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INTEREST IN INHALED INSULIN GROWS

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This document is divided into two parts:

- 1) The *Highlights* section contains brief comments patterned after the “abstract” placed on the first page of many studies reported in journals. *Highlights* condenses the content of studies, and allows a quick review of pertinent points of each article.

The *Editorial Comments* are the editor’s assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of *Practical Pointers*.

- 2) The main *Abstracts* section is designed as a reference. It presents structured summaries of the content of articles in much more detail.

An *Index* containing all the Highlights is published twice a year. In an evening or two, the reader can refresh memory of the entire content of practical points abstracted from 6 major journals over the 6-month period.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr, M.D.

Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS* SEPTEMBER 2005

9-1 “THE MEDICAL HUMANITIES”, For Lack Of A Better Term

So, what are “The medical humanities” anyway?

The commentator (an established poet and essayist) finds it very difficult to define.

We know intuitively that the way medicine is now taught and practiced is simply wrong—that the humane is being supplanted by unfeeling science and uncaring economics. The medical literature describes the practice of medicine in the modern era as increasingly dominated by economic constraints and technological hubris.

Medicine, in losing sight of how the arts and humanities inform and elevate the work of healing, is following the footsteps of larger societal trends.

“Distancing” is the process whereby physicians remove themselves from the particulars of patients’ experiences of illness so that they may render accurate diagnosis and treatment. It imperils the work of doctoring, and has converted it from a sacred vocation, borne of a desire and duty to alleviate suffering, into a mere financially rewarded, technically challenging line of work.

The view of any kind of work as simply a means to the all-important paycheck is widespread nowadays. “Distancing” pervades most human interactions.

Perhaps it is expedient to blame the shortcomings of modern biomedicine on the stereotypically bespectacled, heartless philistine hiding behind his bleeping machines in his white coat, rather than to look more critically at the economic pressures that have so harshly changed medical practice. Can we really expect beleaguered clinicians and medical educators to teach ethical thinking or to nurture compassion in trainees who come to their prospective profession lacking in these fundamental personal virtues that more appropriately ought to have been instilled in them by their parents, or by immersion in what should be a healthier, more universally humane society?

Only with omnipresent and immediately accessible humanities resources for ourselves and our trainees can we nourish in our profession “the art of medicine” from which we have become so estranged.

I do not agree that medical care is being “dehumanized”. I do not agree that unfeeling science and uncaring economics are supplanting the “humane” in medicine.

In my view, the editorialist’s criticism is much too harsh. I do not believe that physicians are less “humane” (ie, less caring; less empathetic) than they were in the 18th, 19th and 20th centuries. Many health care practitioners simply do not have the opportunity to establish an empathetic relation with patients. It takes time to develop a “connection”. They are much more involved in the difficult task of providing the best of evidence-based medicine and technology. (Little of evidence-based medicine and present day technology existed before the mid-1900s.) They nevertheless retain a desire and duty to alleviate suffering, and they do indeed alleviate suffering. They are “humane” in a new and different way.

Conscientiously applying the best of modern therapy and diagnosis to each patient is an expression of caring (“humaneness”). Expert use of a blinking machine, which will often benefit patients’ health and increase

longevity, is an important part of caring. I doubt many patients (including the editorialist) would be willing to exchange the miracles of modern medicine, surgery, imaging, and anesthesia in favor of a more consistent and personal “caring” connection with every health-care provider.

Caring and technology are not mutually exclusive. Primary care clinicians are blessed with the opportunity to combine the two. They care for patients and families over time. This provides opportunity to connect and give support to the cares and concerns of their patients; to elicit, understand, and respond to each patient’s “story” in addition to attending the presenting complaint.

Has the practice of medicine been “converted into a mere financially rewarding line of work”? Not by a long shot. I do not believe young aspiring physicians enter the profession for the purpose of making money.

Nowadays, in contrast to the past, maintaining an office staff is costly. Technology is expensive. I doubt the income of the average physician, especially primary care clinicians, exceeds that of other professions. Few become “rich” as a result of their medical practice. But, it is important to earn enough to provide the family with a comfortable, safe home, a good education, and to save for retirement. This is also a form of “caring”.

Many physicians give generously of their income to charitable organizations and church. Many express humaneness by pro-bono work, caring for the less fortunate in one of the many free clinics scattered throughout the country.

The healing professions do not lack humaneness. The way it is expressed has changed.

9-2 “THE MEDICAL HUMANITIES”: Attempting A Definition

“A Humanity” is any product of human creativity and any human relationship which promotes understanding, kindness, good will, compassion, care, and caring.

“The Humanities” is the totality of all “A Humanity”.

“A Medical Humanity” (“The Medical Humanities”) does not differ from any other. However, medical professionals (nurses, therapists, dieticians, and physicians) may have more opportunity to express “A Humanity” because they care for others when the others are most vulnerable.

“Doing It In The Doctor’s Waiting Room May Be Better Than Doing It At Home.”

9-3 SELF MONITORING OF HIGH BLOOD PRESSURE

This issue of BMJ reports a randomized trial on self monitoring BP *in the physician’s office*. The self measured and the professionally measured BPs were comparable. This suggests that hypertension guidelines are applicable to self monitoring.

Patients were welcomed into the BP measuring room of the practice and encouraged to measure their own BP at least once a month using an electronic BP machine. They received instructions on how to use the machine on their first visit. Patients were given an instruction card showing their BP target (140/85). Monthly BP readings were recorded on the card. Patients were asked to see the practitioner or nurse if BP exceeded target on successive months, or if it was very high. More than 90% of patients were seen by the medical staff during the year.

This is a switch from the usual studies on self monitoring BP at home.

I wonder if some primary care clinicians would be tempted to place a validated electronic device in an alcove of the waiting room allowing any patients who are waiting to measure their BP. I believe this would be more meaningful and accurate than self measuring in a drug store.

9-4 THE METABOLIC SYNDROME—A New Worldwide Definition

The ultimate importance of the MS is that it identifies individuals at high risk for type 2 diabetes (**DM2**) and cardiovascular disease (**CVD**).

The International Diabetes Federation (2004) felt there was a strong need for one practical definition that would be useful in any country for the identification of high risk of DM2 and CVD:

1) Central (abdominal) obesity is a prerequisite to the diagnosis of the MS.

Waist circumference 94 cm or more for white men of European origin; 80 cm or more for women.

(The cut points for other ethnic groups have been changed (See text). In the USA, cut points of 100 cm and 88 cm are likely to be retained in the definition.

Central obesity is related to each of the other components of the MS. If it is not present, the MS is not diagnosed.

Plus any two of the following four factors:

2) Triglycerides 150 mg/dL and above.

3) HDL-cholesterol under 40 mg/dL in man and under 50 mg in women.

Both 2) and 3) are commonly observed in patients with DM2 and insulin resistance.

Both are risk factors for CVD.

4) BP 130 systolic and above; diastolic 85 and above, or previously treated hypertension.

5) Fasting blood glucose 100 and above, or previously diagnosed diabetes.

If above 100, a glucose tolerance test is strongly recommended.

Note that persons with 2), 3), 4) and 5) who do not have abdominal obesity are not defined as having the MS. Nevertheless, they are at increased risk. Not all 5 factors carry the same weight. But, the more factors present, the higher the risk. Of course, the other factors should be determined and treated.

I would wager that most men over age 50 in the USA have an abdominal girth over 100 cm (40 inches). And that men with obvious abdominal obesity have the MS.

It would be reasonable to immediately recommend life-style changes for them. Indeed, the need for lifestyle changes in the USA is universal.

I garnered some details from the web site of the IDF.

http://www.idf.org/webdata/docs/Metac_syndrome_def.pdf

The Big Question—Will It Mutate To Facilitate Human-To-Human Transmission?

9-5 INFLUENZA A (“Bird Flu”; H5N1): *Will It Become The Next Pandemic Influenza? Are We Ready?*

Experts have predicted a next pandemic flu for many years. They believe that the question is not whether another pandemic will occur, but when. They fear an event like the Spanish flu of 1918-19 (H1N1) which rapidly

caused death of millions and reduced the average life expectancy in the USA by 13 years. The 1918-19 pandemic affected mostly young, previously healthy adults. Death occurred within a week due to a hemorrhagic, necrotizing, viral (not bacterial) pneumonia.

Avian influenza (influenza A H5N1) appears to have a similar potential.

Most flu viruses occur in birds. Aquatic waterfowl are their natural reservoir. Only a few types of the virus have circulated widely in humans. "Bird flu" refers to both influenza in birds and to instances when the virus jumps the species barrier to cause human disease.

To cause a global pandemic the virus needs three properties: 1) ability to infect people, 2) substantially new antigenic properties to which humans are not immune, and 3) efficient person-to-person transmission. H5N1 has the first 2 properties, but there is only minimal evidence of 3).

Amantadine and rimantadine are not active against H5N1 even though it is a type A virus. Oseltamivir (*Tamiflu*; given orally) and zanamivir (*Relenza*; given by inhalation) are active in vitro and in animal models. Clinical utility for treatment and prevention of H5N1 has not been rigorously studied. The supply is inadequate for a global pandemic. Antiviral resistance does occur.

What about drug treatment and prophylaxis? Early administration of antiviral agents appears to be beneficial. Patients with suspected H5N1 should promptly receive a neuraminidase inhibitor pending diagnosis by laboratory testing. The optimal dose and duration of treatment are uncertain. Currently approved regimens likely represent the minimum required. High levels of resistance to *Tamiflu* have been detected in several patients with H5N1. Amantadine and rimantadine are not effective for H5N1. For prophylaxis, *Tamiflu* is warranted for persons who have had a possible exposure to H5N1.

Current supplies of Tamiflu and Relenza are grossly insufficient for prophylaxis and treatment of H5N1. Those of us who are knowledgeable about H5N1 and affluent enough to afford Tamiflu may be tempted to purchase and hoard a supply for possible use. There are serious objections to this. The limited supply should be reserved for treatment of individuals who are infected with the flu virus. "Ring" prophylaxis may be a reasonable control measure. This involves quarantine and prophylactic drug therapy of individuals (eg, family; health care workers) in close contact with a patient with proven influenza. This may reduce likelihood of spread in the community.

The North Carolina Department of Health has issued a statement strongly discouraging personal stockpiling of Tamiflu. It points out: 1) There has been no sustained human-to-human transmission in Asia; 2) There is no H5N1 in the USA. No poultry have been infected; 3) Supplies are limited and should be reserved for people who will need it for prevention of regular influenza this season; 4) If a pandemic occurs, Tamiflu should be used by priority groups rather than for personal stockpiles; 5) Inappropriate use may lead to resistance.

"Cutting Down" Reduces Risk Of Lung Cancer, But Not Risk Of Myocardial Infarction And COPD.

9-6 EFFECT OF SMOKING REDUCTION ON LUNG CANCER RISK

This study asks - Would "cutting down" reduce risk of LC?

Divided into 6 groups according to smoking habits:

- 1) Continued heavy smokers (> 15 cigarettes daily; mean = 20).

- 2) Reducers reduced smoking from > 15 per day by a minimum of 50% without quitting.
- 3) Continued light smokers (1-14 per day).
- 4) Quitters (stopped between 1st and 2nd examinations).
- 5) Stable ex-smokers.
- 6) Never smokers.

Groups:	1)	2)	3)	4)	5)	6)
Number	7351	832	3199	1355	2881	4066
Pack years at baseline	31	27	14	19	14	
Number of LCs	576	52	104	52	52	28
% with LC	7.8	6.3	3.3	3.6	1.8	0.7
Adjusted hazard ratio for LC:	1.00	0.73	0.44	0.50	0.17	0.09

Absolute difference, continued heavy smokers vs those who reduced consumption by 50% = 7.8% - 6.3% = 1.5%. Sixty two smokers would have to cut consumption by 50% to prevent one LC. Twenty four would have to quit completely to prevent one LC.

The authors previously investigated the all-cause mortality, fatal and non-fatal myocardial infarction, and hospitalization for COPD in smokers. They found no reduction in risk associated with smoking reduction. “Cutting down” does not reduce these risks. LC is more likely to demonstrate a dose-response to cutting down. *See the following report on snuff. RTJ*

Would You Advise Snuff For Nicotine Replacement?

9-7 MIXED FEELINGS ON SNUS

The British American Tobacco (**BAT**) company markets “snus” in Sweden. “Snus” is a finely ground snuff that is pasteurized to diminish the carcinogenic nitrosamines sometime found in high levels in snuff as well as in cigarettes. (The sale of snus is illegal in the European Union except in Sweden.)

BAT is trying to....”extend the appeal of snus to more adults smokers who have not heard of snus to try it.” BAT claims that the move is part of their “continuing efforts in harm reduction”. They claimed that the biggest group of quitters in Sweden used snus as “the main aid in quitting”.

Is it true that snus is a harm-reduction product? It certainly is much less harmful than cigarettes. It has not been associated with any increase in lung cancer. But, it is classified as a carcinogen by the International Agency for Research on Cancer. A recent study reported an increased risk of pancreatic cancer. Snus is not harmless.

Is it effective as an aid to quitting cigarettes? Evidence is inadequate, but suggests that it may be effective for some smokers. Many nicotine users favor it over tobacco smoke. The fact that more Swedes choose snus rather than therapeutic nicotine replacement for routine use suggests that it offers a better “fix”.

Is it addictive? This is controversial. Nicotine replacement therapy is relatively non-addictive, but there is a view that, if such therapy is to replace cigarettes it needs to be more competitive, and this means more addictive.

It is possible (however reluctantly) to agree that snus is a harm-reduction product, but only when compared with cigarettes.

In view of the ban on cigarettes in many restaurants and bars, tobacco companies are encouraging smokers to try snuff as an alternative where smoking is forbidden. Is this ethical?

I abstracted this article to ask myself—if my patient stated he had absolutely no intention of quitting, or was unable to quit after many tries, would I suggest his switching to snuff? (Snuff in the USA is probably more carcinogenic than snus.) Would I suggest snuff as a drug (nicotine replacement) hoping to enable cessation, or at least a reduction in cigarette smoking?

We accept risk with every drug we prescribe. With preventive therapy, (eg, aspirin, statin drugs; antihypertension drugs) patients seem quite willing to accept the risks. I abstracted this article to ask—should we consider snuff a preventive drug (ie, one that reduces risk)? Would the patient sue if he developed oral cancer after being informed of the risk and accepting it?

I would merely point this article out to the patient and let him decide on his own. I would not prescribe snuff. Indeed, I would place in the record that I advise cessation of all tobacco products.

9-8 SCABIES: *Diagnosis And Treatment*

Eight clinical points.

“Suicide Headache”

9-9 CLUSTER HEADACHE

Cluster headache (CH) is one of the most severe pain syndromes. It is underdiagnosed and suboptimally managed in primary care. It has substantial effects on functioning, even when appropriate treatments are used.

Headaches often start about 1 to 2 hours after falling asleep, or in the early morning. Attacks can strike up to 8 times a day, are relatively short-lived (18 to 180 minutes), and are characterized by very severe unilateral head pain localized in or around the eye. Attacks may occur daily for some weeks followed by a period of complete remission. (CH is cyclic.)

Patients with CH, unlike those with migraine, are restless and prefer to pace about or sit and rock back and forth. Some will isolate themselves or leave the house to get into cold air. Some become aggressive.

Unilateral autonomic symptoms ipsilateral to the pain occur only during attacks: ptosis and pupil constriction (a partial Horner’s syndrome); as well as lacrimation, conjunctival injection, rhinorrhea, and nasal congestion. This indicates parasympathetic hyperactivity, and sympathetic impairment. Sweating and blood flow to the skin increase on the painful side.

The author presents a long list of suggested drugs for treatment and prevention. (The rather large number of choices suggests that none is “best” and individual trials are necessary. RTJ)

Primary care clinicians, if they practice long enough, will encounter a patient with CH. Recognition and treatment will provide most welcome relief, and may even be life-saving. (CH has been termed the “Suicide Headache” because the severe unremitting pain may drive some patients to take their own life.)

Therapy may be tried in primary care. Complicated cases require referral to a headache clinic.

Primary Prevention Is Much More Rewarding

9-10 MODELLING THE DECLINE IN CORONARY HEART DISEASE DEATHS IN ENGLAND AND WALES 1981-2000: *Comparing Contributions From Primary Prevention And Secondary Prevention*

Since the 1980s, coronary heart disease (CHD) mortality rates have halved. Studies consistently suggest that 50% to 75% of the decrease in cardiac deaths can be attributed to population-wide improvements in the major risk factors, particularly smoking, cholesterol, and high blood pressure. Modern cardiological treatments for CHD generally explain the remaining 25% to 50% of the fall in mortality.

Fall in mortality from CHD attributable to changes in risk factors:

		Deaths prevented or postponed yearly (2000 vs 1981)		
	% changes*	Primary prevention	Secondary prevention	Total
Smoking	- 35%	24 000	5000	29 000
Cholesterol	- 4.2	4700	3100	7900
Blood pressure	-7.7	7200	500	7700
All 3		36 000	8700	45 000

(* % changes in the risk factor level in the population)

This article places our efforts to reduce risks (by enthusiastic prescription and by example) in concrete terms.

This is a major public health achievement. Congratulations to all involved

If weight reduction and physical activity were also considered, benefits would be larger.

We never know, however, which individuals in our practices and in the general population are benefited.

This should not deter us.

I abstracted this article mainly to point out how important improvements in public health are. Certainly, primary care clinicians contributed a great deal.

Note the “Spin”

9-11 PREVENTION OF CARDIOVASCULAR EVENTS WITH AN ANTIHYPERTENSIVE REGIMEN OF AMLODIPINE, ADDING PERINDOPRIL AS REQUIRED, VERSUS ATENOLOL, ADDING BENDROFLUMETHIAZIDE AS REQUIRED.

This study asked—Would a regimen based on a calcium channel blocker (CCB) + an angiotensin converting enzyme inhibitor (ACE) lead to more favorable outcomes than a regimen based on a beta-blocker (BB) + a **Thiazide** diuretic?

The study was stopped prematurely after a median of 5.5 years (over 106 000 patient-years) because fewer patients in the CCB-ACE group had the primary endpoint. (*Note: this did not reach statistical significance.*)

Outcomes over 5.5 years	ACE + CCB (n = 9639)	BB + Thiazide (n = 9618)	NNT*
Primary endpoint	429	474	208**
Stroke (fatal & non-fatal)	327	422	65
Total cardiovascular events & procedures	1362	1602	25

All-cause mortality	738	820	116
Incidence of diabetes	567	799	24***

(* NNT for 5.5 years to benefit one patient. ** Not statistically significant. The authors attributed this to under powering of the study. *** NNT to harm one patient (develop diabetes) (*My calculations. RTJ*)

“The findings of ASCOT-BPLA show that in hypertensive patients at moderate risk of developing cardiovascular events, an antihypertensive drug regimen starting with amlodipine adding perindopril, as required, is better than one starting with atenolol adding a thiazide, as required, in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and in terms of risk of subsequent new-onset diabetes.”

“Pending further information, we believe the combination of a beta-blocker and a diuretic should not be recommended in preference to the comparator regimen used in ASCOT-BPLA for routine use, but only for specific circumstances.”

This is an extraordinary (and expensive) study. I congratulate the investigators on their persistence. I feel they (and Pfizer) are disappointed with the outcome.

Benefits of antihypertension drug therapy would be much less when used for primary prevention.

But, there is an extraordinary degree of “spin” in this detailed 12-page article. As noted, the absolute differences between groups is small. And the NNT to benefit one patient over 5.5 years is large (25 to 208).

I believe these differences are of little clinical significance.

The number needed to treat unnecessarily for 5.5 years, with the amlodipine regimen as compared with the atenolol regimen, to achieve benefit for one patient is high, varying from 24 to 207.

I calculated the MNT (money needed to treat) for 5.5 years to benefit one patient. According to my pharmacy:

	Cost per day \$	Cost for 5.5 years \$	Total \$
Atenolol 50 mg	0.15	240	
Hydrochlorothiazide 25 mg			
<i>(I could not access cost of bendroflumethiazide)</i>	0.09	180	481
Amlodipine (Norvasc 2.5 mg)	1.45	2910	
Perindopril (Aceon 2 mg)	1.15	2308	5,218

Money needed to treat (MNT) with CCB + ACE vs BB + thiazide (at minimal doses) to prevent one adverse outcome over 5.5 years:

To treat 208 patients for 5.5 years to prevent one MI or one cardiovascular death::

$$CCB + ACE = 5218 \times 208 = \$1,085,344$$

$$BB + thiazide = 481 \times 208 = \$100,048$$

$$\text{Difference} = \$985,296$$

To treat 25 patients for 5.5 years to prevent total cardiovascular events and procedures =

$$\$130,450 \text{ and } \$12,025$$

$$\text{Difference} = \$118,425$$

(My calculations RTJ)

Application of lifestyle interventions would be much more effective at no cost.

Study supported mainly by Pfizer.

See the following abstract for additional analysis.

More “Spin”

9-12 ROLE OF BLOOD PRESSURE AND OTHER VARIABLES IN THE DIFFERENTIAL CARDIOVASCULAR EVENT RATES NOTED IN THE ANGLO SCANDINAVIAN CARDIAC OUTCOMES TRIAL-BLOOD PRESSURE LOWERING ARM (ASCOT-BPLA)

(This article, by the same investigators, expands on the previous trial)

Differences between the groups included BP, HDL-cholesterol, triglycerides, potassium, fasting glucose, heart rate, and body mass index. All of these variables were significantly associated with rates of coronary events and stroke during the trial. (CCB-ACE, in addition to a slightly greater reduction in BP, was associated with reductions in other risk factors.) The investigators offer no explanation except . . .”That it remains possible that differential effects of the two treatment regimens on other variables also contributed to the different rates noted”.

These factors influenced outcomes favoring the CCB-ACE group. After adjusting for these factors the investigators determined that they accounted for about half the reported difference in coronary events and about 40% of the differences in stroke noted between the two groups. (Ie, the reported benefits in the CCB-ACE group were attenuated because, overall, the differences in risk factors favored this group.)

Note—the “spin” continues. If there is any benefit of CCB - ACE over BB-Thiazide, it is certainly minimal. This additional analysis markedly increases the number of patients needed-to-treat to more clinically insignificant levels. It also greatly increases the NNT(unnecessarily) and the “Money Needed to Treat” to benefit one patient.

It does not convince me to change first-line therapy away from BB- Thiazide. I would begin with a diuretic.

The Difference Between Relative Risk Reduction And Absolute Risk Reduction

9-13 EVIDENCE THAT NEW ANTIHYPERTENSIVES ARE SUPERIOR TO OLDER DRUGS

(This editorial comments, in generally favorable terms, on the preceding articles.)

“The amlodipine-based regimen in ASCOT . . . reduced major cardiovascular endpoints by 16%, stroke by 23%, and cardiovascular and total mortality by 24% and 11% respectively, compared with the beta-blocker atenolol, with or without bendroflumethiazide.”

“On balance, the ASCOT results endorse the European guidelines for the treatment of hypertension, which leave the choice of drug class for antihypertensive treatment to the doctor.”

Note again how misleading relative risk reductions can be. In absolute terms, the percentage reductions are by my calculation:

	<i>Relative risk reduction (%)</i>	<i>Absolute risk reduction (%)</i>
<i>Major C-V endpoints</i>	<i>16</i>	<i>0.5</i>
<i>Stroke</i>	<i>23</i>	<i>1.0</i>
<i>Cardiovascular mortality</i>	<i>24</i>	<i>0.5</i>
<i>Total mortality</i>	<i>11</i>	<i>0.9</i>

*Absolute risk would be further reduced if the adjustments cited in the second study were considered.
Journal editors and investigators should not present relative risk reductions in their studies.*

Equivalent Efficacy For Treating Early and Latent Syphilis, but Resistance May Occur

9-14 SINGLE-DOSE AZITHROMYCIN VERSUS PENICILLIN G BENZATHINE FOR THE TREATMENT OF EARLY SYPHILIS

A single intramuscular dose of 2.4 million units of penicillin G benzathine (*Bicillin LA*) is the recommended therapy for early syphilis. It is low cost. Adherence is no problem. Disadvantages include pain, the relatively high prevalence of self-reported penicillin allergy, and the need for injection equipment and trained personnel. In addition, there is some risk of transmission of blood-borne infections if the injection equipment is reused.

Azithromycin (*Zithromax*), a macrolide antibiotic with a long half-life (68 hours), would overcome some of these disadvantages. Efficacy against *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Haemophilus ducreyi* has been established. (Penicillin is not indicated and is ineffective against these organisms.)

Azithromycin is a promising candidate for treatment of primary and latent syphilis. [Latent syphilis is defined by 1) a positive serological test, 2) a normal CSF, and 3) no clinical manifestations.]

This study compared effectiveness of oral azithromycin vs intramuscular penicillin G benzathine in Tanzania. Cure rates at 9 months were 98% in the azithromycin group and 95% in the penicillin group.

There have been reports of azithromycin-resistant strains *T pallidum* in the USA and in Ireland. There was no evidence of resistance in Tanzania.

An accompanying editorial comments on two important reasons for caution: 1) The sustained success (50 years) of penicillin G benzathine. 2) The recent emergence of resistance to azithromycin.

Penicillin G benzathine is marketed as Bicillin LA. Bicillin LA is composed of one molecule of dibenzylethylene diamine + two molecules of penicillin G. Given intramuscularly, it maintains blood levels for 2 weeks or more.

It has been confused with Bicillin C-R, a combination of penicillin G benzathine and penicillin procaine G which produces blood levels more rapidly and of shorter duration. It is not indicated for treatment of syphilis.

Not too long ago, syphilis was considered a major stand-alone course in medical school. I remember well giving treatment with arsphenamine and neo-arsphenamine intravenously. The miracle of penicillin changed all that. The problem of syphilis remains, but is less a problem, at least in the USA.

Environmental Incivilities And Graffiti Have An Adverse Effect On Health

9-15 GRAFFITI, GREENERY, AND OBESITY

Independently of individual characteristics, the place of residence may be associated with health outcomes, including body size, and health-related behaviors such as the level of physical exercise. Perceived attractiveness of neighborhoods has been related to levels of physical activity. Incivilities, such as litter and graffiti, are associated with adverse effects on general wellbeing.

This study hypothesized that areas which are unpleasant, with many incivilities and few green areas, might discourage people from exercising, and thus influence the levels of obesity.

For individuals living in neighborhoods with high amounts of greenery, the likelihood of being more active was more than 3 times as high as that of those living in neighborhoods with low levels of greenery.

For respondents whose residential environment contained high levels of incivilities, the likelihood of being more physically active was about 50% less, and the likelihood of being overweight/obese was about 50% higher.

“In efforts to promote physical activity and reduce weight, attention should be paid to environmental facilitators and barriers as well as individual factors.”

What does this have to do about primary care? A great deal. Economically disadvantaged patients are also medically disadvantaged. Those who live in dangerous neighborhoods will, with good reason, not walk the recommended mile or two daily. And they do not have the means to go to a spa.

I recall an article I abstracted in December 2004 “Economics of Obesity” (Practical Pointers December 2004 [12-6]). This suggests that economics plays a large part in the obesity epidemic. Foods high in fat and sugar have become less expensive as obesity rates have risen. The poor are more likely to depend on these foods. The economic situation of low-income people forces them to adopt “obesogenic” diets. “If you live in the inner city you aren’t going to suddenly start eating mangos and playing tennis.”

These articles should make us more understanding and compassionate, and less critical. “Non-adherence” and “non-compliance” are often not due to lack of motivation, but to poverty and lack of opportunity.

Of course, obesity also occurs more and more frequently in the affluent. Just observe the crowd in an upscale Mall.

The cause of obesity is multi-factorial. Down-graded neighborhoods and lack of economic advantages is an important factor.

Coming Soon? Maybe

9-16 INTEREST IN INHALED INSULIN GROWS

The lungs provide a large surface area for drug absorption. Inhaled insulin is absorbed more rapidly than regular insulin given subcutaneously. The time to peak concentration of most inhaled insulins is nearly superimposable with the rapid-acting insulin analogues.

Controlled trials compared *Exubera* (one brand of inhaled insulin) + oral agents with injected insulin + oral agents. After 2 years, *Exubera* provided continuing glycemic control. HbA1c decreased 1.8%, compared with a 1.5% decrease in the injected insulin group.

Is it safe? Some studies have reported no adverse pulmonary events; some have reported cough as the most common side effect. A slight decline in carbon-monoxide-diffusing capacity occurred. Hypoglycemia, headache and dizziness have been reported. Patients with asthma absorbed lower amounts of insulin.

Longer term studies (a decade or more) are required to evaluate pulmonary function and insulin-binding antibodies, as well as use in children and smokers.

ABSTRACTS SEPTEMBER 2005

9-1 “THE MEDICAL HUMANITIES”, For Lack Of A Better Term

The essayist presents this provocative essay in more eloquent language than I have indicated in the abstract. I chose a few points on which to comment. Read the original. I believe most primary care clinicians will disagree with many of his observations. RTJ

Recently, an international conference of scientists and artists entitled “The Medical Humanities” was held in London. All attendees, scientists and artists, were deeply concerned about the growing dehumanization of medical care, yet unsure about how it might be combated.

So, what are “The medical humanities” anyway?

The commentator (an established poet and essayist) finds it very difficult to define.

We know intuitively that the way medicine is now taught and practiced is simply wrong—that the humane is being supplanted by unfeeling science and uncaring economics. The medical literature describes the practice of medicine in the modern era as increasingly dominated by economic constraints and technological hubris.

“Distancing” is the process whereby physicians remove themselves from the particulars of patients’ experiences of illness so that they may render accurate diagnosis and treatment. It imperils the work of doctoring, converting it from a sacred vocation, borne of a desire and duty to alleviate suffering, into a mere financially rewarded, technically challenging line of work.

Medicine, in losing sight of how the arts and humanities inform and elevate the work of healing, is following the footsteps of larger societal trends. The view of any kind of work as simply a means to the all-important paycheck is widespread nowadays. Many find themselves looking instinctively to the humanities as a source of renewal, reconnection, and meaning. Alas, “the medical humanities” may ultimately provide little help in relieving the predicament. It does not assert the goal of educating aspiring physicians to be more empathetic. It fails to stipulate just what in its far-reaching realm is truly relevant to the ill and their caregivers.

Perhaps it is expedient to blame the shortcomings of modern biomedicine on the stereotypically bespectacled, heartless philistine hiding behind his bleeping machines in his white coat, rather than to look more critically at the economic pressures that have so harshly changed medical practice. Can we really expect beleaguered clinicians and medical educators to teach ethical thinking or to nurture compassion in trainees who come to their prospective profession lacking in these fundamental personal virtues that more appropriately ought to have been instilled in them by their parents, or by immersion in what should be a healthier, more universally humane society? Can we even be sure that teaching humanities in a medical context might in fact humanize medical care? Would it ultimately provide more patient-centered, and thus more attentive and probably more effective care?

Only with omnipresent and immediately accessible humanities resources for ourselves and our trainees can we nourish in our profession “the art of medicine” from which we have become so estranged.

Thus, many of us find ourselves looking instinctively to the humanities as a source of renewal, reconnection, and meaning.

9-2 “THE MEDICAL HUMANITIES”: Attempting A Definition

I tried, along with the editorialist, to more clearly define “The Medical Humanities”, or more specifically “Humanities” It became confusing. Consider these definitions supplied by my dictionary:

HUMAN

Noun: A bipedal animal of the family Hominidae, species *Homo sapiens*.

A human being.

Man, broadly, as distinguished from a divine entity and from lower animals. [*My dictionary is dated.*]

HUMANITY

Noun: The state of being human

HUMANE; HUMANENESS

Adjective: 1) Marked by compassion, sympathy, or consideration for humans and animals.

2) Having the good qualities of human beings—kindness, mercy, compassion.

Noun: Used as a noun “The Humane” encompasses all the above qualities.

HUMANITIES

Noun: The branches of learning (philosophy, arts, language) that investigate human constructs and concerns as opposite to natural processes and social relations.

Those branches of knowledge concerned with man and his culture, as philosophy, literature, and fine arts.

The study of classical languages and literature—Latin and Greek.

If to be “human” is to have all the attributes of being “man”, logically this would include both:

1) The benevolent attributes (compassion, sympathy, caring, kindness, mercy, and consideration for others) and,

2) The malevolent attributes (brutality, oppression, hubris, domination, injustice, racism, sexism, elitism, violence, war, genocide, arrogance, greed, and 100 other evils.)

It seems to me that over human history 2) has outweighed 1).

Thus, it seems contradictory to morph “human” (good and evil) into humane. Ironically, adding the

“e” eliminates 2) and focuses only on 1) What a switch!

The question remains - What are “The Medical Humanities”?

The goal of the discipline is to help individuals attain the most complete maturity possible. A most important aspect of becoming a complete adult in our society is the ability to accurately comprehend the feelings of others and to act on them. This is not easily achieved. The “art of comprehending”, just as “the art of listening”, is a life-long quest. Very few individuals attain complete maturity..

How do we help ourselves and others attain complete maturity?

I agree with the editorialist that the ability and the desire to care for others are best instilled from an early age, by example and instruction at home. I also believe that an appreciation of “The Humanities” can and should be taught in college and graduate school. I applaud the change in emphasis of premedical training over the decades from the “sciences” to history, art, languages, and social studies. Perhaps “humaneness” can be taught in formal terms. But, that is only a part of the learning curve.

The editorialist asks—“What high-powered, busy professional—lawyer, banker, architect, or business executive—has the imaginative wherewithal, or even the inclination to integrate an appreciation of Bach or O’Keeffe amidst his or her daily tasks? Would this make anyone more “humane”? Does reading great literature add to one’s “humaneness”? The ability to address a patient in his own language certainly does help to “connect”.

Perhaps a study of “The Humanities” can help one achieve a higher degree of maturity. But I believe humaneness is best taught by example. A medical trainee would more likely remember and be guided by an example of caring demonstrated by a mentor than to remember the content of a course on bioethics. Achieving “humaneness” is a lifelong quest. Developing full “medical humanity” (the art of medicine) is a life-long quest. Just as is its counterpart, “the art of listening.”

So, to attempt a definition:

“A Humanity” is any product of human creativity and any human relationship which promotes understanding, kindness, good will, compassion, care, and caring.

“The Humanities” is the totality of all “A Humanity”.

“A Medical Humanity” (“The Medical Humanities”) does not differ from any other. However, medical professionals (nurses, therapists, dieticians, and physicians) may have more opportunity to express “A Humanity” because they care for others when the others are most vulnerable.

Practical Pointers September 2005, Commentary by the Editor.

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“Doing It In The Doctor’s Waiting Room May Be Better Than Doing It At Home.”

9-3 SELF MONITORING OF HIGH BLOOD PRESSURE

Effective care of hypertension requires rigorous management with regular review and willingness to intensify drug treatment. The outcome of regular care depends on patients as much, or more than, it does on practitioners. Managing chronic diseases such as asthma and diabetes emphasizes the value of patients’ participation. The same is probably true for self monitoring of blood pressure.

Validated electronic measuring devices are now available to the public. Self monitoring satisfies the public’s demand for more self control and knowledge about health and disease.

This issue of BMJ reports a randomized trial¹ on self monitoring BP *in the physician’s office*. The self measured and the professionally measured BPs were comparable. This suggests that hypertension guidelines are applicable to self monitoring.

The study reported a cost effective reduction in treatment of hypertension with no increase in anxiety.

Previous studies reported that home monitoring is more effective in controlling BP and achieving targets. This is probably explained by the absence of a white coat effect and better adherence to treatment.

Self monitoring of BP should be part of a plan to include patients in decisions about treatments. It allows active participation by patients without losing professional supervision. Office self monitoring may prove an advantage over self monitoring at home.

[BMJ September 5, 2005; 331: 466-67](#) Editorial, first author J Carel Bakx, Radboud University, Nijmegen Medical Centre, Nijmegen, Netherlands.

1 “Targets and Self Monitoring in Hypertension” BMJ September 3, 2005; 331: 493-96 Original investigation first author R J McManus, University of Birmingham, UK.

Note that this study assessed patient self determination of BP in the doctor’s office, not at home.

Patients were welcomed into the BP measuring room of the practice and encouraged to measure their own BP at least once a month using an electronic BP machine. They received instructions on how to use the machine on their first visit. Patients were given an instruction card showing their BP target (140/85). Monthly BP readings were recorded on the card. Patients were asked to see the practitioner or nurse if BP exceeded target on successive months, or if it was very high. More than 90% of patients were seen by the medical staff during the year.

9-4 THE METABOLIC SYNDROME—A New Worldwide Definition

The metabolic syndrome (**MS**) (visceral obesity, dyslipidemia, hyperglycemia, and hypertension) has become a major public-health challenge world wide.

The association of several of these risk factors has been known for 80 years, but received scant attention until Reaven in 1988 described “Syndrome X”: insulin resistance, hypertension, low HDL-cholesterol, and raised VLDL-triglycerides. He omitted obesity (especially central obesity) which is now considered an essential component of the MS.

Several definitions have been proposed over the years.

Several of the factors are related to life-style.

The ultimate importance of the MS is that it identifies individuals at high risk for type 2 diabetes (**DM2**) and cardiovascular disease (**CVD**).

The conceptual framework used to underpin the MS (and hence drive definitions) has not been agreed upon. Opinions vary as to whether MS should be defined mainly to indicate insulin resistance, the metabolic consequences of obesity, or simply a collection of statistically related factors. The prevalence of the syndrome has been similar in any given population regardless of which definition is used, but different individuals are identified.

Another difficulty has been the applicability of the MS to different ethnic groups.

The International Diabetes Federation (2004) felt there was a strong need for one practical definition that would be useful in any country for the identification of high risk of DM2 and CVD:

1) Central (abdominal) obesity is a prerequisite to the diagnosis of the MS.

Waist circumference 94 cm or more for white men of European origin; 80 cm or more for women.

(The cut points for other ethnic groups have been changed (See text) In the USA, cut points of 100 cm and 88 cm are likely to be retained in the definition.

Waist circumference is highly related to insulin sensitivity.

If body mass index is over 30, central obesity can be assumed, and waist circumference does not need to be measured.

Central obesity is related to each of the other components of the MS. If it is not present, the MS is not diagnosed.

Plus any two of the following four factors:

2) Triglycerides 150 mg/dL and above.

3) HDL-cholesterol under 40 mg/dL in man and under 50 mg in women.

Both 2) and 3) are commonly observed in patients with DM2 and insulin resistance.

Both are risk factors for CVD.

4) BP 130 systolic and above; diastolic 85 and above, or previously treated hypertension.

5) Fasting blood glucose 100 and above, or previously diagnosed diabetes.

If above 100, a glucose tolerance test is strongly recommended.

Insulin resistance, which is difficult to measure, is not included.

Clinicians should use the new criteria for the identification of high-risk individuals.

Preventive measures are needed for those identified. Lifestyle modification with weight loss and increased physical activity will be beneficial. Drug therapy may be needed to address individual abnormalities if lifestyle therapy fails. There is no specific treatment.

Primary intervention

Moderate calorie restriction to achieve up to 10% loss of body weight in the first year.

Moderate increase in physical activity.

Change in dietary composition.

Clinical benefits are associated with small weight loss in terms of preventing (or at least delaying) conversion of persons with glucose intolerance to clinical DM2.

Secondary intervention:

In persons for whom lifestyle changes are not enough and who are considered at high risk for CVD, drug therapy for individual components of the MS may be required:

1) Dyslipidemia: Lower triglycerides; Raise HDL-c levels; Lower LDL-c levels

Fibrates improve all components of the dyslipidemia. They appear to reduce the risk of CVD in persons with the MS.

Statins reduce LDL-c. Several studies have confirmed the benefits of statins in the MS.

- 2) Elevated BP: Categorical hypertension (140/90 and above; 130/80 and above for diabetics) should be treated. The majority of clinical trials suggest that the risk reduction is due to BP lowering per se, and not due to a particular type of drug.
- 3) Insulin resistance and hyperglycemia: There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of DM2 and reduce CVD risk. Metformin in patients with prediabetes will prevent or delay development of DM2. Thiazolidinediones, acarbose, and orlistat may have some benefit.

The authors stress, these new criteria are not the final word. Hopefully they will help identify people at increased risk.

[Lancet September 24, 2005; 366: 105962](#) “Comment”, first author K George M M Alberti, St. Marys Hospital, London, UK, for the IDF Epidemiology Task Force Consensus Group.

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The Big Question—Will It Mutate To Facilitate Human To Human Transmission?

9-5 INFLUENZA A (“Bird Flu”; H5N1): *Will It Become The Next Pandemic Influenza? Are We Ready?*

Experts have predicted a next pandemic flu for many years. They believe that the question is not whether another pandemic will occur, but when. They fear an event like the Spanish flu of 1918-19 (H1N1) which rapidly caused death of millions and reduced the average life expectancy in the USA by 13 years. The 1918-19 pandemic affected mostly young, previously healthy adults. Death occurred within a week due to a hemorrhagic, necrotizing, viral (not bacterial) pneumonia.

Avian influenza (influenza A H5N1) appears to have a similar potential.

Most flu viruses occur in birds. Aquatic waterfowl are their natural reservoir. Only a few types of the virus have circulated widely in humans. “Bird flu” refers to both influenza in birds and to instances when the virus jumps the species barrier to cause human disease.

Two major glycoproteins exist on the surface of the virus: hemagglutinin (H) and neuraminidase (N). The subtypes of H and N are antigenically distinct—16 H subtypes and 9 N subtypes. All are found in birds. Thus far, only H1, H2, and H3 have caused pandemic or epidemics in humans. The viruses are constantly evolving into new antigenic variants to which humans are not immune. This accounts for the vulnerability of flu in humans and the need for annual vaccination with vaccines trying to match the virus most likely to cause the disease in the next year.

In 1997, a cluster of avian influenza (H5N1) occurred in Hong Kong. This outbreak was unique and alarming because it was the first recognized direct transmission from birds (poultry) to humans. It was highly fatal. In 2003 and 2004, new outbreaks of H5N1 occurred in poultry in 8 Asian countries. Over 100 cases (poultry to human) occurred, with high mortality in young adults and children. The pathological features were similar to the H1N1 infection of 1918.

To cause a global pandemic the virus needs three properties: 1) ability to infect people, 2) substantially new antigenic properties to which humans are not immune, and 3) efficient person-to-person transmission. H5N1 has the first 2 properties, but there is only minimal evidence of 3).

A H5N1 vaccine is currently in human trials, The hemagglutinin (H5) may be a poor antigen. Necessary studies needed to assess efficacy and safety may require extended time. The virus may traverse the globe before the vaccine is mass produced.

Amantadine and rimantadine are not active against H5N1 even though it is a type A virus. Oseltamivir (*Tamiflu*; given orally) and zanamivir (*Relenza*; given by inhalation) are active in vitro and in animal models. Clinical utility for treatment and prevention of H5N1 has not been rigorously studied. The supply is inadequate for a global pandemic. Antiviral resistance does occur.

Some have argued since, after its 9-year presence in poultry, there is no evidence that the virus has mutated to permit human-to-human transmission, if a pandemic were to happen it would have happened already.

We must not ignore the possibility of a pandemic. Even if it does not materialize, the planning and development of effective interventions will provide the necessary preparations in the event that another avian strain, to which humans have no immunity, jumps the species barrier.

[Annals Int Med September 20, 2005; 460-62](#) Editorial, first author John G Bartlett, Johns Hopkins University, Baltimore, MD.

An article in NEJM September 29, 2005; 353: 1374-85 from the WHO provides some additional details.

The big question is: Will H5N1 mutate so that human-to-human spread occurs with a facility similar to H1N1 “Spanish flu”? If so, since humans have not had exposure to H5N1 and have no immunity to it, a pandemic may result. Thus far, there is no strong evidence that human-to-human transmission occurs easily. Indeed, bird-to-human transmission is not very efficient. Species barriers to acquisition of H5N1 is substantial. Serologic studies of exposed health-care workers indicate that transmission is inefficient.

What about drug treatment and prophylaxis? Early administration of antiviral agents appears to be beneficial. Patients with suspected H5N1 should promptly receive a neuraminidase inhibitor pending diagnosis by laboratory testing. The optimal dose and duration of treatment are uncertain. Currently approved regimens likely represent the minimum required. *Tamiflu* and *Relenza* are active against H5N1 in animal models. High levels of resistance to *Tamiflu* have been detected in several patients with H5N1. Amantadine and rimantadine are not effective for H5N1. For prophylaxis, *Tamiflu* is warranted for persons who have had a possible exposure to H5N1.

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“Cutting Down” Reduces Risk Of Lung Cancer, But Not Risk Of Myocardial Infarction And COPD.

9-6 EFFECT OF SMOKING REDUCTION ON LUNG CANCER RISK

Lung cancer (LC) is the leading cause of cancer death worldwide; 90% of cases are tobacco-related.

The efficacy of smoking cessation intervention is limited. Many smokers are unwilling or unable to quit.

This study asks - Would “cutting down” reduce risk of LC?

Conclusion: The risk of LC was significantly reduced in heavy smokers who reduced smoking by 50%.

STUDY

1. Observations, population-based cohort study followed over 19 500 individual smokers for up to 31 years.
Mean pack-years ranged from 15 to 31.
2. Subjects attended 2 consecutive examinations at a 5- to 10-year interval between 1964 and 1988. They completed self-filled questionnaires asking about life-style habits.
3. Divided into 6 groups according to smoking habits:
 - 1) Continued heavy smokers (> 15 cigarettes daily; mean = 20).
 - 2) Reducers reduced smoking from > 15 per day by a minimum of 50% without quitting.
 - 3) Continued light smokers (1-14 per day).
 - 4) Quitters (stopped between 1st and 2nd examinations).
 - 5) Stable ex-smokers.
 - 6) Never smokers.
4. Determined incident LC from the National Cancer Registry until 2003.

RESULTS

1. Incident LC occurred in 864 individuals (4.3%).

2. Groups:	1)	2)	3)	4)	5)	6)
Number	7351	832	3199	1355	2881	4066
Pack years at baseline	31	27	14	19	14	
Number of LCs	576	52	104	52	52	28
% with LC	7.8	6.3	3.3	3.6	1.8	0.7
Adjusted hazard ratio for LC:	1.00	0.73	0.44	0.50	0.17	0.09

3. Absolute difference, continued heavy smokers vs those who reduced consumption by 50% = 7.8% - 6.3% = 1.5%
4. Sixty two smokers would have to cut consumption by 50% to prevent one LC.
5. Twenty four would have to quit completely to prevent one LC.

DISCUSSION

1. A large reduction in tobacco consumption between baseline and follow-up was associated with a decrease in subsequent LC. A mean decrease in 62% of cigarettes smoked was associated with a 27% reduction in risk.
2. Participants who were light smokers throughout the study and those who quit had considerably lower risk.
3. Participants who were ex-smokers at baseline had a much lower risk. Another study reported that cessation before middle-age was associated with a more than 90% reduction in LC.
4. Only a minority of smokers are able to achieve and sustain a considerable reduction, even with the aid of *ad libitum* nicotine replacement. Subsequent compensatory smoking may occur in those who reduce intake. (Ie, they may inhale more deeply and use more of the cigarette.)

5. The authors previously investigated the all-cause mortality, fatal and non-fatal myocardial infarction, and hospitalization for COPD in smokers. They found no reduction in risk associated with smoking reduction. “Cutting down” does not reduce these risks. LC is more likely to demonstrate a dose-response to cutting down.
6. Nevertheless, the risk of LC continues to some extent over the long-term even in those who quit.

CONCLUSION

Smoking reduction from an average of 20 cigarettes per day to less than 10 per day was associated with a reduction in risk of LC by about 25%.

[JAMA September 28, 205; 294: 1505-10](#) Original investigation, first author Nina S Gotfredsen, Copenhagen University Hospital, Copenhagen, Denmark.

Is cutting down worthwhile? Considering that LC is fatal, it is.

An accompanying editorial “Reducing The Risk Of Lung Cancer”, first author Lawrence J Dacey, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, comments and expands:

Cigarette smoking causes about 5 million deaths each year around the world. In the USA, LC is the leading cause of cancer-related death. For both men and women, the 5-year survival is an abysmal 14%. Direct costs for treatment are about 5 billion annually.

“Fortunately, it is never too early or too late to stop smoking.” There is always a health benefit to be gained by quitting. One study reported that a lifetime male smoker who lived to age 75 had a 16% cumulative risk (a one in six) chance of getting LC. If that individual had quit at age 60, the cumulative risk decreased to 10%. Stopping at age 50 would reduce risk to 6%; at age 40 to 3%; at age 30 to 1.7%.

Quitting well into middle life dramatically reduces risk. Quitting before middle age reduces risk by at least 90%.

More than 2/3 of smokers say they want to quit. Only a minority will succeed. It is essential to find better ways to help them quit. Intensive cessation programs combined with nicotine replacement have some success.

How should clinicians advise patients who cannot or will not quit? Some have no intention of doing so because they enjoy smoking so much. Is there anything physicians can offer beside more lectures, stern admonitions, and grim statistics?

The preceding study presents some benefits from cutting down. It is important to inform smokers that the more they can reduce the number of cigarettes they smoke, the more they will decrease the risk of LC. “They should stop smoking completely, but cutting down is clearly beneficial.”

See the following report on snuff. RTJ

Would You Advise Snuff For Nicotine Replacement?

9-7 MIXED FEELINGS ON SNUS

“Public health often requires balancing risks and benefits. This can be complex, especially with tobacco.”

The British American Tobacco (**BAT**) company markets “snus” in Sweden. “Snus” is a finely ground snuff that is pasteurized to diminish the carcinogenic nitrosamines sometime found in high levels in snuff as well as in cigarettes. (The sale of snus is illegal in the European Union except in Sweden.)

BAT is trying to . . .”extend the appeal of snus to more adult smokers who have not heard of snus to try it.” BAT claims that the move is part of their “continuing efforts in harm reduction”. They claimed that the biggest group of quitters in Sweden used snus as “the main aid in quitting”.

Is it true that snus is a harm-reduction product? It certainly is much less harmful than cigarettes. It has not been associated with any increase in lung cancer. But, it is classified as a carcinogen by the International Agency for Research on Cancer. A recent study reported an increased risk of pancreatic cancer. Snus is not harmless.

Is it effective as an aid to quitting cigarettes? Evidence is inadequate, but suggests that it may be effective for some smokers. Many nicotine users favor it over tobacco smoke. The fact that more Swedes choose snus rather than therapeutic nicotine replacement for routine use suggests that it offers a better “fix”.

Is it addictive? This is controversial. Nicotine replacement therapy is relatively non-addictive, but there is a view that, if such therapy is to replace cigarettes it needs to be more competitive, and this means more addictive.

Should public health workers advocate legalization of snus? Many are opposed to the concept of harm-reduction, particularly one that introduces another tobacco product. Tobacco contains carcinogens other than nitrosamines. It is possible (however reluctantly) to agree that snus is a harm-reduction product, but only when compared with cigarettes.

For snus to be legally available, it must be regulated. Snus is quite a long way from the market in Europe.

[Lancet, September 17, 2005; 366; 966 -67](#) “Comment” by Nigel Gray, International Agency for Research on Cancer, Lyon France.

9-8 SCABIES: *Diagnosis And Treatment*

(I enjoyed this concise review. I abstracted 8 clinical points. RTJ)

- 1) A history of itching in several family members over the same period is almost pathognomonic.
- 2) Consider scabies in any adult with widespread eczema or pruritus of new onset, or with widespread impetigo.
- 3) In men, itchy papules on the scrotum and penis are virtually pathognomonic.
- 4) The pathognomonic sign is the burrow. They may be missed if the skin has been scratched, has become secondarily infected, or if eczema is present.
- 5) Permethrin 5% dermal cream is the treatment of choice. It must be applied correctly. Apply to the whole body (except head and neck) with 2 applications, one week apart. Wash off at 12 hours. Only a small amount is absorbed through the skin and this is rapidly detoxified in the body.
- 6) Malathion is a second choice. The oral antiparasitic drug ivermectin is also effective.
- 7) Lindane is less effective than permethrin. It has been withdrawn in many countries because of reports of aplastic anemia. It is neurotoxic if ingested or excessive absorption occurs.

- 7) If itching persists after treatment, topical corticosteroids with or without topical antibiotics (depending on secondary infection) may be used.
- 8) Treatment should be started if scabies is suspected clinically, even if it cannot be confirmed by microscopy.

[BMJ September 17, 2005; 331: 619-22](#) “Clinical Review”, first author Graham Johnston, Leicester Royal Infirmary, UK

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“Suicide Headache”

9-9 CLUSTER HEADACHE

Clinical features:

Cluster headache (**CH**) is one of the most severe pain syndromes. It is underdiagnosed and suboptimally managed in primary care. It has substantial effects on functioning, even when appropriate treatments are used.

Headaches often start about 1 to 2 hours after falling asleep, or in the early morning. Attacks can strike up to 8 times a day, are relatively short-lived (18 to 180 minutes), and are characterized by very severe unilateral head pain localized in or around the eye. Attacks may occur daily for some weeks followed by a period of complete remission. (CH is cyclic.)

Patients with CH, unlike those with migraine, are restless and prefer to pace about or sit and rock back and forth. Some will isolate themselves or leave the house to get into cold air. Some become aggressive.

Unilateral autonomic symptoms ipsilateral to the pain occur only during attacks: ptosis and pupil constriction (a partial Horner’s syndrome); as well as lacrimation, conjunctival injection, rhinorrhea, and nasal congestion. This indicates parasympathetic hyperactivity, and sympathetic impairment. Sweating and blood flow to the skin increase on the painful side.

Epidemiology and genetics:

Compared with migraine, CH is uncommon. It mostly affects men. There are some reports of an increased history of head trauma with brain concussion, but a cause and effect relation is not established. Chronic headache is more common in smokers. But quitting has no benefit. Alcohol and nitrates can trigger an attack.

A 14-fold increase in risk in first-degree relatives, and a 2-fold risk in second-degree relatives has been reported. Genetic factors may be important, but no precise mechanism of inheritance has been described.

Pathophysiology:

The hypothalamus is involved in CH. Hypothalamic activation occurs with secondary activation of the trigeminal and facial nerves. The autonomic symptoms and the headache may be generated entirely through central mechanisms. The hypothalamus is the key site for triggering pain and controlling the cycling aspects of CH.

Diagnosis:

Is exclusively clinical. In its typical form, CH is unmistakable.

The International Classification of Headache Disorders lists criteria on page 848.

Treatment:

Based entirely on empirical data. Drug treatment shows a placebo effect similar to that of migraine.

A. Treatment of acute attack:

- 1) 100% oxygen inhalation is effective in stopping attacks.. There are obvious logistical problems.
The mechanism of action is not understood.
- 2) Triptans (selective 5-hydroxytryptamine agonists as used for migraine):
Sumatriptan (*Imitrex*) injected subcutaneously and by nasal spray.
Zolmitriptan (*Zonig*) orally and by nasal spray.
- 3) Lidocaine by nasal application.

B. Preventive therapy:

The primary goal is to suppress attacks and to maintain suppression over the expected duration of the CH.
An individual regimen must be formulated with each patient.

- 1) The cornerstone is the calcium blocker, verapamil (*Generic*) Daily dose 240 to 360 mg (occasionally up to 480-720 mg) is the established therapy. It is generally well tolerated, but dose should be increased gradually until it is effective. It must be monitored by regular ECGs. It can be used safely with sumatriptan.
- 2) Corticosteroids may be given in the first 2 weeks of verapamil therapy. Open label trials have reported efficacy. No randomized trials are available.
- 3) Methysergide and corticosteroids are also used short-term. Care—methysergide is metabolized into an active compound, methylergometrine. Long term use has been associated with pulmonary and retroperitoneal fibrosis.
- 4) Ergotamine and triptans have also been used effectively as an initial prophylactic therapy.
5. Combinations of drugs have been used.

(The rather large number of choices suggests that none is “best” and individual trials are necessary. RTJ)

[Lancet September 3, 2005; 366: 843-55](#) “Seminar”, review article by Arne May, Universitats-Krankenhaus Eppendorf, Hamburg Germany.

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Primary Prevention Is Much More Rewarding

9-10 MODELLING THE DECLINE IN CORONARY HEART DISEASE DEATHS IN ENGLAND AND WALES 1981-2000: *Comparing Contributions From Primary Prevention And Secondary Prevention*

Since the 1980s, coronary heart disease (CHD) mortality rates have halved. Studies consistently suggest that 50% to 75% of the decrease in cardiac deaths can be attributed to population-wide improvements in the major risk factors, particularly smoking, cholesterol, and high blood pressure. Modern cardiological treatments for CHD generally explain the remaining 25% to 50% of the fall in mortality.

Risk factor reduction should be a central component of all CHD policies. Disagreement continues about whether to prioritize risk factor reduction across the whole population (primary prevention), or mainly to target CHD patients (secondary prevention).

This study analyzed the decrease in CHD mortality between 1981-2000, and estimated the proportions attributable to changes in major cardiovascular risk factors in apparently healthy people (primary prevention) and in patients with CHD (secondary prevention).

Conclusion: Primary prevention was by far the most important factor in reducing deaths due to CHD.

STUDY

1. Used a model to synthesize data describing CHD patient numbers, uptake of specific treatments, trends in major cardiovascular risk factors, and the mortality benefits of specific risk factor changes in healthy people and in patients with CHD.

RESULTS

1. Over the 30 years between 1981 and 2000, overall there was a 54% fall in CHD mortality; about 68 000 fewer deaths from CHD in 2000 than in 1981.
2. Fall in mortality from CHD attributable to changes in risk factors:

		Deaths prevented or postponed yearly (2000 vs 1981)		
	% changes *	Primary prevention	Secondary prevention	Total
Smoking	- 35%	24 000	5000	29 000
Cholesterol	- 4.2	4700	3100	7900
Blood pressure	-7.7	7200	500	7700
All 3		36 000	8700	45 000

(* % changes in the risk factor level in the population)

3. For the change in all 3 factors, 81% of the benefit occurred in primary prevention; 19% in secondary prevention.

DISCUSSION

1. Mortality from CHD fell by 54% between 1981 and 2000. About half of this reduction could be attributed to primary prevention, defined as reductions in the 3 major risk factors in persons without recognized CHD.
2. Primary prevention had a fourfold greater benefit than secondary prevention.
3. The fourfold advantage becomes 12-fold greater when life-years gained are considered. A death prevented or postponed in a patient with CHD gains an additional 7 years of life, compared with 21 years for primary prevention in a healthy person.
4. The biggest single contributor was a decrease in overall smoking.

CONCLUSION

About half of the recent large falls in CHD deaths can be attributed to primary prevention in three major risk factors in people without recognized CHD.

Primary prevention has a fourfold bigger impact on mortality than secondary prevention.

[BMJ September 17, 2005; 331: 614-17](#) Original investigation, first author Belgin Unal, Dokuz Eylul University School of Medicine, Ismir, Turkey

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Note the “Spin”

9-11 PREVENTION OF CARDIOVASCULAR EVENTS WITH AN ANTIHYPERTENSIVE REGIMEN OF AMLODIPINE, ADDING PERINDOPRIL AS REQUIRED, VERSUS ATENOLOL, ADDING BENDROFLUMETHIAZIDE AS REQUIRED.

The benefits of antihypertension drugs for prevention of cardiovascular mortality and morbidity are well established. Trials using standard diuretic or beta-blocker therapy, or both, indicate a lowering of BP is associated with a significant fall in coronary heart disease (**CHD**) events.

“The issue of which antihypertensive agent should be used in first-line treatment has been controversial for almost two decades.”

This study asked—Would a regimen based on a calcium channel blocker (**CCB**) + an angiotensin converting enzyme inhibitor (**ACE**) lead to more favorable outcomes than a regimen based on a beta-blocker (**BB**) + a **Thiazide** diuretic?

Conclusion: The amlodipine-based regimen prevented more major cardiovascular events than the beta-blocker based regimen.

STUDY

1. Prospective, randomized trial entered over 19 000 patients with hypertension. (Mean BP = 164/95) About 60% were over age 60; mean age not stated.) None had a history of coronary heart disease. All had at least three other cardiovascular risk factors (a high risk group). Other risk factors: left ventricular hypertrophy; type 2 diabetes; peripheral artery disease; previous stroke of TIA; male sex; age 55 or over; microalbuminuria or proteinuria; smoking; high ratio of total cholesterol/HDL-cholesterol; family history of premature cardiovascular disease.
2. All had BP of 160/100 or more, or treated hypertension with BP of 140/90 or more. Mean baseline BMI = 29. Target BP = < 140/90 (<130/80 for patients with diabetes).
3. Randomized to:
 - 1) A calcium channel blocker (**CCB**; amlodipine; *Norvasc*) 5-10 mg + addition of an angiotensin converting enzyme (**ACE** inhibitor; perindopril; *Aceon*) 4-8 mg, if required to lower BP to target, vs
 - 2) A beta-blocker (**BB**; atenolol; generic) 50-100 mg + addition of a thiazide diuretic bendroflumethiazide (*Naturetin*) 1.25-2.5 mg if required to reach target BP.
(Other drugs could be continued or added to reach target.)

4. Primary endpoint = combined non-fatal myocardial infarct (including silent infarct) + fatal CHD.

RESULTS

1. The study was stopped prematurely after a median of 5.5 years (over 106 000 patient-years) because fewer patients in the CCB-ACE group had the primary endpoint.

(Note: this did not reach statistical significance.)

2. End mean BP = 137.7/79.2 for BB group; 136.1/77.4 for CCB group. Difference = 1.6/1.8 in favor of CCB.

3. The majority of subjects took at least two antihypertensive drugs. The average numbers of drugs were 2.2 and 2.3. About 1/5 crossed over to a drug included in the group to which they were not assigned.

4. Outcomes over 5.5 years	ACE + CCB (n = 9639)	BB + Thiazide (n = 9618)	NNT*
Primary endpoint	429	474	208**
Stroke (fatal & non-fatal)	327	422	65
Total cardiovascular events & procedures	1362	1602	25
All-cause mortality	738	820	116
Incidence of diabetes	567	799	24***

(* NNT for 5.5 years to benefit one patient. ** Not statistically significant. The authors attributed this to under powering of the study. *** NNT to harm one patient (develop diabetes) *(My calculations. RTJ)*

5. At trial close-out, only 53% of patients had reached both systolic and diastolic BP targets.

6. Adverse effects:

	ACE group (%)	BB group (%)
Cough	19	8
Dizziness	12	16
Dyspnea	6	10
Fatigue	8	16
Joint swelling	14	3
Peripheral edema	23	6

7. Overall 25% of subjects stopped therapy because of adverse events—with no significant difference between groups. Serious side effects (not specified) occurred in 2% vs 3%.

DISCUSSION

1. This study demonstrated that BP can be lowered effectively in most patients.

2. “The findings of ASCOT-BPLA show that in hypertensive patients at moderate risk of developing cardiovascular events, an antihypertensive drug regimen starting with amlodipine adding perindopril, as required, is better than one starting with atenolol adding a thiazide, as required, in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and in terms of risk of subsequent new-onset diabetes.”

(1 *In my view, the study group was at high risk for cardiovascular events. All had hypertension and had three additional risk factors. RTJ*)

3. “We...feel an appropriate reflection of contemporary medical practice would be to consider the primary endpoint plus coronary revascularizations for which a significant difference exists in favour of the amlodipine-based regimen.”
4. The average number of drugs used to reach target BP was 2.2; 8% of patients were on 4 or more. This lends support to the use of, and adherence to, standardized treatment algorithms for lowering BP effectively unless contraindications exist or side-effects arise.
5. Much data exists that the size of the absolute BP reduction is a more important determinant of the relative effects on total cardiovascular events than the choice of antihypertensive drugs.
6. “Pending further information, we believe the combination of a beta-blocker and a diuretic should not be recommended in preference to the comparator regimen used in ASCOT-BPLA for routine use, but only for specific circumstances.”
7. Since the absolute benefits associated with the amlodipine-based regimen are small, the authors admit there are cost implications.

CONCLUSION

The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen.

[Lancet September 10, 2005; 366: 895-906](#) original investigation, The Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm (ASCOT-BPLA), first author Bjorn Dahlöf, Sahlgrenska University Hospital, Goteborg, Sweden

More “Spin”

9-12 ROLE OF BLOOD PRESSURE AND OTHER VARIABLES IN THE DIFFERENTIAL CARDIOVASCULAR EVENT RATES NOTED IN THE ANGLO SCANDINAVIAN CARDIAC OUTCOMES TRIAL-BLOOD PRESSURE LOWERING ARM (ASCOT-BPLA)

(This article, by the same investigators, expands on the previous trial)

In the preceding study, there were differences during the follow-up period in BP and other risk factors between the BB-Thiazide group and the CCB-ACE group. This additional study assessed the extent to which these differences influenced the outcome. During the first year of the study, more events occurred in the CCB-ACE group than in the BB-Thiazide group. Thereafter, outcomes favored the CCB-ACE group.

Differences between the groups included BP, HDL-cholesterol, triglycerides, potassium, fasting glucose, heart rate, and body mass index. All of these variables were significantly associated with rates of coronary events and stroke during the trial. (CCB-ACE, in addition to a slightly greater reduction in BP, was associated with

reductions in other risk factors.) The investigators offer no explanation except . . .”That it remains possible that differential effects of the two treatment regimens on other variables also contributed to the different rates noted”.

These factors influenced outcomes favoring the CCB-ACE group. After adjusting for these factors the investigators determined that they accounted for about half the reported difference in coronary events and about 40% of the differences in stroke noted between the two groups. (Ie, the reported benefits in the CCB-ACE group were attenuated because, overall, the differences in risk factors favored this group.)

Differences in HDL-cholesterol had the largest effect on the differences in coronary events. (Ie, HDL was higher in the CCB-ACE group during follow-up.)

“Overall, after adjustment of the combined effect of differences in weight, heart rate, biochemical variables, and blood pressure, the differences in the effects of treatments on coronary and stroke events were no longer significant. This adjustment, however, only explained about 50% and 40% of the differences in coronary and stroke events, respectively.”

“Irrespective of the mechanism of action, the amlodipine-based regimen was more effective in reducing cardiovascular events than the atenolol-based regimen.”

“For many patients benefits of the amlodipine-based regimen, in terms of lowering blood pressure and prevention of cardiovascular events, are greater than the well-established benefits of the standard combination therapy of beta-blockers plus a diuretic.”

[Lancet September 10, 2005; 366: 907-13](#) Original investigation, first author Neil R Poulter, Imperial College London, London, UK.

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The Difference Between Relative Risk Reduction And Absolute Risk Reduction

9-13 EVIDENCE THAT NEW ANTIHYPERTENSIVES ARE SUPERIOR TO OLDER DRUGS

(This editorial comments, in generally favorable terms, on the preceding articles.)

“The amlodipine-based regimen in ASCOT . . . reduced major cardiovascular endpoints by 16%, stroke by 23%, and cardiovascular and total mortality by 24% and 11% respectively, compared with the beta-blocker atenolol, with or without bendroflumethiazide.”

How should clinicians translate ASCOT into day-to-day practice?

“On balance, the ASCOT results endorse the European guidelines for the treatment of hypertension, which leave the choice of drug class for antihypertensive treatment to the doctor.”

“ASCOT also supports the use of newer drugs, especially in patients with complicated hypertension, associated risk factors, or metabolic disturbances.”

Of note, at the end of the study, as in most other trials, BP was properly controlled in only 32% of the diabetic and 60% of the non-diabetic population. “These dismal statistics underscore the need for use of multiple drug combinations spanning newer and older drug classes in a large group of hypertensive patients and a need to up-titrate treatment more rapidly.”

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Equivalent Efficacy For Treating Early and Latent Syphilis, but Resistance May Occur

9-14 SINGLE-DOSE AZITHROMYCIN VERSUS PENICILLIN G BENZATHINE FOR THE TREATMENT OF EARLY SYPHILIS

A single intramuscular dose of 2.4 million units of penicillin G benzathine (*Bicillin LA*) is the recommended therapy for early syphilis. It is low cost. Adherence is no problem. Disadvantages include pain, the relatively high prevalence of self-reported penicillin allergy, and the need for injection equipment and trained personnel. In addition, there is some risk of transmission of blood-borne infections if the injection equipment is reused.

Azithromycin (*Zithromax*), a macrolide antibiotic with a long half-life (68 hours), would overcome some of these disadvantages. Efficacy against *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Haemophilus ducreyi* has been established. (Penicillin is not indicated and is ineffective against these organisms.)

Azithromycin is a promising candidate for treatment of primary and latent syphilis. [Latent syphilis is defined by 1) a positive serological test, 2) a normal CSF, and 3) no clinical manifestations.]

This study compared effectiveness of oral azithromycin vs intramuscular penicillin G benzathine in Tanzania.

Conclusion: Single-dose azithromycin was effective.

STUDY

1. Followed 328 subjects (25 with primary syphilis) and 303 with latent syphilis [high titer (at least 1:8) on a rapid plasma regain (RPR) test]. All had been recruited and detected by screening. Over 50% were also positive for HIV.
2. Randomized to a single dose of: 1) azithromycin 2 gram orally, or 2) intramuscular penicillin G benzathine 2.4 million units intramuscularly.
3. Primary outcome was serological cure, defined by a decline in RPR titer of at least two dilutions by nine months, or by epithelization of primary ulcers at 1 to 2 weeks.

RESULTS

1. Cure rates at 9 months were 98% in the azithromycin group and 95% in the penicillin group.
2. In the groups treated with azithromycin, mild to moderate adverse effects, primarily gastrointestinal in about 10%. (Ie, no higher than that reported previously with lower doses.)

DISCUSSION

1. Azithromycin was clearly as effective as penicillin in treating early syphilis in this group of patients.
2. There have been reports of azithromycin-resistant strains *T pallidum* in the USA and in Ireland. There was no evidence of resistance in Tanzania.
3. Azithromycin was just as effective in HIV positive individuals as in those without this infection.

4. "Our results are applicable to a mixed population of persons with early and latent cases, making them highly relevant to syphilis-control strategies in developing countries in which . . . the duration of infection is usually unknown."
5. A major problem affecting research on syphilis treatment is the imprecision of the definition of serologic cure. Such imprecision may have led to either an overestimation or to an underestimation to the true rates of cure.
6. Continued monitoring for azithromycin resistance will be essential.
7. Given the logistical advantage of oral treatment, particularly in resource-poor settings in developing countries, and the efficacy of azithromycin in treatment other common sexually transmitted infections, these findings support wider use of this alternative treatment.

[NEJM September 22, 2005; 353: 1236-44](#) Original investigation, first author Gabriele Reidner, London School of Tropical Medicine, London, UK.

An editorial in this issue of NEJM (pp 1291-93) by King K Holmes, University of Washington, Seattle, comments on the study:

What innovations, if any, are now warranted in the management of early syphilis? Can azithromycin be substituted for penicillin? Should azithromycin be dispensed to patients with early syphilis to deliver to their sexual partners in a manner analogous to that of patient-delivered partner therapy for gonorrhea and chlamydial infections?

Two important reasons for caution: 1) The sustained success (50 years) of penicillin G benzathine. 2) The recent emergence of resistance to azithromycin.

Resistance is due to a point mutation in a RNA gene in *T pallidum*. This is as common as 88% in Ireland. Almost all azithromycin-resistant strains came from men who reported having sex with other men.

Given the sustained effectiveness of penicillin G benzathine and the rapid emergence of resistance to azithromycin, there seems little reason to change the STD treatment guidelines.

For those with penicillin allergy, the forthcoming US guidelines list 100 mg doxycycline given orally twice daily for 14 days; 1 gram ceftriaxone given I M daily for 10 days; or 2 gram azithromycin orally as a single dose as possible alternatives for treatment of primary and latent syphilis. Close follow-up is essential.

Environmental Incivilities And Graffiti Have An Adverse Effect On Health

9-15 GRAFFITI, GREENERY, AND OBESITY

Independently of individual characteristics, the place of residence may be associated with health outcomes, including body size, and health-related behaviors, such as the level of physical exercise. Perceived attractiveness of neighborhoods has been related to levels of physical activity. Incivilities, such as litter and graffiti, are associated with an adverse effect on general wellbeing.

This study hypothesized that areas which are unpleasant, with many incivilities and few green areas, might discourage people from exercising, and thus influence the levels of obesity.

Conclusion: Low levels of greenery, and high levels of graffiti were associated with overweight/obesity

STUDY

1. Drew upon data collected in the “Large Analysis and Review of European Housing and Health Status” (LARES) which was done in 2002-03 in 8 countries.
2. Housing and health questionnaires obtained self-reported data on health, body mass index, level of physical activity, and the surrounding environment.
3. Trained observers inspected the immediate residential environments for the amount of graffiti, litter, and dog mess—as well as the level of visible vegetation and greenery. They arbitrarily divided environments into 5 levels—from a low amount of greenery to a high amount; and from a low amount of litter and graffiti to a high amount.
4. Recorded degree of physical activity in the neighborhoods.

RESULTS

1. Effect of litter, graffiti, and greenery on likelihood of being overweight/obese, and being frequently physically active:

A. Overweight/obese	Adjusted odds ratio
Greenery	
1 (low amount)	1.00
5 (high amount)	0.63
Litter and graffiti	
1 (low amount)	1.00
5 (high amount)	1.42
B. Frequent physical activity	
Greenery	
1 (low amount)	1.00
5 (high amount)	3.30
Litter and graffiti	
1 low amount)	1.00
5 (high amount)	0.53

DISCUSSION

1. For individuals living in neighborhoods with high amounts of greenery, the likelihood of being more active was more than 3 times as high as that of those living in neighborhoods with low levels of greenery.
2. For respondents whose residential environment contained high levels of incivilities, the likelihood of being more physically active was about 50% less, and the likelihood of being overweight/obese was about 50% higher.
3. “In efforts to promote physical activity and reduce weight, attention should be paid to environmental facilitators and barriers as well as individual factors.”

CONCLUSION

Environmental incivilities and graffiti have an adverse effect on health.

[BMJ September 17, 2005; 331: 611-12](#) Original investigation, first author Anne Ellaway, University of Glasgow, Scotland.

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Coming Soon? Maybe

9-16 INTEREST IN INHALED INSULIN GROWS

“Is the era of insulin injections for patients with diabetes drawing to a close? Probably not, at least yet. Even so, some researchers believe that inhaled insulin is now on the fast track and could emerge as viable. Phase three trials are now in progress. “Inhaled insulin should meet regulatory requirements of approval.”

Using the lung as an absorption pathway has appeal for patients who dread the discomfort and inconvenience of injections.

The lungs provide a large surface area for drug absorption. Inhaled insulin is absorbed more rapidly than regular insulin given subcutaneously. The time to peak concentration of most inhaled insulins is nearly superimposable with the rapid-acting insulin analogues.

At least 6 new pulmonary insulin drugs and delivery systems are in active development. They use either liquid or dry powder formulations of regular insulin, with particle sizes appropriate for pulmonary delivery. They differ in efficiency. In general, 60% to 80% of insulin molecules do not reach the lung and alveolar tissue. Most molecules are degraded or exhaled.

Exubera (a dry powder human insulin) uses a mechanical aerosol delivery device. The powder is packaged in foil blisters. An inhaler generates a pulse of compressed air that turns the powder into a fog-like form delivered into a reservoir from which the insulin is then inhaled.

Controlled trials compared *Exubera* + oral agents with injected insulin + oral agents. After 2 years, *Exubera* provided continuing glycemic control. HbA1c decreased 1.8%, compared with a 1.5% decrease in the injected insulin group.

Is it safe? Some studies have reported no adverse pulmonary events; some have reported cough as the most common side effect. A slight decline in carbon-monoxide-diffusing capacity occurred. Hypoglycemia, headache and dizziness have been reported. Patients with asthma absorbed lower amounts of insulin.

Longer term studies (a decade or more) are required to evaluate pulmonary function and insulin-binding antibodies, as well as use in children and smokers.

“We are talking about life-long administration of insulin into the lung, so indeed, further studies will be needed.”

[JAMA September 14, 2005; 294: 1195-96](#) “Medical News and Perspectives” reported by Richard Trubo, JAMA staff.