Strokes

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INTRODUCTION

The term "stroke" refers, in its broadest sense, to any neurological event in the brain of vascular origin, whether short-lived or prolonged, mild or serious.

Strokes may be produced by a number of causes, but the pathogenesis may be resolved into one of three fundamental vascular processes — hemorrhage, embolism and thrombosis. The relative frequency of each is still somewhat controversial. Thrombosis, however, is believed to be the commonest — producing 50-70% of strokes. Hemorrhage is said to be responsible for 15-20% of cases; and embolism, while formerly thought to occur uncommonly, is now being recognized with increasing frequency and some implicate it in as many as 35% of cases.

Cerebrovascular lesions are a very important cause of illness, disability, and death. As a cause of death they are exceeded only by heart disease and malignancy. In the United States in 1952, for example, 170,000 people died and 1,800,000 persons were disabled by these lesions. British figures for the same year implicate them in 14% of all deaths.

The therapy of conditions predisposing to cerebrovascular lesions and the management of stroke victims thus is of importance to every practitioner.

ANATOMY

A brief review of the cerebral circulation may be useful at this point.

Arterial blood reaches the brain through four main vessels, the paired vertebral and internal carotid arteries. In general, the vertebrals supply the posterior half and the internal carotids the anterior half of the brain.

The two vertebral arteries, after entering the cranial cavity through the foramen magnum, unite to form the basilar artery at the point of junction of medulla and pons. The basilar, which gives off supplying branches to the cerebellum, bifurcates into the posterior cerebral arteries where pons and midbrain meet. These latter vessels supply the inferior surfaces of the temporal lobes and the entire occipital lobes.

Each internal carotid artery, after entering the skull via the carotid canal, runs forward within the cavernous sinus and enters the subarachnoid space medial to the anterior clinoid process. Then, at the medial end of the lateral cerebral fissure, it divides into its terminal branches, the anterior and middle cerebral arteries, which supply blood to the medial and lateral portions of the hemispheres.

The Circle of Willis, at the base of the brain, joins the vertebral and carotid systems and provides for anastomatic blood flow between them. In addition, anterior, middle, and posterior cerebral arteries are joined by many small, but potentially anastomotic, channels over the cortex.

From the above mentioned larger vessels, smaller, but important, penetrating arteries arise which supply all areas of cerebral tissue. Functionally, these penetrating vessels are "end arteries" so that stoppage of the blood flow in them results in infarction in the particular area supplied. In a location where tracts and functions are highly concentrated such an occurrence produces marked findings.

The venous return from the brain is via the external and internal cerebral
veins. The external group course over the hemispheres and empty into the dural venous sinuses. The internal cerebral veins join the inferior sagittal sinus to form the straight sinus.

**PHYSIOLOGY**

Cerebral tissue is easily damaged by anoxic conditions and so the brain is extremely dependent on an adequate supply of oxygenated blood. Normally, the flow to this structure is remarkably constant, being about 12% of the output of the left heart.

The constancy of flow results from alterations in the blood pressure-peripheral resistance balance. The peripheral resistance is affected by changes in intracranial pressure, blood chemistry and consistency, and the automatic nervous balance (although this latter influence is less in the cerebral circulation than elsewhere in the body). With increasing peripheral resistance, the blood pressure increases to maintain flow and vice versa.

**ETIOLOGY, PATHOGENESIS AND PATHOLOGY**

I. Cerebral Embolism

Sudden stoppage of the flow of blood in a cerebral artery by impaction of the lumen with material carried in the blood stream from elsewhere in the body constitutes a cerebral embolism. The embolic material is usually a piece of thrombus or clot. Occasionally, however, fragments of valvular vegetations, fat, bone marrow, tumor cells, atheromatous material, air or parasites are involved.

Emboli arise from several sources, the most frequent of which is the heart. Emboli may be dislodged from a mural thrombus which has formed over an area of myocardial infarction — particularly when the auricles are fibrillating. Atherosclerotic areas in the arteries leading to the brain provide post-cardiac sites for thrombus formation and embolus production. Clots forming in the vast venous bed of the lungs also may be carried to the head. Pre-cardiac venous thrombi — as in the veins of the lower extremities, abdominal or pelvic cavities — may rarely produce cerebral embolization by passing through a patent foramen ovale.

In considering embolic materials one should remember the vegetations of subacute bacterial endocarditis and bacterial endocarditis on the left heart valves, the possibility of fat and bits of bone marrow entering the circulation from fracture sites, and the hematogenous dissemination of tumor cell clumps. The set-up for air embolization can be present whenever a needle is in a vessel. Parasitic embolization must be a rare occurrence.

The embolus — whatever its nature — is swept along in the circulation until it encounters a point in a cerebral vessel where the lumen is smaller than the embolus. The common points of stoppage are at bifurcations and areas of atherosclerosis. The sudden interruption of blood flow allows no time for collateral circulation to develop so that the infarcted area corresponds quite exactly to the area of tissue normally supplied by the blocked vessel. The cerebral infarction may be pale — if the embolus does not move distally after the initial blockage — or hemorrhagic — if it does move on and blocked vessels re-open. Sometimes emboli disintegrate and the fragments are carried on into peripheral small vessels so that the pathological findings of cerebral embolism are seen without discovering an embolus at the expected place.

Normally, the pathological picture in the infarcted area is one of early softening, followed by liquefaction. This is modified, however, in the presence of infective elements as in subacute bacterial endocarditis and bacterial endocarditis.
II. Cerebral Hemorrhage

There are two types of cerebral hemorrhage, primary and secondary. Primary cerebral hemorrhage results from hypertension—the intraluminal pressure exceeding the strength of the vessel wall. Secondary cerebral hemorrhage results from a variety of conditions, which may be local (e.g., cerebral hemangioma) or general (e.g., thrombocytopenia), and where the cerebral bleeding is one manifestation of another pathological process.

The pathogenesis of primary cerebral hemorrhage—the type with which we are chiefly concerned here—is not known definitely. Some believe that "simple" rupture of healthy cerebral vessels in the face of excessive pressure is the explanation. Others state that rupture occurs through an atheromatous plaque of a diseased vessel wall. While the latter theory is widely held, proponents of the "simple" rupture theory cite cases of cerebral hemorrhage occurring in young individuals with a temporary hypertension—as in an overdosage of adrenaline—where atherosclerosis is absent or minimal. The controversy will probably be resolved when the site of a cerebral hemorrhage is accurately visualized. At present there is no clear idea of the size of the vessel and the size of the lesion for which to look. Since the average volume of a fatal intracerebral hemorrhage is 50-70 c.c., a small hole in a small vessel would suffice to produce this lesion. For example, this volume of blood would accumulate if one drop of blood escaped with every four heart beats during one hour.

Pathologically, the hemorrhage may be classified according to its size—massive, small, slit, or petechial. Massive hemorrhages are extensive to begin with, gradually enlarge, and often rupture into the ventricular system. They are prone to occur in the putamen and the white matter immediately adjacent, the thalamus, the pons, and the cerebellum. Small hemorrhages are abortive ones which occur in the same regions but do not terminate fatally. Slit hemorrhages are small ones which occur at the junction of white and grey matter. They are less common than the previous two types. Petechial hemorrhages occur terminally in cases of acute hypertensive encephalopathy associated with brain edema.

Secondary cerebral hemorrhage, as already noted, may result from general or local pathological states. Examples of the former are hemorrhagic diseases—such as hypoprothrombinemia, thrombocytopenic purpura, scurvy, anaphylactoid purpura, and various infections, and iatrogenic causes such as vigorous anticoagulant therapy and treatment with arsenical compounds. Local pathological conditions include vessel damage resultant from trauma, hemangiomas, cerebral tumors, and aneurysms of the mycotic, arteriovenous, or berry type.

The pathological findings in cerebral hemorrhage consist of blood, surrounded by an area of cerebral tissue which is compressed and may be edematous. As the lesion ages, the blood is absorbed and may be replaced by a neuroglial scar or by a cavity containing a yellow serous fluid.

III. Cerebral Thrombosis

Cerebral thrombosis—the clotting of blood in cerebral vessels during life—may be produced by a number of causes.

The commonest cause, by far, is cerebral atherosclerosis. The atherosclerotic process here is no different from that seen in arteries elsewhere in the body, although ulceration of the surface of the plaques rarely occurs. Thus, thrombus formation in cerebral arteries is likely on the basis of slowed blood flow and stagnation proximal to the area of atherosclerotic narrowing. This gradual slowing of blood flow through the involved vessel leads to the prodromata sometimes seen before complete thrombotic occlusion occurs.

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There are important differences in the atherosclerotic pattern found in normotensive persons when compared with hypertensive individuals.

The normotensive person tends to have the larger arteries involved with a focal type of atherosclerosis which shows definite preferential sites — namely, branches, bifurcations, and bends. Common sites are the carotid sinus, the internal carotid at the paraclinoid portion, and at its bifurcation into anterior and middle cerebral arteries, the first bifurcation of the middle cerebral, the tip of the vertebrae as it enters the spinal canal, the lower and upper bifurcations of the basilar artery, the posterior cerebral artery in the region of the peduncle, and the anterior cerebral as it bends upwards around the corpus callosum.

Thrombus formation most commonly occurs in the internal carotid artery, followed in frequency by vertebral, basilar, and posterior cerebral thrombosis. The large vessels at the base of the brain are less frequently involved in thrombosis than in embolism and hemorrhage; and thrombosis of the middle cerebral artery — a location frequently thought of in the visualization of a thrombotic stroke — is apparently quite uncommon.

The pathological picture resulting from thrombosis in the above-mentioned vessels depend on the condition of the collateral circulation. Usually an area of infarction occurs, but sometimes, since these are larger vessels and the process of occlusion may be gradual, sufficient collateral circulation is present to prevent tissue death.

The hypertensive individual, on the other hand, tends to have a generalized atherosclerosis of the larger vessels rather than the focal type mentioned previously. In addition, and of considerable importance, is the atherosclerotic involvement of the smaller vessels — especially the penetrating branches — found where hypertension exists. The penetrating branches of the middle cerebral arteries (the lenticulostriate group), the thalamic branches of the basilar system along with its pontine and cerebellar branches, as well as other small vessels, such as the posterior inferior cerebellar artery or the central artery of the retina, are frequently affected.

The sites of thrombotic occlusion common in hypertensives are in the small vessels leading to the lenticular nucleus, internal capsule, thalamus, and basis pontis. Since these small vessels are functional end arteries and collateral flow is minimal, small areas of infarction and softening develop in the above areas. This process produces the picture of repeated minor strokes so often seen clinically in hypertensive patients.

Other causes of cerebral thrombosis include syphilitic arteritis, tuberculous or other inflammatory conditions of the meninges, polycythemia, tumors which compress or constrict vessels, and polyarteritis nodosa.

Occasionally a stroke-like picture can result from obstruction of venous outflow by thrombophlebitis of venous sinuses or surface veins. Instead of the usual pathological findings of pale infarction and softening, edema and hemorrhagic infarction of the involved area are seen.

It should be mentioned that infarcted areas of cerebral tissue are found sometimes at post-mortem with no demonstrable occluding mass in the supplying vessels. Some state that this phenomenon is due to cerebral vasospasm alone, while others maintain that this condition results from blockage by an embolus or thrombus which then disintegrates and is washed through into the smaller vessels.

**DIAGNOSIS**

The diagnosis of strokes involves a consideration of the following symptoms, signs, and laboratory and special procedures.
I. History

The patient is usually middle-aged or elderly. Strokes due to thrombosis, on the basis of a syphilitic arteritis, or to hemorrhage, from a Berry aneurysm, are seen in the younger age groups, however. Embolic lesions, naturally, may occur at any age.

The mode of onset is of considerable diagnostic importance. Sudden onset is the story in a majority of cases. Primary hemorrhage and embolism strike without preliminary manifestations. Thrombosis, on the other hand, fairly often produces prodromal transient episodes of paresis, parasthesia, aphasia, dizziness, visual field defects or blindness, confusion or dementia, dysarthria, dysphagia, etc. — on the basis of gradual occlusion and ischemia — before the appearance of the frank stroke. Other times, and especially in hypertensives, however, cerebral thrombosis is not heralded by such warning phenomena.

The pattern of symptom development may be helpful also. In cerebral embolism one finds complete development within 10-30 seconds of the onset. The picture in hemorrhage usually worsens over a period of several minutes, an hour, or very rarely a day, and is dependent on the size and location of the arterial leak. In cerebral thrombosis one sometimes sees a more gradual development — which may be spread over several days — in which the neurological deficit is added to in an interrupted staccato manner — never in a smooth, gradual progression.

Some deductions from the time of and activities at onset may be made. Cerebral hemorrhage most often occurs during the day and frequently with exercise or exertion when the blood pressure is higher. Cerebral thrombosis, on the other hand, tends to occur during periods of lowered blood pressure and slow flow over atheromatous lesions, and so frequently comes on during sleep or shock — e.g. following myocardial infarction. Cerebral embolism, of course, may occur either during the waking or sleeping hours.

Loss of consciousness is a frequent complaint. In embolism and hemorrhage unconsciousness usually follows quite quickly and, especially in hemorrhage, deep coma may ensue. Unconsciousness may be quite transient, may last several hours, or in the case of hemorrhage may persist until death. In cerebral thrombosis the degree of cerebral upset varies from slight confusion to coma.

Paralysis is another frequent report. It may be evidenced by a slumping to the ground during the waking hours or a falling to the floor on getting out of bed in the morning, when the lower extremities are involved.

Other symptoms include paresis, ataxia, parasthesia, visual disturbances, confusion, dysphagia, and dysarthria or aphasia. Generalized or focal convulsions are occasionally reported and are usually associated with cerebral hemorrhage. Headache and vomiting are other symptoms more frequently encountered with hemorrhage than in embolism or thrombosis.

The neurological complaints, of course, depend on the area of cerebral tissue involved — hemiplegia and disturbance of speech being among the more common deficits noted.

II. Physical Examination

The physical findings in stroke cases may be divided into general signs — which are useful in diagnosing the lesions — and neurological findings — which aid in the localization of them.

The blood pressure level should be determined. Hypertension is found in primary cerebral hemorrhage which, for practical purposes, should not be diagnosed in its absence. Hypertension may also be present in certain cases of cerebral thrombosis — namely, those where occlusion of the smaller vessels occurs. Con-
Contrary to the general impression, there is no significant drop in the blood pressure immediately after the onset and the pressure, as first measured, is probably an accurate indicator of the pre-stroke level. Normotensive levels, on the other hand, are found in cerebral thrombosis of the larger vessels and may or may not be present in cases of cerebral embolization.

The respirations are usually labored in the comatose patient. Persistent coma for more than 48 hours and Cheyne-Stokes respiration are bad prognostic signs and favor the diagnosis of hemorrhage.

The body temperature level is variable, usually being elevated, but sometimes normal or subnormal. In fatal cases, regardless of the type of cerebrovascular lesion, there is a progressive rise in the temperature, pulse, and respiratory rate as the patient progresses downhill and the vital centres collapse.

The following findings in the general physical examination may often suggest the diagnosis of vascular lesions involving cerebral tissue. Arteriosclerosis of the retinal or peripheral vessels, hypertensive changes in the fundi, and other evidence of vascular disease, may be seen in cases of cerebral hemorrhage and thrombosis. Similarly, the presence of auricular fibrillation, a recent coronary thrombosis, or findings of bacterial endocarditis are often noted in cases of cerebral embolism. Absence of internal carotid pulsation would indicate occlusion of the vessel on that side and the discovery of neck rigidity could suggest blood in the cerebrospinal fluid from hemorrhage.

The determination of the presence or absence of paralysis is of great importance. This is relatively easy in the conscious person but is more difficult in the stuporous or comatose patient. The paralysis is usually flaccid in type — upper motor neurone lesions exhibiting the phenomenon of neuronal or spinal shock for the first 2-3 weeks before spasticity ensues, and lower motor neurone lesions being flaccid throughout. Observation of the face is rewarding, paralysis being indicated by deviation of the head and eyes to one side — usually the side of the lesion, by facial asymmetry and sagging of one corner of the mouth, and by a bulging of one cheek during expiration. The pupils may be unequal in size and sluggish in reaction to light. Paralysis of the extremities can be determined by lifting each one and allowing it to fall to the bed. Normal limbs sink down gradually; paralysed limbs fall heavily to the bed. In very deep coma, this differentiation may not be possible since unparalysed, as well as paralysed limbs fall heavily. Vigorous or painful stimulation of the palms or soles produce withdrawal of unparalysed limbs but no movement of paralysed extremities occurs. Paralysed lower extremities show an extensor plantar response.

Specific neurological findings naturally depend on the site and the size of the lesion. Lesions in “silent areas” of the brain produce little in the way of focal neurological signs; lesions in other areas, however, may be localized by a consideration of the altered neurological findings. Time does not permit a discussion of the various syndromes resultant from specific cerebro-vascular lesions. Instead, a brief consideration of some basic neurological principles useful in the localization of cerebral lesions follows.

1. Sensory-motor function of one side of the body is chiefly handled by the cortex of the contralateral hemisphere. The only cortical function having unilateral representation is that of speech, which is located in the dominant hemisphere — the left hemisphere in a right handed person and vice versa.

2. Upper motor neurone lesions produce — after the stage of spinal shock — a spastic paralysis, increased deep reflexes of the involved part, and no neurological atrophy of the involved muscles. (Disuse atrophy may later set in, however.) Lower
motor neurone lesions, on the other hand, give a flaccid paralysis, decreased or abolished reflexes, and marked atrophy of muscles.

3. The completeness of paralysis seen following a unilateral pyramidal tract lesion varies with the muscle groups involved. Some groups are innervated by the motor area of the contralateral cortex entirely; others receive homolateral, as well as contralateral, cortical innervation. On this basis three general groups of muscles are recognized:

(a) Those controlled by the opposite hemisphere entirely and where paralysis is marked on the side opposite the lesion — included here are the muscles of the arm and leg, the lower facial muscles, and much of the trapezius.

(b) Those muscles which have some degree of homolateral innervation, as well as the usual contralateral, and where some weakness rather than complete paralysis occurs — included here are the trunk muscles and the tongue muscles.

(c) Muscles whose control is sufficiently bilateral that unilateral pyramidal lesions fail to produce clinically demonstrable effects — included here are the extraocular muscles (especially the orbicularis and frontalis), the muscles of mastication, the muscles of deglutition (excluding the tongue), muscles of the larynx, sternomastoid and upper portion of trapezius, and the diaphragm.

4. The point of cross-over of pyramidal fibres from contralateral to homolateral side varies. The fibres of the corticobulbar tract cross at the level of the cranial nuclei which they supply. Of the fibres of the corticospinal tract, 85-90% decussate at the caudal end of the medulla; the remaining fibres cross-over in the cord at the level of the structures they supply.

5. Regarding sensation, it should be remembered that certain modalities travel together in the central nervous system. Muscle, joint, and tendon sense, vibration sense, and discriminative touch do so. Pain and temperature sensation travel together also. Simple touch and pressure sensation do likewise.

6. The level of cross-over of sensory fibres on their way to the contralateral cortex varies. Pain and temperature sensation from the body cross almost immediately on entering the cord; that from the head runs posteriorly and crosses at the level of the medulla. Muscle, joint, tendon, vibration and fine touch sensation from the body cross in the medulla cephalad to the decussation of the pyramidal tracts. The anatomical pathways of these modalities from the head are not yet clear. Most simple touch and pressure fibres from the body cross shortly after entering the cord but a few do so at the medulla. The pathways for these sensations in the head are, once again, not definitely worked out.

7. The points of cross-over of the various modalities of sensation and the fibres of the pyramidal system are important in the analysis of situations where sensory disturbances are noted on one side of the body and loss of motor function on the other.

8. Lesions involving the autonomic nervous system outflow may do so in the hypothalamic area — the headquarters of this system — or more distally. If the oculomotor nucleus or nerve is involved, dilation of the pupil on that side will be noted. If the sympathetic outflow to the eye is interrupted, ptosis and miosis will be observed. Disturbances of bowel and bladder function — incontinence or retention — will be seen where autonomic imbalance — parasympathetic or sympathetic dominance, respectively — occurs in the

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smooth muscle of bladder and rectum as a result of a cerebrovascular lesion. Similarly, the absence of sweating and vasodilation in an area marks loss of sympathetic impulses and parasympathetic dominance.

9. A brief word regarding some of the functions of the following structures may aid in the localization of a vascular lesion, when a disturbance of their activities is observed.

(a) Cerebellum — this structure functions in three general ways — in equilibration, in postural reflexes and muscle coordination, and in smoothing and stabilizing the more complex movements from the motor area. Disturbances thus include ataxia, intention tremor, decomposition of movement, dysdiadochokinesis, dysmetria, past-pointing, nystagmus, and muscular hypotonia.

(b) Corpus Striatum — this structure also functions in producing smooth, coordinated muscle movement and normal muscle tonus. It is responsible, in addition, for certain automatic associated movements such as swinging the arms when walking and changing facial expression with emotions. Disturbances here include involuntary movements — as in chorea and athetosis, increased muscle tonus and tremor at rest, and "mask-like facies".

(c) Interruption of the reticular formation of the extrapyramidal system at the midbrain level removes its smoothing and coordinating influence on muscular movement and tone and produces the characteristic posture of decerebrate rigidity.

10. The highest cerebral functions may be impaired and personality alterations frequently follow on a cerebrovascular lesion.

III. Laboratory Aids and Special Procedures

In general, the laboratory aids are not specifically diagnostic in cerebrovascular lesions but are used to corroborate the clinical diagnosis.

Useful tests include urinalysis, blood count and chemistry, and cerebrospinal fluid examination. Hyperglycemia and sugar in the urine are common findings during the first 24 hours after the lesion occurs. A mild or moderate leucocytosis is often present in cases of cerebral hemorrhage. The cerebrospinal fluid is bloody and under increased pressure in cases of hemorrhage, generally speaking. Deep seated lesions far removed from the subarachnoid or ventricular spaces may present initially clear fluid, however.

X-ray examination, ventriculography, cerebral angiography, and electroencephalography may, on occasion, be employed. Pineal displacement and ventricular distortion may be revealed by the first two means. Cerebral angiography can demonstrate sites of arterial occlusion and localize aneurysms and intracerebral clots. It is particularly useful when a surgical attack upon the lesion is contemplated. E.E.G. examination may give positive findings but a normal tracing does not exclude these lesions.

DIFFERENTIAL DIAGNOSIS

Cerebrovascular lesions present a twofold differential problem. First, one must rule out other conditions which produce a somewhat similar clinical picture. Secondly, one must try to determine whether cerebral embolism, thrombosis, or hemorrhage has occurred.

With regard to the first problem, some of the commoner differential conditions which one must keep in mind are:

1. Diabetic coma.
2. Uremia—It must be remembered that cerebrovascular lesions are a complication of this condition.
3. Acute alcoholism.
4. Extradural hemorrhage.
5. Subdural hemorrhage.
6. Brain tumor or abscess.
7. Epilepsy.
8. Subarachnoid hemorrhage.

The differentiation may be relatively easy or quite difficult, depending on whether a good history is obtainable — to add to the physical signs and laboratory findings — or whether the patient is comatose and one has to rely on these two diagnostic methods alone. In cases of this latter type, a careful physical examination — including a check for head trauma, the size and reaction of the pupils, the odor of the breath, the state of the optic discs, the respiratory characteristics, the temperature and pulse, the blood pressure level, neck stiffness, and paralysis — and the use of certain laboratory procedures — especially urinalysis, blood sugar and N.P.N. determinations, and cerebrospinal fluid examination — are essential.

Having established the presence of a cerebrovascular lesion one must then attempt to determine whether it is a cause of embolism, thrombosis, or hemorrhage. This is of some prognostic and therapeutic import. The chief differential points have already been discussed under diagnosis so that it suffices now to merely list them. One should consider:

1. The mode of onset — whether there were prodromata.
2. The time taken for the full-blown clinical picture to develop.
3. Whether hypertension enters into the case.
4. Whether the attack occurred during the day or night and whether the patient was exerting himself.
5. Whether loss of consciousness occurred.
6. Whether other conditions predisposing to a particular lesion are present.
7. The relative predominance of certain findings — e.g. headache, nausea, vomiting, and convulsions favoring hemorrhage over thrombosis.
8. The presence or absence of neck stiffness and the spinal fluid findings.

In spite of these points, the typing of a particular lesion can be difficult, especially if the mode and characteristics of the onset and prodromata — if any — are unknown.

CLINICAL COURSE AND PROGNOSIS

This varies with the type of lesion, its extent and site, and the presence or absence of other complicating factors.

Cerebrovascular lesions, with the exception of rupture of large basilar aneurysms, rarely cause sudden death. Cerebral hemorrhage in general, however, carries a very poor prognosis. Those of any appreciable size usually terminate in death within 2-14 days of the onset.

Cases of cerebral thrombosis or embolism end fatally if a major vessel is involved. This usually occurs within 10-21 days of the onset as a result of secondary complications, such as bronchopneumonia or other serious disease present which is capable of causing death by itself. In the majority of cases, however, the patient survives the first attack and one becomes concerned with the neurological deficit which will remain. The degree of permanent damage cannot be accurately predicted early, since part of the picture may be due to a temporary interruption of function due to edema rather than necrosis. Usually there is some improvement in the focal neurological signs and occasionally complete
recovery. The improvement often proceeds over a period of 6 months or so and the deficit should not be considered permanent until at least that time has passed.

If the etiological factors responsible for the first lesion are not amenable to treatment, those who recover, of course, can, and often do, suffer subsequent attacks.

**TREATMENT**

The treatment of cerebrovascular lesions may be considered under the headings of prophylactic and active measures.

**(a) Prophylaxis**

Prophylactic steps should be considered whenever situations favoring strokes are present. Thus when cerebral embolism is a possibility, appropriate treatment of the underlying conditions — with anticoagulants, quinidine, or antibiotics, as indicated — may prevent this cerebrovascular complication. Similarly, hypotensive therapy may abort a primary cerebral hemorrhage and active treatment of the predisposing conditions to secondary cerebral hemorrhage may prevent this type from occurring. Cerebral thrombosis on atherosclerotic areas may be averted if anticoagulant therapy is instituted during the phase of prodromal symptoms and signs, should they present. Active antibiotic therapy may help prevent thrombosis due to inflammatory conditions — such as syphilis and tuberculous meningitis.

**(b) Active Treatment**

Once a cerebrovascular lesion has occurred, the active treatment program begins. It may be divided into two parts, namely, that stage immediately after the onset — when the primary concern is the saving of life, and the second stage — which entails the handling of residual defects.

(1) **First Stage:**

During the first stage, strokes of all three types require the same general care. This includes good nursing, fluid and liquid nourishment by mouth, if possible, otherwise parenterally, inlying catheter to prevent overdistension of the bladder, enemas or cathartics to aid elimination, frequent alteration of the position in bed to prevent hypostatic pneumonia and bed sores, and the judicious use of sedatives, avoiding opiates and their respiratory depression.

Specific care for the cerebral lesion is to be attempted wherever possible. In cases of cerebral embolization or thrombosis attempts have been made to improve the cerebral circulation by reducing any consequent vasospasm via stellate block. Some feel that this procedure is valueless while other observers report good results in cases of marked vasospasm — which they state to be as frequent as every third or fourth case. Vasodilation with substances such as nicotinic acid has been attempted also with indifferent results.

In cerebral thrombosis the use of anticoagulants is believed to be of some value. Their prophylactic use has already been mentioned, but when a frank thrombosis has occurred anticoagulant therapy is often employed to prevent extension of the thrombus already formed and to reduce the likelihood of new clots forming.

In patients suffering from cerebral hemorrhage who survive the initial shock, operative removal of the clot should be considered. It is absorbed slowly and is apt to behave like a tumor if not removed, so that surgery, in selected cases, may be life-saving and reduce the final neurological disability. Anticoagulant therapy, of course, is definitely contraindicated in cases of cerebral hemorrhage and this condition must always be ruled out before its administration.
(2) **Second Stage:**

During the second stage of active treatment one has to try to minimize the disabilities due to residual neurological damage. Physio-therapy — in the form of light massage and passive movements — can be begun on paralysed limbs while the patient is still confined to bed. This helps to keep paralysed muscles in good condition and prevents joint stiffness. The patient should be encouraged to try to use the paralysed muscles while they are being moved passively, as the degree of functional recovery will largely depend on such effort and re-education. These exercises should not be overly prolonged since the patient will become fatigued and discouraged. Hand exercises — squeezing a rubber ball and putting it down and picking it up — help restore function in this part of the body. The development of arm contractures should be avoided by the use of well-padded splints and if foot-drop appears splintage there, is necessary also. These splints need not be kept on at all times. As the general condition and strength of the patient improves he may be allowed out of bed into a chair and from there ambulated gradually using the support of attendants or canes as required.

The treatment of aphasia or disorders of the speech, when present, poses a problem which can only be handled by a persistent patient and a patient physician. In the presence of both, and incomplete involvement of the speech areas, complete or nearly complete control of speech often returns.

These measures, along with encouragement and emotional support by all those attending the patient — who is often quite upset and anxious in the face of his new disabilities — will enable him to live the remainder of his life, be it short or long, as independently and as happily as possible.

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Essential Hypertension

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INTRODUCTION

Essential hypertension is a disease of unknown etiology, characterized by a significant elevation in blood pressure. The upper limit of normal for the blood pressure as determined by standard clinical methods has not been definitely established. A compromising hypothetical value might be taken as 140/90. It has been shown that there is a greater tendency to develop hypertension, and/or arteriosclerotic disease in individuals with blood pressures above this level, than in those with lower blood pressures.

The blood pressure as determined by the universally employed auscultatory method, corresponds closely to the blood pressure as measured by intra-arterial manometers. In individuals with short obese arms, however, the former method may give an excessively high reading. Intermittent elevations of blood pressure often suggest an unstable neurovascular mechanism and may be the forerunner of frank sustained hypertension. The percentage of individuals with transient elevations of their blood pressure, in whom essential hypertension subsequently becomes manifest, is far higher than in the general population. This observation has led to the designation of the "labile", and "pre-hypertensive" states.

ETIOLOGY

Although the basic etiology of essential hypertension is unknown, a variety of factors contribute to its cause and pathogenesis. These factors include hereditary, environmental, racial, neurogenic, endocrine, metabolic and humoral influences. Females show a somewhat higher incidence of hypertensive disease than males. It has been estimated that if one, or both parents have high blood pressure, the incidence of hypertension in their children will be about 30%, and 45%, respectively. When both parents are normotensive, only about 3% of their children will develop hypertensive disease. Pyknic types and obese individuals show a definitely higher incidence of essential hypertension than the general population. It is rather difficult to assess the influence of such nebulous factors as temperament, emotions, and the environment.

PATHOGENESIS

Despite intensive investigation, the pathogenesis of essential hypertension remains obscure. Since cardiac output and blood viscosity remain constant, the rise in blood pressure is likely due to an increase in the peripheral resistance. There is good evidence to show that this increase in peripheral resistance occurs in the arterioles, especially those of the kidney. Initially, increased resistance is due to increased sympathetic tone, rather than to structural changes in the arterioles; but such organic changes do occur in time. The mechanism responsible for altered sympathetic tone has not been definitely established. A theory has been suggested whereby neurogenic stimuli at the level of the hypothalamus so upset the sympathetic-parasympathetic control over the arterioles that there is subsequent vasoconstriction.

As the result of renal ischemia, renin is released. Renin combines with a globulin precursor in the blood (hypertensinogen) converting it to hypertensin, (angiotonin). Hypertensinogen is an active pressor agent. A vicious cycle is established, which is further aggravated by structural changes in the arterioles. This theory may be satisfactory in some in-
stances, but it fails to explain all cases of essential hypertension.

PATHOLOGY

The pathological lesions associated with essential hypertension are more likely the result of the disturbance than its cause. The characteristic changes occur in the arterioles, where intimal and medial thickening result in narrowing of the lumina. The kidneys may appear essentially normal, or they may reveal evidence of profound renal disintegration and breakdown.

In fully developed benign nephrosclerosis, the kidneys appear granular and slightly contracted. The capsule is usually firm, and adherent to the underlying cortex. The microscopic appearance varies considerably, due to the patchy distribution of the lesions. The architecture may appear normal, except for partial fibrosis in a number of glomeruli, or there may be evidence of extensive glomerular obliteration. Progressive renal ischemia results in atrophy, collapse, and the disappearance of large numbers of tubules, with connective tissue replacement of these elements. Arteriosclerosis and hyaline thickening of the intima in the small arterioles, especially the afferent arterioles, are the most readily recognized vascular lesions. Intralobular and medium sized arteries show extensive intimal thickening, due mainly to reduplication of the internal elastic lamina. In the malignant variant of essential hypertension, additional vascular lesions are encountered. These are hyperplastic arteriolar sclerosis and necrotizing arteriolitis. The latter lesion is rarely seen in the absence of renal insufficiency.

In hypertension of short duration, the heart may be of normal size. Usually, however, there is some degree of left ventricular hypertrophy. If failure has occurred, the hypertrophy is more diffuse and there will be some element of dilation present. Arteriosclerotic changes are frequently encountered in the coronary arteries.

The pathological features of hypertension found in the brain are primarily confined to the cerebral vessels. Often these show arteriosclerotic degeneration. The surrounding nervous tissue is frequently gliosed from the progressive ischemia associated with this condition. Other pathological features may be demonstrated elsewhere in the body, but they are not so characteristically or as clinically significant as those already described.

CLINICAL FEATURES

Essential hypertension is often asymptomatic, and many cases are first discovered on routine physical examinations. Early symptoms are difficult to differentiate from constitutional characteristics. These are: loss of energy, fatigue, nervousness, irritability and insomnia. Later features which often prove troublesome are headache, dizziness, epistaxis, and impairment of memory and concentration.

Although it is not invariably true, it appears that the higher the blood pressure, within the range of normality, the greater is the predisposition to the development of hypertension in later years. Borderline hypertensives and labile hypertensives are often found to have unstable blood pressures.

Secondary manifestations of essential hypertension can often be discovered by an examination of the eye grounds, and by an assessment of cardiac, cerebral, and renal function.

Eye Ground Changes

A hypertensive patient may present with visual symptoms. Blurring of vision, scotomata, field defects, diplopia, deterioration of vision, or sudden blindness, are among the complaints encountered.

The fundamental eyeground changes are:
(1) Angiopathy

Localized or generalized arteriolar-sclerosis and phlebosclerosis. Focal arteriolar constriction and generalized attenuation and narrowing.

(2) Retinopathy

Cotton wool patches of edema, edema residues, (hyaline patches), and flame shaped hemorrhages. Complications include arteriolar and venous thrombosis, retinal detachment, and the accumulation of exudates in the region of the macula, (macular star formation).

(3) Neuropathy—papilledema

An evaluation of the fundi in hypertensive disease is usually based upon one of two commonly employed classifications.

The American Ophthalmological Association classification of the eye ground changes in essential hypertension:

Grade 1: A-V ratio 1:2
Slight arteriolar constriction (to 2/3 normal diameter).
Increased light reflex from the arterioles.

Grade 2: A-V ratio 1:3
Moderate arteriolar constriction (to 1/2 normal diameter).
Copper wire arterioles and arterio-venous nicking.

Grade 3: A-V ratio 1:4
Considerable arteriolar constriction (to 1/3 normal diameter).
Silver wire arterioles.

Grade 4: Arterioles are thread-like or invisible

The Keith-Wagener-Baker classification distinguishes progressive vasospasm in grades 1 and 2, the occurrence of hemorrhages and exudates in grade 3, and papilledema in grade 4. Although the examination of the optic fundi should not be over-emphasized in the total evaluation of the hypertensive patient, it should be pointed out that the ophthalmoscopic findings have considerable prognostic importance and may, at times, serve as a sensitive indication of the course of hypertensive disease.

Cardiac Manifestations

Involvement of the heart is the complication of paramount importance, since it accounts for about 60% of deaths in hypertensive patients that cannot be attributed to incidental disease. Cardiac output is at first maintained by an increased force of contraction and subsequent left ventricular hypertrophy.

Symptomatology depends upon the degree of cardiac compensation. Classically, there is a history of increasing shortness of breath on exertion, and eventually while at rest, paroxysmal nocturnal dyspnea, orthopnea, and periodic (Cheyne-Stokes) respiration.

Physical examination reveals a powerful cardiac impulse, which is displaced to the left and inferiorly, an increased area of cardiac dullness, accentuation of the first heart sound in the mitral region and of the second heart sound in the aortic region. There may be a mitral systolic murmur, indicative of relative mitral insufficiency.

Often a patient with hypertension has angina pectoris. He may or may not have a significant degree of coronary sclerosis. The angina in the latter case is explained by the increased work demand of a hypertrophied myocardium with insufficient blood supply. Eventually, normal sinus rhythm may give way to a gallop rhythm and pulsus alternans. Radiological evidence will confirm cardiac enlargement and engorgement of the pulmonary vessels will be apparent in some instances.
The EKG will show evidence of left ventricular hypertrophy. As the heart becomes decompensated, bilateral basal rales are detected in the lung fields and eventually all the peripheral signs of congestive failure become manifest. The above picture is frequently complicated by coronary artery disease, as evidenced by angina pectoris or myocardial infarction.

Cerebral Manifestations

Cerebral manifestations of hypertensive disease accounts for about 30% of deaths attributable to this condition. The anatomical arrangement of the cerebral vessels, and the susceptibility of nervous tissue to anoxia, readily account for vascular and ischemic complications. Minor symptoms include paraesthesia, transitory weakness, headache, and dizziness. More serious disturbances are hypertensive encephalopathy, cerebral hemorrhage and cerebral thrombosis. Concomitant atherosclerotic changes in the cerebral vessels and the resultant ischemia of cortical tissue, account for the gradual mental deterioration which is sometimes observed.

Renal Manifestations

The end result of hypertension is renal vascular damage. Impairment of kidney function occurs late in benign essential hypertension, where progressive arterial and arteriolar occlusion is followed by ischemic atrophy of the nephron. In the malignant variant of hypertensive disease, however, there is early progressive arteriolar necrosis, with subsequent embarrassment of kidney function. In terminal cases, the clinical picture of hypertensive disease is often complicated by the symptoms and signs of uremia. Drowsiness, confusion, coma, anorexia, nausea and vomiting are suggestive of such a course. An ammoniacal odor to the breath, urea frost, and a pericardial friction rub, lend further support to the diagnosis. The renal manifestations of essential hypertension have been estimated to be responsible for about 10% of deaths attributable to this condition.

Malignant hypertension is a clinical term applied to the variety of essential hypertension which pursues a fulminating course. This phase, or variety of hypertensive disease, is also characterized by the presence of papilledema, primary affection of the kidneys, and its predisposition for males in the 20-50 year age group.

DIAGNOSIS

The diagnosis of essential hypertension is best made on the basis of an accurate history, careful physical examination, and the judicious use of laboratory tests and ancillary methods of investigation, where indicated. The other causes of high blood pressure must be ruled out. A definite diagnosis should be withheld, if possible, until the patient has been observed and studied on a number of occasions. An attempt has been made to correlate a number of pressor tests (the most popular of which has been the cold pressor test), with the susceptibility to the development of essential hypertension. These tests are equivocal and cannot be accepted as reliable indices. In young subjects with intermittent elevations of blood pressure, it is frequent to find eye ground changes and a family history of hypertension. Occasionally, it is necessary to follow such subjects for a prolonged period of time before making a definite diagnosis.

DIFFERENTIAL DIAGNOSIS

(1) Normal Aging

A rise in systolic, with little change in the diastolic blood pressure, often occurs as a normal manifestation of the aging process, and should not be considered as evidence of essential hypertension. The mechanism for such a change in blood pressure has been shown to be a progressive diminution in the elasticity of the aorta and its primary branches.
(2) Conditions with Elevated Systolic and Diastolic Pressures

(a) Renal Lesions

The blood pressure is elevated in most cases of acute and chronic glomerulonephritis and chronic pyelonephritis, but it is rare for hypertension to accompany acute pyelonephritis. Some cases of nephritic hypertension progress to the malignant phase. Essential hypertension can usually be differentiated from nephritic hypertension on the basis of concomitant clinical findings, but occasionally this distinction is difficult or impossible to make.

A difficult problem is often posed by patients with hypertension and unilateral kidney disease. The majority of these patients have been shown to have chronic pyelonephritis in the affected organ. It must be stressed, however, that the number of patients with true Goldblatt kidneys is rare. Nephrectomy is only indicated for hypertension in such cases where there is little or no function in the diseased organ and where the opposite kidney is able to compensate adequately.

Rare causes of hypertension associated with kidney lesions:

(1) Trauma
(2) Polycystic disease of the kidneys
(3) Hydronephrosis
(4) Neoplasms
(5) Amyloidosis
(6) Infarction of the kidney

A routine urinalysis, NPN, and intravenous pyelogram should be performed on all patients suspected to have essential hypertension. Other laboratory tests and ancillary methods of investigation are indicated if these suggest primary renal pathology.

(b) Endocrine Disorders

i. Diabetes Mellitus:

Hypertension eventually develops in the majority of patients with the Kimmelstiel-Wilson syndrome. Differentiation from essential hypertension may pose a problem. It is primarily based on the finding of proteinuria, prior to the onset of hypertension, the characteristic picture of diabetic retinopathy, and other evidence of long-standing diabetes mellitus.

ii. Cushing Syndrome:

Elevation of the blood pressure is an integral feature of the Cushing syndrome, whether the cause be due to primary adrenal hyperplasia or tumor, or to a basophil adenoma of the pituitary. Diagnosis of this condition rests upon an assessment of clinical features, estimation of the urinary-17-ketosteroids, and upon other special diagnostic procedures. Overdosage with adrenal steroids may give rise to a Cushing-like picture.

iii. Pheochromocytoma:

Classically, pheochromocytoma was described as producing paroxysmal hypertension. Many cases present with sustained elevations of the blood pressure. Some cases of essential hypertension, the "labile" hypertensives, display a fluctuating pattern, which may closely mimic pheochromocytoma. The diagnosis of a secreting chromaffin tumor primarily rests upon the use of laboratory tests:

(1) Measurement of urinary catechols.
(2) The injection of substances that will cause the secretion of adrenaline and/or noradrenaline.

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(3) The injection of adrenolytic agents.

Occasionally, abdominal palpation with frequent blood pressure recordings may facilitate the diagnosis. Compression of the tumor by this maneuver sometimes precipitates an episode of hypertension.

(c) Toxemia of Pregnancy

Hypertension in pregnancy is most often due to the syndrome referred to as toxemia. Since this condition rarely appears prior to the thirtieth week of gestation, and never before the twenty-fourth week (except in the presence of hydatidiform mole), hypertension before the sixth month of pregnancy must be attributed to some other cause. This is usually essential or nephritic hypertension. In toxemia, hypertension generally precedes the proteinuria, and there is evidence of abnormal water retention plus other clinical findings.

Post-toxemic hypertension presents a special problem. It is impossible to differentiate this condition from essential hypertension, unless the patient is known to have been normotensive prior to her pregnancy.

(d) Coarctation of Aorta

The presence of coarctation of the aorta must always be entertained when assessing a patient with high blood pressure. The diagnosis of this condition is based upon the discrepancy in blood pressure as measured in the arms and legs, absent or diminished pulses in the feet, auscultation of the chest, and upon characteristic X-ray findings.

(e) Intracranial Lesions

Essential hypertension can usually be distinguished from hypertension due to C.N.S. lesions by the history, physical findings and an examination of the spinal fluid. Among the causes of hypertension due to such lesions are:

(1) Increased intracranial pressure
(2) Cerebral lesions
   (a) Trauma
   (b) Encephalitis
   (c) Neoplasm
(3) Diencephalic syndrome.

A psychogenic basis for hypertension must always be considered. Differentiation from essential hypertension may prove difficult in this instance, for the role played by the psyche in the pathogenesis of essential hypertension has not been definitely established.

(3) Conditions with Elevated Systolic, and Normal or Decreased Diastolic Pressures

(a) Aortic regurgitation
(b) Patent ductus arteriosus
(c) Arterio-venous fistula
(d) Hyperthyroidism

(4) Rare Causes of Hypertension

(a) Polycythemia rubra vera
(b) Collagen diseases
   i. Periarteritis nodosa
   ii. Disseminated Lupus erythematosus
(c) Toxic Factors
   i. Acute Plumbism
   ii. Systemic Infections
(d) Amyloidosis

In each case of hypertension, the organic, psychogenic, and laboratory findings must be considered before making a final diagnosis.
TREATMENT

(A) Treatment of Hypertension

As yet, no specific cure has been discovered for essential hypertension. Assuming that the pathogenesis of this condition involves a number of interrelated factors, it is obvious that no single chemical, surgical or medical measure, aimed at neutralizing one of the several influences will be effective in all cases. Each patient must be considered as an individual problem. Factors to consider in therapy are:

(1) The necessity of definite antihypertensive treatment.

(2) The choice of therapy, considering:

(a) The possible complications of treatment.

(b) The availability of hospital facilities, including laboratory services.

(c) The skill and experience of the physician.

(d) Problems presenting in the individual patient.

(3) Careful management once the mode of therapy has been decided upon.

Occasionally it is advisable to do nothing in a definite way for the hypertensive patient. An important factor in any form of therapy is reassurance, coupled with physical and mental rest. Exercise, however, within the limit of the patients capacity, should be encouraged. A life full of interest and activity should be the main objective in each case.

The efficacy of any form of therapy may be evaluated according to a number of criteria:

(1) Reduction in systolic and diastolic blood pressure.

(2) Relief of symptoms.

(3) Reduction in morbidity and mortality rates from causes attributable to hypertensive disease.

I. Diet

The diet of hypertensive patients should be adequate, but a reduction in weight is advisable in obese patients. A great deal of controversy surrounds the question of low sodium diets in the management of essential hypertension. Some authors claim that rigid sodium restriction may, in itself, be sufficient to control the blood pressure; while others only use such a regime in the management of hypertensive disease with cardiac decompensation. As yet there is insufficient information concerning the influence of rice diets, or prolonged rigid sodium restriction, on the course of hypertensive disease. Even if such a mechanism existed, however, the severe dietary discipline would prove unacceptable to many patients.

II. Psychotherapy

While it is generally agreed that psychotherapy is a valuable adjuvant to all forms of therapy for essential hypertension, it is of little value when used alone, except in cases of mild or labile hypertension, with an obvious psychogenic basis.

III. Surgery

Various forms of sympathectomy and splanchecotomy have been practised in the last twenty years in an attempt to reduce vasomotor tone in patients with essential hypertension. More recently, adrenalectomy and combined adrenalectomy-sympathectomy procedures have been recommended. Adequate surgical sympa-
thectomy unquestionably prolongs life when it lowers the blood pressure, but in many cases it fails to relieve hypertension permanently.

The assessment of long term results and the establishment of criteria for the selection of patients is impossible at this time. Until such information is available, surgery should be reserved for uncooperative patients and for patients who fail to be adequately controlled on a chemotherapeutic regime.

IV. Chemotherapy

With the recent introduction of a number of useful hypotensive agents, the treatment of essential hypertension has taken on a new and more optimistic light. It now appears that the chemotherapeutic approach to this condition will furnish the most satisfactory results. In recent years a myriad of drugs have been advocated for the reduction and control of blood pressure. Many, however, have proved impractical, because of their undesirable side effects, difficulty in regulation of dosage, expense, or because they were unable to control the blood pressure adequately for a sufficient length of time.

The various drugs used in the pharmacotherapy of essential hypertension may be considered as: (a) sedative or tranquillizing agents, (b) drugs designed to reduce the blood pressure directly.

(a) Sedative or Tranquillizing Drugs

(1) Barbiturates

The most frequently prescribed drugs for the treatment of essential hypertension are the barbiturates (notably, phenobarbital). Preparations such as this, aid in promoting relaxation, and tend to give relief from anxiety, emotional tension, and insomnia. Caution must always be employed, however, to prevent over-consumption and habituation.

(2) Rauwolfia

The latest drugs to gain popularity have been rauwolfia and its related extracts and alkaloids. These preparations are only mild antihypertensives, their widespread use being related to the simplicity and safety of their administration, and to their relatively few undesirable, or serious side effects. The rauwolfia drugs appear to exert their hypotensive action by a disruption of the sympathetic-parasympathetic balance at the level of the hypothalamus, and by a direct action on the vasomotor centre. The generalized vasodilatation which results, lowers the blood pressure. By depressing cerebral centres, the rauwolfia compounds exert a mild tranquilizing effect. This is particularly effective in relieving the anxiety and tension so frequently encountered in mild, labile hypertensives.

Untoward reactions are often encountered, but they are seldom serious and usually disappear when the drug is withdrawn, or when the dose is reduced. Nasal congestion, increased appetite, lassitude, drowsiness, unpleasant dreams, muscle aches and pains, dyspnea, impotence, diarrhea, depression, and rarely, a frank psychosis, have been described.

Rauwolfia is the drug of choice in initiating hypotensive treatment, for it decreases the severity of unpleasant side effects, and the total dosage requirements of more potent chemotherapeutic agents. When used alone, rauwolfia is most effective in
the treatment of mild hypertensives who have little cardiac, cerebral, or renal damage.

(b) Drugs Designed to Reduce the Blood Pressure Directly

(1) Thiocyanates

Thiocyanates were among the first drugs to be studied as possible agents for the control of essential hypertension. Many bizarre hypotheses have been suggested concerning their mechanism of action. None have been consistently supported by experimental investigation. These drugs are effective in mild and moderate hypertension, providing the proper laboratory facilities are available for blood level determinations every 2-4 weeks until therapy is established, and every 4-6 weeks thereafter. The desired therapeutic level is about 7-11 mgs. %. Serious complications are rare if the dosage is properly regulated and based upon frequent thiocyanate blood level determinations. The introduction of other hypotensive drugs in the last few years has largely relegated the thiocyanates to a position of historical interest.

(2) Veratrum Alkaloids

The hypotension induced by veratrum alkaloids is likely due to a reflex inhibition of central vasoconstrictor impulses, with subsequent peripheral vasodilatation. Alone, these drugs are of limited value in the treatment of essential hypertension, because of the relatively narrow range between therapeutic and toxic doses. The oral dose of Veraloid is 3-5 mg. TID. Tolerance is also a problem with these compounds. Side effects include bradycardia, hypotension, nausea and vomiting.

Veratrum alkaloids have been used less extensively in the treatment of essential hypertension than in the hypertension associated with toxemia of pregnancy.

(3) Hydrazinohalazine

Hydralazine (apresoline) is unique in its property of increasing cardiac output and renal blood flow. It acts directly on the smooth muscle of arterioles. In addition, there is a peripheral vasodilation due to a central vasomotor action, the mechanism of which is not clear. When used alone the oral dose of apresoline is 20-100 mg. QID. The development of tolerance, the possibility of serious toxicity, and the high incidence of untoward reactions have limited the usefulness of this drug. Side effects include headache, tachycardia, palpitation, and more rarely, edema, anemia, and skin rashes. Psychoses, pancytopenia, rheumatoid arthritis, and disseminated lupus erythematosus have been described following prolonged therapy employing large doses of the drug.

Hydrazine is used in some chemotherapeutic combinations. It has proved most useful in the management of hypertension, in which there is considerable embarrassment of kidney function.

(4) Ganglionic Blocking Agents

Hexamethonium and the pentolinium salts have been valuable additions to the armamentarium of anti-hypertensive drugs. Methonium compounds lower the blood pressure and enhance peripheral blood flow by blocking sympathetic vasomotor impulses. In hypertensive patients, cardiac output, stroke volume, and left ventricular effort are reduced, but there is no appreciable diminution in coronary or cerebral blood flow.

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flow. Renal blood flow is diminished initially, but there is rapid recovery, despite continued hypotension. There is great individualism with these drugs. The methonium compounds exhibit frequent and sometimes serious side effects. Postural hypotension is a common problem. This can often be ameliorated by instructing the patient to move slowly from the recumbent to the erect position, and by the use of an abdominal binder. Failure of visual accommodation, dry mouth, paralytic ileus and urinary retention may also prove troublesome, but the simultaneous administration of a parasympathomimetic will often prevent their occurrence.

Hexamethonium has been the most extensively studied methonium compound. The inconvenience of administration, the great individual variation in its effectiveness, the development of tolerance, and the not infrequent occurrence of troublesome side effects, has restricted its use to cases of essential hypertension that cannot be adequately controlled by less potent chemotherapeutic agents. Another methonium compound, pentapyrrolodinium, has been introduced recently and promises to be superior to hexamethonium in many respects.

(5) Sympathetic Blocking Agents

Many other hypotensive agents have been recommended for the treatment of essential hypertension. The majority, however, have proven impractical because of their inefficiency, side effects, expense, or difficulty of administration. Perhaps the most disappointing preparations have been the sympathetically blocking agents, dibenzyline, dibenamine, tolazoline, benzazoline (Priscoline), dibenzazepine (Illidar), and the dihydrogenated ergot alkaloids. Doses sufficient to produce adequate hypotensive effect were intolerable when taken for any extended period. They are rarely used today.

(c) Chemotherapeutic Combinations

Of the hypotensive agents, a few have been used conveniently together. In some cases the actions of the components are mutually synergistic. The principal advantage of therapeutic combinations is the reduction in the dosage of the components, made possible by their use together. The incidence of untoward reactions is markedly reduced.

Rauwolfia and veratrum have been used together in the treatment of moderately severe hypertension. This combination of rauwolfia with one of the methonium compounds seems to be the most effective chemotherapeutic combination for the management of severe hypertension. Whether or not hydrazinothalazine should be added to these two is debatable. While the individual dosage of the components can be lowered still further, there is danger of developing the rather serious side effects of hydralazine.

(B) Management of Complications

A discussion of the management of complications of essential hypertension is quite beyond the scope of this brief account. Suffice it to say, the therapist must treat the patient, as well as the elevated blood pressure.

Among the more serious complications of hypertensive disease are congestive heart failure, angina pectoris, myocardial infarction, cerebral thrombosis and hemorrhage, and renal failure.

Symptomatic and supportive measures and the management of concomitant conditions depends upon their severity, and upon problems presenting in the individual case.
Essential Hypertension

PROGNOSIS

It is difficult to make an accurate prognosis in essential hypertension because of the many unpredictable variables. With the introduction of more effective chemotherapeutic agents within the last few years, the disease has taken on a new and more optimistic outlook.

There is a definite correlation between the presence of hypertension and the development of arteriosclerosis. The majority of hypertensives ultimately succumb to arteriosclerotic complications in the heart and brain. It is a pertinent problem to determine in each case the contribution of each factor to the clinical picture. This information will influence the type of therapy employed and the results which can be anticipated from such treatment. The injudicious use of potent hypotensive drugs or radical antihypertensive procedures can, in a patient with severe arteriosclerosis, result in thrombotic episodes in the heart or brain. This is particularly apparent in a patient who has developed an anginal syndrome. Similarly, a fall in systemic blood pressure can produce acute cerebrovascular insufficiency with a profound effect on cerebral activity.

Only long term studies are capable of establishing the efficacy of present management. The adaptation of the patient to his condition and the empirical control of the blood pressure will remain as the principal features in any form of treatment until further knowledge is gained concerning the etiology and pathogenesis of this condition.

THE RELATIONSHIP OF CIRRHOSIS OF THE LIVER TO HYPERTENSION

A Study of 504 Cases of Liver Cirrhosis:

H. F. Loyke:


A number of investigators have commented on the absence of experimental and clinical hypertension with liver disease. Recent studies have tended to confirm these ideas, when it was found that the frequency and degree of hypertension were substantially higher in a control group than in patients with subacute liver atrophy who later come to post-mortem examination. It was concluded that hypertension could not occur in the presence of more than minimal liver damage. In view of this report, the author sought to examine the nature and frequency of hypertension a consecutive series of cases with liver cirrhosis; 504 cases with a positive diagnosis of hepatic cirrhosis were studied.

This study confirmed the impression that hypertension is less likely to occur in cirrhotics than in normal patients. However, the renal and neurogenic mechanisms capable of elevating the blood pressure remain intact in the presence of liver cirrhosis. In some cases hypertension was existent but disappeared as hepatic failure advanced. A large proportion of cases in which blood pressure fell as liver failure progressed, constitute most impressive evidence of the dependence of "essential" hypertension on adequate liver function. In these cases there is no evidence of any progressive malnutrition, cachexia or salt restriction, which if present, could have been causative in the lowered blood pressure.

The conclusions therefore are, that hypertension does not usually occur in the presence of hepatic cirrhosis; that hypertension may occur if renal disease develops in cirrhotics, and that established hypertension may disappear with the onset of liver cirrhosis.

—James G. Goodwin, Meds ’57

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Hypothermia in Surgery

DUNCAN McPHERSON, Meds '56

INTRODUCTION

General hypothermia has been defined as the physical state of an homeothermic individual in whom the body temperature is below the normal range for that individual. At the present time a great deal of research is in progress toward a better understanding of this state. Hypothermia is in regular clinical use in many centers already, and the advances which this technique has made possible in the fields of neurosurgery and cardiovascular surgery should soon justify its discussion in the curriculum for the medical student.

Hypothermia is only the most recent of many great advances in anesthesia which have extended the scope of the surgeon. Endotracheal techniques aided operations upon the head and neck; while controlled respiration allowed the opening of the chest cavities. Curare and related compounds have given greater muscle relaxation with less anesthetic, and controlled hypotension has allowed operations that otherwise would be impossible because of hemorrhage. General hypothermia is the cooling of the patient by a variety of techniques, down to temperatures of 25°C to 28°C, where oxygen consumption is greatly reduced. This has made possible the exclusion of gas from the circulation for an appreciable length of time, or the interruption of the circulation of the blood completely for advanced surgery.

HISTORY

Cold has never seemed to occupy such a prominent place in the physician's armamentarium as heat. With a few scattered exceptions, it is only in the past twenty years that cold and its effect in the human body has been studied scientifically.

As early as 1646, Marcio Aurelis Severino employed freezing mixtures of snow and ice to secure surgical anesthesia. During the Napoleonic Wars, observers noted that wounded soldiers often seemed to survive better if left in the cold than when brought at once into warm surroundings. Baron Larrey, army surgeon to Napoleon, recorded that amputations done in cold weather, that is, below 19°C, were relatively painless and seemed to do well.

The anesthetic effects of cold were first studied in human beings in a controlled experiment by Smith and Fay in the late 1930's. They used general hypothermia to alleviate the intractable pain of cases of advanced breast carcinoma. Although successful, the method was technically not practiced and fell into disrepute.

It has required the stimulus of war, when large numbers of people are exposed to low temperatures, to cause a revival of cold research. Methods were developed during World War II for the resuscitation of survivors of torpedoed ships or airmen ditched in the sea who had been exposed to severe immersion hypothermia. At the present time the more general climatic effects of cold are of national interest with the possibility of war in arctic areas.

The past five years have seen hypothermia emerge as a recognized adjuvant to rather advanced surgery. The chief exponents of it are Bigelow in Toronto, Swan in Denver, Laborit and Huguenard.
in Paris, and Delorme and Ross in England. Each of these groups has a different method of securing lowered temperatures, but the physiological changes which occur are the same in all cases except for minor differences to be pointed out as each technique is described later.

PHYSIOLOGY OF HYPOTHERMIA

It has been assumed generally that maintenance of body temperature at 37°C was a necessity to avoid irreversible damage to cell and enzyme systems. Now it becomes apparent that cooling to lower temperatures is not harmful and may in fact be life-saving.

Normally, the body responds to a cold environment in (a) attempting to preserve heat by peripheral vaso-constriction, (b) producing more heat by shivering. If shivering be prevented, the body temperature falls.

Other Variables Than Cold

(1) the respiratory rate and type of induced respiratory cycle, which can significantly alter electrolyte and water distribution, in turn influencing cardiac irritability and myocardial competence.

(2) the anesthetic agents and preoperative indications which affect myocardial tolerance to cold, the oxygen consumption, and metabolic pattern of response to hypothermia, especially the sympathetic-parasympathetic balance as it affects cardiac functions.

(3) the pre-existing state of the heart—the diseased heart being less tolerant to the effects of cold.

(4) age and pre-existing hypoxia.

The limiting factor in cooling is cardiac irritability which, especially below 28°C, leads to ventricular fibrillation, the chief danger in hypothermia.

General Observation

Spontaneous respiration ceases at 25-28°C, hence the need arises for positive pressure respiration with oxygen. As cooling progresses, the heart rate, cardiac output, blood pressure, and cardiac conductions are all decreased—at the same time, cardiac irritability increases.

Advantages of Hypothermia

The chief advantage being sought is a decreased oxygen consumption in the tissues, which makes possible the interruption of the circulation for short periods without cellular changes in the affected tissues. Bigelow has found that oxygen consumption by the tissues falls about 5% for each degree centigrade down to 27°C, and less rapidly below that. From this, he postulates an eventual state of suspended animation at a temperature near 10°C. This means that at 30°C, oxygen need is 65% of normal, and at 28°C, it is only 50% of normal values. The factor of cardiac irritability, however, sets up a barrier at about 24°C.

An important factor is that cooled tissues do not incur an oxygen debt provided the supply is within other limits just given. Thus oxygen need—temperature relations allow complete arrest of the general circulation for 6 to 8 minutes at 28°C, with perfect safety; which is time enough to allow repair of intra-cardiac defects by direct-vision procedures.

Previous mention has been made of the anesthetic property of cold. Swan observes surgical anesthesia at 28°C, even though major organ function continues. This is important in that it allows use of lesser amounts of anesthetic agents which are toxic to the body and are responsible for the post-operative nausea, vomiting, etc.

Requirements

Acid-base balance must be maintained by positive pressure respiration with oxy-
It has been shown that hyperventilation, a method to secure a slightly higher pH than normal (about 7.5), is desirable because it lessens the incidence of cardiac irregularities.

The fall of blood pressure due to the lessened heart action varies greatly with the individual, often going as low as 60 systolic at 25-30°C. For this reason, it is best recorded by intra-arterial methods. Most investigators employ a nor-adrenaline drip to keep blood pressure up to a reasonable level. There is apparently little risk to the tissues in general.

Precautionary Measures

Swan states that there is no specific cellular pathology above 20°C., even in periods of several hours. The conclusion has been reached by most investigators that cooling and re-warming in the range of 37-25°C. is totally innocuous per se, if the usual precautions of maintaining adequate respiration and blood pressure levels are observed. The only drawback to the procedure is the lowered threshold of ventricular fibrillation seen in both dogs and man near 28°C.

Many theories have been advanced as to the cause of the ventricular fibrillation—most of them logical, but none proven as yet to be the real cause. Temperature gradients across the myocardium due to the right heart blood being colder in cooling; and circulating adrenaline due to cold stress are two recently suggested. Swan feels it is due to a disturbance of potassium balance in the myocardium. He employs deliberate hyperventilation with oxygen throughout the procedure to maintain potassium balance in heart muscle—always being sure that the pH of the right auricular blood is at least 7.5 before occluding circulation for a cardiotomy.

There is reason to believe that a disturbed sympathetic parasympathetic balance might be a contributing factor in this irritability problem. Swan, who has done the most work in this subject, has found that cold depresses vagus function more than sympathetic functions. Administration of acetyl choline, neostigmine and stimulation of the peripheral end of the vagus nerve all inhibited ventricular fibrillation in dogs under hypothermia. Applying this knowledge to human beings, Swan administers a small dose of neostigmine into the root of the clamped aorta so as to get coronary perfusion of the neostigmine. As a safeguard, should the dose prove too large and cause the heart to slowly stop, calcium may be given to counteract the neostigmine which has a potassium-like effect. The same rationale applies for the avoidance of the use of pre-operative atropine.

Disturbed myocardial functions evidenced as ventricular fibrillation is the major cause of death in hypothermic surgery. The risk of this occurring rises sharply in:

(a) diseased heart,
(b) occlusion time beyond eight minutes,
(c) temperatures below 26°C.

This discussion of the physiology of hypothermia is admittedly brief. Most writers devote their articles to a description of actual techniques rather than the changes recorded in the patient. As Swan emphasizes, each case is different and no hard and fast rule can be set as to what schedule to follow in inducing hypothermia. It is a physiological adventure with danger and limitations, but these must in each case be weighed against the advantages to be gained by its use in the attainment of the operative objectives.

TECHNIQUES TO HYPOTHERMIA

In the field of hypothermia there are two very different schools, with gradations between them. Depending on the type of hypothermia employed, different
Hypothermia in Surgery

objectives are sought. At one end of the scale is the European concept of artificial hibernation as practiced since 1950 by Laborit and Huguenard. At the other extreme are the deep cooling techniques of Swan, Bigelow, Delorme, and Ross. Between these two schools are many others who employ methods that are a mixture of two techniques.

"Artificial Hibernation" Method

The type of hypothermia used in Europe is better thought of as a modified anesthetic technique, and is called by its proponents, "artificial hibernation". It is not suited to the extensive cardiac and brain operations done under low temperatures by Swan and other advocates of deep physical cooling. Artificial hibernation aims to produce a general state of hypoventilation so that the body can efficiently counter-act lesion-causing syndromes that would be fatal in all other circumstances.

Laborit believes that death is in many cases due to an over-action of the autonomic nervous system in an attempt to preserve the constancy of the internal environment. In this way the reserves of the body are rapidly used up in a futile attempt to keep temperature, blood pressure, and so on, at normal levels. If the autonomic influences could be blocked, then these general metabolic processes would slow down and allow recovery at a lower level of inner activity. Laborit and Huguenard employ a mixture of drugs to produce a central neuroplegia and so prevent the pituitary-adrenal complex from reacting to the stress in the first place. The mixture used is aptly called a "lytic cocktail", and with variations, consists of 50 mg. promethazine; 50 mg. chlorpromazine; and 100 mg. nupéridine given intravenously by a drip before operation. By this means he secures a non-specific, diffuse autonomic block, and stability of the central nervous system and cardio-vascular system at a temperature of 33-35°C. However, oxygen consumption is little affected at this level, and some others employ wet sheets or ice packs to reduce the temperature further.

Laborit was the first to use this method; he had read accounts of soldiers during the Napoleonic Wars, surviving great ordeals if at low temperatures. In cases of severe aggression, for example burns, shock from injury, surgery, perhaps refrigeration would be the avenue to allow the body to passively accept the aggression. He argues that physical cooling, using anesthetic and curare to inhibit shivering and other natural responses to the cold, is bad, and says that "surgery in such cases is done at the stage of final dissolution of the subject". The lytic cocktail on the other hand, has certain advantages. It acts from within with chlorpromazine or largactil as the main active principle. The properties claimed for the drug are its inhibitions of the autonomic nervous system, especially the sympathetic portion, and its depression of the central nervous system to give hypothermic, hypnotic, anti-pyretic, anti-convulsant, and anti-emetic effects.

Its hypothermic effect is due to a direct action on the thermo-regulating center in the central nervous system, thereby preventing shivering and other responses to cold such as peripheral vasoconstriction. Chlorpromazine also potentiates the relaxation due to curariform and has a quinidine-like effect on the heart. Also it should be remembered that the drug potentiates barbiturates and is irritant to veins, so must be well diluted for intravenous use.

Skeptics call the French method "polypharmacy" and claim the "lytic cocktail" has no more cooling effect than the use of relaxants plus pentobarbital.

Laborit makes great claims for it but acknowledges its limitations. He hopes to develop a state of the body analogous to that of the hibernating animal through
the use of drugs. Practical trials of the method have given good results. Smith and Fairer in England report thirty-six cases of major operations in poor risk patients. They give the cocktail, with thiopentane relaxants, and oxygen is needed. During operation, respiration is shallow, heart rate constant, and blood pressure about 100 systolic. Body temperature falls to 35-36°C, and returns to normal in 6 hours. They claim better results in serious cases than would be possible with ordinary anesthetic techniques and have no undesirable aftereffects such as nausea and vomiting or headache. Intravenous is used only to replace the actual measured blood loss. This method is said to be best for feeble patients or for difficult and prolonged operations, and it is claimed to reduce greatly the body's unfavorable responses to surgical trauma. Barclay, Grizo, Stevenson, and Walsh report another small series of "last-ditch" cases done with autonomic block plus wet sheet and ice cooling to 30°C, with good results. They also emphasize that in the hypothermic state, blood and fluid replacement should not exceed the measured loss.

"Physical Cooling" Method

A method of hypothermia which seems to offer most for advanced types of surgery is that being studied by Henry Swan of Denver. Dr. Swan has recently published a report of 100 clinical trials along with a description of his techniques. His object is to secure a bloodless field for operation by temporary occlusion of the blood circulation. The low temperature used to prolong the time-tolerance to ischemia have made possible the repair of cardiac defects hitherto considered impossible.

Indications (Swan):

(i) for open direct vision cardiac procedures and cerebrovascular opera-

ations, using occlusion to secure a bloodless field,

(ii) to improve the risk in patients with cyanotic, congenital or acquired heart disease,

(iii) to achieve a physiological hypotension and lower the operative blood loss even in absence of complete occlusion,

(iv) hypothermia is anesthetic itself, so less use need be made of toxic anesthetic agents, an important advantage in portal-caval shunts in cirrhosis.

The method used by Swan is typical in most respects of hypothermia as employed on this continent in the repair of cardiac defects. The apparatus used is fairly simple.

Pre-operative drugs used are:

(a) digitalis for failure,

(b) penicillin routinely,

(c) barbiturates, morphine, or demerol sedative.

Technique

Anesthesia is with ether, and a slow intravenous glucose drip is given in the arm. An electro-cardiogram with needle electrodes, rectal thermometer, and intrarterial blood pressure recordings are made continuously. After induction, the patient is placed in a tub of cold water and given curare if shivering is noted. As the body temperature starts to fall, ice is added to the water. At 31°C, the anesthetic is stopped and ether is washed out with hyperventilation using pure oxygen. The patient is removed from the ice water now before the desired temperature is reached because he will keep on cooling by about two-thirds the temperature loss while in the ice bath. Cooling requires about 45 minutes in an adult.
After carefully drying the patient, the lower abdomen is wrapped in felt and surrounded by a diathermy coil to be used in re-warming. The operation now commences and the heart is exposed. Blood is replaced as it is lost.

In heart operations, curare is given before circulatory occlusion to prevent diaphragm contraction as respiration is resumed after the occlusion. The blood pH of the right auricle should be 7.5. As inflow veins are clamped, and after a slight delay while the heart empties and arterial changes are applied, a small dose of neostigmine is given into the base of the aorta. The breathing apparatus is discontinued. The patient is motionless, the circulation is stopped and repair of heart defects must be done within eight minutes.

After cardiotomy is closed, the occlusion clamps are released, and ventilation with pure oxygen is resumed to blow off the accumulated carbon dioxide. The diathermy is turned on to warm the patient and raise the blood pressure so that the latent bleeders can be found and tied before the chest is closed. Diathermy has been found to rewarm just as rapidly as hot water immersion, and with less danger of rewarming shock since deep and superficial tissues are warmed at the same time.

The average waking temperature is 34°C. The endotracheal tube is removed after spontaneous breathing is established. The patient continues to look very pale for two to four hours post-operatively due to peripheral vasoconstriction.

The dangers to guard against are:

(a) ventricular fibrillation,
(b) coronary air embolism.

Treatment for Complications

To treat ventricular fibrillation rewarming is started at once, potassium chloride given by coronary perfusion and then electric defibrillator is applied. Manual compression restores coronary circulation. Adrenaline into the right auricle is a last resort.

Coronary air embolism is easily taken care of by massaging the air through into the venous side of the coronary circulation—also by observing care in closure of the heart under saline.

Assessment

The cases reported by Swan comprised fifty-nine direct vision cardiac procedures, twenty-one closed cardiac procedures, and twenty non-cardiac operations. The mortality was 22%, of these eight were unrelated to hypothermia, while fourteen were adjudged as probably due to hypothermic technique. Of the fourteen, eleven were due to ventricular fibrillation or standstill as a primary cause, the other three died of thrombo-embolism and heart failure. From the study of these, it was concluded that the presence of a diseased heart is the main factor in the incidence of ventricular fibrillation under hypothermia and that there is a very low risk of ventricular fibrillation in non-cardiac procedures in persons with normal hearts. When viewing the mortality rate, remember that these were all serious operations and it was believed in many that hypothermic surgery offered the best if not the only chance of life.

There are arguments for and against Swan’s method of surface cooling. Some say it can not help but stimulate the sympathetic response to cold and in this way upset the balance of homeostatic mechanisms. Others object to the use of sedation and anesthetic to abolish the cold responses. To its advantage is the relative simplicity of the method, provided that the operating team is experienced. The paper by Swan is impressive and this certainly seems to be the most practical method so far.
Extra-Corporeal Blood Stream Cooling

This is used by Delorme and Ross of England and involves extra-corporeal blood stream cooling to achieve lowered body temperatures.

Technique

Pre-operatively, blood and electrolyte levels are carefully checked. Presence of cold agglutinins must also be ruled out. Pre-medication and anesthesia are given as usual and ventilation is carried on by positive pressure apparatus, with the exception of the period of circulatory arrest. Continuous records are made of electrocardiograms and temperature of pharynx and chest. The saphenous vein is cannulated in the femoral triangle and a saline drip is connected. The chest is opened and the heart is exposed at normal temperature. There is no danger of ventricular fibrillation as yet. Now the decision is reached as to whether cooling will be needed or not. If hypothermia is needed, a cannula is placed into the right auricular appendage and up into the superior vena cava. Blood is removed from the superior vena cava end, and run through a refrigerated coil and back into the body via the saphenous vein. The total cooling time is forty-five minutes, and then the cardiotomy may be done. After cardiac repair is completed, rewarming is carried out by the same means up to 35°C. A nor-adrenaline drip is used here also to preserve systolic blood pressure above 80.

Advantages

Blood stream cooling gives good control of rate and depth of cooling. Since it employs only venous blood, it avoids damage to major arteries, and the harmful effect of creating an arterio-venous fistula. This method is restricted to surgery of the heart and great vessels, but for this it has some advantages.

Delorme claims that the fall of eosinophils and rise of blood sugar in surface cooling are evidences of an adrenaline response to cold stress. These changes are not seen in perivascular cooling theoretically, because of an absence of surface stimulation, and a direct and early depression of endocrine and neural mechanism by cold. Of lesser importance is the absence of any local cold injury which is seen occasionally with ice baths. A better control of temperature is possible by avoidance of the after-drip seen in surface techniques due to re-circulation in chilled surface tissues, remembering that the outer two centimeters of the human body comprises about one-half of its mass.

No drugs need be used, just anesthetic for induction. Cold itself produces response mechanisms. Although it has these advantages, perivascular cooling is not likely to offer as much as surface cooling techniques, because of the apparatus needed, and the fact that it is limited for the most part to cardiac operations.

CONCLUSION

Other techniques in use are just variations of the three already described. Hypothermia is still experimental and risky, but it has great promise of widening the field of surgery. The main drawback so far is ventricular fibrillation which awaits a better understanding of heart physiology for its solution.

Hypothermia may be of value in any condition which is benefited by the reduced oxygen need of the tissues, physiological hypotension, and generally decreased temperature which it makes possible.

The most publicized use is in the field of cardiovascular surgery and neurosurgery. Many other conditions come to mind where it might be used more as a therapeutic agent than as an adjunct to surgery. For instance, acute lung disease;
anemic and hypertensive crises; internal hemorrhage; and hyperpyrexic states of various causes would all stand to gain by the lowered oxygen need, hypotension, and low temperature.

The list of possible uses will grow with time and it is hoped that this discussion will enable a better understanding of hypothermia as it comes into more general application.

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Myxedema and Myxedema Heart

DAVE BARNES, Meds '57

INTRODUCTION

The name myxedema is of Greek derivation, myxa meaning mucous and oidema meaning swelling. Myxedema is generally applied to the condition which results from atrophy or loss of function of the thyroid gland in later life. It occurs primarily in women of middle age. The prognosis for complete relief is very favorable if treated with thyroid hormone. If it is untreated, death ensues due to the degenerative processes secondary to the tissue changes of myxedema; before the advent of antibiotics, however, death was due to secondary infections.

Myxedema has been recognized as a clinical entity for little more than a century. In 1850, Curling recognized the importance of the thyroid gland in certain hypothyroid conditions; and in 1856 Schiff published a paper on the effect of thyroidectomies on dogs. These papers were certainly instrumental in the work of Gull, who in 1873 gave the classical description of myxedema, and discovered its cause. Schiff in 1884 made a further contribution by discovering that thyroidectomized dogs could be saved by a thyroid transplant. This experiment ultimately led to the treatment of myxedema with thyroid extracts which gave excellent results.

MYXEDEMA

Rarely are we presented with a more classical picture in clinical medicine than the short, frequently overweight, pugly-faced, somewhat expressionless individual who responds to questioning slowly but accurately in a hoarse voice and complains only of extreme weakness. This is the full-blown picture of adult myxedema, all too frequently the stage in which it is first recognized.

Clinical Manifestations

The clinical manifestations of myxedema are numerous and extensive. The most pertinent in order of their frequency are:

1. **Solid, non-pitting pseudo-edema of the skin and mucous membranes** caused by infiltration with an acid mucopolysaccharide.

2. **Weakness**, due to a lowered metabolic rate and secondary anemia.

3. **Coarseness and dryness of skin**, caused by the absence of stimulation of the sebaceous and sweat glands by the thyroid hormone.

4. **Sensitivity to cold**, due in major part to nature's effort to conserve heat.

5. **Apathy**, resulting from lower emotional level, extreme complacency and lack of initiative.

6. **Slowness of speech** is caused by a swollen thick tongue and the accompanying mental changes.

7. **Edema of eyelids and face**.

8. **Impairment of memory**.

9. **Coarseness of hair**, which is a result of a lowered nutritional status of individual cells and alterations in the metabolism of cholesterol.
10. Thick tongue, probably due to myxedematous infiltration.

11. Increase in weight. This is not fat but is due to added fluid occasioned by myxedematous infiltration. In more severe cases, however, a decrease in weight may be seen.

12. Loss of hair, caused by lowered nutritional status of the cells. It might be interesting to note here that thinning of the outer portion of the eyebrows is not as characteristic of myxedema as originally believed, for it occurs rather infrequently and may be seen in a number of other conditions.

13. Enlargement of the heart or myxedema heart, which will be discussed later.

14. Myxedematous pallor of skin and lips due to an associated carotenemia resulting from hepatic insufficiency. The carotene is not converted to vitamin A.

15. Other manifestations are hoarseness, constipation, dyspnea, irregularities in menstruation, anorexia, nervousness and irritability, pericardial pain, palpitation, weakened heart sounds.

In brief, the manifestations of myxedema may be observed in the following spheres:—

—mental and psychic
—the nervous system
—body weight
—the skin and appendages
—cardiovascular
—gastro-intestinal
—genital system
—interglandular relations.

Etiological Factors

McGavack presented a five-fold division in his etiological classification of myxedema.

1. Secondary to thyrotoxicosis—When hyperplasia of the thyroid has persisted a sufficiently long time, it may result in atrophy associated with hypothyroidism.

2. Secondary to hypofunction of anterior lobe of the pituitary—This is a rare condition and may be differentiated from other forms of myxedema through signs and symptoms of the severe dysfunction which exists concomitantly in other glands of internal secretion.

3. Secondary to simple atrophy of the thyroid—The etiology of which is still undetermined although exhaustion atrophy has been suggested.

4. Secondary to chronic thyroiditis—This cause is extremely rare.

5. Artificial myxedema—Artificial myxedema is due to thyroidectomy, or secondary to administration of certain drugs such as thiouracil and Iodine 131.

Additional predisposing factors have been suggested by Joll and Levitt—pregnancy, complicated by mental anguish and infection, unsanitary conditions, defective diet, infections and toxic states. Several cases may occur in one family and hereditary tendencies have been recorded. Many of the causes of myxedema are unknown, but the main etiological factors seem to be hereditary, hormonal, infectious, and artificial.

MYXEDEMA HEART

The myxedema heart is an extremely controversial subject. Some authorities have described this as a definite clinical and pathological entity, while others have claimed its non-existence.

Gross Features

The heart is enlarged, soft, and pale, and fibrosis may follow due to athero-
sclerosis in many cases. Some papers, however, have denied any specific changes in a myxedema heart.

The enlargement has been attributed to several factors, but is as yet undecided. Pericardial effusion, myxedematous swelling of the myocardium and dilation due to degeneration in the myocardium have been suggested.

The pericardial effusion described by some is of high protein and cholesterol content, and is undoubtedly due to increased capillary permeability, and perhaps a disturbance in the electrolyte balance. There are E.C.G. reports to substantiate this theory in some cases of myxedema. Some say that this is the main or only cause of the enlarged myxedema heart. Others say it occurs occasionally.

Not infrequently the enlargement of the heart has been attributed to myxedematous infiltration of the myocardium by a mucopolysaccharide.

Others believe that the enlargement is due to a dilation of all heart chambers. This dilation is caused by degenerative changes in the myocardium which may lead to fibrosis, hence a weakening of the myocardium and a subsequent dilation. Other gross features such as softness and paleness are due to myxedematous infiltration and degeneration of the myocardium.

Microscopic Features

Microscopically, hydropic vacuolation of the sarcoplasm is often found. This is in close association with loss of striation, fragmentation, pale staining and ultimate fibrosis. Muscle fibers are swollen and edematous; nuclear changes have also been noticed. Interstitial edema and edema of epicardial fat have also been described.

Physiological Manifestations

These are numerous and include changes in the electro-cardiogram tracings, cardiac activity, and blood changes.

(a) E.C.G. Changes: The characteristic change in the E.C.G. tracings have been described as lowering of the voltage in tracing with the T-wave often inverted and a prolonged P-R interval. These changes do not occur in patients with hypometabolism from other causes, and are rarely, if ever, absent in severe hypothyroidism; but are not specific for this condition. Some authors, however, point out a similarity in E.C.G. tracings from patients with pericardial effusions and from patients with myxedema. This suggests a common origin but has not been proven.

The cause of this typical E.C.G. change is attributed to pericardial effusion by some, others say the change is due to mucous infiltration of the Bundle of His, increased vagal tone, low B.M.R., or associated anemia and myocardial anoxia. Still others suggest a lowered nutritional level as the cause.

(b) Cardiac Changes: There have been some other fairly constant cardiac findings in connection with myxedema. Feeble impulses are invariably found and the heart rate is slow. Consequently heart sounds are faint and cardiac output per minute volume is decreased. Arrhythmias and palpitations have occasionally been observed.

Impairment of the heart function, that is a feeble and slow beat, is due to edema of the muscle fibers. On the basis of experiments with the cat heart, Gould says that bradycardia of hypothyroidism is caused by changes of sensitivity of adrenergic and cholinergic heart effectors to the respective neuro-transmitters.

MAY, 1956
(c) Blood Findings: Certain blood findings are also important in considering the myxedema heart. A high serum Cholesterol is invariably recorded and has been known to reach a level of 700 mgm.% (the upper limit of normal being 300 mgm.%). Some authorities have attempted to point out correlation between B.M.R. and blood cholesterol levels. This remains a very debatable point.

High cholesterol level in the blood may be explained by several factors, the most important of which seem to be lessened destruction, lessened excretion in the intestine, and a decrease in the use of cholesterol in hepatic synthesis. It might also be noticed that in myxedema there is marked atrophy of the adrenal cortex, where there is normally a high cholesterol turnover. This might also tend to increase blood cholesterol levels.

Another change in the blood is the lowering of the blood sugar. This is due to an underfunction of the adrenal cortex.

The nourishing power of the blood is diminished due to a secondary anemia that is often associated with myxedema. This anemia is caused by an iron deficiency or it may be attributed to the low activity of the bone marrow due to lack of stimulation by thyroxin.

Vascular Aspects

The myxedema heart cannot be adequately covered without considering the manifestations of the coronary vessels. Most authorities associate coronary atherosclerosis with the myxedema heart. These men tend to connect the atheromatous plaques with the high serum cholesterol, but this inference is far from being conclusive.

Nutrient arteries of the heart have been observed to be partially occluded either by pressure of the edema in the myocardium or as more frequently described by coronary sclerosis. Recently workers have had great success in producing atherosclerosis in animals by maintaining high levels of serum cholesterol. There is also a strong clinical inference in favor of the correlation of high serum cholesterol to the incidence of atherosclerosis. This correlation is, however, far from being confirmed; in fact, in one paper Blumgart very convincingly showed that atherosclerosis plaques were not present in excess of normal in artificially induced myxedema.

The other outstanding vascular change is an increase in capillary permeability. This is a common finding in myxedema.

Summarizing the explanations of the various manifestations, we find the increase in heart size is due to pericardial effusion, myxedematous infiltration or dilation of the chambers. E.C.G. changes are caused by effusion, mucous infiltration of the conducting system, increased vagal tone, low B.M.R. or anemia. Impairment of heart function is due to edema or a nerve block. High blood cholesterol is due to lessened destruction, excretion and metabolism of cholesterol. Occluding of the vessels is caused by pressure of edema and atherosclerosis.

Treatment

The treatment of the patient with cardiac manifestations in myxedema is very important and should be undertaken with great care.

If moderate or large doses of thyroid are given carelessly and indiscriminantly, great harm can be done, resulting in infarcts, angina pectoris, cardiac failure, etc. On the administration of thyroid extract the body metabolism is soon increased. This places an increased demand on the
heart almost immediately; but does not allow the heart time to resorb interstitial edema in the myocardium or lipid materials in the vessel walls or repair any other myocardial changes. The adrenal cortex has had no opportunity to regenerate and thus the blood sugar is still low — too low to supply the new demand of the heart. The net result is an additional strain on the already overburdened heart.

Considering these facts, treatment should be very moderate. One should start with as little as .025 grains of desiccated thyroid substance, gradually increasing this dose over many weeks to a maintenance dose of approximately 1.5 grains, depending on the patient's B.M.R. and general condition. The maintenance dose should be continued indefinitely and if any signs of cardiac malfunction occur the dosage should be decreased.

Treatment in cases of the myxedema heart should be very conservative, thus allowing heart damage to be repaired and it should be modified if there are cardiac manifestations.

Conclusion

The most important clinical manifestations and the etiology of myxedema have been presented.

The manifestations found in myxedema heart include:

(a) grossly a large, pale heart
(b) microscopically, hydropic degeneration

(c) physiologically, changes in the E.C.G., cardiac output and blood
(d) vascular changes which are narrowing of the nutrient arteries and increased capillary permeability.

The necessity of conservative treatment in cases of myxedema heart has been explained.

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All the books are on open shelves and the students have access to all books and current periodicals. Recent acquisitions by the library are placed on the new book shelves where they are left for the staff and student appraisal and consideration. Of these new books, we have selected the most recent and the most outstanding for your immediate attention.

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PHYSICS

U.W.O. MEDICAL JOURNAL
SOME PHYSIOLOGICAL VARIABLES IN HYPOTHERMIA

by Capt. T. G. Barila, M.C.
Col. H. C. Slocum, M.C.
Washington, D.C.
Rocky Mountain Medical Journal
Vol. 52, No. 8, August 1955.

Surgical Hypothermia, with body temperature below 36°C., is "moderate" (between 36-32°C.) and "deep" (32°C. and lower). Moderate hypothermia is adequate in the surgical treatment of cyanotic congenital heart diseases where tissue oxygen requirements must be depressed so as to be satisfied by the inadequate circulation. Deep hypothermia was preferred for most adults treated since these involved aneurysms and more complex thoracic procedures. Physiological differences were qualitative.

1. Nervous System
   Below 28°C. cold acts as a narcotic. Analgesia and amnesia are complete. Hypothalamic function is depressed and autonomic reflexes irritability is gradually lost.

2. Blood
   Increased red blood cells, hematocrit, and hemoglobin concentration increase the load of the heart but provide adequate CO₂ and O₂ transport. Renal blood flow persists at 20°C. White blood cell and platelet counts are decreased. This may be a factor in preventing major thromboses.

3. Respiration
   Vigorous respiratory assistance is a prerequisite in decreasing liability to ventricular fibrillation. It also assists in maintaining the blood pressure.

4. Heart
   Conduction time is prolonged. Effects are in order:
   i) bradycardia and prolongation of the Q-T interval,
   ii) at 30°C., the pacemaker wanders and P wave disappears,
   iii) spread of the QRS complex (the clinical end point),
   iv) flattening of the T wave and ventricular fibrillation.

5. Metabolism
   Metabolism of liver and kidney are depressed although, in spite of falling blood pressure, vital circulation remains adequate. Shivering is a complication above 22°C.

6. Endocrine
   Although release of ACTH is decreased, anesthetics are still required to avoid severe stress.

Two important limitations are: duration of safe interruption of blood supply to the nervous system, and increased danger of ventricular fibrillation.

—Ian D. Graham, Meds '58
## Intern Placements

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<tr>
<th>NAME</th>
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<td>ANDRY, Harold</td>
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(Continued on Page 152)
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