends that all women capable of becoming pregnant should consume 0.4 mg of folic acid daily to prevent the serious and common birth defects spina bifida and anencephaly.[2-4] It is important for women and their physicians not to be confused by these messages. They need to understand that the daily consumption of a single multivitamin preparation containing folic acid and no more than the U.S. Recommended Daily Allowance (RDA) of vitamin A for pregnant women (8000 IU) is beneficial.

Retinol and retinyl esters, the common dietary forms of preformed vitamin A (here referred to as vitamin A), cause similar birth defects in many animals, although the teratogenic dose varies substantially among species.[5] Provitamin A compounds, such as beta carotene, are also found in the diet, but they do not cause birth defects in animals. Retinol, retinyl esters, and beta carotene are all used in various dietary supplements.

The drug isotretinoin (13-*cis*-retinoic acid, used in the treatment of severe cystic acne) is a chemical with vitamin A activity that causes a characteristic set of birth defects, including malformed or absent external ears or auditory canals and conotruncal heart defects.[6] Isotretinoin is thought to interfere with cranial-neural-crest cells, which contribute to the development of both the ear and the conotruncal area of the heart. Because of the teratogenicity of vitamin A in animals and of isotretinoin in humans, vitamin A (but not beta carotene) has been assumed to be a human teratogen even though the direct evidence consists largely of anecdotal reports of serious ear malformations in infants whose mothers consumed 25,000 IU or more of vitamin A per day during pregnancy.[7,8]

In 1987 the Centers for Disease Control, the Teratology Society, and the Council for Responsible Nutrition independently published recommendations designed to reduce pregnant women's exposure to high amounts of vitamin A from supplements.[8-10] These recommendations were made because teratogenesis was assumed to occur at some undetermined level above 8000 IU of vitamin A per day and because pregnant women in the United States do not appear to benefit from additional vitamin A. The recommendations included limiting vitamin A in prenatal multivitamin preparations to 5000 to 8000 IU and the vitamin A content of all multivitamin preparations to 10,000 IU; suggesting that women should not take 10,000 IU or more of vitamin A without consulting a physician; using beta carotene rather than vitamin A in supplements; and specifying the amounts of retinol, retinyl esters, and beta carotene on supplement labels. When we recently looked at vitamin products for sale in our neighborhood, we found that some manufacturers of vitamin A products are following some of these recommendations.

Since 1987, two case–control studies have been published that focused on the relation between vitamin A consumption and birth defects in humans. Martinez-Frias and Salvador found an association limited to the consumption of more than 40,000 IU of vitamin A daily.[11] The birth defects in children exposed prenatally to this level of vitamin A were not similar to those caused by isotretinoin. Werler et al. conducted a study of birth defects possibly due to abnormal development of the cranial neural crest.[12] For women who consumed only the vitamin A contained in multivitamin supplements, they found no association and could exclude a relative risk of 1.2 or greater. For women who consumed supplements containing only vitamin A, they found a relative risk of 2.0 for birth defects. Many of these women also consumed a multivitamin containing vitamin A. Since preparations containing 25,000 IU of vitamin A were available during the years when the infants in the study by Werler et al. were born, it seems reasonable to conclude that the users of supplements of vitamin A alone included some women who consumed at least 25,000 IU per day.

The results of these two case–control studies provide evidence suggesting that the children born to women who consume supplemental vitamin A at levels found in current multivitamin preparations are not at increased risk for birth defects. Evidence supporting the safety of vitamin A at the levels in the usual multivitamin preparations is also found in studies that show that folic acid prevents spina bifida and anencephaly.[4] A randomized, controlled trial in Hungary compared a multivitamin containing 4000 or 6000 IU of vitamin A and 0.8 mg of folic acid with a control preparation and found a lower incidence of spina bifida and anencephaly among the infants of multivitamin users.[3] The infants born to the vitamin users also had a significantly lower rate of all birth defects other than spina bifida and anencephaly. Two recent case–control studies in the United States of conotruncal heart defects, which arise in part from cranial-neural-crest cells, have also found a lower risk among women who used multivitamin preparations during the periconceptional period than among those who did not.[13,14] Most multivitamin preparations sold in the United States contain vitamin A.

Rothman et al.[1] sought to clarify further the association between vitamin A intake and birth defects, using data from a nonrandomized, prospective study. They report findings consistent with those of other studies, suggesting that the consumption of less than 10,000 IU of vitamin A per day from vitamin supplements is safe. They also report data consistent with the hypothesis that the mother's consumption of more than 10,000 IU of vitamin A per day from supplements is associated with an increased risk of birth defects in the infant. The key question that remains is at what levels, if any, vitamin A in supplements causes birth defects. It would

have been useful if Rothman et al. had presented more detailed data on the amounts consumed by the women who took 10,000 IU or more of vitamin A per day and on the birth defects in their infants. Since the mean vitamin A intake in this group of women was 21,675 IU per day, it is likely that some fetuses were exposed to more than 25,000 IU per day. It would be helpful to know just how much of the apparent association between vitamin A consumption and birth defects in this study resulted from the consumption of vitamin A at these higher levels. Without further knowledge of this sort, we do not recommend using the dose–response curve in the study by Rothman et al. for the purpose of advising pregnant women who have consumed more than the RDA of vitamin A about the specific risk of malformation in their offspring. We cannot make good estimates of the teratogenicity of this vitamin at higher consumption levels unless more data become available.

Given the gaps in the existing data, what advice do we have for women and their physicians? Women who are, or who might become, pregnant should avoid consuming daily supplements containing more than 8000 IU of vitamin A and should consume liver and liver products only in moderation because they contain large amounts of vitamin A. Producers of vitamin supplements should follow the 1987 recommendations regarding vitamin A dosage. Women of reproductive age should be encouraged to follow the Public Health Service's recommendation that they consume 0.4 mg of folic acid daily to prevent spina bifida and anencephaly in their infants. Women can be assured that one safe and effective way to meet this requirement is to take a single, daily multivitamin preparation that contains 0.4 mg of folic acid and no more than 8000 IU of vitamin A.

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THE CHANGING CONCEPTS OF GUILLAIN–BARRÉ SYNDROME

GUILLAIN–BARRÉ syndrome[1,2] is a leading cause of acute paralysis. It occurs worldwide, in patients of all ages and both sexes. The weakness develops in a matter of days, sometimes with frightening rapidity and severity. Thirty percent of patients require treatment in critical care units, where ingenuity and resources are taxed to their maximum, and the stress on the patient and family is enormous. Nonetheless, modern management has reduced the mortality rate from 30 to 3 percent, and 75 percent of patients recover completely in 6 to 12 months.

Guillain–Barré syndrome has traditionally been regarded as a poorly understood immune-mediated attack on the myelin sheath of peripheral nerve, hence the descriptive term acute inflammatory demyelinating polyneuropathy. However, new insights from investigations in the past 10 years have dramatically altered this restricted viewpoint. It is known that in demyelinating Guillain–Barré syndrome the severe inflammation may induce a secondary axonal degeneration — a "bystander" effect.[3] Recovery in such instances is more prolonged. In 1986, however, Feasby et al.[4] described five patients with unusually severe Guillain–Barré syndrome in whom electrophysiologic and pathological studies suggested a primary axonal degeneration, a condition now termed acute motor and sensory axonal neuropathy. Earlier results from northern China in 1979[5-7] and more recent clinical, electrophysiologic, and pathological studies by McKhann et al.[8] in the Chinese patients revealed an acute motor axonal neuropathy in children and young adults, similar to Guillain–Barré syndrome except that, again, there was a primary axonal degeneration, and it affected only the motor fibers. During the past 30 years, similar patients had been described in other countries and regions, including Mexico, Spain, South America, Japan, South Korea, India, and, most recently, North America.[8] These cases tend to occur in the summer and have been linked to infection with *Campylobacter jejuni*. *C. jejuni* is the most common cause of diarrheal illness in developed countries and is ingested in poultry, raw milk, or contaminated water. It must now be regarded as the chief precipitant of Guillain–Barré syndrome. Cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, and vaccinia are less common causes.[9] Certain strains of *C. jejuni* — Pen 19,

Lior 11, and Lau 19 and 3/25 — are most likely to precipitate Guillain–Barré syndrome.[9] Stool cultures may be negative by the time the syndrome appears, usually one to three weeks after the diarrheal illness. Hence, serologic testing for elevated levels of serum IgA, IgM, and IgG, specific to *C. jejuni,* should be performed, in addition to stool culture.

The report by Rees et al. in this issue of the *Journal*[10] further clarifies the relations between *C. jejuni* and Guillain–Barré syndrome. In a prospective study of 96 patients with the syndrome who were identified during one and a half years in England and Wales, 27 (26 percent) had bacteriologic and serologic evidence of preceding *C. jejuni* infection, as compared with an incidence of 2 percent in household and hospital controls. Patients with the more severe, axonal, form — whether primary or secondary to demyelination — were more likely to have *C. jejuni* infection. The group with poor outcomes — six patients who died and seven who were severely disabled — were older and more often were *C. jejuni*–positive, required ventilatory support, and became bedbound within two days of the onset of neuropathic symptoms. For the *C. jejuni*–positive patients, the median time to regain the ability to walk was 89 days, as compared with only 45 days for *C. jejuni*–negative patients.

The *C. jejuni* story offers new insights into the pathogenesis of Guillain–Barré syndrome.[11] The immune mechanism of "molecular mimicry" now seems tenable. Peripheral nerves may share epitopes, or antigenic sites, with *C. jejuni;* thus, the immune response initially mounted to attack *C. jejuni* is misdirected to peripheral nerve. Although proof of this theory is still lacking, it is tempting to speculate that since infection with *C. jejuni* may be associated with either primary demyelinating or primary axonal degeneration, the target epitope may reside in the myelin sheath, the axon, or both. Certain neuronal systems seem more susceptible in some patients than in others. Thus, a variant of Guillain–Barré syndrome, the Miller Fisher syndrome, has also been linked to *C. jejuni.*[10] In this syndrome, ophthalmoplegia and sensory ataxia predominate, and there is probably a primary axonal degeneration of cranial-nerve motor axons and peripheral-nerve sensory axons. Future investigations may explain more precisely the recognized variants of Guillain–Barré syndrome: acute inflammatory demyelinating polyneuropathy, acute motor sensory axonal neuropathy, acute motor axonal neuropathy, and Miller Fisher syndrome.

Some have wondered whether the axonal form of Guillain–Barré syndrome is the same as the polyneuropathy of critical illness, an often occult, potentially reversible motor and sensory axonal polyneuropathy confined largely to patients in critical care units. However, critical-illness polyneuropathy occurs as a nonimmune response to severe infection or trauma of virtually any type, including sepsis with what is now termed the systemic inflammatory response syndrome. In sepsis the mechanism is probably a complex disturbance of the systemic microcirculation, in which peripheral nerves suffer impaired perfusion, leading to severe energy deficits and a predominantly distal axonal degeneration.[12]

These changing concepts have practical implications. The identification of only 96 patients with Guillain–Barré syndrome in England and Wales during one and one half years, while 2 percent of hospital or household controls had serum samples positive for *C. jejuni,* means the chances that Guillain–Barré syndrome will develop after *C. jejuni* infection must be extremely small. Moreover, *C. jejuni* infection is usually a relatively benign, self-limiting illness not requiring antibiotic treatment. It spreads chiefly by animal-to-human rather than human-to-human contact. Thus, although public health measures to prevent *C. jejuni* and other, similar, infections are indicated, investigating and then treating each case of suspected *C. jejuni* infection with antibiotics simply to prevent the unlikely complication of Guillain–Barré syndrome seems impractical and is still of unproved benefit. If the syndrome does develop, however, a history of diarrheal illness and positive cultures or positive serologic tests for *C. jejuni* (the results of serologic tests should be available within 48 hours) may signal a potentially more severe axonal disease. This evidence of *C. jejuni* infection may be the only early warning, since electrophysiologic studies, although valuable in establishing the presence of polyneuropathy, may fail to distinguish axonal from demyelinating disease in the first three weeks.[13] However, it must be emphasized that *C. jejuni* in some patients may be associated with a pure demyelinating or a milder axonal neuropathy, with early recovery; even patients with a severe axonal neuropathy may eventually recover.[14] Thus, all patients should receive optimal care, if possible by immediate referral to a tertiary care center. There, investigations, monitoring, and if necessary, intervention by management in a critical care unit can be instituted. Such interventions may include treatment with plasmapheresis or intravenous immune globulin, which may be effective, although perhaps to a lesser degree, against the axonal as well as the demyelinating form of Guillain–Barré syndrome.[9,15]

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P-GLYCOPROTEIN — A MARKER OF CANCER-CELL BEHAVIOR

RESISTANCE to a broad array of cytotoxic drugs — multidrug resistance — is thought to be a major reason chemotherapy fails to cure most cancers. Multidrug resistance has been studied intensively since the human *MDR1* gene was identified almost 10 years ago.[1] Increased levels of the *MDR1* product, called P-glycoprotein, are often associated in vitro with reduced intracellular concentrations of several anticancer drugs derived from plants, such as anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), vinca alkaloids (e.g., vincristine), dactinomycin, and paclitaxel. When cells are grown in increasing concentrations of one of these cytotoxic drugs, populations of cells that overexpress the *MDR1* gene may be selected. These cells, selected by only one drug, have cross-resistance to all the above-mentioned drugs.

P-glycoprotein is a transmembrane glycoprotein that is normally present in cells of the adrenal cortex, biliary canaliculi, endothelium of the blood–brain and blood–testicle barriers, placenta, gastrointestinal epithelium, proximal renal tubuli, and some bone marrow stem cells.[2] In many of these organs, P-glycoprotein is thought to act as a detoxifying agent by pumping toxins or xenobiotics (including anticancer drugs) out of cells. In other organs, such as the adrenal gland and the gravid uterus, it may transport steroid hormones. P-glycoprotein belongs to a large superfamily of highly conserved ATP-binding cassette transport proteins, and its amino acid sequence resembles those of many bacterial and eukaryotic transport proteins.[3]

Increased levels of P-glycoprotein are common in cancer cells. Moreover, levels of the glycoprotein can increase after chemotherapy, when the tumor becomes refractory to treatment.[4] The presence of increased levels of P-glycoprotein in several types of tumor has been correlated with poor responses to chemotherapy and short progression-free survival and overall survival.[5]

In this issue of the *Journal*, Baldini et al.[6] report a strong correlation between the presence of increased levels of P-glycoprotein and the prognosis in patients with osteosarcoma. Osteosarcoma is a rare and extremely aggressive cancer that most commonly affects adolescents. Preoperative and adjuvant chemotherapy has dramatically improved the prognosis of patients with nonmetastatic osteosarcoma. Nevertheless, about 50 percent of patients who undergo radical surgical resection and receive aggressive combination chemotherapy relapse. Salvage therapy (chemotherapy with or without surgery) benefits only a minority of these patients. So far, the most important predictor of disease-free survival and overall survival is the histologic response to preoperative chemotherapy — that is, the amount of chemotherapy-induced necrosis in the tumor.

Baldini et al. found that the P-glycoprotein status of the primary biopsy specimen was a better prognostic marker than tumor necrosis. Patients with tumors that had high levels of P-glycoprotein, as assessed immunohistochemically, had twice the relapse rate of patients with P-glycoprotein–negative tumors. This difference was independent of the amount of tumor necrosis found in the surgical specimen after preoperative chemotherapy.

These findings suggest that P-glycoprotein status might be used to identify patients with osteosarcoma who are at higher-than-usual risk of metastases and thereby serve as a marker to select patients for aggressive therapy, such as high-dose chemotherapy with transplantation of peripheral stem cells. The authors suggest that the use of drugs, such as cyclosporine, that can impair the pumping function of P-glycoprotein and thus reverse multidrug resistance may be effective in patients who have relapsed or may prevent multidrug resistance in previously untreated patients whose tumors have increased levels of P-glycoprotein.

It is interesting that Baldini et al. did not observe any correlation between P-glycoprotein status and the extent of tumor necrosis. In other words, the expression of P-glycoprotein was unrelated to the response of tumor cells to chemotherapy. In fact, these two phenomena remained independent variables in a multivariate analysis. This suggests that, at least in patients with osteosarcoma, the presence of P-glycoprotein may be not simply a marker of tumor chemosensitivity but also a sign of tumor aggressiveness. Similar observations have been made in colon cancer,[7] in which 50 percent of the invading carcinoma cells at the leading edge of the tumor expressed P-glycoprotein. The expression of P-glycoprotein by these carcinoma cells was strongly correlated with a greater-than-usual incidence of vessel invasion and lymph-node metastases.[7] Moreover, in half the patients with P-glycoprotein–negative tumors, the lymph nodes expressed P-glycoprotein. Another relevant finding is that P-glycoprotein is more frequently expressed in locally advanced breast cancers, which are often very aggressive, than in smaller, more indolent tu-

mors.[8] One could hypothesize that cancer cells use P-glycoprotein to pump out the cytokines that mediate the process of invasion and metastasis.

In the study by Baldini et al., as in several others like it, it is difficult to conclude that the ability of P-glycoprotein to extrude drugs from the tumor cells was clinically important. The chemotherapy given to the patients included methotrexate, cisplatin, and ifosfamide, which are not substrates of P-glycoprotein. In another study of the problem, the expression of a different molecule related to drug resistance, lung resistance protein, which is not on the cell surface but in the cytoplasm, correlated with the prognosis of patients with ovarian cancer who were being treated with cisplatin.[9] It would therefore be interesting to see whether the presence of lung resistance protein is a marker of resistance in osteosarcoma, in which cisplatin also has a major therapeutic role.

Several drugs, such as calcium-channel blockers and cyclosporine, can efficiently reverse the multidrug-resistance phenotype in vitro. These compounds act mainly through inhibition of the drug pumping by P-glycoprotein. As a result, they enhance the intracellular concentration of cytotoxic drugs (Fig. 1). Clinical studies of such agents given in combination with chemotherapy have been performed in patients with hematologic cancers or solid tumors. Many of these studies attempted to achieve plasma concentrations of these agents that matched the concentrations that were effective in vitro. However, the importance of the plasma concentration is unclear, because we have virtually no knowledge of the concentrations of these agents and cytotoxic drugs in tumors. Moreover, many reversing agents have been too toxic at doses that mimic the conditions in vitro; consequently, a number of studies actually used suboptimal concentrations.

Cortisol and probably several other endogenously produced substances are also extruded by P-glycoprotein. These endogenous products may compete with exogenous drugs for the P-glycoprotein pump.[10] It is thus not surprising that agents that reverse the multidrug-resistance phenotype are of limited benefit.

Despite occasional responses in patients with hematologic cancers, in which tumor cells are more directly exposed to a drug than are the cells in solid tumors, and despite the positive results of a small, randomized study of the addition of verapamil to chemotherapy in untreated non–small-cell lung cancer,[11] three recent large, randomized trials failed to show any benefit of agents that reverse the multidrug-resistance phenotype in terms of the response to chemotherapy or the length of survival. The addition of verapamil to a regimen consisting of vincristine, doxorubicin, and dexamethasone had no effect in patients with refractory multiple myeloma.[12] Two other large, randomized studies of untreated patients with small-cell lung cancer[13] and breast cancer[14] also failed to demonstrate any benefit of adding verapamil or quinidine to chemotherapy. Drug resistance is very likely multifactorial. For example, cells with defective transport of antineoplastic drugs have been shown to have increased levels of yet another ATP-binding cassette transport protein, called MRP (multidrug-resistance–associated protein).[15]

Some agents that reverse the multidrug-resistance phenotype, such as verapamil and cyclosporine, influence the pharmacokinetics of anticancer drugs, possibly by decreasing their elimination and increasing their plasma concentrations by 40 to 60 percent, thereby increasing their toxicity. Apart from the adequacy of plasma concentrations of the reversing agents, other factors must be considered when one is designing clinical studies of the treatment of osteosarcoma. The role of these agents can be assessed only by a randomized study in which the target plasma concentration of the anticancer drug over time is matched in the group given the reversing

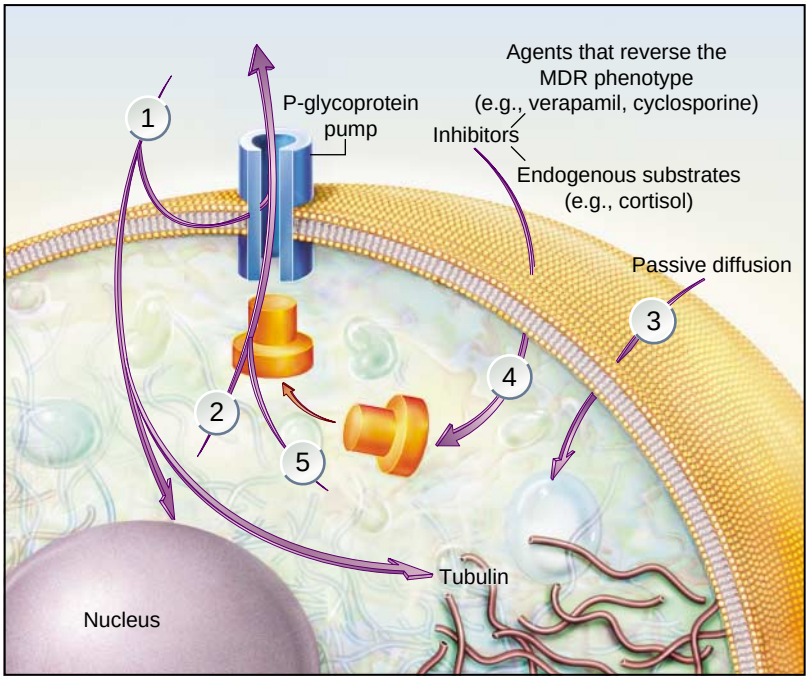

Figure 1. The P-Glycoprotein Pump.

P-glycoprotein may transport cytotoxic drugs directly from the cell membrane, before such drugs enter the cytoplasm (1), or from the cytoplasm (2), limiting the concentration of such drugs at the target (DNA or tubulin). Highly lipophilic drugs enter the cell by passive diffusion (3). Inhibitors of P-glycoprotein–mediated transport may be carried through the blood supply (e.g., steroid hormones and agents that reverse the multidrug-resistance [MDR] phenotype) (4), or hypothetical natural substrates may be produced in the cell (5).

agent and the group not given the agent. The steep dose–response relation of several anticancer drugs is well known. Moreover, the plasma concentration of doxorubicinol, the chief metabolite of doxorubicin, increases more than threefold when doxorubicin is given together with cyclosporine.[16] Because doxorubicinol is a less potent anticancer drug and may be more cardiotoxic than its parent, proposed studies of agents that may reverse the multidrug-resistance phenotype are not without risk.

Given the disappointing results of clinical trials of agents that reverse the multidrug-resistance phenotype and the uncertain role of P-glycoprotein expression in inducing drug resistance in human cancers, other approaches, such as high-dose myeloablative chemotherapy followed by the transfusion of peripheral stem cells, may have higher priority in patients whose tumors have high levels of P-glycoprotein.

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THE COMPUTER-BASED PATIENT RECORD AND CONFIDENTIALITY

IN various ways computers can help people become more active participants in their own health care and that of family members, as emphasized earlier by Kassirer.[1] Computers can help people acquire medical information, interact with care givers, connect with support groups when illness strikes, and in some cases, carry out a treatment plan. Electronic linkage of patients and their families to support groups and medical libraries is well under way and is likely to increase in popularity as computers become standard equipment in the American home. Information bestows power, and making medical information more easily accessible is a way of empowering patients. In theory at least, the better-informed patient will be in a better position to consider various options in addressing a medical problem and to evaluate medical advice.

Most advocates of the use of the computer in medical care have different aims. They are more interested in the benefits of computer-based medicine to the health care industry and, not incidentally, to the computer industry. In 1991 the Institute of Medicine (IOM) released an influential report, *The Computer-Based Patient Record: An Essential Technology for Health Care*.[2] It advocated the adoption of the computer-based patient record as standard medical practice in the United States. As the report said, "CPRs [computer-based patient records] and CPR systems can respond to health care's need for a 'central nervous system' to manage the complexities of modern medicine — from patient care to public health to health care policy."[2] The report described the computer-based patient record as a continuous chronologic history of a patient's medical care linked to various aids for users, such as reminders and alerts to clinicians, and clinical decision-making systems.

The IOM report led to the creation of the Computer-Based Patient Record Institute, an advocacy group that is supported by corporations in the health care, insurance, data-processing, and computer industries, as well as by some professional groups. Last year's proposals for health care reform and some bills currently before Congress include provisions for the establishment of a National Health Care Data Network. Such a network would contain records on every medical encounter in the United States. These measures at the federal level reflect the effectiveness of efforts to promote the computer-based patient record.

In spite of the computer's obvious usefulness, its use in medical care is replete with problems. The greatest concern is the threat to confidentiality. Even before the introduction of the computer, confidentiality deteriorated as care provided by large groups became more

common. But computerized records, particularly if embedded in large networks designed to collect comprehensive lifelong data, can rapidly accelerate that trend. As Gostin has acknowledged, the difficulty of controlling the behavior of large groups limits the value of security measures, such as passwords and encryption, in any system in which large numbers of people are given access to data.[3]

Other issues arise with respect to changes in the character of the medical record. The computerized record is envisioned as a newly designed, multipurpose document with a standardized format and nomenclature.[2] This reconstruction of the record raises serious methodologic questions. The frequent claim, for example, that the computer-based patient record will be complete and accurate reflects naiveté about the inherent problems with standardized formats and record keeping. The suitability of a single record for many purposes — business, clinical, research, and public health — is also questionable.

These problems, and others, need to be recognized and addressed by the medical profession and the public before we forge ahead with a commitment to paperless records. In this article, I focus only on the effect of the computer-based patient record on medical confidentiality and some possible consequences.

In the setting of private practice, medical information that identifies a patient is supposed to be transferred from physician to physician only with the written informed consent of the patient. In an institutional setting, information is generally passed around without obtaining consent from the patient, as considered necessary on the basis of a "need to know."[4] The current restructuring of medical care is rapidly reducing the ranks of those who obtain their medical care in the more protected environment of a private physician's office. In the context of the newly merged health care networks and integrated delivery systems, computers and computer-based patient records are to be used as tools to link geographically separate facilities. As outpatient care is increasingly given within such networks, traditional standards of confidentiality will be diminished unless patients are given new forms of control over access to their records.

Growing Claims of a Need to Know

The number of people authorized to read medical records has increased dramatically in the past two decades because of the growing reliance on insurance to pay medical bills and the growth of oversight activities. In the words of one legal scholar, "A widening audience of outside observers now watch the performance of doctors, nurses, and patients."[5] Anticipation of the availability of computerized patient records appears to be generating even more extensive claims of a need to know. The authors of the IOM report stated that the number of parties with a potential need to know was so large that they would not even attempt to provide a complete list. The authors nevertheless listed many parties not directly involved in patient care.[2]

The computer-based patient record not only will be seen by more parties than the traditional record but also will contain a wider array of data. For example, a 1994 report sponsored by the IOM suggests that the record should contain assessments of the patient's physical functioning, mental and emotional well-being, cognitive functioning, social and role functioning, and perceptions of health.[6] Various techniques may be used to gather information for business, research, or other purposes without the patient's understanding why the information is being sought or how it will be used.

At the same time that claims of a need to know are expanding, there is an increase in the number of parties with a desire to know the contents of medical records. Medical information is considered valuable by many commercial enterprises (including health maintenance organizations [HMOs] and various kinds of health care networks, insurers, pharmaceutical firms, medical-equipment firms, and research enterprises), as well as by employers, detectives and information brokers, political campaign managers, and others. Parties with a desire to know the contents of medical records use various strategies, some of them illegal or of borderline legality, to obtain information from those who have access to the records on the basis of a need to know.

Easy Access, Improper Disclosure

At present, most hospitals and health care networks do not restrict access to computerized information about a patient to the personnel directly involved in providing services to that patient. The advocates of unrestricted access justify it on the grounds that it facilitates the efficient provision of health care services. But the disadvantages are clear. Insiders (employees and affiliated personnel), who may number in the thousands in some health care networks and hospitals, become a tempting target for the growing number of people outside the hospital who wish to have access to medical records. Among the many insiders with access, some will be willing to sell information, to share a password, or to subvert the system in some other manner.

The recent indictment of 24 people in Maryland in connection with a scheme in which clerks sold information about identified individual patients, obtained from the state's Medicaid data base, to four HMOs is a case in point.[7] In a different context, the ease with which private investigators have acquired information in the National Crime Information Center's computerized files shows that presumably restricted information is available from insiders when there are buyers for it.[8]

Easy access by insiders also facilitates record browsing. Documented cases of browsing by insiders in large computer networks indicate that the behavior is not uncommon, even when officially prohibited,[9] and that it may be carried out for such diverse reasons as curiosity (e.g., about friends, neighbors, relatives, or celebrities), perversity (e.g., sexual interests), anger (e.g., on the part of an employee who is about to be or has recently been dismissed), or a desire for financial or political gain.

The effects of particular violations of the confidentiality of patient records will be as multifarious as the motives for the violations. Past cases of improper view-

ing of patients' medical records and improper disclosure of their contents have led to detrimental publicity, ostracism by family members, mistreatment by coworkers or schoolmates, and blackmail. In a recent case, a convicted child rapist, who obtained a job at a Boston-area hospital and gained access to nearly a thousand patient records with an improperly acquired password, made repeated telephone calls to young children and their families over a period of several months.[10] In the current social climate, one might also worry about adverse consequences for women with a medical history of abortion if this information became more easily accessible.

As the Maryland HMO case demonstrates, improper disclosure can also lead to improprieties in business practices and in the solicitation of business. The linkage of medical data bases with other data bases, which will be quite easy with some record-numbering systems, will create further opportunities for inflicting harm.[11] An example is the case of the Maryland banker who cross-referenced a list of patients with cancer against a list of people who had outstanding loans at his bank and then called in the loans.[12]

Unauthorized viewing is not the only potential source of harm to patients. One can also anticipate harmful consequences from the increased numbers of authorized viewers. Many patients would not be reassured, for example, by the Computer-Based Patient Record Institute's inclusion of employers among those who may "require access to data for reasons not directly related to treatment of the patient."[13] Given past practices, patients have reason to worry about whether medical, lifestyle, and genetic information will be used by employers, insurers, bankers, school administrators, and others in a discriminatory fashion, even if such discrimination is illegal.

Semipublic Records

In fact, corporations, whether in the role of employers or investors, are increasingly acting as the managers of our health care system and of the information it generates. It is the plans of these corporations, and of some government agencies, to conduct widespread investigations in the name of oversight and cost control that make it so difficult to solve the problem of limiting access to computerized medical records. In this context the computer is being viewed not as a technical device to make an essentially private record quickly available to physicians (and, in exceptional circumstances, to other parties), but instead as a device to transform the medical record into a semipublic record used routinely for a wide range of investigations. Many of these investigations are more likely to be of benefit to their corporate sponsors than to either patients or physicians. At present, there is virtually no legislation that sharply restricts the use of medical records by corporations.

Two years ago, in an article on the privacy of personal information in a new health care system, Gostin and his colleagues wrote, "Individuals have the right to expect, and the health care system has the obligation to provide, assurances . . . that records will be confidential and maintained in a secure system."[14] But more recently, Gostin seems to have concluded otherwise. Although he now acknowledges the conflict between privacy and extensive data collection, Gostin opts for data collection: "A health care system supported by data on almost any relevant subject, accessible to a diverse and significant number of users, is an integral part of the vision for health care reform."[3] Some statisticians and physicians have questioned the reliability of the kinds of studies that are proposed,[15,16] but Gostin is convinced that high-quality information can be obtained by collecting huge volumes of uniform data in electronic form and that the benefits of such data collection are worth the price in loss of privacy: "A complex modern society cannot elevate each person's interest in privacy above other societal interests."[3]

Why Not Privacy?

Generally, claims that are meant to protect the individual against the collective weight of society or government are couched in the language of rights. But even if we limit ourselves to the language of interests, a case can and should be made for the interest that society has in protecting privacy. In the medical arena it is easy to rationalize data gathering as an activity undertaken for the sake of the individual and society. But information may be used for many purposes that are not benevolent, and the collection of medical data can easily turn into medical surveillance. Such surveillance, in turn, can lead to unprecedented forms of supervision of personal life. Already, a representative of a large employer group has stated that attention is going to be paid to "the psychology of patient behavior" and that "what happens between doctor visits will become just as actively attended to and managed as what happens during doctors' visits and hospital stays."[17]

Such developments will affect the actions of consumers. If they perceive their records as semipublic and the use of health care services as a threat to personal autonomy, then decisions about when and how to obtain these services will be affected. Some patients may forgo them entirely. Others may choose to pay for their care out of pocket and to avoid networks and hospitals with computer systems (to the extent possible). Alternative (unconventional) forms of health care will probably be sought more often. And what patients say in the health care setting will almost certainly be influenced by the knowledge that others may be reading the record. One can also anticipate more frequent attempts by patients to disguise their identities. These defensive measures, in turn, will affect research based on computerized medical records.

A more general approach to the protection of privacy requires legislative action. Unfortunately, the bills currently before Congress that pertain to medical information contain numerous provisions that are inimical to privacy. Strong legislation would require concerted action by organizations representing both physicians and consumers and by leaders of the medical profession.

Stuart Horner, chairman of the British Medical Association's Ethics Committee, has provided an example

of this kind of leadership. At the association's annual meeting in July, he urged that doctors in Britain boycott a computer network that the government wishes to set up, unless stringent legal and technical protections for patients are established.[18] In this country, the Privacy Committee of the American Civil Liberties Union of Massachusetts is advocating legislation that would give the patient control over decisions about which personal medical information goes into a computer network and which information does not. The committee maintains that entering data into a computer network is a form of publication and, like any other publication of personal medical information, should require the patient's consent.

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