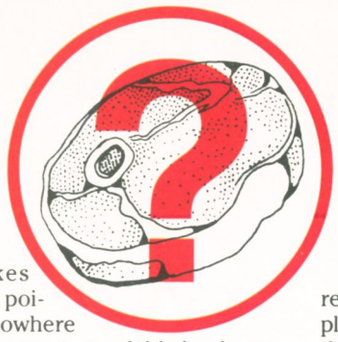

Paring Protein

Low-protein cuisines may slow aging

By JANET RALOFF

Dose makes the poison. And nowhere do we get a better taste of this fundamental tenet of toxicology than in our diet.

"It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that [cause cancer in rodents]," states a report in the Oct. 8 SCIENCE by Bruce N. Ames of the University of California, Berkeley, and his coworkers. Because coffee, tea, beer, and wine do too, foods and beverages provide humans an "enormous background of exposure" to carcinogens, the researchers contend. But they conclude that most of these carcinogens should pose little health risk at typical dietary levels.

Indeed, the traditional focus on trace contaminants in foods has distracted attention from a far more pervasive dietary threat: the sheer size of modern Western diets.

A growing number of animal studies indicate that restricting calorie consumption – to amounts some might characterize as near-starvation rations – may extend the life span by reducing the incidence of chronic, deadly disease (SN: 8/27/88, p.142; 10/5/91, p.215). Though largely unappealing, the take-home message for human diners has been that protracted underindulgence may pave the way to longevity.

But wait. There may be a more palatable alternative, argues Linda D. Youngman, a nutritional biochemist at the Imperial Cancer Research Fund Cancer Studies Unit at the University of Oxford in England. Rather than limit calories, limit protein, she suggests. In a pair of new papers, Youngman and her colleagues show that animals fed low-protein diets can chow down as much as they want – and derive many of the same benefits as animals with calorie restrictions.

Youngman and T. Colin Campbell of Cornell University used diet restriction to cut cancer rates in rats exposed to aflatoxin, a liver carcinogen. But they limited protein, not calories. Indeed, they allowed their 800 animals to eat all they wanted.

The researchers randomly assigned rats to low-, medium-, or high-protein diets – containing by weight 6, 14, and 22 percent casein, the primary protein in milk. Only the 6-percent-casein diet fell below the recommended daily protein allowance for growing rats (roughly 14 percent as casein); to prevent deficiency-related disease, this chow included supplements of certain essential amino acids, the basic building blocks of proteins.

Although rats eating low-protein feed consumed more calories than rats in the other two groups, they grew significantly less, Youngman and Campbell report in the September CARCINOGENESIS. More important, "the incidence of early [precancerous] lesions, the incidence of early tumors, and the incidence of advanced tumors and metastases were definitely lower in the low-protein-fed animals" than in those eating 22 percent protein, Youngman says. And this held true at every time point studied: 6, 12, 40, 58, and 100 weeks – "when they're quite geriatric," she notes. Tumor rates for animals feeding on the medium-protein chow fell somewhere in between.

Nor was the antitumor effect of protein restriction confined to chemically induced liver cancers. "At the end of my study, I looked at the incidence of other tumors – kidney, lung, any kind," Youngman says. And again, the incidence was far lower in the low-protein-fed group than in the high-protein-fed animals, she says. "The difference was quite striking."

Looking for a mechanism to explain the low-protein diet's effects, Youngman collaborated with Ames and his colleagues at Berkeley. They fed 3-week-old rats calorie- or protein-restricted diets for 6 or 12 weeks. They also gave the animals a high, sublethal dose of radiation twice each week to generate free radicals – reactive molecular fragments that produce cellular damage that mimics aging.

In the Oct. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, the Youngman-Ames team reports that both calorie-restricted and protein-restricted animals incurred less radiation-induced free-radical damage to their body proteins than did cohorts allowed to eat their fill of a typical, high-protein chow.

These and related animal studies suggest that protein and calorie restriction offer a number of common benefits, Youngman says. Such benefits include inhibition of tumors, extension of functional life, reduced body weight, improved cell-mediated immunity, and increased antioxidant defenses.

"I don't think any one of these is *the* functional mechanism," she adds. "They probably work together to protect [against disease]."

Protein restriction may offer other benefits as well. Researchers led by Erkki Ruoslahti of the La Jolla (Calif.) Cancer Research Foundation have shown, for instance, that low-protein diets reduce the production of transforming growth factor-beta (TGF-beta), at least in rat kidneys.

TGF-beta induces formation of extracellular matrix. Accumulations of this structural material not only make up scar tissue, but also can clog the filtering apparatus (glomeruli) within the kidneys, leading to potentially life-threatening inflammations.

In the Nov. 1, 1991 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Ruoslahti and colleagues at the University of Utah in Salt Lake City note that rats fed very low levels of protein (7 percent casein), compared with rats fed normal levels (25 percent casein), secrete less TGF-beta and avoid a buildup of extracellular matrix within the glomeruli of the kidneys.

Because TGF-beta is a tumor promoter and because it occurs throughout the body, these findings suggest another mechanism whereby low-protein diets might fight cancer, Ruoslahti notes.

They also highlight another similarity to calorie restriction. "Our [animal] studies – and we've been working on calorie restriction for about six years – indicate that calorie restriction works [to increase longevity] by altering the hormonal and growth-factor status of an animal," says Angelo Turturro of the National Center for Toxicological Research in Jefferson, Ark. Severe calorie restriction, he says, essentially shuts down production of many hormones and growth factors, causing cancer rates to drop, hypertension to disappear, heart stress to diminish, and immunity to increase. "Everything changes," he says, "including [rates of] DNA repair."

In rabbit studies conducted over the past several years, consumption of proteins from meat, eggs, or milk elevated concentrations of cholesterol in the blood – even in the absence of dietary cholesterol – and gave the animals atherosclerosis, says Kenneth K. Carroll of the University of Western Ontario in London, Ontario. Protein derived from soybeans caused no similar cholesterol changes, he notes. Carroll's findings suggest that essential amino acids are responsible.

And then there's ammonia. Willard J. Visek, a nutritionist at the University of Illinois at Urbana-Champaign, has found that intestinal concentrations of this

compound – a metabolite of proteins – increase as the protein content of the diet increases. Moreover, studies by his team have shown that at levels typically found in the gut, ammonia can damage cells, spur cell proliferation (a potentially precancerous event), and promote the development of chemically induced colon cancer in rats.

Youngman and her collaborators now offer "even more convincing evidence" of protein's dietary risks, Visek says.

Those data are still not convincing enough, however, for Edward J. Masoro of the University of Texas Health Science Center at San Antonio.

The interpretation that Youngman and her collaborators put on their findings "gives the impression that protein is very effective – and possibly as effective as energy restriction" at suppressing tumors and aging-related changes, Masoro says. "But from all of our studies, I reach the opposite conclusion."

In an investigation reported in the November 1991 JOURNAL OF GERONTOLOGY: BIOLOGICAL SCIENCES, his team looked for spontaneous tumors arising in the same strain of rats used by Youngman. Though calorie restriction delays tumor occurrence in these animals, "we found no evidence at all that reducing protein has even a mildly retarding effect," Masoro told SCIENCE NEWS. And if such an effect existed, "we should have seen it," he says, because this study used a diet containing 12.6 percent protein – a concentration comparable to the medium-protein intake that reduced liver cancer rates in the study Youngman conducted at Cornell.

This leads Masoro to suspect that the tumor reduction seen by Youngman's team represents a response specific to the liver – where spontaneous cancers occur only rarely – or to the aflatoxin used to induce the tumors.

Research chemist Juliette C. Howe adds another note of caution, based on rat studies her group conducted during the early 1980s at the U.S. Department of Agriculture's Human Nutrition Research Center in Beltsville, Md. They found that female rats fed a 6-percent-casein diet after weaning experienced "severe" reproductive problems.

Howe and her co-workers had intended to study three generations of animals, comparing the effects of diets with low (6 percent), medium (8 percent), high (20 percent), and excessive (45 percent) amounts of protein. However, females in the lowest-protein group had trouble becoming pregnant, maintaining a pregnancy, or giving birth to live pups. Part of the problem, Howe suspects, was the females' size – about one-third that of normal dams. Even the medium-protein group provided too few pups to allow statistical analyses.

These findings suggest that protein restriction should not begin before sexual maturity and "would have to be curbed if a woman became pregnant," Howe says.

To be fair, Masoro says, "the jury is still out. [None] of our groups has studied a sufficient spectrum of intake to be sure who is right" about protein's role.

"The data are far more definitive for calorie restriction," Youngman acknowledges. Calorie restriction's benefits may also prove greater, she says. "But I would argue that because low protein is a far more feasible alternative for humans, it deserves more study."

How much protein might we need to cut out? "Data definitely suggest that people would be far more healthy if they cut protein intake to the recommended daily allowance (RDA)," Youngman argues. According to the National Academy of Sciences' Food and Nutrition Board, U.S. men typically consume about twice the RDA for protein, women some 50 to 75 percent more than the RDA. □