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ERADICATION OF A DISEASE: How We Cured Symptomless Prostate Cancer

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SMOKING AND ALANINE AMINOTRANSFERASE LEVELS IN HEPATITIS C VIRUS INFECTION

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HIGHLIGHTS APRIL 2002

4-1 ERADICATION OF A DISEASE: How We Cured Symptomless Prostate Cancer

"Certainly SPC was common. And now, in the new millennium, what is the frequency of this disease? Perhaps we haven't progressed quite as far as with smallpox, but we are getting close. Symptomless prostate cancer is no longer a very rare disease."

What key discovery led to this remarkable reduction in frequency of SPC? The key was an inexpensive blood test called prostate specific antigen (**PSA**) which provided patients and their doctors with evidence of the presence of PC cells. An avalanche of studies in the past 15 years assured the end of peaceful co-existence between microscopic deposits of PC cells and their symptom-free hosts. "No longer do patients arrive for yearly checkups, enjoying their lives in blissful ignorance of their cancer. They now arrive monthly, flustered and anxious, some of them with graphs in hand. They no longer have *symptomless* PC, but *symptomatic* PC."

Practical point: Patients should be informed about the potential harms as well as the potential benefits of PCA testing before the test is performed.

4-2 GASTROESOPHAGEAL REFLUX, BARRETT ESOPHAGUS, AND ESOPHAGEAL CANCER

Although strong evidence links GERD and adenocarcinoma, the risk in any given individual is low. Given the low incidence of cancer, and the lack of demonstrated efficacy of endoscopic screening, insufficient evidence exists to endorse routine endoscopy screening for patients with chronic symptoms.

Practical point: Patients with chronic, severe symptoms of GERD may be given the results of this study, and then decide for themselves. Primary care clinicians should treat these patients with proton pump inhibitors. This will reduce the risk of erosion caused by the acid reflux.

4-3 LONG-TERM EFFECTIVENESS AND SAFETY OF PRAVASTATIN IN 9014 PATIENTS WITH CORONARY HEART DISEASE AND AVERAGE CHOLESTEROL CONCENTRATIONS: THE LIPID TRIAL FOLLOW-UP

Long-term therapy (8 years) yields benefits in addition to 6 years treatment. Benefits of therapy continued to accumulate after years of therapy. Older patients, women, and patients with cholesterol <210 mg/dL benefit. Incidence of stroke is reduced.

Practical point: Almost all patients with established coronary atherosclerotic heart disease should be treated with long-term statins.

4-4 TOO MUCH MEDICINE?

Death, pain, and sickness are part of being human. All cultures have developed means to help people cope with all three. Indeed good health care can even be defined as being successful in coping with these realities.

Modern medicine has launched an inhuman attempt to defeat death, pain, and sickness. It has sapped the will of the people to suffer reality. "People are conditioned to *get* things rather than to *do* them. They want to be taught, moved, treated, and guided rather than to learn, to heal, and to find their own way."

The more a society spends on health care, the more likely are its inhabitants to regard themselves as sick.

The concept of what is and what is not a "disease" is extremely slippery. It is easy to create new diseases and new treatments. Many of life's normal processes – birth, aging, sexuality, unhappiness, and death can be medicalized.

Practical point: Primary care clinicians bear the responsibility of balancing medicalization with undertreatment. (Application of the "art" of medicine to the individual.)

4-5 UNDERSTANDING THE TREATMENT PREFERENCES OF SERIOUSLY ILL PEOPLE

The desirability of an intervention depends heavily on its outcome. Elicitation of patients' preferences should be based on outcomes rather than specific treatments

Planning should take into account patients' attitudes toward the burden of treatment, and the likelihood of adverse functional and cognitive outcomes. Discussions of advanced care planning should shift from whether patients would accept or reject specific treatments, to what they consider acceptable in terms of quality-of-life, the burdens of treatment, and the probability of successful outcome

"Clearly, treatment outcomes are a strong determinant of patients' preferences."

Practical point: We should try to give terminally patients the best advice about possible outcomes and then let them choose the course.

4-6 BETWEEN HOPE AND ACCEPTANCE: The Medicalization of Dying

An active, rather than a passive approach to the care of dying people, is supplanting the fatalistic resignation of the doctor ("There is nothing more we can do"). We are challenged to find new and imaginative ways to continue caring up to the end of life.

The challenge for palliative physicians is no different from that facing their counterparts elsewhere in medicine: how to reconcile high expectations of technical expertise with calls for a humanistic and ethical orientation.

Practical point: Primary care clinicians should continue care and caring until the end of life.

4-7 NONALCOHOLIC FATTY LIVER DISEASE

"NAFLD is the most common cause of abnormal liver-test results among adults in the USA. " Obesity, type 2 diabetes, and hyperlipidemia frequently coexist. NAFLD is histologically indistinguishable from liver damage due to alcohol abuse. A net retention of lipids within hepatocytes, mostly triglycerides, is a prerequisite for NAFLD.

Insulin resistance is the most reproducible factor. Insulin resistance and hyperinsulinism leads to fat accumulation in hepatocytes.

Although symptoms of liver disease rarely develop in patients with steatotic livers they may be vulnerable to further injury when challenged by additional insults.

Practical point: Another good reason to prevent and treat obesity, diabetes, and dyslipidemia.

4-8 TREATING *HELICOBACTER PYLORI* INFECTION IN PRIMARY CARE PATIENTS WITH UNINVESTIGATED DYSPEPSIA

"Testing (with C-urea breath test) and treating" to eradicate *H pylori* in patients with uninvestigated dyspepsia provided long-term relief of symptoms and reduced health costs.

Practical point: Patients in the USA with *H pylori* infection (with or without dyspepsia) should be treated.

4-9 SINGLE FLEXIBLE SIGMOIDOSCOPY SCREENING TO PREVENT COLORECTAL CANCER

This flex-sig screening regimen was acceptable, feasible, and safe. The prevalence of neoplasia detected was high.

Practical point: Some patients who refuse colonoscopy may accept this less stressful procedure, even if they know it is incomplete screening.

4-10 MALE CIRCUMCISION, PENILE HUMAN PAPILLOMA VIRUS INFECTION, AND CERVICAL CANCER IN FEMALE PARTNERS.

Male circumcision was associated with a reduced risk of penile HPV.

In the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer was evident in their current female partner.

Practical point: A reasonable indication for circumcision.

4-11 BLOOD LEVELS OF LONG CHAIN N-3 FATTY ACIDS AND THE RISK OF SUDDEN DEATH.

These prospective data suggest that long chain n-3FA found in fish may reduce the risk of sudden death from cardiac causes, even in men without a history of cardiovascular disease. More than 50% of all sudden deaths from cardiac causes occur in people with no history of cardiac disease. Practical point: Fish are an important part of the healthy diet.

4-12 ERYTHROMYCIN-RESISTANT GROUP A STREPTOCOCCI IN SCHOOLCHILDREN IN PITTSBURGH

A longitudinal study of schoolchildren detected the emergence of erythromycin resistance in pharyngeal isolates of group A streptococci. The clonal outbreak also affected the wider community.

Practical point: "We recommend that macrolide antibiotics not be used for the routine treatment of pharyngitis due to group A streptococci until more epidemiological information is available.

4-13 THROMBOLYTIC THERAPY VS PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR MYOCARDIAL INFARCTION IN PATIENTS PRESENTING TO HOSPITALS WITHOUT ON-SITE CARDIAC SURGERY.

After an extensive development program, primary PCI can be performed safely, promptly, and effectively in the community hospitals without an elective PCI or cardiac surgery program.

Compared with thrombolysis, the availability of primary PCI resulted in a reduction in deaths, recurrent MI, and stroke.

In this study, the absolute reduction in mortality in patients with acute ST-elevation MI was 5.5% with primary PCI vs 7.6% for thrombolysis. (NNT to prevent one death = 43). Intracranial hemorrhage was essentially eliminated.

Practical point: "Primary PCI is considered a superior strategy both for efficacy and safety." It should be made more available in the community.

4-14 SMOKING AND ALANINE AMINOTRANSFERASE LEVELS IN HEPATITIS C VIRUS INFECTION

Alcohol and cigarette consumption were independently associated with elevated ALT levels among persons with HCV infection, but not among those infected with hepatitis B. "Smoking, like alcohol, is an independent promoting factor for hepatic necroinflammation."

The liver is a target organ for the chemicals in tobacco and alcohol. Abstinence from both would probably slow the progression of hepatitis.

Practical point: Patients with HCV infection are strongly advised not to smoke as well as to abstain from alcohol.

Not Symptomless Any More. PSAdnyia is a Common Disease

4-1 ERADICATION OF A DISEASE: How We Cured Symptomless Prostate Cancer

"Medical knowledge advances in small steps – the more time passes, the smaller the steps. Thus to be able to report a striking reduction in the prevalence of a common disease such as symptomless prostate cancer (**SPC**) in a little more than a decade is remarkable." Unfortunately SPC is not recorded as a distinct entity in cancer registries, making precise calculation of epidemiological characteristics difficult. However, necropsy studies show a high frequency of SPC in elderly men who died of other causes.

Certainly SPC was common. "And now, in the new millennium, what is the frequency of this disease? Perhaps we haven't progressed quite as far as with smallpox, but we are getting close. Symptomless prostate cancer is no longer a very rare disease."

What key discovery led to this remarkable reduction in frequency of SPC? The key was an inexpensive blood test called prostate specific antigen (**PSA**) which provided patients and their doctors with reliable evidence of the presence of PC cells. An avalanche of studies in the past 15 years assured the end of peaceful co-existence between microscopic deposits of PC cells and their symptom-free hosts. "No longer do patients arrive for yearly checkups, enjoying their lives in blissful ignorance of their cancer. They now arrive monthly, flustered and anxious, some of them with graphs in hand. They no longer have symptomless PC, but symptomatic PC." We have added another symptom of PC, possibly the most common of all, to ensure that almost every patient who has a prostate cancer cell shall suffer from, rather than live with, the disease. That symptom is disabling anxiety resulting from the knowledge of their prostate cancer, a state known as PSAdynia. "Is it for this that we have cured symptomless prostate cancer?"

What have we gained? Experts have almost come to blows when discussing the merits of using PSA as a screen. This suggests that supporting evidence is not very great. A serum marker is useful if it can be used to detect disease before symptoms or signs arise, thereby increasing the probability of cure or duration of survival. Screening can detect PC in men who are symptom free. Since introduction of PSA the incidence of PC has doubled in the US, but increased only slightly in the UK where the test is used less frequently. Every PC patient diagnosed represents a decrease in the prevalence of symptomless PC. About 75% would never have been diagnosed in the absence of PSA screening. And only one in four men with screen-detected PC would have died of PC within 15 years.

There has been a small decline in mortality from PC in the US. But, mortality has fallen too soon after widespread introduction of PSA to be attributed to the effects of screening. A small decline in PC deaths might be explained by the detection of high-grade PC before their metastasis. However, similar mortality rates have been recorded in regions of the US with high and low levels of screening. Whether screening improves survival remains unclear. Treatments for localized PC, including radical prostatectomy and radical radiotherapy have not been shown to improve overall survival. There are indeed some younger patients who have survived for years after

treatment. There are almost certainly some who otherwise would have died of the disease who have been cured. However, this apparent benefit might be offset by a low, but definite treatment-related mortality. Large numbers of men who otherwise might never have developed symptoms of the disease, develop symptoms related to treatment.

Further, PSA has been used to follow patients who have already been diagnosed and treated. When the disease recurs, PSA rises for a median of 8 years before symptoms return. "We have a new term for this – biochemical failure. What does a patient gain by being informed of his biochemical failure?" Certainly, a great deal of anxiety and an immediate loss of quality of life. Some men may benefit from early aggressive hormonal therapy. However, the merit of these benefits for a few men compared with the loss of a symptom-free interval for many, if they had never known about their PSA, remains debatable. "Perhaps a better definition of biochemical failure might be biochemical testing of a man who is symptom-free, thereby providing him with evidence of our inability to cure his disease."

"Unfortunately, in medicine some discoveries lead to more harm than good."

Lancet April 13, 2002; 359: 1341-42 "Viewpoint", editorial by Ian F Tannock, University of Toronto, Canada. **www.thelancet.com**

Comment:

Does the editorialist overstate his case? I believe not much. Many primary care clinicians automatically screen their male patients with PSA, not even informing them or discussing beforehand the possible benefits and harms. This is poor practice.

For MDs and their patients this is another good example of uncertainty in medical practice. Can we determine which individuals might have a curable PC and those who might unnecessarily receive invasive therapy leading to incontinence and impotence without cure? RTJ

Reasoning against routine screening

4-2 GASTROESOPHAGEAL REFLUX, BARRETT ESOPHAGUS, AND ESOPHAGEAL CANCER

Symptoms of gastroesophageal reflux disease (**GERD**) are among the most common complaints encountered by primary care clinicians. GERD has potentially serious complications: stricture; erosive esophagitis; development of Barrett esophagus (**BE**), and adenocarcinoma of the esophagus (**ACE**).

ACE is a rare cancer. Its incidence is increasing. Some authorities recommend patients with chronic GERD undergo upper endoscopy to assess for BE and to screen for cancer.

This study reviewed the evidence linking GERD and BE to esophageal adenocarcinoma and examined the utility of upper endoscopy as a screening tool for adenocarcinoma among individuals with GERD.

Conclusion: Although strong evidence links GERD and adenocarcinoma, the risk of cancer in any given individual is low. Given the low incidence of cancer, and the lack of demonstrated efficacy of endoscopic screening, insufficient evidence exists to endorse routine endoscopy screening.

STUDY

1. Medline search of GERD, BE, and ACE.

RESULTS

1. *What is the prevalence of GERD? What degree of reflux is pathologic?*

Cohort studies demonstrate that symptoms of GERD occur monthly in almost 50% of US adults.

Because most individuals usually experience several episodes of undetected acid reflux daily, and because many others experience symptomatic reflux only rarely, defining what degree of reflux constitutes disease is uncertain. If only those who sustain tissue damage are considered to have GERD, the 30% to 70% of individuals who have painful, treatable reflux symptoms but non-erosive disease would be excluded. If all who experience occasional symptoms are labeled as having GERD, the problem may be overmedicalization, defining a symptom as a disease.

2. *What is Barrett esophagus?*

BE is associated with increased risk of adenocarcinoma.

BE is a metaplastic change from the normal squamous epithelium to a specialized intestinal-type columnar lining – ie, containing goblet cells. The first step is destruction of the squamous epithelium by acid. Whether BE is a necessary precursor in all cases of ACE is not known. The relative contributions of acid, pepsin, and duodenal refluxates are unclear. There are no prospective cohort studies of reflux patients to assess cancer risk.

Individuals with erosive esophagitis and BE have, on average, more severe reflux symptoms. The degree of overlap of symptoms of those with severe tissue injury and non-erosive disease may make it difficult to identify individuals with the potential to develop complications. Even short segments of BE can evolve into CE. Length is not a risk factor.

Five percent to 15% of those with long term reflux symptoms will have BE of some length. But even patients with only mild symptoms can develop BE. The number of individuals in the US with BE may be higher than 3 million.

BE progresses through degrees of dysplasia before development of ACE.. The most predictive factor in progression of BE to ACE is the degree of dysplasia. The risk of ACE in those with high-grade dysplasia exceeds 25%. Some authorities have recommended resection of the esophagus for those with high grade dysplasia.. Others, citing the low incidence of incurable metastatic disease among those developing cancer suggest patients be observed closely with frequent endoscopy, reserving resection only for those who develop ACE. The optimum treatment is still undecided.

It is clear that proton pump inhibitors do not avert progression nor cause regression.[1] The reason for proton pump inhibitors in treating BE is only to relieve reflux symptoms. [1] It is unclear if surgical anti-reflux procedures diminish the likelihood of developing ACE. Endoscopic ablation treatment results are also not clear. At present these therapies are considered experimental.

3. *What is the association between GERD and adenocarcinoma of the esophagus?*

Three large case-control studies demonstrated a positive association between reflux symptoms and risk of adenocarcinoma of the esophagus. The more prolonged and severe the symptoms the greater the risk. However, because of the low incidence of adenocarcinoma and the ubiquity of reflux symptoms, the risk of cancer in any given individual is low.

Despite the increase in incidence of adenocarcinoma over the past 40 years, the absolute numbers of persons with the condition in the US remains low. About half of the 13 000 cancers of the esophagus seen annually in the USA are adenocarcinoma. White men have the highest risk.

Subjects with esophageal adenocarcinoma are almost 8 times more likely to report at least weekly symptoms of reflux or regurgitation. A dose response relation exists. For long term (20 years) and severe symptoms the adjusted odds ratio of developing ACE is 43. However, since the cancer is rare even among those with frequent severe symptoms, the absolute risk in patients with GERD is low. The annual cancer incidence has been calculated to be 6500 cases for every 10 million reflux patients.

Another problem using reflux symptoms as a marker is that many patients developing ACE never experience severe chronic reflux symptoms. The annual incidence of ACE in those who report severe GERD symptoms is less than 1 in 1000. About 40% of those who

develop ACE do not have frequent symptoms. The use of reflux symptoms to stratify risk is associated with multiple epidemiological problems.

4. *Does endoscopy for those with GERD avert death from ACE?*

No randomized trials are available to demonstrate either decreased cancer incidence or increased life expectancy in individuals who undergo screening endoscopy.

Alarm symptoms are associated with development of ACE (dysphagia, odynophagia, anemia, weight loss, hemetemesis). These call for endoscopic diagnosis, or barium swallow.

It is less clear if patients with classic reflux without alarm symptoms should undergo further testing. The American College of Gastroenterology guidelines recommend patients over age 50 with long-standing GERD have screening endoscopy to assess for the presence of BE, and presumably for ACE at a more curable stage. Despite the ACG recommendations, there are no prospective data demonstrating that periodic endoscopic surveillance prolongs life expectancy or decreases cancer mortality.

The commentator considers these recommendations too aggressive. The incidence of ACE is low; overall risk is small. Major complications of endoscopy are approximately 1 in 1000. Mass screening of the 10 million GERD patients over age 50 would be expected to yield about 10 000 major complications to detect a cancer with an annual incidence of about 6500. The costs would be prohibitive.

We should not ignore the potential psychosocial effects of giving patients a diagnosis of BE. “Many patients with BE are terrified that they are doomed to develop esophageal cancer.” In our zeal to prevent an uncommon cancer, we physicians should not recommend unproved and potentially harmful therapies.

Even if BE is identified, it is not clear whether the patient will derive any benefit from this knowledge. “This message must be transmitted to patients choosing to undergo surveillance.” Even if screening endoscopy were limited to individuals considered at high risk, more than 500 yearly endoscopies would be necessary to find one ACE.

It is not clear whether the benefits of screening endoscopy outweigh its monetary and quality-of-life costs.

CONCLUSION

Given the low absolute risk of ACE in those with chronic GERD, and the lack of demonstrated efficacy of endoscopic screening, insufficient evidence exists to endorse routine screening

JAMA April 17, 2002; 1972-81 Review article, first author Nicholas Shaheen, University of North Carolina, Chapel Hill. **www.jama.com**

Comment:

1 If the acid-GERD-erosive esophagitis-BE-ACE progression is etiologically valid, would it not be reasonable to believe that long-term suppression of acid would reduce risk of ACE?

So, what should the primary care clinician do when confronted with a patient with severe, chronic GERD? Certainly treat with long-term proton pump inhibitors. What should we advise about endoscopy? It is indicated if the patient has alarm symptoms. What about the patient who has read about BE and is fearful? Fortunately, we can always fall back on the individual patient’s choice (after we inform about risks, costs, and benefits). If the patient expresses no concern, I would not mention the possibility of endoscopy. If the patient asks for referral to a gastroenterologist, it is very likely that he will subsequently undergo endoscopy.

Major complications of endoscopy likely outweigh yield. Proton pump inhibitors are safe long-term. They can give total relief of symptoms. Many patients will accept them, even with the costs. Risk of complications

from surgery (and death, although rare) also outweigh risk of ACE. Surgery should not be undertaken to reduce risk of ACE. RTJ

Benefits of statin therapy extend over many years

4-3 LONG-TERM EFFECTIVENESS AND SAFETY OF PRAVASTATIN IN 9014 PATIENTS WITH CORONARY HEART DISEASE AND AVERAGE CHOLESTEROL CONCENTRATIONS: THE LIPID TRIAL FOLLOW-UP

The previously reported LIPID trial[1] showed that pravastatin (*Pravachol*) therapy over 6 years reduced mortality and cardiovascular events in patients with previous acute coronary events and average cholesterol levels. (*A secondary prevention trial*.)

This extension of the study followed patients for an additional 2 years to assess longer-term effects of treatment on cardiovascular events and mortality (a total of 8 years).

Conclusion: Continuing long term treatment was beneficial and safe.

STUDY

1. The original 6-year study followed over 9000 patients with previous MI or unstable angina randomized to pravastatin or placebo. All had a baseline cholesterol of 150 to 270 mg/dL (4.0 to 7.0 mmol/L).
2. After completion of the original study, over 7500 of these patients were continued on open label pravastatin. Those originally receiving pravastatin were continued; the control patients were started on pravastatin:
   A. 3766 originally received pravastatin 6 years then open label pravastatin for an additional 2 years.
   B. 3914 received placebo controls 6 years then open label pravastatin 2 years.

RESULTS

1. After start of the second phase (both groups on pravastatin) mean total cholesterol and LDL-cholesterol were identical in the 2 groups for the ensuing 2 years. [174 and 102 mg/dL; 4.52; 2.65 mmol/L]

2. Outcomes <u>second 2 years</u>:

	1) Pravastatin-pravastatin	2) Control-pravastatin	Absolute difference	NNT
Death (all causes)	5.6%	6.8%	1.2%	83
Coronary deaths	2.8%	3.6%	0.8%	125
CHD death or non-fatal MI	4.5%	5.2%	0.7%	143

(Ie, continuing pravastatin for 2 years after 6 years provided additional benefit. The first 2 years of pravastatin after 6 years of placebo was not as beneficial.)

3. Outcomes <u>total 8 years</u>

Death (all causes)	15.9%	19.7%	3.8%	26
CHD mortality	8.8%	11.3%	2.5%	40
Myocardial infarction	9.6%	12.7%	3.1%	33
Stroke	5.0%	6.0%	1.0%	100

4. There was strong evidence of treatment benefits in subgroups in the pravastatin-pravastatin group:

Women	15%	18%	3%	33
Patients over age 70	15%	28%	5%	20
Total cholesterol under 210	15%	18%	3%	33

5. Pravastatin had no significant adverse effects.

DISCUSSION

1. The absolute benefits of treatment and the strength of the evidence for effectiveness were greater for the 8-year follow-up than over the 6-year follow-up. [*Ie, the difference between group 1) and group 2) in total mortality, CHD death, and stroke continued to diverge, favoring the pravastatin-pravastatin group*.]
2. For every 1000 patients treated with pravastatin for 6 years, death and MI were prevented in 47. With treatment extended for 8 years, these events were prevented in 58 of 1000. With this extended follow-up, the benefits of the first 6 years of cholesterol-lowering treatment continued to accumulate at least for an additional 2 years. (Ie, the benefits in the pravastatin-pravastatin group over the additional 2 years could be attributed only to the first 6 years of treatment.)
3. The findings support the thesis that full treatment effects of statin therapy are delayed. (Ie, in the control-pravastatin group, 2 years of statin therapy did not confer as much benefit as 2 years of additional pravastatin therapy after 6 years of pravastatin therapy.
4. The long term benefits of statin drugs could be underestimated if trials extend only for 5 years.
5. There is evidence that statins reduce risks within 6 months, but not immediately This may be mediated by plaque stabilization, improved endothelial function and vascular reactivity, and reduced thrombotic tendency. Now there is evidence that reduction in risk continues to expand after 6 years.
6. The results also strengthen the evidence that long-term statins reduce risk of stroke.
7. Almost all patients with established coronary atherosclerotic heart disease should be treated with long-term statins.

CONCLUSION

Long-term (8 years) of pravastatin therapy resulted in accumulating benefits.

Lancet April 20, 2002; 359: 1379-87 Original investigation by the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, Clinical Trials Centre, University of Sydney, Australia. **www.thelancet.com**

1 NEJM 1998; 3339: 1349-57

Comment:

The study re-enforces the benefits of statins in secondary prevention in several important ways:

1. Long-term therapy (8 years) yields additional benefits in risk reduction. Benefits of therapy continued to accumulate after years of therapy.
2. Older patients, women, and patients with cholesterol <210 mg/dL benefit. benefit.
3. Incidence of stroke is reduced.

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"Dying has become the ultimate form of consumer resistance."

4-4 TOO MUCH MEDICINE? ***Almost certainly***

We all know medicine's power to be a force for good. However, some observers might accept the concept that increasing medical inputs will, at some point, become counterproductive and produce more harm than good. So where is that point, and might we have reached it already? There is no clear answer. Presumably no one wants to keep cutting back on education, the arts, scientific research, good food, travel, and much else on which we spend more and more of our resources on an unwinnable battle against death, pain, and sickness. Do we in the rich world want to keep developing increasingly expensive treatments that achieve marginal benefits when most in the developing world do not have the undoubted benefits that come with simple measures like sanitation, clean water, and immunizations?

Death, pain, and sickness are part of being human. All cultures have developed means to help people cope with all three. Indeed good health care can even be defined as being successful in coping with these realities.

Modern medicine has launched an inhuman attempt to defeat death, pain, and sickness. It has sapped the will of the people to suffer reality. "People are conditioned to *get* things rather than to *do* them. They want to be taught, moved, treated, and guided rather than to learn, to heal, and to find their own way."

The more a society spends on health care, the more likely are its inhabitants to regard themselves as sick.

The move to patient partnership may be shifting power from doctors back to people. People may increasingly take charge, more consciously weighing the costs and benefits of the "medicalization" of their lives. They may be more judiciously assessing the real value of medicine's never ending regimen of tests and treatments.

Many forces encourage greater medicalization. Patients and their professional advocacy groups can gain moral and financial benefits from having their condition defined as a disease. Doctors may welcome the boost to status, influence, and income that comes when new territory is defined as medical. Advances in genetics open up the possibility of defining almost all of us as "sick". Pharmaceutical companies have a clear interest in medicalizing life's problems. There is now a pill for every ill. Companies manufacturing diagnostic equipment or tests for specific diseases can grow rich on the medicalization of risk.

The concept of what is and what is not a "disease" is extremely slippery. It is easy to create new diseases and new treatments. Many of life's normal processes – birth, aging, sexuality, unhappiness, and death can be medicalized. Conversely, there is much undertreatment. The challenge is to get the balance right.

The cost of trying to defeat death, pain, and sickness is unlimited. Beyond a certain point every penny spent may make the problem worse, eroding still further the human capacity to cope with reality.

Without increased spending, doctors and their organizations will pay a personal price. They will try to cope with increasing demand with inadequate resources. "Indeed, this is one of the sources of worldwide unhappiness among doctors. Although seen by many as the perpetrators of medicalization, doctors may actually be some of its most prominent victims."

The move to patient partnership may be shifting power from doctors back to people. People may increasingly take charge, more consciously weighing the costs and benefits of the "medicalization" of their lives. They may be more judiciously assessing the real value of medicine's never ending regimen of tests and treatments.
BMJ April 13, 2002; 324: 859-60 Editorial, first author Ray Monyhan, Journalist, Australian Financial Review, Sydney **www.bmj.com/cgi/content/full324/7342/859**

Comment:

Some points of the editorial are based on Ivan Illich's book "Limits to Medicine. Medical Nemesis; The Expropriation of Health", reviewed in this issue of BMJ (p 923). The editor of BMJ recommends it highly. "Health, argues Illich, is the capacity to cope with the human reality of death, pain, and sickness. Technology can help, but modern medicine has gone too far – launching into a Godlike battle to eradicate death, pain and sickness. In doing so, it turns people into consumers of objects, destroying their capacity for health."

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Based On Understanding Outcomes Rather Than on Advanced Directives

4-5 UNDERSTANDING THE TREATMENT PREFERENCES OF SERIOUSLY ILL PEOPLE

Honoring the preferences of patients is critical for the provision of high-quality care at the end of life. Preferences are often elicited through advance directives which ask patients whether they would want to receive or forgo specific life-sustaining treatments. There are limitations to this approach.

The desirability of an intervention depends heavily on its outcome. Elicitation of patients' preferences should be based on outcomes rather than specific treatments. (Eg, intubation of a patient with a curable pneumonia is fundamentally different from intubation of a patient with terminal cancer.)

Previous investigations support the importance of considering outcomes in treatment preferences. Patients weigh the burden of treatment against the possible outcomes.

This study examined the effects of the burden of treatment on a variety of possible outcomes of care expressed by seriously ill patients.

Conclusion: Planning should take into account patients' attitudes toward the burden of treatments, the possible outcomes, and the likelihood of adverse functional and cognitive impairment.

STUDY

1. Questionnaire asked 226 patients about treatment preferences. All were over age 60 (mean age = 73) and had a limited life expectancy due to cancer, heart failure or chronic obstructive pulmonary disease.
2. Asked whether they would want to receive a given treatment 1) when the outcome was known with certainty and 2) when different likelihoods of an adverse outcome were possible.
3. The outcome without treatment was specified as death from the underlying disease.

RESULTS

1. The burden of treatment (ie, the length of hospital stay, extent of testing, and invasiveness of interventions), and the likelihood of adverse outcomes all influenced treatment preferences.

2. The number who said they would choose treatment declined as the likelihood of adverse outcome increased. Fewer participants would choose treatment when the likely outcome was functional or cognitive impairment.
3. For a low burden treatment with restoration of current health, almost all said they would choose the treatment (rather than not receive it and die). Eleven percent of the participants would not choose the treatment if it had a high burden even if non-treatment led to death.
4. If the outcome was survival with severe functional impairment, 75% would choose not to receive treatment. If the outcome was cognitive impairment, 89% would refuse treatment. (*Note: fear of loss of cognition was greater*. *RTJ*)

DISCUSSION

1. The burden of treatment and the likelihood of outcomes all influenced treatment preferences. "Clearly, treatment outcomes are a strong determinant of patients' preferences."
2. Almost all would choose low-burden treatments if the alternative was death. But, for low-burden treatments with an outcome of cognitive impairment, almost 90% would not want therapy.
3. The proportion of participants who wished to receive therapy changed, but to a lesser degree, when the burden differed but the outcome was the same. More than 10% rejected or were undecided about high burden therapy vs only 2% who would reject low-burden therapy.
4. Many patients would not wish to receive aggressive therapy if they knew they were dying. But, uncertainty about the prognosis coupled with a "deeply held desire not to be dead" makes patients willing to undergo therapy even when they are seriously ill but not close to death. The study forced participants to choose between a particular treatment and certain death. In reality, the choice may not be so simple. If preferences are to be honored, they first must be understood. Understanding depends on assessment of how patients view the burden of treatment in relation to outcomes.
5. The predominant clinical approach now focuses on preferences with regard to specific interventions. In the absence of probability of different outcomes, this may be misleading. (Eg, the proportion of persons who say they would want to undergo cardiopulmonary resuscitation is much lower after they have been told the low probability of survival. Uninformed estimates of survival after resuscitation have been mistakenly high.)
6. Identification and correction of misconceptions are especially important. Many patients would not want to receive therapy if there was a 50% chance of severe impairment. "The possibility of functional and cognitive impairment has a particularly important role in patients' preferences."

CONCLUSION

Advance care planning should take into account patient's toward the burden of treatment, the possible outcomes, and their likelihood. The likelihood of adverse functional and cognitive outcomes requires explicit consideration.

NEJM April 4, 2002; 1061-66 First author Terri R Fried, Yale University School of Medicine, New Haven, Conn.

www.nejm.org

An editorial in this issue (pp 1087- 89), first author Diane E Meier, comments:

Many argue that it is ethical to provide marginal effective treatments if sick patients want them, regardless of the resulting quality of life. A long legal and cultural tradition emphasizes the autonomy of patients as the dominant principle guiding medical decision-making.

Advance directives are based on the assumption that patients can anticipate their choices under future circumstances in which death is imminent. There is little evidence that the decisions they make when relatively healthy predict their choices when death is immanent. Preferences for life-sustaining treatments appear only moderately stable. The likelihood of choosing treatments increases as patients' health worsens.

The study suggests that discussions of advanced care planning should shift from whether patients would accept or reject specific treatments to what they consider acceptable in terms of quality-of-life, the burdens of treatment, and the probability of successful outcome. Unfortunately, it is difficult for very sick persons to engage in graded, probabilistic thinking.

When desperately ill patients and their families opt for desperate treatments, they should also be asked under what circumstances death would be preferable to life with severe impairment, and whether treatment should be discontinued if these circumstances occur. Patients, families, and doctors need an escape route like a limited trial of therapy. If the worst happens, life-sustaining treatments can be stopped according to the patient's wishes.

What seriously ill patients really want is relief of suffering, help in minimizing the burden on families, closer relationships with family, and a sense of control.

Comment:

Primary care clinicians must be aware of individual and ethnic differences, given the diversity of their patients.

I believe this study is clinically applicable in primary care. Patients, families, and primary care-givers may ask their physician – What would you do faced with this decision? Giving direct advice negates autonomy. For terminally ill mentally competent patients, the physician may cite the study as an example of other patients' feelings. If the terminally ill patient is not competent, families may take some comfort knowing the decisions of other patients at the end of life. RTJ

"A Determination To Find New And Imaginative Ways To Continue Caring Up To The End Of Life."

4-6 BETWEEN HOPE AND ACCEPTANCE: The Medicalization of Dying

"We have grown used to speaking of medicalization as a byword for all things negative about the influence of modern medicine on life and society." The term has become synonymous with the sense of a profession reaching too far: into the body, the mind, and even the soul itself. Its use now is almost always pejorative, negative, and antagonistic. An original critique of medicalization claimed that modern medicine had "brought the epoch of natural death to an end". (*Ivan Illich – 1970*)

Yet, well before Illich, a climate of concern was developing about contemporary means of dying, and medicine's part in them. The emergence of terminal and hospice care and subsequent endorsement of the specialty

of palliative care is a clear expression of this. In the USA, a reaction to futile treatments in the face of suffering and inevitable death began to take root.

Four particular interventions can be identified:

1. A shift in the literature on the care of dying people, from anecdote to systemic observation and research. This suggested ways in which terminal care could be promoted.
2. A view of dying began to emerge that sought to foster concepts of dignity and meaning along with a new openness about terminal sedation.
3. An active, rather than a passive approach to the care of dying people was promoted in which fatalistic resignation of the doctor ("There is nothing more we can do") was supplanted by a determination to find new and imaginative ways to continue caring up to the end of life.
4. A growing recognition of the interdependency of mental and physical distress created the potential for a more embodied notion of suffering. This constituted a profound challenge to the body-mind dualism on which so much medical practice of the period was predicated. The notion of "total pain" emerged.

The hospice movement began and the term "palliative care" came to symbolize this broadening orientation toward greater dignity at the end of life.

But just as palliative care emerged, parallel developments in the medical system emerged to redouble efforts in the opposite direction. Creeping medicalization entered palliative care. The problem of treatments that are futile and have a low probability of having a benefit, or produce an effect that is of no benefit is one aspect of this.

Problems arose from the widespread assumption in society that every cause of death can be resisted, postponed, or avoided. Many elderly patients with advanced cancer have received intensive non-palliative treatments during their final days. Many with dementia and cancer received enteral tube feeding, and many still had the tube in place at the time of death. Dying patients were caught up in a medical juggernaut driven by a logic of its own, one less focused on human suffering and dignity than on the struggle to maintain vital functions. Patients in hospitals became socially isolated. Dying was dehumanized. Medical technology failed to co-exist appropriately with dignified dying.

As these increasingly technical approaches to care at the end of life gained influence, the newly formed specialty of palliative care concentrated on two areas:

1. An impetus to move palliative care further upstream in the disease progression, seeking integration with curative medicine and rehabilitation therapies and shifting the focus beyond terminal care.
2. A growing interest in extending the benefits of palliative care to those diseases other than cancer to make "palliative care for all" a reality. This new specialty is delicately balanced, trying to blend technical interventions with a humanistic orientation to dying patients.

However, in print, in conferences, and in their daily work, specialists in palliative care seem to lack clarity and confidence when defining precisely what they do and how it differs from other health care. "Palliative medicine relates to the *stage* of a patient's condition rather than its pathology." It lacks a specific disease, bodily organ, or life stage to call its own. It has been drawn towards a model that overarches the course of illness and is unified by quality of life goals. Yet the adoption of "quality of life" as a goal of palliative care conceals many problems, several of which are structural, economic, and social, and lie beyond the immediate influence of clinical medicine. To attend to suffering rather than quality of life may therefore seem a more realistic aim for palliative care, one

that is more compatible with the wider goals of medicine, and which might help to address problems about futility and overtreatment. But it has raised fears of selling out to a medical model in which (*physical*) suffering is the only problem to be solved and specialists in palliative care become symptomologists in just another specialty.

From the outset, achievement of the "good death" has figured as a goal of palliative care. But the shift from "terminal" to "palliative" care has brought about a diminished emphasis of the good death, which now has a reduced significance in the discourse of pain and symptom management. "Mainstreaming" palliative care into the central functions of the health care system produces a greater concentration on the problems of the living than the dying population. A shift "upstream" in earlier stages in the disease process – and the inclusion of chronic, life limiting conditions – promotes the rhetoric of quality of life versus a good death.

Paradoxically, what we are seeing is the medicalization of palliative care, a specialty that opens up a space somewhere between the hope of cure, and the acceptance of death.

Medicine has become more dissembled and further divided into micro-specialisms. In this context, is palliative medicine contributing to the medicalization of death, despite its early intentions? The answer is probably yes. For some, pain and other physical suffering are better controlled. The challenge for palliative physicians is no different from that facing their counterparts elsewhere in medicine: how to reconcile high expectations of technical expertise with calls for a humanistic and ethical orientation for which they are largely unselected and only partially trained.

Elements of a "good death" in modern Western culture.

- Pain-free death
- Open acknowledgement of the imminence of death
- Death at home, surrounded by family and friends
- An "aware" death – in which personal conflicts and unfinished business are resolved
- Death as personal growth
- Death according to personal preference and in a manner that resonates with the person's individuality.

BMJ April 13, 2002; 324 Editorial by David Clark, University of Sheffield, UK

www.bmj.com/cgi/content/full/324/7342/905

The article adds a box (an "endpiece"):

Trapped Between Two Evils

"The consequences of this continuing modernist deconstruction of mortality have brought us to the current postmodernist impasse in which dying patients are trapped between two evils: a runaway medical technology of ventilators, surgeries, and organ transplants that can keep bodies alive indefinitely, and – as if this prospect were not frightening enough – an understandable but reckless public clamor for physician-assisted suicide as the only alternative to such ignominious physician-assisted suffering."

David B Morrris "*Illness and Culture in the Postmodern Age*"

Comment***:***

I am not as pessimistic as the author. I believe the profession and patients are gradually coming more and more to accept the inevitability of death and to plan for it.

Care of the dying still lies mainly in primary care – often with the help of Hospice. We may learn from specialists in palliative care, but still bear most of the opportunity and responsibility.

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The most common liver disease?

4-7 NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (**NAFLD**) is increasingly recognized. It may progress to end-stage liver disease. Pathologically it resembles alcohol-induced liver injury, but it occurs in persons who do not abuse alcohol.

A number of names has been given to the condition, including non-alcoholic steatohepatitis. Nonalcoholic fatty liver disease is becoming the preferred term. This refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis.

The clinical implications of NAFLD are derived mostly from its common occurrence in the general population and its potential to progress to liver failure.

Risk factors:

Obesity, type 2 diabetes, and hyperlipidemia frequently coexist. Prevalence of NAFLD in persons with a body mass index (**BMI**) over 30 is about 5 times that of non-obese persons. Type 2 diabetes is an important risk factor regardless of BMI. One study found NAFLD in about half of persons with hyperlipidemia. The risk factor is hypertriglyceridemia rather than hypercholesterolemia. A typical patient is a middle-aged woman.

Prevalence

Up to 25% of persons in some countries. Up to 75% in obese persons. Up to 50% in obese children. "NAFLD is the most common cause of abnormal liver-test results among adults in the USA." An estimated 30 million obese adults in the USA have NAFLD; and about 8 million have steatohepatitis. About 50% of persons with diabetes have NAFLD. Combined obesity-diabetes increases risk: almost all have NAFLD; about half have steatohepatitis; 20% have cirrhosis.

Clinical features

Most are asymptomatic. Some report fatigue and malaise and a sensation of fullness in the right upper quadrant. Hepatomegaly is the only physical finding in most patients. "A high proportion of patients with cryptogenic cirrhosis share many of the features of NAFLD." This suggests that their cirrhosis is due to NAFLD.

Laboratory abnormalities

Mild to moderate elevations of aminotransferases are the most common and often the only abnormality. Alanine aminotransferase (**ALT**) is usually higher than aspartate aminotransferase (**AST**). Elevated ferritin levels are found in half the patients. Other markers: hypoalbuminuria, prolonged prothrombin time, and hyperbilirubinemia may be found in the cirrhotic stage.

Imaging studies

Fatty infiltration of the liver produces a diffuse increase in echogenicity on ultrasound of the liver as compared with the kidney. Ultrasound has reasonably good sensitivity and specificity. A low density hepatic parenchyma is seen on CT scan.

Histologic findings

NAFLD is histologically indistinguishable from liver damage due to alcohol abuse. Features include; steatosis, inflammatory cell infiltration, hepatocyte ballooning and necrosis, and fibrosis. The spectrum of NAFLD is widespread. Fibrosis suggests a more advanced and severe liver injury. The combination of steatosis, infiltration of inflammatory cells, hepatocyte ballooning, and spotty necrosis is known as non-alcoholic steatohepatitis. Most patients with steatohepatitis have some degree of fibrosis.

Pathogenesis

It is not understood why some patients develop simple steatosis and some go on to progressive disease. A net retention of lipids within hepatocytes, mostly triglycerides, is a prerequisite for NAFLD. Insulin resistance is the most reproducible factor. Insulin resistance (and hyperinsulinism) leads to fat accumulation in hepatocytes.

Although symptoms of liver disease rarely develop in patients who are obese, have diabetes, or have hyperlipidemia, the steatotic liver may be vulnerable to further injury when challenged by additional insults.

Diagnosis

Usually suspected when elevated aminotransferase levels are found in asymptomatic patients. Unexplained hepatomegaly may be present. The clinical suspicion of NAFLD and its severity can be confirmed only with a liver biopsy. Diagnosis requires exclusion of alcohol abuse. A daily intake as low as 20 g in women and 30 g in men may be sufficient to cause alcohol-induced liver disease in some patients.**1**. Viruses, autoimmune disease, drugs and toxins should be ruled out. Age over 45, presence of obesity, type 2 diabetes, and a ratio of ALT/AST over 1 are indicators of advanced disease and fibrosis. Higher levels of ALT and triglycerides also indicate more advanced disease.

Role of the liver biopsy

This is the best diagnostic and prognostic tool.

Natural history

Is determined by the severity of the histologic change. Many patients have a relatively benign course. Others progress to cirrhosis. There is a trend toward more liver-related deaths among patients with steatohepatitis. An occasional liver transplant is performed for end-stage steatohepatitis.

Management

Good metabolic control of diabetes and hyperlipidemia. Weight loss is important, but too rapid loss may reduce necroinflammation fibrosis and bile stasis. (Not more than 500 g/wk in children and 1600 g/wk in adults.)

Drugs: Metformin (*Glucophage* **),** gemfibrozil, and vitamin E have been reported to benefit.

General recommendations: Gradual weight loss; appropriate control of glucose and lipid levels may be the only steps needed for those with pure steatosis. Liver transplant is the last resort. NAFLD may recur in the allograft.

CONCLUSION

NAFLD affects a large proportion of the world's population. Liver biopsy is the most sensitive and specific means of providing prognostic information. Simple steatosis may have the best prognosis, but has the potential to progress to steatohepatitis, fibrosis, and cirrhosis. Sustained weight reduction may lead to improvement. Pharmacotherapy holds promise. Liver transplant is the last resort.

NEJM April 18, 2002; 346: 1221-1231 "Medical Progress", Review article by Paul Angulo, Mayo Clinic and Foundation, Rochester, Minn. **www.nejm.org**

1 Diabetes is included among the conditions widely reported to respond beneficially to daily intake of one to two drinks. Now there is a caution expressed in diabetics with NAFLD.

Comment:

A long list of nutritional, drug, metabolic, genetic and other causes is presented in table 1, p 1222.

My main response to the article – Is NAFLD really that common? I was not aware of this before. If so, NAFLD must be one of the most common diseases in the USA. It follows the pattern of increasing obesity and diabetes. RTJ

H Pylori Infection Should Be Treated

4-8 TREATING *HELICOBACTER PYLORI* INFECTION IN PRIMARY CARE PATIENTS WITH UNINVESTIGATED DYSPEPSIA

Dyspepsia is one of the most common conditions presenting to primary care. Most patients are not investigated and the cause is usually not known. Primary care clinicians are comfortable treating patients without an initial diagnosis and prescribe up to 2.5 courses of empirical drugs before referring for investigation. The majority of investigations are normal and the diagnosis is functional dyspepsia.

A suggested strategy for managing uninvestigated dyspepsia is to screen patients under age 50 with a non-invasive test for *H pylori* and to eradicate the infection in those with positive results.

This study determined whether a non-invasive *H pylori* "test and treat" strategy for primary care adult patients of any age with uninvestigated dyspepsia would result in improvement or cure of dyspepsia.

Conclusion: A "test and treat" strategy resulted in significant symptomatic benefit.

STUDY

1. Randomized, placebo-controlled trial entered 294 patients with dyspepsia. All had a positive *H pylori* ^{13}C-urea breath test.
2. Defined dyspepsia as a symptom complex of epigastric pain or discomfort thought to originate in the upper gi tract. It included any of the following *additional* symptoms: heartburn, acid regurgitation, excessive belching, increased abdominal bloating, nausea, feelings of slow or abnormal digestion, early satiety. (Ie, symptoms frequently encountered in uninvestigated patients seen in primary care.)

3. Patients with *only* heartburn, regurgitation, or both were considered to have gastro-esophageal reflux disease and were not included.
4. Randomized to treatment for 7 days with: 1) omeprazole (*Prilosec*), metronidazole (*Flagyl*) and clarithromycin (*Biaxin*), or 2) omeprazole + placebos.
5. Otherwise treated as usual by their primary care clinicians.
6. Treatment success defined as no symptoms or minimal symptoms of dyspepsia at the end of one year.

RESULTS

1. Eradication treatment cured the infection in 80%
2. At one year, eradication treatment was significantly more effective than placebo in relieving symptoms. Absolute reduction = 14% (50% success rate vs 36% for placebo. NNT = 7.)
3. Test and treat strategy reduced annual costs, primarily through decreased visits to physicians and use of fewer drugs.
4. Quality-of life showed greater improvement in the eradicated group.

DISCUSSION

1. *H pylori* is known to cause peptic ulcers and is linked to gastric cancer. Its association with dyspepsia remains unclear.
2. Most studies have been done in patients with investigated dyspepsia. They show at best a small benefit, about 6%.
3. Symptoms do not reliably predict endoscopic findings or allow reliable diagnosis. Symptoms of heartburn and acid regurgitation are defined as synonymous with gastro-esophageal reflux disease (**GERD**). (Note, in the study patients with some of these symptoms were included if they were present in addition to other symptoms of dyspepsia.) Eradication treatment of patients with GERD who test positive for *H pylori* either does not affect clinical course, or may worsen it.
4. Most patients with dyspepsia have multiple overlapping symptoms.
5. “Our study showed consistent results in favour of eradication of *H pylori* for most outcome measures.” This is consistent with the hypothesis that *H pylori* is responsible for dyspepsia in some patients.
6. “Our results are robust and generalizable to primary care.” Nevertheless, at least half of treated patients will require further treatment for dyspepsia.

CONCLUSION

“Testing (with C-urea breath test) and treating” to eradicate *H pylori* in patients with uninvestigated dyspepsia provided long-term relief of symptoms and reduced health costs in primary care patients.

BMJ April 27, 2002; 324: 1012-16 Original investigation, the Canadian Adult Dyspepsia Empiric Treatment – *Helicobacter pylori* (CADET-Hp) trial, first author Naoki Chiba, McMaster University, Hamilton, Ontario, Canada. **www.bmj.com/cgi/content/full/324/7344/1012**

Comment:

I enjoyed this article. It applies to the way primary care medicine is generally practiced.

I believe treating *H pylori* –related dyspepsia is indicated. There is some difference between studies about the effectiveness of eradication in dyspeptic symptoms. This article reported more effective elimination of symptoms than most studies. Removing some of the threat of peptic ulcer disease and gastric cancer are reasons enough to eradicate the infection. Additionally, elimination of *H pylori* infection lessens the risk of development of gastric ulcer formation in patients started on long-term NSAID therapy.

H pylori produces urease. This is the basis of the ^{13}C-urea breath test. Labeled urea is given by mouth. If *H pylori* are present in the stomach, the urea is split into CO2 and ammonia. The ^{13}CO2 is exhaled and easily measured. RTJ

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A Reasonable Alternative to Colonoscopy

4-9 SINGLE FLEXIBLE SIGMOIDOSCOPY SCREENING TO PREVENT COLORECTAL CANCER

A randomized trial is being conducted in the UK to examine the hypothesis that a single flexible sigmoidoscopy (**flex-sig**) offered at about age 60 can lower the incidence and mortality of colorectal cancer (**CRC**). A single screening by flex-sig might be a cost effective way of lowering incidence rates. The rate of distal adenomas increases with age until the late fifties, and then appears to level off. This suggests that most people destined to develop distal CRC will have developed a distal adenoma by this age.

The low survival characteristics of CRC is the result of the advanced stage at diagnosis. When the disease is early, localized, and in most cases symptomless, cure rates exceed 90%. CRC is potentially preventable by population screening. The development of CRC from an precursor adenoma is a slow process, taking 10 years on the average. There is sufficient time for adenoma detection and removal..

Two methods of screening are under consideration in the UK for implementation in a national program: 1) fecal occult blood testing (**FOBT**), and 2) flexible sigmoidoscopy. FOBT lowers mortality rates by about 15% if testing is offered every 2 years, mainly through detection of early CRC. In the UK, flex-sig is judged a more suitable tool for population screening than colonoscopy because: it is safer; cheaper; quicker; more convenient; and because acceptability (uptake rate) is much higher. "Two thirds of adenomas and cancers are within reach of the flexible sigmoidoscope." The procedure takes only 5 minutes. It requires no sedation, and only a self-administered enema to clear the bowel.

Conclusion: This flex-sig screening program is acceptable, feasible, and safe. The prevalence of adenomas is high.

STUDY

1. A questionnaire mailed to over 350 000 persons in the UK asked about their interest in attending for flex-sig screening. 55% responded positively.
2. Over 40 000 eligible individuals (age 55-64) underwent flex-sig.
3. Patients were prepared with a self-administered phosphate enema one hour before leaving home.
4. Flex-sig was undertaken with a 60 cm video-endoscope. Carbon dioxide was used to insufflate the bowel. The endoscope was advanced as far as could be achieved without causing undue pain or distress (usually to the junction of the sigmoid and the descending colon). Sedatives were rarely used. The examination was not expected to take longer than 5 minutes.
5. Small polyps were removed during screening. Colonoscopy was undertaken for those with high-risk: (three or more adenomas; size 1 cm or greater; villous, severely dysplastic, or malignant adenomas).

RESULTS

1. Among those receiving flex-sig: 5% were classified as high-risk and referred for colonoscopy. The remainder with no polyps or with only low-risk polyps (which were removed) were discharged.
2. Flex-sig completed to junction of sigmoid and descending colon depended on patients' experience of pain -- 93% of those without pain were completed; 68% of the 3% of patients who had severe pain received a complete examination.

3. Numbers with distal adenomas	Men (n = 20 000)	Women (n = 20 000)
Any	16%	8%
Three or more	1%	0.2%
Tubulovillous or villous	3.2%	1.6%
Severe dysplasia	1.1%	0.4%
High risk lesions	6.4%	2.9%
Cancer	0.5%	0.2%

4. Numbers with adenomas or cancer in the proximal colon

	Men (n = 1396)	Women (n = 655)
Any	23%	11%
Three or more	5%	2%
Tubulovillous or villous	4%	2.4%
Severe dysplasia	1.4%	0.6%
Advanced adenomas	6%	4%
Cancers	0.6%	0.2%

(*This was my first encounter with a remarkable difference in prevalence between the sexes. The authors mention the difference, but gave no reason. RTJ*)

5. 62% of cancers were Dukes' stage A.
6. There was one perforation after flex-sig; 4 after colonoscopy. Twelve of the flex-sig group were hospitalized for bleeding

7. Almost all said they were glad they had the test.

DISCUSSION

1. Evidence already exists from case-control studies that a single sigmoidoscopy leads to reduction in risk of fatal distal CRC by about 60%.
2. The wider use of flex-sig in the USA and removal of adenomas has been suggested as an explanation for the reduction incidence of distal (but not proximal) CRC in the USA over the past 8 years.
3. Detection rate of large adenomas with flex-sig is about 4 times higher than detection with a single FOBT. (The sensitivity of FOBT increases on repeated testing.)
4. With increasing age, the prevalence of advanced proximal neoplasia increases. A strategy to prevent proximal CRC would be more cost-effective if focused on older people.
5. In the future, nurses or technicians might be able to undertake flex-sig examining.
6. The cost differential (flex-sig vs colonoscopy) would be tremendous. This is offset by the numbers of proximal cancers which would remain undiscovered.

CONCLUSION

This flex-sig screening regimen was acceptable, feasible, and safe. The prevalence of neoplasia detected was high.

Lancet April 13, 2002; 359: 1291-300 Original investigation by the UK Flexible Sigmoidoscopy Screening Trial Investigators **www.thelancet.com**

Comment:

A July 2002 issue of the Annals of Internal Medicine (July 16, 2002;127) reports that screening (vs no screening) for CRC is cost-effective in persons over age 50 and reduces death (due to removal of adenomatous polyps). Considering FBOT, FBOT + sigmoidoscopy, and colonoscopy, the optimum strategy cannot be determined from current data.. Physicians should inform patients about advantages and disadvantages to determine patients' personal preference.

Would sigmoidoscopy (admittedly an incomplete screening procedure) be acceptable in the USA where colonoscopy has become the standard? I believe many individuals avoid colonoscopy for obvious reasons. This group would be much more likely to accept the much simpler, more convenient, and less painful procedure knowing that it will miss some significant lesions. The increasing prevalence of proximal lesions in the elderly is reason for caution in recommending flex-sig for this group.

Would it be reasonable to do a flex-sig as a follow-up procedure after an initial colonoscopy? Should it be combined with FBOT?

In the UK, flex-sig is judged a more suitable tool for population screening than colonoscopy because; it is safer; cheaper; quicker; more convenient; and because acceptability (uptake rate) is much higher. "Two thirds of adenomas and cancers are within reach of the flexible sigmoidoscope." The procedure takes only 5 minutes. It requires no sedation, and only a self-administered enema to clear the bowel.

This flex-sig screening program is acceptable, feasible, and safe. The prevalence of adenomas is high.

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A Reasonable Recommendation For Circumcision

4-10 MALE CIRCUMCISION, PENILE HUMAN PAPILLOMA VIRUS INFECTION, AND CERVICAL CANCER IN FEMALE PARTNERS.

Hutchinson in 1855 suggested that circumcision might prevent syphilis. Studies have suggested that circumcision may reduce risk of penile cancer, urinary tract infections, and common sexually transmitted infections, including human immunodeficiency virus (**HIV**) infection.

Little is known about effect of circumcision on risk of acquiring human papilloma virus (**HPV**). HPV causes genital warts and has been linked to cancers of the cervix, vulva, vagina, anus, and penis.

Cervical cancer is the 2nd most common cancer in women. Up to 99% of all cases may be attributed to infection by oncogenic types of HPV. Factors that reduce probability of acquiring or transmitting HPV may reduce risk of cervical cancer.

This study asked if male circumcision reduces risks of penile HPV in men and cervical cancer in their female partners.

Conclusion: Circumcision reduced both.

STUDY

1. Enrolled over 1900 couples in case-control studies of cervical carcinoma in situ and cervical cancer.

2. Women:
   Cases: 977 had invasive cervical cancer or cervical carcinoma in situ.
   Controls: 936 were matched controls recruited from the general population.
3. Determined male circumcision status by self-report in stable partners of the women (defined as reporting regular intercourse for at least 6 months).
4. Determined HPV status of the penis and cervix by polymerase-chain reaction.
   (Valid result obtained in 1139 men.)

RESULTS

1. Men: penile HPV status:
   Circumcised 6%
   Uncircumcised 20%

After adjustment for multiple potential confounders, circumcised men were less likely to have HPV. (Odds ratio = 0.37)

2. Women who were monogamous and whose circumcised male partners had 6 or more lifetime sexual partners had a lower risk of cervical cancer than monogamous women whose uncircumcised partners had 6 or more lifetime sexual partners (Odds ratio = 0.42).

DISCUSSION

1. In men, circumcision was associated with a reduced risk of penile HPV infection.
2. There was an inverse association between circumcision and risk of cervical cancers in women whose male partners engaged in sexual practices known to increase the risks of HPV infections (such as having multiple sexual partners).
3. Epidemiological evidence suggests that, in the absence of circumcision, there is an increased risk of phimosis, poor genital hygiene, genital warts, and HPV infection.
4. What mechanisms might removal of the foreskin protect against HPV? -- maintaining good penile hygiene, and less exposure to a non-keratinized mucosa. (The keratinized stratified squamous epithelium of the glans is less vulnerable to invasion by the virus than the non-keratinized mucosa of the foreskin.)
5. That male circumcision may reduce risk of cervical cancer is highly plausible. It reduces risk of penile HPV. Penile HPV infection is associated with a four-fold increase in risk of cervical cancer in the female partner. And cervical HPV is associated with a 77-fold increase in the risk of cervical cancer.

CONCLUSION

Male circumcision is associated with a reduced risk of penile HPV.

In the case of circumcised men with a history of multiple sexual partners, a reduced risk of cervical cancer was evident in their current female partner.

NEJM April 11, 2002; 346: 1105-12 Original investigation for the International Agency for Research on Cancer: Multicenter Cervical Cancer Study Group, first author Xavier Castellsague, Servei d'Epidemiologia i Registre del Cancer, Barcelona, Spain. **www.nejm.org**

An editorial in this issue of NEJM comments:

The American Academy of Pediatrics has recently issued a statement that the medical benefits are "not sufficient to recommend routine neonatal circumcision. "

Notwithstanding this statement, it is generally accepted that circumcision reduces the prevalence of several infectious diseases. There is evidence that circumcision reduces risk of HIV, and now, HPV.

The oncogenic subspecies of HPV (especially 16 and 18) are considered to be the main cause of both premalignant and malignant lesions of the cervix.

Prophylactic vaccination against HPV is now being evaluated in clinical trials. It could substantially reduce the rates of HPV infection and cervical cancer.

Eat More Fish!

4-11 BLOOD LEVELS OF LONG CHAIN N-3 FATTY ACIDS AND THE RISK OF SUDDEN DEATH.

Previous studies have reported that fish consumption is associated with a reduced risk of sudden death. It is hypothesized that long chain n-3 polyunsaturated fatty acids (**n-3FA**) found in fish may be responsible. Experimental data suggest these n-3FA have antiarrhythmic properties. A recent secondary prevention study of myocardial infarction (**MI**) survivors reported a 45% reduction in risk of sudden death in those taking n-3FA with no effect on nonfatal MI.

This study asks -- Is there benefit of n-3FA among persons without a history of cardiovascular disease? (Primary prevention)

Conclusion: Consumption of n-3FA from fish was strongly associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease.

STUDY

1. The Physician's Health Study entered over 22 000 male physicians in a prospective case-control study.
2. None had history of MI, stroke, TIA, of cancer.
3. Determined FA composition on previously collected blood on:
   Cases – 94 men in whom sudden death occurred as the first manifestation of cardiovascular disease.
   Controls – 184 controls matched for age and smoking status.
4. Follow-up = 17 years.

RESULTS

1. Blood levels of long chain n-3FA were inversely related to risk of sudden death
2. Compared with men with blood levels of n-3FA in the lowest quartile, the relative risk of death of those in the 3rd and 4th quartiles was significantly lower. (Relative risk = 0.28 and 0.19)

DISCUSSION

1. "In this prospective case-control study of healthy male physicians without evidence of cardiovascular disease at enrollment, the base-line blood level of long chain n-3 fatty acids was inversely associated with the subsequent risk of sudden death after known confounders had been controlled for."
2. The association was linear. As compared with men with the lowest quartile of n-3FA, those in the highest quartile had an 81 percent lower risk of sudden death.
3. The benefit may be in part to the anti-arrhythmic effects of n-3FA.
4. If the association is causal, increasing intake of n-3FA by eating more fish or by taking supplements is an intervention that could be applied with little risk.

CONCLUSION

These prospective data suggest that long chain n-3FA found in fish may reduce the risk of sudden death from cardiac causes, even in men without a history of cardiovascular disease. More than 50% of all sudden deaths from cardiac causes occur in people with no history of cardiac disease.

NEJM April 11, 2002; 336: 1113-18 Original investigation, first author Christine M Albert, Brigham and Woman's Hospital, Boston, Mass**. www.nejm.org**

Comment:

I have wondered how much n-3FA there is now in the fish we eat. The n-3FA content of ocean fish arises in plankton which ascend the food chain and end up in fish. Many of the fish we eat now are raised on farms. I do not know if there is much n-3FA in the feed they eat. If there is little, the conclusions of the study would be less applicable.

Of over 17 000 men only 94 died suddenly over 17 years. The number needed to treat with increased fish intake would be very large to prevent one sudden death. However, since there are so many sudden cardiac deaths annually, if all individuals in the country ate fish regularly, the public health benefit would be clinically evident.

Taking 80 mg of aspirin daily is much more convenient and effective.

A similar article appeared in JAMA April 10, 2002;287: 1815-21. This concerned over 84 000 women in the Nurses' Health Study. During 16 years of follow-up, there was a linear decrease in incident non-fatal MI and sudden coronary death as fish intake increased from less than once a month to 5 or more times weekly. Taking aspirin blunted the beneficial effect. Intake of supplements of fish oil has also been associated with lower risk of sudden death. Several years ago there was a flurry of advertisement about supplementary fish oil capsules. They were generally available at drug stores. The enthusiasm has waned. Fewer than 2% of the women in this study were taking supplements of fish oil.

The health benefits of fish extend beyond the effect on sudden death. RTJ

Another battle in the microbe-antibiotic war. Antibiotics are losing.

4-12 ERYTHROMYCIN-RESISTANT GROUP A STREPTOCOCCI IN SCHOOLCHILDREN IN PITTSBURGH

Group A streptococci **(GAS**) are the most frequent and important cause of bacterial pharyngitis in children and adults. Penicillin V remains the treatment drug of choice. Erythromycin has been prescribed for persons allergic to penicillin. Azithromycin (*Zithromax*) is not recommended as first-line therapy, but many clinicians find the 5-day regimen of one dose daily attractive. Azithromycin and other macrolides are also frequently prescribed for non-streptococcal pharyngitis and other upper respiratory infections. The number of prescriptions for azithromycin has increased. The rate of resistance to erythromycin among isolates correlates with increased use of macrolides.

Heretofore erythromycin resistant GAS have been very uncommon in the USA.

This study examined the antibiotic susceptibility patterns of pharyngeal isolates of GAS in school children and evaluated the sudden emergence and rapid spread of erythromycin resistance

Conclusion: A longitudinal study detected rapid emergence and spread of erythromycin-resistant GAS.

STUDY

1. Obtained surveillance throat cultures twice monthly -- October 2000 to May 2001-- in school children without infections, as well as from children with new respiratory illness.
2. Tested for erythromycin resistance.
3. Used the polymerase-chain-reaction to identify the resistance genes.

RESULTS

1. Obtained over 1700 throat cultures from 100 children.
2. Of these, 18% were positive for GAS.
3. Forty -eight % of the 18% were resistant to erythromycin. (Total of 9% of 1700)
4. Of 100 random cultures of children in the community, 38 were resistant to erythromycin.
5. None were resistant to clindamycin. (*Cleocin*)
6. The outbreak was due to a single mutated strain of GAS.

DISCUSSION

1. Beginning in the 1980s, the incidence of acute rheumatic fever increased, and serious invasive complications caused by GAS occurred while the incidence of pharyngitis due to group A remained stable. This emphasizes the need for correct diagnosis of streptococcal pharyngitis.
2. Prompt initiation of appropriate antibiotics will prevent suppurative and some non-suppurative complications of GAS. It will also reduce the pool of patients from which adults and other children acquire the infection.
3. The susceptibility of GAS to commonly prescribed antibiotics has been very stable in the USA. However, in many other countries, a high percentage of isolates are resistant to erythromycin and other macrolides. In Finland, the rates of erythromycin resistance prompted an intense effort to reduce use of macrolides. This resulted in a dramatic reduction in prevalence of resistance.
4. “We found an unexpectedly high incidence of erythromycin resistant group A streptococci among children in a single school; also a high prevalence in the community. The isolate spread very rapidly.”
5. The outbreak was due to a single clone of GAS.
6. The use of macrolide antibiotics in the USA has increased, accelerated by the wide use of short courses of azithromycin for treatment of pharyngitis, sinusitis, otitis media, and community-acquired pneumonia.
7. The children in the study were treated for GAS pharyngitis only if they had respiratory symptoms and a new positive culture for GAS. Children with resistant GAS were treated with amoxicillin, penicillin or clindamycin.
8. Children with streptococcal pharyngitis usually recover within several days, even in the absence of treatment. Only in the event of increased frequency of suppurative, invasive, or non-suppurative complications of erythromycin-resistant GAS might this trend toward resistance be detected.
9. “We recommend that macrolide antibiotics *not* be used for the routine treatment of pharyngitis due to group

A streptococci until more epidemiological information is available, or unless susceptibility testing is first performed."

CONCLUSION

A longitudinal study of schoolchildren detected the emergence of erythromycin resistance in pharyngeal isolates of group A streptococci. The clonal outbreak also affected the wider community.

"We recommend that macrolide antibiotics not be used for the routine treatment of pharyngitis due to group A streptococci until more epidemiological information is available, or unless susceptibility testing is first performed."

NEJM April 18, 2002; 346: 1200-06 Original investigation, first author Judith M Martin, University of Pittsburgh, PA **www.nejm.org**

An editorial in this issue (pp1243-44) comments:

"Too often antibiotics . . . are used to satisfy patients' needs rather than out of clinical necessity." Macrolides have become enormously popular as empirical therapy for upper respiratory infections. A worrisome report recently linked macrolide resistance to invasiveness of GAS. Since GAS are intracellular, macrolide resistant strains may escape the effects, not only of macrolides, but also of beta-lactam antibiotics, which have their greatest effect outside cells.

For erythromycin-susceptible GAS, the minimal inhibitory concentration is less than 0.5 mg/L. In the study the MIC was 4 to 16 mg/L. High level resistance can reach an MIC of over 128 mg/L.

Within a few months, the resistant erythromycin GAS clone spread among schoolchildren and the community.

Physicians must know the prevalence of resistance in their communities.

It is fortunate and remarkable that group A strep over many years has remained susceptible to penicillin. Also that reducing the nation-wide use of macrolides can result in regain of susceptibility.

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Expanding Interventional Cardiology To Community Hospitals

4-13 THROMBOLYTIC THERAPY VS PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR MYOCARDIAL INFARCTION IN PATIENTS PRESENTING TO HOSPITALS WITHOUT ON-SITE CARDIAC SURGERY.

Trials have reported that primary percutaneous coronary intervention (**PPCI**) is superior to thrombolytic therapy in patients with acute ST-elevation myocardial infarctions (**MI**). However, PPCI is often limited to hospitals that have on-site cardiac surgery programs to which most MI patients do not have access.

If it can be applied promptly, PPCI is the better therapy. If it cannot be applied, as now is the case in hospitals without on-site cardiac surgery backup, thrombolysis is the standard of care. Thus, whether a patient receives the better therapy (PPCI or thrombolysis) depends on the hospital to which the patient presents – a matter of chance and geography.

This study was undertaken to determine whether PPCI produces outcomes at 6 months superior to thrombolysis when applied at hospitals without on-site surgery. If PPCI is the better therapy, then access to it might be extended to hospitals to which many patients with acute MI present.

Conclusion: PPCI at hospitals without on-site cardiac surgery was associated with better outcomes than accelerated thrombolysis.

STUDY

1. Entered 11 community hospitals where neither on-site surgery nor PPCI was available.
2. Completed a formal PPCI training program at all hospitals.
3. Randomized 451 acute ST elevation MI patients (mean age = 64) to receive: 1) PPCI, or 2) accelerated tissue plasminogen activator therapy.
4. Stents and glycoprotein IIb/IIIa receptor antagonists were widely available.
5. Main outcome = composite incidence of death, recurrent MI, and stroke at 6 months.

RESULTS

1. Outcomes at 6 months:

	Thrombolysis (%)	PPCI(%)	Absolute difference	NNT
Death	7.6	5.3	2.3	43
Recurrent MI	10.9	4.7	5.2	19
Stroke	3.8	1.8	2.0	50
Composite	20.4	9.9	10.5	10

2. Median length of stay in the PPCI group was 4.5 days vs 6.0 days in the thrombolysis group.
3. No patient in the PPCI group was sent for emergency CABG surgery for a PPCI-related complication.
4. Sixty nine percent of the thrombolysis group was sent to a tertiary hospital for additional care vs 31% of the PPCI group.

DISCUSSION

1. Development of this method of care must include careful, detailed attention to standards, training, logistics, and quality and error management.
2. In other studies, PPCI was superior to thrombolytic therapy only at hospitals with higher procedure volumes.
3. Median door-to-thrombolysis was 46 minutes; median time for door-to-balloon time for PPCI was 105 minutes.
4. These results are applicable only to patients with acute ST elevation MI or left bundle branch block on presenting ECG.
5. “Our study adds to the evidence suggesting that there is no need for on-site cardiac surgery to back

up primary PCI." Abrupt closure or dissection requiring emergency surgery did not occur in the trial. Actually these complications (*in acute ST-elevation MI*) are extremely rare in primary PCI because the infarction-related artery is usually totally occluded from the outset.

6. Coronary perforation did not occur.
7. Access to PPCI capability can be increased by extending PPCI to hospitals without on-site cardiac surgery.
8. The results do not apply to patients with unstable angina or non-diagnostic EKGs, or to elective PCI.

CONCLUSION

After an extensive development program, primary PCI can be performed safely, promptly, and effectively in the community hospital without an elective PCI or cardiac surgery program.

Compared with thrombolysis, the availability of PPCI produced a reduction in deaths, recurrent MI, and stroke.

JAMA April 17,2002; 287: 1943-51 Original investigation by the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT), first author Thomas Aversano, John Hopkins Hospital, Baltimore MD

www.jama.com

An editorial in this issue of JAMA by Christopher P Canon, Harvard Medical School, Boston MA (pp 1987-89) comments:

Many trials have shown clear benefit of primary PCI compared with thrombolysis in the treatment of acute ST-elevation MI. In this study, the absolute reduction in mortality was 5.3% with PPCI vs 7.6% for thrombolysis. (NNT to prevent one death = 43). Intracranial hemorrhage was essentially eliminated.

"Primary PCI is considered a superior strategy both for efficacy and safety."

Interventional cardiology has advanced dramatically with the advent of stents and glycoprotein IIb/IIIa inhibitors. These interventions have made a difference in outcomes in patients with unstable angina and non-ST elevation MI.

Experience makes a difference. Outcomes are better at high volume centers. But even at low volume centers there was an overall advantage for primary PCI.

Door-to-balloon time is significant. Compared to one hour, a more than two hour delay increases mortality by about 50%.

Data suggest that immediate surgical backup may not be required because complications of primary PCI are quite low in the current era of stenting.

"After a careful training program, primary PCI can be performed successfully at community hospitals." The implications are profound. If community hospitals make a strong commitment to establish a comprehensive program, primary PCI will benefit many patients. Policy may need to be modified so that patients with acute ST-elevation MI are transferred to a cardiac center that has primary PCI available 24 hours a day.

Comment:

I believe more of our well-trained younger interventional cardiologists will now branch out into community hospitals.

When PPCI is generally available, primary care clinicians will have to assume more responsibility to diagnose and refer patietns with acute ST-elevation MI. RTJ

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Smoking, as well as alcohol, increases hepatic inflammation

4-14 SMOKING AND ALANINE AMINOTRANSFERASE LEVELS IN HEPATITIS C VIRUS INFECTION

Serum alanine aminotransferase (**ALT**) is the most suitable and useful protein enzyme used in evaluation of hepatocellular damage.

An additive, or possibly synergistic effect exists between alcohol consumption and elevation of ALT levels in HCV patients.

This study asks—does smoking also cause elevation of ALT in patients with HCV?

Conclusion: Smoking and alcohol consumption were independently associated with elevated ALT levels.

STUDY

1. Collected a cross-sectional sample of over 6000 inhabitants in a community with hyperendemic hepatitis B and C virus infections.
2. Assayed levels of ALT, hepatitis B surface antigen, and anti-hepatitis C virus antibody.
3. Determined relation between alcohol intake and cigarette smoking and elevated ALT (defined as over 40 IU/L)

among persons with different hepatitis virus infections.

RESULTS

1. ALT level	Under 40 U/L	Over 40 U/L
Seropositive for hepatitis B	639	80 (11%)
Seropositive for hepatitis C	635	282 (31%)

2. Individuals with elevated ALT were more likely to be male, to drink alcohol, and to smoke.
3. Relation of elevated ALT with smoking and alcohol consumption in those positive for HCV:

Smoking 1 pack or more daily + frequent drinking	71%
Smoking 1 pack or more daily + rare drinking	50%
No smoking; frequent drinking	44%
No smoking; occasional drinking	42%
Smoking less than 1 pack daily and rare drinking	32%
No smoking; rare drinking	25%

5. Compared with abstainers, odds of elevated ALT was 7-times higher for HCV seropositive patients who smoked 1 or more packs of cigarettes daily and frequently drank alcohol.
6. No significant relation of alcohol and smoking with elevated ALT among those seropositive to

hepatitis B surface antigen.

DISCUSSION

1. Consumption of alcohol and cigarettes was associated with elevated ALT levels in patients positive for antibody to hepatitis C, but not among those positive for hepatitis B surface antigen.
2. Seventy five percent of those with antibodies to HCV who did not smoke or drink had normal ALT levels. Cigarettes and alcohol had an additive effect on prevalence of elevated ALT.
3. The prevalence of elevated ALT in heavy smokers who did not drink alcohol was as great as those who drank frequently and did not smoke. “Smoking, like alcohol, is an independent promoting factor for hepatic necroinflammation.”
4. The liver is a target organ for the chemicals in tobacco and alcohol. Abstinence from both would probably slow the progression of hepatitis.
5. Smoking has been shown to influence all aspects of the immune system, including alterations in humoral and cellular immunity.

CONCLUSION

Alcohol and cigarette consumption were independently associated with elevated ALT levels among persons with HCV infection, but not among those infected with hepatitis B.

Patients with HCV infection are strongly advised not to smoke and drink alcohol.

“Smoking, like alcohol, is an independent promoting factor for hepatic necroinflammation.”

The liver is a target organ for the chemicals in tobacco and alcohol. Abstinence from both would probably slow the progression of hepatitis.

Archives Int Med April 8, 2002; 162: 811-15 Original investigation, first author Chong-Shan Wang, A-Lein Community Health Center, Taiwan. **www.archinternmed,com**

Comment:

This was my first encounter of a relation between smoking and liver damage. RTJ

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