What to Eat - and Why?

Edwin Cox, M.D.

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The goals: a long, and healthy, life

To live as long as possible (maximum lifespan)

To stay as well as possible (maximum healthspan) within the lifespan



The Facts of Life

There are certainties - and uncertainties

Certainty

- · We will die
- \cdot Many will develop diseases that impair quality of life

Uncertainty

- Can we live longer by lifestyle choices?
- · Can we avoid illness and disability by lifestyle choices?

This course will answer those questions affirmatively

Lifestyle

- * Physical activity
- * Food
- * Drink
- Smoking, alcohol, recreational drugs

Occupation

Social interaction (church, civic organizations, clubs) Hobbies



"No, you won't live longer if you give up sex and alcohol. But it'll seem like it."

The goal: a long and healthy life

What can we can do in our daily life and behavior (diet, exercise)...

- \cdot to live as long as possible (maximum lifespan), and
- to stay as well as possible (maximum healthspan)?
- I wanted to know for *myself* what I should be eating!

Perhaps I could pass the insights to my children and grandchildren to help them optimize *their* prospects for health and longevity

What triggered my interest...

- My sister and her family went vegan
- · Was I missing an important opportunity if I didn't do the same?
- My medical training and experience did not shed light...

First stop: The popular media

Current best-selling books

Articles in newspapers and magazines

Websites and blogs

Especially respected medical centers,
specialists and governmental authorities

But, the Diet Gurus didn't agree

Nutrition advisors say...

- Atkins Diet: Carbohydrate is the culprit; restrict carbohydrates, consume mainly protein and fat; animal sourced foods are fine
- Campbell Diet: Animal proteins are toxic; plant-based, whole-food diet avoids harm
- USDA: Fats, especially saturated fat, cause heart attacks and strokes; eat low-fat diet with as much carbohydrate as you want

They reach mutually exclusive conclusions - they can't all be right!

All have elements of truth, but each misses the mark, due to "cherry-picking" data!

Just give up? Que sera, sera?

We've been conditioned to think, "what will be, will be"

Just accept that nobody *really* knows what to do to stay alive and well

We might as well eat, drink and be merry

When disease strikes, look to doctors to push back, i.e., pills, surgery, chemotherapy

But, doing that just makes us pawns of powerful commercial forces – the "manufactured food" industry

• They wants us to buy prepared foods that yield them big profits but expose us to disease and premature death

My approach: Let the evidence speak!

What I did as a physician when faced with challenging patients

• Consult original sources in the medical literature for the best current treatment results Accept nothing pre-processed through anyone else's filter

Leverage my background in statistics and epidemiology to rigorously evaluate data

Yet, there was no guarantee that I would find much of value

- · Perhaps diet wasn't as important as some people made it out to be
- · Or maybe the right research had not been done
- · Or maybe the necessary diet was just too limited and unappealing to be practical

Timing... is everything!

My research started in 2013

- Numerous large, high-quality studies were just bearing fruit
- I focused on published research dealing with individual questions
- · How does total mortality relate to dairy consumption?
- · What is the incidence of diabetes relative to nut consumption?
- · Does eating more fiber prevent colon cancer?

No single researcher had compiled an complete overview that synthesized the results into a comprehensive plan

• My goal was a holistic approach to lifestyle, weighing the pros and cons of all elements to arrive at a balanced approach

Success!

A wide array of conclusions and recommendations were gleaned

I compiled my findings into this course

I've continued to research and update knowledge base

The course is now in its eleventh iteration, with several useful new findings from 2019 research reports



All you need to know

Base diet around nuts, whole grains, vegetables, fruits, beans, fish, poultry, olive oil, vegetable oils

Modest amounts of dairy, eggs

Avoid - or sparing amounts of - red meat, processed meats, sugary beverages, refined grains (white bread, rice, cereal, desserts)

Alcohol in small amounts if not otherwise excluded Regular physical activity

Harvard Healthy Eating Pyramid



Now you know what to eat. Why ask why?

Know the rationale for eating specific foods and avoiding others, empowering you to...

- Think for yourself
- Make informed choices
- · Develop willingness to try new foods that are good for you
- · Resist being swept along with each new fad
- · Gain skills to critically evaluate new recommendations
- · Reduce enticing foods that are detrimental
- · Satisfy curiosity

Diseases to focus on: Sutton's law

When famed serial bank robber Willie Sutton was asked, "Why do you rob banks?", he replied, "That's where they keep the money!"

Let's focus on common impactful diseases highly influenced by lifestyle

Diseases where diet, exercise and/or smoking make a difference



Impactful "lifestyle" diseases

Diet and exercise

- · Coronary heart disease ("heart attacks")
- · Cerebrovascular disease ("strokes")
- · Type 2 diabetes mellitus & metabolic syndrome
- · Obesity and its complications
- · Cancer all types

Smoking

- · Lung cancer
- · Head, neck and esophageal cancer
- · Bladder cancer
- · Cardiovascular diseases

Epidemiology

"The science that studies patterns, causes and effects of health and disease conditions in defined populations"

Etymology: closely related to "epidemic"

- · epi (Gr.) "upon, among"
- · demos (Gr.) "people, district"
- · logos (Gr.) "study, word, discourse"

Nutritional Epidemiology

Branch of epidemiology that focuses on relationship of diet to health and disease

The Evidence: Types of studies

The purpose of studies is to infer causes

- For example, meat causes coronary heart disease or sugar shortens life span
- Basic research
- Randomized controlled trials
- Cohort (observational) studies

Basic research

Genomics

 Look for genes that are associated with diseases and susceptibility to exposures

Environmental factors

- Exposures correlated with disease causation and progression
- Mechanisms of benefit or harm
- · How do walnuts lower LDL-cholesterol?

Randomized controlled trials

Subjects allocated to different treatment arms by randomization

Outcomes of treatment arms evaluated by statistical tests

Statistically significant results allow us to infer causality

Drawbacks with respect to nutritional epidemiology

- · Long, expensive, intrusive
- · Short-term studies inconclusive
- · Rarely practical in nutritional research
- · False positives and false negatives

Randomized Clinical Trials

Lyon Diet Heart Study (France)

- · 300 subjects with existing heart disease (secondary prevention)
- · Followup: 5 yrs
- PREDIMED (Spain)
- · 8000 subjects at risk for heart disease (primary prevention)
- · Followup: 5 yrs
- Both studied Mediterranean Diet

Both showed significant benefit in reducing coronary heart disease compared to control diet

Observational studies

Obtain a large sample of individuals with some well defined common attributes (nationality, occupation, age, etc)

Record age, weight, height, blood pressure, educational level, exercise level, blood tests

Obtain dietary history by food frequency questionnaire (FFQ), food diary, or 24 hr recall

Follow up to determine end points: death, cause of death, and/or onset of specific diseases

Food frequency questionnaire

BREADS (include use as toast and sandwiches)	Never or rarely	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day	Standard Serving Size	Standard	1/2 or less	11/2 Or more
White bread, rolls, buns, or French bread	0	0	0	0	0	0	0	0	0	2 slices or 1 bun/roll	0	0	0
Whole grain bread, rolls, buns, or oatmeal bread	0	0	0	0	0	0	0	0	0	2 slices or 1 bun/roll	0	0	0
Corn bread, Johnnycake	0	0	0	0	0	0	0	0	0	2 slices or pieces	0	0	0
Other breads, bagels, biscuits you eat? (<i>please write them in - use</i> CAPITAL <i>letters</i>):										2 plines or			
1	0	0	0	0	0	0	0	0	0	2 slices or pieces	0	0	0

National Nutrition Database for Standard Reference



Full Report (All Nutrients) 45102292, BREAD, MADE WITH WHOLE GRAIN, UPC: 071301047179

					1
Nutrient	Unit	Data points	Std. Error	2.0 SLICES 57g	Value Per100 g
Proximates					
Energy	kcal			150	263
Protein	g			5.00	8.77
Total lipid (fat)	g			2.00	3.51
Carbohydrate, by difference	g			28.00	49.12
Fiber, total dietary	g			2.0	3.5
Sugars, total	g			3.00	5.26
Minerals					
Calcium, Ca	mg			200	351
Iron, Fe	mg			1.58	2.77
Sodium, Na	mg			280	491
Vitamins					
Vitamin C, total ascorbic acid	mg			0.0	0.0
Thiamin	mg			0.000	0.000
Riboflavin	mg			0.136	0.239
Niacin	mg			1.754	3.077
Vitamin A, IU	IU			0	0
Lipids					
Fatty acids, total saturated	g			0.000	0.000
Fatty acids, total monounsaturated	g			0.000	0.000
Fatty acids, total polyunsaturated	g			0.502	0.880
Fatty acids, total trans	g			0.000	0.000
Cholesterol	mg			0	0

Observational study analysis

Evaluate outcomes with respect to the "risk factors" (demographic, personal and diet data) with statistical tests

 Example: Heart attack rate is higher in people eating more processed meat

Statistical significance indicates association between risk factors and outcome

Association does not prove causation

- · Achilles' heel of observational studies
- Replication in different settings, plausible biological mechanisms can validate

Major observational studies

Nurses Health Study (NHS) 100K 30yrs

Health Professional Followup Study (HPFS) 50K 25yrs

Physicians' Health Study (PHS) 50K 25yrs

NIH-AARP Diet and Health Study (AARP) 500K 10yrs

European Prospective Investigation into Cancer and Nutrition (EPIC) 500K 18yrs

Adventist Health Study (AHS)

Health Survey for England (HSE)

Statistics

A field devoted to planning and analyzing results of research studies

Descriptive statistics

- · Summarizing observed data
- Shape of distribution (e.g., classical "bell-shaped")
- Central measure (e.g., mean) and dispersion (e.g., standard deviation)

Inferential statistics

· Drawing conclusions about relationship between factors

Drawing Conclusions: Inference

"There's something going on here. We've got to get to the bottom of it" - or maybe not!

Put forward a proposition, collect data to test it, chose a statistical model that applies, and either confirm or reject it

Conclusions can guide future actions and policies

 If increasing amounts of fiber in the diet lowers one's rate of heart attacks, diabetes onset, and death, without offsetting adverse effects, one would give strong consideration to eating as much fiber as practical

Inference making

Similar to trying a crime suspect

Four possible outcomes:

- Defendant guilty, found guilty
- · Defendant innocent, found innocent
- · Defendant guilty, found innocent (ERROR! Criminal getting off)
- · Defendant innocent, found guilty (ERROR! Innocent punished)

Goals:

- Maximize rates of correct conclusion
- · Minimize error rates, according to impacts of the different types of error
- Determine magnitude and meaningfulness of effects

Hypothesis testing

Formal name for process of making inferences

State the null hypothesis

• There is no relationship between fiber intake and onset of coronary heart disease State the alternative hypothesis

• There is a relationship ...

Analyze data with appropriate model

Acknowledge that result could have happened by chance

Determine the probability that the observed result could have happened by chance

If that probability is sufficiently low, conventionally 5% or less, declare that the observed result probably did not happen due to chance \rightarrow "statistically significant"

Hypothesis testing

Formal name for process of making inferences

State the null hypothesis

• There is no relationship between fiber intake and onset of coronary heart disease

State the alternative hypothesis

• There is a relationship ...

Analyze data with appropriate model

Likelihood of observed outcome or more extreme due to chance alone

- · Likely: Do not reject the null hypothesis
- · Unlikely: Reject the null hypothesis \rightarrow Accept alternative hypothesis

Example of hypothesis testing

Situation: Coin tossing

Hypothesis: The coin is fair, i.e., equal probability of heads and tails

Alternative hypothesis: The coin is biased, i.e., more likely to land heads than tails, or vice versa

Data: Toss the coin 10 times. It lands 'HHHHHHHHH'

Model: Tossing a fair coin, the probability of landing all heads (or all tails) is 2 in 2^{10} , or 2 in 1024.

Conclusion: An event with 0.2% occurrence is a rare event by chance alone. Therefore, we reject the null hypothesis of a fair coin and accept the alternative that the coin is biased.

Discussion: Rejecting the null hypothesis is not declaring certainty; rather it points to fruitful areas for further exploration. Repeating the experiment and obtaining similar results lends more credence. Having a plausible cause \rightarrow effect mechanism bolsters conclusion (coin is found to have been filed).

Walnut feeding experiment

Sabaté et al - NEJM - 1993

18 healthy men fed a cholesterol-lowering diet for 8weeks in a research kitchen at Loma Linda University;30% calories from fat

During 4 of the weeks, 20% of the calories came from walnuts, about 3 oz / 2500 Cal

Cross-over design, so each man was on both arms of the experiment, with and without walnuts, the order randomly assigned and stratified

Walnut feeding study - results

LDL fell 16% during the walnut feeding

Total cholesterol fell 12% during walnut feeding

HDL fell 5%

But, were these changes due to chance, and not to eating walnuts?





All 18 subjects followed each diet, but 10 followed the walnut diet first (○) and 8 followed the reference diet first (■).

Cholesterol vs. walnut consumption

Table 4. Serum Lipid and Lipoprotein Levels at the End of Each Diet Period.

VADIABI E*	Reference Diet [†]	WALNUT DIET [†]	ESTIMATED DIFFERENCE IN DIFT EFFECTS [‡]	PERCENT
ARIABLE	Dibit	2121		CHARGE
Total cholesterol (mg/dl)	182±23	160 ± 23	-22.4 (-28.2 to -16.6; P<0.001)	-12.4
LDL cholesterol (mg/dl)	112 ± 16	94±17	-18.2 (-23.2 to -13.2; P<0.001)	-16.3
HDL cholesterol (mg/dl)	47±11	45±10	-2.3 (-3.9 to -0.7 ; P = 0.009)	-4.9
LDL cholesterol:HDL cholesterol	2.5±0.6	2.2±0.7	-0.3 (-0.4 to -0.2; P<0.001)	-12.0
Triglycerides (mg/dl)	114±59	103±45	-9.5 (-20.5 to 1.5; P = 0.101)	-8.3

*To convert values for total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

†Values are means ±SD.

[‡]Reference-diet values were subtracted from walnut-diet values according to methods described by Fleiss.¹⁴ Because of minor adjustments for the diet-period effect, the estimated differences do not exactly equal the difference between the values for each diet. Values in parentheses are 95 percent confidence intervals.

P<0.001 means "a difference this great would happen by chance 1 in a thousand or less"

Correlation / linear regression



Figure 7.16: Gift aid and family income for a random sample of 50 freshman students from Elmhurst College, shown with the least squares regression line.

Survival analysis

Area of statistical analysis

Duration of time until an event happens

- · Death
- · Onset of disease
- · Relapse from remission
- · Industrial Failure of component

Developed for life insurance

- · Rate individuals, set premiums
- · Base predictions on risk factors (BP, smoking)

Survival analysis - example

Mortality in British physicians re: smoking

Conducted by UK epidemiologist Richard Doll

Study included 35,000 male doctors

Study began 1948, last follow-up 2000

25,000 died, 5,000 remained alive, 4,000 withdrew

Cohort: Doctors aged 30-39

Doctors born 1921-1930: 7,385

1,713 never smoked up to age at entry

- 51 had died by age 50 (3.0%)
- · Average annual mortality = 3.0%/15 yr = 0.2%/yr (2.0/1000/yr)

2,252 currently smoked at entry

- · 158 had died by age 50 (7.0%)
- · Average annual mortality = 7.0%/15 yr = 0.48%/yr (4.8/1000/yr)
- 3,420 former smokers
- Excluded from analysis

Longevity UK Doctors at Age 35



Mortality rates and ratios

Mortality rates

- · Current smokers: 4.8/1000/yr
- · Never smokers: 2.0/1000/yr

Mortality ratio (AKA relative risk, risk ratio, hazard ratio)

- MR = RR = HR = 4.8/2.0 = 2.4
- · RR > 1: factor has adverse effect on mortality
- · RR < 1: factor has beneficial effect on mortality
- · RR = 1: factor has no effect on mortality

Interpretation

- "Current smokers at age 35 die 2.4 times as fast in the next 15 years compared to neversmokers"
- "Current smokers have 140% higher mortality rate than never-smokers"

Mortality rate and ratios another example

Study of milk product consumption and mortality in men: Netherlands

- 50,000 men, divided into 5 groups by amount of total dairy consumed
- 10,000 deaths over 10 years
- 1,980 deaths in highest fifth (560 g/d avg.)
- 2,020 deaths in lowest fifth (80 g/d avg.)

Mortality ratio

Mortality rate, exposed

· 1,980/10,000 = 19.8% = 19.8/1000/yr

Mortality rate, not exposed

· 2,020/10,000 = 20.2% =20.2/1000/yr

Mortality ratio

· 19.8/20.2 = 0.98, or 98%

Lower means better, but how much better?

- · 1.0, or 100%, is the ratio of "no difference"
- 100%-98% = 2% reduction
- 95% confidence interval for the mortality ratio is 0.92-1.04 (98%-104%)

How meaningful are mortality ratios?

Pretend you are the Surgeon General

· You have to make decisions on policy and advise the public

Smoking increases mortality by 140%

Milk consumption lowers mortality by 2%

Are these real differences, or could they have occurred by chance?

Assuming these are representative samples from larger populations, what generalization can we make?

- What is the effect of smoking in all British males? in all males globally? in men and women?
- · What is the effect of drinking milk in Dutch males? all males? men and women?

Relevance of study results

Statistical aspect

• Statistical theory provides us guidance on the reliability of the results we have observed - often the easiest aspect to deal with

Sampling aspect

• How representative is the sample we observed of the underlying population to which we would like to apply our results?

Effect size

• Is the result large enough to be of practical importance, or is it statistically significant but biologically trivial?

Measurement errors

- Dietary history methods are subject to error
- Error can be minimized by various means: biomarkers, different methods of collecting diet history
- Errors tend to reduce or obscure effects, not exaggerate or suggest false effects

Statistical aspect of reliability

Statistical theory provides reliability guidelines

"95% confidence interval"

- Smoking: 1.73 to 3.21 (+73% to +221%)
- Milk consumption 0.92 to 1.04 (-8% to +4%)
- · With 95% confidence, the "true value" of the mortality ratio lies within that interval

A mortality ratio of 1.0 is the ratio of "no effect"

- · Exposed and unexposed subjects have the same mortality rate
- If 1.0 falls within the 95% confidence interval, we are unable to declare a significant difference between the exposed and unexposed subjects in the outcome
- · Mortality is not significantly related to milk consumption

A mortality ratio whose 95% confidence interval does not include 1.0 is significant

· Mortality is significantly related to smoking

Mortality ratio with confidence interval

Confidence interval depends on number of subjects as well as the effect size

 The larger the number of subjects, the smaller the confidence interval, and the more precise the estimate of the true effect of the exposure

More subjects are required when we are trying to detect small effects

Extremely large samples may find statistically significant results that are not practically meaningful

Forest plots

Compact graphical depiction of RR and 95% CI Combining data from multiple studies: Meta-analysis Comparing data from multiple factors Icon size indicates relative number of subjects Horizontal line spans CI, usually 95% CI



Dose-response: Smoking

Addressing the question: "Is smoking all-or-none, or does the harm increase with dose (number of cigarettes smoked per day)?"

Reference (comparison) is non-smokers

Cigarettes/day	0	1-14	15-24	>24
Mortality rate	19	29	35	45
Mortality ratio	1.0	1.5	1.8	2.4

Dose-response analysis: graphical



Mortality Ratio

How does outcome (mortality, disease incidence) relate to level of exposure to factor?

Smoking has a direct (adverse) effect on mortality

Quantiles

Grouping subjects into equal-sized groups

- · Halves 2 groups
- · Tertiles 3 groups
- · Quartiles 4 groups
- · Quintiles 5 groups
- · Deciles 10 groups

Comparisons are made between each quantile and the reference group

- In this example, subjects are groups in quintiles
- Reference group is quintile 1, the lowest fiber intake
- RR for each other group is its comparison to the first quintile

Dietary fiber and mortality							
Quintile 1 2 3 4 5							
Fiber, g/d	13	16	19	23	29		
RR	1.00	0.77	0.68	0.59	0.53		

Dose-response analysis

How does outcome (mortality, disease incidence) relate to level of exposure to factor?

Dietary fiber has a inverse (beneficial) effect on mortality



Mortality and dietary fiber

You can cut your mortality rate in half just by doubling your fiber intake?!?

But wait! Those eating less fiber are more likely to smoke cigarettes, are less likely to exercise, have higher body mass index, i.e., have additional risk factors

How do you take the effects of these co-factors into account?

- Multivariable statistical methods
- · Proportional hazards survival analysis
- Multiple linear regression

Dose-response, adjusted for risk factors



Dietary fiber and mortality								
Quintile	1	2	3	4	5			
Fiber, g/d	13	16	19	23	29			
RR	1.00	0.77	0.68	0.59	0.53			
Adjusted RR	1.00	0.94	0.90	0.82	0.78			

Multiple regression analysis

Estimates effect of main factor after taking effects of other cofactors into account

Fiber effect falls from 47% reduction in mortality to 22% after accounting for co-factors

Causation vs. correlation

Regression analysis finds *associations* (correlation) between outcome and risk factors

Correlation does not prove causation

However, causation becomes more tenable when:

- A biologically plausible mechanism exists to support a cause-effect linkage
- · Multiple studies replicate relationship
- · Reverse causation is excluded

Lack of correlation does not disprove causation

A negative study does not establish the lack of an effect of a factor Accurate measurement of intake levels is a gnarly problem in dietary studies

- · Total sugar intake especially inaccurate
- · Bias in measurements related to gender, BMI, other factors

Mis-measurement drives relative risks toward the null (RR of 1.0, non-significant)

Biomarkers may be used to correct for bias and yield more accurate estimates of intake

· Urinary sugar excretion can be used to adjust for diet questionaire bias

Meta-analysis

- A study of studies
- Results from multiple similar studies are combined
- Increases ability to detect small effects that can't be detected in individual studies
- Often presented as forest plots
- Special tests to check for biases that could invalidate results (publication bias, inhomogeneity)

Dose-response curve

Plotting mortality ratio vs. magnitude of the exposure



Mortality Risk Ratio: Dose-Response

Servings

Dose-response curve

Rising D-R \rightarrow higher risk of death; harmful

Falling D-R \rightarrow lower risk of death; beneficial

U-shaped D-R \rightarrow beneficial at low dose, but harm with increasing dose



Mortality Risk Ratio: Dose-Response

Servings

Diet or diet

"diet": The technical term for "the composition and amount of what we eat and drink"

May be qualified by adjectives such as low-sodium, low-carb, vegetarian, vegan, lacto-ovo-vegetarian, or pescetarian

"Diet": A term used, capitalized, accompanied by a specifying adjective, to indicate a deliberate pattern of food and drink selection to meet a particular set of objectives.

• The Pritikin Diet, the Mediterranian Diet, the Adkins Diet, and so on. Distinction not always crystal-clear.

Diet by Chemical Composition

Water

Carbohydrates (50% Cal)

- · Sugars
- · Starches
- · Fiber
- Lipids (35% Cal)
- · Saturated Fats
- · Monounsaturated Fatty Acids
- Polyunsaturated Fatty Acids
- · Cholesterol

Proteins (15% Cal)

Vitamins

- Fat-soluble (A,D,E)
- Water-soluble (B complex, C)

Minerals

- · Calcium
- · Sodium
- · Potassium
- Magnesium
- Antioxidants
- Phytosterols

Diet by Roles of Food Components

Fuel

Hydration

Building Blocks (Growth & Repair)

- · Amino Acids \rightarrow Proteins (structural, enzymes)
- · Lipids \rightarrow Membranes, hormones, transport
- · Sugars & Starches \rightarrow Glycogen, polysaccharides

Minerals

Vitamins

Probiotics

Prebiotics

Diet by Type of Food

Plant-sourced

- · Grains Cereals
 - Whole grain
 - Refined
- · Roots Tubers
- · Leaves
- · Fruits
 - Nuts
 - Legumes
 - Other

Animal-sourced

· Dairy

- Milk
- Butter
- Cheese
- Other
- · Red meat
- · White meat
- Processed meat
- · Eggs
- · Fish / seafood

Diet definitions

Omnivore

- · All food types animal- and plant-sourced
- Vegan or Strict Vegetarian
- · Only plant-sourced foods
- Lacto-ovo-vegetarian
- · Plant-sourced foods plus eggs & dairy

Pescotarian

· Plant-sourced foods plus seafood, eggs & dairy

Semi-vegetarian

· Plant-sources foods plus animal-source foods less than once per week

More information

Web site for our class:

http://olli-what-to-eat-and-why.weebly.com

My email address: Ed Cox <<u>ebcox@yahoo.com</u>>