Graves' disease, toxic multinodular goiter and a toxic autonomous nodule or nodules. RAI has also been increasingly used in euthyroid patients with multinodular goiters in order to reduce their size and before the onset of hyperthyroidism.

**Contraindications:** Radioactive iodine is contraindicated in patients who are pregnant, nursing and those women planning to conceive within the next few months. Some physicians also avoid RAI in those patients with significant ophthalmopathy. Others treat such patients with radioactive iodine and subsequent steroids for 3 to 12 months (6, 7). Radioactive iodine may also initially aggravate hyperthyroidism secondary to release of thyroid hormone into the periphery from necrosed cells. There is also a risk of gland swelling and where the trachea is already compressed by a large gland, the patient must be carefully watched (6). Patients with hyperthyroid Graves' disease and a single hypofunctioning nodule need a fine needle biopsy of their nodule prior to ablation with radioactive iodine. If there is a suspicion of malignancy, surgery is the preferred treatment (3).

**RAI in younger patients:** Historically, there has been concern about treating young patients with radioactive iodine for the fear of inducing secondary neoplasia. However, the American Thyroid Association and the American Association of Clinical Endocrinologists do not list youth as a contraindication for radioactive iodine therapy. One exception would be young patients with single toxic adenomas as there may be the theoretical risk of developing additional thyroid nodules.

**Dosing:** There is no consensus regarding how to dose radioactive iodine. We recommend full ablative doses (15-25 mCi) as this strategy increases the likelihood of cure and subsequent hypothyroidism is predictable and easy to treat. Dosing should be based on gland size, patient age, severity of symptoms and TSH receptor antibody levels. In our opinion, patients who are likely to be lost to follow up should be given full ablative dosing (25-29 mCi) and started on levothyroxine replacement as soon as free $T_4$ is normalized.

**Pretreatment with antithyroid drugs:** Pretreatment with thionamides can reduce the severity of radiation induced exacerbations by depleting thyroid hormone stores. The thionamides must be stopped for at least 3 days prior to radioactive iodine (6). To avoid the danger of arrhythmias we believe that all elderly patients should be rendered euthyroid before radioactive iodine treatment. However, patients who are pretreated with thionamides may require higher radioactive iodine doses (4). Other drugs have also been used as pretreatment, most commonly the beta antagonists and, less commonly, lithium and steroids.

**Post-treatment with antithyroid drugs:** Thionamides can be restarted within several days after radioactive iodine treatment to control hyperthyroidism and then tapered off based on clinical and biochemical evidence. Stable iodide can also be used to control severe thyrotoxicosis after radioactive iodine but the patient will eventually overcome this benefit via the Wolff-Chaikoff effect. Beta adrenergic blockade may also be indicated to control symptoms. In patients with preexisting significant orbitopathy, we recommend low dose corticosteroid use (eg. prednisone 20mg daily), starting on the day of radioactive iodine administration and continuing for 3 months. We do not use radioactive iodine in patients with severe orbitopathy except under steroid coverage.

**Follow up after radioactive iodine treatment:** Follow up after radioactive iodine treatment should be based on the dose of radioactive iodine, disease severity, patient symptoms and the concurrent use of antithyroid medications. Free $T_4$ is the test of choice at this time as TSH levels can remain suppressed for twelve weeks or longer and may not reflect actual thyroid function. Patients must be followed closely as hypothyroidism can develop any time from weeks to years after ablation (6).

### Thyroid Surgery and Hyperthyroidism

**Indications:** Surgery in hyperthyroid patients should be reserved for (a) Patients with very large glands, especially those with low radioactive iodine uptakes, (b) patients with moderate to severe Graves' ophthalmopathy who are unlikely to be cured by antithyroid drugs, (c) patients with a hot nodule who want to be sure to avoid the hypothyroidism of RAI, (d) Pregnant patients who cannot tolerate and/or are not controlled by antithyroid drugs, (e) Patients with local tracheal compressive symptoms, (f) children and young patients with toxic autonomous nodules (4, 6) and (g) patients needing an immediate cure of their Graves' disease (eg. amiodarone induced hyperthyroidism in a heart failure patient).

**Advantages and Disadvantages:** The advantages of surgery include a rapid cure of the hyperthyroidism as well as the cosmetic advantage in a patient with a large gland. The disadvantages of surgery are the inherent risks of anesthesia and surgery, the scar, the risk of recurrent laryngeal nerve damage and hypoparathyroidism. Rarely, the risk of thyroid storm or severe

thyrotoxicosis occurs in a patient who is not adequately controlled preoperatively. In addition, patients treated with surgery often require thyroid hormone repletion, depending on the extent of surgery.

**Pretreatment for surgery:** It is critical that the patient be rendered euthyroid prior to surgery. The three drugs which are classically used are the combination of oral iodides, propanolol and thionamides. Propanolol and thionamides are given for 4 to 6 weeks pre-operatively while the oral iodide is given for 7-14 days preoperatively. Longer administration of oral iodide is not recommended preoperatively as patients may escape from the Wolff-Chaikoff effect and become hyperthyroid. An alternative pre-operative management strategy is the use of ipodate, dexamethasone and propanolol for 5 days preoperatively (2).

**The surgery:** Surgery must be performed only be an experienced surgeon. Wherever possible, danger to the parathyroid glands and recurrent laryngeal nerves must be avoided. This is most easily accomplished by subtotal thyroidectomy or hemithyroidectomy which allows the back of the gland to be retained. Where there are very many nodules in a toxic MNG then total removal may be indicated to prevent recurrence. A number of surgeons are performing these procedures as day surgery but post operative management must still include observation for hemorrhage and hypocalcemia as well as for tracheal collapse following the removal of large glands.

**Follow up after surgery:** Following surgery, thyroid functions should be followed and levothyroxine treatment initiated as hypothyroidism develops. Once stable thyroid function is achieved, thyroid functions should be tested yearly or as symptoms develop.

### Special Situations

**Toxic Multinodular Goiter and Toxic Adenoma:** Patients with toxic multinodular goiters and toxic adenomas are unlikely to be cured with thionamides and treatment would need to be lifelong. We, therefore, recommend treatment with radioactive iodine or surgery. Thionamides are reserved for early treatment when a rapid return to clinical euthyroidism is important (the elderly or cardiac patients) and as pretreatment for surgery or radioactive iodine. Oral iodide is not recommended as treatment for toxic multinodular goiters as this may precipitate hyperthyroidism, especially in iodine-deplete regions (2).

**Hyperthyroidism in Pregnancy and Lactation:** Pregnant patients with hyperthyroidism should be treated medically. The natural history of Graves' disease in pregnancy is remission during the pregnancy and a flare postpartum due to loss of the immunosuppression of pregnancy. PTU is considered to be generally safe in pregnancy and lactation as it minimally crosses the placenta and large quantities do not appear in breast milk (1). One human study suggested that MMI crossed the placenta in greater quantity than PTU; but, clinical experience has found that both drugs are effective in controlling fetal thyroid status in utero (8). However, MMI has been associated with the rare condition of aplasia cutis congenita while PTU has not. It is important to monitor the newborn for possible transient thyrotoxicosis caused by maternal-fetal transmission of TSH receptor antibodies. This situation is likely if maternal TSH receptor antibody levels remain elevated at the end of pregnancy. Thionamides are generally considered to be safe in lactation, at doses up to 20 mg of MMI a day or 450 mg of PTU daily. The drug should be taken immediately after the mother breast feeds (8).

**Accelerated Hyperthyroidism (Thyroid Storm):** This severe form of thyrotoxicosis is a medical emergency associated with a high mortality. The symptoms are fever, tachycardia, weakness and agitation. Accelerated hyperthyroidism should be treated with large doses of corticosteroids (4mg dexamethasone bid), thionamides, beta blockers, and Lugol's iodine (or SSKI) (3-4 drops bid). It is preferable to administer the thionamide at least 2 hours prior to giving the iodide as the iodide load can potentially worsen hyperthyroidism in the absence of pre-blockade of thyroid hormone synthesis (2).

**Thyroiditis-related hyperthyroidism:** Thyroiditis is a condition characterized by gland inflammation, but hyperthyroidism may result from release of stored thyroid hormone. Thyroiditis may be viral in etiology (DeQuervain's) or autoimmune (early Hashimoto's disease as seen in postpartum thyroiditis). It may also be painful (typically viral) or painless (either etiology). DeQuervain's thyroiditis is the classical painful subacute form of thyroiditis but it may also be non-painful and referred to as silent thyroiditis. The sedimentation rate is elevated in viral thyroiditis and the gland RAI uptake is low or absent. Thionamides and radioactive iodine are of no use in treating thyroiditis since the hyperthyroidism is from tissue breakdown and release. Based on symptoms, physicians may chose to treat with medications such as non-steroidal anti-inflammatories, cox-2 inhibitors, corticosteroids and beta blockade. Some physicians administer $T_4$ to

allow the patient's thyroid gland to rest. Patients should be closely monitored for the subsequent development of hypothyroidism, which can be transient or permanent.

**Drug-induced Thyrotoxicosis:** Amiodarone and iodinated contrast dyes can induce thyrotoxicosis. Amiodarone contains 37% iodine (2). Amiodarone-induced hyperthyroidism occurs via an inflammatory thyroiditis or, in iodine deplete areas, iodine-induced thyrotoxicosis. Treatment of the inflammatory thyroiditis should be with anti-inflammatory agents and corticosteroids. Treatment of the iodide-induced thyrotoxicosis should be with medical therapy. Surgery is indicated if the hyperthyroidism persists in a case where amiodarone cannot be discontinued and when medical therapy is unsuccessful (2). Iodinated contrast dyes and topical agents can also cause hyperthyroidism. Treatment should be with medical therapy as these conditions usually resolve with discontinuation of the offending agent. Surgery should be considered if the underlying gland is not normal or if the patient fails medical therapy (2).

**Subclinical hyperthyroidism:** Subclinical hyperthyroidism occurs when there is a suppressed TSH (<0.05 uU/ml) and normal free $T_4$ and $T_3$ levels. We believe that patients with subclinical hyperthyroidism should be treated as this condition may precipitate atrial fibrillation and contribute to osteoporosis. Treatment should be based on the underlying pathology, typically antithyroid drugs for mild Graves' disease and radioactive iodine for toxic multinodular goiters. Patients with TSH levels below the normal range but above 0.05 uU/ml should be observed first.

## Conclusions

**Hyperthyroidism can be treated with medications, radioactive iodine or surgery. There is no perfect therapy and the treatment strategy should be based on physician and patient preference and the underlying pathology. Regardless of the treatment regimen, patients should be monitored closely for potential side effects, complications and failure of the treatment regimen. Long-term cure for hyperthyroidism is an achievable goal, although often at the expense of resultant hypothyroidism.**

**TREATMENTS FOR THYROTOXICOSIS BASED ON UNDERLYING**

| CONDITION | MEDICAL TREATMENT |
|---|---|
| **Grave's disease** | Thionamides<br>Beta blockade<br>Oral iodides<br>Lithium<br>Steroids<br>Oral cholecystographic agents |
| **Toxic Multinodular Goiter** | Thionamides<br>Beta Blockade<br>Lithium<br>Steroids/No long term cure |
| **Toxic Uninodular Goiter** | Thionamides<br>Beta Blockade<br>Lithium<br>Steroids/No long term cure |
| **Acute/Subacute Thyroiditis** | NSAIDS,<br>steroids,<br>beta blockade |
| **Iatrogenic/Factitious thyrotoxicosis** | Bile acid sequestrants,<br>beta blockade,<br>steroids |
| **Central hyperthyroidism** | Beta blockade,<br>Steroids, octreotride,<br>dopamine receptor agonists,<br>3,5,3'-triiodothyroacetic acid |
| **Thyroid Storm** | Thionamides<br>Beta blockade<br>Oral iodides<br>Lithium<br>Steroids<br>Oral cholecystographic agents |
| **Amiodarone and Iodinated Contrast Dye Induced Thyroiditis** | Thionamides<br>Beta blockade<br>Lithium<br>Steroids |

## DISEASE

| RAI | SURGERY |
|---|---|
| Effective/Indicated only after a trial of thionamides; majority develop hypothyroidism | Effective/indicated if patient fails medical therapy and has a contraindication to RAI, has compressive symptoms, has suspicious nodule |
| Effective in high doses | Effective/Indicated for long term cure of large glands |
| Effective but may cause hypothyroidism | Effective/Indicated for long term cure |
| Not indicated/ Ineffective | Not indicated/ Ineffective |
| Not indicated/ Ineffective | Not indicated/ Ineffective |
| Not indicated/ Ineffective | Not indicated/ Ineffective |
| Must be delayed until medically stable and administered iodides have been excreted | Contraindicated secondary to patient instability |
| Not indicated/ Ineffective | Effective/Indicated when pt fails medical therapy, drug cannot be stopped, pt has suspicious nodule |

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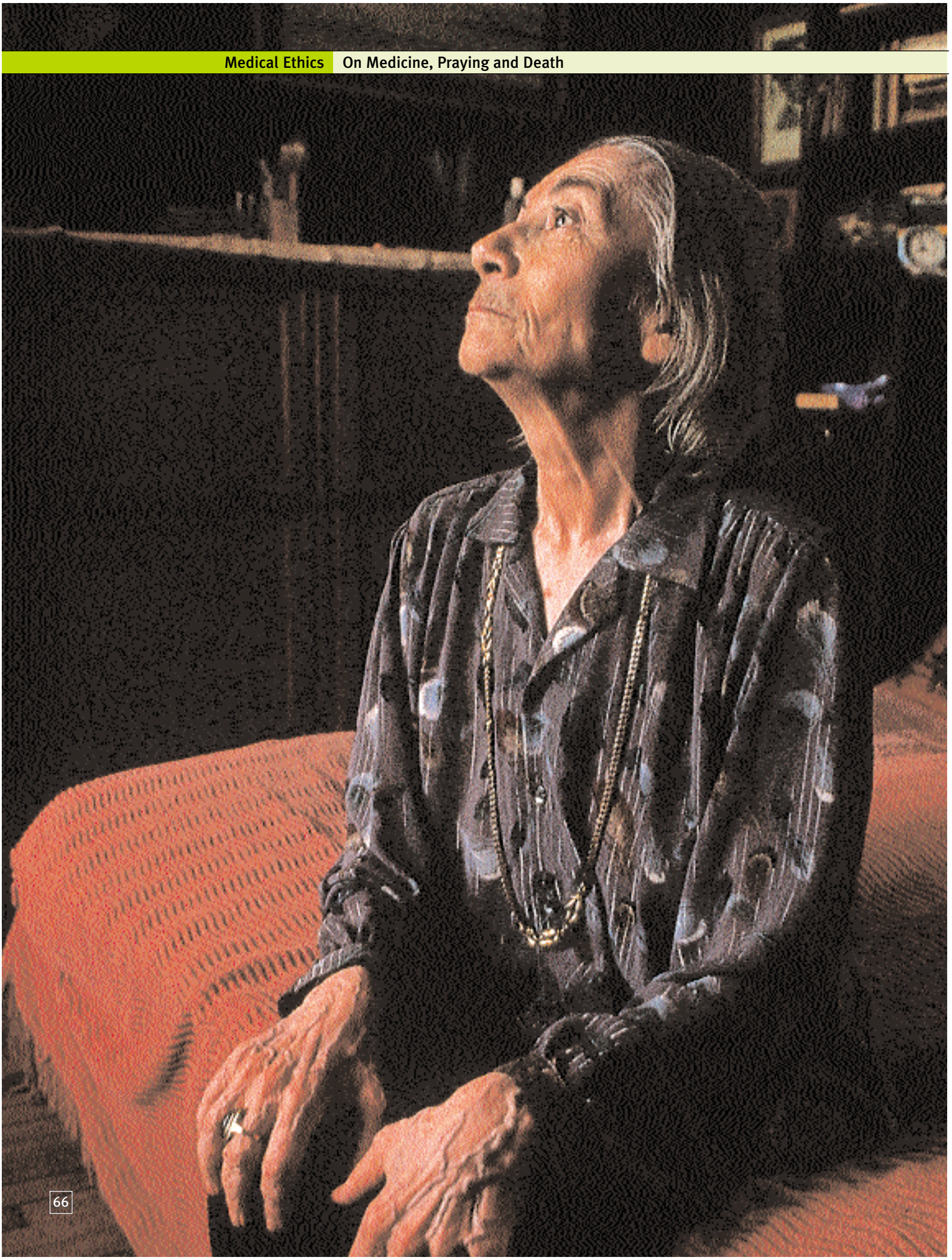


Maxine Gold

Medical Ethics

# ON MEDICINE, PRAYING & DEATH

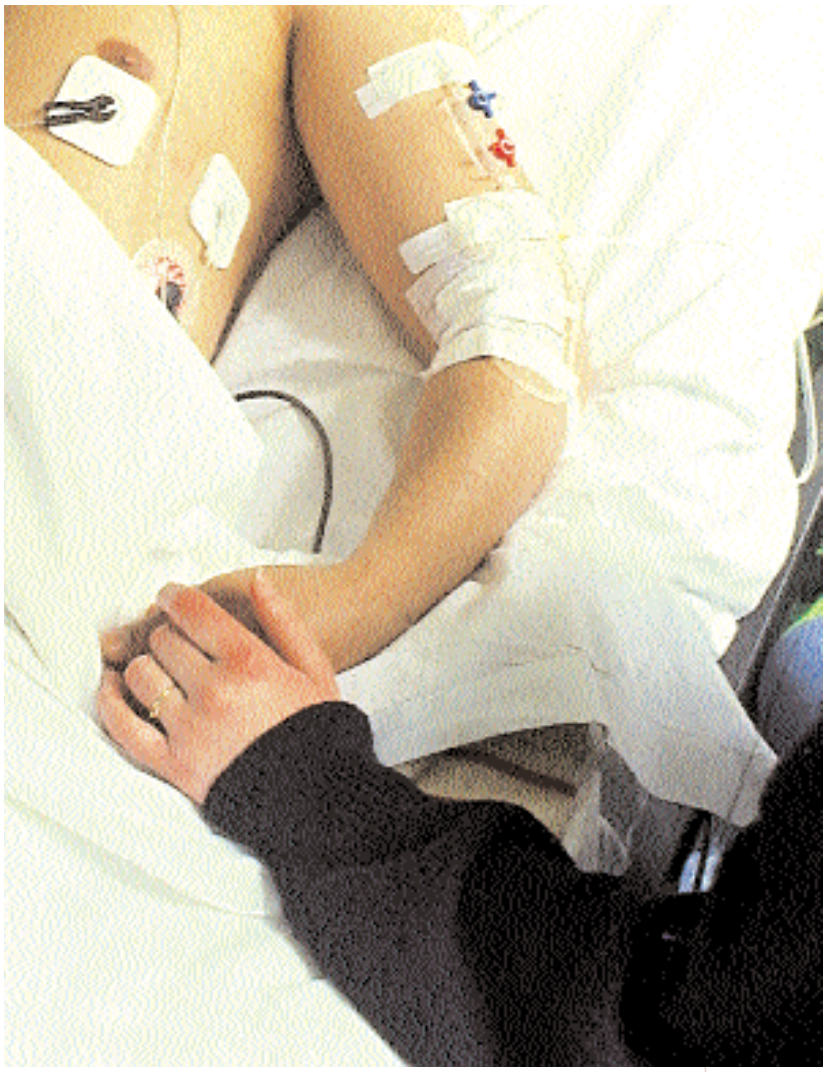
**Larry Norton, M.D., newly elected president of the American Society of Clinical Oncology and head of the division of solid tumor oncology at Memorial Sloan-Kettering Cancer Center in New York City, and Rabbi Harlan Wechsler, founding Rabbi of Congregation Or Zarua, also in New York City, recently held a lively public conversation on the subject of "Life, Death, Medicine & Judaism" at New York's 92nd Street Y.**

The two "healers," one a man of science, the other a man of God, both men of great humanity and wisdom, agreed that medicine and religion both touch people's lives at very good, and at very bad times, and that at those times their roles often merge. Together they explored the notions of prayer, miracles and hope in coping with illness and imminent death.

## Praying allays anxiety

Take, for example, the act of prayer. Science has shown us that the physical act of praying can affect the body by allaying anxiety, which in turn can help the healing process. Norton has observed in his practice that the kind of people who engage in prayer generally do better than those who don't. "Do better?" one might well ask. According to Norton, people who pray are people who look forward, who have hope, who deal better with difficulties and illness, and seek the highest possible quality of life. "The act of praying," he said, "is associated with a positive outcome." For Wechsler, however, the slant is slightly different: God hears – and answers – our prayers; all Israel hears our prayers. "Frequently the answer is no; sometimes the answer is yes," he hastened to add. Norton, however, although a

Norton has observed in his practice that the kind of people who engage in prayer generally do better than those who don't.



believer, does not quite accompany the Rabbi to the end of that road.

It is essential to understand that by "positive outcome" Norton does not necessarily mean "cure." What he does mean is that a patient who exhibits confidence that all will turn out well leads to a better prognosis because such a patient is willing to do everything necessary in the pursuit of a realistic goal. Even if this patient loses the struggle for survival, his/her quality of life leading up to the end will be greater. And Norton himself has often called a minyan together at the bedside of a patient if he feels it is appropriate and that it will help the patient cope.

Norton also sees social integration as a crucial ingredient in a good prognosis. Communal connection and support, including communal prayer, – all aspects integral to the practice of Judaism – have been shown to enhance patient outcome. He made clear, however, that one must pray for something rational and attainable. He suggests, for example, that one pray to be able to deal with one's illness. Implicit in this act is a person's ability to visualize the future in a positive way, to have an intrinsic confidence in the future. The Rabbi, who also teaches medical ethics at the Jewish Theological Seminary of America, seconded this concept, noting that the Talmud teaches the value of rational as opposed to vain prayer.

## The law is the law

Both men agreed that one should remain forever mindful of the fact that we are all part of the universal and immutable laws of nature, that we are all players in the grand and complex and miraculous cycle of life and death. "My greatest dilemma," said Norton, "is in the moment when a patient has come to terms with his imminent demise. He is ready. He wants to go. But the family is not at the same point of acceptance. How do I reconcile the fact that medically and ethically it is time to withhold treatment, that it is more important to alleviate pain and suffering than to postpone death with the desire to grant the family's wishes?" Noting that patients often make the transition before families do, he added that it is often the deeply religious who want to delay the process, because they believe that there is always the possibility of divine intervention and they want to create the opportunity for that to happen.

Rabbi Wechsler emphasized that from the religious point of view, miracles notwithstanding, it is not acceptable to go beyond what is appropriate for the patient. Paraphrasing the well-known passage from Ecclesiastes, Wechsler said, "There is a time to live, a time to die...."

Religion and medicine meet at every significant life event – birth, death, illness and recovery – in the form of hope. Norton feels that it is valid and appropriate for the physician to offer patients the opportunity to hope, to believe that they can have a positive outcome. "A positive outlook leads to a positive outcome," he said. Hopelessness can change into hopefulness with the help of a doctor or a Rabbi, he said. "One never knows the consequences of one's actions. An article on some small aspect of an ongoing research project can conceivably save the life of someone on the other side of the globe. What is important is to take action."

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# PETER Z. MALKIN

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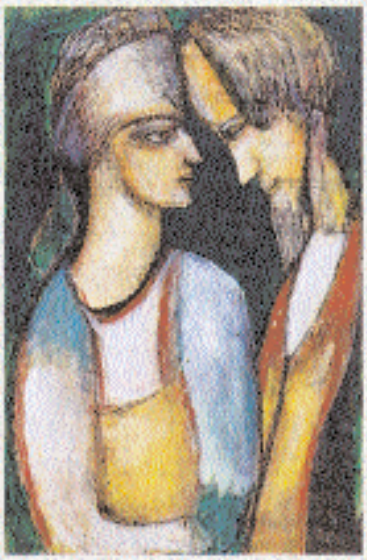

"Lovers Across the Street"

"Light Through Window"

Peter Z. Malkin was born in Palestine and spent his early childhood in Poland. In 1963, his family returned to Palestine; his sister, Fruma and her three children who remained behind together with 150 other relatives, died in the Nazi Holocaust. During the fight for independence, Malkin joined the Haganah as an expert in explosives. In 1950, he was recruited by the Mossad, which he left in 1976 as head of operations. All the time he worked for the Mossad, painting was his cover. On May 11, 1960, Malkin physically captured Adolph Eichmann, with an elite commando team in Argentina. He recounts this story in his compelling memoir, Eichmann In My Hands, made into a TNT movie, "The Man Who Captured Eichmann" starring Robert Duvall in 1966. During his historic mission, he painted words and images on the maps in an Argentina guidebook.

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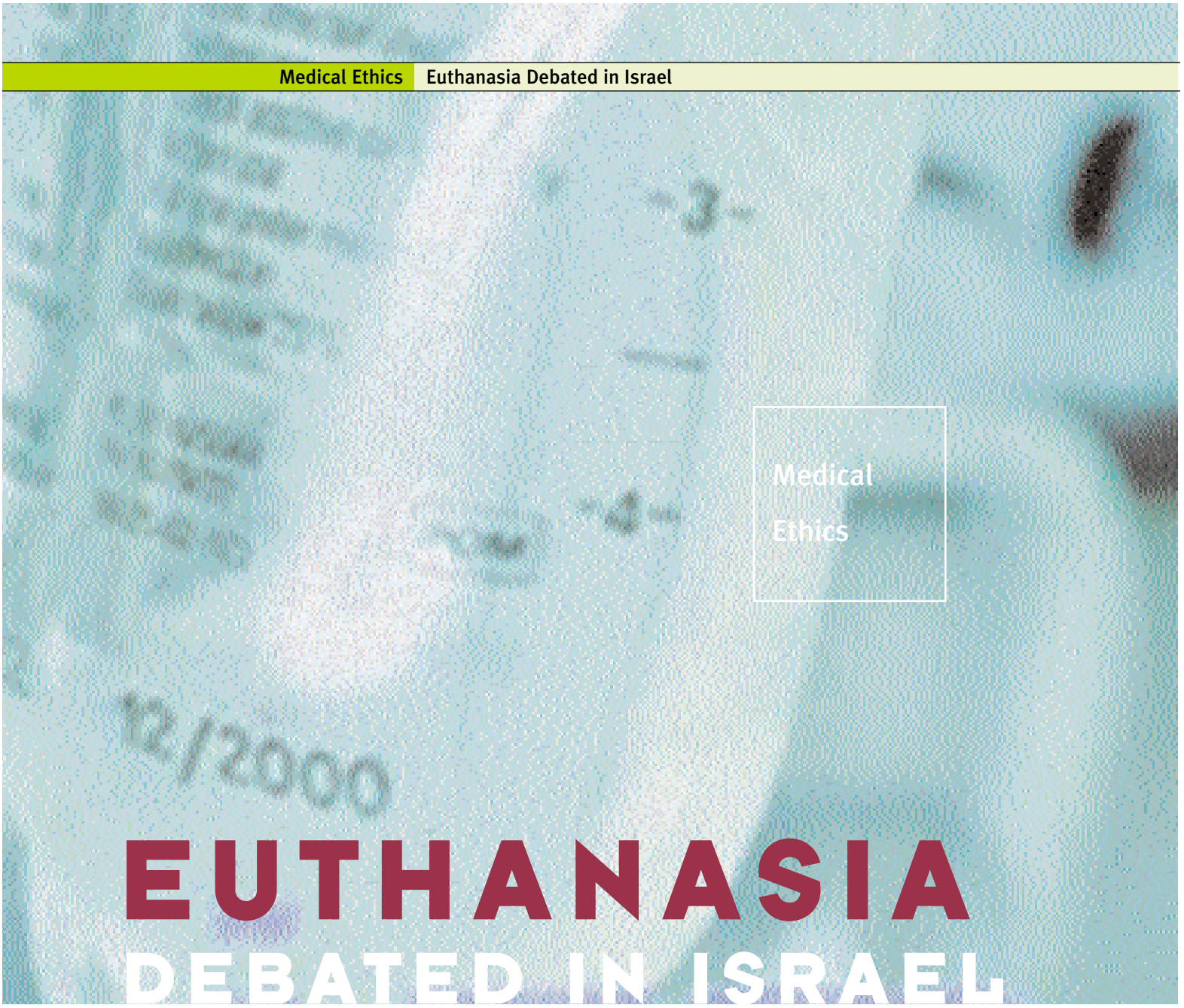



# EUTHANASIA DEBATED IN ISRAEL

**After the Holocaust, active euthanasia in Israel is inconceivable. Putting terminal patients to death — even if they beg to die and the only parts of their body they are able to move are their eyelids, is "not suited to Israeli society," says Prof. Avinoam Reches, who has been working hard for years to persuade the authorities to allow passive euthanasia.**

Legalization of active euthanasia for terminal patients — which was formally adopted recently in the upper house of Holland's parliament — will never be accepted here, insists Reches, a senior neurologist at Hadassah-University Hospital in Jerusalem's Ein Kerem; Reches has spent years fighting for legalization of passive euthanasia.

Reches, who is also chairman of the ethics committee of the Israel Medical Association, says that even the use of the term euthanasia ("good death") is inappropriate and confusing in this country. The average Israeli confuses active euthanasia (in which incurable patients are disconnected from life-maintaining devices or injected with drugs that kill them) and passive euthanasia (when terminally ill, suffering patients who

want to die can ask in advance not to undergo treatment or be attached to machines that keep them alive, or when a device is removed when it is clear that this will not immediately cause their death). Reches therefore went before the Israel Language Academy, which coins new Hebrew words; after three sessions in 2000, he won its approval for a new Hebrew term for passive euthanasia — *mitat hesed* (literally "mercy dying") rather than the popularly used *hamatat hesed* ("mercy killing").

Reches made headlines in late 1998 when it was revealed he had assisted in the passive euthanasia of Itai Arad, a 49-year-old former Israel Air Force pilot who suffered from the devastating neurological disorder amyotropic lateral sclerosis (ALS, or Lou Gehrig's disease). He couldn't swallow, talk, or move a muscle except for batting his eyelids. Arad persisted in begging Reches to let him die and repeatedly expressed this wish by blinking his eyes in response to questions. Reches consulted with senior Health Ministry officials and finally was permitted to proceed. He administered morphine to reduce pain from asphyxiation and removed Arad's breathing tube, certain he would continue to breathe on his own for a while. Arad died about 24 hours later — "from the ALS, not from the extubation," Reches said.

**"passive euthanasia is unofficially carried out every day in hospitals around the country. It's better than the active euthanasia, which is known to occur in some oncology departments and other wards -- a doctor gives a fatal injection when no one is looking..."**

"I didn't kill Itai; his disease did. He was given the chance to die with dignity, without suffering, with his family around him,"Reches told the Knesset (parliament's ) labor, social affairs and health committee session held to discuss the case. The Hadassah neurologist said he called in experts about the amount of narcotics that he could administer to put Arad into "terminal sedation" (unconsciousness) without having the drugs cause his death. Then he disconnected the respirator, "knowing for certain that Arad wouldn't die as a result. He had breathed alone many times before, but not efficiently. And he died the next day."

The neurologist conceded that if he had erred in his calculations and Arad had died immediately from suffocation, he would have felt "terrible." He told the committee with emotion that "passive euthanasia is unofficially carried out every day in hospitals around the country. It's better than the active euthanasia, which is known to occur in some oncology departments and other wards — a doctor gives a fatal injection when no one is looking. But this was the first case of passive euthanasia that was completely transparent and approved by the authorities according to a specified process."

Reches continued to keep the issue in the public eye when, in February 2000 he organized an unprecedented medical conference at the Hebrew University-Hadassah Medical Faculty. It attracted such a large audience that the proceedings had to be piped into the nearby dental school via closed-circuit TV from the medical school auditorium.

Hebrew University president Prof. Menahem Megidor said many of his colleagues had told him before the event that they felt "embarrassed and uncomfortable" about the gathering — the first public discussion at the medical school of dying with dignity — as doctors "are taught to fight for lives to the end." But Megidor told them they should not feel that way, as "death is part of life, and shouldn't be avoided."

Then-health minister Shlomo Benizri, a rabbi representing the haredi (ultra-Orthodox) Shas party, went out of his way to address the seminar. He said that halachic Judaism "sees man not just as a physical body but also as the bearer of a soul who regards time on earth as a gift. Man wants to live so he can create." Benizri added that while rabbinical sages are not completely unanimous in their views about either form of euthanasia, the majority allow the withholding of treatment that would keep alive those who are hopelessly ill and in pain; but they oppose active euthanasia that kills the patient.

Britain's late chief rabbi Immanuel Jakobovits, in his seminal work, *Jewish Medical Ethics,* published in 1959, wrote: "It is clear, then, that even when the patient is already known to be on his deathbed and close to the end, any form of active euthanasia is strictly prohibited. In fact, it is condemned as plain murder." But he noted that Jewish law "sanctions, and perhaps even demands, the withdrawal of any factor — whether extraneous to the patient himself or not — which may artificially delay his demise in the final phase. It might be argued that this modification implies the legality of expediting the death of an incurable patient in acute agony by withholding from him such medicaments as sustain his continued life by unnatural means."

Benizri announced at the Jerusalem conference that he would appoint a committee to study the issue of "dying with dignity," and within a short time he named the members. This body, which is due soon to present a formal draft of recommendation, is headed by Prof. Avraham Steinberg, a *haredi* pediatric neurologist at Jerusalem's Shaare Zedek, chairman of the medical ethics department at the Hebrew University-Hadassah Medical Faculty and a recent Israel Prize winner who has produced a massive encyclopedia on medicine and Jewish law. Steinberg, who was also present at the Jerusalem conference, said that while Reches was "covered from a legal point of view, the case overstepped the line from a public point of view." He worried about the "slippery slope." A law, he said, "has to be passed setting down what is permitted or forbidden — now — or we won't be able to stop it. If nothing is done, any hospital in the periphery will be able to do this without the requisite controls and transparency."

**Under the bill, a terminal patient would be able to request that his doctors not prolong his life artificially. A physician would not bear criminal responsibility if he avoided attaching the patient to a respirator, gave cardiopulmonary resuscitation, dialysis, chemotherapy, radiation, or infusions — on condition that the patient filled out and signed a formal living will signed by two witnesses**

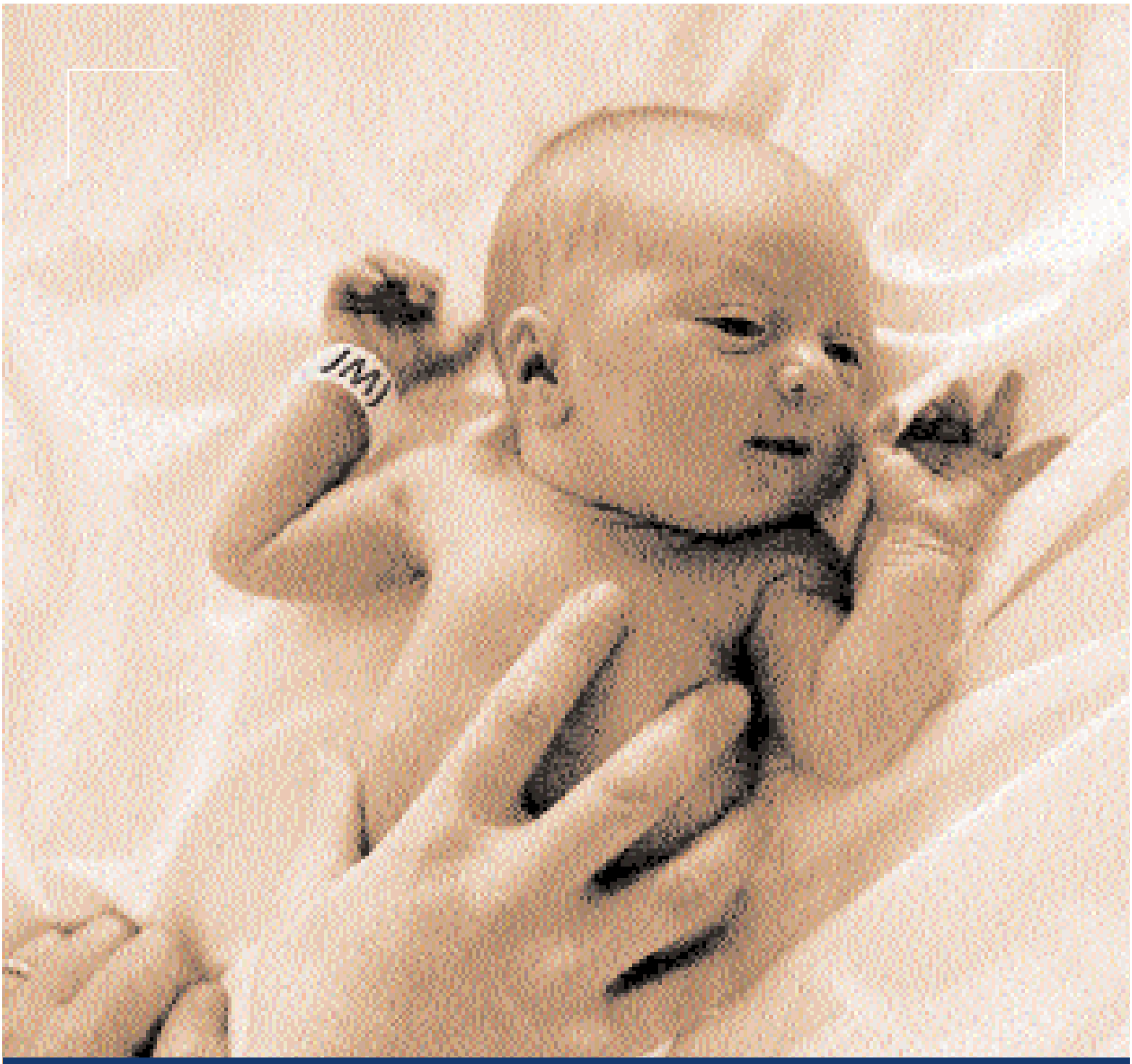
The Steinberg Committee's appointment was speeded up by the initiation of a private member's bill by two left-wing Knesset members. Anat Maor and Avi Yehezkel proposed that doctors be allowed to carry out passive euthanasia as set down in terminal patient's "living wills." Unsurprisingly supported by Reches and surprisingly backed by the Shas Party (which chairs the Labor, Social Affairs and Health Committee) and the other haredi party, United Torah Judaism, after receiving approval by their rabbis, the bill passed its first reading last March.

Under the bill, a terminal patient would be able to request that his doctors not prolong his life artificially. A physician would not bear criminal responsibility if he avoided attaching the patient to a respirator, gave cardiopulmonary resuscitation, dialysis, chemotherapy, radiation, or infusions — on condition that the patient filled out and signed a formal living will signed by two witnesses (neither of whom is in line to inherit). The patient would be able to change his mind and cancel the living will, even orally, at any time.

Reches welcomed the committee vote, saying it was an "historic" decision because it would give legal status to living wills and protect physicians from prosecution when they carry out their patients' request for passive euthanasia. However, the bill does not go as far as discussing withdrawal of existing life-support systems.

Ghita Dror, head nurse in the respiratory intensive-care unit at Hadassah-University Hospital in Jerusalem's Ein Kerem, sums up by giving her profession's perspective: "In each of these beds lies a patient, a person, a unique human being — many a time only his eyes express some spark of life, of light that often fades into darkness.... As medicine progresses so does longevity, bringing with it the complications and implications of such a system. Consequently, we in the intensive-care unit are increasingly required to care for disabled elderly who are mentally crippled and handicapped, riddled with pressure sores and constrictions."

"Within this group, there are the fortunate — or unfortunate — who do not find peace through death... But what of those who do not die? Are we interfering and saving their lives at all costs, or are we many times only prolonging the pain and suffering of patient and family? My values and beliefs tell me this is not life... The patient can no longer be healed or saved. For me, man is more than a set of biological functions. He is more than meters of tubing and drains and bottles and needles. For me, life is related to the autonomy of the individual; to the dignity and self-respect of the person; to self-determination and independence; to the ability to care for oneself, to control one's body. It is immoral to allow someone to live on in an ICU, gradually losing all form of human shape, becoming more crippled and deformed by the very same equipment that offers him life... Quality of life, freedom of the spirit, a will, and a purpose to life must be the values that rise over sheer existence, "Dror concludes," and modern medicine must come to terms with the fact that... death in itself is not a failure."



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**1 ABOUT APF:** The "Home" link is our current front-page, acting like a portal to our different sections and links to other Internet sites. By clicking on one of the lines in this section, you will discover our main programs and the names of APF's officers and trustees.

**2 GET INVOLVED:** Time for action. Find out about how to become part of our endeavours to advance the state of medical education, research and health care in Israel. Become a member of APF, make tax-deductible donations, choose your APF Fund – or create your own.

**3 AFFILIATE PROGRAMS:** If you wish to be more involved in Women's Health, in Environmental Medicine or in Allergology, this is where to click. Our Affiliate Programs will take you to your field of interest.

**4 NEWS AND EVENTS:** You wish to find out about an APF event near you? This section will keep you posted. You can also browse through our Press releases and General information.

**5 ARCHIVES & LIBRARY:** A reference in a past APF publication? This is where to look for it. The APF Library contains past and present publications of the APF for your convenience. Others links will lead to the Chevra/SIG Library and to other sites of interest on the Internet.

**6 WELCOME TO THE APF:** Click on the "Read more..." line and you will learn all you wanted to know about the American Physicians Fellowship for Medicine in Israel –who, what, where, when and more.

**7 DOWNLOAD:** APF sponsors annual consultations to Israel led by American experts in the field of women's health, co-sponsored by IAAWH and Hadassah Israel, have planted the seeds for the adoption of women's health curriculum at Israel's medical schools. Other projects are focusing on breast cancer, cardiovascular disease and other aspects of women's health. Read the Heart disease chapter after downloading it through this link.

**8 WHAT'S NEW:** Discover our Discussion Board, read *Good Medicine: Israeli Innovations In Health Care That Could Benefit Americans,* an AICE publication sponsored by the APF, pay a virtual visit to our Photo Gallery of 50 Years of APF History. And if you have any questions, comments, or problems, this is where to report it to our Webmaster.

5TH INTERNATIONAL CONGRESS ORGANISED BY
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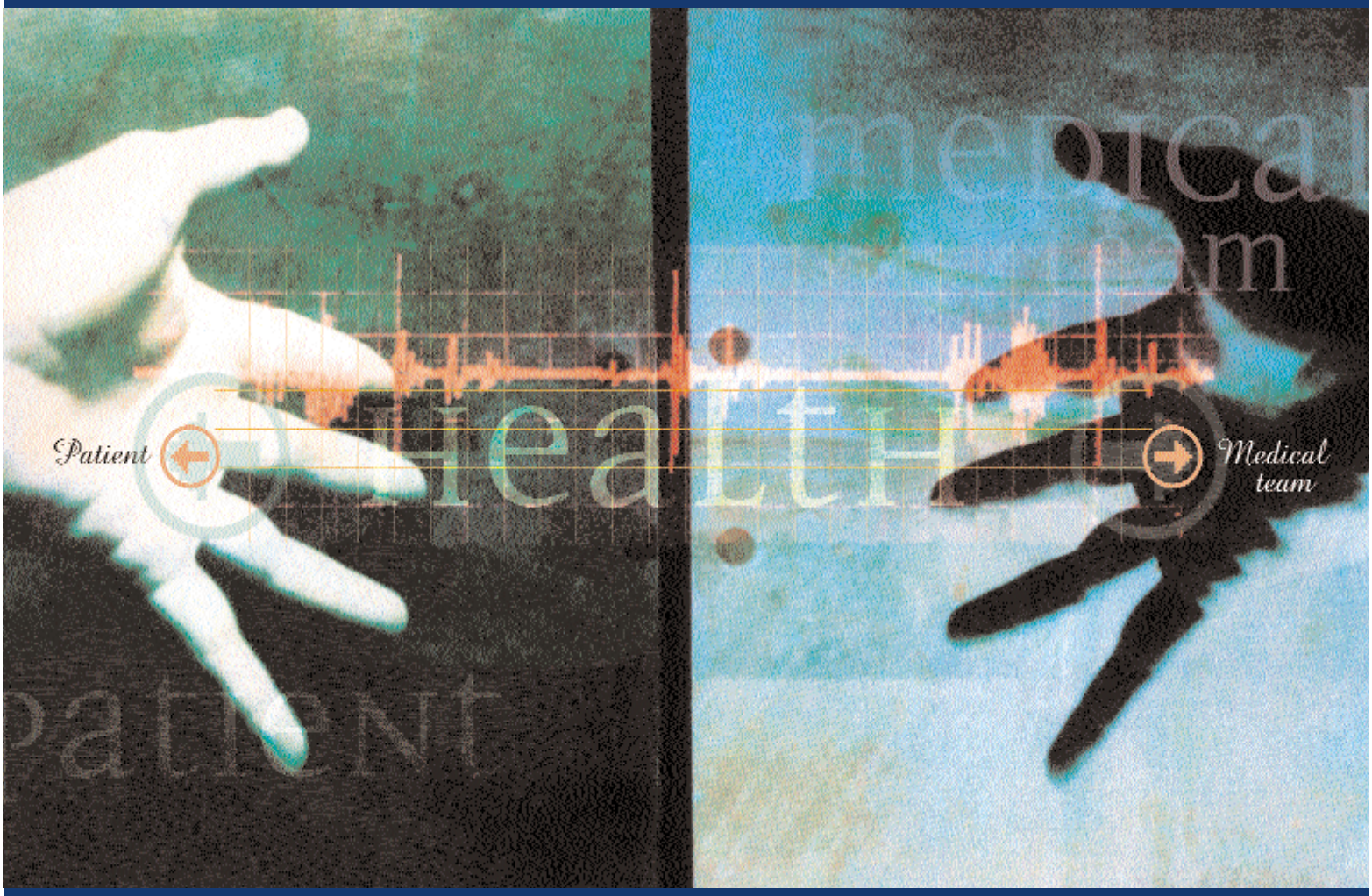


# Patients, physicians & decisions in quality of life:

## *A global perspective ?*

OCTOBER 30-31, 2002
NOVEMBER 1, 2002

INFORMATIONS

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The NEW YORK ACADEMY of MEDICINE

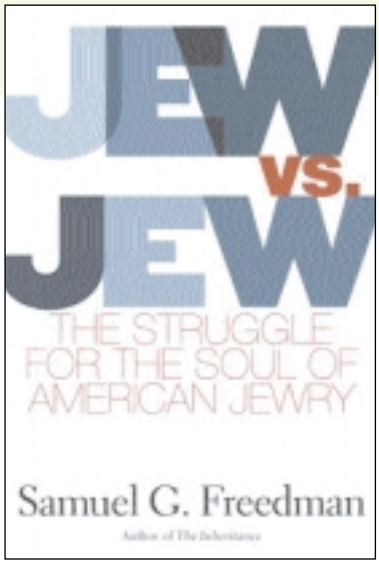
**Jew vs. Jew:** *The Struggle for the Soul of American Jewry,*
Samuel G. Freedman,
New York, Simon & Schuster, 2000, (397 pp.)

Just as the defeat of Communism has exposed the ethnic, cultural and political diversity of the peoples of the former Soviet bloc, so has the defeat of the Nazis, the creation of the state of Israel and the relative freedom from anti-Semitism that American Jews enjoy begun to reveal many cracks in the walls of a previously more unified Jewish community.

It is these schisms that Samuel Freedman, author and Columbia University journalism professor, examines in depth as he criss-crosses America, and Israel, observing and documenting what he sees as the fragmentation of the Jewish community in this post-World War II, post-1948 world.

"From the suburban streets of Great Neck [Long Island] to the foot of the Western Wall," he states in his prologue, "I have witnessed the struggle for the soul of American Jewry. It is a struggle that pits secularist against believer, denomination against denomination, gender against gender, liberal against conservative, traditionalist against modernist even within each branch." He goes on to elucidate other areas of struggle: issues of conversion standards, the peace process in Israel, land use, and the role of women in worship.

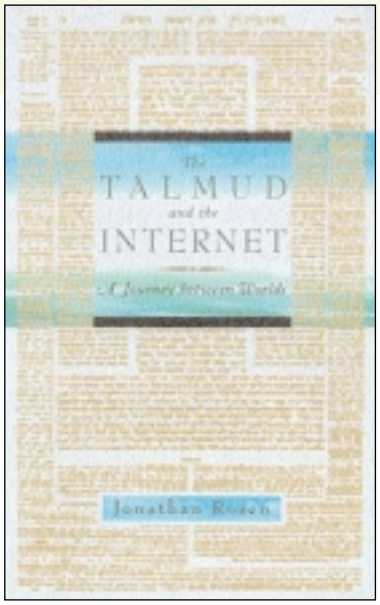
Wherever Freedman takes us in his wide-ranging, comprehensive assessment of the state of Judaism in the new millennium, the opposing and incompatible themes of unity and




pluralism are never far from the surface. In *Jew vs. Jew*, the reader will confront the nettlesome issues with great clarity and a minimum of sentimentality. Moreover, Freedman offers no easy answers.

This is an important, thought-provoking book, especially for all who call themselves Jews.

**The Talmud and the Internet: A Journey between Worlds,**
by Jonathan Rosen, Farrar, Straus & Giroux,
New York, 2000, (132 pp.)




Question: Where can one find discussions of sex, commerce and God juxtaposed and immediately accessible? If your answer is the Internet, you are right; if your answer is the Talmud, you are also right. This simplistic exercise neatly sums up Jonathan Rosen's voyage between the ancient world of the Talmud and the contemporary one of the Internet in his attempt, as he himself puts it, to "harmonize unlikely elements." Along the way, he discovers startling affinities between these two seemingly disparate vehicles of accumulated knowledge, wisdom, or at the very least, information, each a living repository of an entire civilization, each "a book that is more than a book."

Admitting that he is "proficient in neither, [but] a child of both," Rosen says, "When I look at a page of the Talmud and see all those texts tucked intimately and intrusively onto the same page, like immigrant children sharing a single bed, I do think of the interrupting, jumbled culture of the Internet. For hundreds of years, responsa, questions on virtually every aspect of Jewish life, winged back and forth between scattered Jews and various centers of Talmudic learning. The Internet is also a world of unbounded curiosity, of argument and information where anyone with a modem can wander out of the wilderness for a while, ask a question and receive an answer. I take comfort in thinking that a modern technological medium echoes an ancient one." This thoughtful, beautifully written, high-minded and at the same time deeply personal meditation makes us see each of these achievements of their respective cultures in a new way: Suddenly, the Talmud does not seem so distant, nor does the Internet seem all that new. The first began as the physical embodiment of a place (the Temple) no longer available to the Jews, and remains to this day the "place" where the Jews of the Diaspora (and Israel) go to seek knowledge, spiritual sustenance, and most of all, connection to 2,000 years of history. The Internet began as a communications tool for the military, but soon transformed itself into the space where a modern-day "diaspora" (the realities of the global economy attest to a kind of breakdown of national identity) comes to seek information as well as to connect with the inhabitants of a new global village – and its marketplace

Rosen began the book as an elegy for his beloved grandmother. Fortunately for us, his notes for the project were erased from his computer, sending him in search of a technician who knew the secrets of mining the depths of cyberspace to retrieve lost memory. His notes were eventually restored, but the incident led him in an entirely new direction, and the result is this original, superbly written essay that weaves together past, present and future in a most engaging and enlightening way.

Michael Nevins, M.D.

**In 13th century France there was an enclave of Jewish physicians living in Provence who distinguished themselves as translators of Greek and Arabic texts into Hebrew. They also worked closely with Maimonides, who at that time was living in Egypt. The ethical will that Dr. Judah ibn Tibbon left to his son provides marvelous insight into Jewish medical education during that period.**

Jewish Roots

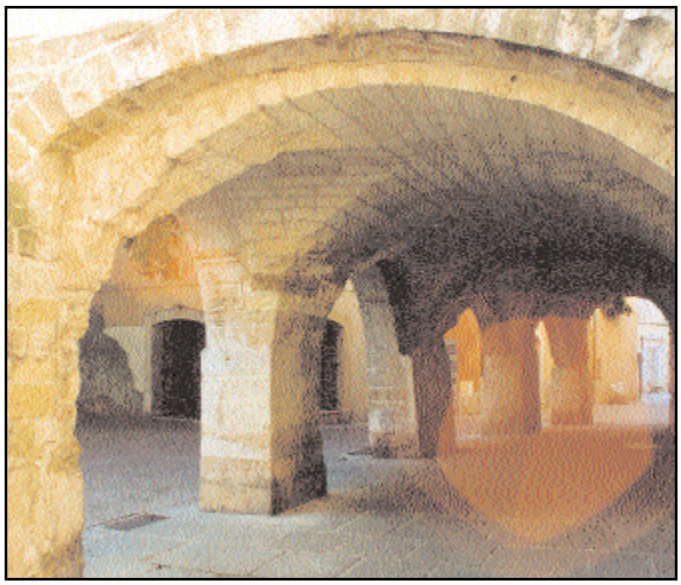
# THE COMPANY OF LUNEL

The 12th century Jewish itinerant Benjamin of Tudela wrote "from Montpellier it is four parasangs to Lunel in which there is a congregation of Israelites who study the Law day and night... The community has wise, understanding and saintly men of great benevolence who lend a helping hand to all their brethren both far and near. The congregation consists of about 300 Jews — may the Lord preserve them."

The leader of this Jewish enclave in Southern France was Meshullam ben Jacob (d. 1170 CE), a wealthy philanthropist, who along with his five sons attracted a cadre of immigrant scholars from Spain who were skilled in language. They sometimes were referred to as "the company of Lunel."
Unlike most earlier Jewish scholars, Meshullam was interested in obtaining general knowledge in addition to studying Talmud. He commissioned the émigrés to translate and transcribe philosophic and scientific works from Arabic into Hebrew, primarily works by Maimonides and other Jews living in Moorish countries, but also by Greek and Arabic writers.

In 1248 a fanatical Arabic group from North Africa invaded Spain and many Jews fled for their lives. Among them was the family of the ten year old Moses ben Maimon (Maimonides) who after years of wandering eventually settled in a suburb of Cairo. Shortly after the Maimons left Cordoba, a physician Judah ibn Tibbon (1120 - c. 1190) and his family departed from Granada and joined the scholars of Lunel where soon he too began to translate and transcribe.

In his remarkable will and testament ("A Father's Admonition"), Judah harangued his idle son, Samuel ( c. 1150 -- c. 1230) to attend to his studies and follow his father's example. The document is reproduced extensively here, as it appears in Jacob Marcus' medieval source book, because it provides unique insight into the process of medical education during this period:
"My son, listen to my precepts, neglect none of my injunctions. Set my admonition before thine eyes; thus shalt thou prosper and prolong thy days in pleasantness!...
Thou knowest my son, how I swaddled thee and brought thee up, how I led thee in the paths of wisdom and virtue. I fed and clothed thee; I spent myself in educating and protecting thee. I sacrificed my sleep to make thee wise beyond thy fellows and to raise thee to the highest degree of science and morals. These twelve years I have denied myself the usual pleasures and relaxations of men for thy sake, and I still toil for thine inheritance. (After the death of his wife the father devoted his time to Samuel, his son.)
I have honored thee by providing an extensive library for thy



**Street in the ancient city of Lunel**

use, and have thus relieved thee of the necessity to borrow books. Most students must bustle about to seek books, often without finding them. But thou, thanks be to God, lendest and borrowest not. Of many books, indeed, thou ownest two or three copies. I have besides made for thee books on all sciences, hoping that thy hand might find them all as a nest.

Seeing that thy Creator had graced thee with a wise and understanding heart, I journeyed to the ends of the earth and fetched for thee a teacher in secular sciences. I minded neither the expense nor the danger of the ways. Untold evil might have befallen me and thee on those travels, had not the Lord been with us!

But thou my son! didst deceive my hopes. Thou didst choose to employ thine abilities, hiding thyself from all thy books, not caring to know them or even their titles. Hadst thou seen thine own books in the hands of others, thou wouldst mot have recognized them; hadst thou needed one of them, thou wouldst not have known whether it was with thee or not, without asking me; thou dist not even consult the catalogue of thy library...

Therefore, my son! Stay not thy hand when I have left thee, but devote thyself to the study of the Torah and to the science of medicine. But chiefly occupy thyself with the Torah, for thou hast a wise and understanding heart, and all that is needful on thy part is ambition and application. I know that thou wilt repent of the past, as many have repented before thee of their youthful indolence....

Let thy countenance shine upon the sons of men; tend their sick, and may thine advice cure them. Though thou takest fees from the rich, heal the poor gratuitously; the Lord will requite thee. Thereby shalt thou find favor and good understanding in the sight of God and man. Thus wilt thou win the respect of high and low among Jews and non-Jews, and thy good name will go forth far and wide. Thou wilt rejoice thy friends and make thy foes envious. For remember what is written in the Choice of Pearls ( of Ibn Gabirol): "How shall one take vengeance on an enemy? By increasing one's own good qualities."....

My son! Examine regularly, once a week, thy drugs and medicinal herbs, and do not employ an ingredient whose properties are unknown to thee. I have often impressed this on thee in vain..."

(After several paragraphs concerning how to treat his wife, Judah continues)

"Examine thy Hebrew books at every New Moon, the Arabic volumes once in two months, and the bound codices once every quarter. (Arabic and Latin were the languages of science in Spaine, the Provence and southern Italy.) Arrange thy library in fair order so as to avoid wearying thyself in searching for the book thou needest. Always know the case and the chest where the book should be. A good plan would be to set in each compartment a written list of the books therein contained. If, then, thou art looking for a book, thou canst see from the list the exact shelf it occupies without disarranging all the books in the search for one. Examine the loose leaves in the volumes and bundles, and preserve them. These fragments contain very important matters which I collected and copied out. Do not destroy any writing or letter of all that I have left. And cast thine eye frequently over the catalogue so as to remember what books are in thy library.

Never intermit thy regular readings with thy teacher; study in the college of thy master on certain evenings before sitting down to read with the young. Whatever thou hast learned from me or from thy teachers, impart it again regularly to worthy pupils so that thou mayest retain it, for by teaching it to others thou wilt know it by heart, and their questions will compell thee to precision and remove any doubts from thine own mind.

Never refuse to lend books to anyone who has not the means to purchase books for himself, but only act thus to those who can be trusted to return the volumes. Thou knowest what oursages said in the Talmud, on the text 'Wealth and riches are in his house; and his merit endureth for ever'. But 'Withhold not good from him to whom it is due' and take particular care of thy books. Cover the bookcases with rugs of fine quality and preserve them from damp and mice, and from all manner of injury, for thy books are thy good treasure. If thou lendest a volume, make a memorandum

before it leaves thy house, and when it is returned, draw thy pen over the entry. Every Passover and Tabernacles (that is, every six months) call in all books out on lean....
I enjoin on thee, my son, to read this, my testament, once daily, at morn or at eve. Apply thy heart to the fulfilment of its behests, and to the performance of all theirin written. Then wilt thou make thy ways prosperous, then shalt thou have good success."

The document reveals how the transmission of medical knowledge was a personal process and a cheaper alternative to formal education during times when Jews were denied entrance to the emerging medical schools. Knowledge was a commodity that couldn't be taken away; a medical education was portable and allowed the bearer to live by his wits.

If overbearing and pedantic, Judah Tibbon's fatherly advice evidently had a salutatory effect for Samuel went on to surpass his father. If Judah later was called "the patriarch of translators", his son Samuel was described as "the prince of translators." He translated works by Galen and Aristotle into Hebrew, but his outstanding contribution was his translation of Maimonides' Guide For The Perplexed which had been written in Arabic. Maimonides was still alive and the Lunel community first wrote to him asking that he translate the work himself. The author begged off because of lack of time and energy for the project, but his reply, written in 1202 two years before his death, is enlightening:
"My friends and colleagues, be strong and of courageous hearts in this difficult period. You and those who live in your vicinity are the only ones who carry high the banner of Moses. You study the Talmud and cultivate the other sciences as well. But here in the East, the men of wisdom are decreasing and dying out.....Thus, salvation can reach us only from you. Be therefore strong and courageous and stand by the Law. You cannot rely on my labors. I can no longer come and go. I am old and weary, not with the burden of years, but because of my suffering body. The Lord grant you assistance and preserve you for blessing and glory in this world."

Samuel ibn Tibbon taught at the medical school in nearby Montpellier as did several other Jewish colleagues. Many of this younger generation lionized Maimonides and their translations of his work into Latin helped spread the Rambam's influence in the Christian world as well.
Indeed, throughout the 13th and 14th centuries there were insufficient numbers of Christian physicians, and Jews either were recruited or banned from treating the gentile population. They were exiled from France in 1306, but permitted to return in the

**Mikveh (ritual bath) of the School of Lunel house**

1360s out of sheer necessity in the aftermath of the Black Death of 1348-50.
Whenever they were tolerated, the Jewish physicians in southern France transmitted the knowledge that they had learned in Moorish Spain and distinguished themselves both in religious learning and in medical practice.

In a recent analysis titled Jews, Medicine, and Medieval Society, Joseph Shatzmiller observed, "A comparison with what happened around this time in money lending, the other major Jewish occupation, is revealing. In the same way that Jews' involvement with usury was a product of the growing demand for credit in all sectors of society, so their entry into medicine was related to the growing demand for medical services. In both instances their progress was facilitated by the church, which adopted a negative stance and was not sensitive enough to the new needs of society. Considering that other professional avenues were closed to Jews, it is not surprising that they leaped at the opportunities in finance and medicine. They found ways of creating the necessary learning tools and they turned Hebrew into a language of medical education".

From *Case Reports, Stories about Jewish Doctors,*
by Michael Nevins, M.D.

*Many Sephardic Marrano Jewish physicians fleeing Spain and Portugal settled in Holland.*
*The article in our next issue will describe one such physician who flourished there – Rembrandt's friend Dr. Ephraim Bueno.*

# LISTED EVENTS 2001/2002

| EVENT | SUBJECT ATTENDENCE | LOCATION | ORGANIZER | FROM... TO DATE | COMMITEE |
|---|---|---|---|---|---|
| International Conference on Tumor Microenvironment Progression, Therapy and Prevention | Medicine 400 | Tiberias | Kenes Ltd. | October or November, 2001 | |
| 14th Congress of the European Association for Tissue Banking | Medicine 250 | Royal Beach Hotel, Eilat | Dan Knassim Ltd. | 14/10/01 18/10/01 | |
| 11th International Symposium on Cholinergic Mechanisms | Medicine 400 | Eilat | Kenes Ltd. | 21/10/01 26/10/01 | |
| American Association for Cancer Research | Medicine 400 | Royal Beach Hotel, Eilat | Kenes Ltd. | November, 2001 | |
| 2nd International Conference on Tumor Microenvironment: Progression, Therapy & Prevention | Medicine | Tel Aviv | Kenes Ltd. | 04/11/01 07/11/01 | |
| ATSMHI 2000 | Medicine 300 | Jerusalem | Unitours | 12/11/01 16/11/01 | Dr Silvio Gutkovski, |
| First International Congress on Natural Spa Therapy | Medicine | Dead Sea | Ofakim Convention Ltd | 21/11/01 24/11/01 | |
| Regional Conference on Spinal Cord Injury | Medicine 500 | Eilat | Ortra Ltd. | 25/11/01 28/11/01 | Prof Avi Ohry |
| Meeting of the Israel Society of Obstetrics and Gynecology | Medicine 500 | | Kenes Ltd. | December, 2001 | |
| 7th International Symposium on Hypertension in the Community: Screening, Investigation and Therapy | Medicine 350 | Daniel Hotel, Herzliya | Carmel, Organizers of Conferences and Events | 03/12/01 03/12/01 | Prof Talma Rosenthal |
| Annual Meeting of the Israel Orthopedic Association | Medicine | David Inter-Continental Hotel, Tel Aviv | Israel Orthopedic Association | 04/12/01 05/12/01 | Israel Orthopedic Association in conjunction with the French Orthopedic Association |
| 8th Biennial European Society of Medical Decision Making | Medicine 200 | Kibbutz Shefayim | Target Tours, Ltd. | Year 2002 | |
| 6th International Symposium on Cardiac Arrhythmias and Device Therapy | Medicine 600 | Tel Aviv | Kenes Ltd. | 05/03/02 08/03/02 | |
| 11th World Congress on Human Reproduction | Medicine | David Inter-Continental Hotel, Tel Aviv | Kenes Ltd. | 10/03/02 14/03/02 | |
| Sixth Eilat Conference on New Antiepileptic Drugs | Medicine 300 | Eilat | Target Tours, Ltd. | 07/04/02 11/04/02 | |
| 5th Conference of the European Parkinson Disease Association (EPDA) | Medicine 400 | Jerusalem | Ortra Ltd. | 19/04/02 25/04/02 | Mr Raphael Medan Prof Martin Rabey |
| 4th International Congress of Neuropsychiatry | Medicine 500 | Jerusalem | Kenes Ltd. | 28/04/02 02/05/02 | |
| 3rd International Conference on Ocular Infections | Medicine 400 | Jerusalem | Kenes Ltd. | 09/06/02 13/06/02 | |

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# CLARITIN®
## brand of loratadine
## TABLETS, SYRUP, and RAPIDLY-DISINTEGRATING TABLETS

**Brief Summary (For full Prescribing Information, see package insert.)**

**INDICATIONS AND USAGE** CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 2 years of age or older.

**CONTRAINDICATIONS** CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

**PRECAUTIONS** **General:** Patients with liver impairment or renal insufficiency (GFR < 30 ml/min) should be given a lower initial dose (10 mg every other day). **(See CLINICAL PHARMACOLOGY: Special Populations.)**

**Drug Interactions:** Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), these were not clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on $QT_C$ intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These adverse findings are summarized in the following table:

Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine
After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers

| | Loratadine: | Descarboethoxyloratadine |
|---|---|---|
| Erythromycin (500 mg Q8h) | ↑ 40% | +46% |
| Cimetidine (300 mg Q6h) | ↑ 103% | ↑ 0% |
| Ketoconazole (200 mg Q12h) | +307% | ↑73% |

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility.** In an 18 month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure in mice given 40 mg/kg of loratadine was 8.6 (loratadine) and 18 (descarboethoxyloratadine) times the exposure in adults and 5 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times the exposure in adults and 40 (loratadine) and 98 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. Mice were given 40 mg/kg and a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg, and males and females given 25 mg/kg. Exposure of rats given 10 mg/kg of loratadine was 10 (loratadine) and 15 (descarboethoxyloratadine) times the exposure in adults and 15 (loratadine) and 20 (descarboethoxyloratadine) times the exposure in children given the maximum recommended daily oral dose. The clinical significance of these findings during long term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in mouse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m² basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m² basis).

**Pregnancy Category B** There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m² basis). There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an $AUC_{breast milk}/AUC_{plasma}$ ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.05% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

**Pediatric Use:** The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 180 pediatric patients 6 to 12 years of age in placebo controlled 2 week trials. The safety and tolerability of CLARITIN Syrup at a daily dose of 5 mg has been demonstrated in 60 pediatric patients 2 to 5 years of age in a double blind, placebo-controlled, 2-week study. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children aged 2 to 12 years is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric populations is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN in children under 2 years of age have not been established.

**ADVERSE REACTIONS** **CLARITIN Tablets:** Approximately 80,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day involved over 2 weeks' (in 6 months' duration. The rate of premature withdrawal from these trials was approximately 3% in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE GREATER THAN 2% IN PATIENTS TREATED WITH CLARITIN TABLETS IN ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER

PERCENT OF PATIENTS REPORTING

| | LORATADINE 10 mg QD n = 1926 | PLACEBO n = 1545 | CLEMASTINE 1 mg BID n = 526 | TERFENADINE 60 mg BID n = 691 |
|---|---|---|---|---|
| Headache | 12 | 11 | 8 | 8 |
| Somnolence | 8 | 6 | 22 | 9 |
| Fatigue | 4 | 3 | 10 | 2 |
| Dry Mouth | 3 | 2 | 4 | 3 |

Adverse events reported in placebo controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

**CLARITIN REDITABS (loratadine rapidly-disintegrating tablets):** Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

**CLARITIN Syrup:** Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 10 to 15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF > 2% IN LORATADINE SYRUP-TREATED PATIENTS (6 TO 12 YEARS OLD) IN PLACEBO CONTROLLED TRIAL S, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP

PERCENT OF PATIENTS REPORTING

| | LORATADINE 10 mg QD n = 188 | PLACEBO n = 262 | CHLORPHENIRAMINE 2-4 mg BID/TID n = 170 |
|---|---|---|---|
| Nervousness | 4 | 2 | 2 |
| Wheezing | 4 | 2 | 5 |
| Fatigue | 3 | 2 | 5 |
| Hyperkinesia | 3 | 1 | 1 |
| Abdominal Pain | 2 | 0 | 0 |
| Conjunctivitis | 2 | <1 | 1 |
| Dyspepsia | 2 | <1 | 0 |
| Malaise | 2 | 0 | 1 |
| Upper Respiratory Tract Infection | 2 | <1 | 0 |

Sixty pediatric patients 2 to 5 years of age received 5 mg loratadine once daily in a double blind, placebo-controlled clinical trial for a period of 14 days. No unexpected adverse events were seen given the known safety profile of loratadine and likely adverse reactions for this patient population. The following adverse events occurred with a frequency of 2 to 3 percent in the loratadine syrup-treated patients (2 to 5 years old) during the placebo controlled trial, and were frequently than in the placebo group: diarrhea, epistaxis, pharyngitis, influenza-like symptoms, fatigue, stomatitis, tooth disorder, earache, viral infection, and rash.

In addition to these adverse events reported above (> 2%), the following adverse events have been reported in at least one patient in CLARITIN clinical trials in adult and pediatric patients:

*Autonomic Nervous System:* altered lacrimation, altered salivation, flushing, hyperhidrosis, impotence, increased sweating, thirst.

*Body as a Whole:* angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, weight gain.

*Cardiovascular System:* hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

*Central and Peripheral Nervous System:* blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

*Gastrointestinal System:* altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, loose stools, nausea, vomiting.

*Musculoskeletal System:* arthralgia, myalgia.

*Psychiatric:* agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paranoia.

*Reproductive System:* breast pain, dysmenorrhea, menorrhagia, vaginitis.

*Respiratory System:* bronchitis, bronchospasm, cough(ing), dyspnea, hemoptysis, laryngitis, nasal dryness, sinusitis, sneezing.

*Skin and Appendages:* dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, urticaria.

*Urinary System:* altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice; hepatitis; and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; thrombocytopenia; and seizures.

**OVERDOSAGE** In adults, somnolence, tachycardia, and headache have been reported with overdosage (greater than 10 mg with the tablet formulation [40 mg-180 mg]). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in mice (approximately 1700 and 1400 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). No deaths occurred at oral doses up to 5000 mg/kg in weanling rats (approximately 2400 and 2000 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). However, lethality occurred in juvenile rats at an oral dose of 175 mg/kg (approximately 100 and 70 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis). No deaths occurred at oral doses up to 1700 mg/kg in monkeys (approximately 2100 and 1500 times, respectively, the maximum recommended daily oral dose in adults and children on a mg/m² basis).

Schering.

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Rev. 9/00

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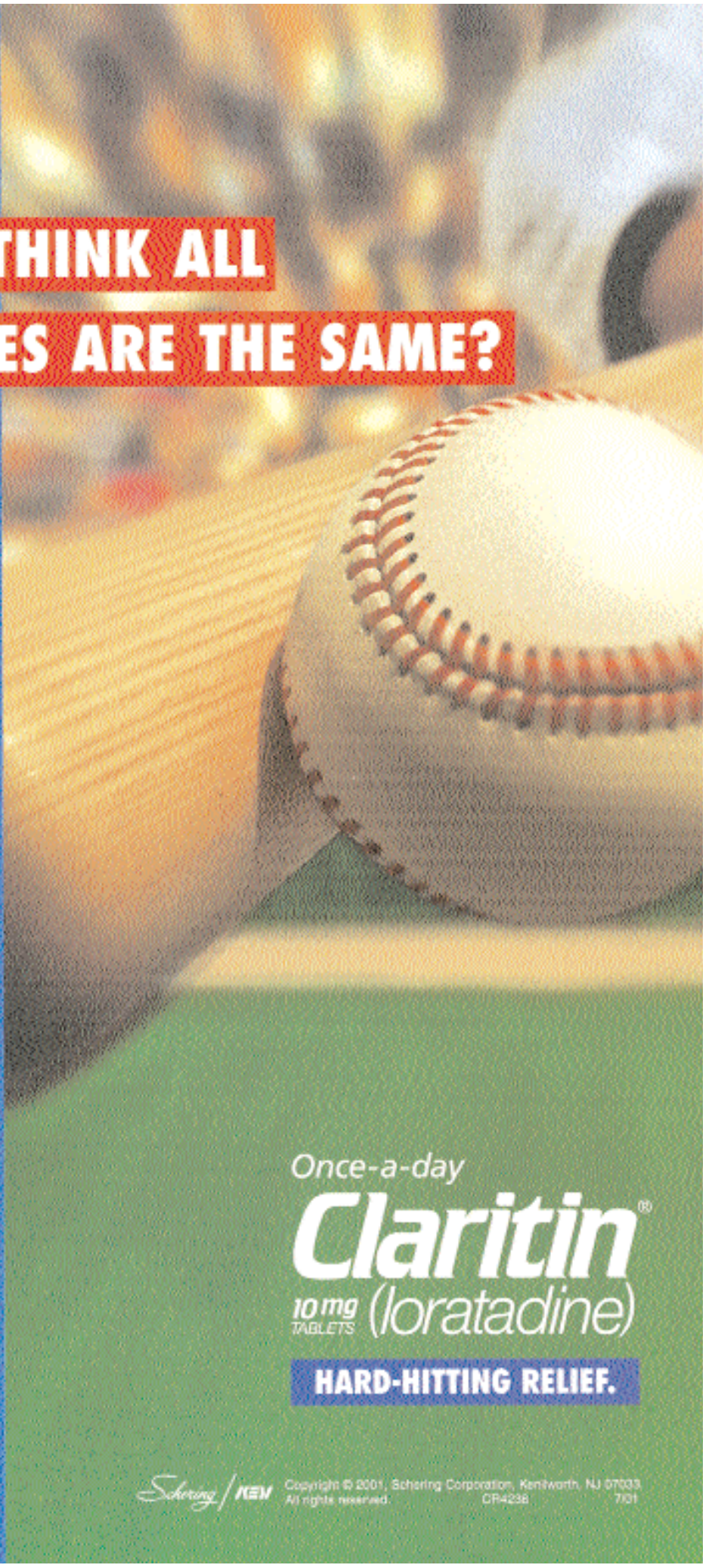
**CLARITIN REDITABS (loratadine rapidly-disintegrating tablets)** are manufactured for Schering Corporation by Schering-Plough, England.

U.S. Patent Nos. 4,282,233 and 4,371,516.



For the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria...

# DO YOU STILL THINK ALL ANTIHISTAMINES ARE THE SAME?

## *Only CLARITIN® delivers...*

- The #1 prescription antihistamine in the world [1]
- A family of five formulations to meet your patients' needs
- Over 10 billion patient days of experience*

## *Plus...*

- No food restrictions
- QD nonsedating† relief
- Accepted on over 96% of managed care formularies

In controlled clinical trials in seasonal allergic rhinitis patients using the recommended dose, the incidence of adverse events with CLARITIN® was similar to placebo (headache 12%, placebo 11%; somnolence 8%, placebo 6%; fatigue 4%, placebo 3%; dry mouth 3%, placebo 2%).

* Based on the CLARITIN® family of products.
† The incidence of sedation with CLARITIN® (8%) was similar to that of placebo (6%) at the recommended dose. In studies with CLARITIN® at doses 2 to 4 times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed.

**Reference**

1. Based on MAT, December 1995 to December 2000. IMS prescription data.

**Please see brief summary of Prescribing Information on adjacent page.**

Once-a-day

**Claritin®**

10 mg TABLETS (loratadine)

**HARD-HITTING RELIEF.**

Schering / NEW



CR4236 7/01