cer rate has occurred in several parts of the country.

Perhaps not surprisingly, both the investigators who support and those who oppose the idea of an estrogen-cancer link manage to interpret this downturn in favor of their own theory. The supporters suggest that the downturn reflects the decreased use of estrogens occurring as a result of the reports that the drugs cause endometrial cancer. The decrease occurred very rapidly, but this is consistent with the possibility that estrogens are tumor promoters rather than true carcinogens as some investigators propose. Tumor promoters do not cause cancer by themselves but speed up the development of tumors initiated by carcinogens (*Science*, 11 August, p. 515). The effects of promoters are reversible, at least up to a point, and the tumors do not develop if exposure to the promotor stops before this point is reached.

In contrast to this point of view, Horwitz and Feinstein propose that the increase in endometrial cancer was itself the result of increased detection. More D & C's and hysterectomies have been performed in the past decade or so and this would lead to more endometrial cancers being found. Now that the excess cancers have been detected, the incidence of disease is returning to its true level.

At present, seven epidemiological studies favor a link between estrogens and endometrial cancer. Five of the seven studies have been published and two are in press at the *New England Journal of Medicine*. Because two earlier studies, which were performed in a manner similar to that advanced by Horwitz and Feinstein, also discount the existence of the link, the score now stands at seven to three in favor of a causal connection between estrogens and endometrial cancer. But Horwitz and Feinstein quote the late epidemiologist Harold Dorn on epidemiological research of this type. Dorn said: "reproducibility does not establish validity, since the same mistake can be made repeatedly," an argument that can also be cited by the other side in this dispute.

As a result of the reports linking estrogen use to endometrial cancer, the Food and Drug Administration currently requires that the label for the drugs carry a warning that they are associated with an increased risk of the cancer; the label also advises physicians to prescribe estrogen in the lowest doses and for the shortest time required to control menopausal symptoms in order to minimize that risk. The FDA is reviewing the work of Horwitz and Feinstein, a process that should take about a month, to determine whether a change in the policy on estrogen use is warranted.—JEAN L. MARX

Hair: A Diagnostic Tool to Complement Blood Serum and Urine

Hair has the potential to become a remarkable diagnostic tool. It is easily collected without trauma on the part of the donor, it can be stored without deterioration, and its contents can be analyzed relatively easily. Trace elements, in particular, are accumulated in hair at concentrations that are generally at least ten times higher than those present in blood serum or urine and may provide a continuous record of nutritional status and exposure to heavy metal pollutants. Some drugs have already been shown to accumulate in hair, and it seems likely that other organic chemicals may be identified there when sufficiently accurate analytical techniques are developed. Hair analysis thus promises to be an ideal complement to serum and urine analysis as a diagnostic tool.

Much of the original interest in analysis of hair involved its application to forensic science. Early investigators hoped that measurement of the concentrations of 10 to 15 trace elements in hair might make it possible to link a hair sample obtained at the scene of a crime with a specific individual. Subsequent work has shown that hair analysis has limited forensic value; profiles of trace element concentrations vary significantly in hairs collected from different parts of the head, and profiles obtained with many hairs change appreciably with time. In the process, though, investigators found that hair analysis can indicate exposure to certain pollutants and can serve as a probe of physiological functions.

The best results have been obtained with heavy metal pollutants such as lead, arsenic, cadmium, and mercury. Several investigators in Japan, Sweden, Canada, and the United States have shown that concentrations of these elements in the hair provide an accurate and relatively permanent record of exposure, and that there is a good correlation between concentrations in hair and concentrations in internal organs. Typical examples of such measurements were provided by Amares Chattopadyyay of Dalhousie University at the Second Human Hair Symposium, which was held in October in Atlanta.

Chattopadyyay found, for example, that the concentration of lead in hair was lowest in rural population groups, higher in urban groups, and highest in individuals who live close to lead smelters. These differences are presumed to reflect differing exposures to lead in automobile exhaust, paint, and industrial emissions. He also observed the highest concentrations of mercury and cadmium in hair from individuals with known exposure to the metals. Similar results have been reported by other investigators, but the absolute concentrations reported differ appreciably because of differences in technique (see box). Chattopadyyay and others have also shown that the approximate time of occurrence of short, intense exposures to heavy metals can be determined by sectioning hairs along their length and analyzing each section.

Several groups are thus compiling baseline data about normal concentrations of trace elements so that hair analysis can be used to monitor exposure to pollutants. The most notable effort is that of the International Atomic Energy Agency (IAEA) in Vienna. Yu S. Ryabuahin of the IAEA is collecting analytical data on more than 40 elements from laboratories in 13 countries. Several individual investigators are doing the same thing on a smaller scale. Still others, such as Harold G. Petering of the University of Cincinnati College of Medicine, are feeding the heavy metals to animals in measured quantities and monitoring concentrations in hair in an effort to correlate exposure and concentrations.

Animal hair might also be used to monitor environmental pollutants. Norman F. Mangelson and his colleagues at Brigham Young University, for example, are analyzing trace element concentrations in the hair of rodents collected in Utah's Lake Powell Recreation Area, the site of a proposed coal-fired power plant. Once they have established baseline concentrations, they plan to contin-

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Growing Pains for a New Field

The science of hair analysis has undergone several growing pains, due, in large part, to the failure of early investigators, in their seeming haste to produce useful results, to develop or adopt uniform procedures for collecting, preparing, and analyzing hair. In consequence, measurements made in any laboratory today can generally be assumed to be accurate, but comparisons of data obtained from different laboratories often show large variations in absolute values. There is, furthermore, little agreement about precisely what constitutes normal concentrations of trace elements in hair. Until this situation is corrected, advancements in the field will be impeded. Fortunately, some corrective measures are being taken.

One of the principal problems of hair analysis—also one of its chief advantages—is the accessibility of hair to the external environment. Air and water deposit many trace elements on the surface of hair; sweat does the same. Grooming habits compound the problem. Some antidandruff shampoos, for example, contain zinc or selenium and some hair sprays contain manganese and other metals. Many of these elements may become irreversibly bound to the hair.

Thus, notes Adon A. Gordus of the University of Michigan, the concentration of many elements increases with increasing distance from the scalp and there may be as much as a 30-fold difference in concentration of some elements between opposite ends of hair strands. The problem can be minimized by analyzing only the portion of the hair closest to the scalp, and most investigators now do this; some data produced earlier, however, are not consistent with current data because this restriction was not observed.

A more severe problem is the removal of external contaminants. The obvious solution is to wash the hair before analysis, but there is no consensus about how this should be accomplished. Some laboratories wash hair in distilled water, some use detergents, some use a combination of aqueous detergents and organic solvents, and still others use chelating agents to trap metal ions. Data indicating the effects of these washing procedures are scant, but it is clear that the different procedures remove different contaminants and different proportions of trace elements. Washing procedures are a major source of inconsistencies among laboratories and, at present, there appears to be no agreement about which should be adopted universally.

The actual hair analysis is generally performed by neutron activation analysis, photon activation analysis, atomic absorption spectrometry, or particle-induced x-ray emission analysis. Each of these is highly sensitive and can detect very small quantities of many elements in hair. Comparisons of results obtained with the different techniques are reliable, however, only if there are standard reference materials with which to calibrate the instruments. At present, there are no such materials, but the International Atomic Energy Agency—which is particularly interested in nuclear techniques for hair analysis—is attempting to develop some. If such standards become available, and if investigators can be induced to use a standard method for sample preparation, results should become more consistent.

Another problem results from the preliminary successes already achieved through hair analysis. Commercial laboratories that perform hair analyses are springing up throughout the country, but particularly on the West Coast. These laboratories, Gordus says, often produce elaborate and impressive computer printouts that would seem to indicate the nutritional status of the client—despite the fact that the technique has never been demonstrated to be effective for this purpose.

In most cases, therapies proposed on the basis of hair analysis appear to involve relatively harmless dietary supplementation with, for example, zinc or other essential elements. In some cases, though, chelation therapy has been suggested for clients whose hair shows slightly above-normal concentrations of toxic heavy metals. Chelating agents, which bind to metal ions to speed their elimination from the body, can also remove essential metals, and, however, their use is generally recommended by physicians only in cases of exceptionally high exposure. Many investigators thus think that the operations of such laboratories should be severely restricted.—T.H.M.

ue testing rodent hair to monitor potential emission of pollutants by the power plant.

Unusual concentrations of trace elements in hair may also provide a tool for the diagnosis and therapy of diseases. Harry Shwachman of the Children's Hospital Medical Center in Boston and Louis Kopito of the Massachusetts Institute of Technology, for instance, have shown that children with cystic fibrosis have as much as five times the normal concentration of sodium in their hair, but only about 10 percent of the normal concentration of tightly bound calcium. Analysis of these two elements in hair, Shwachman says, is thus a useful tool both for screening for cystic fibrosis and for assisting in diagnosis of the disease.

Shwachman and Kopito have also found that there is less sodium than potassium in the hair of patients with celiac disease, a disorder in the digestion and utilization of fats; there is generally three to four times as much sodium as potassium in the hair of healthy individuals. The ratio of sodium to potassium returns to normal with improvement in the condition, so it is a potentially useful monitor of therapy. They have also shown that hair from victims of phenylketonuria, an inborn error of metabolism, contains below-normal concentrations of magnesium and much-below-normal concentrations of calcium, and that hair from victims of a severe protein-calorie malnutrition known as Kwashiorkor has markedly increased concentrations of zinc.

Several investigators, such as Ananda S. Prasad of the Wayne State University Medical School and Petering, have shown that marginal zinc deficiencies in the diet can be identified by below-normal concentrations of zinc in hair. (Severe zinc deficiencies are generally characterized by extensive loss of hair, but the little hair that does grow contains normal concentrations of zinc.) Such deficiencies can produce retardation of both growth and sexual maturation. They may occur more often than has been expected, according to K. Michael Hambidge of the University of Colorado Medical Center, because diets of many low-income people provide relatively little zinc.

Hambidge tested children in Denver's Head Start program—which is designed to assist children from low-income families—and found that both their hair and blood serum contained significantly lower concentrations of zinc than specimens from children of middle-income families. In general, the lowest concentrations of zinc were obtained in the smallest children. Hambidge picked six of the children with the lowest zinc concentrations in their hair for further testing and found that taste perception was impaired in five. Addition of small zinc supplements to the children's diets restored their taste perception and increased zinc concentrations in their hair to normal.

Other investigators, such as Delbert J. Eatough of Brigham Young University, have found that iron deficiencies can be detected by hair analysis. This application appears to have less value, however, since the normal concentration of iron in the blood is relatively high and alternative techniques for monitoring iron deficiencies are already in widespread use.

Another area of interest is the relation between sugar metabolism and chromium. Hambidge and Walter Mertz of the U.S. Department of Agriculture in Beltsville, Maryland, have independently demonstrated below-normal concentrations of chromium in the hair of victims of juvenile-onset diabetes. This finding is supported by biochemical evidence that demonstrates low concentrations of chromium in the blood of some patients with juvenile-onset diabetes. Interestingly, Eatough and his colleagues have shown that chromium concentrations are normal in the hair of maturity-onset diabetics from the Pima Indian nation, which has a very high incidence of diabetes. Most diabetologists now believe that juvenile- and maturity-onset diabetes have different causes, and this finding appears to support that conclusion.

To further delineate this relation, Emily Sheard and Richard Carter of the Clinical Chemistry division of the Center for Disease Control (CDC) have been developing a standarized technique for measuring chromium in hair. The CDC is the central laboratory for the National Center for Health Statistics' Health and Nutrition Examination Survey (HANES). In the current phase of HANES, data are being collected from some 21,000 individuals to provide statistical data about normal health; glucose tolerance tests will be conducted on a third of the individuals. Sheard and Carter hope to persuade the investigators also to collect hair samples from each of these individuals so that chromium concentrations can be correlated with the results of glucose tolerance tests. If the initial results are confirmed, hair analysis might provide a useful tool for screening for diabetes.

One of the more controversial aspects of hair analysis involves the relation between trace elements in hair and intelligence or learning ability. One of the first indications of a link was obtained in 1973 when Adon A. Gordus of the University of Michigan reported that the hair of students with high academic marks contains substantially more zinc and copper and less iodine, lead, and cadmium than the hair of students with low marks. Subsequent work by Gordus has shown that the differences are not so pronounced as they were first thought to be, but are nonetheless real. Gordus notes that the literature contains much data indicating an association between zinc deficiencies and learning deficits in rodents.

Link to Learning Disabilities

Last year, Robert O. Pihl and his colleagues at McGill University reported that they could distinguish between normal children and those with learning disabilities with 98 percent accuracy by analyzing concentrations of 14 elements in hair. Particularly important in the differentiation, they found, were increased levels of lead, cadmium, and manganese, and reduced levels of lithium and chromium. A follow-up study of these children after 2 years of behavioral and nutritional therapy, Pihl told the symposium, indicated that both their behavior and the trace element profile in their hair had returned almost to normal. Pihl and others are now attempting to reproduce these results, but Pihl, at least, has encountered some methodological problems in the analytical procedure. In his most recent studies, however, he also has observed an association between low zinc concentrations in hair and certain types of learning disabilities.

P. J. Barlow of the University of Aston in Birmingham, England, and M. Kapel of the University of Leeds have observed a relation between trace element profiles in hair and four different types of mental abnormality. In hair from 67 women with Down's syndrome, also known as Mongolism, they observed below-normal concentrations of calcium, copper, and manganese (some other abnormalities in the hair appeared to be related to environment). Low concentrations of calcium had previously been observed in the blood of Down's patients.

In hair from 37 patients with schizophrenia, Barlow and Kapel observed below-normal concentrations of cadmium and manganese, and above-normal concentrations of lead and iron. The low manganese may be particularly important, Barlow told the hair symposium, because some reports suggest that manganese chloride may be effective in therapy of schizophrenia. In hair from a group of 25 severely subnormal young people in a hospital in Denmark, the two investigators observed below-normal concentrations of manganese, iron, lead, and copper, and above-normal concentrations of zinc. And, finally, in hair from five patients with ataxia telangiectasia, they observed low concentrations of copper. This hereditary disease is manifested in a number of symptoms, including mental retardation, enhanced susceptibility to damage from radiation, and enhanced susceptibility to damage from x-rays. The low concentrations of copper may be particularly relevant, Barlow says, because copper is involved in DNA repair mechanisms.

The utility of hair analysis has been expanded somewhat by Peter F. Jones and Annette M. Baumgartner of The Aerospace Corporation in Los Angeles and Werner Baumgartner of the Los Angeles Veterans Administration Hospital. Previous investigators had shown, using relatively insensitive techniques, that barbiturates, amphetamines, and dopamines can be detected in animal hair if large enough amounts of hair are used. The Los Angeles investigators used the more sensitive technique of radioimmunoassay to extend these results to humans. In their initial studies, they demonstrated that morphine is present at concentrations of 1 to 10 nanograms per milligram in the hair of mice that had previously been injected with the drug. They also found that the drug remains in the hair for at least 3 months after injection and that, by sectioning the hair lengthwise, it is possible to tell approximately when the drug was injected. Subsequent studies among patients at a drug abuse clinic indicated the presence of heroin metabolites in hair samples from each of 60 patients who admitted prior drug use. Conventional urinalysis indicated the presence of the drug in only 30 percent of the patients—an indication that 70 percent of the subjects had used the drug at least 2 days prior to specimen collection.

Jones and Baumgartner are now trying to develop similar assays for barbiturates and amphetamines, and Jones thinks it possible that there may be many other organic chemicals locked into hair. They are thus trying to adapt highly sensitive chromatography-mass spectrometry techniques to the study of hair in the hope that other drugs of abuse, chemotherapeutic agents, and perhaps even biochemical intermediates may be detected. If this should be the case, a completely new dimension of hair analysis will be opened.—THOMAS H. MAUGH II