APF news

APF

Co-Sponsors

Women's Health

Symposium in Jerusalem

The American Physicians Fellowship for Medicine in Israel, based in Boston, recently co-sponsored a symposium on women's health and the delivery of health services in Israel, as part of National Women's Health Week.

Organized by Israel Association for the Advancement of Women's Health (IAAWH), the symposium drew 150 health care professionals, representatives of women's organizations, and others to Jerusalem, a wonderful achievement in these difficult days. The meeting was fascinating and a great professional success.

Dr. Amy Avgar, executive director of IAAWH, said one goal of the symposium was to encourage Israel's health care system to examine different models for the delivery of health care services to women, including the adoption of a more holistic focus. Sponsored by the APF, the principal guest speaker was Prof. Marcel Kornitzer, a noted cardiologist and epidemiologist at the School of Public Health, Free University of Brussels, Belgium. Prof. Kornitzer pointed out that breast cancer is the most common cause of cancer mortality in women, and that women are more prone to developing Type 2 diabetes, thyroid disorders, osteoporosis, arthritis, and colitis. His studies also show that women suffer from greater job stress caused, in part, by their lack of control in the work environment and little social support, as well as a greater incidence of depression and other mood disorders. Prof. Kornitzer called for greater focus on the specific needs of women in creating guidelines for detection, prevention, and treatment.

A particularly interesting session focused on the health needs in three sub-groups of women living in Israel: Arab women, immigrants from the former Soviet Union, and Haredi women. The presenters pointed out the particular barriers to health care women in these groups face, especially those related to cultural mores, and the attempts being made to help them overcome these barriers. For example, Haredi women are less inclined to espouse early detection and prevention of disease, especially breast cancer. There is a clear need for greater education about the importance of mammography and clinical examination and also for rabbinic approval to make these "legitimate" within the community. The presenter on the subject of Arab women was Dr. Bishara Bisharat, the medical director of General Health Services' Northern District. Dr. Bisharat was an APF Fellow during his year of study at the Harvard Institute of Social and Economic Policy in the Middle East 11 years ago.

The APF has been supporting the introduction of the field of women's health in Israel since 1995. During this time, the effort has brought a number of leading women's health experts to Israel, to lecture, teach, and meet with women activists and medical leaders. The organization is committed to continue supporting this important work.

APF news

SHERWOOD GORBACH, M.D., COMPLETES HIS TERM AS BOARD PRESIDENT

Almighty God, Thou hast created the human body with infinite wisdom. Ten thousand times ten thousand organs hast Thou combined in it that act unceasingly and harmoniously to preserve the whole in all its beauty, the body which is the envelope of the immortal soul. They are ever acting in perfect order, agreement, and accord. Yet, when the frailty of matter or the unbridling of passions deranges this order or interrupts this accord, then forces clash and the body crumbles into the primal dust from which it came. Thou sendest to man diseases as beneficent messengers to foretell approaching danger and to urge him to avert it.

Grant that my patients have confidence in me and my art and follow my directions and my counsel. Remove from their midst all charlatans and the whole host of officious relatives and know-all nurses, cruel people who arrogantly frustrate the wisest purposes of our art and often lead Thy creatures to their death.

– Attributed to Moses Maimonides, a 12th-century Jewish physician in Egypt.

Dr. Gorbach (l.) was presented with an engraved "Maimonides Prayer" plaque by Dr. I. Kelman Cohen.

These excerpts from the Maimonides prayer were intentionally selected for Dr. Sherwood Gorbach, our immediate past president. Dr. Gorbach is a professor of Community Health and Medicine, Tufts University School of Medicine, chief of Nutrition/Infection Section. The Maimonides prayer addresses the spiritual responsibility of medicine as opposed to limiting one's practice to the physical healing of medicine.

On Sunday, January 20, 2002, Sherwood L. Gorbach, M.D., president of the board of trustees, completed a four-year term in office. Dr. Gorbach has led the APF in a number of capacities for almost a decade. Thanks to his dedication, APF was able to expand its services to underserved communities of Israel. He was instrumental in creating new linkages throughout Israel. He also worked diligently to expand the organization's financial support. Finally, Dr. Gorbach was able to successfully work with other members of the board to create this journal.

In a gesture of the organization's deep appreciation and regard for him, Dr. Gorbach was presented with an engraved "Maimonides Prayer" plaque by Dr. I. Kelman Cohen, the incoming president. Dr. Gorbach is truly the embodiment of Moses Maimonides' teachings, both professionally and personally. We are pleased to report that Dr. Gorbach will continue to serve on the board of trustees. Congratulations on a successful tenure!

APF news

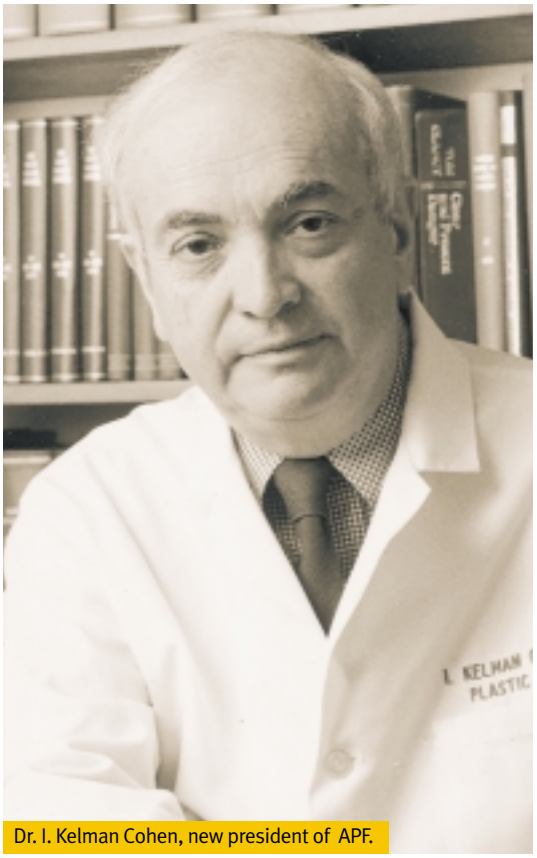
RICHMOND SURGEON ELECTED PRESIDENT OF APF

I. Kelman Cohen, M.D., emeritus chairman of the Division of Plastic and Reconstructive Surgery and professor of surgery at the Medical College of Virginia in Richmond, has been elected president of the American Physicians Fellowship for Medicine in Israel (APF). He has been a member of APF since 1981.

Dr. Cohen, a resident of Richmond, received his bachelor's degree from Columbia University in New York City, and his M.D. from the University of North Carolina in Chapel Hill.

He completed his advanced surgical training at the Mary Hitchcock Hospital; North Carolina Memorial Hospital at the University of North Carolina; and the Johns Hopkins Hospital. He is professor emeritus and Chairman of Plastic Surgery at Virginia Commonwealth University Health Science Center. He was a founder of the Arab-Jewish dialogue group of Richmond and a recipient of the Maimonides Physician of the Year award in Richmond. He is board-certified in both general and plastic surgery.

APF, a Boston-based, nonprofit organization, founded in 1950, comprises a group of North American and Israeli physicians and laypersons dedicated to advancing the state of medical education, research, and health care in Israel. Among its primary initiatives are awarding fellowship grants for medical scholars who come to North America to advance their training; a registry of volunteer physicians on call to go to Israel in cases of emergency; and a scholarship program for Israeli nurses training in North America.



Dr. I. Kelman Cohen, new president of APF.

"My vision as president is to improve health education and health care for all religious groups in Israel and to reach out to the needs of Jews and others in third-world countries," Dr. Cohen said. "After the tragedies of the past year and the realistic threats of further devastation, I would like to see our organization do its part to help bring about better understanding between Jews and other religious and ethnic groups throughout the world through the power of medical healing and education."

APF's Fellowship program provides supplementary grants to Israeli doctors coming to North America for specialty training. Each year the program provides grants to approximately 40 Israeli physicians, by supplementing the costs related to temporary relocation in the U.S. and Canada. Once their fellowships are completed, these physicians return to Israel, and many have gone on to assume leading positions in Israeli medical education, research, and clinical care.

Its Emergency Medical Volunteers for Israel program maintains a registry of some 350 North American physicians who have volunteered to be on call in case of an emergency, in which case they are flown to Israel to provide help where needed, particularly in the areas of surgical and critical care. This program was started during the 1973 Yom Kippur War, when a small group of American Jewish physicians went to Israel to provide essential medical assistance. Israel recognized the contributions of APF by granting it exclusive rights to establish an emergency registry of American medical volunteers who would be at the ready to serve in future national emergencies.

Now, in light of the current events in Israel, with almost daily suicide bombings, heightened discord because of the Palestinian issue, and the threat of bioterrorism, APF's Emergency Medical Volunteer program is more crucial and more relevant than ever.

Since 1988, the Nursing Specialty Awards program has sponsored more than 36 Israeli nurses for specialty training in leading U.S. and Canadian medical centers through its Solomon Hirsh Memorial Fund.

Dr. Cohen said that in the short term, his goal as president will be to further enhance the organization's scholarship program for Israeli health care workers and to step up the organization's fund-raising efforts to help meet educational and health care goals.

APF news

MESSAGE
from the President of APF

This third volume of the journal comes at a time when the State of Israel is at war. It is a time when those physicians in Israel who have trained with funds provided over the years by APF are now using their knowledge and judgment to save the lives of the innocent victims of Palestinian terrorism. You who have contributed to the APF effort should be proud that the knowledge acquired from your dollars is paying off. The educational opportunities you have provided through APF are helping in the decision-making of doctors and nurses as they treat the victims of Palestinian terrorists. Spawned from the same radical groups that attacked the World Trade Center, they must be eradicated from the Holy Land.

But there is more going on with your APF dollar. The government of Israel has given us the responsibility to have a team of physicians and nurses ready in the United States to meet the health care needs of civilians, should this war escalate. Although we have about 400 registered volunteers, we would like to have more in the way of nurses, neurosurgeons, plastic surgeons, general surgeons, vascular surgeons, anesthesiologists, burn experts and radiologists. Other skilled physicians and nurses should register as well—just in case you are needed. Putting this program together has been no small task and the organizational costs have been significant. We are fortunate to have a well-organized team of Israelis to guide us and, in the U.S.A., great leadership from two of the country's leading emergency trauma physicians. PLEASE, sign up now by contacting.

APF
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Boston, MA 02135-7771
Phone: (617) 232-5382
e-mail: Barbara@apfmed.org

Finally, in my first three months as your president, your generous donations and the personal notes I have received have gratified me so very much. We need your financial help now, more then ever, to run our two major programs. This week, we will have conference calls with each of the deans of the Israeli medical schools to learn how we can better serve them when we are able to raise the money to do so. I will keep you informed about our progress. APF has very limited funds and, under the leadership of Paul Scheer, we will be increasing our fund-raising activities. Please help as much as you can.

Let us all pray that peace comes soon. In the meantime, we must do everything we can to help our brothers and sisters in Israel.

Sincerely,

I. Kelman Cohen, M.D.
President of APF

APF news

THE BOSTON-HAIFA MEDICAL CONNECTION

Health professionals in Boston and Haifa are finding exciting and innovative ways to act as partners. The American Physicians Fellowship for Medicine in Israel (APF) and the Combined Jewish Philanthropies of Greater Boston (CJP) are helping make the connection. This year, six health care professionals from Haifa were awarded short-term fellowships to study in Boston.

Dalia Magal, an admissions department manager at B'nai Zion Hospital in Haifa, was hosted by three Boston hospitals – Beth Israel Deaconess, Mount Auburn, and Deaconess Glover. Her training focused on admissions and dismissal systems and gave her an insight into the American health system. Dalia was hosted by four Boston families and enjoyed the opportunity to experience the Jewish way of life in America.

Dalia Magal (l.).

Arieh Eden Oppenheim, M.D.

Arieh Eden Oppenheim, M.D., a Carmel Hospital anesthesiologist, was awarded a fellowship to do advanced study with Dr. Stanton Sherman and at the Department of Anesthesiology at the Brigham and Women's Hospital. His area of interest is transesophageal echocardiography and cardiac anesthesia. Dr. Oppenheim recently returned to Haifa and expressed his gratitude for all he was able to accomplish during his short stay.

Four more physicians will be coming to Boston shortly for two weeks of study and exchange ideas. Plans are under way to send physicians from Boston to Haifa for a similar exchange

APF has strong institutional and personal ties with Haifa University, B'nai Zion Hospital, Carmel Hospital, Rambam Medical Center, Flieman Hospital, and the Faculty of Medicine at the Technion - Israel Institute of Technology. APF also provided fellowship support to more than 50 Haifa physicians and nurses who came to the U.S. for advanced study between 1988 and 2002.

EMERGENCY MEDICAL REGISTRY

American Physicians Fellowship for Israel is the official organization designated by the State of Israel to maintain a registry of medical volunteers willing to go to Israel in case of a national emergency. Volunteers are needed particularly in the surgical, critical care, and nursing specialties. Those who can provide such assistance will be flown to Israel and housed at the expense of the Ministry of Labor.

For more information on the Boston-Haifa medical connection or to volunteer in our Emergency Medical Volunteer program for Israel, please E-mail Helen@apfmed.org.

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DESCRIPTION

PROSED®/DS is a dark blue tablet for oral administration. Each tablet contains: Methenamine 81.6 mg, Phenyl Salicylate 36.2 mg, Methylene Blue 10.8 mg, Benzoic Acid 9.0 mg, Atropine Sulfate 0.06 mg, and Hyoscyamine Sulfate 0.06 mg.

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PHENYL SALICYLATE (2-hydroxybenzoic acid phenyl ester) exists as white crystals with a melting point of 40-43˚C. It is very slightly soluble in water and freely soluble in alcohol.
METHYLENE BLUE (methylthionine chloride) exists as dark green crystals. It is soluble in water and in chloroform; sparingly soluble in alcohol.
BENZOIC ACID (benzenecarboxylic acid) exists as white crystals, scales or needles. It has a slight odor and is slightly soluble in water; freely soluble in alcohol, in chloroform and in ether.
ATROPINE SULFATE is an alkaloid of belladonna. It exists as an odorless, white crystalline powder that is slowly affected by light. It is very soluble in water and freely soluble in alcohol.
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INDICATIONS AND USAGE

PROSED®/DS is indicated for the relief of discomfort of the lower urinary tract caused by hypermotility resulting from inflammation or diagnostic procedures and in the treatment of cystitis, urethritis and trigonitis when caused by organisms which maintain or produce an acid urine and are susceptible to formaldehyde.

CONTRAINDICATIONS

Risk-benefit should be considered when the following medical problems exist: glaucoma, urinary bladder neck obstruction, pyloric or duodenal obstruction or cardiospasm. Hypersensitivity to any of the ingredients.

WARNINGS

Do not exceed recommended dosage. If rapid pulse, dizziness, or blurring of vision occurs, discontinue use immediately.

PRECAUTIONS

Cross sensitivity and/or related problems: Patients intolerant of other belladonna alkaloids or other salicylates may be intolerant of this medication also. Delay in gastric emptying could complicate the management of gastric ulcers.

Pregnancy/Reproduction (FDA Pregnancy Category C): Atropine, hyoscyamine and methenamine cross the placenta. Studies have not been done in either animals or humans. It is not known whether **PROSED®/DS** tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **PROSED®/DS** tablets should be given to a pregnant woman only if clearly needed.

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Prolonged use: There have been no studies to establish the safety of prolonged use in humans. No known long-term animal studies have been performed to evaluate carcinogenic potential.

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Gastrointestinal – dry mouth, nausea/vomiting

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Adults: One tablet orally 4 times per day followed by liberal fluid intake.
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AFI news

AFI Meets in New York


Ms. Sarah Lehman of Pfizer and Dr. Albert Lefkowitz

At the meeting of Allergists for Israel (AFI) held at the Manahattan Club at Rosie O'Grady's, on March 4, 2002, Lyndon Mansfield thanked everyone for coming and recognized Pfizer and UCB Pharma for helping to sponsor the event. He then introduced Bill Silvers, who also expressed gratitude to Pfizer and UCB Pharma for their support. "I'd also like to thank Lyndon and Randee for helping to organize this, and APF and Regimedia. I had nothing to do with putting this evening together, and maybe that is why it's so successful!" He went on to say how much he was looking forward to the exchange of ideas and the opportunity to "bond together more fully and help the field of allergy in Israel."

He gave the floor back to Mansfield, who proceeded to present a short history of the AFI. "Allergists for Israel was the dream, I suppose, of really one person that I love a lot. And because of his dreaming, some 20 years ago, we decided that we wanted somehow to express our caring for Israel and for the field of allergy in particular. And so an idea was born."

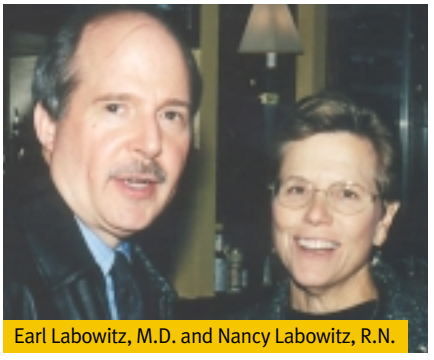
He continued, stating that he hoped that the message of the evening's gathering would be "that we do care and that we will try to do things to make things [in Israel] a little better if not perfect. After all, we weren't supposed to make it all perfect, but just to try to make it perfect. This is the contract of tikkun olam that Jews have with God."

He added, "With a lot of help from many people, including Pfizer and UCB Pharma, the projects that the AFI will undertake this year. I think are steps in the right direction toward making "chevra" again among our colleagues, our chaverim in Israel, and us here in America, who are perhaps a little insulated from some of the turmoil and difficulty."

He announced that with the funding obtained by AFI, the organization, under the leadership of Jonathan Bernstein, will institute a project that will allow four Israeli Allergy Fellows to come to the U.S. to spend a month at one of three centers: the University of California-Irvine, the University of Cincinnati, and a site in San Diego. "We'll see what other sites develop, but we hope to make it a unique educational experience for the Israeli Fellows," he said.

Mansfield's next announcement was that a number of AFI members would be going to Israel, on the suggestion of "our Israeli colleagues," as visiting lecturers in allergy and

Dr. Lyndon Mansfield, Chairman of AFI


Earl Labowitz, M.D. and Nancy Labowitz, R.N.


David Rosenstreich, M.D., Sydney Simon, M.D., Rebecca Rosenstreich

asthma at some of the smaller medical centers. "We will start by going to Afula," he said, "not just for terrific falafel but also to lecture at Afula Medical Center, to help foster understanding of the diseases we are knowledgeable about." This project will be realized with the support, in part, of Pfizer. "If we do it well, hopefully we'll be able to raise the status of allergy and immunology as a medical specialty in Israel, and we'll get good press, we hope. And that's our goal, and obviously along the way we'll make some friendships, and we will build stronger bridges between us."

He then went on to discuss another project – a National Aerobiology Program for Israel. As of now, the funding for this project is not there, but Jack Pinnas and Jay Portnoy are willing to help set up a national aerobiology networking program for Israel. Mansfield reported that these two experts in the field will be counting on multiple sites in Israel.

In closing his report, Mansfield told the attendees about "an excellent project and one that I will attend to personally – that before the end of this year there will be a Web site for AFI." He said that an Internet site would make it possible for people in Israel to get information in Hebrew or English about allergy, and that the site would also provide links to other organizations throughout the world.

A highlight of the evening was the introduction of Sarah Lehman from Pfizer's Zyrtec™ marketing team.

"For those of you that aren't from the Big Apple," she said, "I hope that you have a chance to get out into the city and see the great things that the city has to offer you. I'm actually glad that we had the opportunity to move your group from a hotel room to a nice restaurant so I hope you enjoy the fine fare. We appreciate the opportunity to partner with you and as an organization committed to your specialty, we certainly look forward to opportunities in the near future. Enjoy the evening and thank you again."


Ms. Sarah Lehman and Dr Lyndon Mansfield

Following Lehman's remarks and recognition of others who helped with the event, Bruno Cohen, CEO of Regimedia addressed the group.
"I'm really happy to be here. I was not supposed to prepare a speech so I'll keep it short. Tonight is very special for me because this is the first event we have organized in the U.S. and I'm really happy to do this with Lyndon, the APF, and the AFI, of course. This is just a start. Thank you so much to so many people. "


Ms. Sarah Lehman of Pfizer

"I want to tell you about a very important event that we are organizing with Elie Wiesel on April 30th at the New York Academy of Medicine. It is a symposium on "Bioterrorism. New Threats: Perspectives from the US and Israel." We secured the presence of Brigadier General Arieh Eldad, who was until a few weeks ago surgeon general of the Israel Defense Force Medical Corps. Professor Eldad will discuss Israel's concepts for preparedness. Nobel Prize laureate Stanley Prusiner will lecture on the response of academic medicine to the bioterrorist threat. Many other distinguished speakers will join us and we really hope that you will be part of this event of great significance."


Dr. William Silvers, Dr. Paul Goldberg, and Jared Goldberg, medical student at NYU


Howard Druce, M.D. (Pfizer), and William Silvers M.D.


DIABETIC
SEE WALLET CARD

Richard D. Siegel, M.D.
Assistant Professor of Medicine
Tufts University School of Medicine
Division of Endocrinology, Diabetes, Metabolism and Molecular Medicine
New England Medical Center, Boston, MA.

Medical Research & Practices Updates

Update on pharmacologic treatment of DIABETES MELLITUS

The past five years have seen many advances in the pharmacological treatment of diabetes mellitus. In the United States, prior to the approval of metformin, sulfonylureas were the only class of oral drugs available. Now, several new classes of medications have allowed type 2 diabetics to be free of insulin for a longer period of time. The advent of insulin analogues has improved the treatment of type 1 diabetics as well as type 2 diabetics who require insulin.

ORAL MEDICATION FOR TYPE 2 DIABETICS

There are presently four main classes of oral medications available for the treatment of type 2 diabetes. Each of the classes works on a different aspect of the pathophysiology of the disease process (Table 1).

Insulin Secretagogues

The insulin secretagogues have expanded in the last several years beyond the sulfonylureas that have been used for several decades. Glimepiride (Amaryl) was introduced in 1996 and was the first sulfonylurea approved by the U.S. Food and Drug Administration for use with insulin. As with the original sulfonylureas, it acts at the sulfonylurea receptor on the pancreatic beta cell that eventually leads to insulin secretion after closure of an ATP-sensitive potassium channel and cellular depolarization. There is some evidence that glimepiride may increase insulin sensitivity under mild to moderate hyperinsulinemic conditions by translocation of the glucose transporter GLUT4 in fat and muscle cells. In one study, it was associated with less of an increase in fasting insulin and C-peptide and fewer hypoglycemic episodes when compared with glyburide. Glimepiride has also been associated with less weight gain compared with other sulfonylureas. It is taken once daily in doses ranging from 1-8 mg, which allows for titration.

Repaglinide (Prandin) was approved in 1998 and is classified as a meglitinide, which is structurally different from the sulfonylureas. It still binds to a different part of the sulfonylurea receptor causing eventual insulin secretion. It is a short-acting agent (plasma half life of about one hour) that is meant to be taken before each meal in doses from 0.5 mg-4 mg. Plasma insulin levels rise after taking the medication and fall to baseline by the next meal. It can be titrated for the meal size, especially carbohydrate portions, in an effort to limit hypoglycemia. In initial clinical studies, it appeared to have a lower risk of hypoglycemia compared with sulfonylureas. With the short half life, it is a useful medication for patients with erratic eating schedules. If a meal is missed, the medication is skipped. There are limited data to suggest that repaglinide may be used safely in patients with renal insufficiency. In comparison with glyburide as monotherapy, mean glycemic control was the same, but fasting glucose levels were lower with glyburide and postprandial glucoses were lower with repaglinide. Repaglinide is approved with metformin and appears to be synergistic in combination.

Nateglinide (Starlix) is a d-phenylalanine derivative that is the most recent insulin secretagogue to be approved by the FDA during 2001. While it also activates part of the sulfonylurea receptor, it specifically enhances early insulin release (first phase) to provide postprandial glucose control. Similar to repaglinide, nateglinide is short acting and is designed to be taken immediately before meals. It has only two doses at 60 or 120 mg. While there have not been any head-to-head clinical trials with repaglinide, nateglinide was reported to cause only 2.4 percent risk of hypoglycemia in phase III trials compared with 31 percent of patients treated with repaglinide. One small study in 15 healthy nondiabetics suggested that nateglinide produced a more rapid and short-lived stimulation of insulin release compared with repaglinide, resulting in lower postprandial glucose levels. Nateglinide is also approved with metformin. The latter helps to lower fasting glucose while nateglinide lowers postprandial glucose. With recent studies suggesting that postprandial glucose levels are associated with cardiovascular morbidity and mortality, both repaglinide and nateglinide represent an advance, since they focus on lowering postprandial glucose. It is unclear at the present time if either drug is superior to the other or to the sulfonylureas for lowering cardiovascular disease, as there are not yet any outcome studies showing that normalizing postprandial glucoses improves cardiovascular event rates.

Metformin - Extended Release and Combination with Glyburide

Metformin (Glucophage), available since 1995, went off of patent in September 2000. This has led to the release of two new versions of the drug. Extended-release metformin (Glucophage XR) was approved in 2001 with a large direct-to-consumer advertisement campaign. While the exact mechanism of metformin is not known, it primarily lowers hepatic glucose production, possibly by acting at the mitochondria. To a lesser extent, the medication increases the peripheral uptake of glucose. The original form of the medication is taken twice or three times daily. Extended-release metformin is meant to be taken once daily with supper, with dose titration from 500-2000 mg daily. There may be a lower incidence of diarrhea and gastrointestinal upset with the extended-release version, which along with its once-daily administration, could improve compliance. The 30-day cost also is lower with the newer version of the medication by about $8. As with the original version, the medication should be stopped in patients with renal insufficiency or other illness where there is a risk of hypoxia due to the small risk of lactic acidosis. There is also a risk of B12 deficiency with chronic administration by lowering the absorption of this vitamin.

The glyburide/metformin combination (Glucovance) was approved in 2000. This is the only combination medication approved at present for treatment of type 2 diabetes. By using the two drugs in combination, better control of blood sugars can be achieved as compared to either drug used alone. Many endocrinologists advocate starting combination therapy with two antidiabetic agents that work on different aspects of the pathophysiology at the onset rather than a stepped, add-on approach. Compared with glyburide alone, there is a significant drop in both HbA1C (1.6 percent) and fasting plasma glucose (74 mg/dl) with the glyburide/metformin combination. There are three-dose combinations including 1.25 mg (glyburide)/250 mg (metformin), 2.5/500, and 5/500. Maximum dosage would be 10/1000 twice daily. The side-effect profile is the same as that seen with each medication individually, with hypoglycemia and gastrointestinal side effects predominating. The main disadvantage of this combination is the somewhat limited flexibility of the fixed-dosage combination. The medication is less expensive than the combination of the drugs used individually, though this may change when generic metformin is available. Cutting down the number of pills taken daily with a combination such as this may improve compliance for many patients, especially given that many diabetics take several other medications for hypertension, hyperlipidemia, and other comorbidities. Other combinations of antidiabetic agents are likely to be approved in the future.

TABLE 1 - CLASSES OF ORAL AGENTS FOR TYPE 2 DIABETES

(all trade names in parentheses are those used in the United States)

Insulin Secretagogues

Act on pancreatic beta cells to increase insulin secretion

Sulfonylureas

- First generation (rarely used at present)
  - Tolbutamide (Orinase)
  - Chlorpropamide (Diabinese)
  - Acetohexamide (Dymelor)
  - Tolazamide (Tolinase)
- Second generation
  - Glyburide (Micronase, Diabeta, Glynase)
  - Glipizide (Glucotrol, Glucotrol XL)
- Third generation
  - Glimepiride (Amaryl)

Meglitinide

- Repaglinide (Prandin)

D-Phenylalanine derivative

- Nateglinide (Starlix)

Biguanides

Decrease hepatic gluconeogenesis (primary), improve glucose utilization at muscle

- Metformin (Glucophage, Glucophage XR)
- Glyburide/Metformin (Glucovance)

Thiazolidinediones

Improve insulin sensitivity at muscle, fat, liver

- Rosiglitazone (Avandia)
- Pioglitazone (Actos)

Alpha glucosidase inhibitors

Decrease carbohydrate absorption in small intestine

- Acarbose (Precose)
- Miglitol (Glyset)

Thiazolidinediones ("Glitazones")

In 1997, troglitazone was approved as the first drug in a novel class of agents known as the thiazolidinediones or "glitazones." The drugs in this class are insulin sensitizers and work as ligands for nuclear peroxisome proliferator-activated receptors or PPARs. By binding primarily PPAR- g, they lead to an increase in transcription of insulin-responsive genes. They also increase adipocyte differentiation and are involved in lipid metabolism.

Troglitazone was removed from pharmacies in March 2000 owing to several cases of idiosyncratic hepatic toxicity with associated hepatic failure and death. The FDA in mid-1999 approved the second and third drugs in the class, rosiglitazone (Avandia) and pioglitazone (Actos). As research continues with the drugs in this class, it is clear that they will be useful beyond treatment of type 2 diabetes. Future indications could include treatment of the insulin-resistance syndrome ("syndrome X"), polycystic ovarian syndrome,which is often characterized by insulin resistance, and possibly coronary artery disease, given that preliminary evidence suggests these agents may have an antiatherosclerotic effect.

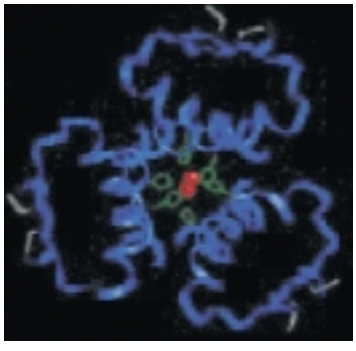
Rosiglitazone is approved for use as monotherapy or combined with metformin or sulfonylureas. It is taken once or twice daily with doses from 2-8 mg per day. Twice-daily administration may be slightly more effective than taking it once daily. When used by itself or with metformin, there is no risk of hypoglycemia, given that both of these drugs tend to lower insulin levels by working at organs other than the pancreas. Hypoglycemia may occur if the drug is used with an insulin secretagogue. The primary side effects that have been seen with rosiglitazone include weight gain, peripheral edema, and mild anemia. To date, there have only been a few case reports suggesting hepatic toxicity with rosiglitazone. The package insert continues to suggest measuring ALT values every two months for the first year of use and then periodically afterward. In early 2001, the FDA added to the package insert that rosiglitazone was not indicated for use together with insulin owing to an increase in the risk of clinical heart failure in patients taking this combination. The cause of the fluid retention in this class of medications is not clear, but may limit its use in many patients who might benefit from it. Rosiglitazone tends to raise both LDL and HDL cholesterol with variable effects on triglycerides. No clinically important drug interactions have been reported with it.

Pioglitazone was approved shortly after rosiglitazone. It is approved for use with insulin as well as monotherapy, with metformin and sulfonylureas. Dosing is once daily from 15-45 mg. There are no direct head-to-head comparisons between pioglitazone and rosiglitazone, though one may be in the planning stage. This medication has a similar side-effect profile to rosiglitazone and also has not been noted to have any significant hepatic toxicity (one case report suggesting a possible association). Liver monitoring is as listed above for rosiglitzone. Pioglitazone may be a partial agonist at PPARa and thus has lipid effects similar to the fibrates. Compared with rosiglitazone, there is minimal effect on LDL cholesterol. Triglycerides tend to fall and HDL cholesterol increases in most patients. The drug is partly metabolized by CYP3A4 and has potential for interactions with other drugs that may inhibit this cytochrome, such as ketoconazole.

Alpha-glucosidase inhibitors

Acarbose (Precose) is an alpha-glucosidase inhibitor, which binds with sucrases in the intestinal enterocytes. Because its binding affinity is so much higher than that of the oligosaccharides, acarbose interferes with their digestion, so that instead of being digested and absorbed in the upper jejunum, these complex sugars are digested in the distal jejunum and the ileum, and their products are then not absorbed. This accounts for the lower postprandial glucose observed after the ingestion of acarbose in both diabetic patients and normals. Acarbose also decreases insulin and C-peptide postprandial levels. In patients with type 2 diabetes, the postprandial peak of glucose rise is diminished by 40-60 mg/dl. The effect of acarbose on the fasting level of glucose is much more moderate and averages 15-30 mg/dl. The primary side effects of acarbose are increased flatulence, abdominal discomfort, and occasional diarrhea. These effects are caused by formation of carbohydrates that reach the colon and are metabolized by normal flora. The side effects are dose-related. Miglitol (Glyset) is the second drug in the class and may have a lower incidence of flatulence as a side effect.

INSULIN REPLACEMENT (TABLE 2)



Insulin therapy has been around since the 1920s when the first insulin was purified from pancreatic extracts for treatment of diabetic patients at the University of Toronto. Advances in the decades since then primarily involved modifying the insulin preparation with protamine or zinc to affect their absorption profile. In 1996 the first of the insulin analogues appeared, allowing diabetics requiring insulin to move closer toward more physiological insulin delivery. Lispro insulin (Humalog) was prepared by recombinant DNA technology using E. coli and differs from human insulin by switching lysine and proline from their natural positions on the B-chain on the molecule. This new molecule is absorbed more quickly than regular insulin owing to the fact that it aggregates into dimers and hexamers to a lesser extent. While regular insulin must be injected about 30 minutes before a meal for an optimal effect, lispro may be injected at the meal or up to 15 minutes before the meal. Its peak levels are higher than regular insulin and occur at 30 to 60 minutes. Its duration is only three to five hours, compared with six to eight hours for regular insulin. Due to its kinetics, lispro insulin lowers postprandial insulin more effectively than regular insulin. When used at the evening meal, it is associated with a lower risk of nocturnal hypoglycemia. There may be a slightly altered absorption when lispro is mixed with NPH insulin. A new premixed insulin with 25 percent lispro and 75 percent neutral protamine lispro

TABLE 2 - INSULIN PREPARATIONS

Bolus Insulin	Onset	Peak Time	Duration
Rapid Acting			
Insulin Lispro (Humalog)	.25 hours	0.5 - 1.5 hrs	3-5 hrs
Insulin Aspart (Novalog)	.25 hours	0.5 - 1.5 hrs	3-5 hrs
Short Acting			
Regular	0.5 hrs	2-5 hrs	5-8 hrs
Basal Insulins			
Intermediate Acting			
NPH	1-3 hrs	6-12 hrs	16-24 hrs
Lente	1-3 hrs	8-16 hrs	18-28 hrs
Long Acting			
Ultralente	6-10 hrs	10-16 hrs	18-24 hrs
Insulin Glargine (Lantus)	1-2 hrs	No Peak	24 hrs
Combination Therapies (Basal/Bolus)			
70/30 Insulin			
Lispro 75/25 Mix			

(NPL) is also available as an alternative to the older 70/30 insulin, which contains 30 percent regular insulin and 70 percent NPH. Premixed insulins are useful to help achieve adequate glycemic control with fewer shots per day.

Aspart insulin (Novolog) was approved in 2001 and is the second rapid-acting insulin to be approved. It differs from human insulin by the substitution of aspartic acid for proline in the 28th position on the B-chain. Aspart insulin has very similar pharmacokinetics to lispro insulin. A small study in type 1 diabetics comparing the two insulin analogues found similar glucose and insulin concentrations. Lispro was absorbed and declined more rapidly than aspart. As with lispro insulin, late postprandial and nocturnal hypoglycemia appears to be less with aspart as compared with regular insulin. Dosing of each of these insulins will depend on the meal content and possibly the blood sugar prior to the meal. Doses should be adjusted based on blood sugar trends aiming to keep postprandial sugars in a goal range of 100-140 mg/dl (ideally). Both insulin analogues are available in 10cc vials or cartridges made to fit pen injectors. Lispro insulin is also available in a prefilled disposable pen. Insulin pens have improved compliance with multiple insulin injection regimens where rapid-acting insulin is taken before each meal, which best mimics normal physiology.

In type 1 diabetics, it is essential that basal insulin be used along with bolus insulins such as lispro or aspart. NPH, Lente, and Ultralente have been the basal insulin in use through the 20th century. The 21st century has brought us insulin glargine (Lantus), the first long-acting insulin analogue to be approved by the FDA for both type 1 and type 2 diabetes. Glargine is also a product of recombinant DNA technology and differs from human insulin at position 21 in the A-chain where glycine replaces asparagine and at the C-terminus of the B-chain where two arginines were added. It is absorbed slowly over 20 to 24 hours without a peak concentration. The slow absorption profile is due to the fact that the solution has an acidic pH of 4 when injected and becomes neutralized in subcutaneous tissue, forming microprecipitates that dissolve slowly. Of note is the fact that glargine is a clear solution unlike the older basal insulins, which are cloudy. The insulin is suggested for injection nightly at bedtime. Patients may be switched unit for unit to glargine if they are once daily NPH or Ultralente. If these insulins are taken twice daily, the starting dosage of glargine should be about 20 percent less than the prior total basal dosage. The dose should be adjusted to achieve a fasting blood sugar of under 110 mg/dl without hypoglycemia. Glargine insulin, due to its lack of a peak, leads to less nocturnal hypoglycemia as compared to NPH insulin as well as slightly less weight gain. It should not be mixed with any other insulin.

In conclusion, the pharmacological treatment of diabetes has gone through a distinct evolution over the past decade. New oral medication classes in type 2 diabetes treat both relative insulin deficiency and insulin resistance. Insulin analogues have better pharmacological profiles than older insulins, allowing more physiologic insulin replacement. The next several decades will bring more new classes of oral drugs for type 2 diabetes and advances toward creating an "artificial pancreas" through pancreatic islet transplant, implantable insulin pumps, and possibly stem-cell therapy.

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