Atherosclerosis: The Cholesterol Connection

Nobody doubts that cholesterol is a major component of atherosclerotic lesions. That has been known for more than 100 years. The major questions that investigators have been trying to resolve concern the route by which cholesterol gets into the lesions, its role in their initiation and development, and—most important—whether lesion formation can be prevented or reversed with a consequent savings of some of the 900,000 lives lost every year to atherosclerotic disease in the United States alone.

This is the third in a series of Research News articles examining recent developments in research on heart disease.

Investigators have been using three approaches in their attempts to pin down the role played by cholesterol in the etiology of atherosclerosis. One involves epidemiological or statistical studies (*Science*, 29 Oct., p. 509). These have shown a correlation between high concentrations of blood cholesterol and an increased risk of having a heart attack, which may occur as a result of the formation of atherosclerotic lesions in the arteries that supply blood to the heart muscle. But the epidemiological studies have been criticized for a variety of reasons, and not all investigators think that the correlation is adequate proof of a causative relationship.

Another way to get at the problem involves studying the biochemistry of cholesterol in both normal and disease states. And the third approach encompasses studies designed to show whether lowering the concentration of cholesterol in the blood by means of diet, drugs, or surgery will interfere with the progression of atherosclerosis and actually prevent heart attacks.

The biochemical studies have resulted in a better understanding of how cholesterol is transported in the body and how its synthesis and utilization are controlled. Information of this kind may eventually lead to an unraveling of the mechanisms underlying the formation of atherosclerotic plaques and thus permit intervention to block the process. For example, high concentrations of one form of blood cholesterol apparently favor plaque formation. Investigators have made considerable progress in determining how the blood concentrations of this material are regulated.

Since cholesterol is a sterol (a steroid bearing an alcohol group), it is practically insoluble in water, and virtually all of the material in the blood is carried in the form of lipoproteins. These complexes of proteins with lipids are constructed with the charged or polar molecules, the proteins, for example, on the surface. The nonpolar molecules, such as triglycerides (esters of glycerol and three long-chain fatty acids) and esters of cholesterol, are on the inside. Seventy percent of the cholesterol in lipoproteins is present as esters. The free or nonesterified cholesterol is on the surface of the lipoproteins.

There are four main types of lipoproteins, which are classified according to their size and density. These are the chylomicrons, the very low density lipoproteins (VLDL), the low density lipoproteins (LDL), and the high density lipoproteins (HDL). Recently, attention has focused on the LDL, which are known to carry most of the cholesterol found in blood, as playing a key role in both the development of atherosclerotic lesions and in the regulation of cholesterol metabolism in cells other than liver. Much of the interest stems from the work of Michael Brown and Joseph Goldstein of the University of Texas Southwestern Medical School.

These investigators have evidence that human fibroblasts and certain other kinds of cells normally contain specific receptors for LDL, and that interaction of the lipoprotein with the receptors is a necessary first step before the degradation of LDL and the suppression of cholesterol synthesis can occur in the cells. If these two events are prevented then large quantities of the cholesterol-bearing LDL may accumulate in the bloodstream. This is apparently what happens to persons with the genetic disease called familial hypercholesteremia. According to Brown and Goldstein, fibroblasts from these individuals lack receptors with the capacity to bind LDL.

Persons who inherit two copies of the gene that transmits this disease have concentrations of plasma cholesterol that may exceed 800 milligrams per 100 milliliters—roughly four times the normal value. They develop symptoms of atherosclerosis at a very early age and often die of heart attacks before their 20th birthday. Individuals who inherit one copy of the gene have plasma cholesterol concentrations that are about twice the normal value; they, too, develop symptoms of atherosclerosis prematurely but usually not before they are 30 years old.

However, only a small fraction—about 20 percent, according to some estimates—of persons with high blood concentrations of LDL actually have typical familial hypercholesteremia. The condition of most is the result of a poorly understood combination of hereditary and environmental factors. Nevertheless, the single-gene form of familial hypercholesteremia afflicts about one person in 500. And the fact that a single genetic defect results in both high concentrations of LDL in the blood and also severe atherosclerotic disease strengthens the case that blood cholesterol, most of which is carried in the LDL, is causally involved in atherogenesis.

Most, if not all, of the cells of the body have the capacity to synthesize cholesterol, a substance essential as a building block for cell membranes and also as a precursor for the synthesis of other steroids, including the bile acids and a number of hormones. Liver cells are especially active at synthesizing cholesterol, but synthesis is suppressed when the intake of dietary cholesterol is high. According to Marvin Siperstein of the University of Texas Southwestern Medical School, the dietary cholesterol acts by suppressing the synthesis of a key regulatory enzyme (3-hydroxy-3-methylglutaryl coenzyme A reductase) needed for cholesterol synthesis.

The results of John Bailey at George Washington University Medical School and George Rothblat at the Wistar Institute implied that a similar feedback inhibition was operating in peripheral cells. They observed that removal of cholesterol from the medium in which cultured mammalian fibroblasts are incubated enhances synthesis of the sterol by the cells. Brown and Goldstein then showed that the LDL suppress cholesterol synthesis by cultured human fibroblasts and that binding of the lipoprotein to the specific receptors on the fibroblast surface is a necessary first step toward the suppression.

According to the investigators, fibroblasts from patients with two genes for familial hypercholesteremia either have no receptors for LDL or else have defective receptors that bind LDL very poorly. They have observed both situations in the cultured cells. Fibroblasts from persons with one defective gene have half the normal number of functional receptors.

Brown and Goldstein suggest that, following binding of LDL to the receptors of normal cells, the membrane invaginates to form vesicles containing LDL inside the cell. With Richard Anderson, also at the University of Texas, they have shown that LDL labeled with ferri-

tin, a protein that contains a large quantity of iron and can thus be seen in electron micrographs, binds to the membrane of normal cells at certain areas that are indented and have fuzzy coats. Other investigators have suggested that these areas are the sites where formation of the internal vesicles is initiated. Although cells from patients with familial hypercholesteremia have the indented areas, they do not bind the ferritin-labeled LDL the way normal cells do.

The next step is the merger of the vesicles with the lysosomes (membranous sacs containing enzymes that break down a variety of biological molecules). The enzymes digest the protein components of LDL and split the cholesterol esters with the release of free cholesterol, which is the form used by cells to synthesize membranes. In addition, the liberated cholesterol has three important regulatory roles. It reduces cholesterol synthesis by suppressing the key regulatory enzyme; it activates another enzyme (cholesterol acyltransferase), which catalyzes the formation of new cholesterol esters for storage; and it suppresses the synthesis of the LDL receptor and thus prevents accumulation of too much cholesterol by the cell.

Support for the role of the lysosome in this scheme comes from experiments in which Brown and Goldstein showed that cells deficient in a lysosomal enzyme that splits cholesterol esters can accumulate LDL in the lysosomes but that the esters are hydrolyzed at a reduced rate. Thus, the release of free cholesterol is delayed, as are the regulatory events.

However, if these cells or the cells lacking the receptors are supplied with free cholesterol in a form that can penetrate the membrane, they will respond to the sterol in the normal manner. That is, the enzyme regulating cholesterol synthesis will be suppressed and the one reesterifying the sterol will be activated. According to Andrew Kandutsch of the Jackson Laboratory, certain oxygenated derivatives of cholesterol are even more effective than the parent compound in producing these responses in both normal cells and those from individuals with familial hypercholesteremia. This could point the way to more effective methods for lowering elevated blood cholesterol concentrations than are now available.

Brown and Goldstein think that the effects of LDL, acting through the receptor, could explain the low rate of cholesterol synthesis normally seen in many cell types in vivo. On the other hand, lack of functional receptors could contribute to elevated LDL concentrations in the blood in two ways. Peripheral cells would be unable to take up and metabolize LDL adequately. In addition, the enzyme regulating cholesterol synthesis would not be suppressed and the cells would continue to produce the sterol in spite of the high plasma concentrations.

Recent epidemiological studies also support the concept that high concentrations of LDL may contribute to the development of atherosclerosis and coronary artery disease. William Kannel, director of the Framingham study, a large prospective epidemiological study designed to identify the risk factors associated with heart disease, says that their data indicate that as the concentration of plasma LDL increases, the risk of having a heart attack also increases. On the other hand, persons with high concentrations of HDL have fewer heart attacks than persons with low concentrations, according to Kannel and William Castelli, also of Framingham. The effects of the two lipoproteins on the risk of coronary heart disease appear to be independent of one another. This result, and those from other investigations, imply that HDL may somehow protect against the development of atherosclerotic lesions.

These findings are consistent with the physiological roles postulated for LDL and HDL in cholesterol transport. Investigators* think that lipoproteins do not just function to solubilize lipids, but that the proteins on the surfaces of the particles carry information that specifies the

Coal Liquefaction Plant Goes Ahead

The Energy Research and Development Administration (ERDA) finally announced last month that it had signed contracts for construction of an experimental coal liquefaction plant at Catlettsburg, Kentucky. Negotiations over the contract had been protracted, and had nearly foundered over the issue of cost-sharing between ERDA and industry. The pilot plant is designed to treat 600 tons of high-sulfur eastern coal per day, converting it to a low-sulfur fuel oil by a catalytic hydrogenation technique known as the H-coal process (*Science*, 3 Sept., p. 873). The plant will be the largest coal conversion facility yet built in the United States.

The plant will be potentially large enough to permit scaling up directly to commercial size, about 10,000 tons per day, without an intermediate step. Construction is to begin 1 December, with operation scheduled to get under way in the autumn of 1978. Three major oil companies—Mobil, Conoco, and Standard of Indiana—are expected to participate in the industrial consortium that will fund a portion of the $180 million plant, in addition to the prime contractors, Hydrocarbon Research, Inc., which initially developed the H-coal process, and a subsidiary of Ashland Oil, which will manage the plant's construction and operation.

The contract is notable as evidence of a significant shift in government policy on risk-sharing for such experimental plants. ERDA will put up $142 million and industry $36 million for this major step toward development of the proprietary liquefaction process. In assuming such a large share of the cost, ERDA is departing from the two-thirds to one-third cost-sharing formula that has prevailed for several years. Apparently, ERDA convinced the Office of Management and Budget of what industry has been saying for some time, that the old formula was too rigid and that government should assume a greater portion of the risk. Observers familiar with the internal discussions say that the arguments for a more flexible approach prevailed some time ago, but this contract is the first tangible evidence of the new policy.

Martin Neuworth, of the ERDA synthetic fuel staff, points out that the H-coal contract is the first real test of industry-government cofunding of a coal conversion project on this scale, since the total industrial contribution to several previous synthetic fuel projects was $40 million spread over 4 years.

Equally encouraging to observers in industry are indications that ERDA will leave day-to-day management of the project largely up to Ashland, indicating, perhaps, that the agency has learned from earlier and largely unsuccessful attempts to manage the nuclear breeder program from Washington. A technical advisory committee representing ERDA and the other consortium partners will oversee major decisions.—ALLEN L. HAMMOND

tissues to which the different classes of lipids are to be delivered. The proteins would do this by recognizing and interacting with receptors on the appropriate cells or by serving as cofactors that are necessary for the action of the enzymes involved in shuttling cholesterol and other lipids from tissue to tissue.

The pathways by which the different lipoproteins are formed, interconverted, and used are complicated, but the view emerging from a large number of studies is that the LDL carry cholesterol, whether obtained from the diet or synthesized in the body, to the peripheral tissues where it is used. Goldstein and Brown think that the bulk of the LDL may be degraded in tissues other than the liver. This hypothesis is supported by findings from the laboratory of Daniel Steinberg of the University of California at San Diego. He showed that removal of the livers of swine did not slow the degradation of cholesterol by the animals and may even have increased it.

On the other hand, the HDL appear to transport cholesterol from the peripheral tissues to the liver. From here it may be excreted into the intestinal tract either as cholesterol or after conversion to the bile acids. Alternatively, it can be incorporated into LDL or VLDL and recycled to the peripheral tissues. But the HDL may provide a route for removal of cholesterol from the tissues and, possibly, for diminishing the likelihood of its ending up in atherosclerotic plaques.

The way in which high concentrations of blood cholesterol contribute to the production of atherosclerotic lesions is still unclear. One hypothesis, proposed by Russell Ross and Lawrence Harker of the University of Washington Medical School, is that chronic elevation of the sterol concentration leads to local injury to the inner lining of the arterial wall. When the investigators increased the blood cholesterol concentration of monkeys by feeding the animals a diet high in the sterol, about 7 percent of the inner surface of their major arteries suffered damage. The arteries of control monkeys remained intact.

Several investigators have suggested that arterial injury is a major factor in the formation of atherosclerotic plaques (*Science*, 5 Nov., p. 592). The idea is that this would expose the smooth muscle cells beneath the injury to blood constituents that stimulate the local proliferation of the smooth muscle cells. Not everyone agrees that arterial injury is the cause of the proliferation but most investigators think that abnormal growth of the smooth muscle cells is a key factor in the formation of atherosclerotic plaques. Moreover, evidence from a number of laboratories, including that of Robert Wissler at the University of Chicago, indicates that the LDL promote the division of arterial smooth muscle cells, possibly by providing lipids for cell membrane formation. Thus, high concentrations of cholesterol-containing LDL may be involved in the initiation of lesion formation as a consequence of injury to the arterial lining and the lipoproteins may also contribute directly to lesion progression.

Cholesterol Accumulation in Plaques

Atherosclerotic plaques contain large deposits of cholesterol. Several factors, acting alone or in combination, could be contributing to the accumulation. The cholesterol could be taken up directly from the blood; elevated concentrations of LDL might facilitate this uptake. The mechanisms by which arterial smooth muscle cells use the cholesterol might be deficient. Or the cells might be synthesizing the sterol in larger than normal quantities. There is evidence for all three of these possibilities.

Smooth muscle cells from human arteries take up large quantities of LDL and VLDL, at least in culture, according to Edwin Bierman and his colleagues at the University of Washington Medical School. They take up lesser quantities of HDL. These results contrast with those the investigators obtained with cultured smooth muscle cells from rat arteries. The latter cells take up more HDL than LDL or VLDL. Bierman points out that the rats are very resistant to the development of atherosclerosis, whereas humans readily develop the condition. He suggests that the ease with which a species develops atherosclerosis may be related to this difference in lipoprotein uptake. According to Bierman, the characteristics of LDL binding and uptake by the cultured cells are consistent with the presence on the arterial cells of receptors similar to those observed by Brown and Goldstein on cultured human fibroblasts.

Bierman has also found that lowering the oxygen content of the atmosphere above the cultured cells decreases the breakdown of the protein portion of the LDL and causes the protein to accumulate in the cells. Since degradation of LDL proteins is part of the normal sequence for breakdown of the LDL, the investigator thinks that oxygen deficiency could promote accumulation of LDL and accelerate the formation of the lipid-laden cells seen in atherosclerotic plaques. He has hypothesized that this may be one way that cigarette smoking, which is a known risk factor for atherosclerosis, contributes to plaque formation. The carbon monoxide inhaled by smokers replaces some of the oxygen that would otherwise be carried by hemoglobin and consequently lowers the arterial oxygen pressure.

Once the lipoproteins have been taken up by the aortic smooth muscle cells, the lysosomes may play an important role in determining whether or not atherosclerotic lesions develop, according to Christian de Duve of the Rockefeller University and the University of Louvain in Belgium. The lysosomes contain the enzyme (cholesteryl esterase) that splits the cholesterol esters that form the bulk of the LDL cholesterol; the splitting occurs after the lysosomes fuse with the vesicles carrying the LDL. A prominent feature of the lesions are the foamy cells which are thought to be formed from smooth muscle cells that have accumulated large quantities of cholesterol and have consequently lost their characteristic structure. Since cholesterol must be released from its esters in order to be used by the cells or transported out of them, de Duve thinks that, if the lysosomes of arterial smooth muscle cells were deficient in cholesteryl esterase, cholesterol esters would accumulate and the foamy cells might result.

De Duve has evidence that this is what occurs when rabbits are fed a high-cholesterol diet and consequently develop atherosclerosis. He and his colleagues have found that the lysosomes of the aortic smooth muscle cells of cholesterol-fed rabbits are much less dense than those of normal animals. This is what would happen if the lysosomes were accumulating lipids of low density. The Rockefeller investigators have also determined that the activity of the cholesteryl esterase in rabbit lysosomes is very low. De Duve hypothesizes that this activity is adequate to split the cholesterol esters ingested by rabbits on their normal vegetarian diet, which contains little of the sterol, but that when the animals are fed high-cholesterol diets the enzyme can no longer handle the esters taken up by the cell and thus they accumulate.

The LDL appear to inhibit cholesterol

*Many investigators have contributed to the elucidation of lipoprotein structure and the pathways by which lipoproteins and the cholesterol contained in them are transported and utilized. They include Donald Fredrickson, now director of the National Institutes of Health; John Glomset of the University of Washington; Antonio Gotto of Baylor Medical School; Richard Havel of the University of California Medical School in San Francisco; Robert Levy, currently director of the National Heart, Lung, and Blood Institute; Angelo Scanu of the University of Chicago; Bernard and Virgie Shore of the Lawrence Livermore Laboratory of the University of California; Olga and Yechezkel Stein of Hebrew University–Hadassah Medical School in Jerusalem; and Donald Zilversmit of Cornell University.

synthesis by aortic smooth muscle cells in culture just as they do in fibroblasts. Brown and Goldstein have observed the inhibition in smooth muscle cells from human aortas, and Steinberg has observed it in swine cells. Steinberg points out that at the concentrations of LDL thought to occur in the fluid bathing aortic smooth muscle cells in vivo, normal cells should be synthesizing very little cholesterol and most of the cholesterol accumulating in atherosclerotic lesions ought to come from the blood. The situation could be quite different in cells from patients with familial hypercholesteremia if they resemble fibroblasts in their lack of feedback inhibition by LDL. Here, cholesterol synthesis by the aortic smooth muscle cells could make an important contribution to the sterol accumulating in the arterial lesions of the patients.

Although the preponderance of the evidence favors the hypothesis that cholesterol, especially that carried by the LDL, is somehow involved in atherogenesis, the big question remains to be answered. That is, will lowering the concentration of cholesterol in the blood prevent or reverse the process of plaque formation and save the lives of persons who would otherwise have died of heart attacks or strokes?

Animal studies do indicate that the lesions will regress when the blood cholesterol is lowered. Many of the species used, however, differ markedly from the human in physiology and diet. There is always the possibility that experimental atherosclerosis in animals like the rabbit is not a good model for the human variety.

Recently, however, encouraging results have been obtained with swine and nonhuman primates, both of which are physiologically similar to the human. For example, Assad Daoud and his colleagues at Albany Medical College observed that advanced atherosclerotic lesions in the arteries of swine would regress if the animals were put on a low-cholesterol diet. The investigators induced the lesions in the first place by a combination of mechanically injuring the arterial lining and feeding a high-cholesterol diet.

Monkeys can also be made to develop advanced atherosclerosis by feeding them appropriate diets. And their lesions will regress if the animals are switched back to a low-cholesterol diet, according to Mark Armstrong of the University of Iowa. In a recent experiment, Wissler and his colleagues fed rhesus monkeys a diet containing large quantities of coconut fat, butterfat, and cholesterol for 18 months. The animals killed at the end of this time all had severe atherosclerotic lesions in the coronary arteries. The remaining monkeys were divided into three groups. One continued to receive the high-fat, high-cholesterol diet; the other two received either a low-cholesterol diet or a low-cholesterol diet plus a drug thought to prevent atherosclerosis in monkeys. According to Wissler, the frequency and severity of the lesions of the monkeys on the low-cholesterol diets were 30 to 50 percent lower than those of the control animals. The drug produced some additional improvement in the appearance of the arteries of the monkeys taking it.

The Coronary Drug Project

Although researchers consider the results of the animal investigations to be encouraging, the only way to tell whether the same is true for humans is by studying humans. In at least one such study, it was not. The Coronary Drug Project, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and completed late in 1974, was designed to determine whether the use of drugs that lower blood cholesterol would decrease the incidence of heart attacks in men who had already had at least one. It turned out that men taking the drugs had as many heart attacks as those receiving a placebo.

However, investigators think that these negative results do not necessarily disprove the value of lowering blood cholesterol concentrations. The average decrease seen in the study was modest at best—less than 10 percent—and possibly too late to do any good. By the time a heart attack occurs the atherosclerotic process may be well advanced.

Another approach is to study individuals whose atherosclerosis is not so far advanced but who are at risk of having a heart attack. The NHLBI is currently sponsoring two major prospective trials involving men thought to be at risk (*Science*, 21 Nov. 1975, p. 764). The first of these, the Lipid Research Clinic Primary Prevention Trial, aims at determining whether otherwise healthy men with high blood cholesterol concentrations can decrease their chances of having a heart attack by lowering the cholesterol concentrations. The second trial, the Multiple Risk Factor Intervention Trial, includes men who have one or more of the three risk factors, high concentrations of blood cholesterol, high blood pressure, and cigarette smoking, considered most predictive of the likelihood of having a heart attack. Attempts will be made to reduce or eliminate all of the risk factors and to determine whether there is a reduction of heart attacks. However, it will be at least 5 years before the results of either of these studies are available.

Meanwhile, there are two techniques that investigators think may permit them to obtain results faster than by long-term prospective studies. One involves using surgery to produce much greater decreases in blood cholesterol than the 10 to 20 percent decreases usually achieved by diets or drugs. This might cause a more rapid regression of plaques. The other requires actual observation of the interiors of arteries to determine what, if any, changes occur as a result of a cholesterol-lowering regimen. Changes in the lesions should be detected earlier than altered incidence of heart attacks.

Henry Buchwald and his colleagues at the University of Minnesota Medical School have devised an operation, the partial ileal bypass, that reduces blood cholesterol concentrations by 30 to 60 percent. In the operation, the last third of the small intestine is disconnected from the intestinal tract to interfere with the absorption of cholesterol and the bile salts. The bile salts are needed to emulsify cholesterol and other lipids so that they can be absorbed. Most of the absorption of lipids and bile salts, which are recycled, occurs in the last third of the small intestine. Thus, after the surgery both the bile salts and cholesterol are excreted in the feces. Moreover, the liver continues to convert additional cholesterol to bile salts in order to replace those that have been lost. These, too, are excreted; this constitutes a further drain on the body's cholesterol. Buchwald says that the only side effects of the operation are diarrhea, which can be controlled with drugs, and a deficiency of vitamin B_{12}, which is also absorbed in the last third of the small intestine. This deficiency can be compensated by injections. An advantage of the surgery is that the patients cannot cheat as they may do with diet or drugs.

More than 100 patients, most of whom have coronary heart disease and high blood cholesterol concentrations, have undergone the operation. Buchwald says that there is evidence that for some of them the condition of the coronary arteries has improved. He performed coronary angiograms on 22 patients before the surgery and then periodically thereafter for up to 3 years. Angiograms permit the visualization of arteries, here the coronary arteries, to see whether or not they have been blocked by atherosclerotic lesions. The atherosclerosis of

(Continued on page 754)

RESEARCH NEWS

(Continued from page 714)

12 patients at least did not progress; that of three patients showed definite improvement; and that of two additional patients may have improved.

This was not a controlled study but the NHLBI is now sponsoring a more extensive clinical trial, involving several clinical centers, to confirm that the surgical technique can cause improvement of atherosclerotic lesions in patients with coronary artery disease. The trial will ultimately include 1000 patients; 500 will undergo the surgery and 500 will be treated conventionally.

A sensitive technique for observing what is happening within the arteries before atherosclerotic lesions become large enough to actually block the vessels and cause symptoms could help to provide information about whether or not early lesions will regress. David Blankenhorn and his colleagues at the University of Southern California have applied computer technology originally developed for analysis of photographic images taken by spacecraft to the analysis of angiograms of the femoral artery of the thigh. With their technique they can visualize the plaques and determine whether they change in size over a period of time.

The investigators have performed a series of angiograms on 25 men who have high concentrations of lipids, including cholesterol, in their blood. Before therapy to reduce the blood lipids and also high blood pressure, where required, the men all had moderately severe atherosclerosis of the femoral artery but did not yet have symptoms of obstruction. Blankenhorn is using a variety of drug and diet therapies on the men. After 13 months of treatment, nine of the 25 patients experienced regression of the lesions, whereas the lesions of 13 got worse and those of three did not change.

Blankenhorn says that the patients whose lesions regressed showed significant declines in blood cholesterol concentration; these decreases did not occur in individuals whose disease progressed. Statistical analysis of the data indicated that decreases in blood pressure made an independent contribution to the rate of change of the atherosclerosis, with a decrease favoring regression. Blankenhorn thinks that the changes in the femoral artery are representative of those that may occur in early lesions of the coronary arteries, but confirmation of this hypothesis will require the development of a similar technique for examining the coronary arteries.—JEAN L. MARX

BOOKS RECEIVED

(Continued from page 718)

A Conference on Key Factor Analysis. A Logic Leading to Social Accountability. Papers from a conference. Irwin M. Jarett and Patricia A. Brady, Eds. Published for the Illinois Regional Medical Program and the Southern Illinois University School of Medicine by Southern Illinois University Press, Carbondale, and Feffer and Simons, London, 1976. xii, 438 pp. Cloth, $10; paper, $4.95.

Contributions to Anthropology. Selected Papers of A. Irving Hallowell. With introductions by Raymond D. Fogelson and five others. University of Chicago Press, Chicago, 1976. xviii, 534 pp. $24.

Controversies in American Voting Behavior. Richard G. Niemi and Herbert F. Weisberg, Eds. Freeman, San Francisco, 1976. xvi, 544 pp., illus. Cloth, $12.95; paper, $6.95.

Electron-Solvent and Anion-Solvent Interactions. Larry Kevan and Brian C. Webster, Eds. Elsevier, New York, 1976, xiv, 360 pp., illus. $57.50.

Elementary Heat Transfer Analysis. Stephen Whitaker. Pergamon, New York, 1976. xviii, 370 pp., illus. Paper, $22.50. Pergamon Unified Engineering Series. Pergamon International Library.

Embryogenesis in Mammals. Proceedings of a symposium, London, June 1975. Elsevier/Excerpta Medica/North-Holland, New York, 1976. viii, 308 pp., illus. $21.95. Ciba Foundation Symposium 40 (new series).

Encyclopedia of Chemical Processing and Design. Vol. 1, Abrasives to Acrylonitrile. John J. McKetta and William A. Cunningham, Eds. Dekker, New York. xvi, 472 pp., illus. $95.

Energy and Conflict. The Life and Times of Edward Teller. Stanley A. Blumberg and Gwinn Owens. Putnam, New York. 1976. xviii, 492 pp. + plates. $9.95.

Energy for Life. Photosynthesis and Respiration. Betty D. Allamong and Thomas R. Mertens. Wiley, New York, 1976, xxii, 194 pp., illus. Paper, $4.95. Self-Teaching Guides.

Environmental Controls. The Impact on Industry. Robert A. Leone, Ed. Lexington Books (Heath), Lexington, Mass., 1976. xviii, 134 pp., illus. $14.

Environmental Law and the Siting of Facilities. Issues in Land Use and Coastal Zone Management. Michael S. Baram with contributions by Timothy Backstrom, Thomas Bracken, Bradley Schrader, and Edward Selig. Ballinger (Lippincott), Cambridge, Mass., 1976. x, 258 pp. $16.50.

Epidemiology of Abortion and Practices of Fertility Regulation in Latin America. Selected Reports. Pan American Health Organization, Washington, D.C., 1975. xii, 142 pp. Paper, $7.50. Scientific Publication No. 306.

Ergebnisse und Probleme der Geo- und Kosmoswissenschaften. Akademie-Verlag, Berlin, 1975. 152 pp., illus. Paper, 12 M. Sitzungsberichte der Akademie der Wissenschaften der DDR, No. 1N.

The Evolution of Man. G. H. R. von Koenigswald. University of Michigan Press, Ann Arbor, ed. 2, 1976. vi, 158 pp., illus. Cloth, $6.95; paper, $2.95. Ann Arbor Science Library.

The Eye and Inborn Errors of Metabolism. Proceedings of a symposium, Oxford, England, Apr. 1975. Daniel Bergsma, Anthony J. Bron, Edward Cotlier, Natalie W. Paul, and Jane Lantz, Eds. Liss, New York, 1976. xxii, 606 pp., illus. + plates. $60. The National