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FOR

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HIGHLIGHTS DECEMBER 2001

12-1 LEFT VENTRICULAR CHANGES IN ISOLATED OFFICE HYPERTENSION

Patients with isolated office ("white coat") hypertension had LV morpho-functional characteristics which differed significantly from normotensive patients and were qualitatively similar to subjects with sustained hypertension.

Isolated office hypertension should not be considered a benign condition.

12-2 PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION AS A PREDICTOR OF CERVICAL INTRAEPITHELIAL NEOPLASIA

The study adds to the body of evidence strongly implicating persistent HPV infections, particularly with oncogenic strains, as a cause of SIL.

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The study adds to the body of evidence strongly implicating persistent HPV infections, particularly with oncogenic strains, as a cause of SIL.

The investigators support the application of repeated type-specific HPV DNA testing in screening for SIL (and by implication prevention of cervical cancer). Vaccines against oncogenic strains (especially type 16 and 18) are a potential for prevention.

Practical point: Watch for developments. Is this the next major step in cancer prevention?

12-3 WHAT VITAMINS SHOULD I BE TAKING, DOCTOR?

Standard advice in the past recommended that vitamin supplements were not needed for persons with an adequate diet. A sea change has occurred. Multivitamin supplements are recommended.

The commentators cite evidence for benefits of folic acid, vitamin B6, vitamin B12, Vitamin D, and vitamin E.

Practical point: Many primary care clinicians now recommend routine use of supplements.

12-4 SUPERIORITY OF AN INTRANASAL CORTICOSTEROID COMPARED WITH AN ORAL ANTIHISTAMINE IN THE AS-NEEDED TREATMENT OF ALLERGIC RHINITIS

As-needed intranasal corticosteroid spray reduced allergic inflammation. It was more effective than *as-needed* H1 blockers in the treatment of seasonal allergic rhinitis.

Practical point: Most patients with troublesome seasonal allergic rhinitis probably take continuing anti-histamine or intranasal steroid during the season. Choice would be personal according to trial and error comparison between the two.

12-5 COMPARISON OF CEFUROXIME WITH AND WITHOUT FLUTICASONE FOR THE TREATMENT OF RHINOSINUSITIS

The addition of fluticasone to xylometazoline and cefuroxime improved clinical success rates and accelerated recovery of patients with a history of chronic recurrent sinusitis who presented with acute sinusitis.

Practical point: Added fluticasone may be a possible benefit in a few patients.

12-6 EFFECT OF OMALIZUMAB ON SYMPTOMS OF SEASONAL ALLERGIC RHINITIS

Omalizumab. an IgE blocking antibody, provided significant relief from allergic rhinitis. And reduced serum free IgE levels.

Practical point: An entirely new development . Watch for additional reports.

12-7 TOTAL CHOLESTEROL/HDL-CHOLESTEROL RATIO VS LDL-CHOLESTEROL/HDL-CHOLESTEROL RATIO AS INDICES OF ISCHEMIC HEART RISK IN MEN

In addition to the well-established conventional risk factors, the Total-c/HDL-c ratio may represent an important cumulative index of the presence of an atherogenic dyslipidemic profile associated with insulin resistance.

It was a simple index of IHD risk in men in this study.

Calculation of the LDL-c/HDL-c ratio may underestimate IHD risk in some patients since it ignores any contribution of the cholesterol in triglycerides.

Practical point: This may be a valid alternative to risk assessment. Calculation or determination of LDL-c may be eliminated, making assessment simpler.

12-8 FREQUENCY OF EATING AND CONCENTRATIONS OF SERUM CHOLESTEROL

In a general population, concentrations of total cholesterol and LDL cholesterol were decreased consistently by increased frequency of eating. "We need to consider not just what we eat, but how often we eat."

Practical point: Nibbling may be healthy; gorging unhealthy. It makes sense not to stress your metabolic machinery.

12-9 INDIGESTION: WHEN IS IT FUNCTIONAL?

Patients often complain of "indigestion". This may be defined differently by individual patients. To some it is heartburn and acid regurgitation; others may describe abdominal rumblings and belching; others, non-painful discomfort in the upper abdomen (fullness, bloating, early satiety).

"Dyspepsia" is best restricted to mean pain or discomfort centered in the upper abdomen.

There are many causes of dyspepsia. But, at least two thirds of patients have no structural or biochemical explanation for their symptoms.

It has been suggested that dyspepsia can be subdivided based on clusters of symptoms. But, subgroups have not proved to be of value in identifying the underlying cause. Symptoms overlap considerably.

Practical point: Perhaps asking patients with troublesome dyspepsia to read this article may help them.

12-10 CYCLO-OXYGENASE INHIBITORS AND THE ANTIPLATELET EFFECTS OF ASPIRIN

Ibuprofen (*Motrin; Advil*) competitively inhibited the prophylactic (anti-thrombotic) effects of aspirin.

Acetaminophen, COX-2 inhibitors, and diclofenac did not have this antagonistic effect.

Practical point: Patients taking low-dose aspirin for primary or secondary prevention of CVD should avoid ibuprofen.

12-11 UNTANGLING VASCULAR DEMENTIA

Questions remain about the mechanism of the interaction between cerebrovascular disease and Alzheimer's in an individual patient. Alzheimer's disease cannot be ruled out by clinical investigation. A diagnosis of vascular dementia does not rule out Alzheimer's. The part that cerebrovascular disease may play in producing symptoms of dementia is particularly difficult to understand when it is accompanied by histological features of Alzheimer's disease.

"It is not surprising that accurate clinical diagnosis of Alzheimer's disease seems to be easier than vascular and mixed dementia. Meanwhile, it is worth noting that although 'pure' vascular dementia exists, vascular disease may be an important and potentially treatable contributor to Alzheimer's disease."

Practical point: We await untangling the pathogenesis of Alzheimer's, and have great hope for development of specific preventive measures for the disease. In the meantime, we can do a great deal to protect the vascular system of the brain. The same prophylactic measures apply to the brain as to the coronary circulation.

12-12 ENGAGING PATIENTS IN MEDICAL DECISION MAKING

Three questions dominate the debate about the role of the patient in making treatment decisions:

Can patients take a leading role in making decisions?

Do they want to?

What if doctors and public health professionals don't like their choices?

Fully informed shared decision making is difficult to conduct in practice. Not all patients want to make their own decisions. Many want to delegate responsibility to their doctors. Yet a desire for information is nearly universal. "Most patients want to see the road map, including alternative routes, even if they don't want to take the wheel."

Fully informed shared decision making is difficult to conduct in practice.

Not all patients want to make their own decisions. Many want to delegate responsibility to their doctors. Yet a desire for information is nearly universal.

Practical point: Determining how much patients wish to be involved is a good start.

2-13 IDENTIFICATION AND FRACTURE OUTCOMES OF UNDIAGNOSED LOW BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN.

About half of a large screened population of postmenopausal women had previously undetected low BMD. Determination of low BMD at peripheral sites (distal radius, heel, finger), as well as at hip and spine, was highly predictive of fracture risk.

Given the economic and social costs of osteoporotic fractures, strategies to identify and manage osteoporosis in the primary care setting need to be established.

Practical point: Some adverse conditions are almost inevitable as age progresses. This includes postmenopausal osteoporosis, atherosclerosis, isolated systolic BP (due to loss of arterial elasticity), and weight gain. Should we wait for confirmatory tests to determine their presence? If so, opportunities for prevention are lost. Or should we assume that preventive measures for these almost universal risks should be started at the earliest reasonable time. Much expense and better prevention would result from empirical and universal primary interventions.

12-14 HELP ARRIVES WITH THE DAWN?

A recent investigation compared 30 minutes of bright light at 0600 hours against placebo and against dawn stimulation. Dawn stimulation consisted of exposure to white light of gradually increasing brightness which started at 0430 h while the patient was asleep. Brightness peaked at 250 lux in 90 minutes. Placebo consisted of dim red light. Dawn stimulation was associated with a significantly higher rate of remission. and a greater reduction in symptoms than either bright light or placebo. Part of the benefit may have been due to the method of delivery which helped patients adhere to a waking time of 0600 h, and thus a regular sleep schedule.

Practical point: Interesting. watch for further reports.

12-15 SIMILAR EFFECTIVENESS OF PAROXETINE, FLUOXETINE, AND SERTRALINE IN PRIMARY CARE.

Three SSRIs, Paroxetine (*Paxil*); Fluoxetine (*Prozac*); and Sertraline (*Zoloft*), were similar in effectiveness and adverse effects for depressive symptoms and domains of health-related quality of life over 9 months.

Practical point: Individual trial and error may come up with the most effective and best tolerated.

12-16 BLOOD PRESSURE REDUCTION AND CARDIOVASCULAR RISK IN HOPE STUDY

The investigatory concluded that ramipril confers substantial benefits *in addition* to those of other BP-lowering drugs. Benefit was greater than expected from the modest lowering of BP which occurred during the trial. But, is there really any benefit in reducing cardiovascular morbidity conferred by a drug in addition to its BP-lowering effect? Controversy remains.

Practical point: The first goal in treatment of hypertension by primary care clinicians should be lowering the BP to recommended levels -- combined by treatment of all risk factors in addition to the BP. I believe that when this is accomplished, any particular drug used will have little additional benefit. RTJ

12-17 PHYSICIAN CHARTER OF PROFESSIONALISM

A campaign to shore up physicians' special place in society has resulted in a *Charter of Professionalism.* The charter reminds physicians that satisfying in full the expectations of a medical professional is still within their control. Physicians may lead a full and satisfying life of medicine.

The Physician Charter of Professionalism contains three fundamental principles:

Primacy of patient welfare

Patient autonomy

Social justice

12-18 GOOD LORD, DELIVER US

"From the inability to let well enough alone; from too much zeal for the new and contempt for what is old; for putting knowledge above wisdom, science before art, and cleverness above common sense; from treating patients as cases; and from making the cure of the disease more grievous than the endurance of the same; Good Lord, deliver us"

Practical point: Amen

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"White-coat" Hypertension is Not Benign

12-1 LEFT VENTRICULAR CHANGES IN ISOLATED OFFICE HYPERTENSION

Isolated office (**IO**) hypertension is frequent. It is characterized by persistently elevated office BP and normal daytime ambulatory BP.

Is IO associated with increased risk of cardiovascular complications of hypertension? Studies vary.

This study compared morpho-functional characteristics of subjects with IO with subjects with normotension and sustained hypertension.

Conclusion: Morphologic and functional changes existed in the left ventricles (**LV**) of patients with IO.

STUDY

1. Enrolled:
   1) Patients with IO hypertension (clinic BP > 140 and/or > 90 and daytime BP < 130/80);
   2) Patients with sustained hypertension (clinic BP > 140 and/or > 90; and
   3) Patients who were normotensive (clinic BP < 135 and/or < 85 and mean daytime BP < 130/80).
2. Forty two individuals were included in each group; mean age = 42. They were matched by age, sex, and body mass index and by mean clinic BP (IO and sustained patients) and mean daytime BP (IO and normotensives). None had been treated for hypertension.
3. Assessed left ventricular morphologic features and function with M-mode echocardiography.

RESULTS

1. Mean BPs:	Normotensive	IO hypertension	Sustained hypertension
Clinic BP	124/73	154/93	153/93
Daytime BP	125/74	126/74	151/97

2. Indices of systolic function were normal in all 3 groups.
3. Compared with normotensive subjects, IO hypertensives had significantly thicker LV walls, increased LV mass, reduced diastolic function, and increased prevalence of diastolic dysfunction.

DISCUSSION

1. IO may place an increased hemodynamic load on the heart. Using a cut-point of 140/90 other studies have reported that IO hypertensive patients have cardiovascular changes similar to those of patients with sustained hypertension, and significantly different from those in normotensive patients.
2. Another study also reported intima-media thickness in the carotid artery increased in like manner.

CONCLUSION

IO hypertensive patients had LV morpho-functional characteristics which differed significantly from normotensive patients and were qualitatively similar to subjects with sustained hypertension.

IO hypertension should not be considered a benign condition.

Archives Int Med December 10/24, 2001; 161: 2677-81 Original investigation, first author Anna M Grandi, University of Insubria, Varese, Italy **www.archinternmed.com**

An editorial in this issue of the Archives (p 2655) comments:

Some investigators have concluded that elevated office BPs ("white coat" hypertension) in not a benign finding. Elevation of casual BP seems to correlate with changes in vascular resistance, presence of LV diastolic dysfunction, and frequently has been associated with elevated triglyceride levels, low HDL-cholesterol levels, increased LDL-cholesterol levels, insulin resistance, and obesity (markers of the "metabolic syndrome"). The higher the office BP, the more cardiovascular events occurred.

Comment:

Should IO hypertensive patients be treated. I believe so. Certainly life style interventions are mandatory. Careful follow-up is required. The occurrence of IO hypertension in many patients seen in primary care clinician's offices will present an excellent opportunity to encourage life-style changes.

Although we do not have any data from randomized trials, I would institute low-dose drug treatment in patients with persistent white coat hypertension if the office BP is high and the patient has other risk factors for cardiovascular disease. This reasoning is strengthened by the recent study from the Framingham Study which found that many patients with "optimal BP" (< 120/80), many with "normal" BP (120-129/80-84), and more with "high normal" BP (130-139/85-89) progress over 4 years to sustained hypertension. I believe it is reasonable to assume that many of these patients also had IO hypertension. NEJM November 1, 2001; 345: 1291-97. Abstracted in Practical Pointers November 2001.

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Is cervical cancer an infectious disease, and potentially preventable?

12-2 PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION AS A PREDICTOR OF CERVICAL INTRAEPITHELIAL NEOPLASIA

Human papilloma virus (**HPV**) is believed to be the central cause of cervical cancer. Recent interest in the development of HPV vaccines has compelled initiation of prospective, long-term studies of the natural history of HPV infection.

This prospective natural history study assessed the risks of cervical neoplasia related to prior persistent HPV infections.

Conclusion: A strong relationship existed between persistent HPV infections and squamous intraepithelial lesions (**SIL**).

STUDY

1. Longitudinal study of the natural history of HPV infections and cervical neoplasia entered over 1600 women (1993-97; mean age - 33). At baseline, none had cytological lesions. HPV status was available at the first 2 visits. (Study conducted in Sao Paulo, Brazil, an area of high endemicity.)
2. Obtained cervical specimens for Papanicolaou cytology every 4 months in the first year, and twice yearly thereafter for up to 5 years.
3. HPV status was determined by polymerase chain reaction at the first 2 visits (including the enrollment visit). Over 25 types of HPV can be detected and grouped by oncogenic potential. (*See p 3108 for a list of 12; 16 and 18 being the most oncogenic*.)
4. Main outcome -- incident cervical cancer precursor lesions (squamous intraepithelial lesions [**SIL**])

RESULTS

1. Overall, 16% of women were HPV positive.
2. All women (except one) had initiated sexual activity by the time of their first follow-up visit, and therefore had been exposed to HPV through sexual transmission. The majority of women had only 1 to 2 partners in their lifetime.
3. Over 1600 women were free of SIL at enrollment:
   Incidence of SIL was high for those + for any oncogenic HPV at enrollment.
   Higher still for types 16 and 18 at one visit
   Higher still for those + for 16 or 18 at both visits.
4. Incidence of SIL:

HPV negative at both visits	3.5%
Positive HPV at either visit for any type	15 %
Positive for 16 or 18 once	8%
Positive for 16 or 18 at both visit	29%

5. Cumulative detection of SIL among those positive for 16 or 18 at both visits approached 40% over 5 years.
6. Younger women (age 18-24) had the highest rates of infection.
7. Most oncogenic strains detected at 2 visits were of the same strain. The relative risk of high grade

SIL among older women with persistent HPV was higher than among the young (29% vs 5%).

8. A small group of women had HPV testing at a third visit. Some eliminated the infection by the third visit. Among these who eliminated the HPV, no persistent SIL was noted regardless of the HPV classification.

DISCUSSION

1. Persistent HPV infection (positive on two or more occasions) , particularly with known oncogenic strains, was associated with a much greater risk of incident SIL than those with HPV on only one occasion.
2. Persistent infection with "non-oncogenic" strains was also associated with increased risk of developing SIL.
3. No incidence of *high* grade SIL was observed among women with non-persistent (implying different types) yet with repeatedly positive HPV types.
4. "The increase in incidence of SIL in women harboring long-term oncogenic HPV infections adds to the evidence for HPV persistence as a key determinant of lesion development."
5. For women who eventually cleared their infection, no persistent SIL lesions were observed.
6. The investigators support the application of repeated type-specific HPV DNA testing in screening for SIL (and by implication prevention of cervical cancer). Vaccines against oncogenic strains (especially type 16 and 18) are a potential for prevention.

CONCLUSION

The study adds to the body of evidence strongly implicating persistent HPV infections, particularly with oncogenic strains, as a cause of SIL.

"A strong relationship exists between persistent HPV infection and SIL incidence, especially for HPV types 16 and 18."

JAMA December 26, 2001; 286: 3106-18 Original investigation, first author Nicholas R Schlecht, McGill University, Montreal, Canada. **www.jama.com**

Comment:

The investigators list 12 "oncogenic" strains. This is certainly a tentative list.

Do all women who develop cervical cancer have HPV infection? Some studies report SIL in persistently HPV negative women. But apparently, most women who develop SIL are infected, especially those with persistent infections. What is the incidence of SIL and cervical cancer in women who remain virgins over their lifetime?

Infections can come and go. (Ie, may be transient and spontaneously clear.) Women who clear the infection apparently are at low risk. Persistent infections or repeated re-infections increase risk. Apparently young women have the highest rates of HPV. Most clear the infection. But, older women have the greatest prevalence of high grade SIL, presumably on the basis of frequent reinfections.

Re-infection is common; strains differ over time. The infection (and therefore cervical cancer) is a venereal disease. Note that few women in this study reported only one or two sexual partners in their lifetime. What does this say about their partners?

The HPV-SIL-cervical cancer story is fascinating. It may be the next big step in cancer prevention. Will cervical cancer turn out to be an essentially preventable disease, as is colon cancer? RTJ

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Supplements now recommended routinely

12-3 WHAT VITAMINS SHOULD I BE TAKING, DOCTOR?

This is one of a NEJM series "Clinical Practice" which begins with a case vignette highlighting a common clinical problem, presents evidence supporting various treatment strategies, reviews formal guidelines, and ends with the author's recommendations.

This vignette concerns a healthy 54 year old woman who expresses confusion about conflicting reports and recommendations about supplemental vitamins.

Medical teaching in the past has been that, in general, the nutritional needs of healthy persons can be met by diet alone. Recent evidence has changed this view. In some circumstances, vitamin intake can be suboptimal without there being any clinical evidence of deficiency.

The authors of this review used all the available evidence to weigh the likelihood of a benefit against the likelihood of harm, while also containing costs. They realize that randomized trials regarding individual vitamins have seldom been done and are not likely be done. They highlight several individual vitamins.

Folic acid:

*Neural tube defects (***NTD***):*

Periconceptional folic acid supplementation is associated with a substantially reduced risk of neural tube defects. In a randomized trial, doses of 800 ug daily reduced incidence of recurrent NTD by 70%. Another trial using a multivitamin that included 800 ug of folic acid in women without a history of NTD was stopped early because of a clear benefit. "This is the only definitively proven benefit of a multivitamin." *(A recent review article in Lancet December 15, 2001; 358: 2069-73 recommends that folic acid fortification levels be increased to 5 mg daily in women planning a pregnancy. RTJ)*

Cardiovascular disease (**CVD**)

Substantial evidence suggests that low folic acid intake increases risk of CVD through its inverse effect on homocysteine. High homocysteine levels are associated with increased risk. Inadequate intake of folic acid, and to a lesser extent inadequate vitamin B6 and B12 intake, leads to increased homocysteine levels. Higher folic acid intake, use of multivitamins, and higher blood folate levels are all associated with a lower risk of CVD.

Although the optimal folic acid intake remains uncertain, an intake of 400 ug daily (the RDA and the amount found in most multivitamin supplements) minimizes blood homocysteine levels in most persons.

Most Americans take in about 200 ug daily in their diet. The new food fortification programs increase intake to about 300 ug. Most consume less than 400 ug. Multivitamin users have lower homocysteine levels than non-users.

Cancer:

Higher intake of folic acid is associated with a lower risk of colon and breast cancer, particularly among persons at increased risk because of daily alcohol consumption. Alcohol interferes with folic acid absorption and metabolism. This may account for the increased folate requirements among drinkers.

Vitamin B6

Intake below the RDA of 2 mg is associated with an increased risk of CVD. It is not clear whether the association is independent of folic acid intake.

Vitamin B12

Low blood levels (<258 pmol/L) are caused primarily by reduced absorption in the elderly with low gastric acidity. Crystalline B12 (the form in multivitamin supplements) does not require gastric acid for absorption. An estimated 12% of elderly Americans are deficient in B12 stores. Low levels are also associated with high homocysteine levels.

Vitamin D:

Sun exposure alone cannot provide adequate vitamin D in Northern latitudes during winter months. The amount produced by sunlight is insufficient to minimize risk of osteoporosis and fractures. Among patients admitted to a Boston hospital, over half were deficient. Few foods naturally contain vitamin D. Fortified milk is the main source. Reasonable evidence suggests that many would benefit from supplemental vitamin D to reach the RDA of 400 IU. Double this amount may be desirable for some persons. An intake up to 2000 IU is considered safe.

Vitamin E

Data are still accruing about benefit in persons at increased risk of coronary disease. "Even assuming a low probability that vitamin E will eventually be proved efficacious (and we view the probability as fairly high) the likelihood of benefit would still outweigh the very low probability of harm." The commentators suggest a supplement of 400 IU daily as the optimum. (*This is much higher than the content in a multivitamin supplement. RTJ)*

Multivitamin preparations:

Prospective studies have reported that daily use is associated with a lower risk of coronary disease, colon cancer, and breast cancer, particularly among regular consumers of alcohol. A randomized trial among elderly persons reported a reduction in the number of days of illness. A supplement reduced risk of stroke in a nutritionally deficient cohort in China.

All these results must be replicated.

Conclusion and Recommendations:

Given the greater likelihood of benefit than harm, and the low cost, the commentators recommend a daily vitamin supplement that does not exceed the RDA of its component vitamins. (*The benefit/harm-cost ratio is very high*) This is especially important in women who may become pregnant, the elderly, those who regularly consume alcohol, and vegans (who require supplemental B12), and poor urban residents who may be unable to afford adequate intake of fruits and vegetables.

NEJM December 20, 2001; 345: 1819-24 "Clinical Practice", commentary by Walter C Willett and Meir J Stampher, Harvard School of Public Health, Boston, Mass. **www.nejm.org**

Comment:

This does indeed, represent a sea change from past recommendations. However, prestigious governmental panels and professional societies still recommend that vitamins and minerals be obtained from food sources rather than supplements. Some do recommend supplements in addition to a good diet to ensure nutritional needs are met. Folic acid supplements are also recommended.

This is a good example of the influence of a combination of low harm and low cost in tilting recommendations toward more universal use.

Supplemental vitamin D combined with calcium is an important clinical application in growing females to build maximum bone density at the end of the growth period. Many young persons do not drink milk.

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Steroids prevent "priming". Antihistamines do not.

12-4 SUPERIORITY OF AN INTRANASAL CORTICOSTEROID COMPARED WITH AN ORAL ANTIHISTAMINE IN THE AS-NEEDED TREATMENT OF ALLERGIC RHINITIS

Guidelines recommend use of histamine (**H1**) blockers as first-line treatment of mild allergic rhinitis. More severe cases are treated with intranasal corticosteroids.

H1 blockers have a rapid onset of action (within hours) and are suitable for as-needed therapy when seeking immediate relief. Intranasal fluticasone given intranasally has an onset of action within 12 hours. A peak effect occurs after several days. Both drugs have proved to be effective.

Allergic individuals challenged with an appropriate allergen react within minutes with an early response characterized by mast cell degranulation, histamine release and typical symptoms. This early response is followed hours later by a cellular influx of eosinophiles and an increase in nasal reactivity to further allergen exposure. This is called "priming". The late response is less dramatic than the early response. Its role has not been clearly defined. Antihistamines have *not* been shown to reduce eosinophile influx, block priming, or reduce symptoms of the late response. Intranasal corticosteroids have profound inhibitory effects on the late response.

These investigators hypothesized that allergic persons who use medications as needed would treat themselves after sensing an early reaction. Taking an antihistamine at this time would not affect the symptoms of an early reaction because symptoms dissipate within minutes, leaving no time for the antihistamine to work. In essence, antihistamines would be effective against symptoms associated with the next *immediate* response, provided the

drug is at therapeutic levels at this time. The antihistamine would not prevent allergic inflammation and priming from developing. Thus, as the season progressed, immediate symptoms in response to further allergen exposure would increase.

An intranasal corticosteroid taken *after* a patient senses the symptoms of an immediate response would be expected to block eosinophile infiltration and priming. It would also be expected to reduce any contribution of the late response to clinical disease. As the season progresses, priming would not occur, and the symptoms due to repeated allergen exposure would be less severe. Therefore, the investigators hypothesized that as-needed use of intranasal corticosteroids would reduce allergic inflammation and provide superior relief compared with as-needed antihistamines.

This study compared effectiveness of as-needed use of an oral histamine blocker (loratidine; *Claratin*) with intranasal fluticasone (*Flonase*).

Conclusion: As-needed fluticasone was more effective than as-needed histamine blocker.

STUDY

1. Randomized, open-label, parallel group study entered 88 persons with seasonal allergic rhinitis.
   All had a positive skin test for ragweed.
2. Randomized to: 1) as needed fluticasone nasal spray -- two 50 ug sprays per nostril (total of 4 sprays) or,
   2) as needed loratidine 10 mg daily.
3. Assessed symptom and quality of life scores.

RESULTS

1. The median total symptom score in the fluticasone group was 4.0 vs 7.0 in the loratadine group.
2. After treatment, the number of eosinophiles was significantly smaller in the fluticasone group.

DISCUSSION

1. In this study, it was assumed that patients would elect to take the medications after the immediate reaction appeared, and before eosinophilic infiltration and changes in reactivity occurred. Thus, as the season progressed, in the fluticasone group, eosinophile infiltration and an increase in reactivity to allergen would not occur.
3. In contrast, as-needed H1 blockers does not prevent eosinophile infiltration and priming.
   Symptoms scores and quality of life would worsen as the season progressed.
4. The study does not exclude the benefits of continuous intranasal corticosteroid use which may offer additional benefits.
5. Other trials, which demonstrated efficacy, used oral antihistamines continuously. Thus, medication was in essence given prophylactically.
6. The investigators question the efficacy of intermittent use of antihistamines when taken after exposure to the allergen.

7. "Our data support the efficacy of fluticasone nasal spray in the treatment of seasonal allergic rhinitis and the superiority of its as-needed use compared with that of an as-needed H1 receptor blocker."
8. It would seem logical to use intranasal corticosteroids as first-line therapy. It could be used regularly to treat severe disease, and used as-needed for mild disease.

CONCLUSION

As-needed intranasal corticosteroid spray reduced allergic inflammation. It was more effective than as-needed H1 blockers in the treatment of seasonal allergic rhinitis.

Archives Int Med November 26, 2001; 161: 2581-87 Original investigation, first author Scott M Kasuba, University of Chicago, IL **www.archinternmed.com**

Comment:

Study supported in part by Glaxco Wellcome

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The combination of more effective

12-5 COMPARISON OF CEFUROXIME WITH AND WITHOUT FLUTICASONE FOR THE TREATMENT OF RHINOSINUSITIS

Inhaled corticosteroids are often combined with antibiotics to treat patients with chronic, persistent sinusitis.

In theory, by decreasing the inflammatory response and reducing mucosal swelling, corticosteroids should promote drainage and increase aeration of sinuses, hastening elimination of infecting organisms.

This study assessed whether the addition of an intranasal corticosteroid to antibiotic therapy would speed recovery. Is the combination beneficial?

Conclusion: The combination improved clinical success rates.

STUDY

1. Double-blind, randomized, placebo-controlled trial followed 88 patients to completion.
   All had a history of recurrent or chronic rhinitis and evidence of acute infection on X-ray or nasal endoscopy.
   All had a history of previously diagnosed sinusitis that necessitated antibiotic therapy.
2. All had at least 2 of 5 major symptoms of sinusitis: headache; facial pain; nasal congestion; thick, colored nasal discharge; olfactory disturbance.
2. Randomized to: 1) Two puffs of fluticasone propionate (*Flonase*; a synthetic corticosteroid) in each nostril daily for 21 days; or 2) Placebo spray.
3. All also received inhaled xylometazoline (*Nature-vent*; over the counter) twice daily for 3 days, and cefuroxime (*Ceftin* -- a broad spectrum cefalosporin) 250 mg twice daily for 10 days.
4. Main outcome—clinical success (cure or much improved). Follow-up at 10, 21, and 56 days.

RESULTS

1. Those receiving fluticasone achieved a significantly higher rate of clinical success than placebo.
   (94% vs 74%)
2. Patients receiving fluticasone improved more rapidly. (6 days vs 10 days)

DISCUSSION

1. Fluticasone is a once-a-day intranasal corticosteroid indicated for management of allergic rhinitis.
2. Cefuroxime has been shown to be effective in treatment of acute bacterial sinusitis.
3.The NNT(benefit one patient - 3 weeks) = 6.
4. Xylometazoline may have aided the distribution of fluticasone in the nasal passages.

CONCLUSION

The addition of fluticasone to xylometazoline and cefuroxime improved clinical success rates and accelerated recovery of patients with a history of chronic recurrent sinusitis who presented with acute sinusitis.

JAMA December 26, 2001; 286: 3097-3105 Original investigation (The Ceftin and Flonase for Sinusitis study; CAFFS) first author Rowena J Dolor, Duke Clinical Research Institute, Durham, NC. **www.jama.com**

Comment:

This is another example of a therapy which may be restricted to few patients in primary care—465 patients were screened; 354 not eligible; 15 eligible patients refused randomization; 95 randomized; 88 completed follow-up (only 19% completed).

Glaxco-SmithKline was involved in the study.

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An entirely new potential therapy

12-6 EFFECT OF OMALIZUMAB ON SYMPTOMS OF SEASONAL ALLERGIC RHINITIS

Allergic rhinitis is an IgE-mediated condition. Symptoms are triggered by exposure to allergens. In sensitive persons, symptoms appear almost as soon as pollenization begins. Many patients are treated in primary care settings with combined intranasal corticosteroids and anti-histamines.

A recombinant humanized anti-IgE antibody (omalizumab) was recently developed. It binds specifically to a unique binding site (epitope) on human free IgE. This blocks the binding of IgE to mast cells and basophiles. Free IgE levels in the circulation are reduced.

This study assessed safety and efficacy of omalizumab for prophylaxis of seasonal allergic rhinitis.

Conclusion: Omalizumab was safe and provided clinical benefit.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 250 patients. All had moderate to

severe ragweed-induced seasonal allergic rhinitis and a positive skin test for ragweed.

2. Randomized to: 1) omalizumab 300 mg subcutaneously, or 2) placebo injection just prior to the ragweed season. Injections were repeated every 3 to 4 weeks during the season. (About 12 weeks)
3. Main outcome measures -- self-assessed symptom severity, rescue antihistamine use, and rhinitis-specific quality of life.

RESULTS

1. Nasal symptom severity and duration scores were significantly lower in patients receiving omalizumab. Use of rescue antihistamine was less frequent. Quality-of-life scores were consistently better.
2. Benefits did not decline during the season.
3. Serum free IgE levels declined in the omalizumab group. Patients with the lowest free IgE had the lowest symptom score.
4. Frequency of adverse events did not differ between groups.

DISCUSSION

1. Lowering free IgE with a specific blocker provided clinical benefit. Benefit continued unabated during the season as injections were repeated every 3 to 4 weeks.
2. Treatment was begun before the onset of the ragweed season. It was hypothesized that beginning before symptoms developed might prevent the priming effect. (*See previous abstract.*)
3. Questions remain: Will blocking IgE activity lower resistance to other infection -- eg, parasitic?

CONCLUSION

Omalizumab. an IgE blocking antibody, provided significant relief from allergic rhinitis. And reduced serum free IgE levels.

JAMA December 19, 2001; 286: 2956-67 Original investigation, first author Thomas B Casale, Creighton University, Omaha Nebraska **www.jama.com**

An editorial in this issue of JAMA (p 3005-06) comments:

Omalizumab does not appear to stimulate an immune response against itself. It can bind more than 95% of free serum IgE. The decrease in IgE induces a rapid and marked decrease in IgE receptors on basophiles and mast cells. This combined action results in a substantial reduction in allergen-stimulated mediator release.

Recent studies have also reported benefit in asthma patients.

Comment:

Study supported in part by Novartis and Genentec.

This is a report of a cutting-edge technology. We await a description of the place it might play in primary care therapy.

The American Academy of Allergy recommends either oral antihistamines (with or without a decongestant) or nasal corticosteroids as first-line therapy for severe rhinitis. Some patients may require a short course of oral corticosteroids.

Practical point: None at this point. I abstracted the article because of its potential.

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A simpler, more accurate measure of risk?

12-7 TOTAL CHOLESTEROL/HDL-CHOLESTEROL RATIO VS LDL-CHOLESTEROL/HDL-CHOLESTEROL RATIO AS INDICES OF ISCHEMIC HEART RISK IN MEN

Both the total-cholesterol/HDL-cholesterol [Total-c/HDL-c] ratio and the LDL-cholesterol/HDL-cholesterol [LDL-c/HDL-c] ratios are used to predict ischemic heart disease. This study asks — which is a better predictor?

There is overwhelming evidence that a high LDL-c is atherogenic and a high HDL-c is cardioprotective. The LDL-c/HDL-c ratio is emphasized by guidelines. This ignores the cholesterol contained in triglycerides (**TG**).

Prospective studies have suggested that a high LDL-c/HDL-c ratio, combined with hypertriglyceridemia is associated with the highest ischemic heart disease (**IHD**) risk. A high LDL-c, low HDL-c, and high TG has been described as the dyslipidemic triad. The investigators believed this approach could be simplified by using the TG/HDL-c ratio. In individuals with elevated TG levels the cholesterol content in the very low density lipoprotein (**VLDL**) fraction is high. Measuring or calculating the LDL-c/HDL-c ratio may underestimate the magnitude of the dyslipidemic state by ignoring the cholesterol content of the TG.

Since there is a high prevalence of hypertriglyceridemia in the population, the total-c /HDL-c ratio may be a better predictor of CHD. (Total cholesterol includes LDL-c, HDL-c and the cholesterol in TG.

Conclusion: The total cholesterol/HDL-c ratio was a useful and simple index of ISD risk in this study.

STUDY

1. Entered over 2100 middle aged men (mean age = 57). None had known ischemic heart disease.
   Excluded men with TG over 400.
2. Measured metabolic profiles in the fasting state. LDL-c was calculated by the Friedewald equation.
   (LDL-c = Total-c - (HDL-c + TG/5)
3. Classified the cohort into tertiles according to the fasting TG levels.
4. Compared total-cholesterol/HDL-c ratio with LDL-c/HDL-c ratio in each tertile of TG. Determined the incidence of CHD in each tertile of TG over 5 years.

RESULTS

1. Overall, those who developed CHD, as expected, had a more unfavorable metabolic profile — higher TG, higher LDL-c, higher T-c, lower HDL-c and higher LDL-c/HDL-c ratio.
2. An elevated TC/HDL-c ratio in men was observed among overweight, hyperinsulinemic

and hypertriglyceridemic individuals. These atherogenic metabolic alterations may not always be reflected by the variation in the LDL-c/HDL-c ratio.

3. The TC/HDL-c ratio was the strongest predictor of ischemic heart disease risk. There was a progressive increase in risk across quintiles as TC/HDL-c ratio increased. Risk of those in the first quintile (TC/HDL-c = 3.7) was considered 1.00 (referent). Odds ratio of risk of ISD increased progressively in each quintile up to quintile 5 (TC/HDL-c = 8.4) where the relative risk was 4.
4. The odds ratio of the LDL-c/HDL-c ratio did not rise as quickly. It was not until the 4th and 5th quintiles of LDL-c/HDL-c ratio that odds ratio increased to above 3.

DISCUSSION

1. High TG-low HDL-c dyslipidemia is often linked to abdominal obesity and insulin resistance.
2. LDL-c levels are usually calculated from 3 measurements — TC, HDL-c and TG.
   [The Friedewald equation: LDL-c = T-c - (HDL-c + Tg/5)]. There is considerable cholesterol in TGs. The higher the TG, the more the cholesterol in TG is ignored in the calculation of the cholesterol risk factor.
3. LDL-c is most often calculated rather than measured. The calculation of TG/HDL-c ratio eliminates this step. As much as 25% variation can occur in the calculated LDL-c depending on the TG level.
4. The men who developed ISD in the study had a mean TG > 177 (considered high) and low HDL-c (< 35), They also had a higher body mass index and elevated insulin levels as compared with normolipidemic men despite identical LDL-c levels in the 2 groups.
5. The relative cholesterol content increased across TG quintiles.
6. The high TC/HDL-c ratio was also associated with an increase in small, dense LDL particles (another risk factor).

CONCLUSION

In addition to the well-established conventional risk factors, the Total-c/HDL-c ratio may represent an important cumulative index of the presence of an atherogenic dyslipidemic profile associated with insulin resistance.

It was a simple index of IHD risk in men in this study.

Calculation of the LDL-c/HDL-c ratio may underestimate IHD risk in some patients.

Annals Int Med December 10/24 2001; 161: 2685-92 Original investigation by the Quebec Cardiovascular Study, first author Isabelle Lemieux, Laval Hospital Sainte-Foy, Quebec, Canada. **www.annals.org**

Comment:

This asks— Should the content of cholesterol in triglycerides (20%) be considered in assessing risk? I believe it should.

Another ratio has been used in some studies is the HDL-c/non-HDL-c. This would include the cholesterol in TG. Only 2 determinations must be made -- total cholesterol and HDL-cholesterol.

Total cholesterol alone is not a good marker for risk, simply because it disregards the protective effect of any increase in HDL-c. The admonition, "Know your cholesterol" should be amended to "Know your total cholesterol and high-density cholesterol".

There is considerable cholesterol in TGs. The higher the TG, the more the cholesterol in TG is ignored in the calculation of the cholesterol risk factor.

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Nibbling versus gorging.

12-8 FREQUENCY OF EATING AND CONCENTRATIONS OF SERUM CHOLESTEROL

Some data suggest that people who eat frequently tend to have lower total and LDL cholesterol as compared with those who eat a gorging diet.

This study examined the relation between self-reported eating frequency and serum lipids.

Conclusion: Total cholesterol and LDL-cholesterol were lower in those eating frequently.

STUDY

1. Cross sectional population study obtained information from a cohort of over 14 500 men and women.
2. Questionnaire determined frequency of eating. "How many times a day do you eat, including meals, snacks, biscuits with coffee breaks."
3. Divided the cohort into 5 categories of eating frequency — one or 2 times daily; three times a day; four times; five times; and six times.
4. Participants also completed a 160 item food frequency questionnaire.
5. Determined concentrations of blood lipids.

RESULTS

1. Mean concentrations of total cholesterol and LDL cholesterol decreased in a continuous manner as frequency of eating increased.
2. In men eating once or twice a day vs 6 times a day, mean total cholesterol was 6.11 vs 5.94 mmol/L (235 vs 228 mg/dL; 3% difference). LDL-cholesterol decreased from 4.06 to 3.86 (156 vs 148). Similar changes in women.
3. But, the HDL-cholesterol also decreased as frequency of eating increased. Thus, the ratio of LDL-cholesterol to HDL-cholesterol remained the same.
4. Increased frequency of eating was associated with higher daily intake of energy, fat, fatty acids, carbohydrate, and protein. Body mass index did not differ between the 1 to 2 meal-daily and the 6 meal-daily groups
5. Observed no consistent relation to waist/hip ratio, or BP.

DISCUSSION

1. The results might be explained by confounding factors. Frequency of eating might be a marker of a particular lifestyle such as physical activity and alcohol intake that might directly affect lipids.
2. The improvement in cholesterol was particularly striking in view of the increased energy intake in the frequent eaters and their increased consumption of fats.
3. Finding lower cholesterol levels with increased frequency of eating is consistent with observational studies and controlled interventions on metabolic wards which show a strong and independent relation between lipid concentrations and frequency of eating.
4. Gorging animals may have an adaptive mechanism—they are able to store energy from a few periodic loads of food, in contrast to nibbling animals. which feed continuously and have steady metabolism. This biological process, called "adaptive hyperlipogenesis", is characterized by higher gastrointestinal absorption of glucose, increased activity of pancreatic enzymes; increased ability to produce fat from glucose (ie, enhanced hepatic lipogenesis probably mediated by insulin action); increased hepatic synthesis of cholesterol; increased total mass of fat; and higher postprandial peaks of insulin and increased sensitivity to insulin in fat tissue. Both lipid and glucose metabolism are affected.
5. The metabolic adaptations of gorging may apply to humans, leading to an increased risk of cardiovascular disease.
6. Although the cholesterol differences were not large, the lower levels in the frequent-eater group were comparable to differences achieved by altering intake of dietary fat. A reduction of LDL-c by 5% has been reported in observational studies to be associated with a reduction in coronary heart disease by 10% to 20%.

CONCLUSION

In a general population, concentrations of total cholesterol and LDL cholesterol were decreased consistently by increased frequency of eating. "We need to consider not just what we eat, but how often we eat."

BMJ December 1, 2001; 323: 1286-88 Original investigation, first author Silvia M O Titan, University of Cambridge, UK **www.bmj.com/cgi/content/full/323/7324/1286**

Comment:

It makes sense to me that binge eating stresses the metabolic system and leads to disturbed glucose and lipid metabolism. Diabetic patients are encouraged to consume foods with a low glycemic index. Frequent small meals would have a lower glycemic index than heavy meals. (Ie, postprandial glucose and insulin levels would be lower), although the duration of post prandial hyperglycemia and insulin elevation may be increased.

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12-9 INDIGESTION: WHEN IS IT FUNCTIONAL?

Patients often complain of "indigestion". This may be defined differently by individual patients. To some it is heartburn and acid regurgitation; others may describe abdominal rumblings and belching; others, non-painful discomfort in the upper abdomen (fullness, bloating, early satiety).

"Dyspepsia" is best restricted to mean pain or discomfort centered in the upper abdomen.

There are many causes of dyspepsia. But, at least two thirds of patients have no structural or biochemical explanation for their symptoms.

It has been suggested that dyspepsia can be subdivided based on clusters of symptoms. But, subgroups have not proved to be of value in identifying the underlying cause. Symptoms overlap considerably.

Causes of dyspepsia:

History taking is the key to identifying likely causes.

Subgroups of symptoms can be:

Ulcer-like	38%
Gastro-esophageal reflux-like	37%
Dysmotility-like	21%
Non-specific	27%

There is considerable over-lap. Some symptoms suggest two categories; a few suggest 3.

Peptic ulcer: Many textbooks continue to propagate the myth that symptoms can accurately identify peptic ulcer disease. Classical ulcer symptoms often occur in patients with functional dyspepsia; many patients with ulcer have atypical complaints. Peptic ulcer is rare in patients who are *H pylori* negative and are not taking NSAIDs.

Gastro-esophageal reflux disease (GERD): It is important to distinguish GERD from other causes of dyspepsia. Frequent heartburn (acid regurgitation) is the cardinal symptom. Characteristically, it is relieved transiently by antacids and precipitated by a meal or by lying down. The majority of patients complain also of epigastric pain or discomfort. The majority of diagnoses can be made by history.

Gastric cancer: Fear of cancer is a main reason patients with dyspepsia present to primary care. It is present in less than 2% of all cases referred for endoscopy. The majority of patients with early cancer initially present with dyspepsia. Under age 55, gastric cancer is rare. Endoscopy is recommended for older patients presenting with new symptoms of dyspepsia and in all patients with alarm symptoms (anemia, anorexia, weight loss, melena, hemetemesis, dysphagia).

Gall stones: Biliary colic is severe, episodic, and constant (rather than colicky) pain in the epigastrium or right upper quadrant. The pain is easily distinguishable from the discomfort of functional dyspepsia. Stones are common in the absence of symptoms. May patients with gall stones complain of bloating, nausea, and other vague upper abdominal symptoms. But, these symptoms are just as common in patients without stones. Cholecystectomy does not reliably result in long term relief of symptoms. Cholecystectomy in a patient with non-biliary type discomfort is likely to result in a diagnosis of post-cholecystectomy syndrome.

Functional (non-ulcer) dyspepsia: commonly, when no abnormalities, or irrelevant abnormalities are found on endoscopy, this label is applied. However, when antisecretory drugs are used, ulcers and esophagitis may be healed and a later endoscopy will miss the diagnosis. These drugs are best not started before endoscopy.

Pathogenesis: Is uncertain. *H pylori* infection is found in many, but is also common in asymptomatic persons. Does *H pylori* cause symptoms in patients without ulcer disease? There is no evidence that specific symptoms identify those with infection.

In functional dyspepsia, gastric and duodenal sensation is disturbed (termed at times the "irritable stomach"). In many patients distention of the stomach induces symptoms at lower pressures or volumes than it does in healthy patients. Delayed gastric emptying can be detected in many with functional dyspepsia. Some have altered intragastric distribution of food, which reflects abnormal gastric relaxation (a "stiff" fundus). There is an increased probability of detecting gastric motor abnormalities in women. There is controversy as to whether functional dyspepsia is a "forme fruste" of the irritable bowel syndrome. They may overlap.

Some patients have anxiety disorder or depression. Whether these are causative remains unclear.

Investigation: Older patients and those with alarm symptoms require prompt endoscopy. Testing for *H pylori* will help guide management. Some infected persons will have peptic ulcer disease. If the patient is infected, two approaches may be made: 1) "test and endoscope", or 2) "test and treat". Eradication will relieve dyspepsia in about 10% of patients with functional dyspepsia who are infected. It will relieve symptoms of peptic ulcer if ulcer is present. Recent trials suggest that "test and treat" is safe and cost effective. Long term outcomes are similar to that of prompt endoscopy. It is gaining widespread acceptance.

Principles of management: Reassurance and explanation remain the key elements of therapy. Advise the patient that it is a real condition and that the symptoms are not imaginary. Reassure that it does not lead to cancer or other serious disease. Modify diet to eliminated provoking foods. A low fat diet may help. (High fat foods delay gastric emptying.) Antacids are no better than placebo–-but the placebo response is high.

Initial treatment: A therapeutic trial of acid suppression is worth while. Trials have reported conflicting results. If patient fails to respond in 4 weeks, it is reasonable to consider a prokinetic drug.

Long-term management: Functional dyspepsia is generally a relapsing and remitting condition. Treatment should not be prolonged. Frequent drug holidays should be prescribed. A trial of antispasmodics or antidepressant drugs may be useful. The diagnosis should be confirmed. Some patients benefit from behavioral therapy or psychotherapy.

BMJ December 1, 2001; 323: 1294-97 "Clinical Review", first author Nicholas J Talley, University of Sydney, Australia. **www.bmj.com/cgi/cintent/full/323/7324/1294**

Comment:

Much of this is "old hat" to seasoned primary care clinicians. But, I thought the review was welcome.

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Ibuprofen negates anti-thrombotic action of aspirin

12-10 CYCLO-OXYGENASE INHIBITORS AND THE ANTIPLATELET EFFECTS OF ASPIRIN

Patients with arthritis and vascular disease often receive both NSAIDs (for symptomatic relief) and low-dose aspirin (for primary and secondary prevention of cardiovascular disease).

This study asked — Is there any interaction between aspirin and NSAIDs?

Conclusion: Ibuprofen antagonizes the platelet-inhibiting action of aspirin.

STUDY

1. To mimic clinical use, aspirin (81 mg, enteric coated) was administered once daily followed by ibuprofen (*Advil; Motrin*) 400 mg three times a day.
2. At 6 days, determined serum levels of thromboxane and degree of platelet aggregation as markers of of platelet cyclo-oxygenase activity.
3. Duplicated the study using, in place of ibuprofen, 1) diclofenac (another NSAID,*Voltarin*; delayed release, 75 mg twice daily) and 2) rofecoxib (a cyclo-oxygenase 2 inhibiting; cyclo-oxygenase-1 sparing NSAID; *Vioxx* 25 mg three times daily), and 3) acetaminophen (*Tylenol* ; 1000 mg).

RESULTS

1. When multiple doses of ibuprofen were given after the one daily dose of aspirin, the beneficial effects of aspirin were blocked. Aspirin's effect on inhibiting production of serum thromboxane and inhibiting platelet aggregation effectively stopped. .
2. Diclofenac, rofecoxib, and acetaminophen had no effect on aspirin's action on platelet aggregation and thromboxane production. Benefits of aspirin continued.

DISCUSSION

1. Aspirin reduces incidence of recurrent myocardial infarction and stroke. Many persons take prophylactic low-dose aspirin. Many also take NSAIDs (often over the counter) for symptomatic relief.
2. Neither NSAIDs nor selective cyclo-oxygenase-2 inhibitors would be expected to afford substantial cardioprotection. Inhibition of platelet aggregability commonly does not persist during dosing with NSAIDs.
3. Platelet cyclo-oxygenase-1 activity is unaffected by cyclo-oxygenase-2 (COX-2) inhibitors.
4. The authors suggest that indomethacin (*Indocin*) may also have this inhibiting effect on aspirin.

CONCLUSION

Ibuprofen competitively inhibited the prophylactic (anti-thrombotic) effects of aspirin.

Acetaminophen, COX-2 inhibitors, and diclofenac did not have this antagonistic effect.

NEJM December 20, 2001; 345: 1809-17 Original investigation, first author Francesca Catella-Lawson, University of Pennsylvania School of Medicine, Philadelphia, PA **www.nejm.org**

An editorial in this issue of NEJM comments: This study was performed in vitro. Clinical studies on the dual effects of combined ibuprofen-aspirin have not been done.

The study reminds us that the COX-2 inhibitors may be thrombogenic. They depress prostaglandin production resulting in increased platelet aggregation. Low-dose aspirin may be given in conjunction to blunt this possible adverse effect. (But at the risk of increasing adverse effects on the stomach.)

Anti-thrombotic effects of aspirin:

Platelets contain cyclo-oxygenase-1. This produces a prostaglandin, the derivative of which is thromboxane. Thromboxane promotes platelet aggregation.

Aspirin acetylates cyclo-oxygenase-1 in platelets. When cyclo-oxygenase-1 is acetylated by aspirin (a non-reversible reaction) , production of thromboxane is impaired. (Anti-thrombotic action.) Since platelets are non-nucleated, aspirin will impede thromboxane production for the lifetime of the platelet. Resumption of production requires the synthesis of new platelets. (Approximately 10% daily.)

Anti-thrombotic effects of traditional NSAIDs

The anti-thrombotic effects of traditional NSAIDs in prevention of thrombotic events is not known. Studies thus far do not support any reduction in rate of occurrence of a first myocardial infarction. NSAIDs, unlike aspirin bind *reversibly* to platelets and depress thromboxane production for only a portion of the dosing interval.

Comment:

The study was much more complicated than I have indicated. I abstracted the portion I believed was clinically applicable.

This has an obviously important clinical message.

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There is a synergistic interaction between the two pathological processes

12-11 UNTANGLING VASCULAR DEMENTIA

The role of cerebrovascular disease in dementia is complex and controversial. The term "vascular dementia" has been introduced to include the full spectrum of cerebrovascular diseases that may cause dementia. Alzheimer's disease and vascular dementia have been conceptionalised as two distinct entities that can be differentiated by careful clinical and necropsy evaluation:

Alzheimer's disease has traditionally been marked by insidious onset of memory loss , followed by gradual progression to dementia in the face of normal findings on neurological examination.

Vascular dementia (or multi-infarct dementia) is characterized by stepwise cognitive decline punctuated by episodes of stroke that are accompanied by focal deficits on neurological examination and imaging abnormalities.

However, the situation may not be so simple. Isolated cerebrovascular disease is an uncommon explanation for dementia. Vascular abnormalities commonly co-exist with histological features of Alzheimer's. There is a synergistic interaction between the two pathological processes. Patients with cerebral infarction seem to require a

lesser amount of Alzheimer neuropathology than those without infarction to show signs of dementia. Emphasis is shifting from a differential diagnosis of these disorders to an approach aimed at understanding their interactions.

A recent study followed patients who had an acute stroke for subsequent development of dementia. A substantial number of patients had progressive cognitive deterioration without occurrence of another stroke. In a large proportion of patients with post-stroke dementia, Alzheimer's disease is likely to be a factor. In many patients, dementia was diagnosed shortly after the index stroke. These individuals probably had pre-existing dementia which would have been termed post-stroke dementia. This suggests that Alzheimer's disease may underlie post-stroke dementia.

The Rotterdam study quantified variables such as carotid wall thickness, blood pressure, cholesterol levels, and measures of peripheral vascular disease. All measurements were related to increased risk of dementia.

Questions remain about the mechanism of the interaction between cerebrovascular disease and Alzheimer's in an individual patient. Alzheimer's disease cannot be ruled out by clinical investigation. A diagnosis of vascular dementia does not rule out Alzheimer's. The part that cerebrovascular disease may play in producing symptoms of dementia is particularly difficult to understand when it is accompanied by histological features of Alzheimer's disease.

"It is not surprising that accurate clinical diagnosis of Alzheimer's disease seems to be easier than vascular and mixed dementia. Meanwhile, it is worth noting that although 'pure' vascular dementia exists, vascular disease may be an important and potentially treatable contributor to Alzheimer's disease."

Lancet December 22/29, 2001; 358: 2097-98 Editorial by William Jagust, University of California, Davis.
www.thelancet.com

Comment:

Whatever the part played by cerebrovascular disease may be, we should prevent it as much as possible. There may be great promise in development means to protecting against Alzheimer's, but this is not feasible now. In the meantime, we should protect our brains as well as our hearts.

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RECOMMENDED READING

12-12 ENGAGING PATIENTS IN MEDICAL DECISION MAKING

The end is worthwhile, but the means need to be more practical

The growing consensus that patients ought to be more involved in their own care lies at the confluence of several powerful ideas: political trends, thinking on ethics, and research on health services. As experienced consumers, patients understand that they have rights. They are much less inclined than they used to be to leave medical decisions entirely to the experts.

Autonomy (what the competent, informed patient wants) trumps beneficence (what the doctor thinks best for the patient) in all but the most extreme circumstances.

Recent studies leave the clear impression that, although respecting patients' preferences is a fundamental goal of medicine, these preferences are vulnerable to manipulation and bias.

Three questions dominate the debate about the role of the patient in making treatment decisions:

Can patients take a leading role in making decisions?

Do they want to?

What if doctors and public health professionals don't like their choices?

Many decisions related to health are complicated. Uncertainty in the scientific evidence, variation in how patients value different states of health, and patient's attitude to risk play a role. Some patients prefer a very bad outcome put off into the future to a moderately bad immediate outcome.

Family and culture also play an important, if poorly understood, role in decisions. Cultural beliefs can have a profound influence on decisions regarding treatment. Fully informed shared decision making is difficult to conduct in practice.

Not all patients want to make their own decisions. Many want to delegate responsibility to their doctors. Yet a desire for information is nearly universal. "Most patients want to see the road map, including alternative routes, even if they don't want to take the wheel."

Patients who make decisions will at times select treatments that are less effective than the recommended approach. (Eg, patients with hypertension value the benefits of drugs less than their doctors do.)

Moving toward the goal of collaborative decision making requires more attention to the realities of clinical practice than is currently evident. The 15-minute consultation leaves little time for eliciting patient's preferences and educating them about risks and benefits. Asking how patients understand the illness and how much they want to be involved in treatment decisions can be a foundation for doctors seeking an informed collaborative model of care.

BJM September 15, 2001; 323: 584-85 Editorial, first author Richard L Kravitz, U C Davis Center for Health Services Research in Primary Care, Sacramento, CA **www.bmj.com/cgi/content/full/323/7313/584**

Comment:

Fortunately, primary care clinicians and their patients don't have to negotiate the treatment contract at one visit. This may evolve.

Chronic long-term illness (diabetes, hypertension, coronary heart disease) and their treatments require more informed consent, more negotiation, and more education about benefits, harms, and costs. Patients visiting for short term illnesses will require little negotiation.

US primary care clinicians must be more aware of cultural differences as the diversity of their patients increases.

Even if a patient wishes to follow advice and to choose the best, it simply may not be available on the basis of cost, illiteracy, inadequate family support, unavailability of expert consultants. Primary care clinicians often have the responsibility of deciding on a best second choice.

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Do all women, as they age, develop osteoporosis?

12-13 IDENTIFICATION AND FRACTURE OUTCOMES OF UNDIAGNOSED LOW BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN.

Low bone mass density (**BMD**) is the single best predictor of fracture risk in asymptomatic postmenopausal women. Dual-energy X-ray absorptiometry of the hip and spine is currently the gold standard for measuring BMD. Other lower cost, small portable technologies are now available to test peripheral skeletal sites. These improve access to testing. BMD at appendicular sites (distal radius, finger, and heel) correlates reasonably well with density at the hip and spine. However, clinicians have been reluctant to rely on results of peripheral BMD measurements for management decisions.

Osteoporosis often remains undiagnosed until a fracture occurs.

This study describes the prevalence of low BMD in postmenopausal women and judges the usefulness of peripheral measurements for short-term prediction of fracture risk.

Conclusion: Over half of the cohort had undiagnosed low BMD. Determining BMD at peripheral bone sites was predictive.

STUDY

1. The National Osteoporosis Risk Assessment was a longitudinal observational study of over 200 000 ambulatory postmenopausal women. Mean age = 65. Excluded women taking a bisphosphonate (eg, *Fosamax*) , calcitonin (*Miacalcin*) , or raloxifene (*Evista*). Those taking current estrogen were not excluded.
2. Measured BMD by peripheral bone densitometry at heel, finger and forearm with several different machines (including ultrasound) in physician's offices. Defined low BMD by WHO criteria -- "T scores":
   - T score of 0 denotes the equivalent of mean peak BMD in a population of healthy 20 to 29 year old women.
   - T score of -1 represents a BMD one standard deviation below this mean.
   - T score between -1 and -2.5 = BMD of 1 to 2.5 standard deviations below the mean, arbitrarily defined as "osteopenia".
   - T score -2.5 and lower = BMD of 2.5 and greater standard deviations below the mean, arbitrarily defined as "osteoporosis".
3. Each standard deviation decline in T score is associated with approximately a doubling of relative risk of fracture.
4. Determined risk factors for osteoporosis by questionnaire.
5. Determined fracture rates at 12 months.

RESULTS

1. 39% of the women had osteopenia; 7% had osteoporosis. Eleven % had previous fracture (after

age 45). Osteoporosis was associated with a 4-fold increase in fracture rate. Osteopenia with a 2-fold increase.

2. Increasing age, personal or family history of fracture, Asian of Hispanic heritage, smoking, and use of cortisone predicted increased fracture risk. The effect of advancing age was independent of all other factors. Compared with women age 50-54, odds ratios of osteoporosis increased from 1.8 for women age 55-59 to 23 for women over 80.
3. Higher body mass index, African American heritage, estrogen use, diuretic use, exercise, and use of alcohol predicted lower risk. Both former and current use of estrogen was associated with a reduction in fracture of 25% to 75% respectively. Alcohol use was protective, even use of over 14 drinks per week.
4. Odds ratio of osteoporosis in current users of estrogen was 0.27

DISCUSSION

1. The study confirms several risk factors — low BMI, history of fracture, cigarette smoking, lack of exercise, and non-use of estrogen.
2. Women found to be osteoporotic at any peripheral site were at markedly increased risk of fracture.
3. Different devices and sites yielded different estimates of low BMD. T scores are calculated by each manufacturer of measuring devices. This may lead to different T scores in the same patient when a different measuring device is used. However, women with T scores of -1 to -2.5 by any device were more likely to have fractures. "All peripheral sites measured in NORA showed similar predictive ability for overall fracture risk after accounting for age."
4. Recent studies report that only about one in 5 patients seen with minimal-trauma fractures had received osteoporosis treatment. Indeed, fracture in postmenopausal women implies osteoporosis unless proven otherwise.

CONCLUSION

About half of a large screened population of postmenopausal women had previously undetected low BMD. Determination of low BMD at peripheral sites (distal radius, heel, finger), as well as at hip and spine, was highly predictive of fracture risk.

Given the economic and social costs of osteoporotic fractures, strategies to identify and manage osteoporosis in the primary care setting need to be established.

JAMA December 12, 2001; 286: 2815-22 Original investigation by The National Osteoporosis Risk Assessment Study (NORA), first author Ethel S Siris, Columbia University College of Physicians and Surgeons, New York.
www.jama.com

Comment:

Measurement of BMD at peripheral sites with less expensive and more universally available equipment would advance diagnosis.

Some adverse conditions are almost inevitable as age progresses. This includes postmenopausal osteoporosis, atherosclerosis, isolated systolic BP (due to loss of arterial elasticity), and weight gain. Should we wait for confirmatory tests to determine their presence? If so, opportunities for prevention are lost. Or should we assume that preventive measures for these almost universal risks should be started at the earliest reasonable time.

It seems to me that much expense and better prevention would result from empirical and universal primary interventions. RTJ

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12-14 SAD -- HELP ARRIVES WITH THE DAWN?

At temperate latitudes, the most common type of seasonal affective disorder (**SAD**) is recurrent winter depression. It remits in the spring and summer. Common symptoms are low mood, anergia, irritability, anxiety, poor concentration, reduced libido, and social withdrawal. Patients often have hypersomnia (with daytime somnolence) and a tendency to eat (predominantly carbohydrates and chocolates), and thus gain weight. About 3% of the population is affected to a clinically significant degree.

Since many persons experience some of these symptoms to some extent, SAD may not be a discrete entity, but is a continuum within the population.

A "phase shift" in melatonin secretion has been proposed as a pathogenic mechanism.

Non-sedative antidepressants such as specific serotonin reuptake inhibitors (**SSRIs**) often treat SAD effectively.

Light therapy (exposure to bright artificial light) has generally proved effective. Morning light is more effective than light administered later in the day

A recent investigation compared 30 minutes of bright light at 0600 hours against placebo and against dawn stimulation. Dawn stimulation consists of exposure to white light of gradually increasing brightness which started at 0430 h while the patient is asleep. Brightness peaked at 250 lux in 90 minutes. Placebo consisted of dim red light. Dawn stimulation was associated with a significantly higher rate of remission. and a greater reduction in symptoms than either bright light or placebo. Part of the benefit may have been due to the method of delivery which helped patients adhere to a waking time of 0600 h, and thus a regular sleep schedule.

It has been widely accepted that bright light, used while eyes are open, is necessary for light therapy to be effective. The effectiveness of relatively dim light (250 lux) is therefore puzzling. It may be that dawn stimulation falls on a particularly sensitive part of the light-phase response curve. The dawn signal may be able to phase-adjust circadian rhythms, even though it is of low illuminance. "Certainly, from an evolutionary perspective, it makes sense that human physiology would be entrained to awaken at fairly low ambient light levels."

Lancet December 22/29 2001; 358: 2100 Commentary by John M Eagles, Royal Crown Hospital, Aberdeen, Scotland. **www.thelancet.com**

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12-15 SIMILAR EFFECTIVENESS OF PAROXETINE, FLUOXETINE, AND SERTRALINE IN PRIMARY CARE.

Selective serotonin reuptake inhibitors (**SSRIs**) have become the most commonly prescribed antidepressants. Compared with tricyclic antidepressants they have more favorable adverse effects, and are less toxic in the event of overdose.

This study asks: Is one SSRI superior to others?

Conclusion: No

STUDY

1. Open label randomized trial compared 3 SSRIs in over 550 patients: Paroxetine (*Paxil*); Fluoxetine (*Prozac*); and Sertraline (*Zoloft*) -- starting daily dose = 20 mg; 20 mg; and 50 mg.
2. All were depressed and considered candidates for antidepression medication by their primary care clinicians. About 75% of patients had a major depression.
3. Clinicians were allowed to switch to a second or third medication if there was inadequate response to the first.
4. Judged response by a Health Survey and a Medical Component Summary score.
5. Follow up = 9 months.

RESULTS

1. Responses to the 3 SSRIs were comparable in all measures and at all time points.
2. Mean improvements in scores ranged from + 16 to + 17. Improvement was more rapid in the first 4 weeks of therapy.
3. Incidence of adverse effects and withdrawals were the same. About 25% discontinued or switched because of adverse effects. About 15% stopped because of lack of benefit.

DISCUSSION

1. These "results unequivocally demonstrate the lack of difference among 3 SSRIs across a broad range of outcomes over 9 months". The magnitudes and time course of benefits was similar.
2. Clinically significant adverse events were similar.
3. A fourth SSRI, citalopram (*Celexa*), was not compared. However, several other comparisons have not demonstrated superiority.

CONCLUSION

The 3 SSRIs were similar in effectiveness and adverse effects for depressive symptoms and domains of health-related quality of life over 9 months.

JAMA December 19, 2001; 286: 2947-55 Original investigation, first author Kurt Kroenke, Indiana University School of Medicine, Indianapolis **www.jama.com**

An editorial in this issue by Gregory Simon, Group Health Cooperative, Seattle WA. (p 3003) comments: The fact that SSRIs are equally effective on average does not mean that they are equally effective for individual patients. Among patients who do not respond to one SSRI, half or more will benefit from another drug of the same class.

Similarly, intolerable adverse effects from one SSRI do not necessarily predict intolerable adverse effects from a similar medication. In addition, SSRIs may differ in potential for drug interactions: fluoxetine and paroxetine are more likely to inhibit action of the cytochrome P450 enzyme in the liver. This is an important consideration since drugs such as beta-blockers, anti-psychotic agents, and many others, are metabolized by this enzyme.

Fewer than half the patients in the trial experienced a good outcome with the original prescription. The remainder discontinued or changed medication because of adverse effects or lack of benefit. "With appropriate dose adjustment or medication changes, the majority of these initial treatment failures can be converted into successes."

Comment:

We would look for a price advantage under these circumstances. There is none. My latest figures for *wholesale* price -- About $2.50 daily.

Note that about 4 out of 10 patients had serious adverse events or withdrew for lack of benefit. The primary care clinician then must ask herself -- What do I do now? The editorialist captures an element of primary care practice regarding drug therapy. Dose adjustments and switching drug classes are standard approaches used regularly to attempt to address individual patient's responses. The risk of adverse effects when multiple drugs are prescribed is increased when the action of cytochrome enzymes is inhibited or enhanced by another drug. I would, as a general rule, if possible, choose a first drug which is not metabolized by the CY P450 system. We can never be sure when a patient might receive a second drug, either prescribed or over-the-counter, which also interferes with the P450 system.

Sertraline (Zoloft) may have the advantage of a lesser effect on the CY P450 system.

There is another consideration regarding drug-drug interactions -- competing effects on protein binding. Drugs highly bound (eg, sertraline) may displace other tightly bound and vice versa.

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12-16 BLOOD PRESSURE REDUCTION AND CARDIOVASCULAR RISK IN HOPE STUDY

Angiotensin-converting enzyme (**ACE**) inhibitors lower BP. Potentially, they have other protective effects.

The HOPE study[1] reported that ramipril (*Altace*), 10 mg daily, lowered BP modestly in *high risk* patients. Most were *normotensive* at baseline. BP declined slightly more in the treatment group than in the placebo group. (A mean of 3.3/1.4 mm Hg.) But the treatment group experienced a 22% relative reduction in cardiovascular outcomes over 5 years.

The benefits of ramipril were much greater than expected from the BP reduction.

The investigatory concluded that ramipril confers substantial benefits *in addition* to any BP-lowering effect, and thus may be superior to other antihypertension drugs.

Lancet December 22/29, 2001; 358: 2130-31 Original study from the HOPE investigators, first author Peter Sleight, John Radcliffe Hospital, Oxford, UK **www.the lancet.com**

1 "Heart Outcomes Prevention Evaluation Study" NEJM 2000; 342: 145-53 See Practical Pointers January 2000 (1-3)

Comment:

I abstracted this brief report as a demonstration of a continuing controversy. Do antihypertension drugs offer any protective benefit beyond that offered by their BP lowering effect? A detailed meta-analysis "Cardiovascular Protection and Blood Pressure Reduction" (Lancet October 20, 2001) reported that all antihypertension drugs have similar long-term efficacy and safety in providing cardiovascular protection.

The first goal in treatment of hypertension by primary care clinicians should be lowering the BP to recommended levels -- combined by treatment of all risk factors in addition to the hypertension. I believe that when this is accomplished, any particular drug used will have little additional benefit. RTJ

For *normotensive* patients who are at high risk of cardiovascular morbidity for reasons beside the BP, I believe data are insufficient to recommend routine prophylaxis with ACE inhibitors.

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RECOMMENDED READING

12-17 PHYSICIAN CHARTER OF PROFESSIONALISM

"Lots of people are terribly worried about what's happening with medicine and what it is forcing physicians to do. Physicians are under a great deal of pressure because of things that are beyond their control.

Physicians need to say –-"This is who we are and what we do" .

A campaign to shore up physicians' special place in society has resulted in a *Charter of Professionalism.* The charter reminds physicians that satisfying in full the expectations of a medical professional is still within their control. Physicians may lead a full and satisfying life of medicine. Physicians take great satisfaction in carrying out their work competently. They love to do the things they do well. They love to know that their patients appreciate their efforts. These are major rewards.

The Physician Charter of Professionalism contains three fundamental principles:

Primacy of patient welfare

Patient autonomy

Social justice

And a set of 10 commitments:

Professional competence

Honesty with patients

Patient confidentiality

Maintaining appropriate relations with patients

Improving quality of care

Improving access to care

Just distribution of finite resources

Scientific knowledge

Maintaining trust by managing conflicts of interest

Professional responsibilities.

Annals Int Med December 26, 2001; 286: 3065-66 "Medical News and Perspectives" Annals of Internal Medicine's Harold Sox, MD, Discusses Physician Charter of Professionalism **www.annals.org**

The charter is a project driven by the American Board of Internal Medicine, The American Society of Internal Medicine Foundation, and the European Federation of Internal Medicine. It is intended as a model across all fields of medicine.

Comment:

They suggest that a copy of the Charter be displayed in the physician's office.

This is a list of daunting responsibilities for the individual physician as well as the profession

I believe it essential to educate the public about the responsibilities their physician accepts.

Post the Charter in the office.

Discuss it with individual patients, explaining the conflicts between best of care and reality of the market place.

Distribute the charter in patient's statements.

Discuss the charter in civic club meetings and letters to the editor of local press.

Goals are important even though they are never completely reached.

Lancet also comments on the charter. February 9, 2002; 359: 520 (www.the lancet.com)

BMJ published a similar "Declaration of a New Doctor" BMJ December 22-29; 323: 1440-41

www.bmj.com/cgi/content/full/323/7327/1440

It's still a privilege to practice medicine.

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12-18 GOOD LORD, DELIVER US

"From the inability to let well enough alone; from too much zeal for the new and contempt for what is old; for putting knowledge above wisdom, science before art, and cleverness above common sense; from treating patients as cases; and from making the cure of the disease more grievous than the endurance of the same; Good Lord, deliver us"

BMJ December 15, 2001; 323" 1397 Quoted form Robert Hutchison BMJ 1953;i:671

www.bmj.com/cgi/content/full/323/7326/1397