THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

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PART III

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Natural History of Ventricular Septal Defect in Patients Surviving Infancy. Daniel K. Bloomfield[1] (Western Reserve Univ.) reviewed clinical data on 424 patients aged 3 and over and hemodynamic data from cardiac catheterization in 288. Twenty-five patients were followed up at an average of 9.4 years and 48 at an average of 24 years. Autopsy data from the literature and from four general hospitals were also reviewed. Groups 1, 2 and 3 included patients with mild, moderate and severe disease, respectively, uncomplicated by elevated pulmonary vascular resistance. Groups 4 and 5 had complicated disease, with pulmonary hypertension and the Eisenmenger complex, respectively. The smaller defects (groups 1 and 2) are separate from the larger ones immediately at birth. Apparent size may differ from real size.

Growth and development in groups 1 and 2 are normal, and early problems are uncommon. About 25% of the defects in these patients will close spontaneously. The risk of bacterial endocarditis is about 30% for a 70-year lifetime and should be considerably lower with judicious penicillin prophylaxis. The lifetime mortal risk of this complication is less than 5%. Group 2 patients will gradually approach group 1 status clinically in the 3d and 4th decades, if not sooner. Diagnosis is more difficult over age 40. These patients seldom die young and they do not acquire pulmonary hypertension. A complication of aging is increased susceptibility to other left ventricular diseases. Weakness from a defective septum, whether open or closed, may initiate early congestive heart failure in the presence of left ventricular disease. The anticipated life expectancy for the 95% of patients surviving bacterial endocarditis is perhaps 65 years. The sur-

[1] Circulation 29:914-933, June 1964

gical approach to these patients is mainly prophylactic —against bacterial endocarditis. The established surgical risk must be below 1%.

Group 3 and 4 patients commonly have congestive failure in the 1st year of life, and there is a high incidence of pneumonia and other respiratory infections, moderate effort intolerance or fatigue and retarded growth. Group 5 patients may have more effort intolerance and cyanosis but less congestive failure and fewer respiratory symptoms. The separate physiologic variants of these three groups tend to fuse toward a single syndrome after age 30, which is characterized chiefly by gradually increasing effort dyspnea and varying degrees of bidirectional shunting. Mean survivorship in patients with large defects surviving infancy is probably 35 years. Patients in groups 3 or 4 who acquire the Eisenmenger complex after 20 years might be prone to early congestive failure. Survivorship among group 4 patients at 8-12 years was poor. Half with reported cases died of congestive failure, often complicated by pneumonia. Another fourth died of bacterial endocarditis.

At present, surgical closure is clearly indicated for groups 3 and 4 and contraindicated for group 5. The theoretical cumulative survival to age 65 of patients with large defects is longer in children not subjected to the higher risk of early surgery (age 1), though as many as 20% of cases become inoperable by age 7. The excess mortality at age 65 in patients having early operation was 448 patient-years per 100 patients per lifetime. The risk of the case of any patient becoming inoperable at age 1-7 is actually closer to 5%.

► [This report is a classic illustration of the type of clinical investigation that needs to be done in the field of congenital heart disease. The rapid surgical advances within the past 20 years have often led to excessive enthusiasm for radical as contrasted with conservative management. Actually, there are as yet many patients with congenital heart disease in whom no one really knows whether surgical treatment is or is not indicated. Such a decision requires two types of information. The first is a clear knowledge of the probable operative hazard. In this respect, the figures in the literature are likely to be misleading because those who have obtained good results naturally report them and those who experience a high mortality tend to keep discreetly silent. The second type of information needed is the natural history of the disease in patients who have not been subjected to operation. This report sets a fine example for studies of the latter type – Ed.]

Systemic-Pulmonary Shunt. A. Voll, F. Marstrander and P. Wexels[2] (Univ. Hosp., Oslo) report the results of clinical, x-ray and hemodynamic studies of 2 patients with shunts from the systemic to the pulmonary circulation.

(2) Dis. Chest 45: 396-401, April, 1964

Case 1.—Woman, 32, was noted to have a systolic murmur at the 3d right intercostal interspace when pregnant 6 years previously. On admission, a continuous systolic-diastolic murmur was heard, and the pulmonary vascular markings were increased in the hilar region, especially on the right. Catheterization studies showed a shunt of arterialized blood to the right pulmonary artery. Aortography revealed an elongated, tortuous and dilated internal mammary artery on the right side, with passage of contrast material into the right pulmonary artery. On chest exploration, many dilated, elongated vessels were found with arterial pulsations and a pronounced thrill, they seemed to be supplied from the markedly dilated right internal mammary artery. The pulsations were traced to the branch of the pulmonary artery to the middle lobe. The anterior segment of this lobe was removed and the greater vessels were ligated. The thrill disappeared. The internal mammary artery was ligated at the level of the 2d right interspace. No complications followed operation.

Case 2.—Man, 33, had dyspnea and palpitations on exertion and sometimes at rest. On auscultation, a continuous systolic-diastolic murmur was heard over the anterior and posterior thoracic wall. Tomography showed many dilated vessels forming a network at the basal and posterior position. Several great vessels joined to form a vessel passing in the direction of the left atrium; the vessel seemed to be a vein. Branches from the area of the vascular network formed a vessel directed into the mediastinum posterior to the right main bronchus, the vessel was supposedly an artery, with an abnormal course and reduced caliber. Pulmonary angiography showed filling of a great branch from the right pulmonary artery, directed at the lung base and giving off several branches to the area of the vascular network. At the venous phase the great posterior vessel showed marked filling with contrast material. Subsequent aortography showed filling of the vessel previously assumed to originate from the aorta and passing to the right lung. The ascending aorta was markedly dilated. Introduction of the catheter into a superior aortic branch gave good filling of an ascending paravertebral branch. A little contrast medium flowed backward into the greater branch to the right lung. Just under this trunk the catheter entered a vessel forming two branches passing into the mediobasal fields of the right lung. About 4-5 cm. from the departure, contrast material passed from this vessel into the greater branch. Operation showed cardiomegaly and considerable dilatation of the ascending aorta. The superior pulmonary vein on the right side was twice its normal size, but the right pulmonary artery was only half its normal thickness. Two great arteries branched off from the aorta, with a marked thrill. The proximal artery immediately divided into two branches, the superior one passing along the thoracic vertebrae; the other branch and the distal artery from the aorta drained into the large pulmonary vein. The two great arteries were divided and the thrill subsided. The postoperative course was uneventful.

The prognosis for these patients is uncertain. Because of the inherent risk of these vascular anomalies, patients should be operated on when the diagnosis is made. The shunt

should be localized on the systemic side The artery should be ligated as close as possible to the starting point, without trying to ligate the many smaller vessels implicated in the shunt at first

Cor Triatriatum: Hemodynamic and Angiocardiographic Diagnosis. In cor triatriatum, an abnormal fibromuscular diaphragm divides the left atrium into a posterosuperior chamber which receives blood from the pulmonary veins and an anteroinferior chamber which communicates with the mitral valve and atrial appendage The diaphragm contains one or, occasionally, several openings, the size of which determines the degree of obstruction to pulmonary venous return The foramen ovale, which may be patent, may communicate with either the upper or lower chamber

Graham A H. Miller, Patrick A Ongley, Milton W Anderson, Owings W Kincaid and H J C Swan (Mayo Clinic and Found.) describe 3 patients studied by cardiac catheterization, in 2 of whom angiocardiography was diagnostic All had increased pulmonary arterial and "wedge" pressures Left ventricular end-diastolic pressures were normal Angiocardiography outlined the intra-atrial diaphragm in 2 patients Removal of the left atrial diaphragm was successful in 2 The third, who had severe pulmonary vascular disease, died on the 1st postoperative day One patient, restudied 11 days after operation, showed considerable reduction in pulmonary arterial and "wedge" pressures and pulmonary resistance Repeat study at 9 months after operation showed only minimal elevation of pulmonary arteriolar resistance, with a further resolution of pulmonary vascular disease. Study of the other patient 1 year after operation showed some residual pulmonary hypertension

Sixty cases of cor triatriatum have been reported, in 5 of which the intra-atrial diaphragm involved the right atrium Hemodynamically, the condition mimics mitral stenosis, and the clinical signs are similar The x-ray appearance of left atrial enlargement and pulmonary venous hypertension suggests obstruction to pulmonary venous drainage.

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(3) Am. Heart J. 68 295-301, September, 1964

RHEUMATIC AND VALVULAR HEART DISEASE

Prognosis of Acute Rheumatic Fever. Alvan R. Feinstein, Edith K Stern and Mario Spagnuolo[1] (New York) correlated the clinical events of acute rheumatic fever with the subsequent cardiac sequelae in 411 children and adolescents who received continuous antimicrobial prophylaxis after rheumatic episodes occurring during 1950-57 Mean follow-up was 7 8 years The proportionate distribution and severity of carditic and noncarditic clinical features in the population were similar to those in a comparable population whose acute rheumatic episodes occurred during 1958 60 At last examination, all 181 patients initially free from carditis remained free from rheumatic heart disease Evidence of cardiac damage had disappeared in 113 of the 260 with carditis initially, whereas 135 had residual heart disease and 12 had died. All but 1 of the 12 had severe carditis initially, and only 1 had evidence of recurrent or persistent acute rheumatic inflammation before death

Disappearance of heart disease was most likely in patients with mild rather than severe carditis; a first rheumatic attack rather than a recurrence; systolic murmurs only rather than diastolic murmurs; murmurs of one valve rather than of two; and arthropathic manifestations rather than no joint symptoms. In the 271 patients whose episodes were first attacks, the cardiac outcome depended on the presence and severity of carditis when treatment was begun and was unrelated to the treatment agent or to the promptness with which treatment was begun after onset of symptoms Evidence of pericarditis was most common in patients with other manifestations of carditis and did not in itself appear to influence prognosis. A prolonged P-R interval occurred in about one third of patients during the acute episodes, regardless of the presence or severity of carditis, and had no direct relationship to the ultimate cardiac state.

Therapeutic correlations showed no superiority of steroids over salicylates in treating patients with first attacks of acute rheumatic fever. The agents had similar long-term

(6) Am. Heart J. 60:817-836, December, 1960.

from rheumatic heart disease. Heart disease disappeared in many patients considered to have it initially. This was most likely to occur in patients who had no attacks of rheumatic fever before the index attack, no cardiomegaly and no diastolic murmurs. All but 1 of the 12 patients who died had evidence of severe carditis in the index attack and remained free from rheumatic recurrences thereafter. A prolonged P-R interval in the ECG had no consistent relationship to other clinical evidence of carditis in the acute attack and was not a useful guide to eventual prognosis.

Diagnosis and Treatment of Tricuspid Stenosis. Arthur Kitchin and Richard Turner[8] (Univ. of Edinburgh) found severe tricuspid stenosis on cardiac catheterization in 19 of 550 patients having mitral valvotomy. Tricuspid valvotomy was performed immediately after relief of mitral stenosis in 17 of these patients. A large flicking *a* wave in the venous pulse, a tricuspid diastolic murmur, right atrial enlargement on x-ray study, right atrial hypertrophy on the ECG and a pressure gradient across the tricuspid valve in diastole offer presumptive evidence for tricuspid stenosis, but all these features may occur in other conditions. In sinus rhythm, the most reliable sign of important tricuspid stenosis is a flicking *a* wave, best seen in the external jugular veins at the root of the neck. Enlargement of the pulmonary artery, congestion of the lung fields and right ventricular hypertrophy do not exclude severe tricuspid stenosis. Valve area calculations are unreliable if incompetence is present. When tricuspid disease is present with atrial fibrillation, a prominent systolic wave in the venous pulse may be associated with severe stenosis and only minor regurgitation. The most consistent confirmatory evidence of severe stenosis in the presence of a tricuspid pressure gradient has proved to be dissociation of right atrial and right ventricular diastolic pressures during respiration. In severe tricuspid stenosis, a systolic murmur from associated incompetence tends to decrease on inspiration.

Tricuspid stenosis causes a disability similar to that in mitral stenosis, but which may be unrelieved by mitral valvotomy. Cardiac output is severely restricted both at rest and on exercise. When atrial fibrillation occurs, the venous pressure remains permanently raised.

Symptoms were relieved in 12 patients after operation.

(8) Brit Heart J 26 354-379, May, 1964

nal population was lost due to lack of attendance, and 81% were regularly observed throughout the study period. Prophylaxis was maintained faithfully by 94% of patients receiving monthly injections of 1,200,000 units of benzathine penicillin and by about 50% of those given sulfadiazine, 1 Gm daily orally, or potassium penicillin G, 200,000 units daily orally.

There were 285 streptococcic infections in the 6-year study period. The attack rates per 100 patient-years of observation were 6% in the benzathine penicillin group, 24% in the sulfadiazine group and 21% in the oral penicillin group. With "carrier" infections excluded, the rates were 4, 18 and 19%, respectively. Forty-eight recurrent episodes of rheumatic fever occurred. Attack rates in the three groups were 0.4, 2.8 and 5.5% per 100 patient-years of observation, respectively. Patients who maintained oral prophylaxis faithfully had fewer streptococcic infections and rheumatic recurrences than those who did not. The benzathine penicillin regimen was more effective than the oral regimens, even when the latter were faithfully maintained. No significant systemic reactions occurred in any group, but benzathine penicillin had to be stopped in about 10% of patients because of persistent local reactions or refusal of the patient to continue treatment. All but 1 of the recurrences of rheumatic fever were associated with significant rise in titer of one or more streptococcic antibodies. The rate of rheumatic recurrence per infection increased with increasing magnitude of clinical symptoms of infection, incremental rise in titer of antibodies, severity of existing heart disease and number of previous rheumatic attacks. The rate decreased with increasing age and with increasing length of time elapsed since the antecedent rheumatic attack. The rate was unaffected by the preinfection antibody titers or by the remoteness of the most recent antecedent infection.

With increasing cardiac damage in the host, the rheumatic recurrences had fewer arthropathic features but more severe cardiopathic effects. In patients with no or questionable carditis in previous attacks, the rheumatic recurrences left no overt permanent valvular damage. In observing 441 patients for almost 8 years, observation being extended beyond the prophylaxis trials, patients free from significant murmurs in the acute "index" attacks were found to remain free

Catheterization was repeated in 5 patients and showed reduction but not abolition of the valve gradient. Right atrial size did not decrease Regression of the P pulmonale pattern in the ECG was usual but not always complete None of the 3 operative deaths was considered to be due to the tricuspid valvotomy itself Traumatic valvular incompetence resulted in only 1 instance Two patients died of the over all effects of severe rheumatic heart disease 1 and 2 years after operation Of the 12 survivors, 11 are well after 2 6 years, whereas 1 had only a fair result

Endocardial Fibroelastosis: Clinical and Anatomic Study of 47 Patients with Emphasis on Its Relationship to Mitral Insufficiency. James H Moller, Russel V Lucas, Jr , Paul Adams, Jr , Ray C Anderson, Joseph Jorgens and Jesse E Edwards* (Univ. of Minnesota) studied 23 patients with primary and 24 with secondary endocardial fibroelastosis All 24 specimens reviewed showed a mitral valve abnormality that appeared to render the valve incompetent All but 5 patients had fibroelastosis of the dilated type, including all 23 with primary disease. The left ventricle in these 23 patients was prominently dilated and thick-walled, and the endocardium consisted of many heavy layers of elastic tissue separated by collagen. In all 11 specimens studied, the mitral valve showed smaller than normal leaflets, particularly the anterior leaflet. The papillary muscles were small and originated higher than normal on the left ventricular wall, the chordae tendineae were shortened and thickened Marked left atrial dilatation and hypertrophy were present. In older patients, the free edge of an anterior mitral leaflet had a rolled appearance. Pathologic evidence of mitral insufficiency was found in all 11 specimens. The presence of this condition was supported by the clinical findings in these patients. Ventriculography, done in 2 patients, showed mitral insufficiency.

Eight patients had congenital aortic stenosis and dilated fibroelastosis. A similar mitral valve abnormality was found in all 4 gross specimens reviewed. The clinical features were those of aortic stenosis. Eight patients had aortic coarctation and dilated fibroelastosis. The 3 patients with a wide ductus arteriosus distal to the coarctation site had evidence of left-to-right flow through the ductus. A bicuspid aortic valve that

was not stenotic was present in 3 of 5 gross specimens studied The mitral valve abnormality was found in all 5 patients The clinical picture was that of aortic coarctation Three patients had endocardial fibroelastosis and anomalous origin of the left coronary artery from the pulmonary trunk In the 1 specimen reviewed, the mitral valve was similar to that seen in the group with primary fibroelastosis

Five patients had aortic hypoplasia with a diminutive left ventricle associated with endocardial fibroelastosis There was a large patent ductus arteriosus The mitral and aortic valves were diminutive in each, and in 2 the left atrium was extremely small Aortic stenosis of unicommissural type was present in 2 patients, and in the others there was aortic stenosis secondary to a stenotic bicuspid valve Each patient showed dilatation and hypertrophy of the right ventricle The mitral valve was small and abnormally formed, but mitral insufficiency did not appear significant in these patients since the left side of the heart was essentially nonfunctional

Many of the clinical and laboratory findings in primary endocardial fibroelastosis could be explained on the basis of mitral insufficiency In patients with associated cardiac anomalies, the hemodynamic consequences appeared to be a summation of the combined effects of the mitral insufficiency, endocardial fibroelastosis and associated anomaly Primary and secondary endocardial fibroelastosis could not be distinguished in these cases by gross or microscopic methods It is preferable to classify cases based on the structural abnormalities present

Idiopathic Hypertrophic Subaortic Stenosis: I. Description of Disease Based on Analysis of 64 Patients is presented by Eugene Braunwald, Costas I Lambrew, S David Rockoff, John Ross, Jr, and Andrew G Morrow[1] (Nat'l Inst of Health) Idiopathic hypertrophic subaortic stenosis is characterized by marked left ventricular hypertrophy, involving especially the interventricular septum and the left ventricular outflow tract During systole, the hypertrophied muscle often narrows the outflow tract enough to obstruct left ventricular ejection Usually the hypertrophy is asymmetrical, but occasionally it is diffuse and the lumen of the outflow tract reduced Marked enlargement of the papillary muscles

(1) Circulation (supp 4) 30-3 119 November 1964.

and trabeculae carneae, deformation of the mitral valve by the thickened septum and thickening of the anterior mitral leaflet are commonly noted

Of the 64 patients studied, 67% were males Average age was 25 7, and females were significantly older than males. A murmur was present before age 1 in 9 patients The 23 patients considered to have the familial form of the disease were members of 11 separate family groups Study indicated that the disease is transmitted in a non-sex linked, autosomal dominant fashion without genetic anticipation Symptoms were present in 48 patients, dyspnea, angina, dizziness and syncope being most common Paradoxical splitting of the 2d sound was present in 22 patients, and the systolic gradient was significantly higher in these An ejection type systolic murmur was heard in all patients Abnormally deep and broad Q waves were significantly more common in familial cases, they are likely related to gross septal hypertrophy. Aortic dilatation is uncommon An inward concavity at the midportion of the right inferior margin of the left ventricular cavity was a common finding on angiograms A long subvalvular area of narrowing commonly appeared to cause the obstruction Nearly half the patients had mitral regurgitation; these patients were significantly older than those without regurgitation and tended to be more disabled

The arterial pulse rises sharply in this condition A carotid pulse with two systolic peaks was recorded in 35 of 47 patients. A systolic pressure gradient within the right ventricular outflow tract was recorded in 10 patients, and the right ventricular end-diastolic pressure was elevated in 21 The mean left atrial pressure was elevated in 18 of 42 patients and the left ventricular end-diastolic pressure in 47 of 64. The peak systolic left ventricular outflow pressure gradient was over 100 mm. Hg in 14 patients, 50-100 mm. Hg in 21 and 10-50 mm. Hg in 15; it was not elevated in 14 patients. There is abnormally low ventricular compliance in this condition Forced slow respiration, discomfort or anxiety, elevation of the legs and general anesthesia all had striking effects on the severity of obstruction. Injection of cardiac glycosides increased the pressure gradient. Isoproterenol usually intensified existing obstruction or resulted in development of a significant pressure gradient. Nethalide prevented the effects

of isoproterenol. Methoxamine or phenylephrine abolished the obstruction, whereas nitroglycerin intensified or provoked it.

In general, this condition is progressive, usually slowly. Six patients died of the disease. Sudden death appears more common in patients with the familial form of the disease and may occur in patients who were previously asymptomatic. It appears likely that hypertrophy precedes and is responsible for the obstruction. The possibility that an abnormal sequence of contraction of the major structural units of ventricular muscle may cause the disease must be considered, and it has been suggested that there is a relation between its eventual development and the hyperkinetic heart syndrome.

Use of Amyl Nitrite in Hemodynamic Assessment of Aortic Valvular and Muscular Subaortic Stenosis was evaluated by Frank I. Marcus, Joseph K. Perloff and Antonio C. DeLeon[2] (Georgetown Univ.). Four patients with aortic valvular stenosis and 4 with muscular subaortic stenosis were studied.

METHOD—Catheterization of the left heart was performed by the retrograde femoral or the transseptal technic. Amyl nitrite was inhaled from a broken phial held lightly over the nose with a small cloth, the subject increased the rate and depth of respiration only slightly. Inhalation usually lasted 10-20 seconds and was stopped when the brachial systolic pressure fell by 25-35 mm Hg

Amyl nitrite consistently increased the left ventriculobrachial arterial systolic gradients in both types of stenosis. Separation of the systolic pressures was achieved primarily by disproportionate decline in brachial arterial pressure. The left ventricular systolic pressure declined or remained unchanged in 5 patients and rose in 3. In 2 patients with valvular aortic stenosis and 2 with muscular subaortic stenosis, nitrite inhalation revealed the presence of outflow obstruction not otherwise apparent since the control systolic gradients were absent or trivial.

Observations indicated that the technic used is a safe, convenient and reproducible means of accentuating the gradient in both types of stenosis. Although it cannot necessarily be used to distinguish one from the other, the diagnosis of muscular subaortic stenosis is suggested if inhalation changes the shape of the arterial pulse to the characteristic double-peaked contour. Amyl nitrite may prove safer than isoproterenol in the diagnostic assessment of aortic stenosis.

(2) Am. Heart J. 68:468-475, October, 1964

since ventricular irritability or coronary insufficiency can be aggravated by the latter drug but not by the former

Total Valve Replacement for Acquired Valvular Heart Disease: Results in 171 Patients having mitral or aortic valve replacement in the past 21 months are reviewed by Denton A Cooley and Thomas G. Nelson (Baylor Univ.) In cases of mitral disease, total replacement was reserved for patients in whom dense calcification or loss of valve substance was present and in whom transventricular commissurotomy or annuloplasty was not considered practical. All patients undergoing operation for acquired aortic valve disease had total replacement The patients selected generally showed progressive cardiac deterioration

Most of the 113 males and 58 females were aged 40-60 Mitral valve replacement was done in 63 patients and aortic valve replacement in 106 Two patients had both valves replaced at the same operation Six patients underwent additional procedures on secondarily involved valves Of the patients, 64% were in class III and 36% in class IV Disability was related predominantly to valve destruction Over 20% of the patients had recurrent incapacity after previous valve surgery No patient was refused treatment because of poor myocardial reserve or disease of the coronary or pulmonary vessels.

At operation, a disposable oxygenator and 5% dextrose prime were used under normothermic conditions Careful venting and refilling technics prevented air embolism The myocardium was perfused with oxygenated blood The Starr-Edwards prosthesis or the Magovern sutureless ball valve was used. The average bypass time for single valve replacement was 30 minutes. Prophylactic antibiotic therapy was given after operation. The average blood replacement for all patients throughout hospitalization was 1,600 ml. Anticoagulation was used prophylactically in selected patients after embolic complications occurred in a few.

The over-all mortality rate was 18.7%; 8 of the 14 early deaths resulted from the first 67 operations Fifteen of the 18 late deaths occurred within 6 months of operation. Myocardial failure caused 34% of deaths and occurred only in class IV patients with unusual degrees of cardiomegaly or pulmonary hypertension. Late complications involving the prosthe-

sis, including thromboembolic accidents, infection and detachment, caused 25% of all deaths. There were 4 deaths from thromboembolism, 2 from systemic infection and 2 from prosthetic detachment with progressive heart failure. Three patients recently underwent reinsertion of a new prosthesis, with 2 successes. Only 3 deaths resulted from coronary artery insufficiency or blockage, despite significant coronary artery disease in one fourth of all patients.

Within 2-3 months of operation, most of the 139 survivors returned to normal activity, had greatly increased exercise tolerance and were relatively free from symptoms. Of 80 operated on more than 6 months ago, 60 are working full time and are virtually free from symptoms, 16 work part time or do normal housework and have minimal symptoms and 4 are partially disabled. One of the 59 patients operated on more recently is partially disabled; all others show greatly improved cardiac function. Most survivors no longer require special diets or diuretics, and many have discontinued the use of digitalis.

The over-all results have been most gratifying in altering the generally grave prognosis of patients with acquired valvular heart disease.

Fatal Hemolysis Following Ball-Valve Replacement of Aortic Valve is reported by William A. Reed and Marvin Dunn[4] (Univ. of Kansas).

Man, 32, was seen for evaluation of a heart murmur known present for about 11 years. The blood pressure was 85/60 mm. Hg and the pulse rate 80. There was marked left ventricular thrust, a grade 4 aortic systolic ejection murmur, a grade 2 aortic diastolic regurgitant murmur at the left sternal border and an Austin-Flint murmur at the apex. The aortic component of the 2d sound was absent, and a loud 3d sound was heard at the apex. The ECG showed ventricular hypertrophy of the systolic overload type. Total ejection time was 0.39 seconds. X-rays showed left ventricular and left auricular enlargement, as well as calcification of the aortic valve and poststenotic dilatation of the aorta. Dyspnea, palpitation, exertional tachycardia and decreased exercise tolerance developed the next year. Right-heart catheterization was normal. A 100-mm. systolic gradient was found across the aortic valve. Left atrial "A" waves peaked at 24 mm. Hg, the left ventricular end-diastolic pressure. Moderate insufficiency was found on Cardio-Green injection.

Operation was performed under bypass with a disk-type oxygenator and a flow rate of 2.2 L./sq. m./minute. The body temperature was reduced and the heart packed in normal saline ice slush. Calcification involved all the aortic valve cusps. The left coronary artery

(4) J. Thoracic & Cardiovas. Surg. 48:436-442, September, 1964

was perfused with blood at 30 C at a rate of 200 ml per minute The valve was removed and an 11A Stan-Edwards valve inserted with interrupted 00 Dacron sutures through the annulus The heart resumed satisfactory function The systolic gradient was 120 mm. Hg before valve insertion and 24 mm Hg after The patient was perfused for 90 minutes

The patient was doing well on the 3d postoperative day on treatment with digitalis, penicillin and streptomycin Hemoglobin and hematocrit decreased on the 4th day The total bilirubin was 1 mg /100 ml and the plasma hemoglobin 4 mg /100 ml Anticoagulant therapy with Coumadin was begun on the 6th day On the 12th, the urine became dark red, it was Hematest positive but contained very few red cells The prothrombin time was 59% and the total bilirubin 1 7 mg /100 ml Methemoglobinemia, methemoglobinuria, methemalbuminemia and methemalbuminuria were present An aortic diastolic regurgitant murmur developed, and the blood pressure changed from 110/70 to 90/45 mm Hg Despite a large urine output, the blood urea nitrogen and creatinine rose gradually Packed red cell transfusions were given, as was 10 mg prednisone every 6 hours Plasma hemoglobin continued to rise The hemolysis was believed due to red cell destruction secondary to partial detachment of the prosthetic valve Angiocardiograms showed regurgitation in the area of the noncoronary sinus, and another operation was performed on the 31st day Regurgitation was noted along the non coronary cusp margin The valve was reattached, with reduction in the systolic gradient from 90 to 40 mm Hg The urine cleared 4 hours after operation, and the plasma hemoglobin was 50 mg /100 ml. The urine again became colored 8 hours after operation, and plasma hemoglobin increased rapidly Renal function deteriorated, and renal shutdown occurred on the 36th day Pulmonary edema developed, and the patient died on the 37th day

Autopsy showed lower nephron nephrosis, with deposits of hemoglobin pigment in all tissues. A reactive bone marrow was present. The prosthesis appeared to be in an excellent position when viewed from the left ventricle, but when viewed from above the aorta encroached on the superior aspect of the cage of the prosthesis With the ball in the open position, the aorta was severely obstructed

Traumatic destruction of red cells appears to be the best explanation for hemolysis in this case. It seems likely that the trauma occurred during systolic ejection, due to partial obstruction and severe blood turbulence. Aortic enlargement or use of a smaller prosthesis might offer a solution to similar problems in the future. Transverse rather than vertical incision of the aorta will also prevent narrowing after closure.

► [One wishes that all cardiac surgeons would report their failures as fully as their successes. The authors of this communication are to be congratulated on having done so.

The frequency of this grave complication of valvular replacement is unknown but it is apparently not excessively rare. Efforts should be directed at devising some method for preoperative detection of those patients who are likely to exhibit the complication. Perhaps the response of the patient's blood

to trauma in some type of apparatus that simulates the action of the artificial valve might be studied – Ed.]

HYPERTENSION: SYSTEMIC AND PULMONARY

Prognosis of Treated Malignant Hypertension. A. Hany, F. Schaub and F. Nager[5] (Univ. of Zurich) define malignant hypertension as a form with poor prognosis, with high diastolic pressure, renal damage (sometimes latent) and severe changes (grades III and IV) in the ocular fundus. The last two findings reflect the rapidly progressive damage to the arterial vascular system. Without treatment, maligant hypertension results in death within a few months to a few years.

From January, 1956, to May, 1964, the authors observed 101 patients with malignant hypertension, of whom 4 could not be followed. Of the remaining 97 patients (54 men), 24 received no therapy. Twenty of 73 patients observed regularly were inadequately treated (because of interruptions, insufficient dosage by the physician or lack of understanding by the patient). In 53 patients, treatment was classified as good, i.e., it was prolonged and sufficiently intensive.

All patients had stage III or IV eye-ground changes and diastolic pressure of at least 120 mm. Hg on admission. The blood rest nitrogen was used as a criterion of renal function, and patients were divided into three groups according to the values: (1) 35 mg./100 ml., or less; (2) 35-80 mg./100 ml.; and (3) over 80 mg./100 ml. The age range was 28-71 years.

The 24 untreated patients (13 women) had an average age of 55 years; all died within 3 years. The average age of the 73 treated patients was 51 years (53 for men and 50 for women); survival times showed no significant difference between the two sexes.

Patients with grade III fundus changes have a better prognosis than those with grade IV changes, especially in the 1st year. The proportion of patients with decreased renal function is higher in those with grade IV changes than in those with grade III changes. With increasing deterioration of kid-

(5) Deutsche med Wchnschr 90:18-26, Jan 1, 1965

ney function, survival rate decreases rapidly; patients with rest nitrogen values over 80 mg./100 ml. died within 1 year.

The 20 patients with insufficient treatment had a definitely decreased survival rate compared with adequately treated patients. The proportion of patients with severe disturbances of renal function was similar in both groups.

In 29 of the 97 treated and untreated patients, elevated blood pressure was first discovered at the time of diagnosis of malignant hypertension. 68 patients had known hyperten sion (55 treated and 13 untreated). No difference in survival rate could be established between patients with a longer (over 1 year), shorter (a few months) or no history of previous hypertension. There was no significant difference in survival rate between patients with malignant hypertension who had been treated and those untreated during the benign stage. Causes of death in those patients treated and those untreated during the malignant stage were about the same. A pancreas infarct was proved at autopsy to be the cause of death in 2 men and was most probable in 1 woman.

Survival rate of treated patients at 1 year was 83%, at 3 years, 56%, at 5 years, 44%; and at 8 years, 25%. Among properly treated patients, the survival rate at 3 years was 61%; at 5 years, 52%, and at 8 years, 35%. In inadequately treated patients, the corresponding survival rates were 42%, 24% and 0%. Thus results of treatment with respect to pro longation of life appear to be directly related to the quality of antihypertensive therapy.

Certain complications greatly influence results of treat ment and prognosis. Of first importance is renal function, both for treated and untreated patients. A lesser but definite prognostic guide is severity of changes in the ocular fundus. Except for extreme increase in diastolic pressure over 150 mm. Hg, height of the blood pressure when the diagnosis is first made is prognostically less important.

[The management of hypertension includes at least three approaches. First, there is the search for and management of the underlying cause when it can be determined. Secondly, there is the treatment of the elevation of blood pressure per se, and finally, the management of the complications which are usually of cardiac, cerebral or renal origin. This report supplies strong evi dence that the second of these aspects of treatment is of genuine impor tance.—Ed.]

Angiotensin-Infusion Tests New Approach to Differential Diagnosis of Renovascular Hypertension. Norman M.

Kaplan and Jack G Silah' (Southwestern Med School) attempted to demonstrate increased levels of circulating angiotensin in patients with renovascular hypertension indirectly by measuring the pressor response to infusion of exogenous angiotensin Patients without recent cerebrovascular accident or coronary artery disease, preferably taking no medication, received an infusion containing 0 3 μg angiotensin II per ml at a rate of 8-10 drops per minute until there was a sustained rise in diastolic blood pressure of 20 mm Hg, the rate being increased every 10 minutes as needed The pressor dose then was calculated in terms of mμg./kg per minute

Patients with functionally significant renovascular hypertension were more resistant to the pressor effect of synthetic angiotensin II than those with other types of nonmalignant hypertension. The former required more than 6 5 mμg /kg. per minute, whereas most patients with other types of nonmalignant hypertension required less than 5 mμg /kg per minute for a pressor response Infusion of 4 mμg /kg per minute over 5 minutes was used as a screening test, a positive result being a rise in diastolic pressure of 20 mm Hg or more during the infusion

The test is invalidated by the presence of malignant hypertension, salt-retaining states and depletion of plasma volume. If done under proper conditions, this simple and safe procedure appears to identify patients with functionally important renovascular hypertension

Similarities between Clinical Toxemia of Pregnancy and Experimental Hypertension: Survey. Louis Tobian' (Univ of Minnesota) points out that hypertension usually appears in toxemia in the latter 4 months of pregnancy and becomes increasingly frequent as the end of pregnancy approaches This pattern is commonly seen in the hypertension produced in the rat with salt or deoxycorticosterone Toxemia and certain forms of experimental hypertension tend to be aggravated by a high sodium intake and prevented by a low intake The later stages of pregnancy are normally associated with a tendency to accumulate more extracellular fluid, as is deoxycorticosterone hypertension in rats. Both types appear more often in the presence of renal disease. Women with diabetes have a higher than normal incidence of pre-eclampsia; this

(6) New England J. Med. 271:536-541, Sept. 10, 1964.
(7) Circulation 30 (supp. 2):50-59, August, 1964

also has its counterpart in experimental hypertension. When pregnancy with pre-eclamptic tendencies occurs in a woman with essential hypertension, there is little antihypertensive action to oppose the specific hypertension of pregnancy, and blood pressure rises. The same phenomenon is probably brought about with deoxycorticosterone Pre-eclampsia is somewhat "dose dependent," just as steroid hypertension is. The larger the dose of steroids given a rat, the more likely is the development of hypertension Similarly, pre-eclampsia is associated with pregnancy, but when the "dose" of pregnancy is higher (as with twins or triplets), both the incidence and the severity of a complicating pre-eclampsia are increased The lesions in vessels of rats given renin, deoxycorticosterone and salt by Masson *et al* were similar to those seen in eclampsia As in some types of experimental hypertension, some patients display persistent essential hypertension after toxemia of pregnancy.

The author hypothesizes that toxemia results from an abnormally high level of a hypothetical steroid hormone in the extracellular fluid. It is probably of placental origin The high plasma level of the hypothetical steroid may result not only from hypersecretion but also from a deficient rate of removal. For hypertensive toxemia to occur, the high level of hypothetic steroid must be present in a woman with marginal antihypertensive action The steroid could cause sodium retention by its action on the kidney tubules and the glomerular endothelium. It would also result in increased amounts of sodium in skeletal muscle cells and in arterial smooth muscle cells, but it would not produce potassium wasting, as deoxycorticosterone does. If the antihypertensive action remained adequate, the syndrome of "edema of pregnancy" without hypertension would occur.

➢ [This paper represents a first-class thought even though definite proof for the hypothesis advanced is lacking. However, one has to pose a question before one can answer it, and the similarities drawn by the author between the experimental and the clinical states are impressive.—Ed.]

Chronic Medical Therapy for Pheochromocytoma: Report of Four Cases in which oral phenoxybenzamine was used is presented by Karl Engelman and Albert Sjoerdsma[a] (Nat'l Inst of Health).

Girl, 12, was a member of a family known to include many persons with neurofibromatosis, pheochromocytoma and Hippel-Lindau disease. Headaches, nervousness, excessive perspiration and weight

loss occurred at age 6, and pheochromocytoma was diagnosed A large, infiltrating tumor was incompletely removed from the region of the aortic bifurcation, and a week later, a left nephrectomy was done because of left ureteral obstruction Irradiation was given The blood pressure began to rise about 2 years before the present admission Two months before, it was 170/120 mm Hg and urinary catecholamine excretion was markedly increased Hepatic metastases were found at laparotomy, and a large mass of recurrent tumor was removed from around the aortic bifurcation On admission, the blood pressure was 140/90 mm Hg Bilateral pulmonary nodules were noted on chest x-rays In the next 9 months, the blood pressure rose and symptoms returned On readmission, the blood pressure was 195/110 mm Hg with the patient supine and 130/90 mm Hg on standing. Spasm of the retinal vessels was noted. The aortic 2d sound was markedly accentuated The liver was felt to descend 1 2 cm below the right costal margin The sedimentation rate was 29 mm per hour and the fasting blood sugar 114 mg. 100 ml Urinary catecholamines and metabolites were elevated, and responses to histamine and tyramine were characteristic of pheochromocytoma Left ventricular hypertrophy was found.

Increasing doses of oral phenoxybenzamine were given to a final dose of 40 mg twice daily, on which the supine blood pressure averaged 140/90 mm Hg The marked orthostatic fall in pressure disappeared, and no further hypertensive crises occurred The patient could engage in normal unrestricted activity and still maintain a normal blood pressure About a year later, the liver was about 1 cm larger than previously, but all tests of liver and kidney functions were normal A chest x-ray showed no change in pulmonary infiltrates or heart size. A trial of therapy with NSD-1034 (N-methyl-N-[3 hydroxybenzyl]-hydrazinium [1+] dihydrogen phosphate) failed to alter the urinary excretion of vanilmandelic acid or the clinical condition, other than causing sedation

All 4 patients were successfully treated on a chronic basis with oral phenoxybenzamine. One patient with catecholamine cardiomyopathy and xanthinuria was treated for over 6 months in preparation for subsequent curative surgery, and the other 3 patients were treated for over 1 year. The effects were manifest in control of the physiologic and metabolic alterations caused by increased catecholamine production.

Alpha-Methyldopa and Hydrochlorothiazide: Controlled Study of Their Comparative Effectiveness as Antihypertensive Agents. Jack M. Colwill, Arthur M. Dutton, James Morrissey and Paul N. Yu[19] (Univ. of Rochester) carried out a double-blind study of these drugs in two series; in the first, the patients participated in four treatment regimens (placebo, alpha-methyldopa, hydrochlorothiazide and the com-

(19) New England J Med 271 696-703, Oct 1 1964

bination), and in the second, the placebo regimen was omitted at the discretion of the referring physician. The hydrochlorothiazide dose was 50 mg. twice daily. The methyldopa dose was gradually increased to 1 Gm. daily in the 1st week, with subsequent weekly increments of 500-750 mg. until the dose was limited by side effects, adequate blood pressure response or attainment of a maximum of 3 Gm. daily. In addition, 2 Gm. potassium chloride was given daily throughout each treatment regimen. The 13 women and 6 men, aged 36-65 (average 50½), had sustained diastolic hypertension of 110 mm. Hg or more. The control supine pressure was 180/115 mm. Hg. Two patients had primary renal disease and the others had essential hypertension. Cardiac or cerebral manifestations of hypertension were present in 11.

On placebo therapy, 9 patients had a decline and 6 a rise in blood pressure, the mean reduction being about 4/2 mm. Hg. With hydrochlorothiazide, the average reduction was about 31/15 mm. Hg, the pressure falling significantly in almost three fourths of the patients. On alpha-methyldopa, there was an average fall of 22/11 mm. Hg, with an added postural effect, the total drop on standing being about 34/19 mm Hg. About 60% of the patients had a significant reduction in the supine position. The average reduction in the supine position with the combination was about 42/21 mm. Hg, with a further drop on standing to 54/29 mm Hg. A significant reduction occurred in 19 patients in the supine position. The augmentation of hypotensive effects with combined therapy over that of either drug was significant in about half the patients. A third of the patients individually seemed to respond significantly better to one drug than to the other, but there was no marked difference for the group as a whole.

Six patients could not continue in the study because of side effects; each was taking methyldopa or the combination of both active drugs. Drug fever associated with abnormal liver function occurred in 4 of these. Drowsiness and dry mouth were the most distressing of the less severe effects, which occurred in most patients. These were closely correlated with methyldopa therapy. Abdominal distress also seemed more severe in those taking methyldopa. Eosinophilia occurred eight times with methyldopa-containing regimens but only twice with placebo or hydrochlorothiazide. The degree of rise

All patients had dilatation and hypertrophy of the right atrium and ventricle, and 9 had a dilated pulmonary artery The foramen ovale was open in 2, and 1 patient had a mural thrombus of the right atrium One patient had Laennec's cirrhosis and 1 had a fatty liver. Pulmonary vascular changes were sufficiently widespread to account for the pulmonary hypertension in 8 patients The other had necrotizing arteritis and mild thickening of the intima in a few branches of the pulmonary artery In 6, there were widespread organizing or recanalizing pulmonary emboli or thrombi. One had subintimal thickening of the muscular arteries, and in another the left pulmonary artery and three of the six major branches of the right were occluded by old adherent clots. Another had multiple intravascular clots. The stages from fresh clot to completely recanalized arteries that were indistinguishable from arteriosclerosis and intimal thickening could be traced.

Since many, if not all, patients with a diagnosis of "primary" pulmonary hypertension may represent cases of recurrent pulmonary emboli, all should be treated as such. Anticoagulants and venous ligation are the treatments of choice. Rigorous therapy to prevent recurrent embolization may arrest progress in many cases otherwise considered to be "primary" pulmonary hypertension. Anticoagulants help prevent the formation of thrombus in pulmonary vessels already damaged by arteriosclerosis.

CORONARY DISEASE

Items of Prognostic Value in Clinical Study: Relationship of Symptoms, Heart Size, Blood Pressure, Electrocardiogram and Ballistocardiogram to After-Histories and to Each Other was evaluated by Isaac Starr, Samuel I. Askovitz and E. M. Mandelbaum[3] (Univ. of Pennsylvania). A previous study indicated that abnormalities of form of force ballistocardiograms were strongly associated with decreased life expectancy. The prognostic value of such records was compared with that of other findings used to assess the severity

(3) J A M A 192 83 87, Apr 12 1965

of heart disease in 221 subjects observed for over 5 years or until death. All were being treated, and 93 died during the study. The high-frequency force ballistocardiogram was recorded within 24 hours of admission.

Clinical findings significantly related to longevity included abnormality of the force ballistocardiogram form; reduced exercise tolerance; increased size of the cardiac silhouette; diagnosis of some form of heart disease; and ECG evidence of myocardial infarction or ischemia. Nonsignificant findings included force ballistocardiographic amplitude; systolic, diastolic and pulse pressure; heart rate; age; weight; pulse pressure to age; atrial fibrillation; and ECG conduction defects. The subject's age was no factor in the relationship between longevity and abnormalities of form of the force ballistocardiogram. The ballistocardiogram was abnormal in 49 subjects despite the absence of a diagnosis of cardiac abnormality Confirmatory evidence of heart disease developed later in all 5 patients with extremely abnormal records and about half of the 44 with moderately or slightly abnormal records. Findings indicate that the detection of physical abnormalities of the heart's performance supplements the classic anatomic and etiologic diagnosis

► [There can be little doubt that the BCG will eventually prove to be of great value in the early detection of decline in myocardial force as age increases Whether this decline is dependent solely on "subclinical" coronary disease as many believe or whether it is a manifestation of "gray hairs in the myocardium" that proceed independently of myocardial ischemia is a matter for future decision — Ed]

Relationship of Nutrient Intake and Exercise to Serum Cholesterol Levels in White Males in Evans County, Georgia. Sarah C Stulb, John R McDonough, B G Greenberg and Curtis G. Hames[1] studied the entire population segment aged 40-74 and a 50% random sample of the segment aged 15-39. Subjects with serum cholesterol levels below 160 mg. and above 260 mg /100 ml were matched by age, and 26 pairs were randomly chosen Each pair consisted of 1 subject with a low and 1 with a high level. Subjects with cardiovascular abnormalities were excluded. The mean values in the two groups were 141.9 mg and 281.3 mg /100 ml

Subjects were studied in the fall and during the following spring Both groups showed changes in the spring, the mean cholesterol level increasing in subjects with low and decreasing in those with high serum cholesterol levels. The

(1) Am J Clin Nutrition 15 236-242 February, 1965

amount of change for most subjects was small compared with the difference between the two groups. Correlations of cholesterol levels with exercise and with 14 independent dietary components were carried out. None of the dietary variables correlated significantly, but 9 were close to being significantly correlated. Correlations with exercise were significant. When the 9 dietary variables and exercise were analyzed in terms of absolute cholesterol levels and per cent change in cholesterol, only exercise had a significant inverse relationship with cholesterol. Removing the effect of exercise had no effect on the relationship of nutrients to cholesterol values. A significant decrease was found from fall to spring in intake of calories, vegetable protein, vegetable fat, carbohydrate and saturated fatty acids. The per cent calories from protein increased significantly; this may be explained by the greater relative decrease in intake of calories as compared with protein.

Any possible relationship between the seasonal dietary pattern and the seasonal pattern of cholesterol appears to be a relationship between cholesterol and caloric intake rather than cholesterol and fat intake as such. However, the nature of the sample was such that the seasonal effect on cholesterol was probably obscured by the overriding influence of regression toward the mean.

Interrelated Effects of Dietary Cholesterol and Fat on Human Serum Lipid Levels. William E. Connor, Daniel B. Stone and Robert E. Hodges[5] (Univ. of Iowa) studied 6 men of average weight, aged 24-48, including 3 healthy men and 3 with unstable, juvenile-type diabetes requiring insulin. The basic diet of mixed, natural foods contained 2,500 calories with 100 Gm. protein, 280 Gm. carbohydrate and 110 Gm. fat; the fat comprised 40% of the total calories and was derived from various mixtures of fats containing only long-chain fatty acids. Caloric intake was determined by body build and estimated energy expenditure so that the body weight would remain constant.

The percentage of total calories from the three main elements was kept similar in all diets. One diet contained 729 mg. cholesterol with 39.9% saturated, 50.6% monounsaturated and 9.5% polyunsaturated fatty acids and an iodine number of about 63, similar to that of the usual American

(5) J Clin Invest 43 1691 1696, August, 1964

diet eaten by the men before the study. In a second diet, cholesterol-containing foods were replaced in the diet by cholesterol-free foods, the fatty acid composition being kept virtually unchanged by the use of vegetable fats. In a third diet, also cholesterol-free, saturated fatty acid was reduced to 18.6% and polyunsaturated fatty acid was increased to 31.4%; the iodine number was raised to 100. A fourth diet contained 725 mg. cholesterol, the fatty acid composition and iodine number remaining the same as in the previous period.

Removal of cholesterol from the diet produced a decrease of 38 mg./100 ml. in the mean serum cholesterol level despite a diet high in saturated fat. Addition of 725 mg. dietary cholesterol increased the mean serum level even when the diet contained a high amount of polyunsaturated fat. Serum lipid levels remained unchanged during the two periods of cholesterol-free intake. The results emphasize the important influence of dietary cholesterol on the serum lipids. The serum lipids of both healthy men and diabetic patients responded similarly to the dietary changes.

Reduction of Serum Triglycerides and Cholesterol by Ethyl p-Chlorophenoxy-Isobutyrate (CPIB). Maurice M. Best and Charles H. Duncan[6] (Univ. of Louisville) studied the relative effectiveness of CPIB with and without androsterone in 10 patients with raised serum cholesterol and triglyceride levels. Patients were followed for 1 year. Each received CPIB alone for 4 months and with androsterone for a second period. Corn-oil placebo was given during a third period. The total daily dose was 1.5 Gm. in 9 subjects and 2.25 Gm. in 1. The daily dose of androsterone was 33 or 49.5 mg.

The mean serum cholesterol and triglyceride levels of most patients were reduced by CPIB with or without androsterone. The mean reduction was 11 and 31%, respectively, without androsterone, and 16 and 34%, respectively, with androsterone. Drug effects were noted within 2 or 3 weeks. No consistent rebound tendency was noted when placebo was given. No effect on plasma free fatty acids was observed, but a moderate decrease may have been obscured by the presence of CPIB in the plasma. There were no consistent weight changes and no increase in serum transaminase levels. The only untoward clinical finding that may have been related to

[6] Am. J. Cardiol. 15: 230-234, February, 1965.

drug administration was the occurrence of two episodes of gouty arthritis in a patient with a serum uric acid elevation before treatment. No patients showed evidence of enhancement of angina pectoris or congestive heart failure. All patients remained in generally the same clinical state throughout the study and experienced no more symptoms when receiving drugs than when receiving placebo.

Results support the conclusion that CPIB is an effective hypolipemic agent and that the addition of androsterone does not increase its effectiveness.

Coronary Artery Anomalies. Hu A Blake, William C Manion, Thomas W. Mattingly and Giorgio Baroldi[7] (Armed Forces Inst. of Pathology) note that major secondary coronary anomalies are found among seriously malformed hearts and are compensatory to the coexisting cardiac pathologic condition. Isolated surgical correction is contraindicated. Major primary anomalies are independent of other cardiac disease. Common to all are features of an abnormal communication between the coronary system and a cardiac chamber or vessel with a constant or intermittently lower pressure: all are thus arteriovenous or arteriovenous-like shunts. These may cause myocardial failure or myocardial ischemia, or be the site of bacterial endocarditis.

If the artery empties into the right atrium or ventricle, coronary sinus or pulmonary artery, features of a true left-to-right shunt are seen. If it communicates with the left atrium or ventricle, a disturbance resembling aortic insufficiency results. The two major coronary arteries may originate from the aorta with a third, smaller accessory one arising from the pulmonary artery; this will often form a sizable connection with an aortic coronary. When both coronary arteries originate from the pulmonary artery, death will likely occur before serious study can be undertaken, but if the pulmonary artery is subjected to systemic pressures, survival may be enhanced. When but one coronary artery originates from the pulmonary trunk and this is the right, the patient may do well with little disability. In contrast, the derangements from an anomalous left coronary artery are severe and the results of surgery far from satisfactory.

When the anomalous artery arises from the aorta, there is

(7) Circulation 30 927 940 December, 1964

no physiologic disturbance, but technical problems in open heart surgery arise. A third artery is present in 23-50% of all hearts and supplies the conal area of the right ventricle. A single coronary artery may or may not be a benign anomaly. The greatest number of coronary arteries reported has been six. An extreme example of a high take-off occurs when the coronary artery seemingly arises from the arch itself. In a series of cases of truncus arteriosus, high take-off occurred in 19% of the left and 9% of the right coronary arteries. It is also frequent in the transpositions. The anomalously placed coronary artery may be a harassment when ventriculotomy is necessary. Most troublesome is a right coronary artery giving rise to an anterior descending branch. Other anomalies include hypoplasia of one coronary artery and a hidden or mural coronary artery.

Prospective Study of Relationship between Personality and Coronary Heart Disease. A. M. Ostfeld, B. Z. Lebovits and R. B. Shekelle (Univ. of Illinois) and O. Paul[a] (Northwestern Univ.) used the Minnesota Multiphasic Personality Inventory (MMPI) and the Sixteen Personality Factor Questionnaire (16PF) to obtain measures of personality from 1,990 men, aged 40-55, who were free from clinical coronary disease at the beginning of the study 4½ years ago. Symptoms of angina pectoris developed in 48 men and 37 others had myocardial infarctions, whereas 1,771 men who remained free from clinical coronary heart disease provided MMPI data; for the 16PF data, the corresponding numbers of patients in the angina, infarct and noncoronary groups were 31, 18 and 1,773.

The findings suggest that the men in the angina group, compared to those with myocardial infarction, were characterized before the clinical appearance of coronary heart disease by a tendency to complain about various somatic symptoms and to be worried about their health even in the absence of objective findings. They also showed greater lability in cardiovascular functioning and greater emotional lability and suggestibility. With respect to the differences between the total coronary and noncoronary groups, it is inferred that the men who later had coronary heart disease, as compared to those who did not, tended to be more inde-

[a] J. Chron. Dis. 17:265-276, March, 1964.

pendent in their social relationships, more suspicious about the motives of other people and to have greater feelings of inner tension.

The results should not be taken as descriptions of "coronary-prone" or "angina-prone" personalities because the data do not by themselves demonstrate the existence of an etiologic relationship between personality and coronary heart disease. The evidence supports the general hypothesis that patterns of behavior are significant in the epidemiology of coronary heart disease in man. It seems likely that persons having attributes of personality like the men in the angina group would be particularly prone, under certain circumstances, to respond favorably to placebo therapy.

► [Although the personality traits that are pinpointed in this paper are not in agreement with those that have been suggested by others, the data of these investigators do substantiate the idea that there is a relationship between such disease and personality traits.—Ed.]

Collaterals and Coronary Artery Narrowing: I. Effect of Coronary Artery Narrowing on Collateral Channels in Swine. George Lumb and Lawrence B. Hardy[9] (James Walker Mem'l Hosp., Wilmington, N.C.) compared the effects of gradual narrowing of the major branches of the left coronary artery with those of right-sided occlusion. Swine were used because their coronary artery distribution and development of natural arterial disease are similar to the human. Hygroscopic constrictors were used to produce gradual occlusion of the left coronary artery; they were applied 5 mm. from the vessel ostium. Postmortem, arteriograms were made with injection of Micropaque.

Collateral channels between the left and right coronary arterial circulations are present but do not appear to be functional in the normal state. Gradual narrowing to occlusion of major vessels stimulated functional collateral circulation. Some animals received 10 mg. pentaerythritol tetranitrate 3 times daily for 2 days before and 7 days after occlusive procedures. There was evidence of increased survival in these animals. Considerably greater functional adequacy results when the left coronary artery acts as the donor vessel than when the right is used as the donor. This may be due in part to differences in intramural ventricular pressure, which favors left-to-right flow. The collateral channels appear to open selectively only into the vessels which are obstructed.

(9) Lab. Invest. 13:1530-1540, December, 1964

Relationship of Cigarette Smoking to Coronary Heart Disease: Second Report of Combined Experience of Albany, N.Y., and Framingham, Mass., Studies is presented by Joseph T. Doyle, Thomas R. Dawber, William B. Kannel, Sandra H. Kinch and Harold A. Kahn.[1] Subjects, who were originally free from heart disease, included 2,282 men aged 30-62 who were followed for 10 years in Framingham, and 1,838 men aged 39-55 who were followed for 8 years in Albany. Both populations were homogeneous in terms of sex, age, race, occupation and diet. Fewer than 1% of each group has been lost to follow-up.

Men reporting habitual consumption of 20 or more cigarettes daily had a death rate from all causes about 3 times greater than that of nonsmokers, former cigarette smokers or pipe and cigar smokers. Heavy cigarette smokers had a similar increase in risk of myocardial infarction compared with non-cigarette smokers. These increased risks were associated with cigarette smoking in all group divisions based on high and low systolic blood pressure and cholesterol levels. The risk of angina pectoris as the sole or initial manifestation of coronary heart disease appeared unrelated to the tobacco habit.

The explanation of the association between heavy cigarette smoking and the increased risk of death from all causes and of death or disability from coronary heart disease in particular remains speculative, but the effect appears relatively immediate No cumulative effect on the development of the underlying atherosclerosis appears evident The inference that stopping cigarette smoking has a beneficial effect in preventing or delaying the onset of the lethal manifestations of coronary heart disease appears warranted.

Coronary Angiography: Technical, Anatomic and Clinical Study. Sven Paulin[2] (Univ of Goteborg) states that, at present, coronary angiography is the only method by which changes in the lumens of vessels or obstructive processes in the coronary arteries can be directly demonstrated in living subjects. Use of the loop catheter eliminates the necessity of interfering with the patient's hemodynamic state during study and of direct selective catheterization of the coronary arteries. The drawbacks can be overcome by designing

(1) JAMA 190:586-590, Dec. 7, 1964.
(2) Acta radiol., supp. 233, 1964.

standardized double-loop catheters. The aim of the x-ray technic is optimal demonstration of anatomic details by means of small focal size of the tube, short exposure time, a secondary diaphragm with fine lead strips and relatively low voltage of the x-ray current. Overlapping of vessels by other structures is avoided by 2 routine injections of contrast medium, during each of which films are exposed with two alternating tubes in stereoscopic position. By these means, films of good quality can be obtained easily and safely.

Study was made of 228 patients, most of whom had coronary artery disease. Injection of contrast material was accompanied by slight to moderate sensation of heat in all patients. Extrasystoles occurred in only 6, and ECG changes were confined to slight ST-T deviations. Brief asystole occurred after injection of a small test dose in 2 patients, and 2 patients reported symptoms of intermittent claudication type. A high incidence of a separate ostium of branches to the pulmonary conus was found. Variations in the arterial supply to the region of the crux and the posterior interventricular sulcus were also common. Early termination of the left anterior descending coronary artery was noted in only a few cases; it was most common in patients with obstruction of the proximal part of the vessel. Among other variations in branches of the left coronary artery was a fairly powerful branch to the left lateral left ventricle, observed in slightly over one third of the patients. Both the sinus node and atrioventricular node artery were seen in a high percentage of patients. In most patients, the lumen of the left main coronary artery was larger than that of the right.

A positive correlation was found between clinical signs of coronary heart disease and obliterative changes in the coronary arteries on angiography. Chest pain of angina pectoris type was rare in patients without stenosis or occlusion. Documented myocardial infarction was found only in patients with at least marked luminal narrowing of a main coronary artery branch.

Repeat study was carried out on 13 patients given various drugs or hemodynamically active agents, and a slight increase in vessel caliber was found in all but 2. Changes in heart rate and/or blood pressure occurred in all 13. The author concluded that improvement in the angiographic depic-

tion of coronary vessels by the slight increase in caliber produced by vasodilator agents is doubtful.

Coronary Vasodilator Therapy for Angina Pectoris is evaluated by George G. Rowe[3] (Univ. of Wisconsin). Few would seriously question that angina pectoris results from a discrepancy between the amount of attainable blood flow in a region of the myocardium and the amount required to sustain a given degree of activity. Study of patients with angina by the nitrous oxide method has shown that resting coronary blood flow per unit weight of myocardium is normal. It is possible that the area of ischemic pain is small in relation to the general myocardial mass and that its reduced flow is lost in the error of the nitrous oxide method. Also, it is probable that severely ischemic areas are replaced by scar tissue. Recent studies have shown that coronary blood flow in patients with angina increases as much or more during exercise as in normal persons, but the coronary sinus oxygen content does not increase with exercise as it does in normal persons. Probably the oxygen content of the coronary venous blood draining from underperfused segments is significantly lowered, and anaerobic metabolism occurs.

Nitroglycerin does not increase the coronary sinus blood oxygen content in persons without coronary artery disease or increased left ventricular work, and myocardial oxygen consumption increases. Coronary blood flow in patients with angina pectoris is not increased by nitroglycerin or erythrol tetranitrate. Vasodilatation during the hypotensive phase of drug action must not be equated with increased blood flow. Some hypotensive agents reduce the frequency of angina attacks in hypertensive patients if the fall in pressure is not excessive. Hydralazine increases coronary flow and coronary sinus blood oxygen content, although it occasionally precipitates attacks of anginal pain in patients with angina pectoris. Clinical use of dipyridamole (Persantin) has had disappointing results in treating angina pectoris. Pathologic studies have shown that a person with angina had had occlusion of at least one coronary artery, and often has a patchy distribution of normal and narrowed sclerotic or occluded coronary arteries. If this narrowing becomes a major factor in determining myocardial blood flow, it is difficult to

[3] Am. Heart J. 68:691-696, November 1964

conceive of any agent that could produce dilatation of the rigid or occluded areas which presumably supply blood to the pain-producing areas in the heart. It, therefore, seems doubtful that effective agents relieve anginal pain by coronary vasodilatation

Agina pectoris is relieved not by increased coronary blood flow but by the reduction of left ventricular work into a range that can be supported by attainable myocardial circulation. Pooling of blood in the dependent part of the body, with reduction of cardiac output and cardiac work, can be achieved by administering the short-acting vasodilator, nitroglycerin. Biologically available coronary vasodilators (adenine nucleotides, dopamine, catecholamines, etc.) increase coronary blood flow considerably more than any of the agents available clinically. It would seem unreasonable to use "long-acting" agents which are potentially detrimental through dilatation of normal vessels for prolonged periods, thereby reducing the pressure head available to diseased vessels, or through reduction of cardiac work over an extended period, thereby reducing the normal stimulus to the growth of new vessels.

► [This abstract and the 2 succeeding ones illustrate some of the difference of opinion concerning the value of coronary vasodilator drugs and their mechanism of action I am convinced that the widespread skepticism concerning the value of these drugs is based on doses that are frequently inadequate in terms of size or frequency Different individuals require widely different doses and the optimal total daily dosage needed must be worked out for each individual patient In most instances, this dose will be that which either produces minimal side effects in terms of headache or hypotension (either postural or recumbent), or will be only slightly less than the dose that causes such effects A careful attempt to individualize the therapy using a diary kept by the patient will lead to highly gratifying effects in almost all patients, and especially in those who are having frequent episodes of angina at rest – Ed]

Effect of Coronary Vasodilator Drugs on Retrograde Flow in Areas of Chronic Myocardial Ischemia. Wadie M. Fam and Maurice McGregor[4] (McGill Univ.) used the retrograde flow technic to study the effects of nitroglycerin and dipyridamole on the coronary collateral flow in 12 dogs with chronic myocardial ischemia and in 5 normal dogs. Ischemia was produced by placing ameroid constrictors on the anterior descending and circumflex branches of the left coronary artery, which occludes the vessels over a period of about 3 weeks. Nitroglycerin, 0.6 or 0.9 mg., or dipyridamole, 5-10 mg., was given intravenously.

(4) Circulation Res 15 355 365, October, 1964

In the ischemic dogs with well-developed collateral circulation, both drugs reduced the systemic blood pressure. Dipyridamole significantly reduced both retrograde flow and peripheral coronary pressure. Nitroglycerin did not significantly reduce these parameters despite a greater fall in mean arterial pressure. When arterial pressure was held constant, nitroglycerin greatly increased retrograde flow in chronic "ischemic" dogs whereas dipyridamole did not. In normal dogs, these differences between the two drugs were not observed. Both reduced retrograde flow and peripheral coronary pressure which paralleled the reduction in systemic pressure Dipyridamole, unlike nitroglycerin, reduced the coronary arteriovenous oxygen difference in both ischemic and normal dogs.

Nitroglycerin may have an action seen only in the presence of well-developed collateral circulation, i.e., to increase flow through collateral channels without significantly altering total coronary artery flow. Dipyridamole does not seem to alter collateral flow but does increase total coronary flow. Thus, the site of action of these two drugs in the coronary vascular tree must be different

Stereoisomeric Nitrates in Treatment of Angina Pectoris. Joseph E. F. Riseman, Sidney Koretsky and George E. Altman[5] (Boston) evaluated and compared the effectiveness of the four stereoisomers of pentitol pentanitrate in the treatment of angina pectoris. The action of these agents was also compared with placebos, a dinitrate, a trinitrate, a tetranitrate and four nonnitrates that have been advocated for use in angina pectoris. Subjects were a typical group of patients with angina, presumably of coronary arteriosclerotic origin; they were observed at weekly intervals for months to years. The subjects mounted and descended a Master two-step staircase repeatedly. The drugs were given for at least 1 week at a time in no fixed order, and periods of placebo administration were interspersed.

The four stereoisomers of pentitol pentanitrate (d-arabitol, l-arabitol, xylitol and adonitol pentanitrate) were found highly effective in the prophylactic treatment of angina pectoris. They were especially effective when given sublingually, but even when enclosed in gelatin capsules and swallowed, their use was followed by an increase in exercise

[5] Am J Cardiol 15:220-229, February, 1965.

tolerance in many patients. Clinically, there was no clear superiority of any one of the preparations over the other three. The optimal dose was 15 mg Larger doses (30 and 45 mg) were no more effective and were occasionally followed by headache. Untoward effects were not striking

Isordil (d-isosorbide dinitrate) was also effective The rapidly soluble sublingual form was much more effective than the more slowly soluble oral preparation. An increase in exercise tolerance became evident within a few minutes of use of the sublingual form and persisted for as long as 1-4 hours in some patients. When taken after induction of pain, this form decreased the duration of discomfort of patients whose attacks were otherwise usually longer than 1 minute The use of sustained-action tablets was not followed by an increase in exercise tolerance, and many patients reported headache. Chlorothiazide and Recordil were of slight value in some patients. The use of Amplivix and Persantin was not followed by any appreciable increase in exercise tolerance

The activity of the nitrates in angina pectoris is not due to the number of $-ONO_2$ groups in the nitrate molecule The lag in onset and the prolonged duration of effect of the nitrates imply that their action is not immediately dependent on the concentration of pure drug in the blood stream

Myocardial Ischemia after Maximal Exercise in Healthy Men: Method for Detecting Potential Coronary Heart Disease? Allen E. Doan, Donald R. Peterson, John R. Blackmon and Robert A. Bruce[6] (Seattle) studied 433 males aged 10-82, including 170 aged 10-30 who were members of physical education classes, 38 aged 30-60 who were employees of the Boeing Company and 225 aged 35-82 who were members of the Seattle YMCA. The last group included 114 subjects who had exercised regularly at least twice a week for 1 year before examination and 111 who had exercised 5 times or less in the preceding year. The standard double Master's two-step test was performed by the 225 YMCA members, and clinical and electrocardiographic monitoring was carried out. The multistage exercise capacity test was performed by all subjects. This measures capacity for exercise on a treadmill by means of progressive increases in speed and grade through seven consecutive 3-minute stages, starting with a slow walk on a slight incline and ending with a fast run up a steep

(6) Am Heart J 69 11 21 January 1965

grade. The test is stopped only if clinical symptoms or ventricular tachycardia develop. A single bipolar precordial lead is used for ECG monitoring, and the ECG usually resembles one obtained with a V_5 precordial lead. The only criterion for a positive Master's test was 0.5 mm. or more of ischemic segmental S-T depression, and for the maximal exercise capacity test, 1 mm. or more of depression.

Without exercise testing, overt cardiovascular abnormalities were found in none of the 170 subjects in the physical education classes or the 38 industrial personnel and in 24 (10.6%) of the 225 YMCA members. The over-all prevalence of myocardial ischemia on the multistage exercise capacity test was 7.4%, the prevalence varying directly with age Of the 201 YMCA men with no cardiovascular abnormalities, only 2 showed a positive response of ischemia on the Master's test, compared with 18 on the multistage test. Of the 24 with clinically detectable abnormalities, 8 (33%) had positive Master's tests and positive responses to maximal exercise. In addition, the multistage test was positive in 5 men who had negative Master's tests, so that this test was 62% more sensitive than the Master's test One man with a healed silent diaphragmatic infarction had normal responses on both exercise tests.

Results show that graded maximal exercise testing is quite practical for men of all ages, body weights and degrees of physical conditioning If future examinations of the men with ECG abnormalities show a high incidence of clinical coronary heart disease, the reliability, specificity and predictive value of the multistage exercise capacity test will be established

Hypopotassemia Resembling Myocardial Ischemia. Michael M Laks and Stephen R Elek[7] (Cedars-Sinai Hosp., Los Angeles) observed a woman, aged 33, who was admitted because of dehydration, nausea, drowsiness and a history of possible hysterical paralysis An ECG showed the S-T segments to be horizontally and deeply depressed in leads V_1 through V_6 and leads I, II, III and aVF Coronary artery disease was diagnosed, but hypokalemia was considered because the S-T segments were shorter in duration than is usually seen in myocardial ischemia. The serum potassium level was 1.8 mEq./L. After intravenous administration of

40 mEq./L. potassium in about 1 hour, the S-T segments were considerably less depressed, the P waves were diminished in amplitude and the U waves, best seen in leads V_2 through V_4, became more prominent. The normal Q-T interval and prolonged Q-U interval were characteristic of hypokalemia, as was the juxtaposition of the U wave to the T wave.

The characteristic changes of hypokalemia are the depressed S-T segments of short duration and prominent U waves juxtaposed to the T waves Inasmuch as the ECG diagnosis of hypopotassemia is often missed and since this is a treatable condition, it is important that the cardiologist be aware of the subtle ECG changes in hypopotassemia.

Serum Creatine Phosphokinase (CPK) Activity in Disorders of Heart and Skeletal Muscle. To assess the usefulness of serum CPK activity as a laboratory aid in clinical medicine, Joseph W. Hess, Roderick P. MacDonald, Richard J Frederick, Robert N. Jones, Joann Neely and David Gross[8] (Detroit) made clinical and laboratory studies.

The serum CPK activity was determined by the enzymatic technic of Tanzer and Gilvarg in 97 healthy ambulatory subjects and 266 hospitalized patients with various diseases The normal subjects (48 males and 49 females) were aged 13-79 years. Six subjects had values greater than 8 units. The equivocal or "gray" area of results due to laboratory and human variations is about 8-17 units. A useful range for normal CPK values is 0-8 units, with 9-17 units considered possibly normal and values above 17 units definitely requiring an explanation.

High values of CPK activity were found in patients with the Duchenne type of muscular dystrophy, polymyositis and acute myocardial infarction. Small to moderate elevations were found in adult types of muscular dystrophy, female relatives of some patients with muscular dystrophy and some patients with coronary insufficiency. Values were normal in patients with acute and chronic liver disease, renal infarction, stabilized chronic renal disease, hemolytic anemia, pulmonary embolism, solid tumors and leukemia.

In human and canine tissue homogenates, highest CPK activity was found in skeletal muscle and heart, followed in order of decreasing activity by brain and smooth muscle-

(8) Ann Int. Med 61 1015 1028 December, 1964

containing organs. Liver, kidney, lung, prostate, pancreas and human red cells had negligible activity.

Intramuscular drug injections, muscle trauma and strenuous exercise may produce transient elevations of serum CPK activity and of other enzymes. If serum CPK is to be determined and drugs must be given parenterally, subcutaneous or intravenous routes should be used if possible. For laboratory confirmation of active myocardial or skeletal muscle disease, serum CPK is more sensitive and specific than serum lactic dehydrogenase or serum glutamic oxalacetic transaminase. It can be especially valuable in patients with hepatocellular damage, pulmonary embolism, hemolytic states or other conditions that may cause elevation of lactic dehydrogenase, glutamic oxalacetic transaminase and other ubiquitous enzymes.

Intelligently used, serum CPK can be a useful laboratory aid in clinical medicine. Isoenzymes of CPK may exist. If skeletal muscle and myocardial CPK can be distinguished in the serum, another important step forward in diagnostic enzymology will have been made.

Serum Creatine Phosphokinase in Diagnosis of Acute Myocardial Infarction. William R. Vincent and Elliot Rapaport[9] (San Francisco) determined serum creatine phosphokinase (CPK) activity 363 times in 146 patients and 32 times in 22 control subjects. A modification of the method of Tanzer and Gilvarg was used. Activity in control subjects ranged from 0.0 to 2.2 units per ml. serum and averaged 0.6 unit. Of 32 measurements made on samples obtained between 12 and 36 hours after onset of precordial pain in patients with unequivocal acute myocardial infarction, 22 were made on refrigerated serums. The peak value of the 22 samples averaged 11.7 units per ml., compared with 44.2 units per ml. in the 10 samples which were assayed immediately. Normal values were found in 12 patients who had pain suggestive of acute coronary insufficiency but no laboratory and ECG evidence of acute infarction. Three of 4 patients with acute pericarditis had normal values, as did 3 of 4 with rapid cardiac arrhythmia of recent origin and all 10 patients with acute or chronic heart failure. Enzyme elevations were encountered in the presence of skeletal muscle and brain dam-

(9) Am. J. Cardiol. 15:14-28, January, 1965.

age, but patients with diseases of the liver and lung consistently had normal serum CPK levels.

The authors concluded that the determination of serum CPK is of value in the diagnosis of acute myocardial infarction because of its increased specificity.

Significance of Ventricular Premature Beats in Diagnosis of Septal Infarction. Jacob Freundlich and Doris Kavanagh-Gray[1] (St. Paul's Hosp., Vancouver, B. C.) reviewed 220 ECGs containing premature ventricular beats and found 20 tracings in which the premature beats were of a pattern that suggested myocardial infarction. The complexes were made up of a significant Q wave followed by a definite R wave and sharply inverted or upright T wave, depending on the age of the lesion. Each of these 20 patients had a history of angina pectoris or myocardial infarction. Autopsy was done in 7, and myocardial infarction was confirmed in each. In 17, both the normally conducted and ectopic ventricular beats showed the typical myocardial infarction pattern In 3 patients, however, only the premature ventricular beats indicated the presence of infarction.

Woman, 55, was admitted about 2 hours after onset of severe precordial pain that radiated down the left arm. The ECG showed depression of RS-T segments in the standard leads and in leads V_4, V_5 and V_6, but there was no definite evidence of infarction In V_2 the premature ventricular beat consisted of a Q wave followed by a broad R wave and an inverted T wave suggesting septal infarction Tracings obtained 12 and 24 hours later did not show any change. The patient died the next day At autopsy, the right coronary artery was completely occluded by a recent thrombus and the left was narrowed by atherosclerotic plaques. Areas of necrosis intermixed with pinpoint hemorrhages were found throughout the entire interventricular septum.

In these 3 cases, in which the ventricular premature beats displayed Q waves, the autopsy findings showed an old or recent septal lesion. It seems probable that the ectopic beats arising in the vicinity of a myocardial lesion are thus better able to display an accurate pattern of a focal lesion.

Aberrant Ventricular Conduction in Diagnosis of Myocardial Infarction. Alvaro Martinez[2] (Detroit Mem'l Hosp.) analyzed 585 ECGs of 326 patients who had postmortem examinations. Myocardial infarction was proved in 108 patients, and in 64 of these (59%) the ECG showed normal

(1) Canad M A J 91 1145-1148 Nov 28, 1964
(2) Am J Cardiol 14 352 356 September 1964

ventricular conduction and was diagnostic of infarction. In 19 other patients, infarction was diagnosed on the ECG when the aberrant ventricular conduction patterns were studied.

Of 89 patients with aberrant ventricular conduction, 41 had anatomically proved myocardial infarction. Necrosis of the septum was suggested from analysis of aberrant conduction patterns in 33 cases, and anatomic study corroborated the ECG diagnosis. The infarction was localized in the anterior or posterior parts of the septal mass in 21 of these cases, while 12 patients showed extension of septal necrosis to the free ventricular wall. In 8 cases, there was definite anatomic evidence of necrosis that showed aberrant ventricular conduction, but no "infarction" pattern was found in the ECGs. Five of these patients had isolated necrotic changes of the free left ventricular wall with no septal involvement; 2 had infarctions of the anterior part of the septum; and 1 had necrosis of the posterobasal aspect of the septal mass which extended to the free left wall.

Abnormal patterns so often regarded vaguely as "only extrasystoles" or masking factors in ECG diagnosis of infarction may yield considerable information when analyzed by the proper criteria. In the precordial leads, qR or QR patterns reflecting the potentials of a specific ventricle were always diagnostic of septal infarction. Absence of "infarction" pattern in aberrant ventricular conduction does not exclude presence of necrosis, especially if only the free ventricular wall is necrosed. The diagnostic accuracy of ECGs was considerably improved when these patterns were studied.

Disturbances of Rate, Rhythm and Conduction in Acute Myocardial Infarction: Prospective Study of 100 Consecutive Unselected Patients with the Aid of Electrocardiographic Monitoring is presented by Desmond G. Julian, Peter A. Valentine and Geoffrey G. Miller[4] (Sydney, Australia, Hosp.). The 76 men and 24 women, aged 37-81 (average 59.6), were admitted with symptoms suggesting acute myocardial infarction within the previous 48 hours between November 1, 1962, and October 18, 1963. Signs of shock were present in 30 and evidence of heart failure in 61. There were 46 instances of anterior infarction, 44 of posterior infarction, 4 of combined anterior and posterior infarction and 6 in which the

location of damage was uncertain. Digitalis was given to patients with more severe failure and those with rapid ventricular rates. Anticoagulants were given to 35 patients. There were 31 deaths. Excluding terminal arrhythmias and those immediately following the treatment of ventricular fibrillation, some disturbance of rate, rhythm or conduction was found in 95 of the 100 patients, and in 56 one or more serious arrhythmias developed. Of these 56 patients, 20 (36%) died, compared with 25% of the other 44. The over-all incidence of arrhythmias was similar at the different sites of infarction.

Sinus tachycardia occurred in 43 patients, 19 of whom died. Sinus bradycardia occurred in 14 patients, 3 of whom died; the bradycardia never had adverse effects. Supraventricular ectopic beats were recorded in 25 patients, 6 of whom died. Atrial fibrillation was associated in 6 patients. Ventricular ectopic beats were recorded in 67 patients, 21 of whom died. The mortality was 41% among those in whom they occurred frequently; ventricular fibrillation developed in 6 of these 32 patients. Of 7 in whom ventricular ectopic beats interrupted the T wave of the preceding complex of sinus origin, 5 died suddenly. Digitalis was implicated in 9 cases. Paroxysmal atrial tachycardia occurred in 4 patients; digitalis was implicated in 3 of these. The attacks were too brief to be important in aggravating cardiac failure. Atrial flutter occurred in 2 patients who had considerable acute cardiac damage. Atrial fibrillation developed in 16 patients, 5 of whom died. The arrhythmia lasted only a few hours in all but 3 of the patients. Twelve of the 16 had cardiac failure, but in only 1 did the arrhythmia seem responsible.

Nodal rhythm of the nonparoxysmal type occurred in 8 patients; 2 died, and digitalis was incriminated in only 1. Posterior infarction was present in 5 patients. Ventricular tachycardia was found in 6, in 4 of whom it was preceded by frequent ventricular ectopic beats. Three patients died of ventricular fibrillation, and another died of shock with cardiac failure. Ventricular fibrillation developed in 10 patients, 9 of whom died. The risk of ventricular fibrillation in the younger males was high. This arrhythmia was prone to develop on the 1st day of illness. No obvious precipitating factors were found. Six patients had frequent ectopic beats, in 4 of the R-on-T variety. Ventricular fibrillation is most likely to

occur in patients who are otherwise progressing satisfactorily.

First-degree heart block was found in 13 patients, 6 of whom died; digitalis was probably responsible in 3. Second-degree block was found in 10 patients, 8 of whom had posterior infarction. The 2d-degree block preceded complete heart block in 3 patients and followed it in 2 others. Three of the 10 died. Complete heart block occurred in 8 patients, 7 of whom had posterior infarction. It lasted for only a short time in each case. Three of the 8 died; treatment almost certainly prevented death in 3 others. Bundle-branch block was found in 13 patients, 8 of whom died. This high mortality was associated with other unfavorable factors rather than any direct effects. One patient had episodes of sinus arrest interrupting 1st-degree block and died of ventricular asystole. Another died of ventricular asystole, and in 2 fatalities the mechanism of death was not determined.

The high frequency of arrhythmias in this series is attributed to ECG monitoring and the inclusion of only those patients who had symptoms of infarction within the 48 hours preceding admission.

Pentaerythritol Tetranitrate as Adjunct Therapy in Immediate Postinfarction Period. Alexander Oscharoff[4] (Queens Hosp Center, Jamaica, N. Y.) conducted a biphasic study in two groups of patients (total 124) hospitalized because of myocardial infarction The effect of 80 mg pentaerythritol tetranitrate (Pentrate) twice daily on blood pressure, pulse rate, morbidity and mortality was determined in the immediate postinfarction period. The latter two effects were determined in a randomized, double-blind, placebo-controlled study.

Measurements failed to show that an 80-mg. sustained-action dose caused sharp fluctuations in blood pressure or pulse rate Preinfarction disease related complications had little or no effect on mortality "Non-disease" related complications, when they occurred singly, did not seriously increase mortality either. Of the various combinations occurring, those involving shock were the most fatal. Significantly fewer patients in the treatment group experienced shock after hospitalization. Whether the drug was responsible for this result could not be determined.

The severity of the acute illness was less eventful in the

[4] Angiology 15:505-514, November, 1964

survivors comprising the drug-treated group. The differences between the mean number of days on which analgesics and oxygen were required were statistically significant, favoring the conclusion that the clinical course was smoother in the drug-treated group The mean number of days required for pulse rate to return to preinfarction levels was not significantly different between the two groups. The over-all mortality in the group of 50 patients who received a placebo besides the regular drug therapy was 22%, compared with 4% of 50 patients given sustained-action doses of pentaerythritol tetranitrate and regular drug therapy. The difference was significant.

Anti-Heart Antibodies in Postpericardiotomy and Postmyocardial-Infarction Syndromes. H. van der Geld[5] (Amsterdam), with the technical assistance of Thea d'Ailly, performed the antiglobulin-consumption test and immunofluorescence studies on 15 patients with the postpericardiotomy syndrome and 14 patients with the postmyocardial-infarction syndrome. Anti-heart antibodies were found in the serums of 13 of the former patients and 8 of the latter. Antinuclear factor was not found in any of the serums studied. With the antiglobulin consumption test, antibodies were found in 23 of 167 patients with various heart diseases and with the immunofluorescent technic, in 17 of 62 patients. No correlation with an increased antistreptolysin-O titer was demonstrated. Transient anti-heart antibodies developed postoperatively in 4 of 17 patients undergoing commissurotomy and in 1 of 7 having closure of an atrial septal defect. None of these patients showed the postpericardiotomy syndrome within a year of operation. On studying 73 serums by both methods, significantly more positive results were obtained with the immunofluorescent technic (47 compared with 30%). In general, in both the postpericardiotomy and postmyocardial-infarction syndrome, antibodies were found only when there were symptoms. The titer declined sharply in the course of the disease in the few cases studied.

The commonest staining pattern in patients with anti-heart antibodies involved fluorescence, especially at the outer edge of the subsarcolemmal sarcoplasm of the myofiber. There was usually a lesser diffuse reaction within the substance of the sarcoplasm. The intermyofibrillary pattern

(5) Lancet 2:617-621, Sept 19, 1964

was less often seen. A striational pattern was never seen. Endomysial fluorescence was observed in 2 cases postoperatively. All positive serums reacted with skeletal muscle. The endomysial pattern, but not the other two patterns, was affected by absorption of serums with thymus, skin, kidney, liver and thyroid. Positive reactions with heart and muscle were obtained with human, horse, calf, rabbit, guinea pig and rat tissue.

ELECTROCARDIOGRAPHY AND ARRHYTHMIAS

P Wave Analysis in Valvular Heart Disease. James J. Morris, Jr., E. Harvey Estes, Jr., Robert E. Whalen, Howard K Thompson, Jr., and Henry D. McIntosh[6] (Duke Univ.) studied 111 consecutive patients with regular sinus rhythm, who had had complete cardiac catheterization with no evidence of intracardiac shunt, and 100 normal controls aged 20-69 Standard 12-lead direct or photographic ECGs were taken Besides the standard P wave measures used, the P wave in lead V_1 was divided into two portions, and the duration and amplitude of each were analyzed The algebraic products of the duration and amplitude were designated the P initial force V_1 and the P terminal force V_1. The measure of P terminal force correctly separated normal subjects from patients with left-sided valvular lesions in 92% of the series. Once a given valve lesion is suspected clinically, the measure permits estimation of the severity of the lesion The measure does not indicate the type of valvular disease, nor does it correlate with any one specific hemodynamic measure

The abnormality does appear to be related, within each separate type of valve disease, to the specific hemodynamic abnormality of that type of valvular involvement In mitral stenosis, the most significant correlation existed between the P terminal force and the catheter measures of the severity of the stenosis. In mitral insufficiency, the best relation was with the degree of insufficiency. When aortic stenosis was present, the systolic gradient was significantly correlated with the abnormal P wave measures. Study of 11 patients with valvular pulmonic stenosis showed that cardiomegaly, digitalis,

edema, etc., play no important role in producing abnormalities of P terminal force found in the patients with aortic and mitral valve disease.

In practice, measurement of the P terminal force is simple. Visual inspection can easily identify an abnormal P wave at V_1. A terminal portion of the P wave at V_1, one box in depth (−1.0 mm.) and one box in duration (0.04 second), yields a P terminal force of 0.04. Any P wave negativity of this size or larger is abnormal.

Clinical Observations Using Electrocardiocorder-AVSEP Continuous Electrocardiographic System: Tentative Standards and Typical Patterns are discussed by John S. Gilson, Norman J. Holter and Wilford R. Glasscock.[7] The Electrocardiocorder-AVSEP (audio-visual superimposed electrocardiographic presentation) system provides long-term, continuous ECG recording and rapid analysis of data from either the ambulatory or confined subject. The Electrocardiocorder is a miniature, portable, self-powered tape recorder, specially designed to permit recording of ECG potentials throughout a wide range of activity. Worn in a holster or carried in a handbag, it continuously records the subject's ECG potentials for 5-15 hours before the tape needs changing. AVSEP is an electronic data reduction device which rapidly reproduces successive ECG complexes as superimposed patterns on an oscilloscope by an accelerated playback technic; 5 hours of recording are reproduced in 5 minutes. The AVSEP patterns may differ in some respects from conventional ECG patterns, but the differences are included in the subject's "basic" pattern, the predominant pattern in any one recording period, which serves as the subject's own reference pattern against which "variation" patterns can be compared. The authors have obtained recordings from 230 subjects, including 65 "normal" ones.

In normal subjects, P waves were usually upright or flat. The QRS complexes were a mixture of transitional and left ventricular type patterns and remained completely stable throughout the trial in all but 3 normal subjects. The S-T segment was depressed in 20% of normal subjects without relationship to sex, age or any other observed variable. Elevated S-T segments were noted in 8% and, like the depressed segments, were not seen in the conventional ECGs. A pre-T

(7) Am J Cardiol. 14 204 217. August, 1964

notch was seen in 45% of normal subjects and simulated a separation of the S-T segment from the T wave itself. In about 10% of subjects, the tallest T waves were over twice as tall as the lowest, or the contour was distorted to a degree. The T wave showed extreme variations, even in the same person from moment to moment. A dip after the T wave was seen in 55% of normal subjects; it seemed to be an overshoot related to the height of the T wave.

Sinus arrhythmia is poorly identified in AVSEP patterns. Sinus tachycardia and sinus bradycardia can be identified, and ventricular ectopic beats are readily identified. Atrial or nodal ectopic beats are difficult to identify without the Arrhythmiagraph, which reproduces cycle lengths as a "picket-fence" pattern on an oscilloscopic screen. Artifact patterns other than those inherent in the electronics of the system are usually brief and infrequent. Even when they are severe, there is often enough of the regular repetitive pattern present so that the experienced eye can "see through" the random artifact potentials. Only 10 of 230 recordings were so badly distorted as to be unsatisfactory; most distortions resulted from broken lead wires.

Effect of Digitalis on Exercise Electrocardiogram. Chuichi Kawai and Herbert N. Hultgren[8] (Stanford Univ.) studied 15 patients with known or suspected cardiac disease and 16 normal subjects A double two-step (Master's) test was performed before and after administration of digoxin, given orally in a dose of 1.5-2 mg. the 1st day, 0.5-1 mg. the 2d day, and 0.25-0.5 mg. the 3d and, in some instances also, the 4th day. Some subjects were studied with inhalation of 100% oxygen, 0.4 mg nitroglycerin, 60-150 mEq. potassium, or inhalation of 10 or 8% oxygen in nitrogen. Final exercise tests were performed 3 weeks after digoxin was discontinued. While receiving digoxin, 14 of the 15 patients and 8 of the 16 normal subjects had positive tests. Five patients and all the normal subjects had negative tests when not receiving digoxin. No evidence was found to suggest that myocardial ischemia was produced by the drug. An effect on intramyocardial potassium seems most likely.

The ECG exercise tests should not be carried out in patients receiving digitalis preparations. Digitalis should be discontinued for at least 3 weeks before an exercise test is

done. Examination of the Q-T ratio may enable differentiation between a false positive test due to digitalis and a true positive exercise test.

Electrocardiographic Abnormalities Associated with Subarachnoid Hemorrhage. S. C. Srivastava and A. O. Robson[9] (Royal Victoria Infirm., Newcastle upon Tyne) describe 4 patients with subarachnoid hemorrhage and ECG abnormalities, in none of whom myocardial damage was found at autopsy.

Woman, 63, had sudden faintness, nausea and loss of consciousness about 3 hours before admission to the hospital The ECG showed upright T waves, a Q-Tc interval of 0 44 second, and elevated S-T segments in leads V_5, V_4 and V_6. A second tracing 4 hours later showed deeply inverted T waves in limb leads and most chest leads, a Q-Tc interval of 0.6 second, Q waves indicating posterior cardiac infarction and extensive ischemic R-wave inversion anteriorly. The serum glutamic oxalacetic transaminase (SGO-T) was 80 Reitman-Frankel units (normal, 10-40 units).

Anticoagulant therapy was given. The next morning, the patient complained of recurrent frontal headache, pain in the right eye and a stiff neck Lumbar puncture showed subarachnoid hemorrhage Anticoagulants were stopped The SGO-T was 30 units An ECG showed grossly inverted T waves and a deformity on the upstroke of inverted T waves, interpreted as possibly due to incorporation of inverted U waves The patient suddenly became comatose on the 3d day and died.

Autopsy showed subarachnoid hemorrhage over the entire base of the brain. A large aneurysm of the right internal carotid artery at its bifurcation had ruptured into the subarachnoid space and into the frontal lobe There was marked "coning" of the cerebellum The heart showed no evidence of infarction The left circumflex coronary artery was narrowed in places, but the lumen was patent, and the other major coronary branches were normal

The ECG abnormality, unassociated with cardiac disease, seen in cases of subarachnoid hemorrhage seems to consist of altered and delayed ventricular repolarization. The changes often develop in the 24-48 hours after hemorrhage and then regress. Electrolyte changes, disturbed autonomic influences and hypothalamic activity have all been blamed for these changes. In all 4 present cases, the hemorrhage was anteriorly placed and close to the frontal lobes.

► [This communication and some of the succeeding ones illustrate what in my opinion is the greatest tragedy and the greatest fallacy in modern cardiology. This tragedy stems from the improper use of one of the greatest tools ever devised in medicine The fallacy is the assumption that the electrocardiogram applies specific and infallible information about etiology. The fact is that the only infallible information in the electrocardiogram concerns the direction and

(9) Lancet 2 431 433, Aug 29, 1964

amplitude of certain electric forces When the type of change that was found in this patient with the subarachnoid hemorrhage is encountered, the odds are strong that one is dealing with a focal anatomic lesion of the myocardium. Infarction simply happens to be the most common of such focal lesions. However, there are many instances illustrated by this patient in which the jump, on a purely statistical basis, to the conclusion that an infarction is in fact responsible is fallacious The electrocardiogram must invariably be interpreted in relation to the total clinical picture Only when so interpreted does it give reliable information —Ed]

Postprandial Electrocardiographic Modifications. Salvador Palma-García and Julio Aspe-Rosas[1] (Mexico City) studied 20 normal subjects and 50 patients with cardiac disease (coronary artery disease, rheumatic heart disease, chronic cor pulmonale and tuberculous pericarditis) or gastrointestinal disease. The ECG tracings were obtained in the best environmental conditions before and after meals and before and after administration of 100 Gm. glucose. The three standard unipolar and precordial leads, V_1 to V_6, were recorded.

Sinus arrhythmia was found in 25% of normal subjects after a meal. Heart rate was increased in 75% and decreased in 10% of the subjects, the average increase being 8 beats per minute. A ±P wave in lead V_1 was present after the meal. The P-R interval was shortened by 0 02 second in 20% of the subjects. The electric axis was shifted 16 degrees to the right in 15% and 10 degrees to the left in 5%. The T wave decreased in 40% and was inverted in D_1 in 5%. The R-ST segment was decreased in the precordial leads in 15%, and 20% showed a shortening of 0 04 second in the Q-T interval.

Heart rate increased in 90% of 10 normal subjects given oral glucose, and 20% showed a ±P wave in lead V_1. One showed a change from sinus arrhythmia to sinus rhythm. The T wave decreased in 40%. The electric axis shifted 10 degrees to the right The Q-T interval decreased 0.03 second in 90% of the subjects.

The changes seen after a meal were present at 60 minutes. They were more marked after glucose intake, but less frequently than after a meal The changes were more pronounced in the cardiac patients Postprandial changes apparently are produced primarily by a decrease in the magnitude of the ventricular gradient, which is modified by an increase in heart rate and a change in permeability of the cardiac fiber membrane to the potassium ion. All ECG trac-

(1) Angiology 15: 174-182, April 1964.

ings should be obtained in the fasting state or 4 or 5 hours after the last meal.

Effect of Saluretics on Pulse Rate, Blood Pressure and Electrocardiogram during Exercise in Normal Subjects. B. Christensson, A. Gustafson and H. Westling[2] (Lasarretet, Lund) recorded ECGs in 13 healthy persons before, during and after exercise on a bicycle ergometer, using successively increasing loads. The following drugs were given: 100 or 200 mg. chlorthalidone daily to 9 persons and 25 mg. hydrochlorothiazide 3 times daily to the other 4. Some received 0.25 Gm. acetylsalicylic acid daily as a "placebo."

Loss in body weight and some hemoconcentration were regularly seen during diuretic therapy. Both drugs decreased sodium and chloride levels in the serum. The change with hydrochlorothiazide was not significant. Chlorthalidone reduced the sodium level from 146 to about 140 mEq./L. and the chloride from 104 to about 95 mEq./L. after 6-8 days' treatment. Hydrochlorothiazide reduced the serum potassium content from 4.3 to 3.5 mEq./L. after 6 days. The lower dose of chlorthalidone (100 mg. daily) reduced the values to 3.3 and 3mEq./L., respectively, in 4 and 8 days, the mean value after 17 days being 3.5 mEq./L. The larger dose (200 mg. daily) reduced the serum potassium level to 3.5 and 2.9 mEq./L. after 3 and 6 days, respectively.

The pulse rate rose on exercise during diuretic therapy; the rise was persistent when the high dose of chlorthalidone was given. The linear relationship between work load and pulse rate persisted during treatment. The higher pulse rate during treatment corresponded to a 20-25% decline in physical working capacity. The higher pulse rate is likely to be due to a decreased stroke volume as a result of dehydration and hemoconcentration. The systolic pressure increased regularly on exercise. Hydrochlorothiazide treatment did not produce any significant changes in pulse rate or blood pressure during exercise. A flattening of the T wave and a positive diastolic after-potential appeared in the ECG at rest during diuretic therapy. In about half the subjects, ECG abnormalities occurred on exercise, when the serum potassium level was about 3 mEq./L. or less. The S-T segments were depressed and the T wave often inverted. The changes disappeared rapidly

(2) Acta med scandinav 175 727-734, June, 1964

after exercise. The ECG changes were more frequent and pronounced with chlorthalidone in the higher dosage.

Serum electrolytes should be analyzed in patients with a pathologic exercise ECG in whom there is suspicion of electrolyte changes, e.g., due to diuretic treatment. Special care should be taken in interpreting exercise ECGs in patients with a resting ECG showing a flat T wave and diastolic after-potential.

Experimental Technics for Improving Effectiveness of Cardiac Resuscitation. Marvin M. Nachlas, Melvin P. Siedband and Philip Bernstein[3] (Baltimore) evaluated three accessory and clinically applicable technics of increasing blood flow when cardiac massage does not produce the desired result. These included cross-clamping of the abdominal aorta, use of vasopressor agents and diastolic perfusion.

METHOD.—Ventricular fibrillation was induced in 51 mongrel dogs and external cardiac massage at a rate of 40 per minute instituted at 2 minutes. The force applied to the sternum varied from 40 to 100 lb., depending on the force required to give an arterial pressure of 50/25 mm. Hg. At 15 and 28 minutes, 20 mEq. sodium bicarbonate was given, and after 30 minutes, external countershocking was begun. Norepinephrine, usually 16 mg./500 ml. of 5% dextrose in water, was infused intravenously until the arterial pressure was stabilized. Only this procedure was carried out on 15 animals. Aortic occlusion was produced in 8 dogs about 3 minutes after onset of fibrillation. Eight others received twice the regular concentration of norepinephrine (64 μg./ml.), beginning about 3 minutes after induction of fibrillation, the pressure was kept at 75/25 mm. Hg or higher during massage. Diastolic pumping was accomplished through the abdominal aorta in 10 dogs and through both femoral arteries and the left carotid artery in 10 others. The Davol assist pump was used. A timing device synchronized the pneumatic external massage pump with the assist pump. Each pump operated for 0.5 second during each 1.5 seconds.

The pupils remained small in most of the 15 control animals. Six were defibrillated after 7 countershocks or less, 4 required more shocks and 5 could not be defibrillated. Over half the dogs could not maintain a satisfactory arterial pressure. Six made a speedy recovery even though massage was performed at a marginal pressure. Of the 8 animals having aortic occlusion, 4 were defibrillated with 1 countershock and had excellent restoration of cardiac and cerebral functions. Five of 8 dogs given increased amounts of norepineph-

[3] Ann. Surg. 161:311-313, March, 1965.

rine made excellent recoveries, and only 1 animal showed no return of spontaneous respiration. Improvement in pressures occurred on diastolic perfusion through the aorta in 6 of 10 animals, but pressure was raised out of the marginal zone of 50/25 mm Hg in only 1. Over-all recovery was good in 5 instances With diastolic pumping through small arteries, 6 of 10 animals still had pressures from which control animals had never been resuscitated. However, recovery in this group of animals was better than that in any other group, only 1 dog requiring more than 4 countershocks to break the fibrillation. Six animals had an adequate blood pressure without vasopressors by 5 minutes after defibrillation.

Findings indicate that all three methods evaluated can be used in clinical attempts at cardiac resuscitation. The technic of diastolic pumping through the peripheral vessels appeared to result in the greatest improvement of cardiac function.

Effect of Steroid Therapy on Normal and Abnormal Atrioventricular Conduction. John L. C Dall[4] (Glasgow) administered prednisolone orally to 25 patients with acute myocardial infarction for 14 days, the dosage decreasing from 30 mg. daily to zero. Electrocardiograms were obtained initially, on the 8th day and at 4 weeks. Study also was made of a control group of 25 patients with infarcts who received no steroids. Another 7 patients with complete heart block of recent onset received oral therapy, with a maximum initial dose of 40 mg. daily, reduced during 14 days: 17 received 10 mg./kg. parenterally in the first 24 hours, this dosage being reduced during 12 days thereafter. Three more patients with partial and 11 with complete chronic heart block were studied.

With normal conduction, the mean P-R interval on day 8 was significantly shortened in treated patients; this did not persist after withdrawal of therapy. Of the 7 patients with acute heart block given oral therapy, 6 converted to normal rhythm and 1 died in a few hours. Average duration of treatment before recovery of sinus rhythm was 6 days. Of 17 patients treated parenterally, 2 died within 2 hours of admission; 15 regained sinus rhythm within 24 hours, the dose of hydrocortisone varying from 300 to 800 mg. in that time. Block did not recur on withdrawal of treatment. One patient

(4) Brit Heart J 26 537 543 July 1964

died after mesenteric embolism on the 10th day. Some shortening of the P-R interval occurred during oral prednisolone therapy in 1 of the 3 patients with chronic latent heart block. Nine of the patients with complete block were uninfluenced by intravenous or oral steroids. One was twice restored to sinus rhythm and reverted to complete block each time. One patient required treatment for 10 months before steroids could be successfully withdrawn. In both recent and chronic groups, Stokes-Adams attacks ceased when treatment was established.

It is suggested that the shortening effect of corticosteroids on atrioventricular conduction in normal subjects or patients with chronic heart block is due to an alteration in the extracellular-intracellular potassium balance. But in the case of a recent infarct with block, corticosteroids may have an anti-inflammatory effect on the disturbance in the conducting tissues, promoting earlier recovery of normal function, as shown by the return of sinus rhythm.

Hemodynamic Studies in Patients with Artificial Pacemakers. Edgar Sowton[5] (St George's Hosp., London) studied 35 patients with complete heart block and reviewed the clinical experience with another 41 treated by artificial pacing for up to 4 years. Treatment by artificial pacing was instituted only after failure of a full medical regimen, the indication in most cases being recurrent Stokes-Adams attacks Pacemakers designed by Davies and giving a 2-msec. square-wave biphasic pulse were used

Cardiac outputs measured 4 minutes after changes in rate were nearly independent of ventricular rate in 14 patients without evidence of myocardial disease, but were critically dependent on rate in 14 patients with myocardial disease, both at rest and on exercise. Most patients had an optimal ventricular rate at rest, at which rate cardiac output was maximal, venous pressure lowest and atrial rate minimal The optimal rates ranged from 55 to 90 beats per minute, with a mean of 71 beats. The optimal rates on exercise for patients with myocardial disease were close to the optimal rates at rest. In all patients, a fixed ventricular rate was acceptable if correctly chosen and permitted moderate activity. Artificial pacing increased the mean cardiac output in 28 patients from 2.9 to 4.4 L. per minute. Exercise with a

fixed ventricular rate increased the mean output in 10 patients from 4 to 10 2 L. per minute. Four of these 10 patients increased their output to 12 L. per minute or more.

Hemodynamic findings with implantable pacemakers producing synchronized atrial and ventricular contractions show considerable improvement over simple ventricular pacing. Until more experience with this unit is available, use of an implantable fixed-rate pacemaker is suggested for long-term artificial pacing.

P Wave Synchrony. Sam E. Stephenson, Jr., and Stanley K Brockman[6] (Vanderbilt Univ.) conducted experiments in 5 mongrel dogs in which complete heart block was produced by the method of Starzl and Gaertner. Standard electrodes fixed to the ventricle and atrium were attached to a stimulator that would function either as a synchronous P wave stimulator or as a stimulator having a fixed, predetermined rate. The dogs had heart rates ranging from 32 to 60 beats per minute. In each experiment, the ventricular rate was brought under complete control by the P wave synchronous pacemaker or by the asynchronous pacemaker. The heart rates ranged from 118 to 156 beats per minute when the ventricle was driven by the P wave pacemaker The atrioventricular delay was adjusted to obtain an optimal P-Q interval as indicated by the aortic and ventricular pressures and stroke volume. This varied between 0.09 and 0.15 second. The aortic pressure, ventricular pressure and stroke volume were always higher during P wave synchronous pacemaking than during direct asynchronous pacing at the same ventricular rate.

The results of these experiments confirm the belief that P wave or synchronous cardiac pacing from an external or internal source is more physiologic and better tolerated by the organism involved.

Four-Year Experience with Implanted Cardiac Pacemaker. Paul M. Zoll, Howard A. Frank and Arthur J. Linenthal[7] (Boston) treated 77 patients since 1960 with long-term cardiac stimulation by implanted pacemakers. Stimulus failure due to rise of threshold has not been seen except in association with sepsis at the implantation site in 3 early cases. Tests in 5 patients 1-3 years after implantation showed thresholds of 1.5-4 volts and 1.3-6 ma. No break has been observed in 23

(6) Ann New York Acad Sc. 111 (art 3) 907-914, 1964
(7) Ann Surg 160 351 365, September 1964

cases with use of electrode wires made of 77 strands of stainless steel, electroplated with gold and platinum and insulated with Teflon. The energy source of the pacemaker is six mercury batteries with an expected life span of 5 years. The output is a 2-msec., 7.5-volt, 10-15 ma. stimulus delivered usually at a rate of about 70 per minute. The electric components are triply sealed in epoxy resin. The unit has functioned perfectly in all but 1 of 55 patients treated since use of the present design was begun. The longest time that an individual pacemaker has functioned has been 30 months.

The method of implantation has been changed little since the authors' previous report (1961). Ability to stimulate the heart is tested in the operating room. β-Propriolactone is used to sterilize the pacemaker system. The retropectoral site is the first choice for implantation. Broad exposure of the left ventricle is desirable. The position of the electrodes is not critical for effective stimulation. The implantation tunnels are aligned in parallel and somewhat obliquely downward and outward toward the lateral ventricular border. The fixing sutures must avoid coronary branches. A cross incision in the pericardium is left open around the wires, which are led upward along the mediastinum and forward in the upper part of the chest to the site of emergence in the 2d or 3d interspace anteriorly.

The patients included 52 men and 25 women. Many were desperately ill, and other serious illnesses besides heart block were frequent. Adams-Stokes disease was present in most cases. All patients but 1 had atrioventricular block, in most, complete and fixed. The entire system was replaced 22 times in 17 patients; 56 other secondary procedures were necessitated by pacemaker failure, wire break or sepsis, nearly all in the early phase of the program.

There were 1 early postoperative death and 16 late deaths. Eight patients died suddenly; the cause of death was a broken wire in 1 case, ventricular fibrillation in 3 cases and unknown in the others. Three other patients had fibrillation but survived. Repetitive responses or ventricular fibrillation from a stimulus in the vulnerable period never were noted. Postoperative morbidity was generally mild. Eight patients had clinically significant bronchitis, atelectasis or pneumonitis. There was no recognized instance of myocardial infarction or pulmonary embolization. Four patients developed the

postpericardiotomy syndrome. The surface materials have proved remarkably nonirritating. Sepsis, when it occurred, persisted and led to prolonged morbidity. Complications some months after operation were a diaphragmatic twitch in 2 patients and a severe pectoral twitch in 1.

Except in instances of wire breakage, attacks due to ventricular standstill have been eliminated and, in general, seizures due to ventricular tachycardia or fibrillation prevented. The pacemaker has been valuable in improving congestive heart failure and other signs of decreased cardiac output. Most patients have been well and able to function without cardiac symptoms at activity levels compatible with their general physical condition. Many patients underwent severe stresses with remarkably little circulatory difficulty

There are few if any patients with Adams-Stokes disease to whom this treatment should not be offered. Congestive heart failure and other signs of decreased cardiac output in patients with slow ventricular rates constitute further indication for surgery Heart block alone in an asymptomatic patient is not an indication for treatment.

Two Years of Clinical Experience with Synchronous Pacer. Sol Center, David Nathan, Chang Yu Wu and Dario Duque[5] report experience with 21 patients operated on during 1962-63. The synchronous pacer now used is 5.5 cm. is diameter and 2.2 cm. thick and weighs 5 oz. It contains five 1.3-volt mercury cell batteries with a shelf life of 5 years. The frequency band of the P wave pick-up is 20-200 cps. The capacitor delivers a negative pulse of 2 msec., 6.5 volts and 10 ma. Sensitivity of the pacer is set at 1 mv. Two diodes previously needed to protect the transistors have been removed. The electrodes terminate in a connector with gold pins, which plugs into the pacer and is covered by a Silastic boot. The electrodes are modified Chardack electrodes of platinum iridium in silicone rubber tubing. Activation of the atria is detected by the atrial electrode and transmitted to the pacer. The time delay equal to that of the normal P-R interval occurs before transmission. The maximal rate of the pacer is 110 cycles per minute, and the minimal rate is 52 cycles per minute A 2:1 block occurs at rates between 110 and 220 and a 3:1 block at rates of 220-230 cycles per minute. Failure of the atrial pick-up electrode or an atrial rate below 52 will

(8) J Thoracic & Cardiovas Surg 48 513-526, October 1964

result in an automatic pacer rate of 52. In event of a return of the patient's own normal sinus rhythm, the pacer will follow but not interfere with the normal conduction of the heart.

Of 18 patients, aged 54-85, undergoing implantation of synchronous pacers for complete heart block, each had a history of Stokes-Adams attacks and 8 were in congestive heart failure at some time before hospitalization. Synchronous pacing was produced immediately in 16 patients. In another, a fixed rate of 52 was present for 2 weeks, with a subsequent change from automatic to synchronous pacing. Synchronization of the P wave never occurred in a patient with a fatty auricular appendage. Atrial fibrillation and/or flutter occurred postoperatively in 2 patients, both of whom responded to digitalis. Two patients acquired postpericardiotomy syndrome and responded to steroid therapy. Postoperative congestive failure was treated successfully in 1 patient, and a thoracotomy wound infection was treated successfully in another. The cardiac output had increased after 3-12 months in all but 1 of 9 patients studied, compared with idioventricular pacing. The increment in cardiac output during exercise was 25-50% in 7 patients studied. Normal sinus rhythm returned after operation in 5 of the 16 long-term survivors. The synchronous pacer was used successfully for protection during asystole in 3 other patients with Stokes-Adams attacks

Pacer pocket infections necessitated exteriorization of the pacer in 2 patients. Electrode problems occurred in 2. Increased ventricular threshold was noted only in the 2 patients with infection at the site of pacer implantation. One patient died suddenly 9 months after implantation, and the pacer was found at autopsy to have an automatic rate of 600 cycles per minute. Another patient died after 16 months, and the pacer was found to have a rate of 52, but it could be artificially stimulated at a rate of 400, it was believed that a pacer-induced tachycardia had probably caused the sudden death of this patient.

Implantation of a synchronous pacer is advised in patients with heart block when drug therapy has proved inadequate to maintain a pulse of 40 or to prevent syncopal attacks and ventricular arrhythmias. Congestive heart failure in patients with complete heart block is also an indication for pacer implantation. In synchronous pacing, the cardiac rate re-

sponds to body demands; ventricular systole occurs synchronously with atrial systole to add to the efficiency of the heart; and the pacer does not interfere with the patient's heart in the event of return to normal sinus rhythm. Maintenance of atrial voltages of 2-4.5 mv. up to 21 months after implantation proves beyond doubt the feasibility of indefinite synchronous pacing.

Effect of Potassium in Restoring Myocardial Response to Subthreshold Cardiac Pacemaker. Weldon J. Walker, John T. Elkins, Jr., and Laurence W. Wood[9] (Walter Reed Gen'l Hosp.) used pharmacologic means to restore responsiveness to partially exhausted pacemakers in 2 patients with complete heart block.

CASE 1 —Woman, 69, had been asymptomatic for 20 months after implantation of a cardiac pacemaker for complete heart block and Adams-Stokes attacks However, she noted a slower heart rate 2 weeks before admission and returned after two syncopal episodes An ECG showed complete heart block with idioventricular rhythm. The ventricle responded to the pacemaker only when the stimulus occurred during the supernormal period of the idioventricular beats. When the stimulus of a catheter pacemaker fell in the supernormal period of the cycle, the ventricle continued to respond to the implanted pacemaker. This supernormal period extended from the latter half of the terminal slope of the T wave to just beyond the peak of the U wave. Infusion of isoproterenol and calcium increased cardiac irritability, and hydrocortisone was ineffective Administration of 75 mg. hydrochlorothiazide and 30 Gm. sodium polystyrene sulfonate reduced extracellular potassium to 3.5 mEq./L and reduced cardiac excitability, the ventricle becoming unresponsive except during the supernormal period of the idioventricular beats. When the stimulus of the catheter pacemaker was increased to 4 ma., the myocardium again became responsive. Administration of 60 mEq. potassium chloride syrup in 4 hours increased responsiveness to the implanted pacemaker Potassium depletion in the next few hours repeatedly caused the myocardium to become refractory to the implanted pacemaker, and potassium administration restored responsiveness. The highest serum potassium level recorded was 4 6 mEq./L. At the time of removal of the pacemaker, it recorded only 0.9 volt

CASE 2 —Woman, 46, began having recurrent convulsions 1 year after implantation of a cardiac pacemaker for Adams-Stokes attacks Complete responsiveness to the pacemaker was restored 7 minutes after oral administration of 30 mEq. potassium chloride in syrup. Potassium depletion caused the myocardium to become refractory to the pacemaker. This sequence was repeated twice before the stimulus for the adjustable cardiac pacemaker was increased.

(9) New England J Med 271 597-601 Sept 17, 1964.

In many patients with implanted pacemakers, a subthreshold stimulus may develop through exhaustion of the battery or decreased myocardial excitability from such factors as fibrosis about the myocardial electrodes. Potassium depletion may be an added cause of pacemaker failure. Oral administration of potassium is advised as a means of restoring myocardial responsiveness to a partially exhausted pacemaker until a replacement can be implanted.

Propranolol (Inderal) in Disturbances of Cardiac Rhythm. D. J. Rowlands, G. Howitt and P. Markman[1] (Manchester, England, Royal Infirm.) studied the effect of propranolol in selected cases of cardiac arrhythmia. In all cases of atrial fibrillation of rheumatic, thyrotoxic and idiopathic origin, a reduction in ventricular rate occurred, even in patients who were already fully digitalized. The drug may be clinically valuable in digitalized patients with mitral stenosis and persistent tachycardia and in those with untreated thyrotoxicosis. In cases of atrial flutter, the atrial rate was unaffected but a significant and consistent reduction in the ventricular rate was induced, especially during exercise. The frequency of ectopic beats was reduced in cases of repetitive paroxysmal ventricular tachycardia, but the abnormal rhythm was not completely abolished. In a single case of exercise-induced bigeminal rhythm, the abnormality was abolished by the drug. The frequency of spontaneous ventricular ectopic beats was not reduced, but propranolol prevented the increased frequency induced by a rebreathing procedure.

In 2 patients with mild, diffuse, obstructive airway disease, wheezing and dyspnea seemed aggravated by propranolol. This is an expected result of sympathetic beta blockade. The drug should be used with caution in such patients.

Propranolol (Inderal) in Persistent Ventricular Fibrillation. Graeme Sloman, James S Robinson and Kenneth McLean[2] (Melbourne) report results in 3 cases of recurrent ventricular fibrillation in which propranolol was used.

Man, 44, had proved anteroseptal myocardial infarction complicated by left ventricular failure at age 40. Subsequently, angina of effort developed. This lasted 8 months and culminated in acute anterior myocardial infarction. On present examination, 3d and 4th heart sounds were heard. Sedation, analgesics and anticoagulant therapy were begun. Pain lasted 48 hours, during which time occasional ventricular extrasystoles were the only ECG abnormality. Moderate

(1) Brit. M. J. 1: 801-804, Apr. 3, 1965
(2) Ibid., pp. 804-806.

left ventricular failure ensued, and the patient was digitalized. The serum glutamic oxalacetic transaminase rose to a peak of 112 units. After walking about 25 yards 21 days after admission, the patient collapsed and was found pulseless. Cardiac massage was begun immediately. Attempts at defibrillation, using an external shock of 400 watt-seconds, were unsuccessful until metabolic acidosis was corrected with 45 Gm. tris (hydroxymethyl)-aminomethane. The arterial pH rose from 7.18 to 7.35 after sinus rhythm was established. Ventricular tachycardia turning into ventricular fibrillation recurred repeatedly that day. The patient was heavily sedated and 2 Gm. procainamide given intravenously over 2 hours without effect. Direct-current defibrillation was required 62 times in the next 30 hours, and 3.7 Gm. procainamide had no significant effect on the number of attacks. Propranolol was given intravenously in a dose of 22 mg. over 10 minutes. After 12 mg., ventricular extrasystoles were less frequent, and after another 10 mg., none were observed. Circulatory failure with severe hypotension persisted, and the patient died 40 minutes later.

Propranolol was effective in suppressing recurrent ventricular fibrillation in all 3 patients after other drug therapy had failed. Complete atrioventricular block occurred after control was achieved in the patient in whom ventricular fibrillation was thought to result from digitalis intoxication. Propranolol was lifesaving in 1 of the 2 patients in whom fibrillation occurred after acute myocardial infarction. When the drug is given to patients with severe infarction, the dose should be kept to a minimum. The maximal single dose should not exceed 10 mg. Propranolol may be of value for preventing ventricular fibrillation in patients with myocardial infarction. A controlled trial of the drug in patients with acute myocardial infarction would be of value.

Diphenylhydantoin Sodium in Cardiac Arrhythmias was evaluated by Robert D. Conn[3] (King County Hosp., Seattle). In a large municipal hospital, numerous patients are treated for a variety of cardiac arrhythmias precipitated by failure to take medicines, digitalis excess, myocardial ischemia and infarction or various metabolic derangements. In such cases, some form of palliative therapy may be of benefit until the primary cause can be identified and corrected.

In the presence of suspected digitalis toxicity or when more specific drugs were not immediately indicated, patients with cardiac arrhythmias with no history of antecedent drug therapy were given diphenylhydantoin sodium intravenously. A dose of 250 mg. in 5 ml. solvent was used; this usually was

(3) New England J Med 272:277-282, Feb. 11, 1965

equivalent to 3.5-5 mg./kg. The drug was given in 1-3 minutes with continuous ECG monitoring for about 5 minutes, and then at intervals of 5-10 minutes until a drug effect could be established. If the ECG showed a response and then the arrhythmia recurred, a similar dose was given again. After a satisfactory response, the patient was maintained on 200-400 mg. intramuscularly or orally, daily, in divided doses until the problem was resolved or other drug therapy was substituted.

Twenty-four patients with a variety of cardiac arrhythmias were treated; occasionally, several different arrhythmias coexisted in the same patient. Three patients with atrial fibrillation and 2 with atrial flutter showed no response. Both patients treated for paroxysmal supraventricular tachycardia reverted promptly to normal sinus rhythm. In 2 patients with atrial tachycardia and block induced by digitalis, a sinus mechanism was restored in 1, while in the other the block was increased Sinus rhythm was restored in a patient with a complex atrioventricular rhythm induced by digitalis or hypoxia and in 1 of 2 patients with atrial tachycardia and wandering atrial pacemakers. Transient block occurred in a patient treated for supraventricular tachycardia after cardioversion for atrial fibrillation. Atrial premature contractions were abolished in all 3 patients given diphenylhydantoin Bigeminal rhythm was abolished in 5 of 6 cases. All 6 patients with multifocal ventricular premature contractions responded. One episode of ventricular tachycardia was treated, and the basic rhythm of chronic atrial fibrillation was restored

All pharmacologic responses occurred in ½-4 minutes One patient developed transient hypotension, and 1 had transient atrioventricular block and bradycardia.

Diphenylhydantoin administered intravenously appears to be useful in controlling supraventricular and ventricular arrhythmias arising from digitalis excess It may serve adequately as a temporary agent in situations in which more specific but slower-acting therapy is indicated and may also be useful in controlling ventricular arrhythmias resulting from myocardial infarction or those occurring during cardiac surgery. It may be ideal for use in cardiac arrest. It may also be effective in arrhythmias unsuccessfully treated with quinidine and procainamide. Diphenylhydantoin appears to

have no place in treatment of atrial flutter and fibrillation and should not be used in patients with bradycardia or a high degree of atrioventricular block.

Experience with "Cardioversion" of Atrial Fibrillation and Flutter is recounted by James J. Morris, Jr., Yihong Kong, William C. North and Henry D. McIntosh[4] (Duke Univ). Direct current countershock was used in 70 patients on 94 occasions. Seven had atrial flutter and 63, atrial fibrillation. Twenty-seven patients had undergone cardiac surgery; in all but 1, cardioversion was not attempted until at least 6 weeks after operation. Ages ranged from 19 to 79; 36% of the patients were over age 50. Rheumatic heart disease was present in 46 patients, ischemic heart disease in 14, hypertensive cardiovascular disease in 3 and miscellaneous conditions in 7. Half the patients had fibrillation for 1 year or longer. Quinidine therapy had been tried in 41 patients.

METHOD—Digitalis was used to control the ventricular rate A cardioverter was programed to discharge a synchronized direct current countershock during the downstroke of the R wave In most patients, electrodes 5 in. in diameter were used, positioned on the anterior and posterior chest wall The initial countershock was usually begun at 50 watt-seconds and advanced 50 or 100 watt-seconds with each attempt until sinus rhythm was restored or an energy level of 400 watt-seconds reached. Intravenous sodium methohexital or sodium thiamylal was used to induce light anesthesia, maintenance was achieved with nitrous oxide and, occasionally, supplemental doses of thiobarbiturates For maintenance, quinidine gluconate was given after reversion in the first 50 cases; a test dose was given before the procedure In the last 20, 0.33 Gm was given every 8 hours, beginning 3 days before cardioversion.

In 90 of 94 episodes, or 66 of 70 patients, sinus rhythm was restored. On follow-up for 1-9 months, 52 (79%) of 66 patients remained in sinus rhythm. The other 14 reverted to atrial fibrillation despite multiple cardioversions and maximally tolerated quinidine therapy. Factors that apparently influenced the chances of maintaining sinus rhythm were duration of fibrillation, type of valvular lesion, functional classification and previous quinidine failure.

From present and reported data, it appears that over 90% of all patients with atrial fibrillation or flutter can safely and effectively be reverted to regular sinus rhythm by this method. A previous history of quinidine failure is not a contraindication. The ability of quinidine to maintain regular sinus rhythm once it is established does not appear related to

(4) Am J Cardiol 14 94 100, July, 1964

its ability to revert the arrhythmia. Cardioversion is not indicated in the first several weeks after acute myocardial infarction unless there are other considerations. The authors have avoided it for 8 weeks after a known embolic episode. It does not appear contraindicated in fibrillation occurring during digitalis intoxication if the rapid rate is contributing to decompensation. Cardioversion may help in supraventricular tachycardia associated with acute myocardial infarction; when the ECG differentiation of supraventricular and ventricular tachycardia is difficult or impossible; or when, in the treatment of supraventricular tachycardia, the difficulty of determining if the patient is under- or overdigitalized arises. The incidence of embolization in the present series was 3%. Multiple attempts at maintaining sinus rhythm are not indicated if a patient has on two occasions reverted to atrial fibrillation in the early postconversion period.

Wolff-Parkinson-White Syndrome is considered by Koo-Young Chung, Thomas J. Walsh and Edward Massie (St. Louis), who reviewed 40 cases and found no difference in the incidence of regular supraventricular tachycardia (paroxysmal atrial tachycardia) between patients with group A ventricular pre-excitation and those with group B type. Atrial fibrillation or flutter was found only in group A patients. There was a significant difference in both groups between the duration of the initial portion of conduction delay in the ECG and that in the vectorcardiogram. The ECGs and vectorcardiograms of group A patients tended to show more marked initial conduction delay. The spatial QRSsE-TsE angle was much narrower (less than 60 degrees) in vectorcardiograms of group A patients than in those of group B patients. However, it could not be established that either a narrow or wide QRSsE-TsE angle has any clinical significance. There is much evidence to justify acceptance of the accessory-pathway theory as the mechanism of the Wolff-Parkinson-White syndrome and the associated arrhythmias. The treatment of choice for most patients with paroxysmal tachycardia is digitalis or quinidine, whereas those with atrial fibrillation and flutter usually require a combination of these medications. External countershock seems appropriate when the patient's condition appears to be deteriorating.

No evidence of organic heart disease was found in 26 pa-

tients (65%). Most of the others were over age 45 and showed evidence of arteriosclerotic heart disease and/or hypertensive cardiovascular disease. Ten patients had psychiatric disorders, mainly manic-depressive psychoses; a similar observation was made by Hejtmancik and associates in 1957. There was 1 case of ventricular and 1 of atrial parasystole, and the Wolff-Parkinson-White syndrome-atrial parasystole combination may be among the first such cases reported.

Paroxysmal Atrial Fibrillation in Wolff-Parkinson-White Syndrome Simulating Ventricular Tachycardia. Joseph H Yahini, Izhar Zahavi and Henry N. Neufeld[6] (Tel-Hashomer Government Hosp., Israel) report 5 proved cases and 1 suspected case of this syndrome.

Man, 35, was seen during an episode of rapid heart action, the second in 3 years. The previous one terminated spontaneously after 2 hours; the ECG was interpreted as indicating ventricular paroxysmal tachycardia. In the second attack, moist pallor, dyspnea, a heart rate of 200-300 beats per minute and a blood pressure of 90/60 mm Hg were noted Carotid sinus compression had no effect The ECG showed a heart rate varying between 170 and 300 per minute without discernible P waves. The QRS complexes were widened, with fluctuations in shape and gradual merging into complexes of normal configuration. The heart rate slowed somewhat after administration of procainamide, but the tracing remained practically unchanged Conversion to sinus rhythm followed injection of 1 mg. digoxin intravenously, and the ECG then showed the characteristic features of Wolff-Parkinson-White syndrome Examination after the attack showed a grade 1 ejection type systolic murmur at the apex The heart appeared normal on x-ray study

These cases lend support to the assumption of others that in young and otherwise healthy adults an irregular ventricular rate of 240 per minute or above with good general state during the attack is practically diagnostic of the Wolff-Parkinson-White syndrome. The ECG shows a grossly irregular ventricular rate, with wide QRS complexes merging gradually into complexes of normal configuration and no discernible P waves. This arrhythmia predominates in males. Thus, the possibility is raised that some cases described as ventricular paroxysmal tachycardia in young healthy adults may actually be Wolff-Parkinson-White syndrome. Rational therapy during the attacks should begin with oral or parenteral quinidine or procainamide. If this fails, digitalis may be added without concern.

(6) Am J Cardiol 14 248-254 August, 1964.

Atrial Tachysystole with Block. Stuart Warren Rosner[7] (USPHS) reports 2 patients who exhibited episodic atrial tachysystole with block.

CASE 1.—Woman, 49, had intermittent dyspnea, fatigue and swelling of ankles for 20 years. She was thought to have rheumatic heart disease with mitral stenosis and regurgitation and aortic stenosis. Digitalis had been given for many years. The first sound at the apex was accentuated, and blowing holosystolic and rumbling presystolic murmurs were present. An opening snap was heard, and a coarse ejection basal systolic murmur radiated into the neck. An electrocardiogram showed sinus bradycardia; first-degree heart block; a prominently negative terminal deflection of the P wave in leads II, III, aV_f and $V_{1,2}$, ST-segment depression; and inversion of the first portion of the T wave in leads I, aV_l and $V_{5,6}$. There was no evidence of thyroid dysfunction.

CASE 2.—Man, 59, complained of dyspnea and productive cough. He was given a diagnosis of pulmonary emphysema and bronchiectasis. He had been taking digitalis for many years. Examination showed persistent bibasilar inspiratory rales and scattered inspiratory and expiratory wheezes. The heart sounds were distant. Mild clubbing was noted. Bronchography showed bilateral lower-lobe cylindrical bronchiectasis. Pulmonary function studies showed moderate airway obstruction. An ECG showed normal sinus rhythm with ST-T wave changes consistent with digitalis effect. An I^{131} uptake was normal.

Application of atrial rate in the region of the arbitrary borderline is not a useful criterion in differentiating paroxysmal atrial tachycardia with block and atrial flutter. Determination of P-wave direction in leads II and III cannot be made in the presence of an undulating base line. The appearance of the base line may not warrant the decisive weight commonly given to it. Alternation of the P-P cycle length is inconstant in paroxysmal atrial tachycardia with block and is not an intrinsic property of the arrhythmia. The occurrence of ventricular premature contractions, response to carotid sinus pressure, and the AV ratio are nonspecific findings. The mode of termination of the arrhythmia may also lack specificity. Restoration of sinus rhythm after potassium administration will at times be coincidental.

The ECG does not provide a means for the clear-cut separation of atrial tachycardia from flutter in certain cases. The term atrial tachysystole with block is offered as a designation for such tracings.

(7) Circulation 29:614-621, April 1964

THE HEART: MISCELLANEOUS

► It is of some interest to compare the number of articles within the various subdivisions of cardiovascular disease with the distribution curve of a few years ago Then, a major fraction of the articles were concerned with congenital heart disease and with cardiovascular surgery because the introduction of cardiac catheterization led to such rapid progress in these areas

That fewer articles are devoted to these topics in the current YEAR BOOK does not signify any lack of significance of these fields, but only that the curve portraying the rate of advance in these areas while formerly exponential, has now become more nearly linear.

In the present YEAR BOOK, the largest numbers of articles are devoted to the topics of coronary disease and of arrhythmias Once again, the reason in the case of the latter is the introduction of new and better methods of treatment It is also being realized that the electrocardiogram has a far broader value than in the interpretation of arrhythmias and the recognition of coronary disease Indeed, it is now clear that the almost Olympian position in which the electrocardiogram was formerly placed in regard to the diagnosis of myocardial infarction was not justifiable The numerous errors, both negative and positive, that resulted from such deification of a valuable instrument, that can tell us much about the electrical function of the heart but can provide little precise information about the specific cause of an abnormality, have tended to diminish the usefulness of an inherently valuable tool The method should not be blamed for the sins of those who misuse it

The emphasis in terms of the number of articles on the field of coronary disease is a reflection both of the importance of the subject and of the large fraction of the total interest in cardiac research that is being devoted to this field

It seems certain that in the future, as in the past, the selection of articles for the YEAR BOOK will be markedly influenced by the rate of progress that is occurring in a given area as well as by the inherent importance of that area —Ed

Genetic View of Cardiovascular Disease: Lewis A. Conner Memorial Lecture. Victor A. McKusick[8] (Johns Hopkins Univ.) points out that cardiovascular malformation is an important feature of triplo-21 mongolism and the XO Turner syndrome and also of trisomies involving a chromosome of group 13-15 and either chromosome 17 or 18. Coarctation of the aorta is the commonest cardiovascular complication in the Turner syndrome. Hypertension without coarctation occurs in some patients. Angiomas of the bowel and lymphedema also occur. Females with the same facial features as those distinguishing the Turner syndrome (low-set ears and low hairline) have congenital heart malformations such as pulmonary stenosis, but with normal sexual development and function. Congenital heart disease, most often a defect

(8) Circulation 30 326-357, September, 1964

of the atrioventricular canal, is present in 35% or more of newborn mongoloid idiots. Ventricular septal defect and dextroposition of the heart occur with an extra chromosome in group D (13-15). Ventricular septal defect and large patent ductus arteriosus are the usual cardiac lesions, accompanied by an extra group E chromosome; whether this is 17 or 18 is debatable.

Among the single gene disorders, the aortic complications of the Marfan syndrome are well known. Vascular changes occur in pseudoxanthoma elasticum; the radial and ulnar arteries are occluded in some cases. Rupture of the great vessels, usually a large branch of the aorta, is a rare feature of the Ehlers-Danlos syndrome. In the Hurler syndrome, the coronary arteries are thickened, with heavy intimal deposits, and pseudoatherosclerosis occurs in the aorta and pulmonary artery. Aortic regurgitation is a feature of the Morquio-Ullrich syndrome, and this was also found in a patient with mucopolysaccharidosis V. In Duchenne's pseudohypertrophic muscular dystrophy, the myocardium has the same biochemical defect as skeletal muscle. Rhabdomyomas of the myocardium occur in neurofibromatosis and the Lindau-von Hippel syndrome. Over half of pulmonary arteriovenous fistulas occur as a feature of the Osler-Rendu-Weber syndrome. Some members of a family with Milroy's disease had hypoplasia of the lymphatic vessels. Peripheral vascular disease and calcific aortic stenosis occur often in the Werner syndrome. Examples of possible single mutants in which the effects appear limited to the heart are endocardial fibroelastosis, idiopathic familial myocardiopathy, muscular subaortic stenosis and supravalvular aortic stenosis.

The genetic component of common forms of cardiovascular disease seems to be polygenic. However, even if the polygenic basis of blood pressure is accepted, it is worthwhile to seek individual gene-determined differences important to blood pressure level. Some familial examples of coronary artery disease undoubtedly are coincidence; the question is whether anything further is involved. Demonstration of the role of the streptococcus in rheumatic fever did not destroy the plausibility that genetic factors are important in susceptibility, but it would not be considered likely that the genetics are simple mendelian. No simple genetic model will account for the features of congenital cardiac malformations. Pol-

ygenic inheritance, or a pathogenesis which is multifactorial in the broad sense, can simulate mendelian inheritance. Transmission through several generations and several collateral lines is more convincing evidence of single gene inheritance

Surgical Risk in Cardiac Patient. John F Skinner and Morton Lee Pearce[9] (Univ. of California, Los Angeles) reviewed all data on cardiac patients undergoing major operations (excluding cardiac) during 1953-59 who had a preoperative evaluation of cardiovascular status. Of the 857 operations reviewed, 766 were first operations. Electronic data processing was used to evaluate 25 parameters. The total mortality was about twice that of the general hospital population undergoing similar surgical procedures. The cardiac patient tolerated minor surgery, including inguinal herniorrhaphy and transurethral resection, well. In major surgery, including thoracotomies and laparotomies, the total mortality was 25%.

Factors that were found to be most sensitive for predicting mortality were the severity of the surgical procedure, functional capacity and type of heart disease. Mortality was 4% in class 1 patients (classification similar to that of the New York Heart Association), 11% in class 2, 25% in class 3 and 67% in class 4. Mortality increased in the following sequence: (1) rheumatic heart disease, (2) arteriosclerotic heart disease and/or hypertensive heart disease and (3) pulmonary heart disease.

Cardiovascular Manifestations of Systemic Lupus Erythematosus. Milton R. Hejtmancik, James C. Wright, Robert Quint and Frank L. Jennings[1] (Univ. of Texas, Galveston) reviewed 142 cases of systemic lupus erythematosus seen during 1945-62. Females constituted 86.6% of the series, and about one third of the patients were Negroes. Incidence was maximal in the 3d decade. Cardiac disease was found clinically in 58% of the patients. Clinical evidence of pericarditis was found in 17%. Myocardial disease was considered to be present in 33%, but it could have been secondary to hypertension in 10 patients and to coronary heart disease in 7. In 21% of the patients the cause was apparently direct involvement of the myocardium by lupus erythematosus. Endocarditis

(9) J Chron Dis 17:57-72, January, 1964
(1) Am Heart J 68:119-130, July, 1964

was found in 6%, hypertension in 22% and congestive failure in 7%, usually due to myocarditis. In 12 patients the presenting symptoms were dominantly cardiac, and only thorough search revealed the underlying disease. The ECGs were definitely abnormal in 43% of patients and suggestively abnormal in another 9%. Chest x-rays showed evidence of cardiac abnormality in 33% of patients and of pulmonary changes in 48%.

Cardiac lesions were found in all 16 autopsied patients and in the various cases was found to involve all structures of the heart. Libman-Sacks valvulitis was found in 8 patients, and in 2 of these a staphylococcic endocarditis was superimposed. The dominant cause of death in this series was cardiac, and 5 patients died of congestive heart failure. Other significant causes of death were renal involvement and infections to which steroid therapy was a predisposing factor.

Primary Myocardial Disease. Ole Storstein[2] (Univ. of Oslo) performed hemodynamic studies in 44 cases of primary myocardial disease. Most patients were aged 40-50 years. Dyspnea was the most prominent first symptom. Almost half the patients had congestive heart failure on admission to the hospital. Electrocardiograms revealed atrioventricular conduction disturbances in 3 patients and auricular fibrillation in 4. The most common x-ray finding was left ventricular enlargement.

There were 22 patients with idiopathic myocardial disease; these cases are either chronic myocarditis or myocardial fibrosis or hypertrophy of unknown cause. Four patients had progressive muscular dystrophy, 4 had scleroderma with myocardial involvement, and 3 had primary amyloidosis. Boeck's sarcoid was found in 1 case, muscular hypertrophy in 2, endocardial fibroelastosis in 4, beriberi in 1 and muscular subaortic stenosis in 3. Nine patients died during observation for up to 5 years. Only 1 patient had a history of excessive alcoholic intake, and embolic episodes were not noted.

The hemodynamic picture was partly dominated by reduction in cardiac output and partly by elevated filling pressure of the heart, most prominent on the left side. Equal elevation of pressure in both atria was found in constrictive pericarditis,

(8) Acta med. scandinav. 176: 731-743, December, 1964

whereas in constrictive myocarditis, the pressure was most elevated in the left atrium. Studies in cases of muscular subaortic stenosis showed a characteristic pressure curve and angiographic picture. In 2 of the 3 cases, there was stenosis on the right side of the septum.

Chronic Effusive Pericarditis. D. Evan Bedford[3] studied 7 patients. A massive chronic pericardial effusion may exist for years without cardiac tamponade or other classic signs of pericardial effusion and may be remarkably well tolerated. Often, it is discovered by chance at routine chest radiography and mistaken for an enlarged heart. Eventually, signs of heart failure or of mild tamponade may appear or, rarely, chronic tamponade with hepatomegaly and ascites simulating constrictive pericarditis. The main diagnostic clue is the discrepancy between the huge heart shadow and the relatively mild symptoms. The shadow is usually pyriform and the contour changes considerably with change in posture. The vascular pedicle is usually short and narrow, the normal arcs of the cardiac contour are ironed out and pulsation is diminished or absent. Selective angiocardiography confirms the diagnosis; only 10-20 ml. contrast medium is required. Once the diagnosis is established, diagnostic paracentesis should be performed, and the fluid removed should be replaced by 100-200 ml. air. The ECG may be normal or may show changes due to the underlying heart lesion. The most characteristic finding is low voltage of QRS and flattened T waves. In cases with sinus rhythm, bifid P waves are sometimes seen, and atrial fibrillation or flutter may eventually occur, as it did in 4 of the author's cases.

Chronic effusive pericarditis may complicate some recognized form of heart disease and may be associated with some recognized general disease, but usually no specific cause can be identified. In 3 of the author's cases the test for antinuclear antibodies was positive, suggesting that an autoimmune mechanism was responsible. The effusion almost always reaccumulates rapidly after paracentesis, and though it may sometimes subside slowly with prolonged diuretic therapy, the only effective treatment is surgery. This involves either pleuropericardial fenestration or a more radical pericardiectomy. Steroid therapy is often effective in treating pleuropericarditis of the postcardiotomy syndrome, in which an au-

(3) Brit Heart J 26 499-512, July, 1964

toimmune reaction has been postulated, and it seems reasonable to try it in cases of chronic effusive pericarditis, at least when immunologic tests are positive.

► [I suspect that I have, from time to time, missed the diagnosis of this condition However, I do have 1 patient now followed for more than 10 years in whom I have long considered this diagnosis to be the correct one, even though it has never been proved by pericardial tap. That particular patient is an elderly woman who has had a very large cardiac shadow for many years and has never had any symptoms of cardiac disability —Ed]

Clinical Course of Tuberculous Pericarditis with Effusion is described by A. Gonin, R. Froment, E. Lachieze-Rey, J. P. Delahaye and A. Perrin[1] (Univ. of Lyon), on the basis of observations in 100 patients, aged 13-73 years, seen during 10 years. The incidence was 0.6% among 15,000 patients hospitalized for cardiopathies on the same service. Among 900 autopsies, 1.1% were cases of tuberculous pericarditis. In the last 4 years of the decade, autopsies revealing tuberculous pericarditis were extremely rare, owing to the effects of modern therapy. Among 190 patients with pericarditis alone (i.e., with no accompanying or later endomyocardial lesion), 52% had tuberculous lesions. This proportion is higher than that reported by other authors (15-38%).

Absolutely certain criteria for diagnosis of tuberculous pericarditis are obtained by bacteriologic or pathologic examination In 6 cases (of 16 punctures), tubercle bacilli were demonstrated by culture or inoculation. The 10 sterile cultures, however, were from patients with definite tuberculous pericarditis, confirming that a negative bacteriologic examination does not justify exclusion of tuberculous etiology The 6 patients with positive bacteriologic findings had grave forms of the disease; 4 later had pathologic examinations either after death or during operation. In 27 cases, histologic examination provided proof of the diagnosis (10 autopsies; 17 specimens removed during pericardiectomies to relieve constriction). Thus the diagnosis was absolutely certain in 33% of the cases

Relatively certain criteria based on clinical findings include a very positive or phlyctenular skin reaction (5 cases) and association of major extrapericardial tuberculous lesions, more or less progressive (miliary pulmonary tracheobronchial adenopathies 5%, tuberculous meningitis 3%, Addison's disease 1%, renal tuberculosis 1%, cutaneous tuberculids 1%, erythema nodosum 1%, cold abscess 1%, keratoconjunctivitis

[1] Mal. cardiovas. 5:493-498, 1964

1%, peritonitis 2%, etc.), alone or in combination. These almost certain criteria were present in 52 cases.

Twelve patients had a markedly positive skin reaction and a history of tuberculosis or of old sequelae of extrapericardial tuberculosis (7 cases). In the last 3 cases, the tuberculous etiology might be questioned, but the diagnosis was made on the basis of a prolonged course (over 3 months) unusual with other causes (neoformations and disseminated lupus erythematosus excepted) and ultimate cure with antibiotic and corticoid treatment of long duration.

In this series, 60% of the patients were males; this accords with findings of other authors. There are two peak periods of incidence, one near the 3d decade with masculine predominance, the other after age 50 with feminine predominance. Pericarditis is not rare at an advanced age; 14 patients were over 60. North Africans constituted 13% of this series; the proportion of all Negroes hospitalized was much lower.

To the traditional chronologic classification of primo-secondary and late reinfection, the authors added examples of tertiary pericarditis and a new type, a complication of pneumonectomy for tuberculosis. Primo-secondary pericarditides (55 cases) supervene in the adolescent or young adult before age 30; 22 of these were contemporaneous with the primary infection and in 12 instances were associated with other manifestations. The other 33 cases developed several months to several years after the primary infection. In this type, there are often more or less latent visceral lesions and polyserositis. Late reinfections (36 cases) generally affect older patients (average 57 years). Otherwise, they are indistinguishable from the preceding group either clinically or prognostically. Tertiary pericarditis, supervening during progressive pulmonary tuberculosis, was seen in 5 cases, and there were 4 cases of pericarditis complicating pulmonary resections.

The classic idea is that tuberculous pericarditis is only exceptionally primary and that it is almost always accompanied by mediastinal adenopathies (which were never lacking in the authors' autopsies). Although direct extension because of contiguity may be responsible, the hematogenous route remains the most probable mode of infection. The prognosis depends in part on degree of mediastinal involvement, which is often latent. Cases with a serious symphysial evolu-

tion usually will correlate with large mediastinal adenopathies, in contrast to those in which the allergic element is dominant or lymphatic involvement is reduced.

Anticoagulant-Induced Hemopericardium with Tamponade: Its Occurrence in Absence of Myocardial Infarction or Pericarditis is reported in 2 cases by Stanley C. Fell, Ira L. Rubin, Charles D. Enselberg and Elliott S. Hurwitt[5] (Montefiore Hosp., New York). One patient died, and the other survived after pericardiectomy.

Man, 40, was admitted with chest pain, nausea and vomiting of several hours' duration He had noted weakness and anorexia 3 weeks previously, and 2 days before admission, he was seen because of left-sided chest pain and dyspnea. Rheumatic heart disease had been present over 10 years. Right-sided hemiparesis developed several weeks after he was first digitalized, about 3 years before admission, and anticoagulant therapy was begun A mitral commissurotomy was performed the following year. A few months later, the patient was converted from atrial fibrillation with quinidine and then maintained on digitalis and warfarin sodium.

On admission, the patient was cyanotic and in shock. The heart was enlarged and an opening snap noted at the apex. The liver was felt 3 fingerbreadths below the right costal margin. An ECG showed a marked right-axis shift, with sharp inversion of T waves and sinus tachycardia The white cell count was 21,200/cu mm , and the urine contained 2+ protein The serum glutamic oxalacetic transaminase was 2,000 units The prothrombin time was 94 seconds, with a control of 12 8 seconds Fluids, metaraminol and oxygen were given, but urine output ceased and the patient died despite treatment with levarterenol and lanatoside C

Autopsy showed 400 ml of blood within the pericardium, with fresh and organizing adhesive pericarditis Microscopic study showed generalized myocardial hypertrophy, with numerous Aschoff bodies Rheumatic mitral valvulitis was present, and the coronary arteries were not remarkable

It appears that this patient was seen in the terminal phase of pericardial tamponade; the hemopericardium must have developed fairly rapidly. The other patient, a man aged 47, was given anticoagulant therapy because of a history strongly suggestive of acute myocardial infarction, despite a lack of supporting evidence. Bleeding occurred in the presence of a prothrombin time within the usual therapeutic range. Hemopericardium apparently developed slowly. No gross evidence of previous myocardial infarction was found at pericardiectomy.

The onset of circulatory collapse in a formerly stable patient given anticoagulants should suggest hemopericardium

(3) New England J. Med. 272:670-674, Apr. 1, 1965

despite the absence of the classic clinical signs of pericardial tamponade. Pericardiocentesis is the most reliable diagnostic procedure and usually affords adequate therapy as well.

► [Two years ago a physician was seen with what had been previously thought to have been intractable heart failure The cardiac shadow was enormous In this instance, the heart failure and the enlargement of the shadow were due to massive hemopericardium consequent to anticoagulant therapy which had been instituted following an infarction

Other complications of anticoagulant therapy include massive adrenal hemorrhage with a picture resembling that of the Waterhouse-Friderichsen syndrome, and likewise profuse retroperitoneal hemorrhage. Either of these conditions may start with severe pain in the back and may be practically impossible to diagnose until the characteristic manifestations are clear In the case of the adrenal hemorrhage, these are the signs of acute adrenal insufficiency with circulatory collapse In the case of the retroperitoneal hemorrhage, there may be back pain followed by hemorrhagic shock and the eventual appearance of a huge mass in either flank The mass, of course, is a hematoma —Ed]

Straight Back Syndrome. K. K. Datey, M. M. Deshmukh, S D. Engineer and C. P. Dalvi[6] (K.E.M. Hosp., Bombay, India) report 6 cases.

Man, 40, was referred because of a thrill and murmur in the pulmonary area There was a history of pulmonary tuberculosis about 10 years previously for which adequate treatment had been given. Examination revealed an asthenic man with a systolic thrill and a harsh grade 4 ejection systolic murmur in the pulmonary area The pulmonary 2d sound was closely split and widened on inspiration The ECG was normal. The posteroanterior chest x-ray showed healed bilateral apical tuberculosis and a prominent pulmonary artery. The cardiothoracic ratio was normal. The dorsal spine was straight in the lateral view, and the anteroposterior diameter of the chest was reduced Catheterization showed normal cardiovascular hemodynamics The pulmonary arterial pressure was 25/10 mm. Hg, and there was no evidence of a shunt or a gradient across the pulmonary valve

In this condition, the upper dorsal spine is straight and there is a loss of the normal kyphotic curve. The distance between the sternum and vertebral column is reduced, resulting in compression of the heart and kinking of the great vessels. The distortion seems to be maximal in the region of the cardiac waist. The right ventricular outflow tract is probably more affected. Distortion of the outflow tract and kinking of the great vessels lead, during cardiac systole, to eddies which convert a laminar blood flow into a turbulent one and produce murmurs generally located in the pulmonic area. The murmur usually diminishes in intensity on sitting up and diminishes further on inspiration. The ECG is normal. The lateral chest x-ray shows loss of the normal spinal

(6) Brit Heart J 26:614-619, September, 1964

curve. The cardiothoracic ratio is within normal limits if the widest thoracic diameter is considered. The widest anteroposterior distance between the spine and sternum was measured, as well as the widest transverse diameter in the posteroanterior view, and the ratio was compared with that of 25 normal adults of comparable age. The ratio was significantly higher in the patients with the straight back syndrome a ratio of 3 or more is almost diagnostic in the absence of other thoracic deformities This is probably a benign condition

Further Observations on Effect of Diuretics on Stasis Edema of Leg. Knut Haeger[7] (Allmanna Hosp., Malmo, Sweden) studied 728 patients with stasis or lymphatic edema of all proportions The mean age was 49.9 Hydroflumethiazide was given to 84, chlorthalidone to 562 and polythiazide to 82. The average state of venous or lymphatic disease was compatible and the ratio of leg ulcers similar in the three treatment groups.

Study of body weight ankle and calf circumference showed that all three drugs had a remarkable effect on reducing the size of the edematous leg and decreasing body weight. Chlorthalidone and polythiazide were similarly effective in the doses used (100 and 2 mg every 2d day, respectively), whereas hydroflumethiazide (25 mg daily) exerted a less pronounced effect. Hydroflumethiazide caused practically no side effects, whereas chlorthalidone caused undesirable reactions in 8% of the patients and polythiazide in 6.2%.

In two groups of patients, an earlier empiric impression of the beneficial effect of diuretics in leg ulcer treatment was confirmed. The healing quotients of one group on standard ulcer therapy of the clinic including diuretics, and of another group on the same therapy with diuretics excluded, were significantly different, favoring the diuretic group. It is concluded that diuretics are beneficial in states of venous stasis edema, with or without leg ulcers.

Diagnosis of Massive Pulmonary Embolism in Man by Radioisotope Scanning. Henry N. Wagner, Jr., David C. Sabiston, Jr., John C. McAfee, Donald Tow and Howard S. Stern[8] (Johns Hopkins Univ.) found radioisotope scanning of

(7) Angiology 15:417-433, September, 1964
(8) New England J. Med. 271:377-394, Aug. 20, 1964

the lungs in 100 patients and 90 dogs after intravenous injection of macroaggregated albumin labeled with I^{131} or Cr^{51} to be a safe, effective means of diagnosing massive pulmonary embolism. Many patients showed a characteristic pattern of avascularity, with decreased pulmonary blood flow to all or part of the right lower and crescent-shaped filling defects on the lateral borders of the lungs To date, no hemodynamic, immunologic or radiation hazard has been observed

The method is an important adjunct to selective pulmonary arteriography, and has distinct advantages in being readily available, fast, technically easy and free from morbidity. It was used as a rapid screening procedure and made possible serial studies at frequent intervals in the same patients. The scanning technic was particularly suitable for evaluating the natural history of massive pulmonary embolism and for determining the effectiveness of surgical procedures, such as vena cava ligation, or of drugs, such as anticoagulants and fibrinolytic agents.

Treatment with urokinase was evaluated in dogs in which thrombosis was produced by leaving a latex balloon containing radiopaque material in place for 48 hours. None of 8 untreated dogs had restoration of pulmonary blood flow within 24 hours; the average time required for spontaneous restoration of flow was over 22 days Of 12 dogs given 2,000-6,000 units of urokinase per kg. body weight just after removal of the balloon, 7 had complete restoration of blood flow within 24 hours, and no thrombosis was found in these dogs at autopsy. Autopsy of the control dogs showed thrombi, fibrosis and atrophy of the involved arteries. Urokinase in the dosage used apparently had a significant thrombolytic effect. The scanning technic permitted evaluation of the pulmonary circulation without sacrifice of the dogs until such time as was indicated by the functional data provided by the scans

Safe Exposure of Men to Severe Heat. C. R. Bell, R. F. Hellon, R. W. Hiorns, P. B Nicol and K A Provins[9] (London) exposed 8 men to hot environments The subjects remained in the heat until they showed signs of distress just before collapsing. Exposure lasted for from 10-15 minutes to 4 hours. The men, aged 19-24, had a mean weight of about 165 lb. and had not been exposed to tropical conditions for at least a

(9) J Appl Physiol 20 288-292, March 1965

year Two groups of 4 subjects each were studied for 2 consecutive weeks Each subject underwent 2 exposures daily for 6 days a week in a climatic chamber where six climates were presented in order of increasing severity

The time taken to reach a state of distress before collapse was found to be hyperbolically related to the severity of the environment when this was expressed as a weighted sum of wet and dry-bulb temperatures Separate hyperbolas were found for standing and working subjects Oral temperature and pulse rate tended to increase with the severity of the climate, as did the rate of sweating Acclimatization was not an important factor in determining tolerance time After the deduction of a suitable safety margin, the resulting curves and their equations made possible the prediction of safe exposure times for severe heat

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PATHOPHYSIOLOGY, DIURETICS AND SHOCK

Stimulus to Hypertrophy of Myocardium is discussed by Henry S. Badeer (American Univ. of Beirut) It has been suggested that in certain conditions, poor nutrition of the myocardium may constitute the stimulus to hypertrophy however, in these disturbances other parameters of cardiac function change concurrently. Clinically, hyperthyroidism does not induce striking increases in heart weight The cardiac findings in adrenal cortical disturbances are believed to be secondary to alterations in the load of the heart rather than a direct effect of corticoids on cardiac muscle mass. One of the most popular notions is that hypertrophy of a given chamber is due to an increase in its external mechanical work. That hypertrophy is a common feature of conditions that increase either the pressure or outflow from one or more heart chambers supports this concept. Repeated muscular activity in healthy persons or animals increases minute output and luminal pressure of the left ventricle, leading presumably to physiologic hypertrophy of the heart. Often the degree of hypertrophy found is not proportional to the calculated external mechanical work of the cardiac cham-

ber. Correlation would be better if stroke work rather than minute work were considered.

It is hypothesized that any condition that increases the metabolic rate of a heart chamber per beat and is maintained long enough may lead to hypertrophy of the chamber wall. Initially one would expect an increase in stroke oxygen uptake per unit mass of heart tissue. As hypertrophy develops, the total mass is increased, and oxygen consumption per beat per unit mass gradually returns to the control value. The stimulus to hypertrophy then ceases. Oxygen consumption per beat is then greater than normal simply because of the increased muscle mass. Hypertrophy would develop more readily in conditions that increase the pressure in a chamber during systole than in those that increase merely the volume of blood ejected. When there is an increase in outflow and cavity pressure remains unchanged, there is little hypertrophy. How an increase in metabolic rate per stroke may bring about structural changes in heart muscle fibers is unknown.

► [I agree in the main with the opinions herein expressed. However, I believe, for reasons that are too detailed to be cited here, that the fundamental stimulus to myocardial hypertrophy is increased tension in the heart muscle.—Ed.]

Some Hemodynamic Aspects of Cardiac Arrhythmias in Man: Clinicophysiologic Correlation. M. Irené Ferrer and Réjane M. Harvey[2] (Columbia Univ.) note that with respect to intermittent arrhythmias, sinus arrhythmia can produce false pulsus alternans, as can atrial premature contractions. True alternans can be initiated in the diseased heart by a single atrial premature contraction. Some variation in atrial pressure follows an atrial contraction that is quite premature, and this may be felt by the patient.

The effect of regurgitation in diminishing stroke output may clarify some of the unexplained variations in arterial pulse pressure with ventricular premature contractions; i.e., beats with tricuspid insufficiency have smaller curves than beats without it. The volume lost in regurgitation may not instantly return to the atria and, if sequestered in other organs, may result in a temporary fall in cardiac output. A central A-V nodal premature contraction is associated with a large pulse wave in the atria when the P wave and atrial systole do not precede but occur simultaneously with the QRS and ventricular systole, respectively. Ventricular asynchronism occurs when a coupled ventricular premature

(2) Am. Heart J. 66:153-163, August, 1964.

contraction produces too small a contraction to open the aortic valve, but the right ventricular contraction and stroke output suffice to open the pulmonic valve This can account for some symptoms reported by patients with ventricular premature contractions and coupling Bouts of paroxysmal ventricular tachycardia can produce symptoms in the central nervous system and splanchnic bed

Two patients with the Wolff-Parkinson White syndrome and episodes of A-V nodal tachycardia showed marked changes in right atrial and superior vena caval pressures and a lesser change in subclavian venous pressure The rise in right atrial pressure is probably due to regurgitation of blood through the tricuspid valve during ventricular-isometric contraction and early ejection, and atrial systolic contraction after the retrograde P wave. Regurgitation occurs because of the absence of a normal atrial systole before ventricular contraction The high peak of atrial pressure probably favors unimpeded retrograde flow into the intrathoracic venous system as far as the first peripheral venous valves Tricuspid regurgitation also occurs in almost every beat during an instance of A V dissociation with interference and His bundle rhythm

In atrial flutter, each electric flutter wave elicits a mechanical atrial systole regardless of the speed of the atrial rhythm, whereas in atrial fibrillation, individual discrete atrial systoles are not seen Tricuspid insufficiency almost invariably occurs in atrial fibrillation, but rarely if ever occurs in atrial flutter When in the course of fibrillation the atrial rate slows and is less than the threshold required to initiate disordered atrial myofibrillar contractions and atrial mechanical paralysis, it is possible for the atrial chambers to respond with discrete mechanical systoles. If pressure or indicator-dilution curves obtained during heart catheterization were to be used as the only criteria to determine the presence of mitral or tricuspid valve insufficiency in a patient being considered for cardiac surgery, errors might result if atrial fibrillation were present. The regurgitant blood may even cause confusion in the interpretation of angiocardiograms by producing a pseudofilling defect with each ventricular systole. Atrial flutter seldom if ever is associated with emboli, whereas these may be fairly common complications with fibrillation. The constant and effective emptying

of the atria in flutter would lessen sludging and clot formation, whereas atrial paralysis plus tricuspid and mitral regurgitation with overdistention of these atrial chambers in fibrillation would favor clotting. In both rhythms the resting level of cardiac output is decreased.

Studies of Starling's Law of Heart: IX. Effects of Impeding Venous Return on Performance of Normal and Failing Human Left Ventricle were investigated by John Ross, Jr., and Eugene Braunwald[3] (Nat'l Inst. of Health). Patterson, Piper and Starling observed that when venous return was augmented in the canine heart-lung preparation, cardiac performance initially increased, but when it was elevated beyond a critical level the performance declined progressively. In general, similar studies on the human heart have indicated that in patients without congestive heart failure, impeding the venous return results in a fall in cardiac output, whereas in those with congestive heart failure small increases in output sometimes occur. In some studies, the relationships between the changes in right heart filling pressure and cardiac output were inconsistent. It appeared that a more direct approach to the problem could be achieved by relating end-diastolic left ventricular pressure to the mechanical activity of this chamber during changes in venous return.

Venous return was impeded by progressively inflating a balloon in the inferior vena cava while left ventricular end-diastolic pressure, output and work were measured in 14 patients, aged 15-51, in the postabsorptive state. Of the 14 patients, 5 had left ventricular disease (1 with relieved and 1 with unrelieved pulmonic stenosis, 2 with systolic arterial hypertension and elevated cardiac indexes, and 1 with a functional cardiac murmur and no organic heart disease), and 9 had left ventricular dysfunction (8 with cardiomyopathy and 1 with arteriosclerotic cardiovascular disease). Four of the latter were in functional class 2 (New York Heart Association Classification), 2 in class 3 and 3 in class 4.

In the 5 patients without clinical or hemodynamic evidence of impaired left ventricular function, the left ventricular end-diastolic pressure fell and the decrease was accompanied by reductions in cardiac index, left ventricular stroke volume and left ventricular stroke work. In the 9 pa-

(3) Circulation 30 719-727, November, 1964

tients with impaired left ventricular function, directionally similar responses were noted, although the left ventricular function curves relating left ventricular end diastolic pressure to left ventricular stroke work were generally flatter and lower than those in the patients without left ventricular disease. In none of the patients did a significant increase in cardiac index, stroke volume or left ventricular stroke work occur during inflation of the balloon.

The Starling relationship appears to operate in a directionally similar manner in both the normal and depressed human left ventricle, and the left ventricles of patients with impaired function are not on a descending limb of the curve. However, a descending limb of the left ventricular Starling curve may become apparent when an added work load is imposed on the diseased ventricle.

► [This study is of fundamental importance. One has to regard the failing heart as being "on" a Starling curve which is placed on a lower level rather than as being "on" the descending limb of the normal Starling curve. If this be correct and the investigations cited here suggest strongly that it is correct then it follows that clinical improvement may result either from measures that tend to increase myocardial performance and thereby raise the level of the curve with an increase in output (digitalis being the classic example) or from measures that decrease the load on the heart (such as diuretics) and thereby may even reduce the output still further. There is little correlation between the clinical state of a patient and the cardiac output, except when the output becomes so low as to produce marked fatigue and lassitude or even a shocklike state.—Ed.]

Dynamic Obstruction of Left Ventricle: Its Production and Abolition by Drugs in Normal Animals was investigated by A. H. De Bono, E. Proctor and Russell Brock.[4] The femoral vessels, aortic arch and left ventricle were cannulated in 20 normal adult mongrel dogs. Pressure changes were noted before and after injections of various drugs.

In 10 dogs, a consistent gradient at the left ventricular outflow tract could be induced with various drugs; these animals were considered reactors. The gradient was indistinguishable from that seen in pressure records in known cases of "functional subaortic stenosis" in man. Depth of anesthesia, atropine, chlorpromazine and wide opening of the pericardium did not affect production of the gradient significantly.

A dose of 2.5 μg. isoprenaline was almost always sufficient to induce a significant gradient of about 100 mm. Hg. with a rise in pressure in the main cavity of the left ventricle to about 200 mm. Hg. A persistent gradient could be main-

[4] Guy's Hosp. Rep. 114: 4-14, 1965.

tained on infusion of about 2.5 μg. per minute In 2 of 3 reactors, 25 μg. norepinephrine induced a gradient of about 100 mm. Hg; in the third, the effect was equivocal. A dose of 10 μg. epinephrine produced a marked intraventricular gradient in all reactors. Intravenous injection of 2 ml. of 10% calcium chloride produced a gradient of about 150 mm. Hg Unlike the catecholamines and calcium chloride, aminophylline produced a gradient lasting up to 1 hour in reactors

Pronethalol, 5 mg., completely abolished the gradient induced by isoprenaline and that produced by epinephrine. The gradient produced by norepinephrine was almost wholly blocked, but those produced by calcium chloride and aminophylline were unaffected. The average pressure gradient from 5 μg. isoprenaline was reduced by prior administration of 4 mg methoxamine from about 100 to 40 mm Hg.

The results are consistent with the view that decreased venous return and increased myocardial contractility can elicit pressure gradients in "latent hypertrophic subaortic stenosis." Combination of three factors, or each factor alone, can produce pressure records identical with those showing left ventricular outflow obstruction; these are ventricular muscle hypertrophy, decreased ventricular filling and increased myocardial contractility.

Changes in Blood Viscosity, Hematocrit Value and Fibrinogen Concentration in Subjects with Congestive Heart Failure. Seymour Eisenberg[5] (Southwestern Med. School), with the technical assistance of Margie Horn and Nola Nelson, measured blood viscosity in 30 patients with congestive heart failure. Treatment included digitalis, salt restriction and bed rest; diuretics were given as necessary, and one phlebotomy was performed. Patients with anemia, cor pulmonale, severe renal disease and thyrotoxicosis were excluded from the study. Measurements were made with the patient recumbent, using a modified Brookfield cone plate viscosimeter.

Restoration of compensation in the 30 patients was associated with a 41.7% increase in blood viscosity. This change was correlated with a significant rise in hematocrit (47.3-53.3%) and fibrinogen concentration (400-525 mg./100 ml.). The erythrocytosis and hyperfibrinogenemia associated with relief of the congestive state may be ascribed to the dispro-

(5) Circulation 30 686-693, November, 1964

portionate decline in plasma volume in relation to red blood cell mass which occurs with diuresis Thus, pre- and post-treatment total circulating fibrinogen was unchanged despite a rise in concentration in the 5 patients on whom these measurements were made

▶ [The implications of this study are obvious Rapid diuresis is dangerous and probably increases markedly the likelihood of thromboembolic disorders When the physician considers rapid diuresis to be imperative, anticoagulant drugs should probably also be used Perhaps the safest course is slow diuresis with or without anticoagulants according to the other indications for them —Ed]

Effects of Dopamine in Man: Augmentation of Sodium Excretion, Glomerular Filtration Rate and Renal Plasma Flow. Robert H McDonald, Jr , Leon I Goldberg, John L McNay and Elbert P Tuttle, Jr (Emory Univ.) administered dopamine intravenously as a dilute solution in 5% dextrose in water to 9 normal men Mean age was 34 The dose was the largest that could be given without increasing mean arterial blood pressure Glomerular filtration rate, effective renal plasma flow, sodium excretion and osmolar clearance increased in each subject and significantly in the group as a whole. Changes in potassium excretion and urine flow were variable. Free water clearance decreased in all but 2 subjects Changes in filtered load of sodium were proportional to changes in glomerular filtration rate The cardiac index increased an average of 1.44 L per minute in the 5 subjects studied Pulse pressure increased in all 9 men, but mean blood pressure did not change significantly The peripheral resistance index decreased in each subject The renal fraction of the cardiac index did not change significantly Six patients with congestive heart failure showed increases in mean glomerular filtration rate, effective renal plasma flow, sodium and potassium excretion and osmolar clearance on dopamine infusion, but only the rise in sodium excretion was significant. Period-to-period variations were considerably larger than in normal subjects. Changes in mean blood pressure or heart rate were not significant, and pulse pressure was not significently increased. Two patients subject to exertional angina had typical angina pectoris on infusion of dopamine, and another had increased ventricular premature contractions.

Findings show that the renal effects of dopamine are different from those reported for other sympathomimetic amines. The reduction of renal resistance in man caused by

dopamine suggests that this substance may have a physiologic role in the regulation of renal blood flow.

► [A study of this importance merits confirmation. Should observations by a variety of investigators on a large number of patients support these findings, a major step forward in the management of congestive failure will have been made - Ed.]

Site and Mechanism of Action of the Diuretic Triamterene was investigated by W. I. Baba, G. R. Tudhope and G. M. Wilson[7] (Univ. of Sheffield). The drug was administered by intragastric tube to male albino Wistar rats after overnight starvation. Water diuresis was induced in some animals. Sodium transport and sodium flux were measured using frog skin.

Autoradiographic studies showed localization of triamterene in the distal tubules 3 hours after administration. Labeled triamterene was found unchanged in the kidney and urine by chromatographic study. Triamterene caused a definite rise in excretion of sodium, chloride and bicarbonate; potassium excretion was depressed. The doses used were proportionate to those commonly used in clinical practice. During water diuresis, triamterene produced increased sodium and decreased potassium excretion, with negligible effects on urine osmolality and free water clearance. The carbonic anhydrase-inhibiting activity of the drug 3 hours after administration was negligible. This was also true when it was added directly to kidney homogenates of untreated rats.

In studies with frog skin, measurement of electric changes showed decrease in both potential differences across skin and short circuit current when triamterene was added to fluid bathing the external surface. Sodium influx and efflux were both decreased by triamterene. Resistance to flow of sodium ions was increased; the effect on the electromotive force was variable.

The results suggest that triamterene inhibits sodium transport in tubular cells. In the distal nephron, where the drug is concentrated, this action interferes with the mechanism for exchange of sodium with potassium and hydrogen ions, accounting for changes produced in electrolyte excretion.

Clinical Trial of the Diuretic Triamterene in 27 subjects is reported by E. Bourke, T. B. Counihan, I. Farrell, P. Keelan

(7) Clin Sc 27 181 193, October 1964

and M. Ryan[8] (Univ. of Dublin). Acute studies were performed in 3 normal subjects, and continued administration was evaluated in 19 edematous patients and 5 nonedematous patients. Intake of salt and water was not restricted, and potassium supplements were not given.

After a single oral dose of 200 mg. triamterene, excretion of urine rose in the 1st hour and reached a plateau in 3-4 hours. Sodium excretion showed a similar pattern. Excretion of bicarbonate and chloride increased considerably; urinary chloride rose early and the rise was sustained. Excretion of potassium decreased. The pH of the urine rose.

Triamterene alone, 100 mg. twice daily for 7 days, was given to 9 patients, 6 of whom had cardiac failure Moderate diuresis occurred in 2 edematous patients, with natriuresis and chloruresis. Urinary potassium remained low during most of the trial.

In a patient with cardiac failure given triamterene and chlorothiazide, marked kaliuresis did not occur, and the potassium-conserving effect of triamterene was maintained for the 16 days of the trial. In 6 patients with mild cardiac failure, the diuresis and natriuresis occurring with triamterene alone were considerably less than that with chlorothiazide added The combination produced greater diuresis than did either drug alone These effects were more obvious in 4 patients with severe failure Two patients with severe failure received triamterene with spironolactone and/or chlorothiazide for 30 days. The combination with spironolactone produced greater diuresis than did the combination of spironolactone with chlorothiazide, and even greater diuresis resulted from triamterene and chlorothiazide, the greatest diuresis followed use of the three drugs together.

A sharp terminal rise in plasma potassium occurred in 5 patients with cardiac failure on triamterene alone. Plasma sodium, measured in 19 edematous patients, did not change appreciably. The blood urea rose in 12 of the 19 patients with cardiac failure, in 4 on the order of 30 mg/100 ml. The glomerular filtration rate fell in 1 of 2 patients studied. Some patients reported nausea, generally not severe.

Triamterene is thought to act directly on the nephron and

not as an aldosterone antagonist. The site of action is presumably the distal tubule, where the drug depresses sodium reabsorption and potassium exchange for sodium. It may have some carbonic anhydrase-inhibiting effect. The main use of the drug is to potentiate action of other diuretics and conserve potassium. It has been found useful as an adjuvant to chlorothiazide or related diuretics in treating severe cardiac failure, especially in cases resistant to other diuretics.

Renotropic Characteristics of Ethacrynic Acid: Phenoxyacetic Saluretic-Diuretic Agent. Karl H. Beyer, John E. Baer, Joan K. Michaelson and Horace F. Russo[9] (West Point, Pa.) studied the effects of ethacrynic acid in trained, unanesthetized, fasted female dogs. This agent contains an α,β-unsaturated ketone structure that combines readily with sulfhydryl groups.

Characteristics of the drug include excellent oral absorption and extremely rapid onset of action when given orally or intravenously. Its dose-response curve has a somewhat greater threshold, a steeper slope and a maximum ceiling in terms of salt or water output per unit time that is several-fold the response to hydrochlorothiazide. Its duration of action is short. It can produce a more substantial reduction in plasma volume and electrolytes than can the thiazides, but differs qualitatively from them in this respect only by a rise in chloride rather than bicarbonate excretion under conditions of sodium bicarbonate-induced alkalosis in the dog. The maximum saluretic-diuretic response to ethacrynic acid is at least as great as that to an organomercurial under conditions of acidosis optimal for the mercurial; the maximum effect is not influenced by acid-base balance or urinary pH.

Ethacrynic acid does not seem to inhibit exchange of sodium for potassium across the distal part of the nephron. Characteristically, it causes the osmolar concentration of urine to approach that of plasma water by increasing incommensurately salt or water output. The sites of action of the drug on sodium transport are interpreted to be the ascending limb of the loop of Henle and both the proximal and distal parts of the nephron. Besides glomerular filtration of the small portion of unbound drug, it is secreted by the probenecid-sensitive proximal secretory mechanism and is reabsorbed

(9) J. Pharmacol. & Exper. Therap. 147: 1-22, January 1965.

more distally. It is eliminated in bile and urine as such and as metabolites including the cysteine adduct

Ethacrynic acid can be given safely either orally or intravenously. Its toxicity is essentially related to its effect on electrolyte excretion. Single large doses can induce in the dog hyponatremic alkalosis with hypokalemia and hypochloremia with dehydration and hemoconcentration. No overt pharmacodynamic effects on organs or functions other than the kidney were observed.

Studies on Ethacrynic Acid in Patients with Refractory Edema. John F. Maher and George E. Schreiner[1] (Georgetown Univ.) performed 137 studies on 38 patients who received 0.5-16 mg. ethacrynic acid per kg. orally every 6 hours. The 38 patients included 9 with nephrotic syndrome, 19 with severe renal failure, 2 with renal ischemia, 2 with idiopathic edema, 3 with heart failure and 3 with hepatic cirrhosis. Urine volume rose to as high as 15% of the estimated glomerular filtration rate, associated with marked natriuresis that exceeded 400 mEq. per 24 hours in some instances. There was a similar increase in chloride excretion, whereas potassium and bicarbonate excretion were less increased. Osmolal and free water clearances increased, and uric acid clearance was reduced. In maximally hydrated normal subjects, free water clearance is reduced.

Results indicated that ethacrynic acid causes blockade of sodium reabsorption proximally and also in the loop of Henle. It appears to be an effective saluretic even under adverse physiologic circumstances. In general, the saluretic response is proportional to the glomerular filtration rate. At high doses the drug is surprisingly effective, even at filtration rates below 20 L. per 24 hours. The drug has been beneficial to patients with the nephrotic syndrome, hepatic cirrhosis, refractory congestive heart failure and idiopathic edema. Notable side effects may occur with high doses, especially in patients with reduced renal function.

Ethacrynic Acid: Effectiveness and Mode of Diuretic Action in Man was investigated by Paul J. Cannon, Henry O. Heinemann, William B. Stason and John H. Laragh[2] (Columbia-Presbyterian Med. Center); in 82 subjects, many of whom had edema that was refractory to treatment with other

(1) Ann. Int. Med. 62: 15-29, January, 1965
(2) Circulation 31: 5-18, January, 1965

diuretic agents. There were 15 normal subjects and 67 patients. The drug was remarkably potent when given intravenously in a dose of 0.5-1 mg./kg. or orally in doses up to 50 mg. 4 times daily. It was especially effective in patients with refractory edema and in those in whom edematous states were accompanied by azotemia or electrolyte disturbances. When the drug was given with other diuretics, its natriuretic effects were additive, and potentiation appeared to occur when it was combined with a carbonic-anhydrase inhibitor. Renal clearance studies showed that it had little effect on glomerular filtration or renal plasma flow, its major action being the blockage of sodium and chloride reabsorption, probably in both proximal and distal parts of the tubules. Ion-exchange mechanisms seemed little affected by the drug, since it characteristically increased both hydrogen and potassium ion excretion. In general, the degree of induced potassium loss correlated well with the rate of endogenous aldosterone secretion. Ethacrynic acid did not cause potassium loss in 1 adrenalectomized subject or in another subject pretreated with an aldosterone antagonist.

Diuresis induced by ethacrynic acid was often accompanied by development of systemic metabolic alkalosis. Factors in this were urinary potassium loss with hypokalemia, urinary hydrogen loss and, in edematous patients, the rapid large loss of relatively bicarbonate-free fluid from the extracellular fluid space. There was compensatory alveolar hypoventilation. Normal subjects showed a marked increase in the rate of aldosterone secretion. More variable effects were noted in patients with heart disease. The higher blood levels of ethacrynic acid produced by intravenous administration were uricosuric. The lower blood levels produced by oral therapy caused renal urate retention and hyperuricemia. Anorexia occurred in 8 patients; transient azotemia in 5, all of whom had renal disease; and asymptomatic hyperuricemia in 8. Excessively rapid diuresis in 1 cardiac patient produced orthostatic hypotension, and massive diuresis in 2 cirrhotic patients induced hepatic precoma and coma.

Most problems associated with ethacrynic acid therapy appeared more related to its pharmacologic potency than to any truly toxic effect. Therefore, the sensitivity and response pattern of each patient should be determined in a stepwise fashion. In most patients with edema, an intermittent dose

schedule produces a more efficient diuretic response and allows time intervals for correction of any electrolyte imbalance If used with a thorough understanding of its pharmacologic effects, ethacrynic acid promises to be a most useful agent in the treatment of patients with difficult or refractory edema

► [This and the preceding several articles deal with two new and apparently very effective diuretics There is a strong probability that each of them will come to play an important role in the management of congestive failure and perhaps other edematous states However, a word of caution is in order During the past 15 years, there have been many new drugs introduced into medicine Some of them have come to occupy a permanent and valuable place On the other hand, it has been learned that many, despite their effectiveness and after widespread use for several years, have produced grave toxic actions that have limited their value and have, in some instances, led to total cessation of their manufacture I urge that not only as regards these two diuretics but as regards all new drugs the greatest caution be utilized until the drug has been in widespread use for at least 5 years —Ed]

Hemodynamic Effects of Rapid Digitalization in Experimental Cardiogenic Shock were investigated by R F P Cronin and T Zsoter* (Montreal, Quebec)

METHOD.—Twenty-three mongrel dogs were anesthetized and all breathed 100% oxygen spontaneously throughout the experiment Cardiogenic shock was produced in 17 animals by Agress' technic of closed chest coronary embolization, using plastic microspheres with a mean diameter of 324 μ during transient acetylcholine arrest and balloon occlusion of the proximal aorta Sham embolization was carried out in 6 control animals Rapid digitalization was accomplished in 13 dogs by infusing 0.5 mg. acetylstrophanthidin in 10 cc of 5% glucose in water over 1 minute. Two dogs received 0.15 mg acetylstrophanthidin and 2, 2 mg

Coronary embolization caused a profound fall in arterial pressure and cardiac output, with a rise in peripheral resistance. Left ventricular stroke work fell markedly, whereas the filling pressure of the left ventricle rose significantly

Rapid digitalization caused a substantial elevation in arterial blood pressure and cardiac output, the rises being roughly proportional. There was a marked increase in left ventricular work in all cases and an average lowering of end-diastolic left ventricular pressure. Other changes included an increase in stroke volume, a widening of the pulse pressure and a more rapid circulation time. Acetylstrophanthidin caused a more rapid upstroke in the arterial pulse pressure, with shortening of the systolic duration in every shocked animal. Serious arrhythmias did not occur in animals given 0.5 mg., although occasional ventricular prema-

* Am. Heart J. 69 233-240, February, 1965

ture beats developed in 2 Both animals given 2 mg. showed ventricular tachycardia. Changes in all parameters in animals given 0.15 mg were comparable to those in animals given 0.5 mg The response to 0.5 mg. in the 3 animals anesthetized with morphine and Dial-urethane-Nembutal was essentially the same as that in the animals anesthetized with pentobarbital. Control animals showed no significant change in any parameter after sham embolization, and the only significant change after acetylstrophanthidin administration was a rise in mean blood pressure. In shocked animals, a marked negative inotrophic effect occurred on embolization This was substantially corrected by treatment.

Results suggest that the use of digitalis glycosides in the treatment of clinical cardiogenic shock deserves further study.

Vasodilator Therapy in Acute Hemorrhagic Shock. James A. Vick, Henry P. Ciuchta, Joseph H. Merickel and Esten O. Lindseth[1] evaluated the effectiveness of an adrenergic blocking agent, phenoxybenzamine (Dibenzyline), in the "post-treatment" of hemorrhagic shock when onset of irreversibility appeared imminent. Healthy adult mongrel dogs were anesthetized and heparinized and bled until mean arterial pressure was 50 mm Hg. Paired animals were divided into control and treated groups 3 hours after hemorrhage, and those in the latter group received phenoxybenzamine, 0.5 mg./kg., intravenously. Survivors were those animals still alive 72 hours after hemorrhage.

An average of 10% of the original blood volume was lost in the first 3 hours after hemorrhage in both groups of animals in addition to the 36% needed to establish the initial pressure of 50 mm. Hg. In the next 7 hours, 46.4% of the original blood volume was recovered by control animals, compared with 32.9% in treated animals Recovery of blood in the treated group was prompt, 14.1% occurring within 15-30 minutes of treatment, compared with 1.8% in the control group. Six hours after hemorrhage, the control and treated animals had recovered 17.4 and 17.2%, respectively Thereafter, recovery increased in the control group, and no control animals were alive at 24 hours. Relatively little change occurred in the treated group after 6 hours, and 18 of 20 animals were alive at 72 hours. Within 5 minutes after a

(1) Circulation Res 16 58-64 January 1965

blood pressure of 50 mm. Hg was reached, the amount of CO_2 in expired air decreased from 5.6 to 3.9% in both groups. At 3 hours, the level was about 2.7%, after which time no significant change occurred in the untreated group. In treated animals, the CO_2 increased and reached a near-control level of 5.1% 7 hours after therapy. Arterial O_2 and venous CO_2 remained constant or rose slightly in untreated animals during hypotensive shock, whereas venous O_2 and arterial CO_2 fell precipitously. In treated animals, venous O_2 and arterial CO_2 increased slowly but progressively and approached control levels 3-4 hours after therapy.

During the early period of hypotension, animals appear to undergo intense vasoconstriction, followed by generalized pooling which ultimately leads to a state of irreversibility. Phenoxybenzamine blocks catecholamine-induced vasoconstriction and histamine-induced venospasm, re-establishing blood flow to vital body areas. Accumulation of metabolic wastes and lack of oxygen in inadequately perfused tissues are reversed, relieving the detrimental effects of prolonged "stagnant anoxia." Adequate fluid replacement is necessary with this form of therapy.

Septic Shock. Jacob Fine[7] (Harvard Med. School) maintains that shock from any cause will become septic shock if it lasts long enough, because the generalized vasoconstriction that shock evokes will impair, among other functions, the endotoxin-detoxifying function of the reticuloendothelial system. This will allow the endotoxins absorbed from the intestine, if from no other source, to exert their property of intensifying vasoconstriction. The inevitable anoxic damage inflicted and the further sustained decline in splanchnic flow eventually lead to paralysis of vascular muscle, so that venous return to the heart falls to a level at which cardiac output can no longer sustain the minimum requirements of vital organs. If vasoconstriction is prevented in the splanchnic circulation, there is no progressive failure of cardiac output, the circulation recovers and the patient survives.

Elimination of bacterial toxins is desirable but not easily achieved. Even in a nonbacterial environment, hypovolemia or nonbacterial toxins will produce vasoconstriction that should prove fatal if it lasts long enough. In the "germ-free" animal, shock is about as fatal as in the ordinary animal.

doubtless because the food it receives contains a substantial amount of dead bacterial bodies The goal of therapy is to preserve vascular integrity by preventing or eliminating persistent vasoconstriction in the splanchnic area. This can be facilitated by eliminating endotoxin as far as possible and by celiac blockade, if not by antiadrenergic agents

PERIPHERAL CIRCULATION

Arteritis of Aorta and Its Major Branches is discussed by V. Schrire and R. A. Asherson[6] (Cape Town, Union of South Africa) on the basis of analysis of 18 cases seen during 1952-63. The disease occurred predominantly in young females, usually aged 10-30 years Four patients died and 3 were brought to autopsy. When first seen, 8 patients had cardiac symptoms and signs, 4, cerebrovascular insufficiency, 5, intermittent claudication, 2, thoracic aneurysm, and 1, constitutional symptoms.

Effort dyspnea was a prominent symptom in 70% of the patients. Congestive cardiac failure developed in 5 patients, and 3 of these died. Mitral incompetence secondary to left heart failure occurred in 3 cases. Aortic incompetence was present in a third of the patients; in 1, it was due to perforation of a small aneurysm through an aortic commissure. Two patients had angina pectoris, and 1 showed marked coronary arteritis at autopsy. Eight patients had severe hypertension; all 5 of these studied had renal involvement. The right renal artery was narrowed in 3 cases and the left artery in 2 Diffuse aortic involvement led to loss of aortic elasticity in 4 cases All but 2 patients had a marked difference in pressure between the two arms or between the arms and legs.

Obliteration or narrowing of the major aortic arch vessels is associated with symptoms secondary to diminished blood flow to the head and neck, and more serious neurologic complications occur in severe cases. Typical claudication is rare; vasomotor disturbances in the upper limbs are more common. Gangrene occurred in 1 case. Two patients had clear evidence of cerebral arterial involvement One had subjec-

(6) Quart J Med 33 439-463, October, 1964

tive ocular involvement Subclavian arterial involvement was noted in 15 cases

In patients with involvement of the lower abdominal aorta and bifurcation, intermittent claudication was the major presenting symptom in 5 and occurred in 2 others Gangrene of the toes occurred in 2 patients One patient showed evidence of venous involvement One of the 2 patients with thoracic aneurysms had hemoptysis and mediastinal obstruction Some patients exhibited signs of constitutional disease one showed all the features of subacute bacterial endocarditis. and another had a prolonged illness beginning with pyrexia of unknown origin extending over many years

The aorta and its branches show diffuse thickening of vessel walls with an irregular intima and, often, marked narrowing of the ostia of the vessels Other vessels are dilated and even aneurysmal Aortic coarctation results from intimal proliferation and medial fibrosis Two patients showed calcification of the aorta Atheromatous changes were present in all cases Histologic changes included necrosis and fragmentation of the medial elastic tissue and internal laminae associated with irregular arteritis presumably secondary to weakening of the wall One patient had coronary arteritis with occasional giant cells

The cause of this disease is entirely unknown It may be a reaction of large arteries to nonspecific stimuli resulting in a form of hypersensitivity angiitis It is characterized by patchy involvement of the aorta anywhere from the aortic valve to the iliac vessels. Most of the symptoms are due to extension of the process to involve the ostia and proximal few centimeters of the aortic branches

Surgical Management of Dissecting Aneurysms of Aorta is described by Michael E. De Bakey, Walter S Henly, Denton A. Cooley, George C. Morris, Jr., E. Stanley Crawford and Arthur C. Beall, Jr.[7] (Baylor Univ.), who treated 179 patients with the disease in the last decade. Dissecting aneurysms may be classified into three groups: type I, in which the dissecting process, along with the intimal tear, arises in the ascending aorta and not infrequently extends into its major terminal branches; type II, in which it is limited to the ascending aorta; and type III, in which it arises in the descending

lesterol crystals may lodge in an arterial lumen and damage the wall Dislodgment of atheromatous material is induced by hemorrhage into atheromas of the aorta, sudden activity or manipulation of an aortic aneurysm at surgery. Arteritis following lodgment of cholesterol crystal emboli is followed by encasement of the crystals by giant cells, which later tend to disappear, leaving the crystals encased by connective tissue. The entire process of embolism and reaction results in obliteration of the lumen. The idea of transformation of thrombi into cholesterol crystals in situ is supported by the production of cholesterol by hemolysis. However, thrombosis occurs more often in veins, whereas cholesterol crystals are seen only in arterial vessels Also, cases of arterial thrombosis far exceed cases with cholesterol crystals in arterial lumens.

Atheromatous embolism should be considered in the patient with disease of sudden onset involving one or multiple organs. It is commoner in gout and syphilitic aortitis than in other states, and diabetes mellitus is not uncommonly an associated condition. Sites of predilection are the kidney, spleen and pancreas, heart, brain, small intestine, skin and lower extremities. Myocardial ischemia or infarction, small strokes, cutaneous nodules, splenic infarction, gastrointestinal bleeding, pancreatitis, hypertension, renal failure and peripheral gangrene are among the clinical manifestations when arteries are occluded by emboli originating in atheromas of the aorta. Syndromes resembling polyarteritis nodosa and bacterial endocarditis may result from widespread embolism to small arteries.

Diagnosis and Treatment of Thromboangiitis Obliterans is discussed by David I. Abramson[1] (Univ. of Illinois). Thromboangiitis obliterans is a rare, chronic, recurrent segmental type of phlebitis and arteritis characterized by remissions and exacerbations. Intermittent claudication is the commonest complaint, the calf muscles usually being involved. Relief usually occurs 2-5 minutes after cessation of exercise. Ischemic neuritis and pain due to impending or existing trophic change also occur. About 34% of patients have a history of thrombosis of small segments of superficial veins in one or both lower extremities. Decreased skin temperature, pallor,

(1) Geriatrics 20 28-41, January 1965

bling a veritable pool of blood On the convexity of the brain, arterial anastomoses are so anatomically rich and functionally adequate that large surface arteries may be ligated without dire effect, but the opposite applies to penetrating arteries that arise from the large vessels at the base of the brain Though the anastomoses of the surface veins are rich, the larger superior cerebral veins must be conserved whenever possible or the brain may overfill with venous blood

The authors believe that, of all the blood in the brain at any given time, exceedingly little is engaged in metabolic processes Therefore, should it be possible for small reserves to be taken from another site, especially from active neighboring territories, this blood will have a great chance of being fully charged with oxygen and nutriment The anatomic patterns observed explain the shape of infarcts that are found in both white and gray matter The radial disposition of arteries in the white matter predetermines the wedge-shaped infarcts with then apex deep toward the ventricle. Cortical infarcts are often cylindric, as are the cortical arterial units

Atheromatous Embolism is discussed by Robert S Eliot, Vladimir J. Kanjuh and Jesse E. Edwards[1] (Univ of Minnesota). Embolism of atheromatous material may originate in the ulcerated atheromatous aorta or arteries Material dislodged from one or several major atheromatous plaques often is of sufficient size to occlude a major systemic artery, including a coronary artery. The ulceration of plaques permits release of cholesterol crystals and other atheromatous components from the plaque In cholesterol embolism the particles are smaller and more numerous than in the other form, and small arteries, often with diameters of 150-200 μ, are usually involved. Cholesterol embolism classically involves multiple vessels in several organs; many emboli go unrecognized. Atheromatous emboli usually involve the abdominal viscera.

Many atheromatous aortic lesions contain considerable amorphous eosinophilic material, lipophages and cholesterol crystals. Emboli in small arteries are composed of this material. When cholesterol crystals predominate in small arteries, it may be assumed that smaller amorphous particles of atheromatous material have passed downstream. The cho-

(1) Circulation 30:611-618, October, 1964.

cyanosis, reduced vibration sense perception, ulceration or gangrene of the dry or wet type may be noted. The average age at which symptoms appear is 29.3 The patients almost invariably smoke About half have signs of impaired circulation in the upper extremities, and about 15% have ulcers and/or gangrene of the fingers Pulsations are absent in the femoral arteries in only about 4% of patients Arteriograms generally show lesions in the smaller arteries of the extremities, and only occasionally are there changes in lumen contour in the common femoral artery The condition is believed to be a clinical entity distinct from arteriosclerosis obliterans.

The only definitive treatment is abstinence from smoking in all forms Generally, the patient who can abstain improves or shows no obvious progression Local care of the extremities is very important, as is avoidance of injury to the involved extremities Anti-inflammatory drugs may be helpful in superficial migratory thrombophlebitis All attempts should be made to encourage the patient to walk Sympathectomy should not be proposed for patients with only intermittent claudication, but it appears to have a place in therapy in the presence of ulcers or gangrene limited to the digits, especially if medical treatment has not helped in healing or preventing extension of the trophic change Vasodilator and adrenergic blocking agents appear to play some role in the treatment of ulcers or gangrene; they are more effective when the patient is at bed rest Indirect or reflex vasodilation, produced by application of heat to distant parts of the body, is also of value in increasing cutaneous blood flow in the hand and foot, as is whiskey taken orally

Drugs for Peripheral Vascular Disease are evaluated by Dale G. Friend[4] (Harvard Med. School). Agents which deplete norepinephrine from the peripheral sites of the sympathetic nervous system are capable of influencing the effect of this hormone on the peripheral blood vessels. Compounds such as the thiazides remove sodium and also have some effect on peripheral vascular tone. Several agents are available which prevent norepinephrine action by blocking receptor sites, and exert some sympatholytic activity by blocking release of norepinephrine at the sympathetic nerve ending. Such agents are widely used in treating peripheral vascular dis-

(5) Clin Pharmacol & Therap. 5:669-672, Sept.-Oct., 1964.

ease. They are useful in treating peripheral vascular spasm in which the spasm is secondary to abnormal vessel sensitivity or to increased norepinephrine release and action.

Azepetine is a potent adrenergic blocking agent which also acts against sympathetic autonomic overactivity and has some vasodilating effect on the wall of small vessels through a direct action on smooth muscle. The dose is increased from 25 mg. 3 times daily to 50 or 75 mg. 3 times daily after about a week. It usually proves helpful in peripheral ischemia or ulceration due to vasospasm. In general, it is well tolerated.

Phentolamine acts both on circulating and endogenously released norepinephrine. It has proved beneficial in Raynaud's syndrome and trophic ulcers secondary to acrocyanosis, emersion foot and the sequelae of frostbite. The initial dose is usually 50 mg. 4-6 times daily, increased according to tolerance to 100 mg. 4-6 times daily. It also is generally well tolerated, but since orthostatic hypotension does follow its use, great care must be taken in patients with cerebrovascular or coronary artery disease.

Phenoxybenzamine is a potent adrenergic blocking agent which acts on the adrenergic receptor cells in a noncompetitive manner. It is effective in Raynaud's syndrome, acrocyanosis, causalgia and ulceration following frostbite. The dose is 10 mg. daily, increased slowly to 20 or 40 mg. daily. Orthostatic hypotension, nasal stuffiness, occasional severe tachycardia and xerostomia may be noted.

Tolazoline closely resembles phentolamine; it is a potent adrenolytic and sympatholytic vasodilating drug and may bring about epinephrine reversal. It may induce increased secretion of hydrochloric acid and ulceration in the stomach, as well as other symptoms. A dose of 25 mg. 4-6 times daily is usually satisfactory, being gradually increased.

Isoxsuprine is a sympathomimetic amine exerting a potent inhibitory effect on the vessel wall leading to relaxation. There are few adverse effects. It is useful to a limited degree in Raynaud's disease, acrocyanosis and perhaps occasionally arteriosclerotic vascular disease. An oral dose of 10-20 mg. 3 or 4 times daily is commonly used.

Nylidrin behaves much like isoxsuprine; occasionally, it has caused dizziness and severe tachycardia. A dose of 6 mg. 3 times daily, which may be increased to 4-6 times daily, is

usually satisfactory It has been used with modest success in Raynaud's disease and acrocyanosis.

The action of cyclandelate is similar to that of papaverine, resulting in the relaxation of smooth muscle Flushing, tingling, sweating, headaches, occasional dizziness and nausea have been observed It has been useful in Raynaud's disease, acrocyanosis and possibly atherosclerotic vascular disease, as well as endarteritis and acute thrombophlebitis It has proved useful in relieving the vascular spasm of ergot A dose of 100 200 mg 3 or 4 times daily is usually sufficient This drug can possibly be used in combination with a catecholamine depletor or even with a catecholamine blocker.

Transluminal Treatment of Arteriosclerotic Obstruction: Description of New Technic and Preliminary Report of Its Application. Charles T Dotter and Melvin P Judkins[3] (Univ of Oregon) developed a safe simple and effective technic for directly overcoming arteriosclerotic narrowing and occlusion in the leg arteries.

Method. – After angiographic survey by retrograde catheterization of the opposite femoral artery 2,000 units of heparin is injected and, under fluoroscopic control, an ordinary coil-spring catheter guide with an outer diameter of about 0.05 in is passed down the lumen until its tip has traversed the stenosis A tapered, radiopaque, Teflon dilating catheter of about 0 1 in outer diameter is slipped over the guide and advanced until it has traversed the block When desirable and possible, a second dilating catheter of nearly 0.2 in outer diameter is passed as well. Exploratory injections of Conray contrast medium diluted with an equal volume of heparin-saline solution are given manually under direct fluoroscopic control It is convenient to monitor the procedure with a Parks mercury strain-gauge plethysmograph. The entire procedure can sometimes be completed in 10 or 15 minutes.

Fifteen procedures were performed on eleven lower extremities of 9 patients; seven extremities were those of diabetic patients with moderate to severe microangiopathy. Most of these patients were scheduled for amputation Six extremities improved markedly, four amputations being averted. Clinical improvement quickly followed increases in blood pressure and circulation. Three extremities were unchanged. Results were based on healed ischemic or gangrenous changes and return of measurable peripheral blood pressure. Symptoms were relieved in extremities that did not receive maximum benefit by these criteria. Failures were not

[3] Circulation 20:658-670, November, 1959

associated with harm to the patient and seemed to reflect early inexperience, the particular disease present, and the inadequacy of the instruments when used in long segment blocks. Recently, the number of treated patients has about doubled, with no further amputations and an improvement in success rate. Late thrombosis appears unlikely in the light of results to date.

Early treatment with this technic may well prevent otherwise serious disease. The authors are satisfied that it is the treatment of choice for many lesions of the femoral and popliteal arteries. It is ready for application to obstructions up to about 10 cm A major instrumental design effort is under way consisting of the development of a device suitable for percutaneous insertion which is capable of externally controlled concentric expansion over a suitable part of its length.

Dextran Therapy in Thrombophlebitis was evaluated by Robert B Sawyer, John A. Moncrief (Fort Sam Houston) and Peter C. Canizaro[4] (Univ. of Texas Southwestern Med. School). Clinical dextran, with an average molecular weight of 75,000, has been found useful in preventing experimental arterial and venous thrombosis. This suggested that dextran would be useful in the treatment of acute thrombophlebitis. Canine jugular veins were occluded proximally and a 5-ma. current passed through the system for 1 hour. The animals then received either sodium chloride solution, 20 cc./kg., heparin, 2 mg./kg., or one of three types of dextran, 1.2 Gm./kg. The dextran used had average molecular weights of 40,000, 75,000 and 185,000, respectively. Clinical dextran protected against thrombus propagation in 82.6% of the preparations, heparin in 76.9% and low-molecular-weight dextran in 60%. High-molecular-weight dextran gave insignificant protection.

Clinical dextran was given as a 6% solution in normal saline to 21 patients with superficial and 18 with deep thrombophlebitis. The initial dose of 600 mg./kg. intravenously over 3-4 hours was followed by daily infusions of 300 mg./kg. until the process subsided. Symptoms resolved in an average of 4.14 days in patients with superficial disease and 4.22 days in those with deep disease. The average time for resolution of symptoms was 4.56 days in 16 patients with symp-

(4) J A M A. 191 740-742. Mar 1. 1965

toms for over 72 hours before treatment and 3 7 days in 2.3 patients with symptoms for less than 72 hours Dramatic improvement occurred in the first 24 hours in 35 patients whereas 4 had gradual subjective improvement Three patients who failed to respond to heparin responded well to dextran In a review of the hospital course of 57 patients treated by conventional means, it was found that 30 patients with deep vein thrombophlebitis who were treated with sodium heparin and bishydroxycoumarin required an average of 15 days for resolution of signs and symptoms Fourteen with superficial thrombophlebitis required an average of 11 days Thirteen with superficial thrombophlebitis treated without anticoagulants required an average of 12 days for resolution

Dextran appeared to be more effective in these patients than heparin or coumarin derivatives Inhibition of thrombus propagation may encourage natural clot resolution The early, dramatic subjective relief seen in most patients may be due to improvement in flow secondary to hemodilution and decreased cellular aggregation

Inferior Vena Cava Obstruction: Clinical Manifestations, Diagnostic Methods and Related Problems are discussed by Morris E. Missal, James A. Robinson and Ronald W Tatum (Rochester, N.Y.), who encountered 5 patients in whom the condition was diagnosed during life. The level of obstruction may be suspected from the pattern of the superficial abdominal veins and from abnormalities in the function of various organs. A prominent periumbilical plexus suggests a bypass via the portal system into the liver and hepatic veins. Absence of central abdominal veins with prominence of lateral abdominal veins suggests patency of the renal veins and/or obstruction in the upper inferior vena cava. Under these circumstances, only extensive inferior to superior vena cava collaterals can function. When hepatic veins are occluded, anastomoses between the superior vena cava and portal vein system assume importance. Venography documents patent channels in the living patient. Probably the most important collateral is the ascending lumbar vein. A collateral channel seldom mentioned involves the renal capsular veins and perinephric veins.

The clinical picture of inferior vena cava obstruction may

result from a number of diverse causes. With some exception, the course or prognosis will depend on the cause and level of obstruction. When thrombosis occurs due to external pressure on the vena cava, there is impaired blood flow and sludging, resulting in retrograde thrombosis behind the level of occlusion. Hypercoagulable states have often been associated with thrombosis of the inferior vena cava, as have a number of generalized and local infections of abdominal organs. Primary tumors of the inferior vena cava are rare, only 11 cases were found in the literature. Occlusion of the vessel by external pressure may be caused by enlargement of the liver or pancreas. The commonest causes are liver abscess, primary or metastatic malignancy and cirrhosis. Retroperitoneal tumor, abscess and cyst, as well as enlarged lymph nodes along the course of the vessel, may lead to external pressure and obstruction. Hypernephroma is one of the commonest causes of actual malignant invasion of the inferior vena cava. Many iatrogenic occlusions were seen when surgical ligation of the vena cava was done more often for recurrent pulmonary embolism. Abdominal aortic aneurysms may, on rare occasions, occlude the inferior vena cava

Patients with complete occlusion to the level of the hepatic veins may be essentially asymptomatic. In those with occlusion below the renal veins, signs and symptoms are restricted to the lower extremities unless pulmonary embolism occurs. Iatrogenic occlusion may produce the same picture. Collateral veins begin to develop about 1 week after complete obstruction and are well developed by the 3d week; maximal efficiency of the collaterals is not reached until 3 months. Severe venous insufficiency may result from occlusion due to direct extension of deep thrombophlebitis. With occlusion at a higher level but below the renal veins, low back pain may be the chief complaint. Symptoms may be suggestive of diseases of the prostate and lumbosacral plexus in males, and profound edema of the genitalia with secondary balanitis may be present. Signs in females may simulate disease of the ovaries or chronic pelvic inflammatory disease. Occlusion of the middle segment of the inferior vena cava may result in thrombosis or obstruction of the renal veins, which usually produces the nephrotic syndrome. Gastrointestinal symptoms may also be present. Sudden occlusion of the upper segment results in liver congestion, impaired liver

function, decreased venous return to the heart, congestive heart failure and death. Gradual occlusion may result in a chronic Budd-Chiari syndrome.

THE KIDNEY

Hypertension Due to Renal Ischemia. According to Harry Goldblatt[6] (Western Res. Univ.), it has been found that a reduction in the amount of blood reaching the functioning components of the kidney occurs in most cases of essential human hypertension. Even unilateral renal ischemia was found to result in elevation of the blood pressure. Hypertension could be made to persist by adequately constricting both main renal arteries or, if the pressure was already considerably elevated due to constriction of one, by removing the contralateral kidney. Moritz and Oldt found pronounced vascular disease almost without exception in 100 patients with essential hypertension coming to autopsy and significant sclerosis in only 1 of 100 normotensive subjects. They concluded that the vascular disease develops first and that hypertension develops only if and when the kidneys become involved to an adequate degree. Animal studies showed that significant impairment of renal excretory function is not necessary for elevation of blood pressure to occur. The ultimate cause was found to be increased peripheral vascular resistance due to generalized arteriolar vasospasm.

A nervous reflex from the ischemic kidneys was excluded as the cause, but this did not exclude the possible effect of psychoneurogenic stimuli. The possible role of these, usually as secondary factors, and the existence of endocrinogenic hypertension have never been denied by the author. Occlusion of both the renal veins and renal arteries of dogs prevented elevation of blood pressure, indicating a humoral cause. It is now generally accepted that renin acts on a substrate in the plasma, angiotensinogen, to produce angiotensin I, which is converted to angiotensin II, a vasoconstrictor which presumably causes the increased peripheral vascular resistance that leads to hypertension. Renin is probably

6. Bull. New York Acad. Med. 40:763-778, October, 1964

formed in the juxtaglomerular apparatus. Recently, Deodhar, Haas and the author induced the development of antirenin by injecting acetylated homologous renin into dogs, rabbits and rats. Antirenin produced with dog renin was effective against human renin. A controlled study of the effect of parenteral injection of acetylated human renin in humans with benign essential hypertension is being conducted.

► [This article carries a note of authority It comes from a distinguished author whose experimental work done more than 30 years ago laid a fundamental basis for the understanding of the mechanism of renal hypertension.

Doctor Goldblatt does not deny the existence of what teachers of medicine call "essential hypertension" in the subconscious hope of making students think the professors know more than they do know Doctor Goldblatt holds only, and I believe correctly, that as we learn more about hypertension fewer and fewer patients belong in this so-called essential—better called unknown—group and more fall into the renal ischemic group Nevertheless, there is ample evidence, as the author concedes, that renal ischemia is not the only primary mechanism Hypertension should be looked on as a manifestation rather than as a disease Of its fairly numerous causes, renal ischemia appears to be the most common of those that are known at present —Ed]

Hypertension as Related to Renal Ischemia is discussed by John Eager Howard[7] (Johns Hopkins Univ.). Ischemia of a kidney in man can result in high blood pressure, with complete and lasting restoration to normotension after nephrectomy or plastic vascular surgery. It seems clear that reduced arterial flow to renal parenchyma results in hypertension. Dead kidney tissue does not do this Proper study of urine derived simultaneously from each kidney can yield precise information when the main renal artery of one kidney is sufficiently stenosed to induce hypertension. It is wiser not to use osmotic diuresis during such tests. These studies are unpleasant to the patient, carry a danger of infection and involve interpretative difficulties when segmental ischemia or pyelonephritis is the offending condition. Biopsy often will not provide helpful information. Aortography has been a great boon. Various renal scanning procedures are useful. With all these procedures and a modicum of common sense, one is in a position to say, with higher than 90% assurance, that operation on a kidney will or will not alleviate hypertension.

The technic devised by Morris for extracting angiotensin seems to be highly specific. The results of determining angiotensin in arterial blood of 135 patients by assay in chemically sympathectomized rats were reviewed. No positive test results were found in blood of normotensive patients or those

(7) Circulation 29 657-663, May, 1964

with essential hypertension, chronic glomerular nephritis, aldosterone tumor, Cushing's syndrome or pheochromocytoma. Tests were also negative in 8 patients who had nephrectomy without benefit to hypertension. The test was positive for all 26 patients whose blood pressure returned to normal after nephrectomy or plastic arterial surgery. In 2 patients with arteriographic evidence of bilateral renal ischemia, the assay was positive in blood derived from each renal vein. After nephrectomy or arterial surgery, angiotensin disappeared promptly from arterial blood. Angiotensin was found in some patients, when they were active and their blood pressure elevated, and was absent in the same patients during bed rest without medication, when the blood pressure was normal or only slightly elevated.

It is difficult not to attribute to angiotensin an etiologic role in the hypertension of these patients with renal ischemia. Studies in dogs have shown that angiotensin directly affects the kidney by reducing filtration and effecting a diuresis of sodium and chloride. These effects are transient, some mechanism supervening within a few hours to restore normal function, despite continued administration of angiotensin. Appropriate stenosis of one renal artery mimicked exactly the effect of angiotensin on the untouched kidney.

Surgically correctable hypertension has been found in patients who have had no more than one fourth of a kidney involved in the ischemic process. Patients have reverted to normotension after 10 years. The presence of renal insufficiency is not necessarily a contraindication to removal of an ischemic kidney. It seems too much to ask that normotension be restored before a renal operation be considered successful.

Experimental Renal Erythrocytosis: Role of the Juxtaglomerular Apparatus in its mechanism was investigated by W. J. Mitus and K. Toyama[a] (Tufts Univ.). Unilateral hydronephrosis was induced in 12 rabbits by ligating the left ureter. Six rabbits received 0.8 mg. cobaltous chloride per kg. daily. The degree of granularity of the juxtaglomerular apparatus was estimated by the method of Hartroft and Hartroft.

Eight of the 12 animals with hydronephrosis had hemoglobin levels of 15 Gm./100 ml. or more at days 25-37 after operation, well above control levels, and total red cell volume also increased. Removal of hydronephrotic kidneys resulted

[a] Arch. Path., 78:676-684, December, 1964.

in return of hemoglobin, hematocrit and total red cell volume to normal. The degree of granularity of the juxtaglomerular apparatus cells of erythrocytotic animals was greatly decreased, compared with other hydronephrotic animals. Hyperplasia in erythrocytotic animals was evidenced by elevated cell counts. Large, round cells with clear cytoplasm were prominent in these animals but not in nonerythrocytotic animals. In animals given cobalt, the granularity of juxtaglomerular cells decreased when hemoglobin levels showed some increase.

It is postulated that hyperplasia and degranulation are indicative of increased juxtaglomerular secretory activity, and that the products of secretion stimulate erythropoiesis and may lead to erythrocytosis. Hydronephrotic pressure may be transmitted through dilated tubules to the macula densa-juxtaglomerular apparatus complex, which may act as a pressure or stretch receptor as well as a secretory organ The pressure may compress and narrow smaller renal vessels and decrease blood flow, the hypoxic blood stimulating the juxtaglomerular apparatus. Changes in urine also could stimulate the juxtaglomerular apparatus.

Urinary Alkaline Phosphatase and LDH Activities in Differential Diagnosis of Renal Disease. Elias Amador, Lionel E. Dorfman and Warren E. C. Wacker[9] (Boston) studied enzyme activities in 88 patients, using 8-hour overnight urine specimens. Alkaline phosphatase activity was determined spectrophotometrically, as was urinary lactic dehydrogenase (LDH) activity, the latter by the "forward" method with dl-lactate as substrate, DPN as coenzyme and pyrophosphate as buffer. The upper limit of normal of urinary alkaline phosphatase activity was 6,100 units in 23 healthy men aged 24-60 and 7,560 units in 39 healthy women aged 24-67. The upper limit of normal of urinary LDH activity in 24 healthy males and 23 females aged 17-80 was 2,050 units.

Urinary LDH activity was normal in the 17 patients with benign hypertension, and alkaline phosphatase activity was normal in the 6 tested. All 5 patients with malignant hypertension had elevated LDH levels, and the 2 tested for alkaline phosphatase had normal levels. Five of the 6 patients with acute urinary tract infection had normal enzyme levels, as did 2 with chronic cystitis. Urinary LDH was elevated in

(9) Ann. Int Med 62 30-40, January, 1965

11 of the 12 patients with chronic pyelonephritis, and 10 had normal alkaline phosphatase activity. LDH was elevated in 3 of 4 patients in this group who had arterial hypertension and unilateral renal atrophy, and 3 of the 4 had normal alkaline phosphatase activity. A fifth patient with a hypoplastic left renal artery and kidney had elevated LDH and normal alkaline phosphatase activity. Both enzyme activities were elevated in 3 patients with acute glomerulonephritis. LDH was raised in all 15 patients with chronic glomerulonephritis, whereas 4 of the 7 with chronic membranous glomerulonephritis and only 1 of the 8 with chronic sclerosing glomerulonephritis had high alkaline phosphatase levels. Urinary enzyme activities were normal in 5 patients with healed glomerulonephritis. LDH activity was elevated in all 10 patients with systemic lupus erythematosus glomerulonephritis, as with alkaline phosphatase activity in the 8 tested. LDH was elevated in 11 of 12 patients with diabetic glomerulosclerosis, and alkaline phosphatase was elevated in 6 of the 8 studied.

The diagnostic sensitivity of elevated urinary enzyme activities permits detection of early renal and urologic disease before irreversible renal damage occurs. Most patients with potentially fatal renal diseases studied have had elevated urinary LDH activity, whereas the alkaline phosphatase activity has been elevated only in patients with certain types of renal disease.

Urinary Lactic Dehydrogenase Activity: IV. Screening Test for Detection of Renal Disease Dissociated and in Association with Arterial Hypertension. Warren E. C. Wacker, Lionel E. Dorfman and Elias Amador[1] (Harvard Med. School) determined urinary lactic dehydrogenase (LDH) activity in 90 patients by the "forward" (lactate to pyruvate) spectrophotometric method. The normal upper limit in 47 healthy adults was 2,050 units.

The urinary LDH activity was normal in all 16 patients with benign essential arterial hypertension and elevated in all 5 with malignant essential hypertension who had resting diastolic pressures above 140 mm. Hg, papilledema and rapidly progressive renal failure. Activity was also elevated in 1 patient whose pressure had been reduced from 250/180 to 220/110 mm. Hg over 3 months by hypotensive drugs, but

[1] J.A.M.A. 189:671-676, May 18, 1964

was normal in 2 in whom prolonged control of malignant hypertension had caused regression of papilledema and renal failure. Urinary LDH activity was normal in all 5 patients with benign arterial hypertension associated with renal cysts and in 2 with benign hypertension associated with adrenocortical hyperplasia The activity was normal in 3 of 4 with acute urinary tract infection but elevated in 1 with acute pyelonephritis caused by Staphylococcus aureus Activity was elevated in 15 patients with chronic pyelonephritis, including 9 with mild disease without azotemia; it was normal in 4 who had severe renal damage and azotemia

Urinary LDH activity was elevated in all 3 patients with acute glomerulonephritis and all 14 with chronic glomerulonephritis It was normal in all 5 with healed glomerulonephritis. All 4 patients with systemic lupus erythematosus had elevated activity, as did 4 with diabetic glomerulosclerosis Two diabetic patients with no evidence of nephropathy had normal activity.

From these studies, the authors concluded that urinary LDH activity is significantly elevated in most patients with potentially fatal renal diseases and normal in those with benign essential hypertension. Measurements of this activity provide a simple but sensitive screening test for renal disease and malignant tumors of the urinary tract in the general population

Phosphate Disappearance from Plasma and Renal Handling of Phosphate after Intravenous Loading in Man. Bengt Arner[2] (Lasarettet, Lund) set up a kinetic model representing the distribution and elimination of inorganic phosphate from plasma after intravenous loading The model is assumed to be valid for a late phase of phosphate disappearance, when the tubular reabsorption is still at its maximum An equation was derived from the model for the relationship between plasma phosphate concentration and time:

$$y = b \quad e^{-k t} + a,$$

where y denotes plasma concentration in mg./100 ml. and t the time in minutes after end of loading. The constant k is equal to $GFR/V_p \times \min^{-1}$, the rate constant of disappearance (GFR is the glomerular filtration rate in ml. per minute, and V_p the apparent volume of distribution for phosphate in ml.). The constant a is equal to $TmP/GFR \times 100$ mg./100 ml.

(2) Acta med scandinav. vol 176, suppl 415, 1964

(asymptote constant), where TmP is the maximal tubular reabsorption of phosphate in mg per minute

Slope analysis of disappearance curves from loading studies on normal subjects and patients showed that a late phase of the disappearance process could be described by equations giving the plasma concentration as the sum of one exponential term and one constant These equations corresponded to the one derived from the kinetic model Data analysis of model experiments showed that the constants k and a could be determined with sufficient accuracy for clinical purposes

The disappearance of phosphate from plasma was studied in 11 normal subjects and 11 patients with impaired renal function. In the latter, the glomerular filtration rate ranged from 126 to 31 ml per minute The values of k and a in normal subjects were of a reasonable order of magnitude The value of k was significantly lower in the patients than in the normal subjects, whereas the constant a was of the same order in both groups. Good agreement between inulin and phosphate clearance was obtained within each urine collection period and in the individual studies as a whole in the 11 patients. Values of TmP calculated in the classic manner and from phosphate data exclusively showed the same close agreement. The means of the quotients GFR_{in}/V_r and $TmP \cdot 100/GFR_{in}$, calculated for each period, were compared with the values of k and a obtained by slope analysis; no significant differences were found. The values of the quotients remained constant throughout the experiments

The results imply that at the concentration levels used (about 10-5 mg./100 ml.), inorganic phosphate in plasma may be considered entirely ultrafilterable. The results do not support the assumption that there is a tubular secretion of phosphate dependent on plasma concentration. During a late phase of phosphate disappearance from plasma, the process of disappearance is in accord with a kinetic model deduced for the distribution and elimination of phosphate Under certain experimental conditions, the glomerular filtration rate and maximal tubular reabsorption may be calculated using only phosphate data.

Treatment of Experimental Nephropathies with Heparin: Prospects of Clinical Application. Immunopathologic lesions, spontaneous or experimentally induced, in any type of tissue are conditioned and controlled by the same fundamen-

tal immunologic process—a tissue reaction of allergic hypersensitivity type In all pathologic processes triggered by this mechanism, there is a specific immune factor, the antibody The role of the antibody, whether humoral or cellular, is capital. But the antigen-antibody antagonism is merely bait for a chain reaction resulting, in the terminal stage, in a tissue lesion. In this chain reaction there are, implicated or active, successively or simultaneously, intermediary factors. enzymes, complement, mononuclear cells Current investigations are striving to determine the role and the place of these factors.

Bernard Halpern, Gilbert LaGrue, Antoinette Fray, Jean-Claude Morard and Paul Milliez[3] (Paris) report such a study on the effect of heparin in immunopathologic syndromes for which heteroimmune nephropathy serves as a model. Heparin is generally used as an anticoagulant, but it also has an effect on development of immunologic processes, apparently related to its anticomplement properties.

Young rabbits free of kidney disease were given a single intravenous injection of 4 or 8 ml. of anti-kidney serum obtained from ducks. The animals then were divided into three groups: A, 19 animals receiving only the anti-kidney serum; B, 17 animals receiving the same doses of anti-kidney serum combined with 100 mg. heparin and then 25 mg. heparin morning and evening for 10 days; and C, 10 animals receiving identical amounts of normal duck serum. In all groups, measurements were made of (1) complement (Roulier method), daily for 8 days after injection and then once a week for variable periods, depending on the experiment, (2) blood urea, twice weekly, (3) urinary volume, proteinuria and hematuria and (4) variations in arterial pressure in the central artery of the ear with Grant's capsule manometer; and careful histologic examinations were made of biopsy specimens between the 10th and 20th day after injection or at autopsy.

All 19 animals in group A had severe nephropathy. Ten died 8-20 days after injection of the antiserum with symptoms of grave renal insufficiency. In all animals of this series, proteinuria varied between 250 and 750 mg./24 hours, hematuria was constant and the blood urea level reached and exceeded 150-300 mg./100 ml.

(3) Presse med 73:57-62, Jan 9, 1965

Of 17 animals in group B, only 1 died with signs of nephritis Proteinuria and hematuria were seen intermittently, but only in animals that had received the high doses of anti-kidney serum In all but 1 animal, the blood urea level remained within normal limits Comparison of results in the two groups of animals demonstrated that heparin attenuated the renal disturbances remarkably

Histologic studies confirmed the clinical findings and showed generalized proliferative endothelial glomerular lesions with features of segmental fibrinoid necrosis An epithelial proliferation with "crescent" formation and massive floccular-capsular synechiae with fibrosis gave the glomeruli a wafer like appearance Besides the glomerular lesions, more discrete alterations of the tubules and glomerular arterioles were often noted

In animals that received anti-kidney serum only, the level of complement fell sharply in the first hours and remained below normal value throughout the course of the nephropathy. In animals that received both antiserum and heparin, complement decreased similarly at the beginning, but the comparative curves rapidly diverged The lowering of complement in animals treated with heparin was only transitory, 2-3 days after the initial injection, the serum complement regained its initial level or surpassed it for several days and then returned to a stable normal level.

In the 10 control animals that received the same amount of normal serum, only transitory albuminuria was observed.

Whether the mechanism operative at initiation of an immune nephropathy is similar to that of Arthus phenomenon or whether it operates by activation of complement implicated in immune cytolysis, heparin should be used. Since in human glomerulonephritis dramatic lowering of complement is the rule and since experimental immune nephropathy is a relatively close replica both pathogenically and histologically, use of heparin therapy in the human disease seems justified.

Experimental findings and preliminary clinical studies indicate that, to be effective, heparin should be administered according to precise rules. It should be given in large amount as early as possible. It should be administered intravenously, with injections repeated often enough to maintain a critical level below which the beneficial effect becomes problematic.

Absence of organotoxicity because of its biologic origin eliminates all restriction in this respect Treatment should be continued as long as the lesion appears to be progressing The only practical inconvenience of heparin therapy is its anticoagulant property. Judicious use of antiheparins should permit maneuvering, with security

Renal Arteriovenous Fistula: Reversible Cause of Hypertension and Heart Failure. Jorge E. Maldonado, Sheldon G Sheps, Philip E. Bernatz, James H. DeWeerd and Edgar G Harrison, Jr[4] (Mayo Clinic and Found) studied changes in circulatory hemodynamics and renal function in 2 patients with renal arteriovenous fistulas and reviewed 53 cases reported during 1928-63.

Woman, 34, was hospitalized with a history of hypertension since her 4th pregnancy about 5 years previously, with progressive increase in blood pressure, which was not successfully controlled by multiple antihypertensive drugs Headaches, congestive heart failure and palpitations became prominent The last pregnancy, about 3 years earlier, was complicated by severe postpartum hemorrhage and shock, the abdomen had been vigorously massaged for an entire day The patient had had three episodes of rheumatic fever in childhood

The blood pressure was 240/130 mm Hg in the right arm, 220/120 in the left arm and 280/130 mm Hg in the right thigh The heart was overactive, a systolic regurgitant murmur was heard over the apex and tricuspid region and an ejection systolic murmur over the pulmonic region The liver was slightly enlarged and the right kidney moderately so, presenting as an ovoid mass over which there was an easily palpable thrill, with a loud bruit The optic fundi showed marked arteriolar narrowing and moderate hypertensive sclerosis An ECG revealed left axis deviation and left ventricular hypertrophy Retrograde aorticorenal arteriography disclosed an aneurysm extending from the origin of the right renal artery to the trifurcation and involving a short part of the primary branches Renal function studies showed bilateral impairment, much greater on the right, and indicated ischemia on the right Indicator dilution studies showed no evidence of shunting.

Exploration revealed a large cystic mass just medial to the right kidney, which was displaced The renal artery was 12-15 mm. in diameter throughout its length This artery and a small inferior accessory renal artery were divided at their origin, and a single renal vein was divided. The aneurysm and the kidney were removed. The blood pressure rose to 190/100 mm Hg on the 4th postoperative day, and bendroflumethiazide and hydralazine were given

When the patient was discharged, the heart was reduced in size and the cardiac murmurs were less intense, the blood pressure averaged 140/100 mm. Hg Six months later, the daily pressure in

the sitting position had averaged 150/105 mm. Hg, and the patient felt well. The optic fundi showed less arteriolar narrowing and sclerosis, radial arterial pressure was 148/85 mm Hg; and function of the left kidney had increased Bendroflumethiazide dosage was increased from 10 to 15 mg daily, and hydralazine was continued at 200 mg daily.

The resected kidney showed slight hydronephrosis. A large zone of incomplete cortical infarction was present on the anterior surface The thin-walled, bilobular arteriovenous aneurysm projected from the hilus and measured 10 × 5 × 3.5 cm. The venous part of the sac involved both the primary vein and its hilar branches The lumen of the renal artery was somewhat dilated The ostium of the fistula was at the primary bifurcation of the artery. Histologic study of the main renal artery showed patchy fragmentation of the internal elastic membrane, decrease in elastic fibers in the media and increase in loose fibrous tissue Sections from the orifice showed interruption of the internal elastic membrane and marked decrease in smooth muscle of the media The renal parenchyma showed an area of incomplete infarction with extensive tubular atrophy.

This case documents for the first time in man renal ischemia distal to a renal arteriovenous fistula. Some features of the fistula suggested that it began as a renal arterial aneurysm which became adherent and then ruptured into the renal vein. The other patient, a woman aged 67 years, was found on arteriography to have vascular lakes within a hypernephroma, with extreme extrarenal venous dilation.

Data for 33 recorded cases of renal arteriovenous fistula with a functioning kidney and for the 2 present cases were adequate for evaluation. There were 21 females and 14 males; the mean age was 39 years. The chief clinical manifestations included intra-abdominal bruit, congestive heart failure, diastolic hypertension and hematuria. Aorticorenal arteriography was performed in 23 cases and was diagnostic or highly suggestive of a fistula in all. The fistula was single in 30 cases and was extrarenal in 17, intrarenal in 12 and both in 1. All 23 patients studied after operation were improved

In 13 cases of postnephrectomy fistula, operation preceded the finding of a fistula by 5 months to 35 years. The mean age of the patients was 50 years. The clinical features were those associated with high cardiac output, but diastolic hypertension was noted only twice. The 11 survivors of operation were notably improved.

An arteriovenous connection should be suspected in all cases of high cardiac output. Preservation of renal function

might be achieved when arterial and venous reconstruction is possible, but the local anatomy and general condition of the patient usually encourage the surgeon to be content with total or partial nephrectomy

Goodpasture Syndrome: Glomerulonephritis with Pulmonary Hemorrhages was first observed by Goodpasture in a youth, aged 18, during an influenza epidemic in 1919 The condition remained unnoticed in the literature until 1948, since then, 41 cases have been reported in the Anglo-American literature. H. Sarre, H. Sieberth and H. Noltenius[5] (Univ. of Freiburg i. Br.) discuss the condition and report the first case in the German literature, that of a youth, aged 20

The so-called Goodpasture syndrome is a rapidly fatal disease with characteristic symptomatology. The average duration is 5 months, only 1 case with survival of over a year is known. In 90% of the cases, the patients were men, and in 85%, the disease appeared before age 30. Coughing up blood is usually the first symptom; this may vary from blood-tinged sputum to massive hemoptysis. Soon before or at the same time, extreme weakness with fatigue and exhaustion appears. Headaches, throat pains with pharyngitis, dyspnea, edema especially of the face, sweating, anorexia, vomiting, fever not over 102.2 F. and, in 1 case, also polyuria and polydipsia are described as accompanying symptoms. Severe hypochromic anemia is always present; it is not attributable solely to the hemoptysis and in many cases was demonstrated before uremia appeared.

Roentgenologically, there is usually a bilateral diffuse infiltrate that may completely regress during the illness, as happened in the authors' patient, while renal insufficiency becomes paramount. From the beginning, there is marked proteinuria with hypo- and dysproteinemia; the urinary sediment always contains numerous erythrocytes, leukocytes and also hyaline and granular casts Within weeks or months, renal insufficiency with oliguria and uremia develops. With deterioration in renal function, the blood pressure often increases. In about 70% of cases, uremia was the direct cause of death; the other patients died of pulmonary hemorrhage or respiratory failure. In 4 patients (including the authors' patient) treated by peritoneal dialysis and hemodialysis, death resulted from refractory cardiac insufficiency

(5) Deutsche med Wchnschr 89 2405 2410 Dec 18, 1964

The diagnosis of Goodpasture syndrome should be considered when the following symptoms occur together: (1) hemoptysis (without tubercle bacilli), (2) nonspecific infiltration in the middle or lower field or both, (3) pronounced proteinuria with erythrocyturia and rapid deterioration of renal function (oliguria, uremia) and (4) severe hypochromic anemia. Treatment is limited to symptomatic measures: blood transfusions, hemostatics, dialyses. Use of antibiotics and corticosteroids does not influence the course of the disease.

Pathogenesis of the syndrome has been attributed to (1) a special form of antigen antibody disease, (2) a vascular disturbance and (3) a hemorrhagic diathesis causing pulmonary hemorrhages. The authors believe the first is the most probable.

Pathologically, there is often a focal, partially necrotizing glomerulonephritis. In the lungs, along with old and fresh hemorrhages, massive hemosiderosis is found, obliterating endophlebitis of small and large veins is often demonstrated. The authors' patient, who was treated for 3 months with extracorporeal dialysis, died of cardiac failure, perhaps as the result of obliterating endophlebitis of numerous pulmonary veins.

Renal Descent during Valsalva Maneuver in Supine Aortography: Simple Means to Improve Detail and Demonstrate Effect of Nephroptosis on Renal Artery. Burton J. Rein and Abraham T. K. Cockett[6] (Univ. of California, Los Angeles) found the Valsalva maneuver useful during aortography in the supine position to improve vessel delineation, reduce overlapping of other arteries and evaluate the reported relationship between renal ptosis, renal artery traction and development of occlusive lesions of the renal artery.

METHOD.—After premedication, a catheter is introduced into the femoral artery (or axillary artery in elderly patients) and passed through the aorta to a level opposite the midportion of the 2d lumbar vertebra. Test doses of 50% sodium diatrizoate (Hypaque) are manually injected under fluoroscopic control to insure correct placement. The patient is told to inspire deeply and strain against a closed glottis. When he begins this maneuver, 30 ml. of 50% Hypaque is injected with a pressure injector and serial films are obtained with a rapid serial filming apparatus.

This technic was used to evaluate renovascular hypertension in 50 patients. It was a convenient means of causing

downward displacement of the kidneys for one vertebral body, or two in the presence of renal ptosis. Improved delineation of the entire arterial length resulted, and overlap of other aortic branches was reduced No complications were encountered

Persistent Nephrotic Syndrome: Renal Biopsy Study in 81 cases of nephrotic syndrome not due to lupus erythematosus, renal amyloidosis, diabetic glomerulosclerosis or a congestive renal state is reported by V J McGovern[7] (Royal Prince Alfred Hosp , Sydney). Seven patients with subsiding acute diffuse proliferative glomerulonephritis had attacks that had quickly merged into frank nephrotic syndromes lasting 3-10 months. Biopsies in these cases showed changes in every glomerulus, some showing prominent endothelial proliferation and segmental obliteration. Eleven patients gradually entered the nephrotic state after an attack of diffuse proliferative glomerulonephritis, and 2 others suddenly entered such a state. All glomeruli showed dense refractile thickening of the basement membrane tending to clublike lobulations, which were converted into hyaline material as the disorder progressed. A few glomeruli resembled those seen in diffuse diabetic glomerulosclerosis. Four of the 13 patients have died.

In 39 patients with initial "pure nephrosis" or the "uncomplicated nephrotic syndrome," occasional glomeruli with foci of proliferated endothelial cells could often be found Fusion of foot processes was noted on electron microscopy. Not infrequently, lipoid-filled cells were found interstitially. Six of 9 patients in whom glomerular sclerosis developed died and were brought to autopsy. Three patients not brought to autopsy died of renal failure, and 4 patients died of nonrenal causes. Seven patients had complete remissions, and 6 have recurrent attacks of the nephrotic syndrome

Seven patients had focal hyaline sclerosis of glomeruli when first biopsies were performed. In some instances, renal insufficiency had occurred. The sclerosis appeared to develop at the sites of focal proliferation of glomerular endothelial cells. Only 1 patient had complete remission. Two of the 7 patients died, making a total of 8 deaths among the 16 patients with focal glomerular sclerosis seen in the last 7 years. Evidence of urinary infection was present in only 2 of the 16

(7) Australasian Ann Med 13 306-312 November, 1964

The other 15 patients in the study had progressive diffuse membranous glomerulonephritis All had insidious onset of the nephrotic state, and the progress of the disorder seemed quite slow One patient has died

In summary, 20 of 81 patients with the nephrotic syndrome have died and another 24 have evidence of renal insufficiency Patients with acute diffuse proliferative glomerulonephritis in whom the nephrotic syndrome develops may be in the subsiding phase of the acute disease, or they may have membranoproliferative changes, in which case a progressive downhill course can be expected The diffuse membranous form of glomerulonephritis seems more slowly progressive than either membranoproliferative or focal sclerosing glomerulonephritis

Kidney Disease Resulting from Phenacetin Abuse has been reported by many authors during the past decade In an attempt to determine how many unreported cases were related to the abuse of phenacetin or other medication, H Sarre and U Rogal[8] (Univ of Freiburg) sent a questionnaire to 500 German clinics and hospitals, 252 responded After exclusion of negative and incomplete answers 63 clinics representing about 10,000 beds reported 176 cases in which clinical conditions could be traced to abuse of analgesics, 122 of these patients had kidney disease related to phenacetin abuse and 50 had blood dyscrasias No skin sensitivities were reported Only 79 of the 122 renal cases were presented in sufficient detail for evaluation; in these, the disease was exclusively related to abuse of a preparation containing phenacetin; other analgesics were not mentioned In 55% of the patients, the medication was taken for years because of headaches (29 cases) and other painful conditions Only 5 patients gave "neuroses" or "occupational strain" as the reason for phenacetin abuse; 7 gave primary kidney disease as the reason for taking the medication; and the other 72 emphatically denied any kidney trouble before the drug abuse.

The various kidney conditions were diagnosed as chronic interstitial nephritis in 51 (9 of which were verified by biopsy), pyelonephritis in 17 (2 histologically confirmed), cystopyelitis in 3, tubular and glomerular insufficiency in 3 and "phenacetin kidney" in 5.

(8) Klin Wchnschr, 58: 2269-2274, Nov 27, 1980

Eighteen of 60 patients with chronic interstitial nephritis died; in 18 the course was chronic, without improvement, and in 24 the condition was chronic but some improvement was observed. Among 51 patients for whom clinical data were furnished, most showed albuminuria and microhematuria, with normal blood pressure, anemia and increased nitrogen retention. Of 49 investigated thoroughly, bacteria were found in the urine of only 15, the urine was sterile in the others. As expected, the correlation between nonprotein nitrogen and phenacetin intake was negligible, but there was a definite increase in azotemia with a consumption of 3 kg phenacetin or more When over 4 kg had been taken, the nonprotein nitrogen levels were mostly over 80 mg 100 ml Among the 18 patients who died, the average amount of phenacetin taken per person was 5.97 kg., the average per year was 0.77 kg. and per day 2.1 Gm.; and the average duration of excessive intake was 7 7 years. For the 18 patients with chronic conditions that had not improved, the corresponding figures were 5.64 kg , 0 58 kg , 1.6 Gm and 9 6 years. For the 24 patients who showed some improvement, the respective figures were 3 84 kg., 0 48 kg., 1 3 Gm and 7 9 years.

Only extremely large doses of phenacetin and protracted abuse lead to kidney damage. To combat the increasing abuse of tablets containing phenacetin, there is only one effective measure, i.e , to require a prescription. In Sweden this was ordered in February, 1961, and the use of phenacetin-containing drugs dropped surprisingly from 33,400,000 tablets in 1959 to 2,250,000 in 1962, and the number of deaths from kidney damage also decreased.

Death Due to Septicemia Following Percutaneous Needle Biopsy of Kidney is reported by William Samellas[9] (State Univ. of New York, Brooklyn).

Man, 34, was admitted because of diabetic gangrene of the right lower extremity, for which an above-the-knee amputation was performed He had been a well-controlled diabetic for 10 years. The ECG was consistent with arteriosclerotic heart disease The blood sugar content was 133 mg 100 ml The urine contained 2+ sugar, 8-10 white blood cells and 10-12 red blood cells per high-power field, and a culture yielded Escherichia coli and Acrobacter aerogenes A right renal biopsy was done with the Franklin-Silverman needle, a core of renal tissue measuring 1 5×0 2 cm being removed easily Some of the glomeruli showed mild glomerulosclerosis Flank pain,

(9) J Urol 91 317 319, April, 1964

gross hematuria, chills and a temperature of 103.8 F developed a few hours after biopsy. The hemoglobin level fell to 8.2 Gm./100 ml. A blood transfusion was given along with 150 mg. Colimycin 3 times daily. The patient felt well by the 5th hospital day and the urine became clear; however, on the 11th day, sudden right flank pain was associated with gross hematuria containing clots. The temperature rose to 104 F. and was accompanied by chills. The blood pressure was 90/65 mm. Hg and the pulse rate 110. The kidney region was tender and red urine was noted. The bladder was distended with clots. The blood urea nitrogen was 23 mg./100 ml. The hemoglobin had fallen to 6.5 Gm./100 ml., and the white blood cell count was 12,500/cu. mm. Transfusion was carried out. An excretory urogram 2 days later showed nonfunction of the right kidney, and retrograde study showed filling defects in the pelvis due to blood clots. Blood cultures were sterile. The patient died suddenly on the 19th day after biopsy.

At autopsy, about 500 cc. dark red semiclotted blood was found in the retroperitoneum surrounding the kidney. The kidney showed a 4-cm. tear in the lateral border, extending to the renal pelvis and representing the site of the needle biopsy tract. A small, loose subcapsular hematoma was seen. Blood clots were present in the renal pelvis and bladder. There were multiple small abscesses in the kidney, liver and spleen, and recent and old small infarcts in both kidneys. The coronary artery was arteriosclerotic and there was an old myocardial infarction. Acute parietal endocarditis, old fibrinous pericarditis and bilateral fibrinous pleuritis were also present.

When urinary tract infection is present, urine cultures should be made and appropriate antibiotics given before biopsy. If fever ensues, vigorous antibiotic therapy should be instituted. A high urinary output must be maintained by infusions, and the bladder should be irrigated with normal saline. The usual 24-48 hours' observation during bed rest after biopsy may not be sufficient. A more cautious attitude is advisable in the presence of urinary tract infection, since needle biopsy is now used to obtain cultures from infected kidneys and to detect pyelonephritis.

Sickle Cell Disease and Hematuria: Report of 29 Cases seen during 1955-63 is made by Terry D. Allen[1] (Southwestern Med. School). This condition basically affects young adults. The 20 females and 9 males were aged 15-60. The bleeding site was evenly divided between the left and right ureteral orifice. Generally, recurrent hematuria was ipsilateral and usually the bleeding was grossly apparent. Transfusion was required in 4 patients, and several others required supplemental iron. Episodes of bleeding commonly lasted from several days to a week or more. Recurrences and re-

(1) J. Urol. 91: 177-183, February, 1964.

missions were not unusual Fully half the patients had previous episodes of hematuria. In 3 patients, bleeding ceased abruptly after renal manipulation, in each, bleeding had been severe or protracted and the cessation of bleeding was abrupt and prolonged.

Negress, 18, was found to have an S C hemoglobinopathy during examination at age 16 On admission, total, gross, painless hematuria originated from the left side X-rays showed filling defects compatible with blood clots in the left renal pelvis Bleeding was brisk, continuous and associated with the passage of clots In 6 days the hemoglobin fell from 11 5 to 5 Gm 100 ml In the next 2 months she required 31 pt blood and received various medications, none of which affected the course of bleeding A transfusion reaction occurred and left renal exploration was carried out Generalized oozing from all the calyceal systems was noted Decapsulation of the kidney was performed and a nephrostomy tube was left indwelling Clear urine was evident on the 1st postoperative day The nephrostomy tube was removed, and the patient was discharged without symptoms and voiding clear urine No further episodes of hematuria have occurred in the 2 years since operation

Electrophoresis disclosed S-A hemoglobin in 18 of 22 patients studied and S-C hemoglobin in 3; S-S hemoglobin was reported once, but this did not coincide with the clinical picture and is questioned. Negative sickle cell examinations were reported initially in 4 patients About a third of the patients had other diseases including cystitis, pyelonephritis, pericarditis, rheumatic fever, evidence of peripheral embolization, prostatism, and 1 patient had adenocarcinoma of the kidney. Several women were pregnant. Renal biopsies were obtained in 2 cases and, aside from some peritubular congestion, were unremarkable

Diagnosis of this syndrome rests on the demonstration of sickle cell disease and the absence of other satisfactory explanations for the hematuria A hemoglobin electrophoresis pattern should be obtained in any suspected case. Conservative treatment is advocated whenever possible.

Human Renal Homotransplantations with Cadaver Kidneys were carried out in 19 patients during 1963-64 by Satoru Nakamoto, Ralph A. Straffon and Willem J Kolff[2] (Cleveland Clinic). All patients were in terminal renal failure and had ceased to respond to conventional therapy. All had required dialysis. All but 2 were hypertensive Five underwent bilateral nephrectomy about 2 months before transplantation, and 8 underwent it about 10-14 days after transplan-

(2) J.A.M.A. 192 302-308 Apr. 26. 1965.

tation Splenectomy was performed on 7 patients and thymectomy on 5 In 2 patients, renal homografts from related living donors had failed Fifteen cadavers served as kidney donors Soon after death of the donor, 200 mg heparin sodium and 500 ml. dextran of low molecular weight were given intravenously and closed chest cardiac massage and artificial respiration instituted The kidneys were removed, flushed with warm then with cold perfusate and kept in cold isotonic saline solution The ischemic time was about 140 minutes in most cases After transplantation, patients received azathioprine, prednisone and cactinomycin Local irradiation to the graft was given when the transplant appeared threatened by rejection and the dose of azathioprine could not be increased Hemodialysis was done in all but 2 recipients

At time of report, 10 patients were living, 9 with functioning transplanted kidneys for 1-12 months, 1 has been on a chronic dialysis program since removal of the transplanted kidney Six patients are able to work Donor kidneys were necrotic at transplantation in 4 cases, total ischemic time was long and cold perfusion was not carried out Intrarenal infection occurred in 2 of the 4 patients In 3 recipients, surgical difficulties led to failure Two patients, 1 of whom was alive at time of report, had necrosis of donor ureters about 1 month after transplantation Agranulocytosis and Escherichia coli septicemia developed in 1 patient, and she died of sepsis. Urine volume increased gradually after transplantation in the 12 patients who lived over 1 month and was sustained after removal of their own kidneys No patient underwent dialysis more than 30 days after transplantation. Creatinine clearance improved, sometimes to low-normal values. Hemoglobin increased at least in the first 3 months and often much longer. No blood transfusion was given after the last hemodialysis.

THE DIGESTIVE SYSTEM

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