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FOR
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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

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 contents of articles in much more detail.

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.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* MARCH 2007

"Patients Generally Received What They Asked For"

3-1 MANAGEMENT OF PATIENT EXPECTATIONS IN PRIMARY CARE PRACTICES

"Patients may approach medical encounters concerned that their expectations will not be met owing to constraints on medical spending, and the intercalation of managed care systems directly in their relationship with the physician." This may be particularly true about expectations for new medications, diagnostic tests, and specialist referrals. Direct-to-consumer marketing and media hype have inflated such expectations.

This study characterized negotiations between patients who had expectations of new medications, tests, or referrals, and their primary care physicians.

Overall, 67% of the expectations were met.

For 73% of unmet expectations, patients stated that the physician gave them a reason for not meeting the expectation. For almost all of these, medical necessity was cited as the reason for providing an alternative choice, or for not granting the request. The great majority of patients reported that the explanation was satisfactory.

Physician post-visit survey:

Physicians reported not meeting 19% of patients' requests.

The most common rationale was that the request was not medically indicated (61%).

The physician would *not* have fulfilled 62 of 138 requests had the patient not asked.

When physicians met the expectations, they sometimes felt "uncomfortable" about doing so. (13% of the time)

Patient satisfaction, trust in physician, and patient empowerment:

90% rated the physician's performance as "excellent" or "very good".

Trust in the physician was generally high.

Over 90% felt involved in the decision-making process. Over 90% reported that their physician "definitely" or "probably" would ask them for help in making the decision between choice of treatments; 81% were often given some control over treatment; 69% were asked to take some responsibility for treatment.

"Unmet expectations did not seem to negatively impact patient's satisfaction with, or trust in, the physician." Alternatives were almost always acceptable to the patient.

"For physicians, learning how to effectively negotiate and respond to patient requests might assist in developing effective paradigms for cost-effective practice that do not negatively affect patient satisfaction."

Conclusion: Patients generally received what they asked for. Physicians often altered their behavior to honor patients' requests.

I enjoyed this article. It portrays the present state of primary care practice.

It is a commentary on the power of the marketing departments of drug companies.

It illustrates the sea change which has led the doctor-patient relationship away from the authoritarian-paternalistic style of previous years, to the now accepted relationship in which patients express their autonomy.

Patients now participate in choosing the type of care they wish to receive, and negotiate with the physician in obtaining it. Patients are taking an active part in their care.

The new paradigm places a requirement for doctors to develop more sensitivity and skill in guiding patients. This will take more time.

It has an upside and a downside:

Including patients in decisions will likely lead to increased responsibility for their own care, to greater compliance, and to increased satisfaction.

The downside is that complying with requests for a different drug (perhaps one recently approved by the FDA and highly advertised), or a more detailed test or examination (perhaps for an expensive laboratory or imaging study), will increase medical costs and dependence on insurance coverage. It may lead patients to unnecessary involvement in the "system" of follow-ups, repeated testing (with the likelihood of more false positive tests), and continuing anxiety. Patients who receive a newly approved drug within several years of approval, run the risk of developing adverse effects which are not uncovered during phase III trials.

I believe physicians should never have to feel "uncomfortable" about filling a patient-request. Such feelings indicate doubts about the appropriateness of the request. If physicians feel the request is not appropriate and will lead to more harm than good, they should deny the request with clear reasons for the denial.

While abstracting this article I thought of a study concerning the doctor-patient relationship. "Effect of Patient Completed Agenda on the Outcome of Consultation" BMJ May 27, 2006; 332: 1238-41 Practical Pointers May 2006 [5-1]. It described a method by which patients record their thoughts and questions about a forthcoming consultation, and express expectations about what they would like the doctor to do. It presents 5 points to help the doctor understand the patient's viewpoint and desires about the consultation. It uncovered a pool of unrecognized patient-needs.

"A Prudent Approach To The Prevention And Treatment Of Diabetes, Heart Disease, And Obesity."

3-2 THE LOW-GLYCEMIC-INDEX DIET: *A Clinical Update*

Recently, the glycemic index (**GI**) has attracted considerable interest with the publication of research linking it to important health outcomes

The GI constitutes an empirical system for classifying carbohydrate-containing foods. It is determined by measuring the 2-hour incremental area-under-the-blood-glucose-curve after consuming a test food (containing 50 g available carbohydrate), relative to that of a control of either white bread or glucose.

A related term, the glycemic load (**GL**)—the average GI multiplied by the carbohydrate amount—takes into account differences in carbohydrate content among foods, meals, and diets.

A high-GI diet elicits a sequence of hormonal events that challenge glucose homeostasis:

1) Shortly after a high-GL meal, blood insulin rises higher than after a low-GL meal with similar nutrients.
2) A high-GL meal inhibits glucagon secretion.
3) The striking increase in the insulin/glucagon ratio constitutes a powerful anabolic stimulus, promoting

uptake of nutrients into the liver, muscle, and fat tissue, and suppressing hepatic glucose output.

4) Within 60 minutes after a high GI meal, blood glucose begins to *fall*, often reaching levels below fasting; release of fatty acids from adipose tissue is suppressed. This stimulates hunger and overeating in the body's attempt to restore concentrations of metabolic fuels to normal.

5) The early postprandial hyperglycemia and hyperinsulinemia and the late postprandial hypoglycemia and counter-regulatory hormone response could adversely affect body composition, and increase risk for diabetes, cardiovascular disease, and cancer.

Most studies report beneficial effects of a low GI-GL diet on health. Virtually no studies have found health benefits with a *high* GI-GL diet.

The low-GI diet, with its focus on carbohydrate *quality* rather than quantity aims to address an underlying physiological cause of diseases arising from excessive swings in post-prandial glycemia. Because this diet does not restrict either fat or carbohydrate, it may be more behaviorally sustainable.

"The clinician should consider a low-GI diet to be a prudent approach to the prevention and treatment of diabetes, heart disease, and obesity."

Would eating 6 small meals a day provide similar benefits? Certainly, we should advise patients to avoid consuming large quantities of food at any meal.

See Practical Punters November 2006 [11-4] for a study reporting that high glycemic load diets increase risk of coronary heart disease.

I do believe that a low glycemic load diet is an important part of the healthy diet. Along with very low saturated fats, low salt, no trans fats, and balanced calorie consumption.

Cardiac-Only Resuscitation By Bystanders Is The Preferable Approach

3-3 CARDIAC ARREST—GUIDELINE CHANGES

Cardiopulmonary resuscitation (**CPR**) is traditionally defined as chest compression and ventilation. The need for chest compression is unquestionable. The need or advisability of intermittent ventilation for out-of-hospital, non-respiratory, primary cardiac arrest has become controversial.

Eliminating the need for mouth-to-mouth ventilation (**M-T-M-V**) will dramatically increase the occurrence of bystander-initiated resuscitation efforts and will increase survival.

An article in this issue of Lancet[1] provides evidence that chest compression without ventilation is preferable.

M-T-M-V is detrimental:

1) It greatly decreases bystander-initiated resuscitation.

2) Survival is better in individuals with cardiac arrest who receive chest compression only, than in those in whom no rescue efforts are started until arrival of emergency personnel.

3) M-T-M-V by single bystanders requires inordinately long interruptions of essential chest compression. Time spent on M-T-M-V takes precious time away from chest compressions that support cerebral and coronary perfusion.

4) M-T-M-V increases intrathoracic pressures, thereby reducing venous return to the chest.

This reduces the already marginal coronary and cerebral blood flow.

A major flaw with the current, and all previous guidelines for cardiac arrest, is that they recommend the same approach of resuscitation for two entirely different clinical conditions: primary cardiac arrest, and respiratory arrest (such as drowning and drug overdose). In the first, arterial blood is well oxygenated; in the latter, the arterial blood is so severely desaturated that it contributes to secondary cardiac arrest. We should continue the old guidelines for assisted ventilations and chest-compressions for respiratory arrest.

The guidelines should promptly be changed to chest compression-alone for witnessed unexpected sudden collapse which is in all probability cardiac arrest.

Conclusion: Cardiac-only resuscitation by bystanders is the preferable approach to resuscitation for adult patients with witnessed out-of-hospital cardiac arrest, especially those with apnea[2], shakable rhythm, or short periods of untreated arrest.

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1 Lancet March 17, 2007; 369: 920-26 "Cardiopulmonary Resuscitation by Bystanders with Chest Compression Only" This was an observational study of over 4000 out-of-hospital cardiac arrests witnessed in Japan:

Overall, any resuscitation attempt was associated with a higher proportion having favorable neurological outcomes than no attempted resuscitation (6.2% vs 2.2%)

In the subset of patients with a shockable rhythm, cardiac-only resuscitation resulted in a favorable outcome in 19.4% vs 11.2% in those receiving M-T-M-V plus chest compression.

Resuscitation started within 4 minutes: favorable outcome in 10.1% for cardiac-only resuscitation vs 5.1% receiving M-T-M-V plus chest compression.

There was no evidence of any benefit from the addition of M-T-M-V in any subgroup.

2 90% of subjects were apneic.

"Lifestyles: First And Foremost Eating Patterns From Preconception On."

3-4 LOW RISK—And the "No More Than 50%" Myth/Dogma

Medical myths/dogmas die hard. New bodies of knowledge for prevention and control of cardiovascular disease have had to disprove and displace myths/dogmas held in the past.

In the1950s:

Atherosclerosis is part of normal aging. Nothing can be done about it.

Cholesterol levels and blood pressure normally rise with age.

Normal blood pressure is 100 plus your age.

Normal cholesterol is as high as 300 mg/dL.

Most high blood pressure is essential hypertension, and of unknown cause.

Treatment of high blood pressure gets at a symptom and not at the underlying disease, and can do more harm than good by lowering blood flow to the brain and heart. Therapeutic nihilism and judicious neglect are right.

All these are now bygone notions, refuted by massive data. But, other longstanding myths/dogmas about the CVD epidemic persist. One long-standing myth/dogma—still bruited about—is contrary to scientific fact. The

dogma persists that the established risk factors for CVD account for no more than 50% of CVD events, and many people who experience CVD events have no risk factors.

In 2005-06, the MrFIT intervention trial expanded the risk factors for atherosclerotic disease to consideration of 5 major factors: total cholesterol, systolic BP; diabetes; smoking; and body mass index.

Based on these factors, low risk was rare. Very few individuals were without all 5 factors:

Only 4% of middle-aged African American women

Only 9% of white American women

Only 3% of African American men

Only 6% of white American men

A key strategic challenge—and opportunity—for medical care and public health is to achieve a progressive increase in the proportion of the population at low risk. "The essence of this advance is progressive steady improvements in lifestyles, first and foremost eating patterns from preconception on."

"The notion that these risk factors account for no more than 50% of CVD events is myth/dogma and is dead wrong."

I abstracted this article as a prelude to the following. The definition of "low risk" of cardiovascular events varies, depending on the number and effect of the individual components. As the number of risk components increases, the number of persons at "low risk" declines. No adults in our society are without some risk. How should we treat them?

Is Drug Therapy Appropriate For Primary Prevention In Individuals At Low-Risk?

3-5 PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

This article raises a number of fundamental questions for the medical and public health communities. Are medical (drug) strategies appropriate for primary prevention in *low-risk individuals*? If preventive strategies are limited to high-risk individuals, the overall population effect on incidence of clinical disease will be relatively minor. A major, yet highly underappreciated problem with the high-risk strategy is that it has a relatively minor effect on overall population incidence of disease. "Low risk" does not mean "no risk". Most of the public burden of disease can be attributed to low-risk individuals with relatively "normal" levels of cholesterol and blood pressure.

Epidemiological data have provided overwhelming evidence that low-risk populations are the source of most clinical disease. This is particularly true for complex, multifactorial diseases such as atherosclerosis, for which continuous variables (including BP and lipids) conspire to increase risk across a wide spectrum of the population. Some have proposed that the low-risk population would be best served by population-based strategies outside the realm of traditional medical testing and therapy. This raises the question: might a medical (drug) strategy be routinely applicable to the low-risk population?

The author defines "low risk" based on the Framingham Risk Score. "Low risk" can be defined many different ways. Definition seems to be in the eye of the beholder.

A tremendous public health burden of clinical atherosclerosis arises from the population of low-risk individuals. Should we apply universal drug therapy to the low risk population?

Consider a non-smoking, physically active 21-year-old with no family history of cardiovascular disease or diabetes, and a BMI of 22, a BP of 115/70, a fasting blood glucose of 70, a LDL-cholesterol of 69, a HDL-cholesterol of 62, and abdominal girth of 30 inches.

Risks are continuous. All persons (no exceptions) over age 50 will be at a higher risk for atherosclerotic disease relative to this 21-year-old. Individuals with levels of risk factors below the arbitrarily set "acceptable" levels will benefit when the risk is lowered toward these baseline levels.

Our classical approach to drug therapy for primary cardiovascular risk prevention is to test first, then treat if the test levels are above the arbitrarily set "acceptable" levels, and then follow-up indefinitely. This limits prevention to a relatively few individuals who are motivated, have access to continuing medical care, and can afford it.

If the risk of disease is universal, should not everyone receive treatment to retard progression as much as possible? We do this now by universal applications of lifestyle interventions. The problem is that lifestyle interventions rarely achieve adequate reductions in risk factors.

A new approach to primary prevention of the epidemic of cardiovascular disease is to prescribe drugs to <u>all</u> persons above a certain age without testing and without follow- up—similar to immunization of the entire population against influenza. We do not determine if individuals are at "high risk" or "low risk" for flu. We immunize everyone.

The purpose is to do much more good than harm to society as a whole, with a low cost. This is, of course, contrary to our classical teaching and practice.

As I was abstracting this article, I kept thinking about the "polypill" (statin drug, aspirin, thiazide diuretic, folic acid, and ACE inhibitor all combined at low dose in one pill). It has been proposed that if all persons over age 50 would take the pill, the prevalence of atherosclerotic disease would decrease dramatically. This universal primary prevention would remove from the population the requirement for screening tests and follow-up. It would represent a sea-change in use of preventive therapy.

A commentary in NEJM January 18, 2007; 356: 212 by Srinath Reddy suggested a pill for general use in India. It consists of aspirin, ACE inhibitor, statin, and beta-blocker. The World Heart Federation announced that it would support the development of such a pill.

A commentary in JAMA July 26, 2006; 296: 377-80 by Bridget M Kuehn, quotes Robert A Rizza, president of the American Diabetes Assn. He suggests a daily generic "polypill" for all patients with diabetes: metformin, aspirin, statin, and an ACE inhibitor. (This "polypill" would also be beneficial for preventive therapy for non-diabetic patients with impaired fasting glucose 110 to 125 mg/dL and impaired glucose tolerance 140 to 199 mg/dl 2 hours after an oral glucose load..)

Any such drug combinations must be at very low cost and be associated with very low risk of adverse effects.

I believe it likely that increasingly more individuals will be taking primary preventive drug therapy in the future.

Does Calorie Restriction Have Benefits Above And Beyond The Effect In Lowering Incidence Of Chronic Diseases?

3-6 AGING, ADIPOSITY AND CALORIE RESTRICTION

Maximum life span, defined as the average life span of the longest-lived decile of a cohort, is often used as a standard for evaluating the aging process.

Life expectancy, defined as the age at which 50% of the population survives after birth, has markedly increased in most developed countries. (From about 45 years in the early 1900s to about 75 years in men and 80 years in women today.) This increase is due primarily to improved sanitation, better hygiene, reduced infant mortality, development of antibiotics and vaccines, and better health care.

Recently, there has been increasing interest in the potential therapeutic use of calorie restriction to obtain optimal health and increase life span in humans. Calorie restriction, defined as a reduction in calorie intake below usual ad libitum intake, (while maintaining adequate nutrition) has been shown to increase maximum life span in many animal species. In laboratory rodents, calorie restriction increases longevity by preventing or delaying onset of chronic diseases (diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, respiratory diseases, and cancer).

The reduction in chronic diseases does not completely explain the increase in lifespan, and the preservation of function at more youthful levels, which occurs in the calorie-restricted rodents. About 1/3 of such rodents die without evidence of organ pathology. “These data support the notion that the common link between aging and chronic disease is not inevitable, and that it is possible to live longer without experiencing a cumulative increase in serious morbidity and disability.”

Data suggest that the effects of calorie restriction on maximum life span are not simply a result of leanness induced by such restriction. Maximum life span does not increase in male rats that maintain a low body fat mass by performing regular exercise. It does increase in sedentary male rats that are food restricted to keep their body weights the same as those of the exercisers.

Conclusion:

1) Calorie restriction is an important determinant of health.
2) Excessive energy intake is a form of malnutrition that leads to unfavorable body composition, organ dysfunction, and premature mortality.
3) The precise caloric intake needed for optimal health and function likely varies for each individual depending on genetic background, age, energy expenditure, and diet composition.
4) The optimal calorie intake needed to slow the aging process is not known. The available data support the notion that calorie restriction in humans leads to many of the same metabolic adaptations and reductions in multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife.
5) Even if calorie restriction does not prolong maximum life span, it could increase life expectancy and the quality of life by reducing the burden of chronic diseases.

I enjoyed this article. I abstracted it in detail because it presents one of the most important health considerations in a somewhat different way. It suggests that properly restricting quantity while maintaining quality of food intake is essential for maintaining health. And that properly restricting quantity per se has a beneficial effect in addition to its effects in controlling body mass index and incidence of chronic disease.

"Calorie restriction" may be a misnomer. "Optimum calorie intake" may be a better term. It is obvious that Americans eat too much. We have the habit of eating to the point of satiety (where ingestion of more food would cause discomfort). A better approach is to save room for dessert, and then skip the dessert.

Ad libitum caloric intake usually means excessive intake, not only intake of the wrong kinds of food, but also the quantity. "Eat yourself to death, Joe". "If you keep on overloading your truck, it will break down sooner." "Eat less than you would like to". If only it were not so difficult long-term.

Animals on an ad libitum diet also eat too much. "Fat cat."

Immunity Wanes With Time. A Second (Booster) Shot Is Recommended.

3-7 LOSS OF VACCINE-INDUCED IMMUNITY TO VARICELLA OVER TIME

This study assessed whether vaccine-induced immunity wanes over time. It examined 10 years (1995-2004) of active surveillance data in a population of 350 000 subjects in a well-defined area in California to determine the incidence and severity of breakthrough varicella. (Onset of rash 43 days or more after vaccination.)

Over 11 000 subjects were reported to have varicella during the surveillance period. Of these, 10% had breakthrough disease. (Ie, had received the vaccine, but had nevertheless experienced clinical chicken pox.)

The annual rate of breakthrough increased from the time since vaccination:

1.6 cases per 1000 person-years within 1 year after vaccination.

9.0 cases per 1000 person-years at 5 years.

58 cases per 1000 person-years at 9 years.

Severity of disease increased with age and as time from vaccination lengthened: children between ages 8 and 12 who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than those who had been vaccinated less than 5 years previously.

Vaccinated children with moderate-to-severe disease were twice as likely to have complications such as pneumonia, ataxia, and skin superinfection as those with mild disease.

"These data suggest a steady decline over a period of years in disease protection afforded by a single dose of vaccine in the context of diminished circulation of wild-type virus."

In June 2006, the Advisory Committee on Immunization Practices recommended that children between ages 4 to 6 receive a second dose of vaccine. The committee also recommended that a second catch-up dose be given to children, adolescents, *and adults* who previously had received one dose.

Conclusion: A second dose of varicella vaccine is now recommended for all children. This could improve protection from both primary vaccine failure and waning of vaccine-induced immunity.

Practical Pointers does not usually abstract articles of interest to the pediatric population.

This article applies to adults for several reasons:

1) Young adults who have not had clinical vaccinia in childhood or adolescence may be subject to the infection regardless of past immunization against varicella. I believe it will take time for this concept to be applied to adults who have received the vaccine. If you were age 20, had received the vaccine as a child, and never had clinical disease, would you be anxious to receive a booster?

2) As the population ages, younger adults who have received the vaccine in childhood may consider themselves to have been protected and never to have had chicken pox, and thus believe they are not a candidate for the herpes zoster vaccine. Past subclinical disease, or forgotten disease may indeed make them subject to shingles as they age.

Recommended For Virtually All Persons above Age 60

3-8 VARICELLA-ZOSTER VACCINE FOR THE PREVENTION OF HERPES ZOSTER

Herpes zoster (**HZ**; "shingles") develops in about 30% of people over a lifetime. Up to 1 million cases occur in the US annually. Risk increases with age, beginning at age 50, when cell-mediated immunity begins to decline. HZ is 10 times as likely in people over age 60 as in younger people. One or more episodes of HZ will develop in up to half of people over age 85. HZ is more common in immunocompromised people.

Post herpetic neuralgia is challenging and debilitating. It can last for weeks, months, and even years. More than 40% of people over age 60 who have had HZ have PHN.

As immunity wanes in older adults, a higher dose of vaccine (as compared with the varicella vaccine given to children) is required to produce immunity. The new HZ vaccine (*Zostavax*; Merck) contains about 14 times the plaque-forming units per dose as the attenuated live chickenpox vaccine given to children. The HZ vaccine increases cell-mediated immunity to a new set point above the "immunological threshold" below which a person is at risk for HZ.

A large clinical study evaluated efficacy of the HZ vaccine in over 38 000 persons over age 60 followed for 3 years. The incidence of HZ was 51% lower in those receiving the vaccine vs placebo. The incidence of PHN was 67% lower The median duration of pain was shorter (21 days vs 24 days), and the severity of pain was lower.

About 17 people would need to be vaccinated to prevent one case of HZ, and about 31 would be needed to treat to prevent one case of PHN. (Estimated costs = $3,300 and $ 6,400.)

Adverse effects were limited to local reactions at the site of the inoculation.

Virtually all persons now age 60 and above have had clinical or subclinical chickenpox. It is not necessary to determine whether there is a history of chickenpox before giving routine HZ vaccine.

Efficacy of the vaccine for people who have had a previous episode of HZ is unknown. The Advisory Committee on Immunization Practices recommends that this group of patients should receive the vaccine.

Administration is advised for all persons over age 60, "unless there is a contraindication".

If vaccine is in short supply, I would postpone administration to patients who have had HZ.

I would not hesitate to administer the vaccine for patients age 50-59 should they request it.

"Overtreatment Is Often The Major Danger For These Patients."

3-9 LOW BACK PAIN: Clinical Update

This article summarizes the basic principles of management and outcome assessment for back pain on which evidence-based daily practice can be based. I included only the points regarding acute back pain (< 6 weeks duration) because primary care clinicians will deal especially with this. See the original article for comments on sub-acute and chronic back pain.

Eleven clinical points. See the full abstract

"The Burden Of Hepatitis E Is Grossly Underestimated." A New Vaccine May Be Effective

3-10 SAFETY AND EFFICACY OF A RECOMBINANT HEPATITIS E VACCINE: A Phase II Trial

Large outbreaks of hepatitis E were first recognized in the early 1980s. It is endemic in some areas of the world, transmitted by the fecal-oral route. (The virus has been found in contaminated waste water and sewage.) Person-to-person transmission is uncommon. Hepatitis E is typically a self-limited acute hepatitis, usually lasting 1 to 4 weeks. It does not progress to chronic disease.

Hepatitis E virus (**HEV**) infection is a major public health problem in many developing countries. Hepatitis E occurs sporadically and in epidemics, and causes substantial rates of death and complications, especially in pregnant women. On the basis of data from serological tests, an estimated one third of the world's population has been infected with the HEV. In India, the lifetime prevalence is more than 60%.

Clinically, the infection is indistinguishable from other types of acute viral hepatitis. The severity of the disease increases with age. The overall fatality rate is estimated to be as high as 3%. Pregnant women who develop the infection have the highest risk of acute hepatic failure. Their case fatality rate is high, as are rates of abortion.

A new recombinant protein vaccine (**rpHEV** vaccine) has been developed.

This study entered 2000 healthy Nepalese Army personnel (almost all male; mean age 25). All were considered susceptible to hepatitis E on the basis of low titers of antibody to HEV at baseline.

Randomized to 1) three doses of vaccine at 0, 1 and 6 months, or 2) three doses of placebo.

Identified acute hepatitis by active surveillance (including hospital). The hepatitis was defined clinically and confirmed by presence of HEV RNA by polymerase-chain-reaction, or by a major rise in anti-HEV antibody.

After 3 doses, hepatitis E developed in 69 subjects—66 in the placebo group and 3 in the vaccine group. Vaccine efficacy was 95%.

The virus may infect travelers to endemic regions. The vaccine may by useful for travelers.

Is there a hepatitis F?

ABSTRACTS MARCH 2007

"Patients Generally Received What They Asked For"

3-1 MANAGEMENT OF PATIENT EXPECTATIONS IN PRIMARY CARE PRACTICES

"Patients may approach medical encounters concerned that their expectations will not be met owing to constraints on medical spending, and the intercalation of managed care systems directly in their relationship with the physician." This may be particularly true about expectations for new medications, diagnostic tests, and specialist referrals. Direct-to-consumer marketing and media hype have inflated such expectations.

When patients bring expectations that cannot be met, or request services that physicians perceive to be medically unnecessary, tension may arise and may challenge patient-physician communication.

When patients voice requests, are physicians likely to honor the requests?

This study characterized negotiations between primary care physicians and patients who had expectations of new medications, tests, or referrals.

Conclusion: Patients generally received what they asked for. Physicians often altered their behavior to honor patients' requests.

STUDY

1. Observational study included 211 patients who voiced specific expectations about a forthcoming consultation, and their consultations with 55 primary care physicians in order to characterize negotiations between physician and patient.
2. Before the consultation, assessed patients' expectations from the visit. Patients were eligible for the study if they endorsed a desire for a new medication, test, or referral.
3. Audiotaped the subsequent clinical encounter to determine: 1) how the expectations were communicated, 2) the physician response, 3) physician rationale for expectations not met, and 4) patient reaction to expectations that were not met.

RESULTS

1. The majority of patients reported a single expectation. A few reported 2 and 3 expectations.
2. Summary of communications by type of previsit expectation: (% of 256 expectations)

	Patient directly requested[a]	Patient mentioned symptoms[b]	Physician initiated[c]
Medication	31%	38%	21%
Tests	42	21	33
Referral	36	38	22
Total	41	30	27

a Patient made the request directly to the physician.

b Patient did not make the request, instead mentioned symptoms related to the expectation.

c Physician initiated discussion about the expectation before any mention by the patient

(In a few cases, the expectations was not mentioned.)

3. Overall, 67% of the expectations were met.
4. Physicians suggested an alternative to the original expectation in 22%. (A different medication; a medication instead of a requested referral.)
5. Of the expectations, 5% were postponed until another visit, or a later time.
6. For 73% of unmet expectations, patients stated that the physician gave them a reason for not meeting the expectation. For almost all of these, medical necessity was cited as the reason for providing an alternative choice, or for not granting the request. The great majority of patients reported that the explanation was satisfactory.
7. Patients openly questioned the physician's decision 8% of the time. A few patients still felt they wanted their pre-visit expectations met.
8. Rationales citing barriers of availability and cost were rare. No physician explicitly cited barriers related to insurance coverage.
9. A higher proportion of expectations were met when a patient made a direct request (78%), or when the physician initiated the discussion about that expectation (76%), compared with expectations in which the patient expressed symptoms as the only means of communication (50%).
10. Expectations for medications and tests were more frequently met than expectations for referral.
11. Physician post-visit survey:
    Physicians reported not meeting 19% of patients' requests.
    The most common rationale was that the request was not medically indicated (61%).
    The physician would *not* have fulfilled 62 of 138 requests had the patient not asked.
    When physicians met the expectations, they sometimes felt "uncomfortable" about doing so. (13% of the time)
12. Patient satisfaction, trust in physician, and patient empowerment:
    90% rated the physician's performance as "excellent" or "very good".
    Trust in the physician was generally high.
    Over 90% felt involved in the decision-making process. Over 90% reported that their physician "definitely" or "probably" would ask the patient for help in making the decision between choice of treatments; 81% were often given some control over treatment; 69% were asked to take some responsibility for treatment.

DISCUSSION

1. Patients' expectations were largely met. Physicians most often provided the services that patients desired.
2. Patients who directly voiced requests were most likely to get what they wanted. When patients expressed their expectations through a nonspecific discussion of symptoms, their expectations were met less frequently.
3. Physicians reported that they would *not* have fulfilled nearly half of the request had the patient not asked. Patients' pressure to have their expectations fulfilled led some physicians to meet the requests despite feeling "uncomfortable" about it.
4. Unmet expectations were satisfactorily explained. For expectations not met, physicians frequently gave the

patient a reason for not meting the request. And 95% of the time, patients reported that the reason was satisfactory. “Unmet expectations did not seem to negatively impact patient’s satisfaction with, or trust in, the physician.”

5. Alternatives were almost always acceptable to the patient.
6. “For physicians, learning how to effectively negotiate and respond to patient requests might assist in developing effective paradigms for cost-effective practice that do not negatively affect patient satisfaction.”

CONCLUSION

Pre-visit expectations for medications, tests, or referrals were discussed at the visit. Physicians met or offered alternatives for nearly 90%. Patients generally received what they asked for, and altered physician behavior nearly half of the time.

Archives Intern Med March 12, 2007; 167: 445-52 Original investigation, first author Sheri A Keitz, Durham Veterans Affairs Medical Center and Duke University Medical Center, Durham NC.

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“Aims To Address An Underlying Physiological Cause Of Diseases”

3-2 THE LOW-GLYCEMIC-INDEX DIET: *A Clinical Update*

For the past half century, the US government and many health agencies have advocated a low-fat diet for the prevention and treatment of obesity, diabetes, and heart disease. “The rationale seemed obvious: fat is energy dense and tasty, making this nutrient easily overconsumed; and saturated fat adversely affects LDL-cholesterol and insulin resistance.” Popular books argued that if you do not want fat on your body or in your coronary arteries, do not eat it, and instead fill up on carbohydrate.

The effects of total fat on bodyweight and health have been called into question in recent years. During the past decade, the pendulum swung far in the other direction with the very-low-carbohydrate (higher fat) diet. Clinical trials reported significant short-term weight loss on diets containing up to 60% energy from fat. However, results from longer-term studies indicated substantial weight regain after 6 months. The popularity of these diets is declining.

Recently, the glycemic index (**GI**) has attracted considerable interest with the publication of research linking it to important health outcomes. Best selling diet books have advocated consumption of a low-GI diet. Is this yet another fad?

The GI constitutes an empirical system for classifying carbohydrate-containing foods. It is determined by measuring the 2-hour incremental area-under-the-blood-glucose-curve after consuming a test food (containing 50 g available carbohydrate), relative to that of a control of either white bread or glucose.

Most varieties of bread, rice, breakfast cereals, and potatoes have a high GI because processing methods allow the starch to become fully hydrated, and therefore rapidly hydrolyzed into glucose in the digestive tract. By

contrast, non-starchy vegetables, legumes, nuts, and fruits have a low GI. Whole kernel and grain products such as stoneground breads, steelcut oats,[2] and pasta tend to have a moderate GI.

A related term, the glycemic load (**GL**)—the average GI multiplied by the carbohydrate amount—takes into account differences in carbohydrate content among foods, meals, and diets.

Before the modern era, the availability of high-GI foods was limited. Before the agricultural revolution, humans did not often consume grain products and concentrated sugars. With domestication of cereal grains, the GI of diets has increased. Prevailing diets have become even higher in GI and GL because of processing of carbohydrates and increases in carbohydrate consumption.

A high-GI diet elicits a sequence of hormonal events that challenge glucose homeostasis:

1) Shortly after a high-GL meal, blood insulin rises higher than after a low-GL meal with similar nutrients.
2) A high-GL meal inhibits glucagon secretion.
3) The striking increase in the insulin/glucagon ratio constitutes a powerful anabolic stimulus, promoting uptake of nutrients into the liver, muscle and fat tissue, and suppressing hepatic glucose output.
4) Within 60 minutes after a high GI meal, blood glucose begins to *fall*, often reaching levels below fasting, and release of fatty acids from adipose tissue is suppressed. This stimulates hunger and overeating in the body's attempt to restore concentrations of metabolic fuels to normal.
5) The early postprandial hyperglycemia and hyperinsulinemia and the late postprandial hypoglycemia and counter-regulatory hormone response could adversely affect body composition, and increase risk for diabetes, cardiovascular disease, and cancer.

Several hundred studies have been published addressing this concept. Most studies report beneficial effects of a low GI-GL diet on health. A significant minority report no health effects. Virtually no studies have found health benefits with a *high* GI-GL diet.

Further evidence of the benefits of delaying carbohydrate absorption comes from studies of alpha-glucosidase inhibitors[1] in the prevention of diabetes and heart disease.

The Food and Agriculture organization of the WHO advocates consumption of a low-GI diet. No government agency in the USA does so.

The principles of a low-GI diet can be summarized (Figure on page 891 presents a low-GI food pyramid):

Top of pyramid: Very limited cookies, pies, pretzels, potatoes, white bread, and cereals.

Middle rows: pasta, grain bread, oils, trans-fat free fats, nuts, milk, fish, eggs.

Bottom row: Increased consumption of vegetables, legumes, and fruits and minimally processed grains. (High in fiber and low in energy density.)

Diets that restrict one major nutrient, either fat or carbohydrate, have produced poor long-term results. Low fat and very-low carbohydrate diets can adversely affect some risk factors for cardiovascular disease.

The low-GI diet, with its focus on carbohydrate *quality* rather than quantity aims to address an underlying physiological cause of diseases arising from excessive swings in post-prandial glycemia. Because this diet does not restrict either fat or carbohydrate, it may be more behaviorally sustainable.

The clinical relevance of the low GI diet debate centers on 3 points:

1) Are the data consistent?

2) How does glycemic response change when several foods are eaten in combination?

3) Is a low-GI diet practical?

Although the data are variable, most published studies report beneficial effects of lowering GI, virtually no study suggests potential of harm.

"The clinician should consider a low-GI diet to be a prudent approach to the prevention and treatment of diabetes, heart disease, and obesity."

Lancet, March 17, 2007; 369: 890-92 "Comment" by David S Ludwig, Children's Hospital, Boston. Mass.

1 Eg, Acarbose (*Precose*; Bayer) An inhibitor of glucosidase. Delays digestion of ingested carbohydrates, resulting in lower blood glucose levels.

2 Steel cut oats ("Irish oatmeal") has a coarse texture. It is derived from the whole oat groates (inner portion of the oat kernel) cut into smaller pieces. It takes longer to cook than our rolled oats ("Instant Oatmeal").

Cardiac-Only Resuscitation By Bystanders Is The Preferable Approach

3-3 CARDIAC ARREST—GUIDELINE CHANGES

Cardiopulmonary resuscitation (**CPR**) is traditionally defined as chest compression and ventilation. The need for chest compression is unquestionable. The need or advisability of intermittent ventilation for out-of-hospital, non-respiratory, primary cardiac arrest has become controversial.

Eliminating the need for mouth-to-mouth ventilation (**M-T-M-V**) will dramatically increase the occurrence of bystander-initiated resuscitation efforts, and will increase survival.

An article in this issue of Lancet[1] provides evidence that chest compression without ventilation is preferable.

M-T-M-V is detrimental for several reasons:

1) It greatly decreases bystander-initiated resuscitation.

2) Survival is better in individuals with cardiac arrest who receive chest compression *only* than in those in whom no rescue efforts are started until arrival of emergency personnel.

3) M-T-M-V by single bystanders requires inordinately long interruptions of essential chest compression. Time spent on M-T-M-V takes precious time away from chest compressions that support cerebral and coronary perfusion.

4) M-T-M-V increases intrathoracic pressures, thereby reducing venous return to the chest. This reduces the already marginal coronary and cerebral blood flow.

5) With sudden cardiac arrest, ventilations are initially neither necessary nor logical. With the onset

of ventricular-fibrillation-induced arrest, the pulmonary veins, the left heart, and the entire arterial system are filled with oxygenated blood. The recommended ventilations do not increase arterial saturation—they only further delay the onset of critical chest compression.

6) M-T-M-V is not necessary in a significant number of victims of witnessed cardiac arrest because they initially gasp, and if chest compressions are started early and continued, many patients will continue to gasp and thereby provide physiological ventilation which facilitates venous return to the heart.

7) Survival from experimentally induced cardiac arrest is better with higher coronary perfusion pressures produced by forceful chest compression.

8) In animals with cardiac arrest, survival is dramatically better with chest-compression-only resuscitation than with ventilations plus chest compression when chest compression is interrupted for a realistic 16 seconds to provide two mouth-to-mouth breaths between each set of 15 chest compressions.

A major flaw with the current and all previous guidelines for cardiac arrest is that they recommend the same approach of resuscitation for two entirely different clinical conditions: primary cardiac arrest, and respiratory arrest (such as drowning and drug overdose). In the first, arterial blood is well oxygenated; in the latter, the arterial blood is so severely desaturated that it contributes to secondary cardiac arrest. We should continue the old guidelines for assisted ventilations and chest-compressions for respiratory arrest. But the guidelines should promptly be changed to chest compression-alone for witnessed unexpected sudden collapse which is in all probability cardiac arrest.

Lancet March 17, 2007; 369: 882-84 "Comment" by Gordon A Ewy, University of Arizona College of Medicine, Tucson.

1 Lancet March 17, 2007; 369: 920-26 "Cardiopulmonary Resuscitation by Bystanders with Chest Compression Only" by the SOS-KANTO Study Group, reported by Ken Nagao, Surugadai Nihon University Hospital, Tokyo, Japan

This large, multicenter, prospective observational study included 4241 out-of-hospital cardiac arrests witnessed by a bystander.

2917 no attempt at resuscitation (72%)

1324 bystander resuscitation:

712 with conventional CPR (18%)

439 cardiac-only resuscitation. (11%)

The primary endpoint was a favorable neurological outcome at one month.

Results:

Overall, any resuscitation attempt was associated with a higher proportion having favorable neurological outcomes than no attempted resuscitation (6.2% vs 2.2%)

In the subset of patients with a shockable rhythm, cardiac-only resuscitation resulted in a favorable outcome in 19.4% vs 11.2% in those receiving M-T-M-V plus chest compression.

Resuscitation started within 4 minutes: favorable outcome in 10.1% for cardiac-only resuscitation vs 5.1% receiving M-T-M-V plus chest compression.

There was no evidence of any benefit from the addition of M-T-M-V in any subgroup.

Conclusion: Cardiac-only resuscitation by bystanders is the preferable approach in adults with witnessed out-of-hospital cardiac arrest, especially those with apnea, shockable rhythm, or short periods of untreated arrest.

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"The Notion That These Risk Factors Account For No More Than 50% Of CVD Events Is Dead Wrong."

3-4 LOW RISK—And the "No More Than 50%" Myth/Dogma

Medical myths/dogmas die hard. New bodies of knowledge for prevention and control of cardiovascular disease have had to disprove and displace myths/dogmas held in the past.

The 1950s:

Atherosclerosis is part of normal aging. Nothing can be done about it.

Cholesterol levels and blood pressure normally rise with age.

Normal blood pressure is 100 plus your age.

Normal cholesterol is as high as 300 mg/dL.[1]

Most high blood pressure is essential hypertension, and of unknown cause.

Treatment of high blood pressure gets at a symptom and not at the underlying disease, and can do more harm than good by lowering blood flow to the brain and heart. Therapeutic nihilism and judicious neglect are right.

Later:

Systolic blood pressure of 140-159 and diastolic 90-104 is mild hypertension, modest in its impact on cardiovascular disease (**CVD**), so pay no attention to it.

Cholesterol is associated with CVD risks only for persons with levels of 240 to 260 and higher.

All these are now bygone notions, refuted by massive data. Other longstanding myths/dogmas about the CVD epidemic persist. One long-standing myth/dogma—still bruited about—is contrary to scientific fact. The dogma persists that the established risk factors for CVD account for no more than 50% of CVD events, and many people who experience CVD events have no risk factors.

In 1992, the Multiple Risk Factor Intervention Trial identified a subgroup of men (less than 10% of the cohort of over 361 000) with favorable baseline levels of 3 readily measured major CVD risk factors: 1) serum cholesterol, 2) blood pressure, and 3) smoking status. (Men with a history of diabetes and myocardial infarction were excluded.) In this low-risk sub-group, fatal CVD was rare.

In 2005-06, expanded findings were reported. Criteria for low risk were updated to include favorable levels of 5 readily measured major risk factors: 1) serum cholesterol < 200 mg/dL (without the use of anti-cholesterolemic drugs), 2) systolic BP less than 120/80 (without use of anti-hypertension drugs), 3) no smoking, 4) no diabetes, and 5) normal body weight (BMI less than 25).

The addition of overweight and obesity to the basic risk factors was welcome because:

Obesity is a major risk factor for type 2 diabetes.

It promotes dyslipidemia, pre-hypertension, and hypertension.

It is related to decades-long CVD risks independent of (and in addition to) other risk factors.

The favorable impact of low risk on CVD prevails for the young—as well as the middle aged—and for women and men. For the few people with favorable levels of all 5 major risk factors the likelihood of a CVD event is small. Most individuals who do experience clinical CVD manifest at least one—often 2 or more—of the 5 major risk factors. “The notion that these risk factors account for no more than 50% of CVD events is myth/dogma and is dead wrong.”

The large favorable impact of “low risk” (so defined) persists for decades, from young adulthood and middle age into older age (with over 30 years of cohort follow-up). This favorable impact of low risk prevails across ethnic groups (African Americans, Hispanic Americans, non-Hispanic white Americans).

Low risk virtually abolishes the generally prevailing higher CVD and all-cause mortality rates of the lower socio-economic strata. Socioeconomic and ethnic differences in CVD risk and longevity have their roots in life-styles, not in genome differences.

Low risk confers not only enhanced longevity, but also, in older age, less likelihood of morbidity, better health related quality of life, and lower costs of medical care.

Based on the 2005-06 criteria, low risk was rare. Very few individuals were without all 5 risk factors:

Only 4% of middle-aged African American women are at low risk.

Only 9% of white American women.

Only 3% of African American men.

Only 6% of white American men.

“With most CVD accounted for by the established major risk factors, (adverse lifestyles, particularly adverse eating patterns, smoking, and sedentary habits), and lifestyle-dependent traits (dyslipidemia, prehypertension/hypertension, overweight/obesity, and diabetes), it is unlikely that the search for new risk factors can find much.” **2**

A key strategic challenge—and opportunity—for medical care and public health is to achieve a progressive increase in the proportion of the population at low risk. “The essence of this advance is steady improvements in lifestyles, first and foremost eating patterns from preconception on.”

Archives Intern Med March 26, 2007; 167: 537-39 Editorial by Jeremiah Stamler, Feinberg School of Medicine, Northwestern University, Chicago, IL

This editorial commented and expanded on a study in this issue of Archives by the Atherosclerosis Risk in Communities Study, “Absolute and Attributable Risks of Cardiovascular Disease Incidence in Relation to Optimal and Borderline Risk Factors”, first author Atsushi Hozawa, University of Minnesota, Minneapolis.

The study considered only 4 risk factors in middle aged subjects (blood pressure, diabetes, cholesterol, and smoking). Based on these risk factors, only 4% to 8% of a cohort of over 14 000 (mean age 54) were considered to be at “low risk”. Over 13 years, mortality and incidence of CVD were much lower in the optimal-risk group.

1 This was determined by the cholesterol levels of a large number of "healthy persons". 97.5% of these individuals had levels of 300 and lower. At that time, it was not considered that these individuals were not really "healthy". Many were at risk for atherosclerotic events.

2 I believe we can sharpen and expand the list of easily determined risk factors Adding to the list will further reduce the numbers of individuals considered to be at low risk. See the following abstract.

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Is Drug Therapy Appropriate For Primary Prevention In Individuals At Low-Risk?

3-5 PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Asymptomatic atherosclerosis poses substantial risks. Among 50-year-old adults enrolled in the Framingham Hart Study, the lifetime risk for developing *symptomatic* disease was 52% in men and 39% in women. For many, the first clinical manifestation is a potentially catastrophic event.

Despite numerous advances, the public disease burden of atherosclerotic disease remains high. Primary prevention (preventing or delaying clinical disease among asymptomatic individuals) remains an issue of major public health interest.

At present, guidelines for asymptomatic patients focus on assessment of individual risk, lifestyle interventions, and when appropriate, drug therapy (anti-hypertension lipid-control drugs, and aspirin).

One recommended approach for primary prevention starts with estimating risk of clinical events using the Framingham Risk Score (FRS)[1] For individuals with an estimated risk of having a cardiovascular event greater than 20% over 10 years, aggressive interventions (drugs) are appropriate. For those with 10% to 20% risk, clinicians should consider testing for high-risk, asymptomatic atherosclerosis with high-sensitivity C-reactive protein, stress-testing, electronbeam computed tomography, measurement of ankle-brachial index, &/or ultrasound measurement of carotid intima-media thickness (**CIMT**). Patients deemed to be at low risk should receive conservative management, focusing on lifestyle interventions.

A study reported in this issue of JAMA[2] poses a serious challenge to this risk-based paradigm. Investigators screened over 5700 asymptomatic adults with carotid ultrasound. All subjects were considered at low risk of atherosclerotic disease (FRS < 10; or having age as the only risk factor [mean age = 57]). Ultrasound identified 984 subjects with substantially increased CIMT. These subjects were randomized to 1) 40 mg rosuvastatin (*Crestor*: AstraZeneca) daily or placebo for 2 years. The investigators hoped to demonstrate a reduction in the CMIT in the treated group. This was not demonstrated. The drug group did achieve stability of the CMIT; in the placebo group CMIT increased. This evidence is not sufficient to conclude that retarding progression of CMIT in low risk individuals will translate into a reduction in clinical events.

"This is a radically different approach to primary prevention than what is recommended by current guidelines."

This report raises a number of fundamental questions for the medical and public health communities. Are medical (drug) strategies appropriate for primary prevention in *low-risk individuals*? If preventive strategies are limited to high-risk individuals, the overall population effect on incidence of clinical disease will be relatively minor. A major, yet highly underappreciated problem with the high-risk strategy is that it has a relatively minor

effect on overall population incidence of disease. "Low risk" does not mean "no risk". Most of the public burden of disease can be attributed to low-risk individuals with relatively "normal" levels of cholesterol and blood pressure.

Epidemiological data have provided overwhelming evidence that low-risk populations are the source of most clinical disease. This is particularly true for complex, multifactorial diseases such as atherosclerosis, for which continuous variables (including BP and lipids) conspire to increase risk across a wide spectrum of the population. Some have proposed that the low-risk population would be best served by population-based strategies outside the realm of traditional medical testing and therapy.[3] This raises the question: might a medical (drug) strategy be applicable to the low-risk population?

JAMA March 28,, 2007; 297: 1376-78 Editorial by Michael S Laurer, Cleveland Clinic, Cleveland Ohio.

The rosuvastatin study provided another risk factor (carotid-intima-media-thickness). It limited preventive therapy to patients who were otherwise considered at low risk for atherosclerotic disease. I believe the manufacturers of rosuvastatin were hoping to demonstrate a reversal of the atherosclerotic process. The study demonstrated only that the process may have been slowed. No clinical benefit was demonstrated. For this intervention the cost would be extremely high (over $3000 for 2 years). Adverse effects of the high dose used (40 mg), if applied universally, would be related to unacceptable numbers of adverse drug effects.

1 The FRS consists of 7 risk factors: age, sex, total cholesterol, HDL-cholesterol, smoking, systolic BP, and history of hypertension. Go to GOOGLE (Framingham Risk Score) to access a risk assessment tool from which individuals may calculate their 10-year risk of developing symptomatic cardiovascular disease.

2 "Effect of Rosuvastatin on Progression of Carotid-Intima-Media Thickness in Low-Risk Individuals with Subclinical Atherosclerosis" JAMA March 28, 2007; 297: 134 4-53, first author John R Crouse, Wake Forest University School of Medicine, Winston-Salem NC.

3 "A Strategy to Reduce Cardiovascular Disease by More than 80%" BMJ June 28, 2003; 326 : 1419-24 by N J Wald and M R Law. The daily "polypill" was aimed at reducing LDL-cholesterol, BP, platelet adhesiveness, and homocysteine. It consists of 6 low-dose generic drugs: a statin, thiazide, beta-blocker, ACE inhibitor, folic acid, and aspirin.

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Does Calorie Restriction Have Benefits Above And Beyond The Effect In Lowering Incidence Of Chronic Diseases?

3-6 AGING, ADIPOSITY AND CALORIE RESTRICTION

Aging results in a progressive decline in multiple organ systems. Aging affects reproductive, metabolic, physical, and cognitive function, and, eventually, survival. *Maximum life span*, defined as the average life span of the longest-lived decile of a cohort, is often used as a standard for evaluating the aging process. However, valid biomarkers of physiological aging have not been identified. The oldest documented person in recent history,

Jeanne Louise Calment, died in 1997 at age 122 years. This represents the near-maximum possible human life span.

It is unlikely that the maximum life span *potential* has changed much in recent history. But *life expectancy*, defined as the age at which 50% of the population survives after birth, has markedly increased in most developed countries—from about 45 years in the early 1900s to about 75 years in men and 80 years in women today. This increase is due primarily to improved sanitation, better hygiene, reduced infant mortality, development of antibiotics and vaccines, and better health care.

Recently, there has been increasing interest in the potential therapeutic use of calorie restriction to obtain optimal health and to increase life span in humans. Calorie restriction (defined as a reduction in calorie intake below usual ad libitum intake while maintaining adequate nutrition) has been shown to increase maximum life span in many animal species.

This systematic review assessed the factors involved in the aging process, and the effect of calorie restriction (with adequate nutritional intake) on disease risk, and life expectancy.

Aging can be conceptualized as the result of 2 interactive and overlapping processes:

1) *Primary* aging (intrinsic senescence) is the progressive deterioration in physical structure and biological function that occurs with advancing age alone, independent of other factors. (Eg, decreased bone mineral density, decreased muscle mass, and accumulation of abdominal fat.)
2) *Secondary* aging is the accelerated deterioration in organ structure and function mediated by diseases, or by harmful environmental and lifestyle factors.

It is not possible to separate the two factors completely.

In a number of animal models, calorie restriction slows aging and increases life span. In rodents, initiating a 30% to 60% reduction in calorie intake started early in life caused a proportionate 30% to 60% increase in life span. A 44% reduction in calorie intake started in adulthood extended life span by 10% to 20%.

In laboratory rodents, calorie restriction increases longevity by preventing or delaying onset of chronic diseases (diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, respiratory diseases, and cancer). In addition, calorie restriction decreases neurodegeneration in the brain and enhances neurogenesis in animal models of Alzheimer disease.

The reduction in chronic diseases does not completely explain the increase in lifespan and the preservation of function at more youthful levels which occurs in the calorie-restricted rodents. About 1/3 of such rodents die without evidence of organ pathology. “These data support the notion that the common link between aging and chronic disease is not inevitable, and that it is possible to live longer without experiencing a cumulative increase in serious morbidity and disability.”

Data suggest that the effects of calorie restriction on life span are not simply a result of leanness induced by such restriction. Life span does not increase in male rats that maintain a low body fat mass by performing regular exercise. It does increase in sedentary male rats that are food restricted to keep their body weights the same as those of the exercisers.

Calorie restriction and aging in humans:

It is difficult to determine whether calorie restriction has beneficial effects on longevity in humans. There are no valid biomarkers of aging. And it is impractical to conduct randomized, diet-controlled trials in humans. Nonetheless, data from epidemiological studies suggest that calorie restriction can have beneficial effects on the factors involved in the pathogenesis of aging, and life expectancy in humans. Food shortages during WWII in some European countries were associated with a sharp decrease in coronary heart disease mortality. (*And type 2 diabetes practically disappeared. RTJ.)* Mortality increased after the war ended. One study reported that inhabitants of Okinawa who eat about 30% fewer calories than the average Japanese have about 35% lower rates of cardiovascular disease and cancer mortality than the Japanese. Okinawans have one of the highest numbers of centenarians in the world.

A small group of individuals lived in the Biosphere (a completely enclosed self-sustaining ecological system) for 18 months. During this period, they ate about 22% fewer calories while sustaining high levels of physical activity. Their average body mass indexes fell from 23 to 19. There was a marked reduction in metabolic risk factors for coronary heart disease, including lipid profiles and blood pressure.

Data from studies of calorie restriction diets have been reported by the Calorie Restriction Society. A small group of lean adults (BMI 19.6) consumed about 1800 kcal per day for 7 years. The diet contained about 30% fewer calories than age-and sex-matched individuals consumed in a typical Western diet. In addition, the diet consisted of nutrient-risk foods (vegetables, fruits, nuts, dairy products, egg whites, wheat and soy proteins, and meat) which supplied more than 100% of the recommended daily intake of all essential nutrients. The diet eliminated processed foods rich in refined carbohydrates and partially hydrogenated oils. The subjects showed many of the same benefits in metabolic and organ function previously reported in calorie-restricted rodents. In addition, left ventricular diastolic function (parameters of elasticity and stiffness) was similar to that of individuals 16 years younger.

“Despite many similarities in the metabolic adaptation to caloric restriction observed in rodents and humans, it is not known if such restriction affects the maximum lifespan.”

Optimal health:

“Optimal health can be defined as the state in which there is the highest attainment of physical, mental, and social well being, and the lowest risk of developing future diseases.” Determining this is difficult. The relationship between biomarkers and disease is a continuum. Cut points have been established to identify individuals at increased risk. Recent data suggests that the threshold for many of the major risk factors for coronary heart disease should be lowered: BP < 115/75; LDL-cholesterol 50 to 70 mg/dl: fasting plasma glucose < 75 mg/dL.

Large population studies suggest that lifestyle factors (eg, physical activity, diet, and adiposity) are responsible for up to 70% of chronic disease and are a major contributor to reduced longevity. The precise amount of calorie intake and body fat mass associated with “optimal health” is not known. The WHO and the National Institutes of Health have proposed that a BMI of 18.5 to 24.9 is “normal”. Values above and below increase the risk for premature mortality. Epidemiologic studies evaluating the relationship between BMI and risk for type 2 diabetes suggest that a BMI ~ 20 is associated with optimal metabolic and cardiovascular health. This correlates

with an average percentage of body fat of ~ 10% in men and ~ 25% in women. The amount of adiposity and BMI values associated with optimum health will vary depending on genetic and environmental influences, body fat distribution, age, and racial/ethnic background.

Conclusion:

1) Calorie restriction (*better said, optimum caloric intake RTJ*) is an important determinant of health.
2) Excessive energy intake is a form of malnutrition that leads to unfavorable body composition, organ dysfunction, and premature mortality.
3) The precise caloric intake needed for optimal health and function likely varies for each individual depending on genetic background, age, energy expenditure, and diet composition.
4) The optimal calorie intake needed to slow the aging process is not known. The available data support the notion that calorie restriction (*optimum calorie intake*) in humans leads to many of the same metabolic adaptations and reductions in multiple chronic disease risk factors that occur in calorie-restricted animal models, even when restriction is started in midlife.
5) Even if calorie restriction does not prolong maximum life span, it could increase life expectancy and the quality of life by reducing the burden of chronic diseases.

JAMA March 7, 2007; 297: 987-94 "Clinical Review" commentary, first author Luigi Fontana, Washington University School of Medicine, St. Louis, MO.

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Immunity Wanes With Time. A Second (Booster) Shot Is Recommended.

3-7 LOSS OF VACCINE-INDUCED IMMUNITY TO VARICELLA OVER TIME

The introduction of universal varicella vaccination[1] in 1995 substantially reduced varicella-related morbidity and mortality. Between 2003 and 2004 the incidence of varicella declined by 85% from 1996 levels. The vaccine is not 100% effective—about 15% of children receiving the vaccine do not have levels of antibody needed to protect them from acquiring the disease.

Exogenous re-exposure to the virus may be needed to boost immunity. As the incidence of varicella has decreased, the opportunities for community exposure to varicella (which is needed to boost vaccine-induced immunity) have also declined.

It is not clear whether vaccine-induced immunity wanes over time. Waning of immunity after vaccination in terms of measurable antibodies has been demonstrated to occur in health care workers. Some outbreaks of varicella in immunized school communities have been reported.

If immunity does wane , the result may be increased susceptibility to varicella later in life, when risk of serious complications may be greater.

It is hypothesized that the time since vaccination may be associated with risk of breakthrough varicella.

This study assessed whether vaccine-induced immunity wanes over time.

Conclusion: Immunity wanes. A second dose of vaccine is now recommended.

STUDY

1. Examined 10 years (1995-2004) of active surveillance data in a population of 350 000 subjects in a well-defined area in California to determine the incidence and severity of *breakthrough* varicella. (Onset of rash 43 days or more after vaccination.)

RESULTS

1. Over 11 000 subjects were reported to have varicella during the surveillance period. Of these, 10% had breakthrough disease. (Ie, had received the vaccine, but had nevertheless experienced clinical chicken pox.)
2. The annual rate of breakthrough increased from the time since vaccination:
   1.6 cases per 1000 person-years within 1 year after vaccination.
   9.0 cases per 1000 person-years at 5 years.
   58 cases per 1000 person-years at 9 years.
3. The proportion of cases that occurred in vaccinated children increased from 1% in 1996 to 18% in 2000, to 60% in 2004.
4. Severity of disease increased with age and as time from vaccination lengthened:
   Children between ages 8 and 12 who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than those who had been vaccinated less than 5 years previously. When assessed according to the time since vaccination, the frequency of moderate-to-severe disease increased to 33% among those vaccinated 5 or more years previously from 23% of those vaccinated less than 5 years previously. Vaccinated children with moderate-to-severe disease were twice as likely to have complications such as pneumonia, ataxia, and skin superinfection as those with mild disease.
   The frequency of moderate-to-severe disease also increased with increasing age regardless of vaccination status, from 22% of children between age 1 and 7 to 44% among those age 13 and older.

DISCUSSION

1. The vaccine was effective in reducing incidence of varicella in all age groups. Varicella declined by 85% from 1995 to 2003. (The vaccine is effective.)
2. Protection afforded by one dose of vaccine waned over time.
3. The incidence and severity of breakthrough disease among children receiving the vaccine increased with time since vaccination. “These data suggest a steady decline over a period of years in disease protection afforded by a single dose of vaccine in the context of diminished circulation of wild-type virus.”
4. In June 2006, the Advisory Committee on Immunization Practices recommended that children between ages 4 to 6 receive a second dose of vaccine. The committee also recommended that a second catch-up dose be given to children, adolescents, *and adults* who previously had received one dose.
5. No long-term data are available on the duration of immunity afforded by the second dose.

CONCLUSION

A second dose of varicella vaccine is now recommended for all children. This could improve protection from both primary vaccine failure and waning of vaccine-induced immunity.

NEJM March 15, 2007; 356: 1121-29 Original investigation, first author Sandra S Chaves, Centers for Disease Control and Prevention, Atlanta, GA.

1 The live attenuated varicella vaccine (*Varivax*; Oka/ Merck)

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Recommended For Virtually All Persons above Age 60

3-8 VARICELLA-ZOSTER VACCINE FOR THE PREVENTION OF HERPES ZOSTER

Varicella-zoster virus (**VZV**) is highly contagious. Before chicken-pox vaccine was available, virtually all people in the USA had evidence of previous VZV infection.

Herpes zoster (**HZ**; "shingles") develops in about 30% of people over a lifetime. Up to 1 million cases occur in the US annually. Risk increases with age, beginning at age 50, when cell-mediated immunity begins to decline. HZ is 10 times as likely in people over age 60 as in younger people. One or more episodes of HZ will develop in up to half of people over age 85. HZ is more common in immunocompromised people.

Complications of HZ include postherpetic neuralgia (**PHN**), encephalitis, myelitis, cranial nerve palsies, and peripheral nerve palsies. PHN is challenging and debilitating. It can last for weeks, months, and even years. More than 40% of people over age 60 who have had HZ have PHN. (Up to 200 000 cases per year in the US.)

After primary VZV infection (chickenpox), latent infection is established in the sensory-nerve ganglia, most commonly in the trigeminal and thoracic ganglia. When the virus is reactivated, viral replication occurs in the ganglia with subsequent destruction of neurons. The virus travels along the affected sensory nerves to the skin, resulting in the characteristic unilateral, dermatonal rash.

Second episodes of HZ do occur, but are not common. (Immunity to the virus is likely boosted by a first episode of HZ.)

As immunity wanes in older adults, a higher dose of vaccine (as compared with the varicella vaccine given to children) is required to produce immunity. The new live, attenuated HZ vaccine (*Zostavax*; Merck) contains about 14 times the plaque-forming units per dose as the attenuated live chickenpox vaccine given to children. The HZ vaccine increases cell-mediated immunity to a new set point above the "immunological threshold" below which a person is at risk for HZ.

A large clinical study[1] evaluated efficacy of the HZ vaccine in over 38 000 persons over age 60, followed for 3 years. The incidence of HZ was 51% lower in those receiving the vaccine vs placebo. The incidence of PHN was 67% lower. The median duration of pain was shorter (21 days vs 24 days), and the severity of pain was lower.

The vaccine is frozen for storage, and is administered subcutaneously as a single 0.65 mL dose. It should be administered immediately after reconstitution with the supplied dilutant. Cost is about $150.00. About 17 people would need to be vaccinated to prevent one case of HZ, and about 31 would be needed to treat to prevent one case of PHN. (Estimated costs per case prevented = $3,300 and $6,400.)

Adverse effects: Varicella-like rash at the injection site in 0.04%; more localized pain, swelling, tenderness, pruritis, and erythema at the injections site. (Up to 35% more than placebo.)

Areas of uncertainty:

1) Cost effectiveness is not yet settled.
2) Use in persons age 50-59 is not approved. Use would be off-label. However, the burden of HZ in this age group is substantial. The commentator does not recommend vaccination in this age group because of the lack of cost-effectiveness and effectiveness data.
3) Wild type VZV infections are declining as a result of universal vaccination in childhood (now including a recommended second dose at age 4 to 6). As consequence, the likelihood that older people will be "boosted" by exposure to a child with chickenpox is declining. What then will be the incidence of HZ over time? How long does immunity conferred by one dose of HZ vaccine last?
4) Should persons who previously received the chickenpox vaccine, as they grow older, be considered to be candidates for HZ vaccination? (They may harbor the virus, and be subject to HZ despite having no history of chickenpox. Many may experience a subclinical "breakthrough" infection. They may not remember they had mild chickenpox years ago.) The commentator suggests that persons who have previously received the chickenpox vaccine should indeed receive the HZ vaccine as they age.
5) The vaccine is not licensed for use in immunocompromised people. Safety and efficacy of the vaccine in this group has not been established. However, this population is at especially high risk for HZ.
6) Efficacy of the vaccine for people who have had a previous episode of HZ is unknown. The Advisory Committee on Immunization Practices recommends that this group of patients should receive the vaccine.

Virtually all persons now age 60 and above have had clinical or subclinical chickenpox. It is not necessary to determine whether there is a history of chickenpox before giving routine HZ vaccine.

Administration of the vaccine is advised for all persons over age 60, "unless there is a contraindication".

NEJM March 29, 2007; 359: 1338-43 "Clinical Therapeutics". Commentary, first author David W Kimberlin, University of Alabama, Birmingham.

1 "A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults" NEJM June 2, 2005; 352: 2271-84 For an abstract see Practical Pointers June 2005 [6-1]

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"Overtreatment Is Often The Major Danger For These Patients."

3-9 LOW BACK PAIN: Clinical Update

- Every year, one in five adults will have low back pain.
- Low back pain is not a clinical entity, but a symptom with different stages of impairment, disability, and chronicity.

- Acute episodes are usually benign, last less than 3 months (90% of cases), and do not need specific treatment. Indeed, "overtreatment is often the major danger for these patients."
- After a brief diagnostic triage, on the basis of identification of specific causes ("red flags") and a limited neurological and musculoskeletal examination, about 85% of patients can be classified as having non-specific low back pain.
- Specific spinal disorders (vertebral fracture, tumors, infections, inflammatory diseases, symptomatic disk herniation, and spinal stenosis) occur in only a few patients with acute low back pain seen in primary care. Five to 15% of acute cases with an established cause do need to be identified at the first consultation and treated accordingly.
- Two key dimensions of pain: intensity (how much), and pain affect (emotional arousal and disruption from the pain experience). Numerical rating scales of pain (eg, a visual analogue scale—1 to 100) are the most practical for ease of administration, scoring, sensitivity, and responsiveness to change.
- A key point in the assessment of pain is the minimum clinically important difference (MCID—the minimum score that constitutes a noteworthy clinical change—a relevant change). For patients with acute lower back pain, the MCID is about 35 units on a 0 to 100 scale.
- Diagnostic imaging is *not* routinely indicated for non-specific low back pain. It should be reserved for patients who are candidates for surgery, or in whom a systemic disease is strongly suspected. "Such tests do not help to plan conservative care. Moreover, they can have a negative effect on the patient's sense of well-being."
- Some of the enthusiasm for radiographic studies can be patient-related (the wish to identify an objective cause of the pain). Others relate to the clinician (fear of missing a severe abnormality). Others are related to the therapeutic interaction (desire to convince the patient that expectations and worries are being taken into account). As a result compliance to this guideline relating to imaging by primary care clinicians is poor.
- The current recommendations for treatment of acute low back pain:

  Adequate information and reassurance

  Advice to stay active and continue normal daily activities if possible, including work

  Analgesia (1^{st} choice acetaminophen; 2^{nd} choice NSAIDs)

  Consider adding a muscle relaxant (short course)

  Consideration of spinal manipulation for patients who are failing to return to normal activities

  Be aware of "yellow flags" (inappropriate attitudes and beliefs about back pain, inappropriate behavior, emotional problems).

  Bed rest, back specific exercises, steroids, and traction are strongly *discouraged.*
- The focus should clearly be placed on reassurance and the provision of adequate information. It is becoming clear that patients' expectations need to be taken into account in the treatment process. Patients wish to be taken seriously. Patients believe it is important that clinicians give a clear and understandable

feedback during the clinical examination, and give reassurance and explanation about the pain, deal with psychosocial issues, and discuss what can be done (by either the patient or the doctor).

Lancet March 3, 2007; 369: 726-28 Commentary, first author Federico Balague, Cantonal Hospital, Zurich, Switzerland.

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"The Burden Of Hepatitis E Is Grossly Underestimated." A New Vaccine May Be Effective

3-10 SAFETY AND EFFICACY OF A RECOMBINANT HEPATITIS E VACCINE: A Phase II Trial

Hepatitis E virus (**HEV**) infection is a major public health problem in many developing countries. Hepatitis E occurs sporadically and in epidemics, and causes substantial rates of death and complications, especially in pregnant women.

On the basis of data from serological tests, an estimated one third of the world's population has been infected with the HEV. In India, the lifetime prevalence is more than 60%.

The infection is usually self-limited and typically occurs in locations where laboratory diagnosis is not available. Consequently, the true prevalence is not known.

Clinically, the infection is indistinguishable from other types of acute viral hepatitis. The severity of the disease increases with age. The overall fatality rate is estimated to be as high as 3%. Pregnant women who develop the infection have the highest risk of acute hepatic failure. Their case fatality rate is high, as are rates of abortion.

HEV is an RNA virus. There are 4 genotypes. Type 1 causes most human disease. All HEVs can be considered to be of one serotype. Thus, a vaccine that has efficacy in one country should provide protection elsewhere.

A genotype-1 HEV recombinant protein vaccine (**rpHEV** vaccine)[1] has been developed.

This study assessed the efficacy and safety of the vaccine in Nepal, where the infection is common.

Conclusion: rpHEV vaccine was effective in prevention of hepatitis E.

STUDY

1. Entered 2000 healthy Nepalese Army personnel (almost all male; mean age 25). All were considered susceptible to hepatitis E on the basis of low titers of antibody to HEV at baseline.
2. Randomized to 1) three doses of vaccine at 0, 1 and 6 months, and 2) three doses of placebo.
3. Identified acute hepatitis by active surveillance (including hospital). The hepatitis was defined clinically and confirmed by presence of HEV RNA by polymerase-chain-reaction or by a major rise in anti-HEV antibody.
4. Primary end point = development of hepatitis E after 3 vaccine doses. Analysis by intention-to-treat.

RESULTS

1. A total of 1794 subjects received all 3 doses of placebo or vaccine. All subjects who received the vaccine developed antibody responses at levels defined as providing protection.
2. The total vaccinated cohort (n = 898) was followed for a median of 800 days.
3. After 3 doses, hepatitis E developed in 69 subjects—66 in the placebo group and 3 in the vaccine group.
4. Vaccine efficacy was 95%.
5. Adverse effects: similar between groups except for injection-site pain in the vaccine group.

DISCUSSION

1. The contribution of hepatitis E to overall morbidity among these subjects was substantial. It was the most common significant medical illness in the placebo group.
2. "The burden of hepatitis E is grossly underestimated."
3. The 3 doses of vaccine were protective against hepatitis E during a median of 800 days. The efficacy was 95%.

CONCLUSION

In a high-risk population, the HEV vaccine was effective in the prevention of hepatitis E.

NEJM March 1, 2007; 356: 985-903 Original investigation from the Walter Reed-Armed Forces Research Institutes of Medical Sciences Research Unit, Nepal and the Nepalese Army, Kathmandu, Nepal, first author Mrigendra Prasad Shrestha

Study supported in part by GlaxoSmithKline

1 A purified polypeptide produced in cells of the Fall Army worm. The worm develops into a beautiful moth in the adult phase.

An editorial in this issue of NEJM by Krzystof Krawczynski, Centers for Disease Control and Prevention, Atlanta, GA comments and expands:

Large outbreaks of hepatitis E were first recognized in the early 1980s. It is endemic in some areas of the world, transmitted by the fecal-oral route. (The virus has been found in contaminated waste water and sewage.) Person-to-person transmission is uncommon.

Sero-prevalence of the disease in some countries where the disease is not endemic has been found in up to 5% of the population, perhaps related to asymptomatic disease. A higher prevalence has been found in swine-handlers, possibly related to the HEV found in swine.

The virus may infect travelers to endemic regions. The vaccine may by useful for travelers.

Hepatitis E hepatitis is typically a self-limited acute hepatitis, usually lasting 1 to 4 weeks. It rarely causes fulminant liver failure. It does not progress to chronic disease.

Fatality rates are higher in pregnant women (up to 25%) who are infected during the 3rd trimester. In some pregnant women, it is rapidly progressive, causing cerebral edema and disseminated intravascular coagulation. *(I was unable to fine any mention in the articles as to the reason for the devastating effects in pregnancy. RTJ)*

The study did not determine if the vaccine prevented *asymptomatic* cases of hepatitis. The trial concerned only subjects who presented with symptoms of acute hepatitis. Asymptomatic HEV infection may be important because subjects without clinical symptoms may continue to shed the virus.

The duration of immunity following vaccination is not known.

A letter to the editor Lancet April 14, 2007; 369: 1260 from, first author Harry Dalton, Corwall Gastrointestinal Unit, UK comments:

Locally acquired hepatitis E in individuals who have not traveled to endemic areas is emerging. The number of documented cases in England and Wales is rapidly increasing owing to increased numbers of genotype 3 in non-travelers. The source is not known, It could be zoonotic from pigs. In the UK, 85% of pigs tested show evidence of asymptomatic infection.

Locally acquired hepatitis E in developed countries in individuals who have not traveled to endemic areas has a predilection to older men, and usually causes a self-limiting hepatitis.

In 2005-06. the authors documented 28 cases of locally acquired hepatitis E in Devon and Cornwall, UK. Three patients, all older men, had previously undiagnosed cirrhosis on biopsy. All presented with jaundice. Two patients died from liver failure at 4 and 5 months.

Hepatitis E can cause adverse outcomes in patients with chronic liver disease, with a mortality of up to 75%. “Our observations suggest that locally acquired genotype 3 hepatitis E in developed countries can cause decompensation and carries a poor prognosis in the context of chronic liver disease.”

“Hepatitis E is a public health issue in the UK.”