TWENTY CENTS

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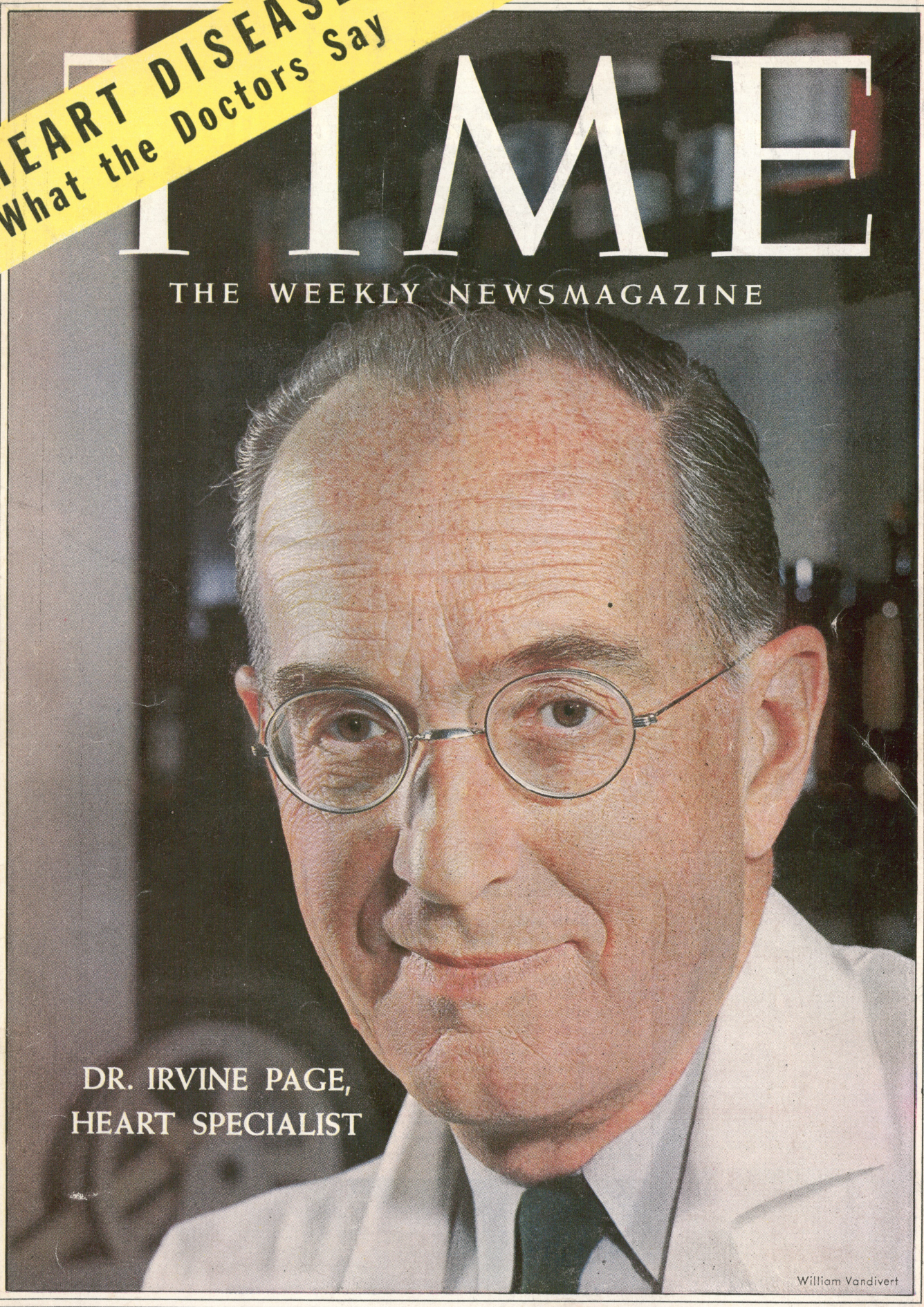
HEART DISEASE
What the Doctors Say

TIME

THE WEEKLY NEWSMAGAZINE



DR. IRVINE PAGE,
HEART SPECIALIST

William Vandivert

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The Specialized Nubbin

(See Cover)

The mightiest of monarchs was dead. The royal embalmers removed most of his vital organs but left enough to show physicians of later ages what ailed him: hardening and narrowing of the vital arteries near the heart. The monarch was Merneptah, Pharaoh of Egypt at the time (some believe) of the Exodus. No fewer than 3,000 years had passed when the chief of the modern world's most powerful state had a heart attack brought on by the same type of disease in the arteries. Yet for all but a handful of these years, nothing had been learned about the causes of heart-and-artery disease, and virtually nothing about its treatment.

Long before President Eisenhower's attack, heart disease became a major American worry. Other diseases were being triumphantly conquered with wonder drugs and new surgical techniques, but one result of keeping people alive longer, it seemed, was to make all the surer that they would eventually have heart attacks. Heart-and-artery disease was pinpointed as the nation's No. 1 killer—with ample statistical reason. It now accounts for 800,000 deaths a year, half the U.S. total.

To many foreign visitors, and some Americans, heart disease has become the typical American illness. The U.S., so the argument goes, is the land of tension and conflict. Men work too hard, play too hard, worry too hard. The image of the tycoon who, at 50, has attained money, success, a yacht and coronary thrombosis is almost part of American folklore. Today, more than ever, anxious men (far more than women) of middle age are scurrying to doctors' offices for a heart checkup. More than two-thirds will be told that they have nothing to worry about; the others can look for no quick cures, but can count on treatment to reduce discomfort and danger. In any case, many tools and techniques used by doctors to examine patients, and virtually everything that they prescribe, have been perfected in the lifetime of a generation no older than Dwight D. Eisenhower.

The Big Mystery. Heart disease is still medicine's most stubborn mystery. Again and again, the killer has eluded its pursuers. From Pharaonic times until this century, the medical profession took a fatalistic attitude that most heart disease was inevitable. Today, a health- and youth-conscious U.S. wants to believe those doctors who insist that no disease process is natural at any age. The pursuit of the killer is proceeding with greater speed—and hope—than ever.

This week top men in charge of that pursuit, 2,000 American heart specialists, met in New Orleans at the 28th scientific convention of the American Heart Association to tell each other how they were doing. An early order of business was installation of a new president. Their choice: Dr. Irvine H. Page, now of Cleveland, at 54 one of the country's leading detectives on the trail of the killer.

Partitioned Patient. What has worried Dr. Page most is that overspecialized modern medicine has not organized itself properly over the years to take broad-front action. Not only the disease but the patient has been senselessly partitioned. A man's brain, if he had a stroke, was in the province of the general internist. The gangrenous toes of his friend who suffered from Buerger's disease went to the angiologist. His heart belonged to the cardiologist, who grudgingly took responsibility for high blood pressure—but could do little for it. His kidneys were annexed by the urologist. Pleaded Dr. Page at New Orleans this week:

"Without coordination we have cardiologists, angiologists, cardiac surgeons, peripheral vascular men and, of late, the more glorious nephrologists . . . Unfortunately there seems to be no term to cover the entire circulation. But in our own thinking, let us make a fresh start and consider the heart as only a 'specialized nubbin' on the whole vascular tree and reintegrate the heart and blood vessels back into the unified system that it really is."

As doctor after doctor reported on his studies and experiments, a unified pattern was, at first, scarcely apparent. Nor would it be from the odder bits of work in progress, ranging from male volunteers who are taking female hormones, willing to run the risk of being feminized in hopes of having their artery-hardening arrested, to Duke University's Dr. James Warren, who is about to head for Africa to learn more about how the giraffe keeps its blood pressure under control.

But all such diverse experiments fit into a growing, if often elusive body of knowledge about the heart.

Where Is the Villain? The earliest, most dramatic progress came in the field of heart surgery. When they could deal with disease by the use of scalpel and mechanical ingenuity, U.S. doctors have worked wonders, *e.g.*, the complex blue-

THE CHANCES FOR RECOVERY

PRESIDENT Eisenhower's attack, and his good recovery to date, have given national urgency to questions that have always troubled heart patients and their families: How good a recovery can a patient make after a coronary thrombosis, and what are his chances of resuming an ordinary, active life? While each case is different, the answer that most heart specialists are now trying to put across to the country is: the chances are far better than generally realized.

The medical profession itself did not fully understand this even 20 years ago. The general feeling used to be: the less activity the better. Recently, searching tests have been conducted to find out just how much or how little an injured but healed heart can stand. Manhattan's Bellevue Hospital and Dr. Arthur M. Master have pioneered in finding out how much work heart sufferers can safely do. Many victims have been found to suffer from nothing but a wrong diagnosis. Others, after recovering from an attack, have been handicapped more by their own anxiety (and occasionally their doctor's) than anything else. About three-fourths can soon go back to work, most at their old jobs, though some must settle for lighter tasks.

Promoted by the American Heart Association, this principle is now being applied nationally through 48 state-federal programs. Classification units grade the patient's capacity for work and such items as his emotional status and especially anxiety about his heart. They also grade the demands of the jobs available, try to fit workers to jobs. Labor unions and industry groups are backing the effort. Some employers shy away because of compensation problems, but the problems have no medical basis: heart cases are more safety-conscious than other workers, likely to be steadier and more reliable. Properly job-graded, they produce as much as their healthier fellows—sometimes more.

Doctors are able to give patients improved care now that they take more and better electrocardiograms (using twelve leads instead of the former three), regulate the diet after an attack, and prescribe permissible exercise. This may range from walking two blocks a day to playing three sets of tennis. The benefits to heart sufferers come not so much from new discoveries or drugs as from spreading a realization, first among doctors and then among laymen, of what the facts are:

¶ At least 80% of coronary victims survive their first attack; among private patients (likely to have better diagnosis and more individual care than ward patients) the rate goes up to 95%.

¶ Among large numbers of patients studied up to 30 years after an attack, 40% have made full recoveries in activity (though some showed electrocardiographic or other signs of hidden damage). Another 40% have made good recoveries with only mild symptoms.

¶ The outlook for those patients who go back to their work is at least as good as it is for those who retire.

baby operation, opening the mitral valve inside the heart, heart-lung machines, even the use of a dog's lung to substitute for the patient's during an operation.

Other successes were scored against heart disease caused by diphtheria and syphilis, both virtually wiped out. Another form of the enemy is being routed largely through penicillin: rheumatic heart disease. But the situation is more complex in regard to the two commonest forms of heart trouble, which account for more than 90% of all heart disease in the U.S.:

¶ Arteriosclerosis (artery hardening), of which atherosclerosis (mushiness and hardening) is one of the commonest forms, and the most dangerous because it so often occurs in the heart's own arteries, the coronaries.

¶ Hypertension (high blood pressure), ranging from a benign form not severe enough to hamper or endanger life to rapidly fatal cases.

Actually, the two disorders are closely related—how, in scientific detail, no one knows. While it is true that many victims of arteriosclerosis show no hypertension, every victim of hypertension examined after death shows arterial damage of some kind. Hardening of the minute arterioles—the slenderest twigs at the extremities of the arterial tree—almost always goes with high blood pressure. Its immediate cause seems to be loss of elasticity in the arterioles' thin muscular walls.

But whether hypertension causes arteriosclerosis, or vice versa, no one knows. A similar change in major arteries is often seen in the aged: the muscular wall hardens so much that the vessels are called "pipe-stem arteries." In an otherwise healthy individual this condition may go undetected and do no apparent harm.

Atherosclerosis is the bugbear. It appears to attack the coronary arteries with especial frequency. And strangely, it is a disease of successful civilization and high living. It is far commoner in the U.S., Britain, Sweden and Denmark than among the poor peasants of Sardinia and southern Italy, the paddyfield workers of China and Japan, or Bantu tribesmen. It is commoner among men than among premenopausal women; after the menopause, women gradually become as susceptible as men, though it takes them until age 80 to catch up. Racial origin, body build, smoking habits and the amount of physical activity also have been implicated. And, of course, the Gog and Magog of modern medicine: stress and strain.

The Question of Fat. The University of Minnesota's Physiologist Ancel Keys recently set up all these theories in a neat line and then charged down it, tilting at them one by one. Items:

¶ "The popular picture of the coronary victim as a burly businessman, fat and soft from overeating and lack of exercise, who smokes and drinks too much because [of his stressful climb to the top] is a caricature." The type exists, but often escapes coronary disease while men of other types fall victim to it.

¶ Families with a "bad heredity" for coronary disease attract attention. Dr. Keys depicted a "family" showing 31 descendants of one great-grandfather: twelve apparently died of coronary disease. But the "family" was fictitious, constructed from U.S. averages. The most that Dr. Keys will concede is a possible "familial tendency."

¶ Race may mean little, because U.S. Negroes living well in Chicago have about the same rates as whites, though Africans whose ancestors escaped slavery in the U.S. are spared the disease. U.S. citizens of Italian descent approximate U.S. average rates, and not those of their second cousins in the old country.

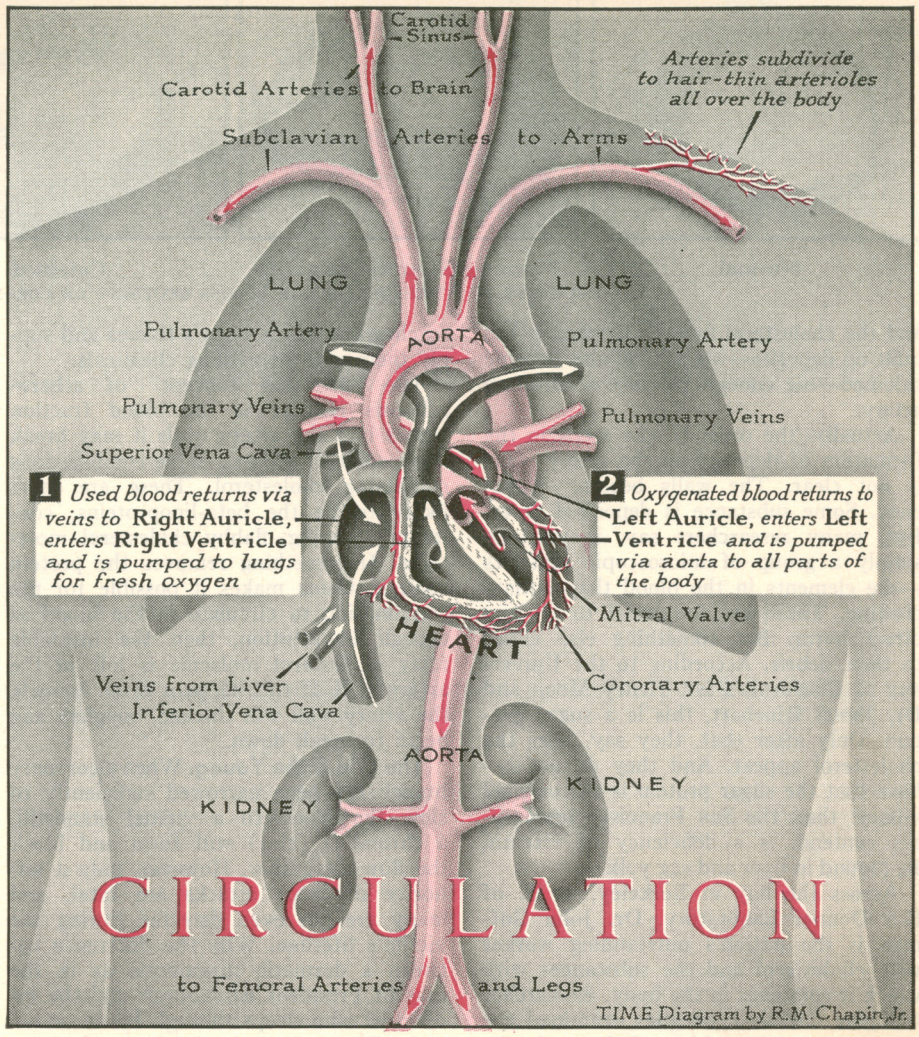
¶ Despite their poverty, many peasant peoples smoke as many cigarettes as they can get, and often down to the last tarry fraction of an inch, without developing heart disease.

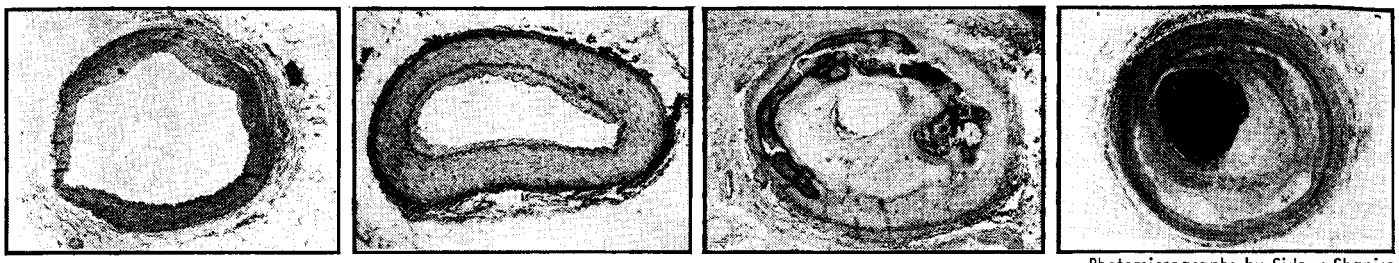
¶ Obesity and overweight are too often confused: a man may be overweight with muscle without being obese, or may have flabby fat on a small frame without being overweight. Without condoning "gross obesity," Dr. Keys could assign it "no more than some aggravating or accelerating influence."

The only factors to which Dr. Keys would give major responsibility were physical exercise (or the lack of it) and diet. He tackles the diet problem from the viewpoint of fat content. The fat in the U.S. diet, he points out, has been going up for 50 years; fats account for as much as 40% of its calories. In Sweden the proportion is 38%. But in Sardinia it is only 22%. The clincher, for Dr. Keys, is to be found among Yemenite Jews who had no coronary disease in their native habitat but have begun to develop it since they migrated to Israel and adopted its high-fat diet. Yet the amiable, blubber-eating Eskimos throw a monkey-wrench into the dietary-fat theory. In Alaska, they live for months at a time on the fat of island seal and whale, but even among their oldsters fatal atherosclerosis is rare.

Surveying the puzzling and contradictory evidence, Dr. Page offers a moderate summation: too much fat in the diet and too little are both bad. Anything below 15% is dangerous (he tried it himself for a year and found that he lost weight, energy and equanimity). Current U.S. levels are needlessly high. A nice balance: 25%. And he sees no decisive difference in the effects of vegetable and animal fats.

The Question of Cholesterol. The hottest of all arguments is over cholesterol. For the last decade or so, some researchers have been casting this fatty alcohol as the villain. It is the predominant substance found in the plaques and patches that form on the roughened inner wall (intima) of the artery, and the amount circulating in the blood is in some rough proportion to the fats in the diet. So it is temptingly simple to draw the conclusion that the dietary fat starts the trouble





Normal | Forming Sclerotic Deposits | Calcified | Blocked by Clot

Photomicrographs by Sidney Shapiro

PROGRESS OF ATHEROSCLEROSIS (CROSS SECTIONS OF CORONARY ARTERY)

and the cholesterol finishes it when it has built up deposits—which may also become calcified—big enough to close a coronary artery.

Actually, the order of the steps in the formation of deposits on the artery walls is not clear. The walls become roughened. Some substance is deposited there. But, many researchers say, it may be simply a group of microscopic platelets —the elements in the blood that initiate clotting. These are too small to do any direct harm. But something else clings to their debris. According to the University of California's Dr. Henry Moon and Dr. James Rinehart, this is a sugar protein. Only after that, they say, does the cholesterol appear. And they do not believe that the sugar protein is the original villain: that, the San Francisco researchers contend, is a deficiency of vitamin B_6 (found in liver and egg yolk).

Across the bay in Berkeley, at U. of C.'s Donner Laboratory, Dr. John Gofman is the nation's outstanding worker with cholesterol and the substances with which it combines in the body. Researcher Gofman and his colleagues examined the combinations in which cholesterol circulates. It enters the bloodstream combined with proteins of different kinds. Cholesterol molecules in the combinations known as alpha-lipoproteins are generally of high density and seem relatively little involved in disease; the beta-lipoproteins contain the fat and flabby cholesterol molecule that is clearly implicated in atherosclerosis.

By taking blood samples from volunteers at regular intervals and analyzing their lipoproteins, Dr. Gofman is now convinced that he has enough experience to forecast whether a given individual will suffer from atherosclerosis. (Other researchers are not sure that he is right. Three laboratories—at Harvard, the University of Pittsburgh and the Cleveland Clinic—have been running experiments to prove or disprove the Gofman thesis.) Still to be explored is the possibility that a more fundamental mechanism is involved: a defect in body chemistry—the way in which an individual metabolizes either fats or proteins.

The Question of Filtration. Then there is a little-known aspect of human circulation on which Dr. Page and others have been working. It may go far to solve the riddle of how atherosclerosis begins. In addition to the direct blood flow down the bore of the arteries to its destination in the capillaries, parts of it also perfuse through the arterial walls. Thus they reach many of the body's tissues and supply them with nourishing chemicals.

The "filtration concept" of atherosclerosis is that as the blood fraction passes into the artery walls it may break down some of the less stable combinations containing cholesterol. These are most likely to be the beta-lipoproteins, containing the big, flabby cholesterol molecules. If something removes the protein coating, which makes it possible for the combination to circulate in the blood as though in solution, then the insoluble fatty cholesterol molecule is left in the artery wall. If this happens often enough, the artery wall will thicken, roughen and begin to break down.

The Old & the Young. When a coronary branch has been narrowed sufficiently to slow the blood to a virtual standstill, a thrombus (clot) will form and block the flow altogether. However, only a minority of heart attacks are fatal, and many are not even detected during the victim's lifetime. Why the difference between a dramatic thrombosis as in the case of President Eisenhower and the individual who sleeps through his heart attack? The answer lies in the gradualness of the process that narrows the coronary artery concerned. If it constricts slowly for months, the heart brings into play its self-repair system and develops collateral circulation, *i.e.*, nearby branches enlarge to carry more blood to neighboring parts of the heart muscle. Thus when the final shutdown comes, its original blood flow has already been diverted. In cases like the President's, the collateral circulation has to develop after the attack.

Walter Sanders—LIFE

RESEARCHER MASTER & TWO-STEP TEST

Moderation in massive doses.

Equally striking is the contrast between the resiliency of many older men after a heart attack and the way in which younger men may succumb. A noted example last week was Cinemactor John Hodiak, 41, who seemed in excellent health—he had just passed an insurance examination—but had a quickly fatal attack while shaving. There are undoubtedly many cases in which a younger man will be killed simply because his disease is new while an older man with slowly developing disease will already have compensated, through collateral circulation, for a shutdown in an artery of the same size.

Treatments. In some cases, threatened heart attacks can be warded off. This happens when narrowing of coronary arteries gives warning of its advance by pain in the chest (angina pectoris). This is felt when the heart cannot deliver extra blood required to digest a big meal, to combat cold, or to sustain unusual effort. The degree of heart impairment can be measured after exercise on a miniature flight of stairs—the Master two-step test. The treatment, besides weight reduction: nitroglycerin pills slipped under the tongue when pain is felt. They dilate blood vessels and relieve pain almost instantly.

What of attacks that strike without warning? Many of these are of the type suffered by the President, and leave no sign of "heart failure." This term, frightening if misunderstood, is a doctor's way of describing the condition when a heart cannot meet the demands upon it and begins to lag. The President's treatment was typical for uncomplicated cases: morphine at once to relieve pain, complete rest, anti-clotting drugs (first heparin, later Dicumarol) and an oxygen tent.

If damage to the heart is so severe as to make it liable to recurrent failure in its pumping action, initial treatment is the same. However, this is then followed by drugs such as digitalis which give the heart added power.

The Question of Blood Pressure. All these experiments and treatments are concerned with one general form of heart disease—arteriosclerosis. The other major form of arterial disease is hypertension. In this case, the heart becomes enlarged from the effort to pump against the increased resistance of hardened, narrowed

arterioles. But as it enlarges, it needs more blood to fuel it, and must work still harder to supply itself. To forestall or arrest this vicious circle is the long-standing aim of Hypertension Specialist Page.

Main trouble is that doctors have no idea what causes 90% to 95% of high blood pressure. This vast majority of the estimated 15 million U.S. cases they list under the misleading label of "essential hypertension." For the small percentage of cases whose origin can be traced, Dr. Page gives four known causes: 1) kidney disorders; 2) hormone upsets, often from tumors of the adrenal glands (astride the kidneys); 3) disorders of the nervous system in which normal impulses are either absent or intensified; 4) hardening and loss of elasticity in the aorta. Whether "essential" or of known origin, hypertension may be either benign or malignant. A patient can live with the benign type for years with only moderate care and little discomfort. The malignant form may kill him within months.

Who gets high blood pressure and why? Many laymen have a pat answer: "It's the pace of modern living." But doctors putting this theory to the test find no proof. Many men under the greatest strain never develop it, while some under the least strain do. Occupation is no guide. Body-and-soul researchers have tried to find a personality type that is especially prone but no clear pattern emerges. Young women are more likely to have heightened pressures than young men, but paradoxically they are less likely to develop disabling disease. After middle age, men are marked for trouble much more often than their wives.

Bedside & Laboratories. Page began his work in 1937 at the Lilly Laboratory for Clinical Research at Indianapolis City Hospital, after three years at Munich's Kaiser Wilhelm Institute and six years at the Rockefeller Institute. With Canadian-born Dr. Arthur Curtis Corcoran, who has been teamed with him since 1936, Page made important discoveries on the workings of renin,* an enzyme secreted by the kidney when it is starved of blood. An injection of renin raises the blood pressure. It also alters the fat-protein combinations in the blood in such a way as to encourage atherosclerosis.

Since 1945, Page has been research chief of the Cleveland Clinic (a private medical center founded by the late Surgeon George Crile). In seven floors of laboratories, Dr. Page and his staff (eight physicians, four other research scientists, 26 technicians) are attacking all phases of hypertension from as many angles as possible, and in 20 research beds in the clinic's adjoining hospital the medical staff cares for patients who agree to cooperate in the study and treatment of their disease. Some of the scientific attacks are so basic that they seem remote from bedside medicine.

Brazilian Dr. Lauro Sollero studies how

* Not to be confused with rennin, a milk-digesting enzyme.

one billionth of a gram of serotonin (a powerful, blood pressure-raising chemical isolated by Page and colleagues) makes a strip of rat uterus contract, and the ways in which serotonin and other body chemicals cancel each other's effects. Dr. James McCubbin is probing breakdowns in nerve impulses that throw blood-pressure control out of kilter. Famed Internist Willem Kolff, who invented the artificial kidney when his native Netherlands was under Nazi occupation, has developed a $14 model in a gallon can. Dr. Page himself spends two or three days a week in the lab—last week he was testing the effects of new chemicals on blood pressure in dogs.

However far apart they seem, says Dr. Page, the pure science researcher and the bedside physician must be brought together, as they are in his own laboratory. From 20 years of personal study and correlating his views with those of other researchers, Dr. Page sums up: "Hypertension is not a single disease. It may be almost as variable as the many different forms of cancer. Neither can it have a single cause. There are at least eight mechanisms in the body operating to maintain an even blood pressure, and these are all interrelated. The balance of one cannot be upset without upsetting the balance of the others."

Treatments. For the relatively mild case of hypertension, Page and colleagues prescribe the obvious—massive doses of moderation. First, they reassure the patient by explaining what they can do about his disease. Then they advise him to do what he can to avoid fatigue and excitement. He should spend ten hours in bed and take short naps, often. Every extra pound of flesh on the patient means work for the heart, so—reduce. Moderation is also prescribed in smoking and drinking, in exercise and sexual activity.

For more severe cases the Cleveland Clinic doctors have a growing list of hopeful treatments. And in some victims, at least, malignant hypertension can actually be reversed. For years Dr. Page used kidney extracts, which helped some patients, and pioneered with fever treatments which had similar moderate success. Not until the spring of 1951 was a drug found to control malignant hypertension. This was hydralazine. In quick succession came a series of hexamethonium compounds (followed by the related pentolinium) and more recently reserpine.

From Cleveland Clinic case histories:

A soft-drink manufacturer turning 50 was in bad shape with an enlarged and failing heart, breathlessness, weakness and fluid retention (the old-time "dropsy"). His blood pressure had soared to 230 over 146. He was the first patient given hydralazine at the clinic, and remains one of its best testimonials. In more than five years he has had no signs of heart failure (though the heart is still enlarged), no worsening of kidney trouble, and he does a full day's work.

In the hypertension area, too, diet is hotly debated. "No salt!" cry many doctors, although the link between salt and blood pressure is not fully understood. Many doctors believe that salt content must drop to an infinitesimal one-tenth of a teaspoonful per day. This can be achieved only by an extreme regimen like the famed "rice diet." But even on this, says Dr. Page, a mere 25% of the patients get their blood pressure down to near-normal levels. So: "Whether one wishes the psychic mortification of the rice diet or the dubious gratification of a planned low-salt diet is up to the individual. So many good low-salt diets and foods are now available that it is not necessary to go to the 'rice-house.' A reliable wife is one of the most useful and often essential adjuncts to a strict low-salt diet."

Ed Nano

RESEARCHERS CORCORAN & PAGE
"We don't want to make invalids."

Heal Thyself. In all but work, Page practices the moderation that he preaches. Waking between 5 and 5:30, he makes his own breakfast and starts work at once. With no visitors or telephone calls to interrupt him he gets his best work done (writing and assembling statistics for his reports) before he leaves for the clinic at 8 a.m.

At 150 lbs., Dr. Page is about the ideal weight for his 5 ft. 8 in.—and proud of it. One thing that helps keep him there is his token lunch, such as a bowl of clear soup and a gobbet of cottage cheese doused with ketchup, washed down with skim milk. Much of his exercise comes from running up and down stairs in the seven-floor lab building: it is quicker than waiting for an elevator and is good for the muscles in the leg arteries. In summer, Page plays singles tennis, but is careful to play only one set a day at first, after the winter's inactivity.

He breaks his long workday by getting home as soon after 5 as possible, taking a shower and a nap before dinner. Page and his wife (a former ballet dancer, author of a promising 1953 novel, *The Bracelet*) have two sons, 13 and 16. At college (Cornell '21), Page used to play "the long-necked banjo" to help pay his tuition. Now he has gone hi-fi, playing Mahler and

Sibelius, while he gets in two or three more hours of medical reading or writing after dinner. Bedtime: 10 or 10:30.

Hope from Surgery. It is too soon for Dr. Page to gauge the long-term value of today's research in his Cleveland Clinic laboratories. This is true of the work on heart-and-artery disease that is being pressed in scores of U.S. laboratories: the field is too new. However, there is solid ground for hope in the very scope of the effort now being made. The American Heart Association pays out $5,000,000 a year in research grants—half of it for basic science. Even more ambitious is the National Heart Institute's program. It is only seven years since the Public Health Service launched the institute with three men, three desks and three filing cabinets in a corner of a temporary building at Bethesda, Md. Now N.H.I. has mushroomed to an expert research force of 400. Of its $18-million budget this year, $5,000,000 will be spent within its own walls and $9,000,000 funneled out to 720 research projects across the country.

Many heart men are returning to the field of their earliest successes—surgery. To check hypertension in some cases of nervous origin there is a formidable two-stage operation, sympathectomy: whole series of nerve bundles beside the spine are cut. Increasingly daring surgery is also coming to the aid of atherosclerosis victims. Surgeons in many cities can now cut out a diseased, bottleneck section of the aorta and use a graft from a frozen artery bank as a splint while the patient's own aorta heals. For similar roadblocks in the femoral (thigh) arteries, the surgeon may slit the artery lengthwise, scrape off the diseased deposits, and sew it up again.

Toronto's Surgeon Gordon Murray has developed a still more daring procedure. The infarct caused by a coronary closure is actually cut out from the wall of the heart itself. Then healthy muscle from each side of the dead area is stitched together. The slightly smaller heart that results is more efficient.

No one can foresee whether the best answers will in the end come through chemicals or the scalpel, or both—or how much longer the tough, miraculous and mysterious sac of muscle will elude man's determination to control it. But one of the most hopeful items in medicine's advancing knowledge is that heart disease and heart attacks need cause far less of the chill dread that used to surround them (*see box*). "Perhaps the most dangerous thing we doctors can do in managing patients with heart or artery disease," says Page, "is to discourage them with too many don'ts. It is disturbing to me to read medical recipes for long life which first prohibit smoking, then alcohol, and tell you to cut out butter and other fats, and end by suggesting that some kinds of cancer can be avoided by total abstention from sexual intercourse. That is limiting life pretty sharply. We don't want to make invalids, but to help these people to live lives that are longer and happier and more useful. I think we are learning how to do that."