Cardiovascular Disturbances in Poliomyelitis

By Louis Weinstein, Ph.D., M.D.

INFECTION by the virus of poliomyelitis is not limited to the anterior horn cells. Clinical observation and anatomic study have indicated that more extensive involvement of the nervous system is not infrequent. Lesions of the precentral gyrus, the reticular formation in the medulla, the roof nuclei and vermis of the cerebellum, the posterior columns of the spinal cord, Auerbach’s and Meissner’s plexi, and the sympathetic ganglia have been demonstrated and, in many instances, related to specific syndromes. That invasion by the virus is not even limited to nervous tissues is suggested by recovery of the agent from the blood, the myocardium, and from lymph nodes. Thus, from the standpoint of viral dissemination and extent of tissue alteration, poliomyelitis is a diffuse disease. Study of large numbers of patients with poliomyelitis, particularly adults, reveals that the clinical manifestations may also be manifold, and not limited to mere loss of muscle power. Dysfunction of organs other than the nervous system is relatively common; in many instances it is secondary to damage of neural structures, in some it may result from direct viral invasion or secondary bacterial infection, and in others more than one mechanism may be responsible. The situations that threaten life in poliomyelitis most seriously and are the most difficult to control arise not infrequently from such involvement. Thus, secondary bacterial invasion of the broncho-pulmonary tissues in the “respirator patient,” acute ulcerations of the gastrointestinal tract with hemorrhage or perforation, infection of the urinary tract, or a variety of cardiovascular abnormalities may terminate life in individuals in whom muscle paralysis, although of extensive degree, readily lends itself to effective management.

One of the systems that may become seriously involved in poliomyelitis, especially during the acute phase, is the cardiovascular apparatus. A variety of disturbances of the heart and vascular tree have been described and are not uncommon, particularly in adults. In some instances these phenomena are of only transient importance in the early stages of the disease, in others they are either directly responsible for or contribute greatly to a fatal termination and, in still others, they may persist late into the convalescent period. The purpose of this paper is to review the cardiovascular abnormalities that have been observed in poliomyelitis, to discuss the mechanisms to which they are thought to be attributable, to point out their importance in determining the clinical course of the disease and measures that may be useful in their prevention and therapy, and to suggest lines for further investigation.

MYOCARDITIS

Anatomic Observations

The first description of the anatomic changes occurring in the heart in poliomyelitis is that of Robertson and Chesley,¹ who recorded the presence of edema of myocardial fibers, pallor and softness of the myocardium, and subendocardial petechial hemorrhages. Although the presence of cyanosis, rapid pulse, and arrhythmias had been commented upon and attributed to cardiac involvement by many students of the disease, it remained for Saphir and Wile² to emphasize myocarditis as a common feature. In 6 of 7 patients studied by these investigators, the heart was noted to be slightly dilated, and the myocardium “flabby.” In instances in which inflammatory changes were slight, there was dilatation of the capillary vessels, which were filled with neutrophils, as

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well as perivascular infiltration with lymphocytes and polymorphonuclear leukocytes. When the alterations were of moderate degree, the same abnormalities were noted, but the inflammatory cells infiltrated the interstitial spaces, and the myocardial fibers showed a varying degree of cloudy swelling. In the most severe myocarditis the principal infiltrating cells were mononuclear and " adventitial"; foci of perivascular collections of neutrophils were frequent. The adventitial cells were often present as " collars" around minute blood vessels. In areas of diffuse inflammatory reaction lymphocytes were predominant although a few neutrophils were also present. In some sites there were small foci of lymphocytes separated by erythrocytes just below the endocardium. Slight swelling and loss of striation of the muscle fibers were noted; for the most part, however, the muscle was well preserved. In some sections of the myocardium individual fibers of some of the larger nerves lying adjacent to branches of the coronary arteries were spread by edema-like material. In a later study, Saphir\(^3\) confirmed these observations. The same type of changes had been noted in the hearts of poliomyelitis patients 20 years earlier by Abramson.\(^4\)

Since publication of the data of Saphir and Wile,\(^2\) other investigators have recorded the presence of interstitial inflammatory reactions, perivascular collections of lymphocytes, and slight but definite changes in myocardial muscle.\(^5\), \(^6\) In addition to these findings, Cowie, Parsons, and Lowenberg\(^2\) observed subepicardial hemorrhages, right-sided cardiac dilatation with relative tricuspid and pulmonary insufficiency, thrombosis of the right atrial appendage, and localized interstitial myocarditis. Peale and Lucchesi\(^6\) found no gross abnormalities of the heart in poliomyelitis, but 6 of 7 cases examined by microscopic study revealed degenerative muscle changes of varying degree, including some loss of striations, fragmentation of muscle bundles, granular necrosis, interstitial edema, and swelling and pyknosis of nuclei; patchy areas of myosclerosis were apparent in some. The lesions could not be related to age of the patients, duration of the disease, or presence of bronchopneumonia.

The largest study of myocardial changes in poliomyelitis is that of Dolgopol and Cragan.\(^8\) Of 92 cases in the acute or convalescent stage of the disease, 16 had focal myocarditis. The duration of the infection in these individuals varied from 2 to 10 days, and their ages from 13 months to 37 years. All had bulbar or spinal involvement of varying severity; several had lesions of the midbrain and cortex. One half of the patients had pneumonia. Three types of focal myocarditis were present: Type I—areas of the myocardium showed isolated, thin, cloudy myocardial fibers, tapering off toward widened edematous stroma with long, wavy nuclei clinging to the fibers. No cytoplasm was present about these nuclei. Type II—collections of cells, usually mononuclear but occasionally neutrophils, were found lying between intact or slightly degenerated myocardial fibers. In some foci the mononuclear cells contained elongated or oval nuclei with little cytoplasm and seemed to be of histiocytic origin. Type III—cellular collections in the interstitial tissues surrounding the blood vessels. The cells were usually histiocytic mononuclears with oval nuclei, but in some cases neutrophils and lymphocytes predominated in the perivascular tissue and infiltrated between the adjacent fibers. In some instances, there were small collections of lymphocytes and polymorphonuclear leukocytes beneath the endocardium and spreading between the underlying myocardial fibers. Subepicardial cellular collections and epicardial, myocardial, and subendocardial petechiae were frequent. Interstitial edema of the myocardium was present in 86 patients; it was apparent not only in the perivascular connective tissue but extended within muscle bundles and between individual myocardial fibers. The heart muscle was remarkably well preserved in the majority of cases of myocarditis. Zenker's degeneration was encountered occasionally in isolated fibers. A peculiar widespread degenerative change was observed in some instances with or without myocarditis; the degenerated fibers showed intrasarcolemmal fragmentation of the fibrillae, which, although still preserving their cross striations, appeared to be cleaved across
the intercalated disks and retracted on either side of the tear.

Interstitial collections of cells, edema of the myocardium, diffuse and focal perivascular infiltration with neutrophils and lymphocytes, and slight changes in the myocardial fibers have been observed in poliomyelitis by several investigators.10-12 Boucek and co-workers13 and Ludden and Edwards14 emphasized the anatomic alterations in the myocardial muscle. They described involvement of single or small groups of muscle fibers. The predominant picture was one of loss of muscle striations and nuclei; the protoplasm was represented by coarse clumps of acidophilic material. Some fibers had a homogeneous nonfibrillar hyaline appearance; others, although retaining their cross striations, were granular and stained more deeply acidophilic than normal, and contained sudanophilic granules. According to Boucek and co-workers12 the “granular character of the muscle fiber is the earliest morphologically recognizable change of myocarditis and the cells showing the protoplasmic clumping and hyaline change represent later stages in the disease process.” Ludden and Edwards14 pointed out that the most conspicuous change in severe acute myocarditis of this type was complete focal necrosis of 1 or 2 adjacent muscle fibers; these were completely replaced by irregular staining disorganized masses of coagulated cytoplasm. In 1 case, they noted a perforation of the posterior wall of the right atrium; the defect was small, had irregular borders, and produced hemorrhage into the surrounding tissues with hemopericardium.

That the lesions in poliomyelitis are not present in all parts of the myocardium to the same degree was stressed by Boucek and associates13 and Jurow and Dolgopol.12 The former observed the most extensive changes in the left atrial appendage, anterolateral wall of the left ventricle, and left posterior papillary muscle. The latter arranged the sites of tissue damage in the heart in the following order of decreasing frequency, intraventricular septum, posterior papillary muscle of the left ventricle, and walls of the atria.

Anatomic changes have also been described in the aortas of patients dying of poliomyelitis.9 Although this organ usually appears grossly normal, microscopic study has revealed a pink, smudgy, edema-like material containing an occasional lymphocyte and separating the elastic lamellae; the intima and adventitia have been unchanged.

**Etiology of Myocarditis**

The etiology of the cardiac damage that may be observed in poliomyelitis has been the subject of considerable speculation. Some investigators have suggested that most of the changes are due to hypoxia, since most patients who die of the disease are suboxogenated for a variable period of time prior to death. Boucek’s group,13 however, have stated categorically that “anoxia is not the cause.” It has been pointed out by Dolgopol and Cragan9 that the lesions of their Type I focal myocarditis are the same as those present in infections by Type A influenza virus. Fifteen years ago Larson9 suggested that myocarditis was produced by invasion by the virus of poliomyelitis. Ludden and Edwards14 postulated that in some epidemics a virus strain with specific cardiotropic properties might be involved. Recent data support the probability that poliomyocarditis is produced by direct invasion of the heart by the infectious agent. Horstmann and her co-workers18 and Sanz-Ibanez16 demonstrated poliomyelitis virus in the hearts of experimental animals. Myocarditis has been found in 25 per cent of experimentally infected chick embryos.17 Jungeblut18 was the first to detect virus in the heart of human beings dying of poliomyelitis, by transfer of cardiac tissue as well as spinal cord from 2 fatal cases of bulbar poliomyelitis to cynomolgus monkeys. Both isolates produced paralysis with classical anterior horn lesions; definite myocardial involvement occurred with several of the subpassages. In a later study, Jungeblut and Edwards19 injected glycerinated fragments of myocardium from 5 patients intracerebrally into cynomolgus monkeys and found virus in 3; only 2 had anatomic evidence of myocarditis. Immunologic studies proved that they were dealing with poliomyelitis virus. The injected animals exhibited myocardial lesions. It was postulated that the infectious agent reached the heart during the period of viremia.
**Electrocardiographic Abnormalities**

Electrocardiographic investigations of large numbers of patients with poliomyelitis have indicated that myocarditis is relatively common, and probably more frequently present than has been suggested by anatomic investigation. The first electrocardiographic study in poliomyelitis was that of Battro and co-workers, who found abnormal tracings in 5 of 20 cases in the acute stage of infection. Since the publication of this paper a number of other investigators have reported electrocardiographic changes in from 12 to 77 per cent of cases of poliomyelitis. The significance of some of these “abnormalities” must be questioned, however, because they have not been evaluated in relation to the presence or absence of fever and tachycardia, both of which may produce transitory, minor alterations in the electrocardiogram regardless of their cause. Gefter’s group noted that the incidence of abnormal tracings rose inconstantly with an increase in the duration of the febrile period. While this suggests a relationship to the acute active phase of the infection, it does not rule out the possibility that some of the abnormalities noted, particularly those involving the T waves and S-T segments, were nonspecifically induced by the elevated temperature and pulse rate characteristic of the early stage of the disease.

A variety of abnormalities in the electrocardiogram have been described. As can be seen in table 1, changes have been observed in all parts of the tracings. The incidence of certain types of alteration has differed considerably from one study to another, however. Thus, prolongation of Q-T has been noted in from 1.6 to 33.3 per cent, T-wave displacement in from 10.7 to 39.3 per cent, and tachycardia (rate over 140 per minute) in from 4 to 42 per cent of patients with poliomyelitis. A number of other changes have been reported without mention of their incidence; these include equivocal Q-T prolongation, Q-T pattern, and sinus bradycardia and low voltage of the QRS complex.

It is obvious that no specific electrocardiographic changes are associated with poliomyelitis. The abnormalities are the same as those noted in a variety of infections due to bacteria, rickettsiae, and other viruses. Of great interest, however, is the relative frequency of prolongation of atrioventricular conduction and the possibility of confusion with acute rheumatic carditis. Occasionally the presence of myocardial infarction may be mistakenly suspected because of a suggestive electrocardiographic pattern. The writer has observed 3 patients with poliomyelitis in whom the tracings were highly suspicious of acute coronary closure; in no case was a myocardial infarct discovered at necropsy. It should be stressed that electrocardiographic abnormalities cannot always be related to demonstrable anatomic changes in the heart, although they are frequently associated.

Electrocardiographic abnormalities usually appear during the first 14 days of poliomyelitis. Fox and his co-workers found changes as early as the first day of the disease but they were most common during the first week; the earliest alterations were present in aVF. Gefter and associates noted the following times of appearance of abnormal tracings: 1 to 3 days, 18 per cent; 4 to 6 days, 17.9 per cent; 7 to 9 days, 10.9 per cent; and 10 to 12 days, 17.6 per cent. Changes did not increase in frequency as the poliomyelitis ran its course; when present, they usually persisted for several weeks. That the duration of electrocardiographic abnormality may be of importance was suggested by Frishknecht and Zellweger; only those cases in which the tracing was abnormal

### Table 1. Types of Electrocardiographic Abnormalities in Patients with Poliomyelitis

<table>
<thead>
<tr>
<th>Type of abnormality</th>
<th>Investigator (reference no.) per cent</th>
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<tbody>
<tr>
<td></td>
<td>11</td>
</tr>
<tr>
<td>T-wave changes</td>
<td>39.3</td>
</tr>
<tr>
<td>ST-T abnormality</td>
<td>50.8</td>
</tr>
<tr>
<td>P-R increased</td>
<td>—</td>
</tr>
<tr>
<td>Q-T increased</td>
<td>1.6</td>
</tr>
<tr>
<td>Extrasystoles</td>
<td>—</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>—</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>—</td>
</tr>
<tr>
<td>Tachycardia (140 or higher)</td>
<td>8.2</td>
</tr>
<tr>
<td>&quot;Arrhythmias&quot;</td>
<td>4.9</td>
</tr>
<tr>
<td>High P waves</td>
<td>—</td>
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for longer than 2 to 3 weeks were thought to be suspicious of myocarditis. Patients with normal records during the acute phase of the infection were not found to develop electrocardiographic evidence of cardiac damage later in the disease.

There is some disagreement concerning the frequency of electrocardiographic abnormalities in different age groups. Gfeter and his associates\textsuperscript{21} found no association between the presence of abnormal records and age. The incidence was 17.4 per cent in cases 1 to 3 years old, and 19 per cent in those 19 to 46 years of age; however, only 6.7 per cent of 4- to 6-year-old children showed such tracings. Weinstein and Shelokov,\textsuperscript{25} on the other hand, detected no electrocardiographic changes in patients older than 16 years, although 50 per cent of the group studied were adults. A tendency toward a greater number of abnormal tracings with increasing age has been suggested by Laake,\textsuperscript{26} he described electrocardiographic changes in 37.6 per cent of individuals over 10 years of age and 24.1 per cent in those younger than 10.

The type and extent of paralytic involvement in poliomyelitis appear to be related to the incidence of electrocardiographic abnormalities. The frequency of abnormal tracings is lowest in the nonparalytic form of the disease\textsuperscript{21, 26} and highest in cases with severe spinal, bulbar, or bulbospinal involvement\textsuperscript{21, 24, 26} (table 2).

Several factors have been suggested as responsible for the electrocardiographic changes in poliomyelitis. The possible role of serum potassium has been ruled out by Manning and Yu.\textsuperscript{27} Disturbances in the sympathetic nervous system have been thought to be of significance in altering the electrocardiogram by Frischknecht and Zellwegger\textsuperscript{28} and Laake.\textsuperscript{26} The latter found that abnormal tracings could be reverted to normal within 45 minutes after the injection of dihydroergotamine, a sympatholytic agent. The state of ventilation, either hypoxia\textsuperscript{24} or hyperventilation, has also been suspected of playing an important part. While it is possible that nervous system dysfunction or abnormalities of ventilation may be responsible for some of the transient and minor electrocardiographic changes, it appears most likely that the alterations of greatest significance and persistence are related to viral invasion of the heart\textsuperscript{13, 19} and resulting myocarditis.

**Physical Findings**

Very few studies of myocarditis in poliomyelitis mention the presence of abnormal physical findings associated with the observed anatomic and electrocardiographic disturbances. In many cases it is difficult to distinguish the exact cause of manifestations consistent with cardiovascular dysfunction because they may arise not only from cardiac involvement, but also from medullary or pulmonary disorders that are frequently present at the same time. It has been suggested\textsuperscript{2} that, although poliomyocarditis produces no specific symptoms, the heart may be considered to be affected if (a) a patient becomes clinically worse and begins to fail rapidly without apparent reason, (b) bradycardia or any type of arrhythmia appears, (c) restlessness becomes prominent, (d) the pulse is feeble, (e) hypotension develops and there is an increase in heart size, and (f) tachycardia out of proportion to the level of fever and cyanosis are present. A critical analysis of these symptoms reveals that, with the exception of cardiomegaly, they are relatively nonspecific, however, and that they may result from disease of the medulla or from disorders of ventilation. Other investigators have described "cardiac failure" or a "clinical picture suggestive of cardiac damage."\textsuperscript{29} In the cases studied by Gfeter and associates,\textsuperscript{21} 7.5 per cent had mitral and 1.5 per cent aortic murmurs, 4 per cent had a heart rate of 140

<p>| Table 2.—Relationship of Type of Poliomyelitis to Incidence of Electrocardiographic Abnormalities |
|-------------------------------------------------|--------------------------------|</p>
<table>
<thead>
<tr>
<th>Type of poliomyelitis</th>
<th>Investigator (reference no.) per cent patients with electrocardiographic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonparalytic</td>
<td>4.3</td>
</tr>
<tr>
<td>Paralysis, 1 extremity</td>
<td>11.4</td>
</tr>
<tr>
<td>Paralysis, 2 or more extremities, bladder, diaphragm</td>
<td>15.6</td>
</tr>
<tr>
<td>Spinal</td>
<td>—</td>
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<tr>
<td>Spinal, moderate</td>
<td>—</td>
</tr>
<tr>
<td>Spinal, &quot;extreme&quot;</td>
<td>—</td>
</tr>
<tr>
<td>Bulbar alone</td>
<td>22</td>
</tr>
<tr>
<td>Bulbar or bulbospinal</td>
<td>26</td>
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weekday
per minute or higher, and 0.01 per cent showed cardiac enlargement. Cardiomegaly and loud apical systolic murmurs have also been noted by Hertz and his co-workers.29 One half of 28 fatal cases of poliomyelitis were thought by Shutkin30 to have died of acute myocardial failure. All of these patients died suddenly, with only a short preterminal phase during which the outstanding abnormalities were moderately rapid pulse of deteriorating quality, normal arterial and venous pressure, normal respiratory function, and cardiac standstill. The individuals with the clinical picture of shock and "peripheral vascular failure" failed to respond to vasopressor agents. Jungeblut31 has stressed the importance of myocarditis in determining the outcome of poliomyelitis: "Since the frequency of myocardial involvement seems to be directly proportional to the severity of the disease, it is not impossible that the fatal outcome in so-called bulbar cases may, at times, be determined more directly by the extent of myocardial damage than by lesions in the respiratory centers of the brain stem. It will also be necessary, on the other hand, to examine carefully the occasional patient with "cryptic" myocarditis of unknown etiology (who shows no obvious signs of paralysis) for the possible presence of poliomyelitis virus, especially when such cases occur at times of epidemics." The points made by Jungeblut are well taken and merit serious consideration.

Considerably more study of the problem of cardiac failure in all types of poliomyelitis, especially the severe case, is necessary. The application of methods of specific measurement, e.g., measurement of venous pressure, circulation time, blood volume, transaminase levels, and cardiac catheterization, etc., may yield information of considerable importance in understanding the nature of cardiovascular dysfunction in poliomyelitis, and lead to more effective management of the disease. It is equally important to investigate the remote effects of poliomyelitis on the heart. Little or nothing of significance is at present known about the natural history of healed poliomyocarditis. Careful study over a number of years of patients known to have developed cardiac involvement during the acute phase of infection is imperative, if the full impact of such damage is to be determined. It is entirely possible that the maximal effect of poliomyocarditis may become most evident many years after recovery from the disease.

Endocarditis and Pericarditis

Endocardial involvement may occur in poliomyelitis. Petechial hemorrhages were present often in the endocardium of the hearts studied by Saphir.5 Luhan32 described a case in which necropsy revealed a verrucous endocarditis involving the mitral valve; there were no embolic phenomena or evidence of chronic congestive failure. Minimal valvular damage, with and without associated endocarditis, was found almost consistently by Ludden and Edwards40 The changes, consisting of separation of the valvular stroma as if by edema, and foci of highly eosinophilic bundles of collagen, were most prominent in the aortic and mitral valves and when myocarditis was present. These investigators also described 2 cases of vegetative endocarditis. In one, the mitral valve was involved; no bacteria were seen but the entire stroma was infiltrated with numerous cells, mainly neutrophils with some lymphocytes, and the vegetation consisted of irregular deposits of fibrin undergoing organization. In the other, a subendothelial circumscribed mass about 2 mm. in diameter was discovered on the inferior aspect of the mitral valve; the lesion contained fibroblasts, budding capillaries, deposits of hemosiderin, and recent hemorrhage. Focal edema of the mitral valve, with minute nodules on the surface of the leaflets was observed in one individual, and hemorrhage in the mitral valve in another, by Weinstein and Shelokov.25 The possibility of acute rheumatic endocarditis was ruled out by the absence of the characteristic anatomic changes.

Although subpericardial hemorrhages have been described in poliomyelitis, involvement of the pericardium itself is apparently rare. Saphir3 noted pericardial hemorrhages in some patients; in one, they were abundant and covered practically the entire visceral layer. In a case studied by Weinstein and Shelokov25 a sterile, creamy effusion containing neutrophils
and fibrin was present in the pericardial sac. The infiltration extended into the superficial layers of the myocardium; a nonbacterial pneumonitis was also observed. This patient had no discoverable bacterial infection and had received no antimicrobial agents. There are no reported instances of symptoms or signs suggestive of pericarditis or cardiac tamponade during life in poliomyelitis. The pathogenesis of pericarditis in this disease is unknown. Possible mechanisms may be spread of virus from infected myocardium, implantation during the viremic phase, or contact with pleura when interstitial pneumonitis, which is occasionally present in poliomyelitis, occurs.

Hypertension

Observations of the blood pressure in patients with poliomyelitis have revealed elevations of varying degree and persistence in a varying number of cases. Considering an increase in diastolic pressure of more than 10 mm. Hg above the expected normal as significant, Grulee and Panos\(^2\) noted hypertension in 72 per cent of 70 patients. Elevation of blood pressure was present in only 7 per cent of the spinal and 12 per cent of the nonparalytic cases. In a study of 428 cases of poliomyelitis Wein- stein and Shelokov\(^2\) found hypertension in 7 per cent. The degree of blood pressure elevation was graded according to the following standards: mild—increase of the systolic level of 20 to 40 mm. Hg; moderate—rise of 40 to 50 mm.; severe—systolic pressure more than 50 mm. higher than normal. Of the 30 patients with hypertension, 22 (73.2 per cent) were over 16 years of age; 5 had spinal, 16 bulbospinal, and 1 bulboencephalitic disease.

Abnormally elevated blood pressure (a diastolic level of over 90 mm. maintained for more than 12 hours) was a striking finding in more than half of the cases of poliomyelitis studied by McDowell and Plum.\(^3\) Of a group of 103 patients, only 1 of whom had hypertension prior to the onset of infection, 45 developed elevated blood pressure during the acute phase of the disease, with the highest incidence in instances of bulbospinal involvement or quadriplegia. Hypertension was of considerably greater degree and longer duration in cases requiring artificial respiration than in those with normal breathing. The average blood pressure in hypertensive respirator patients who survived was 164/104 and the average duration 98 days; in those not requiring artificial respiration, the average blood pressure was 143/96, which persisted for an average of 5.5 days. Of 10 individuals in whom hypertension was still present after 3 to 12 months, all had required treatment with a respirator for at least 2 weeks in the early part of their illness.

Papilledema, generalized seizures, focal convulsions, visual scotomata, retinal arteriolar spasm, retinal hemorrhages, mental deterioration, and progressive renal failure in the absence of pyelonephritis may occur as complications of hypertension in poliomyelitis.\(^34\)–\(^35\) Intensive therapy with hypotensive drugs has been found to be of value in controlling the elevated blood pressure and its sequelae, although reduction to normotensive levels may be difficult to accomplish.\(^34\), \(^35\)

That poliomyelitis may be responsible for hypertension of many years’ duration has been suggested by Vickers,\(^36\) among others. He observed 3 patients, aged 25, 28, and 31 years, in whom there was no evidence of renal disease or other etiologic factors, who had hypertension (180/120, 170/106, and 160/85 mm. Hg) 14, 22, and 23 years respectively after the onset of poliomyelitis; in 2 cases there was residual paralysis.

Several mechanisms, acting singly or in combination, may be responsible for the development of hypertension in poliomyelitis. Hypoxia has been suggested by several investigators\(^35\)–\(^37\), \(^38\), \(^39\) as an important factor, particularly in instances of labile blood pressure levels, because artificial respiration or oxygen or both quickly restore a normotensive state. Grulee and Panos,\(^32\) McDowell and Plum,\(^3\) and Platou\(^40\) do not agree with this hypothesis, however, because hypertension may persist despite adequate ventilation, or may be prolonged long after breathing has returned to normal. A central origin for elevation of the blood pressure in this disease had been postulated\(^31\), \(^41\) on the basis of the presence of lesions in the hypothalamus and the reticular
substance. Another possible mechanism, especially for prolonged hypertension, is renal disease. Infections of the kidney are very common in severely paralyzed poliomyelitis patients who often require prolonged, constant catheterization of the urinary bladder. They occur despite chemoprophylaxis and are very difficult to eradicate even when potent antimicrobial agents are used. It is well known that this type of renal disease, if sufficiently prolonged, may alone be responsible for persistent elevation of the blood pressure. Damage to the vagus or glossopharyngeal nerves that contain pressoreceptor fibers from the carotid and aortic sinuses has also been suggested as a mechanism for the production of hypertension in poliomyelitis.\textsuperscript{38} The reaction of the patient to a situation causing great alarm and apprehension, as occurs in the severely affected case of poliomyelitis, has been thought to play a possible role.\textsuperscript{43} That several factors may be active simultaneously or in sequence has been suggested by McDowell and Plum\textsuperscript{38}: "The potentially harmful circulatory effects resulting from the use of the respirator or the occurrence of transient anoxemia and hypercapnia appeared to be all that was necessary to convert a transient hypertensive state to a seemingly permanent one. Renal hypertensive mechanisms may have been stimulated in this way to produce an irreversible hypertensive state." These investigators reported a high titer of vasoexcitor material in the blood of 5 cases; in 3, the level was "exceptionally high." That some abnormal mechanism involving the autonomic nervous system is involved in the pathogenesis of hypertension in poliomyelitis is suggested by the report of Reilly and Barsanti,\textsuperscript{43} who found that 19.4 per cent of cases of bulbar and spinal forms of the disease developed hypertension following the administration of tolazoline (Priscoline).

It is obvious that hypertension is a problem of varying etiology and significance in poliomyelitis. The transient elevations of blood pressure in severely ill patients, especially those with some degree of ventilatory difficulty, are in all probability related to hypoxia and hypercapnia, since, in most instances, normotension follows procedures that produce adequate oxygenation. Suboxygenation is, however, an inadequate explanation for the hypertension that persists despite restoration of effective ventilation. There seems to be little doubt that disease of the hypothalamus or medulla may be the initiating mechanism in such cases. As has been suggested,\textsuperscript{43} the methods used to produce artificial respiration may play a role in the pathogenesis of blood pressure elevation. Urinary tract infection, with or without obstruction, must be ruled out in every instance.

The hypotensive drugs merit a serious trial in all cases of poliomyelitis in which hypertension is sustained because, if allowed to persist, the elevated blood pressure may add to the already present incapacity or even cost the patient his life. Poliomyelitis offers an important clinical situation for the study of the possible role of neural mechanisms in the pathogenesis of hypertension. In addition, in this disease, the natural history of elevated blood pressure may be investigated from the very moment of its inception through its entire course.

**PULMONARY EDema**

Pulmonary edema is a common event in patients who die of poliomyelitis. It frequently precedes the final episode of "circulatory collapse" or shock and is often difficult to detect because, in most instances, it occurs in individuals who are severely ill in tank respirators, or have "bulbar" disease and are highly susceptible to pneumonia which may be difficult to distinguish from edema of the lungs. The presence of fluid in the pulmonary tissues is often suspected because coughing or tracheal aspiration yields pink, frothy fluid. Persistent hypoxia resistant to all efforts at artificial respiration also suggests the presence of pulmonary edema; in many cases, however, it is discovered only at necropsy.

A number of factors may be involved in the production of pulmonary edema in poliomyelitis.

**Hypoxia.** It has been postulated that hypoxia is the initiating event in pulmonary edema.\textsuperscript{38, 43} While such an association may be inferred from the presence of pulmonary
edema relatively early in the course of inadequate ventilation, it is very often impossible to be certain that edema of the lungs is not the situation responsible for the anoxia. In guinea pigs dying under conditions of hypoxic hypoxia, Hemingway was unable to find pulmonary edema. In these experiments, conditions were so selected that severe hypoxia would occur but the animals were killed before heart failure supervened. Since anoxia and pulmonary edema tend to propagate each other, it is obviously impossible to conclude which is the initiating factor when they are present simultaneously.

Oxygen Poisoning. Although there is no evidence for the incrimination of oxygen poisoning in the pathogenesis of pulmonary edema in poliomyelitis, some recently published experimental observations suggest this as a possibility. When guinea pigs were kept constantly in an environment of 90 to 95 per cent oxygen at barometric pressure of 73 to 75 cm. Hg, they developed edema of the lungs. The condition became progressively worse and death occurred after 4 to 6 days. Studies of the lungs indicated an approximate doubling in their weight and in the soluble protein nitrogen that they contained. Pulmonary hemoglobin, while quite variable in amount in different lungs, did not increase significantly in the entire lung during oxygen poisoning, but histologic examination revealed intense congestion in localized areas. In view of the fact that a great many of the patients with poliomyelitis who require artificial respiration and those with “bulbar” involvement are often treated with high concentrations of oxygen for long periods, oxygen poisoning as a cause of pulmonary edema in this disease merits serious consideration and investigation.

Pulmonary Infection. Many patients with respiratory muscle paralysis or involvement of cranial nerves IX and X develop bacterial infections of the bronchopulmonary tissues, especially if they have been subjected to tracheostomy. Others have an interstitial pneumonitis possibly due to poliomyelitis virus. In a considerable number of such cases pulmonary edema develops. Although mechanisms unrelated to pulmonary infection may be responsible for the edema of the lungs in these instances, the probability that the inflammatory reaction associated with the infectious process may increase the intensity of edema produced by some other factor must be considered. Whether or not pneumonia itself produces pulmonary edema in poliomyelitis remains to be ascertained.

Circulatory Changes Induced by Artificial Respiration. Circulatory changes of varying intensity are produced by artificial respiration, an obligatory method of therapy in patients suffering from paralysis of the muscles of respiration. That such alterations in hemodynamics may be responsible for pulmonary edema is entirely possible. The effect of artificial respiration on circulation is discussed in detail below. Since the life of the individual depends completely on the use of the tank or other type of artificial respiration, little can be done to avoid this possible cause of edema of the lungs. It has been suggested, however, that proper application of breathing apparatus may prevent or eradicate pulmonary edema.

Central Mechanism. Pulmonary edema occurs with greatest frequency in severe bulbar or bulbospinal poliomyelitis. This observation has led to the suggestion that the most important factor in the pathogenesis of edema of the lungs in this infection is involvement of the medulla. The situation has been compared to that which arises when increased intracranial pressure or severe irritation of the brain occurs with other diseases. Very strong circumstantial evidence in favor of this hypothesis is the frequent presence of severe damage of the medulla in cases in which pulmonary edema has been present. While it is possible that medullary involvement may be most important and even the primary initiating event, absolute proof of its significance is still lacking. Austen and co-workers have questioned this hypothesis; they place maximum emphasis on unsaturation of the blood in oxygen as the primary mechanism. The possibility that medullary changes initiate pulmonary edema that is then propagated and increased by the operation of other factors is worthy of investigation.

Involvement of the Heart. Not all cases of
poliomyelitis that develop pulmonary edema have demonstrable cardiac abnormalities. However, myocarditis of varying degree has been found at autopsy in some instances. In 4 patients with edema of the lungs, Weinstein and Shelokov24 noted severe myocarditis in 2, mild interstitial edema of the myocardium in 1, and myocarditis, verrucous mitral endocarditis, and bilateral pleural effusion in 1. It is entirely likely, therefore, that in some individuals pulmonary edema results from congestive failure due to cardiac damage; in those cases in which electrocardiographic and anatomic studies reveal no involvement of the heart, however, this mechanism is of no significance.

Vasoconstriction. On the basis of observation of transient hypertension in patients who subsequently developed edema of the lungs, Hildes, Schaberg, and Alcock45 have postulated that severe vasoconstriction may be an important factor leading to heart failure and pulmonary edema. Such a mechanism would be greatly enhanced by the presence of cardiac damage due to viral myocarditis; this was common in the cases studied.

Overhydration. Dehydration and difficulty in adjustment of fluid and electrolyte balance are common in patients severely ill with poliomyelitis, particularly in those with high temperature, vomiting, and diarrhea. Unless great care is exercised in the administration of water and sodium chloride, overhydration may lead to pulmonary edema. It is very important for the physician to be constantly aware of this possibility and to make every effort to maintain normal electrolyte and fluid balance by frequent study of urine specific gravity, hematocrit, and serum levels of sodium, chloride, and carbon dioxide.

It is apparent from the above review that the etiology of pulmonary edema in a given case of poliomyelitis may be quite obscure. On the basis of studies revealing the presence of severe medullary damage in most patients succumbing with edema of the lungs, the writer is at the moment most inclined toward the theory that disease of the medulla is the primary initiating event; yet it is obvious that other factors may be important contributory causes or, in some instances, may even be solely responsible. Clinical observations suggest strongly that when complications such as myocarditis, pulmonary infection, anoxia, or shock are present, several mechanisms probably operate simultaneously or in sequence to produce pulmonary edema. The probability remains, however, that destruction of the medulla is the keystone of this phenomenon.

Treatment of pulmonary edema in poliomyelitis is difficult and often ineffective. Oxygen should be given in all cases. Positive pressure breathing with the Jefferson ventilator has been thought to alter the process favorably, and merits trial.45 Although various measures designed to combat cardiac failure have been applied, there are no controlled studies to indicate their usefulness; when myocardial damage is evident, this type of therapy might be attempted. If bronchopulmonary infection appears to be a contributing factor, early and intensive administration of a properly selected antimicrobial agent is obviously indicated. The inhalation of alcohol vapor is worthy of consideration. The prevention of pulmonary edema may be more rewarding than any attempts to eradicate it after it has once appeared. Maintenance of proper oxygenation of the blood by insuring adequate ventilation, avoidance of overhydration, the use of hypotensive agents during periods of hypertension,45 guarding against oxygen poisoning, proper regulation of apparatus for artificial respiration so that circulatory disturbances are minimal, and establishment of proper fluid and electrolyte balance may all be of vital importance in preventing the development of edema of the lungs. Unfortunately, there are no methods for preventing or altering the course of the medullary destruction that results from viral invasion and that may be the focal point of the problem.

Circulatory Changes Produced by Artificial Respiration

In addition to the fact that patients severely ill with poliomyelitis, particularly adults, are susceptible to a variety of cardiovascular complications as a result of myocarditis, involvement of the medulla, hypertension, shock
etc., they are also the ones who usually have paralysis of breathing muscles and require artificial respiration. This type of treatment always imposes an additional load on the circulation; in some cases, this may be sufficient to precipitate a serious situation as a result of alteration in hemodynamic equilibrium that may already be unstable.

There is clear-cut evidence that artificial respiration induced by a tank or cuirass respirator under negative pressure is physiologically and mechanically the same as that which results from application of positive pressure to the upper airway.\textsuperscript{47, 50-53} Positive airway and negative intratrunk pressure produce identical changes in intrapulmonic, intrapleural, intracardiac, and systemic arterial and venous pressures. The results of these changes are (a) impairment of the circulation and decrease in cardiac output, (b) increase in cerebral venous and spinal fluid pressures, (c) rise in venous pressure, (d) loss of blood volume, and (e) increased filling of the venous bed and arteriolar constriction.\textsuperscript{55} Adequate ventilation without serious interference with venous return may be accomplished if positive pressure breathing is applied properly.\textsuperscript{54} The positive phase of inspiration should build up slowly, release rapidly, and occupy less than 50 per cent of the total respiratory cycle. Other types of positive pressure curves cause reduction of cardiac output. In the individual who has normal hemodynamics at the time of institution of artificial respiration, compensatory mechanisms that tend to overcome the deleterious circulatory effects are actuated. These have been described clearly and succinctly by Whittenberger and Sarnoff\textsuperscript{47}: “When positive pressure is applied to the airway, a large fraction of the increase is transmitted to the pleural space, great veins, and right auricle. The resulting elevation in right auricular pressure momentarily decreases the venous gradient. Venous return and cardiac output are thus momentarily decreased, but rapidly recover because there occurs a rise in peripheral venous pressure which \textit{reconstitutes the venous gradient} and thus re-establishes venous return. The reconstitution of the venous gradient, therefore, is an essential factor in maintaining normal cardiac output during positive pressure breathing. The mechanism of reconstituting the venous gradient is dependent upon the existing vascular tone, the capacity for reflex vasoconstriction, and the presence of a normal circulating blood volume. This concept is essential to the understanding of circulatory phenomena during artificial respiration.” The increase in peripheral venous pressure required to re-establish the venous gradient causes a rise in capillary filtration pressure, which results in a reduction of the circulating blood volume.\textsuperscript{55, 56}

When the sympathetic pathways are inactive, re-establishment of the venous gradient after the application of positive pressure is either greatly diminished or absent.\textsuperscript{57} Because of this, venous return, cardiac output, and blood pressure fall in direct proportion to the degree of pressure applied. When intense generalized vasoconstriction is present, as is not infrequently the case in severe poliomyelitis where diffuse involvement of the sympathetic nervous system is common, positive pressure breathing produces a decline in arterial pressure, because the mechanisms responsible for reestablishing the venous gradient are already maximally active. If artificial respiration is induced by means of the electrophrenic respirator, which produces negative intrapleural pressure, the arterial pressure is elevated. This type of mechanical breathing is of no value, however, in cases in which phrenic-intercostal nerve involvement is present because stimulation of the phrenic nerve becomes impossible within a short time after onset of paralysis as a result of rapid axon degeneration. Distention of the stomach and intestine often result from the application of positive pressure to the airway by a face mask but not when it is applied through a tracheotomy or endotracheal tube. This complication is serious because of the undesirable reflex vagal effects of gastrointestinal dilatation, the increased difficulty of expanding the lung by any means, and the probable retardation of venous return by a tense abdomen.\textsuperscript{47}

It must be stressed that the effects of negative pressure in a tank respirator are identical with those produced by positive pressure ap-
plied to the airway. Because of this, tank or cuirass respirators produce the same hemodynamic changes as occur when artificial respiration is induced by positive pressure apparatus. As a result, respirators that enclose the body reduce venous return and cardiac output if shock or peripheral vasodilatation is already a problem. Negative tank pressures intensify shock. A decrease in venous return may be desirable, however, in the presence of pulmonary edema. When a significant degree of hypotension is present, the use of an intratank positive pressure phase, alternated with a negative one, both of approximately the same degree, increases venous return.

Circulatory difficulties may arise during the period of "weaning" from the tank respirator. Donhardt" suggested that cardiac damage resulting from poliomyocarditis created unfavorable conditions for the strain that, in some instances, was imposed on the right and also left side of the heart by the resumption of spontaneous respiration. The consequences of hypoxia or hypercapnia or both associated with spontaneous respiration were presumed to be the important feature. Whereas the strain on the left heart might be judged easily on the basis of a rise in the systemic blood pressure, the increase of pressure in the pulmonary circulation resulting from hypoxia could be measured directly only by cardiac catheterization. An important indication of pressure changes of this type was obtained from electrocardiographic study; a shift of the QRS axis and changes in ST and T were considered to be early signs of incipient over-strain. Careful observation of the blood pressure, pulse rate, electrocardiogram, and respiratory function were thought to be helpful in avoiding cardiac damage during the "weaning" period. The use of hypotensive agents was recommended for the management of hypertension; the administration of cardiac glycosides was suggested if electrocardiographic signs of cardiac damage occur despite cautious weaning.

**SHOCK: "CIRCULATORY COLLAPSE"**

The final event in the life of most individuals who succumb to poliomyelitis is shock or "circulatory collapse." This occurs only in cases of bulbar or bulbosepinal disease in which there is involvement of the ninth and tenth cranial nerves, or when respiratory muscle paralysis is present. It may appear very early in advancing bulbar poliomyelitis, or may be delayed for as long as a week in respirator patients with advancing loss of motor power. In some instances, a period of hypertension that may or may not be related to hypoxia precedes the fall in blood pressure. In the early stage of shock, the skin has a flushed, florid appearance, the pulse is rapid and sometimes irregular, and the pulse pressure is small despite the presence of normotension. Later, however, there is intense vasoconstriction with cold, clammy mottled skin, anxiety, restlessness, and confusion. Hypotension of severe degree usually develops very rapidly. At this stage hyperthermia (105 to 110 F.) is common; the pulse is very rapid but usually regular. In cases in which shock occurs early in poliomyelitis, there is often clinical evidence of pulmonary edema.

A number of mechanisms may be involved in the pathogenesis of shock.

**Destruction of the Vasomotor Center.** Baker and his associates have postulated that involvement of the vasomotor center in the medulla is the responsible factor. Histologically, the area of the reticular substance was damaged in most of their patients. Such a lesion should lead to a general absence of sympathetic activity with postural hypotension. Hildes and his co-workers, however, have emphasized the fact that intense vasoconstriction is present when "circulatory collapse" develops. They found severe lesions in the region between the floor of the fourth ventricle and the olivary nucleus in the upper part of the medulla. There was no apparent difference between the patients dying of shock and those in whom death was due to other causes. On the basis of studies of oxygen saturation, Austen and associates have also questioned the significance of disease of the vasomotor center: "The concept of peripheral vasomotor collapse as a direct consequence of involvement of the medullary vasomotor center does not account for the presence of arterial oxygen unsaturation..."
during the normotensive or hypertensive phase.” In this regard, it should be pointed out that medullary involvement may be responsible for the elevated blood pressure. In addition, hypoxia occurring prior to the development of shock may act only to produce an added increment of damage to a medulla injured by the virus of poliomyelitis; this may be sufficient to increase the degree of already present dysfunction to a point where complete failure develops and “circulatory collapse” appears.

**Hypoxia.** For a long time hypoxia has been suggested as a very important factor in the development of shock in poliomyelitis. In this connection, it is important to emphasize that observation of the color of the skin and mucous membranes may be completely misleading, because a considerable degree of arterial oxygen unsaturation may be present in the absence of detectable cyanosis. It is not clear whether shock is directly related to the mere presence of inadequate oxygenation, or, as suggested above, that anoxia produces added damage to the vasomotor center which then results in severe hypotension. It has been suggested by Christie that all deaths from acute poliomyelitis are due to hypoventilation. Although Hildes and his colleagues stated that this cannot be categorically denied on the basis of their observations, the majority of the patients whom they studied were not in respiratory distress at the onset of shock, and no evidence of airway obstruction or asphyxia from other causes was discovered at necropsy. Austen and co-workers considered hypoxia a very important factor in the pathogenesis of shock in poliomyelitis, but attributed the suboxgenation to a pulmonary mechanism such as edema of the lungs rather than to involvement of the vasomotor center. Although there seems to be little doubt that arterial oxygen unsaturation probably plays an important role in the development of “circulatory collapse,” the exact mechanism by which it acts is at present obscure. Whether it produces its effect directly or by altering medullary or cardiac function or both is not clear. The writer has observed a number of patients who have died in a state of cardiovascular collapse in whom, by actual measurement, there was no evidence of hypoxia in the early stages of shock and no obstruction to ventilation at autopsy. In many cases, on the other hand, pulmonary edema and arterial oxygen saturation have been detected prior to death. It is my opinion, nevertheless, that dysfunction of the vasomotor center due to invasion by the poliomyelitis virus is the primary factor responsible for shock, and that this effect is hastened and increased in degree by hypoxia due to pulmonary edema, infection of the lungs, airway obstruction, or failure to produce an adequate degree of artificial respiration.

**Pulmonary Edema.** Since involvement of medullary centers by the virus of poliomyelitis may be concerned both in the production of pulmonary edema and cardiovascular collapse, it is very difficult to attribute an isolated role to edema of the lungs in the pathogenesis of shock. However, because there is good evidence that suboxgenation of the blood may be an important contributing factor, and because pulmonary edema may be responsible for hypoxia, edema of the lungs is probably only of secondary significance. Austen’s group considered that “pulmonary edema is a major factor in the production of circulatory collapse. The effectiveness of increased concentrations of oxygen in reversing the arterial oxygen unsaturation and hypotension is in accordance with this concept.” This suggests that it is not the pulmonary edema itself but the hypoxia secondary to it that is the “major factor.”

**Alteration in Hemodynamics by Artificial Respiration.** As described above, positive pressure applied directly to the airway or negative intratrunk pressure around the body produce impairment of venous return and decreased cardiac output in poliomyelitis patients in whom the sympathetic pathways are inactive, and lead to hypotension and the shock state. The fact that, in individuals without sympathetic dysfunction, artificial respiration does not lead to “circulatory collapse” because of the activity of compensatory mechanisms, suggests that this type of therapy itself may not be a primary factor in the etiology of shock except in certain cases in which it adds sufficient additional burden to unstable blood-
pressure-maintaining mechanisms so that a precarious balance is upset and hypotension results. This hypothesis is supported by observations of respirator patients with secondary infections. I have studied two individuals with bulbospinal poliomyelitis who, while in respirator tanks, developed pneumonia. At the beginning of the infection, the blood pressure was maintained despite the use of negative pressure around the body. In one case, rapidly progressing hypotension occurred very soon after the initiation of the secondary pulmonary disease, while, in the other, it did not appear until about 3 days after the infectious process was established. In both instances, because they were able to sustain unassisted respiration for about 2 hours, the patients were removed from the tank. This led to the prompt restoration of the blood pressure to normal levels. Resumption of artificial respiration quickly resulted in the reappearance of hypotension, despite the use of positive-negative pressure. Removal from the respirator again produced a normotensive state. Treatment over the next few days consisted of giving as much unassisted breathing as possible, the use of the rocking bed, and short periods of rest in the respirator tank consistent with maintenance of normal blood pressure. When the pneumonia had been cured by appropriate chemotherapy, instability of the blood pressure disappeared, and treatment with the tank respirator was continued without event. These cases illustrate the effect of alterations in hemodynamics produced by artificial respiration in contributing to the development of "circulatory collapse" when they are imposed on a situation, infection for example, which itself may produce shock. It appears entirely possible, therefore, that hypotension following artificial respiration in poliomyelitis is for the most part related to hemodynamic changes in patients who are already conditioned by some other mechanism for the development of shock.

Vasoconstriction and Myocarditis. Hildes, Schaberg, and Alcock have suggested that vasoconstriction in combination with myocarditis constitutes the mechanism for the development of cardiovascular collapse. It is possible that the pulmonary edema resulting from the operation of these factors leads to hypoxia that is instrumental in producing the shock state.

Infection. Severe infection of any type may produce "circulatory collapse." The mechanism of this type of shock is unknown. Secondary bacterial infection in poliomyelitis contributes to shock primarily when severe bulbar or bulbospinal disease is present; it rarely causes appreciable hypotension in mild to moderately severe spinal paralytic cases. Although it may occur at any time, shock is most frequent if bacterial infection is superimposed on poliomyelitis during the first 1 or 2 weeks. While pneumonia is the commonest offender in this regard, acute pyelonephritis, a common complication of the use of retention catheters in the urinary bladder, or any infection with associated bacteremia may trigger the development of circulatory collapse. In poliomyelitis, the frequency of "circulatory collapse" following secondary infection is related to the presence of an unstable hemodynamic situation resulting from the primary disease and its treatment, in the majority of instances.

Adrenal Insufficiency. It has been thought that, because of the sudden development of a high grade stress situation in severe poliomyelitis, acute adrenal insufficiency develops rapidly and produces "circulatory collapse." In some cases, the adrenal glands have been found to show a varying degree of the anatomic changes usually associated with stress. There is, however, no chemical evidence to support this hypothesis, and treatment with adrenal steroids is usually without effect in restoring the blood pressure to normal levels.

It is evident that the etiology of "circulatory collapse" in poliomyelitis is not clear. While such factors as hypoxia, medullary damage, pulmonary edema, hemodynamic changes produced by artificial respiration, secondary bacterial infection, and myocarditis with cardiac failure may all be of importance in the pathogenesis of shock, it is impossible to determine the primary mechanism on the basis of the evidence presently available. In a disease like poliomyelitis in which multiple functional derangements are often present, probably no single factor is responsible, but shock results
from the combined effects of 2 or more mechanisms operating simultaneously or in sequence with enhancement of their hypotensive effects. It is my opinion that the 2 most important causes of "circulatory collapse" in poliomyelitis are disease of the vasomotor center and hypoxia. That the medulla may be the focal point of this problem is strongly suggested by the observation of most investigators that shock is practically limited to cases of poliomyelitis in which bulbar (particularly cranial nerves IX and X) or bulbospinal involvement is present. The significance of shock in this disease cannot be overemphasized. The importance of intensive study of this phenomenon and elucidation of its definitive mechanisms is reflected in the fact that shock is practically always the final event in the life of patients with poliomyelitis.

A great variety of measures have been used to treat "circulatory collapse" in poliomyelitis. Although plasma transfusions have been given, there is no evidence to support their usefulness. Adrenal steroids have been administered in many cases without detectable beneficial effect. Nothing can be done to alter the course of events produced by the poliomyelitis virus in the medulla. Much can be done, however, to assure adequate ventilation and prevent arterial oxygen unsaturation by establishing patency of the airway, administering oxygen, and applying adequate artificial respiration. The deleterious effects of positive pressure on hemodynamics can be minimized by proper use of the apparatus employed for artificial respiration. When secondary bacterial infection is related to "circulatory collapse," the most effective therapy is rapid control of the infectious process by early and intensive exhibition of properly selected antimicrobial agents.

Among the drugs most widely used in the treatment of shock in poliomyelitis as well as other infections are the vasopressor compounds, especially norepinephrine. While the intravenous instillation of this agent usually returns the blood pressure rapidly to normal levels, the common experience is that increasing quantities are required until, after 2 to 3 days, refractoriness develops and shock deepens despite the injection of very large doses. Only rarely have I observed a case in which norepinephrine or other vasoconstricting drugs have produced a permanent return of normal blood pressure that was maintained without further therapy. Because of the presence of marked vasoconstriction preceding "circulatory collapse," Hildes and his co-workers suggested that vasoconstrictor drugs would not be expected to be of value; however, norepinephrine seemed to be "of definite benefit" in some of their patients. Remington and associates believed that such drugs might actually be harmful in spite of temporary improvement in blood pressure. On the basis of clinical experience, however, the use of vasoconstrictor agents should be continued until a more effective form of therapy becomes available. Of more importance than the treatment of shock in poliomyelitis is its prevention by elimination of the factors that produce it, or by minimizing their effects if they cannot be eliminated. The treatment of "circulatory collapse" in this disease will become effective only after the investigations necessary to unravel the complex knot of its etiology have been carried out.

**Phlebothrombosis, Thrombophlebitis, and Pulmonary Infarction**

Very little information is available in the medical literature concerning phlebothrombosis, thrombophlebitis, and pulmonary infarction in poliomyelitis. Although mentioned by various investigators, data relative to incidence and predisposing factors are meager. Ferris found 9 instances of thrombophlebitis in 69 cases of chronic or convalescent poliomyelitis with respiratory difficulty. Involvement of the veins occurred in all age groups but was commonest in young to early middle-aged adults. The left leg was affected in every instance, although 1 individual also had venous thrombosis in the right leg. The interval between the onset of nervous system infection and the appearance of vascular occlusion extended from 10 days to several months in the paralyzed patients. Thrombophlebitis and phlebothrombosis occurred most frequently in cases requiring artificial respiration. It must be pointed out, however, that they may appear
even when loss of motor power is limited to a single limb.

Several factors may be involved in the production of peripheral venous thromboses in poliomyelitis. Many episodes of inflammatory occlusive disease of the veins follow a “cut down,” especially if plastic tubing is inserted, because this procedure is associated with a high risk of secondary staphylococcal infection. Thrombophlebitis may occur, however, in the absence of any surgical manipulation. Phlebothrombosis is probably the result of circulatory stasis secondary to immobility of paralyzed muscles, obstruction of venous return by malposition of limbs, direct pressure by supportive pads, vigorous physiotherapeutic measures, delayed weaning from artificial respiration, or elevated hemoglobin levels resulting from dehydration or chronic hypoventilation. That the problem is not restricted to the peripheral veins and that it is a potentially dangerous complication of poliomyelitis are emphasized by the not infrequent occurrence of pulmonary infarction, which is often unsuspected until demonstrated by the pathologist.

The diagnosis and treatment of thrombophlebitis and phlebothrombosis are no different in poliomyelitis than in any other situation in which they occur. The administration of anticoagulants, especially in the early phase of the disease, requires special care, however, because of (a) the possibility of bleeding from gastrointestinal erosions, which are common, and (b) the presence of hypoprothrombinemia, which is frequent in severely ill respirator patients, particularly if they are receiving large quantities of antibiotics. Among the measures that may be of value in decreasing the risk of venous thrombosis are adequate hydration and proper ventilation to avoid hemoconcentration, moving patients about as much as is compatible with the state of their disease, early weaning from the respirator tank, placing patients on rocking beds, avoiding pressure over the veins of the extremities resulting from malposition or supportive pads, and eliminating the use of intravenously placed metal cannulae or plastic catheters for more than short periods of time.

The importance of venous thrombosis in poliomyelitis cannot be overemphasized. Despite the fact that young people with other diseases are much less prone to the development of phlebothrombosis than older individuals, paralytic poliomyelitis presents a situation that makes patients of any age susceptible to this complication and its potentially tragic sequelae. Death in an unknown number of cases of poliomyelitis results from massive pulmonary infarction and not from the virus infection of the nervous system. The physician attending cases of this disease must be constantly sensitive to the possibility of peripheral venous thrombosis and infarction of the lung so that he can carry out the necessary prophylactic and therapeutic measures before the clinical situation gets out of control.

**Blood Vessels**

Involvement of the sympathetic nervous system is common in paralytic poliomyelitis and may be of severe degree. That this leads to vasospasm with the development of a variety of signs and symptoms has been suggested by several investigators. Smith and his co-workers attributed cyanosis to spasm of the pulmonary blood vessels resulting from involvement of the thoracic portion of the nervous system, and also attributed various types of rashes and severe, indolent, necrotic Schick reactions to angiospasm in the skin. Anatomic studies by these observers showed edema of the sympathetic ganglia, small foci of infiltration in the ground substance, and degenerative changes in the ganglion cells, which appeared shrunken with obscured or absent nuclei. Oscillometric studies revealed vascular spasm. Nicotinic acid dilated the normal but not the spastic vessels. They postulated that the blood vessel disturbance in chronic poliomyelitis is like that in Raynaud’s syndrome, and that the cramplike pain is similar to that of peripheral arterial claudication. Zellweger and Morf suggested that vasodilatation is present in the initial phases of poliomyelitis; skin temperature and oscillometric response were both increased in the paralysed extremity. Later in the disease, however, they found vasospasm on the affected side but not on the unaffected one. In another study of chronic poliomyelitis, Kottke and Stillwell observed that vascular changes
were not related to the degree of paresis of an extremity, and occurred in the absence of muscle weakness. The coldness, cyanosis, edema, and pain of the involved areas were presumed to be due to vasoconstriction resulting from sympathetic overactivity. In the constant temperature room, emotional stress increased vasospasticity. These investigators had the following comments to make concerning the etiology of the vasospasm: "The lesions in the spinal cord in poliomyelitis are consistent with these physiological evidences of sympathetic disturbances. Involvement of the sympathetic nuclei in the intermediolateral columns of the cord with destruction both of the internuncial neurons and of the preganglionic sympathetic neurons occurs frequently. Severe lesions of the anterior horns of the spinal cord are always accompanied by lesions of the lateral columns. In some cases, there may be diffuse destruction in both areas without severe muscle paresis. Destruction of internuncial cells might result in release of the spinal sympathetic nuclei from the control of the higher centers. With release from inhibition, the sympathetic neurons show an excessive response to stimuli from other sources. The sympathetic reflexes are exaggerated. Nerve impulses from any origin impinging on the sympathetics result in increased sympathetic activity and vasoconstriction."

 Abramson and his co-workers\textsuperscript{47} were unable to detect any evidence of vasospasm in patients with poliomyelitis. They studied the peripheral circulation in 27 cases of this disease by means of the venous occlusion plethysmographic method. Five were examined within 2 to 4 weeks after termination of the "contagious stage"; the other 22 had had poliomyelitis 1 to 30 years prior to the investigation. No differences could be detected in the blood flow in the 2 groups. In the majority of instances, the peripheral circulation in the paralyzed limb was the same as that in the contralateral normal one; in some, it was even significantly greater. Evidence was obtained that the cutaneous blood vessels in the extremity affected by poliomyelitis responded more markedly to the stimulus of cold than did those of the uninvolved limb. Study of the changes in blood flow during reactive hyperemia following arterial occlusion suggested that the metabolism of muscles atrophied by poliomyelitis was the same as that of normal tissue.

 In an attempt to elicit the pathogenesis of the cold, clammy, and often cyanotic extremities frequently observed in both the early and the late phases of poliomyelitis, Trott, Hellstrom, and Green\textsuperscript{46} made a study of skin and muscle temperatures in the first 40 days after onset of the disease, and in chronic cases; only those with paralysis of a single extremity were investigated. No differences in skin temperature of the paralyzed extremity when compared to the unaffected one could be detected at 0, 21, and 40 days after poliomyelitis first appeared. Ten determinations were made of the temperature of paralyzed gastrocnemius muscles and corresponding uninvolved ones; 5 were studied in the first 20 days, and 5 between 21 and 40 days after the disease started. The values were found to be essentially the same on both sides. In the chronic stage of poliomyelitis, on the other hand, the temperature of the paralyzed gastrocnemius was very much lower than that of the normal muscle. These observations in chronic poliomyelitis are the same as those previously made by Gucker, Green, and Anderson.\textsuperscript{46}

 From the evidence cited above, it appears that, while peripheral vasoconstriction is probably a very common phenomenon in chronically paralyzed muscles, angiospasm may not be a feature of the early phase of poliomyelitis. The mechanism of the cold, blue, clammy, paralyzed extremity that is seen early in the disease is not clear and requires further investigation.

 A very interesting study of the blood vessels in poliomyelitis was carried out by Bloch,\textsuperscript{49} who observed the conjunctivae of patients in the acute phase of the disease with a stereoscopic microscope. He found aggregates of erythrocytes in the circulation in every case; these were frequently associated with various degrees of anemia and low blood volume. The capillaries were plugged and the rate of flow through venules was reduced. A common finding was excessive plasma fluid loss that
resulted in microscopically visible edema of the conjunctiva. A varying degree of hemoconcentration was observed in the small veins of the conjunctiva in every instance. Dilatation and sacculation of the small veins and frank hemorrhage occurred with the maintained reduction in blood flow. There was a progressive and persistent anemia of the arterial blood; associated with this was constriction of the arterioles, capillaries, and venules. Prolonged vasospasm frequently cut off the flow of blood in more than half of the capillary beds in the bulbar conjunctiva. The severity of the intravascular abnormality was roughly proportional to the extent of the symptomatic involvement of the central nervous system.

Because of the clinical impression of decreased vascular supply in paralyzed extremities in poliomyelitis, various measures designed to increase blood flow and to treat shortening of limbs have been employed in the chronic stage of the disease. Harris\textsuperscript{31} performed lumbar sympathectomy in patients with paralysis of a leg and found that the operation produced vasodilatation and paralysis of the sweat glands with increased warmth and dryness of the foot. Calorimetric studies indicated that sympathectomy caused a considerable increase in the blood supply of the affected limb. The beneficial vascular changes appeared to be of prolonged duration, possibly permanent, and rate of growth of the leg was accelerated. When the main arteries of a chronically paralyzed extremity were exposed at operation by Telford and Stopford,\textsuperscript{72, 73} they were found to be much smaller than normal. On the basis of this observation, it was suggested that the loss of normal stimuli created by muscle activity was responsible for the poor development of the arteries and that the latter was proportionate to the loss of voluntary power. Bilateral lumbar sympathectomy was found to be effective in increasing blood supply. Sympathectomy was also carried out by Robertson\textsuperscript{74} and Ogilvie\textsuperscript{75} to restore normal blood flow in paralyzed extremities.

One of the important long-term effects of poliomyelitis is retardation of bone growth and shortening of the involved extremity. Sympathectomy has been found by Harris and McDonald,\textsuperscript{76} White and Smithwick,\textsuperscript{77} and others\textsuperscript{74, 75} to result in resumption of growth in most instances. Of 46 patients operated upon by Harris and McDonald,\textsuperscript{76} 20 had diminution of shortening and 7 showed no change, while in 5 the shortness continued to increase after the surgical procedure. In 12 cases, a beneficial effect present early was later lost.

Other approaches to the problem of increasing blood supply in paralyzed extremities late in poliomyelitis have been the use of tolazoline (Priscoline)\textsuperscript{42, 66, 71} and sympathetic nerve block\textsuperscript{79} (lumbar paravertebral in lower extremity and stellate ganglion block in arm involvement). Although good results have been reported, experiences of different investigators with these procedures differ and they require further evaluation.

**SUMMARY AND COMMENTS**

A review of the cardiovascular phenomena that may occur in poliomyelitis clearly reveals that changes in the heart, alterations in hemodynamics, hypertension, shock, and blood vessel abnormalities, while of variable incidence and severity, may alter the course of the infection unfavorably, or even be responsible for death. These complications may be produced either by direct viral invasion (poliomyocarditis) or be indirectly due to severe damage to the nervous system (persistent hypertension, shock).

Myocarditis with demonstrable anatomic, clinical, and electrocardiographic changes is a well-documented phenomenon in poliomyelitis. There is strongly suggestive evidence that verrucous endocarditis and pericarditis may also occur. Hypertension may be transient or persistent; when of short duration it usually reflects hypoxia, but when prolonged is probably due to hypothalamic involvement. Pulmonary edema and "circulatory collapse" are usually very serious complications and are associated with a very poor prognosis for survival; they appear most frequently in the bulbar (cranial nerves IX and X) or bulbospinal types of the disease. A number of mechanisms have been suggested for these phenomena but
the exact manner of their development is still obscure. Marked alterations in hemodynamics occur when a poliomyelitis patient is given artificial respiration. If normal compensatory mechanisms are active, such changes are transient and harmless; if they are inactive, however, the application of positive pressure to the airway or negative pressure around the body usually results in severe hypotension, shock, and death. Although less common than in elderly patients, phlebothrombosis or thrombophlebitis of the extremities, with or without pulmonary infarction, is a constant threat in young individuals afflicted with poliomyelitis. Angiospasm, while not clearly demonstrable in paralyzed extremities in the early phase of the disease, is a very common feature of the late stages and is probably responsible for color and temperature changes as well as retardation of bone growth.

It is interesting to speculate on the long-term effects of the cardiovascular complications that may occur early in the course of poliomyelitis. Although many patients who develop myocarditis later show no clinical evidence of cardiac dysfunction, there is no evidence to prove or disprove the presence of residual cardiac damage. By analogy with myocarditis occurring in the course of other infections, it is not unrealistic to suggest that the heart once injured by the virus of poliomyelitis is no longer completely normal, though the patient survives. This is a matter worthy of careful investigation by means of long-term follow-up study of all patients paralyzed with poliomyelitis but especially those who are found, by clinical or electrocardiographic study, to have cardiac involvement early in the disease. Although a few cases have been studied carefully for a prolonged period, very little is known about the natural history of the persistent hypertension that may first appear in the course of poliomyelitis. It is very likely that the long-term effects of this type of blood pressure elevation are the same as those that follow hypertension due to other causes, but this possibility needs to be investigated. A small number of patients with paralysis of the breathing muscles become chronic respirator cases and require artificial respiration for very long periods of time. The effects of prolonged positive pressure breathing in these individuals may have slowly progressive deleterious effects; these may account for the occasional case of this type in which, for no discoverable reason, death occurs suddenly 2 or 3 years after the onset of the disease. Although long-term neurologic and orthopedic follow-up study of poliomyelitis is common, there is a need for the same type of investigation with attention focused on the cardiovascular system. This has not been carried out, with the probable neglect of a very important aspect of the disease that bears a significant relationship to the course of a patient's life.

The pathogenesis of 2 extremely important cardiovascular events in poliomyelitis, shock and pulmonary edema, the outcome of which very often determines survival or death, still remains to be elucidated. If the number of survivals in severe bulbar or bulboespinal disease is to be appreciably increased, these problems must be solved. Without a clear understanding of the mechanisms involved, any approach to prevention and treatment must be empiric. The importance of intensive investigation of this aspect of poliomyelitis cannot be overemphasized.

Not many years ago poliomyelitis was considered to be a disease of interest primarily to the pediatrician, neurologist, and orthopedist. The increased incidence of this infection in adults in the past 20 years and the evidence that it is generally much more severe in older than the younger individuals points sharply to the necessity for the internist to acquire and cultivate a serious interest in this disease. The presence of cardiovascular complications, which may be of much greater significance in determining the course and outcome of the infection than mere paralysis of an arm or leg, establishes the need for interest by the cardiologist. Only when all of the phenomena that occur in poliomyelitis are clearly understood and properly related to each other, will it become possible to increase the chance for survival and to decrease the impact of the late effects by
the application of scientifically determined specific principles of management.

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Acetazolamide (Diamox) was given to 7 patients with chronic respiratory acidosis in doses ranging from 0.25 Gm. in a single daily dose to 1.5 Gm. daily in divided doses. In all 7 patients the drug caused a fall in plasma bicarbonate and an increase in the tendency to acidosis. In the majority of the patients the acidosis was restored to the level existing before drug administration by hyperventilation. It is thought that administration of this drug in certain patients with chronic respiratory acidosis is not without hazard. One patient is described in whom the arterial carbon dioxide tension rose to very high levels while receiving small doses of the drug and in whom the acetazolamide seemed to prevent any concomitant compensatory rise of plasma bicarbonate. This was interpreted as an increase in hypercapnia unrelated to the acetazolamide but a fortuitous effect due to fluctuation in the sensitivity of the respiratory center. Similar rapid increases of carbon dioxide tension have been observed, however, in acute pulmonary infections, and patients with acute respiratory acidosis and with carbon dioxide narcosis have been reported to show an unfavorable response to acetazolamide.

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