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Diabetic coma

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A DISCUSSION OF THE TREATMENT OF HEMATOGENOUS
OSTEOMYELITIS

BY

HENRY GRABOW

A THESIS

PRESENTED TO THE COLLEGE OF MEDICINE,
UNIVERSITY OF NEBRASKA.

OMAHA, 1940.
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INTRODUCTION

The treatment of osteomyelitis was chosen as the subject for discussion in this thesis because the disease is so common, its cure so questionable, its course so frequently chronic, and its results so disfiguring, disabling, and often discouraging. In the acute stage, the mortality is high.

It used to be said, "Once an osteomyelitis, always an osteomyelitis." Some men say that that statement is no longer true. Perhaps it isn't, but we do see all too many cases of chronic and recurring osteomyelitis supporting it.

Treatment is probably our greatest weakness concerning osteomyelitis. In the pages which follow we may be able to find out the weakness in our methods and what kind of treatment gives the best results.

We have limited this thesis to the discussion of the treatment of non-tuberculous, hematogenous osteomyelitis of the long bones. It was felt that since osteomyelitis of the long bones is most common, and the principles of treatment essentially the same, there was no need to discuss the treatment in any other specific bones.
DEFINITION

Osteomyelitis is a disease, inflammatory in nature, involving bone and having its origin practically always in the medullary tissue although at times it may originate beneath the periosteum. Also there are frequently two foci, one subperiosteal and one in the medulla. If the infestation is confined to the periosteum it may be spoken of as periostitis, and where the infection is definitely within the bounds of cancellous bone, most surgeons use the term, "osteitis."

HISTORY

Evidence of osteomyelitis is found in fossil reptiles in the topmost strata of the Paleozoic and it probably helped exterminate Mesozoic reptiles and the later fossil mammals. Man has undoubtedly been afflicted with the disease for as long as he has existed. It has been discussed since the beginning of recorded surgical observations (62). Osteomyelitis was first described as a clinical entity by Chassaignac, in 1854, but it had been mentioned earlier in the United States by Nathan Smith in 1789, and by his son, Nathan R. Smith, in 1834 (145).
ANATOMY

There are certain points concerning the anatomy of bones which it is well to keep in mind in dealing with this subject. The periosteum has two surfaces, an outer fibrous one covering the bone and separating it from surrounding structures, and an inner one loosely attached to the bone by many fine strands of connective tissue. When torn away by trauma or lifted up by infection many osteogenic or bone-forming cells go with the inner layer. It is believed that these cells play a major part in the formation of new bone. The periosteum covers the shaft of the long bones and is firmly attached to the cortex at the epiphyseal line, but is not continuous with the articular cartilage. In young persons it dips down into the bone at the epiphyseal line which joins the shaft with the epiphysis. It thus serves as a barrier and delays or prevents infection from reaching the epiphysis from the diaphysis. During the growth stage the epiphyseal line is made of cartilage, from the shaft side of which the bone grows in length. In young persons, the blood supply is abundant along this line, there being numerous end arteries on either side of it. The nutrient artery of the shaft supplies one side, the other
side receives almost as much blood from a circular network or arteries just outside of, and surrounding, the articular cartilage. The blood supplied by the periosteum is of less importance than was once supposed.

BACTERIOLOGY

Staphylococcus pyogenes aureus is the cause of acute osteomyelitis in 75 to 90 per cent of cases. The rest are caused chiefly by the streptococcus, Straphylococcus albus, the colon bacillus, pneumococcus, and very rarely the gonococcus. Osteomyelitis due to the typhoid bacillus is sometimes a complication or sequel of typhoid fever. The organisms are usually blood borne, thus giving to the name, hematogenous osteomyelitis.

Various sources of infection resulting in osteomyelitis are infected teeth and tonsils, sinusitis, mastoiditis, boils, compound fractures, gun shot wounds, operations on bone followed by infection, and rarely, by contiguity from a neighboring joint or infected soft parts. In hematogenous osteomyelitis caused by staphylococci, it is well to look at the skin for the source; if caused by streptococci, look in the mouth, nose, and tonsils.
In acute hematogenous osteomyelitis, or simply, acute osteomyelitis, is blood borne and the infection usually begins in the cancellous bone of the metaphysis bordering the epiphysis. From there it can spread to the marrow of the shaft, across the epiphyseal line into the epiphysis and joint, or peripherally along the epiphyseal line to beneath the periosteum. Contrary to what was formerly believed, the latter is the most common route which it takes. It then elevates the periosteum and extends along the surface of the cortex through which it invades Volkmann's canals and the Haversian system and reaches the medulla. Thus the medullary canal, instead of being invaded early and acting as the chief avenue of widespread infection, is often the last of the bony structures to be involved. Somewhat later pus may be found collected in pools in the medulla, in the joint, beneath the periosteum, and, when it ruptures, in the surrounding soft tissues. Extension through the epiphysis into the neighboring joint is much less common than would be expected. The joint most liable to become infected is one whose ligaments are attached on the diaphyseal side of the epiphysis. The infection
may then break into the joint by penetrating the periosteum at the epiphyseal line. The greatest destruction of bone is due to widespread embolism and thrombosis of blood vessels.

The infecting organism can be recovered from the blood in many cases. Sometimes the septicemia is overwhelming and death may occur from forty-eight to seventy-two hours after the onset of local symptoms. Usually the acute symptoms disappear in a few days, but sooner or later distance complications may arise as a result of the blood stream infection.

The osteogenic cells attached to the raised periosteum soon begin to lay down new bone and form an involucrum around the necrotic shaft. The devitalized bone separates from the living bone in a few weeks or months and forms an infected mass called a sequestrum.

The subacute stage of osteomyelitis begins as soon as the systemic reaction subsides. The patient's life is essentially out of danger, but the local pathology is all too often, very active. In it the involucrum begins to form and the sequestra to separate. There may or may not be draining sinuses present. After three or four months the involucrum is relatively thick and strong and the sequestra...
pretty well separated. From this time on the disease is considered chronic.

Chronic osteomyelitis is the result of neglected or maltreated acute osteomyelitis, traumatism such as compound fractures and gun shot wounds, or may occur without preceding acute damage as in that caused by the typhoid bacillus complicating typhoid fever. It is characterized by a thick involucrum, sequestra, draining sinuses, and a bone with its structure distorted by areas of necrosis.

Occasionally the resistance of the tissues may wall the infection off and confine it to a limited area within the bone or in healing, the drainage channel may heal first and a localized vacuole may remain. Later, a wall of compact bone is built up about it producing a cavity lined with sluggish granulation tissue and containing pus from which the bacteria may disappear. This may remain in a quiescent state many years and is usually known as a Brodie's abscess.

**PREDISPOSING FACTORS**

Acute osteomyelitis is a disease of the young. Most cases occur in children from two to twelve years of age. Often there is a history of local trauma, ex-
posure to cold, or some other factor which might play a part by lowering the local resistance. Boys are affected more often than girls. The bones most often involved are the femur, tibia, and humerus. The acute infections diseases of childhood, acute or chronic infections of the teeth, tonsils, nose, ears, skin and mous membranes often immediately precede or accompany the onset of acute osteomyelitis. These infections like trauma, may reduce local resistance or give rise to infected e-boli and thus aid or initiate the disease.

Acute osteomyelitis is rare in adults. They usually suffer from a chronic osteomyelitis which has never healed, have a recurrence from an old acute or chronic osteomyelitis, or the disease develops from an infected compound fracture, gun shot wound, or similar trauma.

**SYMPTOMS**

In acute osteomyelitis the onset is sudden. Delirium and coma may supervene before localizing signs and symptoms are evident. This is not commonly the case, but often they are desperately ill from the onset of the infection. Whether the onset is sudden or gradual, the outstanding symptom is local pain which is continu-
ous, deep, boring and severs, and the outstanding sign is exquisite tenderness on pressure over the bone, with increase in discomfort brought out by tapping along the shaft of the affected bone.

After twenty-four to forty-eight hours there will often be some edema and tenderness in the soft parts over the endoof the involved bone, and, if the patient is still not treated, suppuration may break through the periosteum into the surrounding tissues.

By this time the patient is very ill with high fever, rapid pulse, dehydration, exhaustion from pain, lack of sleep and infection. Vomiting, acidosis, delirium or coma may develop. The leukocyte count is usually very high.

In chronic osteomyelitis, the symptoms are not acute. The patient will complain of the swelling and dull pain of an unopened abscess, deformed bone, chronically draining sinus, or suffer from a pathological fracture.

A sterile abscess often gives rise to pain in the extremity. Frequently, the pain is not well localized, or is referred to an adjacent joint and the condition goes undiagnosed for months or years.
The early diagnosis of acute osteomyelitis is a matter of great difficulty. One of the features of the disease is that the diagnosis of acute osteomyelitis is often missed until there is positive evidence of it in the X-ray, which takes at least four to seven days.

If a child complains of pain over the end of a bone and does not want it moved or touched, if there is tenderness on deep pressure over a bone, as well as symptoms of an acute infectious process, if the onset of these signs and symptoms has been abrupt and if the evidence of infection are rapidly on the increase, a diagnosis of acute osteomyelitis should be made.

The history is frequently suggestive, but often the clinical picture is vague and inconclusive so that a diagnosis of fracture, epiphyseal separation, acute arthritis, scurvy, rheumatic fever, erysipelas, cellulitis, or lymphangitis is made and delay in treatment results.

The diagnosis of chronic osteomyelitis is easily made from the symptoms, and appearance of the limb with its scars and sinuses. However, the X-ray should be used, not only to make or confirm the diagnosis, but
also to direct treatment. This is also true in the case of chronic bone abscess in which case the lesion can but rarely be definitely diagnosed or located without it.

**COMPLICATIONS**

Septicemia or acute toxemia are the most frequent causes of death in acute osteomyelitis. Much more commonly, there is a bacteremia or pyemia. As a result there may be multiple bone and joint suppuration, suppurative pericarditis, and widespread tissue abscesses. Locally, in either the acute or chronic disease, there may be epiphyseal damage or joint involvement with growth deformity limitation of motion and an ankylosis resulting. Union of fractures is interfered with, pathological fractures frequently occur, and the characteristic scars are very easily injured.

**PROGNOSIS**

In the acute stage, the danger to life is grave. Many cases heal completely in a few weeks following primary operation. Occasionally, the disease will disappear spontaneously with conservative management alone. About one-half of the acute cases go on to chronicity. Most of these can be healed by the use of surgery and
physiotherapy.

After the acute stage, the danger to life is not great. However, many cases remain active for years no matter what is done for them. Frequently amputation is necessary, not so much as a life saving procedure, but because the patient would rather be without his limb than put up with the continual stigma of the infection. The incidence of disability, deformity, and loss of function is high. One of the worst features of this disease, is that all the lesions may heal, but recurrence is frequent. No one can make any predictions; it may recur in a few weeks or months; it may not recur for years; or it may never appear again.
TREATMENT

The only specific thing about the treatment of osteomyelitis is that it is a surgical problem, and some men don't believe that. Results have been far from satisfactory, so the procedures which have been advocated are many and varied. However, no matter what type of treatment a surgeon recommends, it is his honest desire to cure his patient, lower the mortality rate, and prevent sequestration, local metastatic extension, chronicity, and functional impairment and deformity in the shortest possible length of time and with the least expense. Therefore, he uses the type of treatment, which he believes comes the closest to fulfilling that desire.

Acute State

The local supportive measures used by various surgeons are essentially similar and used both pre and post operatively. However, the stress laid on this treatment and the time when it is most used is far from the same. Those who believe in early surgical intervention used them practically not at all, or only for a few hours before operation, while those who belong to the conservative group lay great stress on the pre operative value of this treatment, and do every-
thing in their power to increase the patient's resistance and assist him in living through and overcoming the acute, toxic stage of his disease. These men wait until the virulence of the infection has abated and the bone lesion has localized. They are not afraid to wait until there is x-ray evidence of the disease in the bone. Death, septicemia, phemia, toxemia, metastases, joint involvement and sequestration are to be feared, but they have some very good statistical evidence which shows that their waiting plus the intensive use of general or specific supportive measures, accomplishes more in preventing such complications than early surgery does. It is also to be noted that when these men do operate, they recommend the simplest type of surgery which is usually incision and drainage of the soft tissue or subperiosteal abscess. They prefer to wait until sequestra have separated and an involucrum formed before contemplating any radicle surgery. According to statistics waiting is not only rewarded by a diminished incidence of complications, but many cases heal completely following the primary operation, and rarely the disease resolves without surgery of any kind being necessary. (64, 75, 78, 86, 117, 189)
**Systemic Treatment**

For acute osteomyelitis, the systemic infection is treated with usual supportive measures. Fluids are forced, intravenous dextrose (5-10%) in normal saline being frequently used to combat acidosis and dehydration and to keep up nutrition. The patient should receive a high caloric, high vitamin diet, repeated small transfusions, and enough sedation to allay the pain and keep him resting. (1, 11, 42, 58, 64, 75, 78, 113, 117, 147, 148, 153, 156, 185)

**Specific Medication**

The use of specific medication varies. Gentian violet has been used locally, intravenously, and intramuscularly, but its value is questionable. (174) Sulfonilamide or some of its derivatives may be of some value. (117, 128) It should be particularly useful in osteomyelitis of infants because more than half of those cases are caused by hemolytic streptococci. (129) Klein (94) reports several cases in which he used stannoxyyl with good results. Neosalvarsan was used by Le Cocq (104) and although his series of cases was small the results he reports are very good.
Blood Transfusions

Frequently, blood transfusions are used. Some men use plain blood, while others prefer immuno-transfusions. Their value seems to be questionable, some men believing they are definitely beneficial, especially the immuno-transfusions, while others believe that they are of no use at all. At least, they should assist in combatting the anemia resulting from the infection. (1, 11, 15, 51, 58, 64, 91, 117, 127, 148, 153, 156, 185)

Vaccines and Serum

Autogenous vaccines, stock vaccines, and antitoxins both with, and without surgery have been employed in treating acute and chronic osteomyelitis in all their stages. On reading the various reports one gets the impression that the status of vaccine and antitoxin therapy is unsettled. Vaccine therapy has a few supporters but no good proof of its value has yet been obtained. Dolman (50) whose series of cases is the largest in the literature, reports very favorably on the use of antitoxin in 32 cases of acute osteomyelitis in children. He states that in cases in which there is a positive blood culture the mortality rate, usually 50 per cent, has been reduced to 31 per cent.
In his series the clinical condition of individual patients, and not only statistical considerations, was the chief method of assessing the value of serum therapy. He believes that antitoxic serum therapy has undoubtedly proved a life-saving measure in many instances of osteomyelitis in childhood. He emphasizes the value of early diagnosis and the use of large doses of serum intramuscularly. However, this method of treatment has the danger of serum sensitivity and shock to contend with and since its efficacy is far from established, it is not generally used. ([30, 66, 67, 88, 111, 128, 133, 159, 160])

It is always desirable to run routine cultures on the blood and lesions of a case of acute osteomyelitis. The information they give is valuable in indicating the prognosis and directing the treatment. Septicemia has a high mortality rate. However, when it is caused by a hemolytic streptococcus, specific medication gives frequent cures. Straphylococcic septicemia is highly fatal, yet antitoxins may render enough assistance so that a seemingly hopeless case eventually recovers. Autogenous vaccines or immuno-transfusions with the cultures may occasionally aid materially in causing a favorable resolution of the disease, while organ
isms which produce a low grade infection are very apt to give rise to indolent, but very persistent bone lesions. (64, 91, 117, 133)

**Local Therapy**

Local therapy used before surgery is instituted consists of immobilization of the limb, local heat, and local applications. Immobilization is usually obtained by the use of plaster of Thomas splints. (58, 61, 65, 148)

Physiotherapy is an important adjuvant in both the acute and chronic states and should be used freely. There is probably not much difference in the value of the various methods of applying heat to the involved area. (27, 58) However, Kobak (97) reports that through and through diathermy gives the most prompt and brilliant results.

For local applications, Vignard (183) recommended the use of turpentine packs. He used them exclusively saying that surgery was unnecessary and reported that of 7 patients so treated one failed.

Pennington (149) applied potassium nitrate in rolled oats as a paste over areas of chronic infection. He says it makes surgery unnecessary and treated over 200 successfully. Carruthers (34) used
it on 10 cases with good results. Thorek (179, 180) also recommends its use in the various stages of osteomyelities, but does not advocate its use where radical surgery is indicated. He believes that preoperatively it often facilitates surgery in badly infected cases, and postoperatively often stamps out persisting infection. This may all be true, but we believe that essentially the same could be said for practically any of the various local applications.

**Foci of Infection**

Gannett (61) reminds us that in treating this disease we should not forget that teeth, tonsils, boils, sinuses, ears, and similar foci are possible sources of the infecting bacterial. Whenever, such foci are found their removal may arrest or cure the disease. All conditions which are possibly an underlying cause should be appropriately treated. (140)

**Methods of Operation**

In all operative procedures the patient should be prepared and sterile technic used with the work done in a bloodless field obtained by the use of a tourniquet, as in any orthopedic surgery. The anesthetic used varies with the surgeon, the patient, and
the operation. Incisions should be located along anatomical planes so as to gain adequate exposure with a minimum of functional impairment. Scar tissue formation in osteomyelitis is often very extensive, so in many cases the proper path of approaching a bone lesion may be a real problem. (40)

The operation should always be done as quickly and gently as possible with the least possible tissue damage. The periosteum should not be stripped from the bone any farther than can possibly be avoided. (171) Tools should be used that produce the least amount of trauma. The possibility of fracture is often present, and bone trauma is conducive of shock. (34, 39, 55, 113, 140, 148, 189)

If an operation is done before there is any radiological evidence of bone destruction to locate the lesion, the bone is usually attacked at its point of greatest tenderness. If an abscess is present it frequently indicates the place where surgery is required. (140, 171)

The methods of treating acute osteomyelitis vary from immediate radical drainage to conservative treatment without any surgery. Most men recommend surgery of one type or another, some operate early, others late; some stress preoperative preparation,
while others consider it of minor importance.

For years the complaint has been that the diagnosis of acute osteomyelitis is usually not made soon enough, surgical interference is delayed, and disastrous results follow. The general belief was, as Doran and Brown (51) put it, "If time of onset to surgical treatment is hours, convalescence is weeks; if measured in days, convalescence in months or years." The key-note of their treatment was that acute osteomyelitis should be treated with early drainage. (7, 34, 38, 39, 43, 47, 58, 91, 95, 98, 105, 113, 139, 140, 145, 148, 151, 156, 167, 184, 185)

However, recently some very good evidence has been presented, which indicates that such is not the case. According to Wilensky (187), the treatment of acute hemotogenous osteomyelitis in its early stages has the general infection as its most important item. The mortality statistics of acute hemotogenous osteomyelitis in its early stages reflects accurately the mortality of general bacterial infection and in the absence of any fatal complications or associated lesions, the mortality of the local osseous lesion is nil (46).

It may be that acute osteomyelitis is an incident in a general bacterial infection so that one
may not expect or hope that the mortality of the local osseous lesion will be any less than that of the corresponding and accompanying general infection. Yet, it is believed by some that the generalized infection results from the bone infection and that if it is drained immediately the systemic invasion will not develop. (153, 187)

Rarely, but more commonly that is generally known and understood, foci of hematogenous osteomyelitis subside completely and spontaneously without going on to the stage of sequestration and necrosis. (101, 187)

The extent of operation is a problem the answer to which varies greatly among different surgeons. Many believe that adequate drainage of a subperiosteal or soft tissue abscess is sufficient. (20, 46, 78, 85, 99, 101, 117, 136, 177, 187)

Among those who believe that the bone as well as the soft tissue and subperiosteal abscesses should be drained there is great difference of opinion as to how it should be done, and to what extent. Simple drilling is a commonly used procedure. However, if there is pus present, drilling alone is usually not considered adequate enough so many men then use a chisel, saw, or burr and remove the cortex between
the drill holes, or an even larger portion of it. The amount of cortex removed varies from a narrow groove to two-thirds the width of the bone and extending as far as there is infected and necrosed metaphysis and necrosed medullary tissue beneath it. Sometimes a trough the width and length of the medullary canal is removed. Some men remove all the necrotic tissue, so that nothing but healthy tissue remains. This is not the usual procedure, however, and curetting is generally condemned. Necrotic tissue should be left alone or gently sponged away.

In either drilling or guttering, great care must be taken not to damage the epiphysis and it is often stated that the medullary cavity should not be disturbed unless it is already invaded by infection.

In the absence of a subperiosteal abscess, the men who do either of these operations generally believe that there is no harm in opening the metaphysis on the suspicion that it is infected. If there is no infection found the lesion soon heals, while if

(1, 2, 7, 8, 11, 15, 33, 34, 37, 38, 39, 43, 47, 51, 53, 55, 58, 61, 75, 84, 91, 95, 105, 113, 118, 133, 135, 136, 140, 147, 148, 151, 153, 156, 167, 169, 185, 189)
it is present, drainage is instituted. If suppuration
has not yet occurred, a good avenue has been establish-
ed for the escape of pus when it does appear. (33, 42,
91, 95, 99, 155, 156, 171, 184.)

These men want to drain the bone because infec-
tion in it is surrounded by rigid walls. That causes
pressure to develop which enhances the absorption of
toxins, and bacteria. Thus they believe the patient's
chances of remaining very sick and developing a phemia
or septicemia are great if a decompression is not done;
there is danger of the pressure obliterating the blood
vessels so that bone is destroyed, and it may force
infection into the neighboring epiphysis and joint.
However, many other men believe that the incidence of
these complications is not decreased but, on the con-
trary, increased by surgically invading the bone; in-
stead of the disease subsiding as is desired, it flares
up. (46, 47, 153, 155, 184)

Some men only open the metaphysis when there
is no subperiosteal abscess believing that when it is
present, drainage from the bone is adequate and that
nothing further should be done at the primary opera-
tion. (15, 64, 171, 189)

Occasionally, at primary operation, the bone
is found to be extensively involved, the periosteum
sometimes being literally a bag of pus. Here again, the procedure varies. Those who are conservative merely incise the periosteum and establish adequate drainage. Other resect the necrotic shaft. One man, (155), thought it advisable in some cases to resect part of the shaft and replace it with a glass rod. It would prevent deformity, and it would be easier for a good involucrum to form around it than around a shaft which was loaded with infection. (11, 46, 58, 84, 98, 99, 140)

**Osteomyelitis in Infancy.**

It has been pointed out that acute osteomyelitis in children under two years of age should be treated in a different manner than in patients past that age. In the first place, over half of these cases are apparently caused by streptococci, and the incidence of very acutely ill and toxic cases is much higher than in the older age group. Conservatism, with great stress laid upon general supportive measures, is the treatment most frequently advocated. Because the incidence of streptococcal infection is so high, sulfonilamide or one of its derivatives, may be a life saving procedure. Surgery is usually limited to simple incision and drainage after localization has occurred. Invasion of the
bone also has its advocates here, but that is not the treatment of choice because it has been found that in infants very extensive bone involvement may occur and yet will take place without sequestration if only simple incision of the abscess is done. This abscess is usually in the soft tissues, because the infection quickly extends through the porous bone, and thin periosteum. (65, 92, 129, 138, 175)

It is interesting to note that some men who recommend immediate surgery in older age groups, treat osteomyelitis in infants conservatively. They do so because they say the older patients have greater resistance and can withstand the strain of immediate surgery better. (92) If such is the case, why not let the older patients use that resistance to combat the infection instead of to withstand the onslaught of surgery?

It is not uncommon for osteomyelitis in infants to resolve under general supportive measures and medication, without the use of surgery of any type. If such is to be the case, diagnosis must be early so that both general and specific systemic treatment may be instituted as soon as possible.

While the mortality rate, multiplicity of foci, and incidence of epiphyseal separation is high in infants, the incidence of cases which heal completely
with a complete absence of any residual local or metastatic infection or deformity, is greater than in older patients. (65, 175)

**Mortality**

The mortality rate of acute hemotogenous osteomyelitis is high. (145) Just exactly how high is hard to determine, because each man is prone to report a low mortality rate for the particular method of treatment which he recommends.

Weil, Mettaur and Rohm (185) reported, in 1931, that the average mortality rate in the United States during the preceding 15 years, obtained from a large series of reported cases from the various clinics, was 14.8 per cent. In the British Isles from 1915 to 1927, it was 15 per cent. Yet, Mr. E. Lloyd (189) stated, in 1932, that the mortality of acute osteomyelitis varied from 20 to 60 per cent, and was commonly 30 to 35 per cent. It is generally accepted that the mortality in cases with septicemia also present is about 50 per cent.

According to Key (91) about 20 per cent of the acute cases die, about 30 per cent are cured by early operation and about 50 per cent become chronic.

At least, it can be safely said that the mortal-
ity and morbidity rate is much higher than we think it should be so that every surgeon ought to keep his mind open and give very careful consideration to any suggestions which might aid him in increasing the efficiency of his own method of treatment.

Sequestra

Sequestra form a major problem in the treatment of this disease. They are formed not so much by direct destruction and invasion of osseous tissue by infection, but more by embolic or thrombotic occlusion of the artery supplying a given portion of bone. Early adequate surgical drainage of the infected and necrotic focus in the bone is believed by its advocates to be the best method of preventing such occlusion. They advise against curetting of infected and necrotic tissue, because they fear that such a procedure would release emboli and cause an extension of thrombosis, and caution that all blood vessels encountered must be treated very gently for the same reasons. Also they wish to prevent extensive subperiosteal stripping by their early invasion of the bone. That would prevent medullary infection and thus thrombosis of all or all of the nutrient artery could be avoided. They seem to forget they can just as readi-
ly prevent its becoming infected by simple incision of the subperiosteal abscess since infection usually invades it by way of the Haversian system from such an abscess. The same can be said for preventing joint complication because infection usually enters it from a subperiosteal abscess and only rarely extends directly through the epiphysis. (7, 39, 46, 85, 117, 153, 189)

It is generally agreed, even by those who invade the bone at primary operation, that sequestra should not be removed until they have separated completely, the disease has quieted down, and an involucrum formed. It can best be determined when this has occurred by the use of the x-ray. Rarely a sequestrum which is very accessible and free may be removed at primary operation, although routine primary sequestrectomy is recommended by a few surgeons. Very rarely, but oftener than is suspected, sequestra disappear; they may be absorbed and assist in repairing the bone defect in much the same manner as a bone graft. (1, 64, 75, 91, 117, 136, 167, 187)

**Metastases.**

With metastases, we are confronted with the question as to whether they are foci from a persis-
tent primary focus or an early metastasis which remains quiet for a varying length of time. We cannot answer that question, but perhaps they are both. We do know that most of them appear during the acute phase of osteomyelitis, and thus constitute a definite problem in treating that stage. They sometimes appear after the disease has become chronic, but their treatment should then be essentially the same as during the acute stage. (152)

The consensus of opinion seems to be that they should be treated very conservatively with local physiotherapy, and drained only after suppuration occurs. With conservative management they often disappear spontaneously without the use of any surgery what-so-ever. A few men disagree with this contention and maintain that they should be treated in the same manner as the primary site of bone involvement -- by radical surgery. This may be true in some cases, but probably not in the majority of instances. (175)

Pyogenic metastasis into other tissues of the body should, like any abscess or septic process, be treated according to its size, location, the virulence of the infection, organism involved, and the resistance and condition of the patient.
It would be a real triumph if metastases could be prevented. That was part of the goal of the men who advocated early and varyingly extensive surgery. However, we shall present some statistics which indicate that their incidence is the primary focus is drained lowest when during the second week of the acute stage of the disease. (64, 113, 115)

**Joint Involvement**

Extension of the infection into the neighboring joint is one of the commonest complications of acute hematogenous osteomyelitis. They are also frequently the site of metastatic involvement. The treatment of such joint infection is intimately linked with that of the osteomyelitic process which is often present in the adjoining epiphysis. The treatment of choice seems to be adequate drainage of the joint capsule, when suppuration has occurred. This followed by the generally accepted Willems method of early mobilization of joints has apparently proved of the greatest value in the treatment of infection which has extended into major joints, and is most liable to give a good functional result. (64, 90, 98)

When a neighboring epiphysis is also involved,
it should be treated in essentially the same manner as the primary focus. If it is deemed necessary to attack it surgically, great care should be taken to avoid injury the epiphyseal line. (2) Osteomyelitis of the epiphysis usually results in ankylosis of the joint. When that becomes inevitable, it is the duty of the surgeon to make sure that it occurs in the best functional position. This is done by means of splints, or a case, and with or without the use of traction.

Statistics

So far, what we have said concerning the treatment of the acute stage of hematogenous osteomyelitis has been based chiefly on the therapy which various men have recommended and their opinion concerning its treatment. Now we shall approach it from a statistical point of view. Many articles in the literature contain statistics of various kinds and scope, but the majority of them are too inadequate and presented in such a varied fashion that they do not lend themselves well to correlation. (20, 51, 65, 78, 99, 105, 107, 126, 138, 145, 153, 169, 189)

The following statistics which we quote were chosen because they seemed to be the most comprehensive, unbiased, and complete. All phases of the
therapeutic problem of the acute stage are not con-
sidered, but we believe that the majority of the most
important ones are.

It is of interest to note the dates at which
these statistics were published.

Tables I, II, III, and IV, are concerned with
the results of time of operation and mortality.

TABLE I
MORTALITY PERCENTAGE OF ENTIRE GROUP
IN REFERENCE TO CONDITION OF PA-
IENT AND TIME OF OPERATION.
(Brown (28) 1939

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>Lived</th>
<th>Mortality Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOXIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Operation</td>
<td>22</td>
<td>37</td>
<td>37.3</td>
</tr>
<tr>
<td>Delayed operation</td>
<td>5</td>
<td>13</td>
<td>27.7</td>
</tr>
<tr>
<td><strong>NONTOXIC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Operation</td>
<td>1</td>
<td>24</td>
<td>4.0</td>
</tr>
<tr>
<td>Delayed Operation</td>
<td>1</td>
<td>39</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Operation within 48 hours after the diagnosis
is made is considered immediate.
TABLE II

TIME OF OPERATION AND MORTALITY

Crossan (45) 1936

<table>
<thead>
<tr>
<th>Operation from onset, days inclusive</th>
<th>Number</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 4 days</td>
<td>18</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>5-7</td>
<td>35</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>8-10</td>
<td>12</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>11-14</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15-21</td>
<td>10</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>22-30</td>
<td>10</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Over 30 days</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>26</td>
<td>21.49</td>
</tr>
</tbody>
</table>

TABLE III

MORTALITY ACCORDING TO TIME OF OPERATION AFTER ONSET

Mahorner (117) 1937

<table>
<thead>
<tr>
<th>Time, days</th>
<th>Cases</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-7</td>
<td>57</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>8-10</td>
<td>15</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>11 plus</td>
<td>30</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>26</td>
<td>24.3</td>
</tr>
</tbody>
</table>
TABLE IV
MORTALITY ACCORDING TO TIME OF OPERATION AFTER ADMISSION

Mahorner (117) 1937

<table>
<thead>
<tr>
<th>Time, days</th>
<th>Cases</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>35</td>
<td>31.7</td>
</tr>
<tr>
<td>3 plus</td>
<td>28</td>
<td>1</td>
<td>3.45</td>
</tr>
</tbody>
</table>

No deaths when operated on the fourth day or after. Disease has been present up to 3 weeks.

A consideration of Table I does not leave much room for doubt that, at least in this series, immediate operation in the very toxic and even non-toxic patient was accompanied by a higher mortality, in contrast to those instances in which operation was delayed.

These statistics were compiled from the same series of cases as Table V so that they were operated upon with either the gouge or drill. They thus indicate that immediate operation with opening of the bone whether by gough or drill, upon diagnosis of acute osteomyelitis in an acutely toxic patient, is accompanied by unjustified mortality and, should the patient survive, it is probably in spite of, rather than because of surgery.
Tables II, III, and IV list the time element more accurately than Table I. Table II is definitely in agreement with Table I in indicating that mortality is distinctly higher when operation is early than when it is delayed. However, it indicates in addition that there is an optimum time for operation, which is during the second week after onset of the disease. After that time the mortality goes up, but is still not as high as during the first week. This points out that early diagnosis and treatment which has been stressed for so many years is probably not the optimum treatment.

Table III is not in agreement, however. Only 5 cases were operated upon within the first two days after onset, so we don't know how significant this finding is, but it does tend to support the recommendation that surgical treatment be given early, although the table also shows a low mortality rate for the second week.

Table IV is very interesting and is the only one of its kind we were able to find in the literature. It emphasizes the contention that in order to lower the mortality of acute osteomyelitis the care of the patient's systemic reaction is of far more importance than that of his local lesion.
Tables V, VI, and VII deal chiefly with type of operation, and mortality.

**TABLE V**

RESULTS OF IMMEDIATE AND DELAYED OPERATIONS IN REFERENCE TO DEGREE OF TOXICITY, AND OPERATIVE PROCEDURE

Brown (28) 1939

<table>
<thead>
<tr>
<th></th>
<th>Number of Cases</th>
<th>Deaths</th>
<th>Percentage Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMEDIATE OPERATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very toxic, drill</td>
<td>24</td>
<td>11</td>
<td>45.8</td>
</tr>
<tr>
<td>Very toxic, Gouge</td>
<td>35</td>
<td>11</td>
<td>31.4</td>
</tr>
<tr>
<td>Slightly toxic, drill</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Slightly toxic, gouge</td>
<td>16</td>
<td>1</td>
<td>6.2</td>
</tr>
<tr>
<td><strong>DELAYED OPERATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very toxic, drill</td>
<td>10</td>
<td>2</td>
<td>20.2</td>
</tr>
<tr>
<td>Very toxic, gouge</td>
<td>8</td>
<td>3</td>
<td>37.5</td>
</tr>
<tr>
<td>Slightly toxic, drill</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Slightly toxic, gouge</td>
<td>34</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>NO OPERATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td>18</td>
<td>3</td>
<td>16.6</td>
</tr>
<tr>
<td>Totals</td>
<td>160</td>
<td>32</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Gouge-guttering. Operation within 48 hours after the diagnosis is made is considered immediate.
### TABLE VI

**TYPE OF OPERATION AND MORTALITY IN SEVERELY ILL PATIENTS, TEMP. 103°F.**

**Mahorner** (117) 1937

<table>
<thead>
<tr>
<th>OPERATION</th>
<th>Cases</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple incision</td>
<td>7</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td>Drill</td>
<td>43</td>
<td>16</td>
<td>37.2</td>
</tr>
<tr>
<td>Saucerization or curettage</td>
<td>8</td>
<td>3</td>
<td>37.5</td>
</tr>
<tr>
<td>Subperiosteal reaction</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>31</td>
<td>41</td>
</tr>
</tbody>
</table>

### TABLE VII

**TYPE OF OPERATION AND MORTALITY**

**Crossan** (45) 1936

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMEDIATE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidement</td>
<td>23</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Drilling</td>
<td>18</td>
<td>6</td>
<td>33 - 26%</td>
</tr>
<tr>
<td>Incision</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td><strong>DELAYED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidement</td>
<td>15</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Drilling</td>
<td>14</td>
<td>4</td>
<td>28 - 15%</td>
</tr>
<tr>
<td>Incision</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

This is the work of eight surgeons, Immediate--within 24 hours of admission. Delayed--after 24 hours of admission.
Table V gives the results of immediate and delayed operation with gouge or drill in reference to degree of toxicity. In studying it, we find that in every instance but one (immediate operation of very toxic patients), the mortality was consistently higher when the bone was guttered than when only the drill was used. This indicates that, at least in the majority of instances, the drill is to be preferred.

The mortality in 59 severely ill patients with a temperature of 103 F. or over with regard to type of operation is listed in Table VI. Simple incision with its mortality of 14.3 per cent is apparently by far the safest of the types of operations here recorded.

Table VII is also concerned with the type, as well as time of surgical attack. Again we find it definitely indicated that, in this stage, operation should be delayed, and that simple incision is the safest of the surgical procedures, no matter when the operation is done.
TABLE VIII

OUTCOME IN REFERENCE TO DEVELOPMENT OF SECONDARY FOCI, MORTALITY, AND TIME OF OPERATION.

Brown (28) 1939.

<table>
<thead>
<tr>
<th>SECONDARY FOCI DEVELOPED</th>
<th>Number of Cases</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early operation</td>
<td>36 (33.9%)</td>
<td>10 (27.7%)</td>
</tr>
<tr>
<td>Delayed operation</td>
<td>9 (21.9%)</td>
<td>1 (11.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY FOCI DID NOT DEVELOP</th>
<th>Number of Cases</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early operation</td>
<td>70 (66.1%)</td>
<td>12 (17.9%)</td>
</tr>
<tr>
<td>Delayed operation</td>
<td>32 (78.1%)</td>
<td>4 (12.5%)</td>
</tr>
</tbody>
</table>

In Table VIII the incidence of secondary foci, as well as mortality are considered with regard to time of operation. It was compiled in a clinical review of 160 cases of acute hematogenous osteomyelitis. In studying it, we see that secondary foci are more apt to appear in cases that are operated upon early rather than late, and when such foci appear, the mortality is higher.

Brown (28) from whose report we obtained Tables I, V, and VIII, also found that the time of operation had but little effect on the formation of sequestra—22.4 per cent in the early cases and 28.3 per cent in the late.
### TABLE IX

MORTALITY, AND INCIDENCE OF METASTASES WITH REGARD TO TIME AND TYPE OF OPERATION.

Wilson and McKeever (192) 1936.

<table>
<thead>
<tr>
<th>Time of Drainage</th>
<th>Cases</th>
<th>Mortality</th>
<th>Cases with Metastases</th>
<th>Maximum Number of Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDULLARY CANAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRAINED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 7 days of onset</td>
<td>24</td>
<td>6 (25%)</td>
<td>9 (37.5%)</td>
<td>2</td>
</tr>
<tr>
<td>7-28 days after onset</td>
<td>31</td>
<td>3 (9.7%)</td>
<td>7 (22.5%)</td>
<td>2</td>
</tr>
<tr>
<td>SOFT TISSUE DRAINED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time not given</td>
<td>16</td>
<td>2 (12.5%)</td>
<td>5 (31%)</td>
<td>5</td>
</tr>
<tr>
<td>SPONTANEOUS PERFORATION OF ABSCESS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time not given</td>
<td>23</td>
<td>1 (4.3%)</td>
<td>8 (35%)</td>
<td>6</td>
</tr>
</tbody>
</table>

We compiled Table IX from material given in an article written by Wilson and McKeever (192). They believed these finding suggest that perhaps the answer to the problem is not the earliest possible surgical invasion of the bone, but a well-timed adequate drainage of the medullary canal when the individual's resistance is at the highest possible point.
It should be noted that the mortality rate is lowest in that series of cases in which the abscess perforated the skin spontaneously. However, the incidence of metastases was highest with the greatest number of metastases in a single patient.

We found only one article in which statistics were given concerning joint involvement. McCarrall and Key (121) reviewed 200 consecutive patients admitted to the St. Louis unit of the Shriners' hospital for Crippled Children between the years 1924 and 1938. In all of these cases their condition had apparently resulted from an acute hemogenous osteomyelitis.

In 100 (50%) of the patients there was involvement of the joint adjacent to the focus in the bone, and in 50 (25%) of the patients secondary foci developed in other bones. Thirty-eight of the 50 patients with secondary foci were among the 100 patients in whom the adjacent joint was involved. This indicates a high incidence of joint complications, with metastitic foci being more numerous when the adjacent joint is involved.

Of the 9 patients who had had the bone opened within the first week after onset, the adjacent joint was involved in only 1 (11%) instance and there was
only 1 (11%) secondary focus in another bone. Forty-two patients had had soft tissue drainage in the first week. There were 9 (21%) secondary foci and 17 (40%) with adjacent joint involvement.

This finding concerning the incidence of secondary foci is consistent with Wilson and McKeever's data as given in Table IX, with regard to type of operation, but disagrees with that data and that of Brown in Table VIII, with regard to optimum time of operation, because it indicates operation should be done within seven days after onset.

They attempted to correlate the extent of the bone pathology present on admission with the type of treatment which these patients had received during their acute illness. However, they were unable to draw any definite conclusions although it appeared to them that the degree of bone destruction was not definitely influenced by the early treatment that was given in this series.

Apparently the disease tends to be self limited, the bone is invaded very rapidly, and the amount of bone destroyed varies directly with the virulence of the organism and inversely with the resistance of the individual.

It will be noted that in this statistical study no mention has been made of the incidence of healing.
or cures. Instead, the mortality rate is the chief criterion for measuring the success of treatment. Statistical reports of healing are very sparse in the literature written on the treatment of the acute stage of osteomyelitis.

Thus in accord with the material which we have presented here, judicial conservatism is the proper therapy to be practiced in treating the acute stage hematogenous osteomyelitis. Rest and supportive measures alone should be adopted till the defense mechanism of the body has had time to develop. When surgery is indicated, it should be performed with as little disturbance to the part involved as is consistent with obtaining its objectives.

SUBACUTE and CHRONIC Stages

We shall discuss the treatment of these stages together, because the extent of the pathological lesions can be as great in one as in the other. Surgery is essentially the same in both of them. Their difference lies mostly in the degree to which bone regeneration, especially in the form of involucra, has taken place, and the time the disease has been present.

As in any debilitating disease, the patient
should be kept in the best possible physical condition both pre and post operatively. He should receive an adequate nutritious diet. If he is anemic, it should be properly treated. Every effort should be made to increase his resistance and reparative response, and to re-establish his general health which this disease so often undermines. Physical therapy is an important adjuvant and should be used freely. (15, 27)

Again, as in the acute stage or in any orthopedic surgery, all due consideration must be given to the anesthetic, asepsis, hemostasis, optimum amount and path of surgical exposure, and injury to periosteum, bone and surrounding tissues. (2)

In this regard, Kurtz (102) recommends the use of a large drill attached to a high-speed surgical motor which offers a rapid and ideal method of attack in chronic osteomyelitis. Time of operation and anesthesia is shortened; hemorrhage is reduced to a minimum, with absence of bone concussion which is productive shock.

Operation should be done when something definite is to be gained by it and when infective process is quiescent (85).

All surgery should be directed by proper and carefully conducted roentgenological studies. They
not only locate the pathological lesion, but enable the surgeon to follow its progress or recession, and the extent and stage of repair. (2, 86)

The best technique to follow in the treatment of chronic osteomyelitis depends upon the exact amount and character of bone destruction, the stage of such destruction and bone repair, the bone involved, the joint involvement, the age of the patient, and to some extent upon the convictions of the surgeon (63). One fundamental should be stressed; remove all diseased bone, all new bone possible should be saved (9).

The surgical procedures recommended vary from complete diaphyseal resection to leaving the sequestra in place. Amputation is more extreme, but it is an admission of defeat and when it is at all possible, is strictly avoided.

Resection

Nichols (135) was the prime advocate of resection. His was the most complete article on that subject found in the literature. He based his work on the studies made on bone regeneration by Ollier, in the last half of the nineteenth century. It would seem that resection as he performed it would be a very difficult procedure, but when it worked the results
would be very gratifying. It should be mentioned that although there were several reports in which regeneration failed, healing was usually very kind and the results good when the defect was repaired with a bone graft (18).

Nichols preferred to remove the necrotic shaft from the involucrum when it was young and flexible, but in several cases in which it was old and hard, he obtained good results by removing both the shaft and its involucrum subperiosteally. Most men report failures when they attempt Nichol's method of removing the necrotic shaft. (18, 169) It is very difficult to determine when the involucrum is in the proper stage of development for such an operation.

There are several precautions which should be taken in performing a subperiosteal resection. Great care must be taken with the periosteum. It should be traumatized as little as possible and all of it should be preserved. Best results are obtained when it is sharply dissected (48). Bones such as the femur and humerus, which have no adjacent bone support, should not be resected until an involucrum has formed which is sufficiently strong enough to assist artificial support in preventing deformity due to weight of the limb and muscle spasm. (15, 7)
Resection should not be done unless it is definitely indicated (9). When it is necessary, d'Abreu (46) believes that it should only be done on patients between the ages of 6 and 16 years. He gives as his reasons the facts that in infants wide periosteal stripping may not cause shaft necrosis, and in adults regeneration is too uncertain.

However, although few if any man care to do a subperiosteal resection if then can avoid it, it is frequently the operation of choice, and one of the best means of curing the infection permanently. The latter is especially true when by performing this operation, all the infected and necrotic tissue is removed. Sometimes it is the only method of avoiding amputation. (10, 167)

Subperiosteal resection in some cases of total necrosis of the shaft can be avoided by waiting until a strong involucrum has formed and then removing the sequestrum and most of the involucrum leaving a shallow cavity (12).

**Drill Sequestra**

The other extreme in the treatment of the subacute and chronic stages of osteomyelitis was advocated by Boysan (24). He removes no necrotic tis-
sue and simply bores holes through necrotic bone into living bone. His theory is that granulation tissue will grow into the sequestra from the living bone, they will become revascularized, and healing will follow. Perhaps this will work in some cases, but we have our doubts.

**Debridement and Saucerization**

The technique which is most commonly accepted and used in the treatment of subacute and chronic osteomyelitis was recommended, in 1911, by Beck (12). His surgery was based on three principals: Open broadly leaving the periosteum intact as much as possible; remove all the diseased tissue; and leave no cavity behind.

If necessary, he removed all the bone. He believed that most men fail to remove all the necrotic tissue and leave a cavity which is mechanically difficult or impossible to fill. He left only a shallow through or flat bone in order to avoid the formation of irregular cavities which do not allow a mechanical closure of the wound. X-rays should be taken during after treatment so as to be sure that no dead bone has been left behind and that such forms of bone have been obtained as allow mechanical closure.
However, there are a few men who operate to secure free drainage and to remove sequestra, but they do not believe that all the necrotic tissue should be curretted away. (37, 63, 167)

Bone which is chronically infected has eburnation which extends for a considerable distance up the shaft and this contains minute temporarily walled off islets of granulation tissue which may give rise to an active infection in the future (121). Abscesses continually recur.

This is the type of bone in which resection sometimes gives a very good result (9, 167) It is also the kind which frequently causes the patient to demand amputation. With conservative treatment, or while waiting for the optimum time for radical surgery to be performed, the abscesses are simply treated with local physiotherapy and drained with fluctuation occurs. When abscesses continually recur in the same location, Mr. W. H. Ogilvie (153) institutes permanent drainage with a silver wire extending down to the bone. It should be removed daily and boiled. This type of treatment does not appear to be very desirable.
Sequestra

As we have already mentioned in our discussion of sequestra (pg. 28) they should only be removed after they have completely separated, and after sufficient involucrum has formed (15, 23, 87, 139). That is usually 3 to 6 months after primary operation and drainage of the acute stage. There is no definite time element for their appearance and separation in the chronic stage. The opinion, with few exceptions, is that cure can not and will not take place in the presence of sequestra. (24, 74)

The primary causes for reoperation, in the subacute and chronic stages of osteomyelitis, are usually sequestrum formation, persistent dead space, failure to remove all the diseased tissue, and irregular soft tissue sinus formation (101).

Old persistent sinuses must be eradicated. Many sinuses continue to drain simply because they are lined by a dense layer of chronic granulation tissue. They should either be excised or laid open depending upon their location, type, and extent (101).

Freund (59) calls attention to a method that is harmless and may often render good service in chronic sinuses. He carefully inserts a silver nitrate stick
into the tract and covers the surrounding skin with a thick layer of zinc oxide ointment to decrease the effects of the resulting irritating discharge. Removal of the stick in 2 to 3 days brings the entire tract with it and a sinus tract is left covered by nice, healthy, red granulations.

Sterile Abscess

Brickner (21) called attention to chronic abscesses in the medulla of long bones as a condition but little recognized. They are usually sterile, or the organisms much attenuated, and seem to most often be found some time after a siege of osteomyelitis (22). The bone is usually thickened around them, but they are best located by the use of the x-ray.

Since they are sterile or very nearly so, simple drainage is all that is required. The only other requirements are that infection should not be introduced and the lesion should be made to heal from the bottom. Brickner (22) believed that drainage through a small drill hole was sufficient, and prompt healing followed. Simmons (167) stated that it makes little difference what is done, because they all heal anyway.
Cavities

Sequestrectomy and removal of necrotic bone in chronic osteomyelitis always leaves a variably sized bony cavity. Nature will begin the closure of a large cavernous defect in the interior of a bone by granulations and succeed to a certain point, but there will remain an infected cavity or sinus; persistent sinuses may last indefinitely. Recuretting fails, because the cavity may have become too large to be healed, unaided, by nature's processes. (112)

Treatment of this condition has always been a difficult problem, particularly, before saucerization was used and when the surgeon preferred to close the wound by primary suture. Some of the materials used to fill these defects during that time were Hamilton's (135) sponge grafts (1881), Schede's (135) aseptic blood clot (1886), Senn's (163) decalcified bone chips (1889), and Moorhof's (37, 52, 131) wax (1903). Most of these worked fairly well, and primary closure was successful, if all of the infection were removed during the operation. Moorhof's wax and most of the other techniques required perfect hemostasis and a cavity as smooth and clean as one made in a tooth by a dentist. However, it was too often impossible to fill these requirements so failures were frequent.
Saucerization, which leaves a shallow cavity in the bone, not only leaves a defect which it is mechanical possible for the osseous tissue to repair, but it also allows the soft parts to fall in and fill it. (139, 172) When such soft parts are not available, a muscle or skin flap may be used. (106, 112) The former is preferable. (123, 172) Free fat grafts are preferred by some men, (54, 68, 119) but others have no success with them. (114)

Skin grafts are frequently sued to line these cavities as sliding or pedicle flaps, or pinch grafts.

In many cases it is necessary to use Carrel-Dakin or other irrigations in preparation for the tissue transplant and during the time they are healing. (106, 123)

Many times grafting has lessened the convalescent period in a case of chronic osteomyelitis. However, in the majority of instances the infection is too active to allow the use of grafts or primary suture. It is because of these cases that numerous methods of after treatment have been devised and popularized.

**Scars**

Osteomyelitis scars are usually adherent to
underlying bone. They are often extensive, troublesome and break down easily when bruised. Those on the tibia are especially liable to be injured. In order to give such areas better protection, the thin epithelium which grows in from the surrounding skin can be replaced by large skin grafts. (8, 16, 112, 157)

**AFTER TREATMENT**

There are innumerable methods and variations of after treatment. The majority of them, whether their authors accept or condemn the Orr method, are patterned after it. This is most noticeable with regard to the use of vaseline in place of plain or iodoform gauze; wounds are packed open and granulations thus encouraged to fill the wound from the bottom; immobilization is emphasized; and dressings are infrequent, although used far more often than Orr recommends. In many cases, the Orr method is used in combination with one of the others.

We shall discuss a few of the methods which are best known and standardized. No distinction is made with regard to stage of the disease because their requirements are all essentially the same. Unless otherwise stated, it is to be kept in mind that each
of these methods is to be preceded by careful removal of all the infected and necrotic tissue and saucerization of the bone.

**Carrel-Dakin Technique**

At the suggestion of the Rockefeller Institute, and in co-operation with the United States Steel Corporation, Sherman (166) spent 5 months in England, Scotland, Belgium and France studying the various methods of wound sterilization.

He found the Carrel-Dakin technique to be almost ideal. The solution he recommended was sodium hypochlorite free of caustic alkali, containing only 0.45 to 0.50 per cent of hypochlorite. However, some men use other, but similar solutions such as chloramine, chlorazene, and eusol.

The hypochlorites were supposed to act by the liberation of chlorine in the wound. Sherman found sodium hypochlorite to be 150 to 200 times as bactericidal as carbolic acid.

The success of the treatment is dependent upon the thoroughness with which it is applied and the care given to the most minute details of the technique. Sherman believed Dakin's solution (sodium hypochlorite)
represented 20 per cent, and the Carrel technique 80 per cent of the cure.

Properly perforated Carrel tubes should be used and inserted into the wound so that all its parts are constantly bathed with the solution. Strips of gauze are placed loosely between the tubes to keep them from bunching. The edges of the wound are protected with vaseline gauze.

The wound should be "laked" or "puddled" with the solution, by means of the tubes, every 2 hours, day and night. It should be redressed daily, and every aseptic precaution must be scrupulously exercised to prevent reinfection. The skin should be cleaned and the wound gently sponged free of secretions, necrotic tissue, and other debris, and the tubes reinserted.

It was Sherman's belief that this treatment can clean either an acute or chronic osteomyelitis area within 15 to 25 days if it is opened freely and all parts constantly bathed with Dakin's solution.

The solution should be used until smears from the wound show less than 3 bacteria per high power field of the microscope. Then, after waiting a few days longer, secondary closure can be done. (58, 58)
As a method of active wound antisepsis, the Carrel-Dakin technique is undoubtedly the best that has ever been devised. The methods by which various surgeons have used it are many. We would like to mention one reported by Bauman (10) in 1926. He would resect a diseased diaphysis and sew the periosteum over perforated rubber drainage tubes letting them protrude at either end. The tubes were then used for Carrel-Dakin irrigation and allowed to remain 2 to 5 weeks depending upon the nature of the discharge from the wound.

This method does not harm tissues, it dissolves the wound exudates, and permits nascent chlorine, which it contains, to penetrate to the bacteria in the recesses of the wound. (2) However, Buchman (29) does not agree; he believes that with it there is no particular chemical sterilization, but it acts by physical removal and possibly chemical solution of the wound discharges. He finds that an inert solution with the same technique gives the same results, and that failures and recurrences are frequent.

Albee (2) was one of its most enthusiastic advocates. He found that it was far superior to any other antiseptic used in the World War No. 1, and states
that of 6,000 serious bone cases which came under his care, half owe useful extremities to conquest of wound infection by this method, before reconstruction surgery was attempted.

Yet, there were obvious objections in spite of excellent results. Frequency of dressings and irrigations were distressing to the patient, arduous for the surgeon, and associated with risk of reinfection. They were painful, tedious, and time consuming. Prolonged hospitalization was necessary. The technique rendered necessary immobilization imperfect. Disinfection was working at cross purposes with immobilization and the ultimate goal of bone repair. Within the area of the window in a cast, it induced edema of the granulation and surrounding tissue. Uniform pressure was desirable, but lacking. (1, 29, 145)

The technique of the Carrel-Dakin method is rigid, and requires a well trained and vigilant personnel. It is for those reasons that it so often fails. (60, 180)

Pomeranz (154) found by radiological studies, that regeneration of bone following irrigation (Carrel-Dakin treatment, etc.) is extremely slow and somewhat irregular. Alternating patches of osteosclerosis and osteoporosis are common and recurrences of the infection are not infrequent.
Immobilization is not generally used routinely, but mainly when fracture is feared or with other special indications.

**The Orr Method**

1. Dry wound and wipe out with 10 per cent iodine followed by 95 per cent alcohol, or use another suitable antiseptic.

2. Pack entire wound open firmly, but not tightly with sterile vaseline gauze. Cover with dry sterile pad and bandage on.

3. Then do any reasonable required manipulation to place the part in the correct anatomical position for splinting.

4. Apply a plaster cast or a suitable splint.

5. Leave cast and dressing intact. The wound is not to be dressed except for rise in temperature or other signs of acute sepsis. Dressing usually not necessary for several weeks, and then only because of odor.

6. If a cavity is still present on redressing, repack the wound and apply another cast. Do not hesitate to use an anesthetic for it.

   It will be found when the wound is dressed that it heals from the bottom and healthy granulation tissue gradually pushes the pack to the surface.
The principles upon which this treatment is based are drainage, rest, and prevention of reinfection. The value of drainage in treating infection is not to be denied. With this method it is adequate (19).

Rest has always been considered to be an important factor in the treatment of injuries and inflammation, particularly those of bones and joints. Immobilization does not cause ankylosis of joints if they are not infected. The cast should not have a window in it. That not only decreases the tendency to dress the wound, but causes pressure to be equally distributed over the entire area.

Orr criticizes frequent dressings. He feels that they make proper immobilization impossible. Frequent dressings are liable to destroy a great deal of what has been gained between times, and there is the grave danger that secondary infection will be introduced. He bases this principle on the teachings of Lister.

He admits, that by his method, healing takes longer than first intention, but it involves him in no more anxiety than the primary healing of a clean surgical wound. He feels that there is little distinction between the healing time between the present and long standing cases of osteomyelitis.
important point is that those operated on before sec-
ondary mixed infection occurs recover much more prompt-
ly and with fewer complications than those who must be
reated by his method later.

Some of the advantages of this treatment are
that it is painless and economical Hospitalization
time is decreased. In many instances the patient need
be in the hospital only for his operation, and when
his wound is dressed. Functional results are good.
It is a simple procedure which can easily be carried
out by the average physician or surgeon. It gives good
results in most men's hands, but they dress more fre-
quently than he recommends. The screams of daily dress-
ings are eliminated. The patients are more comfortable
than with any other method. Time of healing is shorten-
ed and bony defects are less. Scars are almost incred-
ibly good. The patients are more comfortable than with
any other treatment. It permits individual attention.

Meehan (126) believes that adherent gauze tears
away many of the granulations. So that nature's handi-
work is torn down, so often the temperature soon rises
soon after dressing. Vaseline gauze and infrequent
dressings prevents those incidents.
Wentworth (186) states that the greatest contribution of the Orr treatment is the elimination of meddlesomeness with nature's process of killing bacteria.

By making careful radiological studies, Pommeranz (154) found that the Orr method bone regeneration usually begins in the excavated area. It is slow in forming and gradually fills the defect made surgically. The new bone is extremely dense and somewhat irregular in character. Reconstruction of a new cortex is not so characteristic as that following maggot treatment, and periosteal thickening is often extensive.

The odor which follows the prolonged immobilization in a cast without redressing is the most frequently cited objection. It undoubtedly also serves as an excuse to redress the wound for those are unable to refrain from the desire to find out how it looks. They don't do it any good by looking at it, but they want to anyway.

Hawk (71) states that the bone itself is rigid, and nature gives immobilization to the n'th degree. All a cast does is render circulation more sluggish.

He advises getting the patient on his feet as
soon as he has recovered from the effects of the operation and the bone is strong enough to support weight. He believes use promotes healing of the tissues and increases resistance to infection.

According to Stewart (173), the Orr method has a high incidence of recurrence, there is much scar tissue, and the poorly nourished fibroid tissue breaks down easily.

Mr. W. H. Ogilvie (189) found that the scars interfered with healing in future operations and there was unnecessary ankylosis of joints.

In other words, some men praise the Orr method, while others criticize the same points. This indicates to us that the results it gives depends a great deal upon the work of the surgeon who uses it.

On the whole, the Orr method has given to surgeons over the country a degree of success that has not been approached by any other form of treatment. (26)

Bacteriophage

Orr's explanation that rest, immobilization, non-interference, and avoidance of reinfection accounted for the marked success of his treatment did not satisfy Albee (2) so he looked elsewhere for the unusual
phenomenon which was befriending both patient and surgeon.

He found that in about 94 per cent of cases of acute and chronic osteomyelitis, a specific bacteriophage appears spontaneously when treated by the Orr method.

The laborator was able to furnish a phange in 3 of the 6 per cent of cases in which it failed to appear that was specific for the organism in question. In the 3 per cent in which the laboratory was unable to cultivate a specific bacteriophage, he frequently found that one later appeared spontaneously, so watchful waiting was in order.

The Orr method should be used and no dressing done for 6 to 10 weeks in order to secure the best effects from the spontaneous appearance of a specific bacteriophage or one that may be introduced. Antiseptics should not be used to swab the bone cavity because they might prevent phage development.

He tries to cultivate a specific phage preoperatively. If one is found, he pours two-thirds of a test tube of it over the wound at operation. He then packs it with a paraffin and vaseline mixture (usually 3/1) to keep the wound open. Being fluid when applied
it can enter every recess of the wound, doesn't adhere to bone or granulations, and is gradually extruded as granulation tissue forms beneath it.

He then inserts one end of a rubber catheter through the tampon into the bone cavity, the other end projecting through the dressing and cast which is applied.

If the laboratory can develop a specific bacteriophage, he injects 10 cubic centimeters into the wound two or three times a week, care being taken not to contaminate the wound.

The cast is removed in 8 weeks, and the wound dressed in a manner similar to the post operative dressing, a cast reapplied, and periodic injections continued. He found that usually three, eight weeks dressings were enough. He states that in 100 cases, the average healing time was six months.

He believes that the method is simple in its application and requires a short period of hospitalization.

Stewart (173) feels that Albee's paraffin vaseline plug inhibits drainage; tissue colbids absorb and inactive for the bacteriophage, and they may be present and inactive for months. He also believes that an antiphage often develops and abolishes its action.
Wentworth (186) also found bacteriophage is present in about 94 per cent of cases treated by the Orr method, but its clinical effect is questionable. It is probably inactive in the presence of mucus, fibrin, pus, blood serum, erythrocytes, and fixed tissue cells.

Mac Neal (116) tried to use bacteriophages intravenously, but found that in the circulating blood it merely seems to exert an opsonic effect.

**Hydrotherapy**

Brockway (25, 26) believes that Orr treatment is very good, but that it has definite shortcomings in cases where the infective process is in close proximity to the major joints, particularly if there is an accompanying suppurative arthritis. Restoration of motion in a pus ridden joint is not best accomplished by a long period of immobilization in a plaster cast. The regeneration of pus-ridden joints and the restoration of function are best accomplished by early evacuation and motion. He prefers to use a 7 per cent warm salt water pool treatment in such cases, and also on some cases where prolonged immobilization and drainage tend to restrict joint motion by
muscle plastering, atrophy, and capsule thickening.

Hudson (80) uses plain tap water in a tub heated to a temperature of about 110 F. He believes Brockway's hypertonic solution should give better results, but has never had such a pool available. Owen (147) also reports on the use of plain water.

These men recommend hydrotherapy because it gives painless motion and no discomfort in the joint on returning to bed, movement is so effortless and painless that the patients soon lose the fear of pain, and active motion returns unconsciously. The warm water is soothing and helps to improve the circulation and hasten healing of the wound. The psychic appeal is more than imaginary.

Hudson finds that the discharge and odor disappear and healthy granulations appear more rapidly than by the use of maggots. The limb does not become water logged, and he has never had any difficulty with spread of infection or superinduced infection.

Brockway found that cultures of the pool remained sterile.

Hudson further claims that cases usually heal in 2 months that would take six months by the Orr method, and that the patients can treat themselves at home.
The technique of these men is to use the Orr method for two to six weeks after operation. The cast is then bivalved, the two halves being used as splints. All packing and dressings are removed and the treatment begun. The patient's entire body is immersed. Brockway uses an electric hoist carrying a stretcher to get the patient in and out of the pool. Light splints may be used the first few times.

The treatment is given for two hours twice every day. After the treatment, the wound is again packed and dressed, and immobilization secured by means of traction, splints, or the bivalved cast.

Maggots

The presence and valuable effects of maggots in infected wounds has been noted and commented upon for centuries. Frequently their presence was encouraged, but, it was not until 1929, that Baer (5) reported a definite attempt to scientifically use them as a method of treating osteomyelitis.

In his first case he worked without any sterilization, without gloves, without washing the skin. That case healed successfully.

Following the usual operative procedure, no an-
tiseptic of any kind should be used. It would inhibit or kill the maggots. The wound is packed for 24 hours to stop the bleeding (often not necessary). It should then be filled with sterile blow fly maggots, and covered by a properly constructed, snugly fitting mesh wire cage. It should not be covered with a bandage, but exposed to the sunlight. Light is essential because maggots abhor it and will penetrate deeper into the wound. Every 4 or 5 days the wound should be washed out with normal saline and filled again with maggots. Dressings have to be that frequent because the larvae only live about 7 days and are not active until they are 2 days old.

Itching can be aided by painting the surrounding skin with collodion. Where a nerve is exposed there is some pain for a time. The wound frequently itches, but most of the patients get used to it although many times sedatives are necessary, especially at night. There is usually a watery discharge from the wound and a slight odor for a time, but both gradually disappear. (5, 6)

The maggots are supposed to produce their effect in the infected wound in several ways. After two or three applications the wound becomes saline
which inhibits bacterial growth. They ingest and destroy bacteria, remove the necrotic tissue, and thus make conditions less favorable for bacterial growth, stimulate drainage, and cause sequestra to separate sooner. (5, 6, 29, 158)

Baer (5) believed maggots prefer dead bone and go directly to it, but stop working on it when it starts to bleed.

The maggots apparently stimulate the growth of granulation tissue, so the period of convalescence is shortened. Healing is frequently complete at the end of 6 or 7 weeks. By the end of that time, the granulation tissues have come directly up to the top of the wound and the epithelium grown over it. There is little or no pitting down into the wound itself. The scars are less extensive, irritable and disfiguring than those obtained with any other method. (5, 29, 53, 61)

It was the belief of Baer and many other workers that there is something formed between the maggots and human body. This belief is enhanced by the fact after 3 or 4 applications the maggots begin to die soon after they are placed in the wound. As the number of applications increases, the life of the maggots decreases. (5, 31) It is hard to explain the benefits
caused by their presence to their physical action alone. For these reasons, many attempts have been made to isolate an active principle.

Livingston (109, 110), alone, and in conjunction with Prince (11), has done a great deal of work along that line. In 1932, he and Prince reported (111) on the use of an extract filtered from the bodies of dead maggots. They stated that the results obtained were better than when only maggots were used. However, they not only used it in conjunction with maggots, but also with polyvalent or autogenous vaccine.

In a later report Livingston (109) stated that his active principle (maggot extract) contained the radicles sulphydryl, natural allantoin, calcium, cysteine, glutathione, and in addition, embryonic growth stimulating substances.

He believes that maggot stimulation of tissue regeneration is due to the substances found in his extract, that is without the psychic trauma, is a more powerful growth stimulant than any of its ingredients, and has wider application than maggots.

In 1932, Buchman and Blair (31) noted that older cases are sometimes complicated by a temperature of 104° to 105°F., 24 to 48 hours after maggots are introduced. In several cases the limbs presented an
erysipeloid appearance with bullae formation. However, the general condition remained good.

Wentworth (186) observed a similar rise in temperature in about one-thirds of cases. He believes it is the result of increased absorption of bacterial toxin through a growing surface of granulation tissue exposed to wound secretions.

Pomeranz (154) studied the repair of bone by means of the x-ray in cases treated according to the Orr, Carrel-Dakin, and Baer methods. He found that after the maggot treatment the bony defect becomes filled with osteoplastic tissue. In about 4 weeks the shape of the bone is re-established and the defect filled with osteoid tissue about as dense as the bone. After about 6 months the excavated area is well rounded and the medulla replaced by dense eburnated bone. He believes that in time the medullary cavity will reform and a new cortex be reconstructed. He is also of the opinion that with this method healing is more rapid and the new bone more nearly normal. Buchman and Blair (29, 31) also found that when maggots are used the new bone is smoothly and evenly calcified, not blotchy as in other methods.

There are several disadvantages to the use
of maggots. The hardest problem is the growth and maintainence of the proper stock of flies. This requires a great deal of equipment and someone who knows how to raise them. If obtained from a supply house, they are very expensive. (53, 173)

There is always the danger that they are not sterile. This greatly increases the difficulty of raising and handling them. Baer (5) lost a case from tetanus because of contaminated maggots. Livingston, gives injections of tetanus routinely when he uses them. They should always be cultured to detect contamination before being introduced into a wound.

The patient has to be hospitalized as long as maggots are being used. The period of convalescence may be shortened somewhat by them, but this is the most expensive of all the methods of after treatment. (31)

Patients are very often opposed to their use. The psychic effect and the tickeling sensation which they produce frequently makes it necessary to administer a sedative so the patient can sleep. (173, 186)

Wentworth also lists a few technical disadvantages. Maggots require oxygen at all times. Lack of food or oxygen in deep wounds, or those filled with secretions drives them out. They are repelled by light, but
will not work down in small dark sinuses. The muscles must be retracted to the depths of the wound and fluid kept at a minimum by aspiration or dependent drainage or they will drown.

Brockway (26) feels that both they and the bacteriophage may be ideal theoretically, but the fact remains they do not greatly alter the stubborn course of the disease. Good results have been attained, but the same is true of most regimens.

Miscellaneous

We shall mention several antiseptics which have been reported in the more recent literature as being very good in the after treatment of osteomyelitis.

Bismuth iodoform paraffin paste, or "Bipp" as it is usually called, was widely used in the treatment of infected wounds before the first World War. It was thought to be a very active wound antiseptic, but Dakin's solution was found to be far superior.

Myers (133) treats osteomyelitis with a modified Orr technique and recommend using "Bipp" impregnated gauze in place of vaseline gauze. "Bipp" may have some antiseptic value, but most of its benefits have probably always been to the fact that it assists in obliterating tissue spaces.
In 1933, Hawk (71) reported that he obtained very good results in treating osteomyelitis by using a mixture of glycerine and magnesium sulfate after proper removal of all necrotic tissue and bone. It was criticized, in 1934, by Stewart (173) who stated that better results were obtained by his more rational treatment which was by the use of picric acid and calcium carbonate.

Wright (195) recommends a mixture of zinc peroxide and cod liver oil.

We do not know just what the value of such materials is, but we are inclined to believe the findings of McCarroll and Key (121) reported in June of 1939. They stated that they have used Carrel-Dakin treatment, various other antiseptics, and hog lard without getting results differing much from those obtained with vaseline. Maggots were not used because they are too expensive. They say, "The infected tissue which is left (after saucerization) is beyond the reach of maggots or of any chemical or other agent which can be applied to the surface of the wound."

It was thought that it might be of value to try and compare some of the statistics which various men have given as evidence of the superior results obtained by the particular method of after treatment which
they advocate. However, we found that it got us no where. Each claims good results, so in order to choose which is the best, one is forced to relegate the statistics to the background, and judge each method chiefly on its rational applicability, and technical details.

Cohn (39), McCarroll and Key (121), and many other surgeons believe that with proper surgery, one type of after treatment is as good as another. After studying many of the methods used, with good results claimed for all of them, we are inclined to agree.

We shall merely say that in reading the literature, the impression is gained that the Orr method is the standard basis of treatment throughout the country; before its advent, the Carrel-Dakin technique was the universal standard, and before it "Bipp" received great acclaim; though maggot therapy caused quite a flurry when Baer introduced it, it is not widely used. Many other methods, some of which we have mentioned, have been advocated and used to some extent, but have not been generally accepted.

**Summary**

In summarizing, we find that in the acute stage of hematogenous osteomyelitis, the patient is usually
very sick and his life is primarily at stake. It is by the use of judicious surgery that the mortality and incidence of complications are reduced.

The surgery used in the sugacute and chronic stages is rather uniform. When it fails it is sometimes the fault of the surgeon, but the location and nature of the disease frequently make cure possible. Tissue which at operation appears entirely healthy may be permeated with a low grade infection so that there is eventually a recurrence of the disease. In the presence of such infection, no method of after treatment has yet been devised which can prevent a recurrence.

It would seem that the best method of both surgery and after treatment is the one which is most suited to a particular case, the surgeon, and the equipment which he has at his disposal.

In no case should the local lesion be treated and the general condition of the patient disregarded or entirely forgotten.

Conclusions

1. Treat the acute stage of osteomyelitis conservatively. Treat the patient first, then do no more surgery than is absolutely necessary at pri-
mary operation. Vaccines and antitoxins may, or may not be of value in either the acute or chronic stages. Sulfonilamide should be of value in cases infected by hemolytic streptococci.

2. Do not remove sequestra until they have separated completely and an involucrum has been formed.

3. In the subacute and chronic stages, use surgery according to the merits of the individual case. When resection is necessary do it, but do not use it as a routine procedure. Most lesions require debridement and saucerization. Sterile abscesses need only be drained. Muscle and skin grafts are often very effective in obtaining a rapid closure of old cavities and sinuses. Skin grafts may be used to replace large, easily injured osteomyelitis scars.

4. No method of after treatment is without its drawbacks and no one is best in all cases. The Orr method is applicable to the largest number of cases, is simple and most widely used.
Bibliography


8. Ibid, A Thick Stage Skin Plastic for Chronic Hematogenous Osteomyelitis, S. Clinic N. America, 5:193, 1925.


64. Gaul, J.S. Problems in Osteomyelitis, South. Surgeon. 6:275, Aug. '37.


85


96. Kline, L.B., Stewart Method (Combination of Picric Acid (Trinitrophenol) and Calcium Carbonate); Preliminary Report. Mil. Surgeon. 75:251, Oct., '34.


116. MacNeal W.J., Infectious Organism; Bacteriophage (Staphylococcus) and Serum (Streptococcus) Therapy, J. Bone and J. Surg. 19:891 Oct., '37.


120. Martin W., The Results of Staphylococcus Infection of Bone, S. Clin. N. Am. 3:409, Apr., '23.


133. Myers, M.T., Bipp (Petrolatum preparation) and autogenous Vaccine, J.M.A. Georgia. 26:565, Dec. '37.


168. Smith, N., Observations on Pathology and Treatment of necrosis, M. Classics. 1:820, April, '37. (Reprint)


173. Stewart, M.A., New Treatment (Combination of Picric Acid (Trinitrophenol) and Calcium Carbonate as Substitute for Maggot Therapy; Preliminary Report, S.G.O. 58:155, Feb., '34.


175. Swoboda, N., Osteomyelitis in Infancy, Pediatrics, 5:33, Jan. 1, 1898.


190. Williams, S.W., Early Treatment (Especially with Antitoxin) of Acute staphylococcal Osteomyelitis, M.J. Australia. 2:459, Sept. 8, '37.


DIABETIC COMA

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SENIOR THESIS

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INTRODUCTION

Diabetic coma was a rather common occurrence in diabetic patients before 1921, for it was only after the discovery of insulin in 1921 by Banting and his associates and its use that it was possible to effectively treat diabetic coma patients. However, even up to the present date, development of coma in diabetic patients is not a rare occurrence for apparently more diabetic individuals are being kept alive by the use of insulin and hence there are more chances for the development of coma.

Coma is as important to the medical man as is an acute abdomen to the surgeon, for it is only by immediate and correct treatment that a patient in coma may be saved. Hence one must look upon it as a medical emergency that needs the immediate attention of the physician. It may be well to keep in mind the statement of Joslin about having the hospital staff practice "coma-drills" as firemen must practice "fire-drills" in their line of duty so as to act quickly and efficiently to secure the desired results.

DEFINITION

Varicous theories have sprung up as to the cause of diabetic coma and as to when an individual shall be placed into this category. Most investigators have taken the carbon dioxide combining power of blood plasma as an
indication of the degree of acidosis and coma (Dillon and Lyer-16).

Baker (3) states that the value 20 volumes per cent of carbon dioxide combining power of the blood plasma is the dividing line between a state of precoma (acidosis) and a state of coma.

In 1917, five years before the introduction of insulin, Joslin reported on 15 patients in diabetic coma who recovered after showing a carbon dioxide tension of alveolar air of 40mm. of mercury or less. The carbon dioxide combining power of the plasma ranged between 4 and 23 volumes per cent. These facts lead Joslin to make use of the value 20 as an arbitrary dividing line between cases of precoma and cases of coma. The latter figure apparently remains, up to the present day, as a good point of division. (Joslin, E.P.; Root; White; Marble; and Joslin, A.P.;-26).

In 1928 Joslin, Root, White, Marble, and Hunt (25) stated that anything below 20 volumes per cent is indicative of coma. However, they also point out that some patients are nearly unconscious when the carbon dioxide value is above 20 while other cases may be quite alert when the carbon dioxide is far below 20 volumes per cent. They give the following conditions as reasons for assuming the above
value. First it has been found that when ketosis has progressed to the point of lowering the plasma carbon dioxide combining power to 20 volumes per cent, unless energetic treatment is given, the danger of development of fatal coma is great. Secondly, before the discovery of insulin, recoveries from coma when the plasma carbon dioxide combining power was above 20 volumes per cent were not uncommon, whereas recoveries when this value was below 20 volumes per cent were extremely rare. The above authors do not believe, that blood sugar, non-protein nitrogen, blood pressure, unconsciousness, nor Kussmaul respirations are adequate indications of the depth of coma.

Allan (3), as a possible aid to the clinician, correlates clinical symptomatology with certain values of the combining power of the blood plasma as follows:

1. A value for carbon dioxide from 40 to 50 indicates mild acidosi; usually with no symptoms.

2. A value for carbon dioxide from 40 to 30; weakness and malaise.

3. A value for carbon dioxide from 30 to 20; prostration, shortness of breath, gastro-intestinal disturbances and aches and pains.
4. A value for carbon dioxide below 20; severe acidosis, extreme prostration and usually loss of consciousness, and air hunger.

INCIDENCE AND MORTALITY

A. Incidence:

Baker (8) gives the following data on the percentage of coma cases in diabetic patients:

1. In his own series of diabetic patients registered at the Mayo Clinic 1.6 per cent were in coma.

2. Joslin's series, 2.8 per cent.

3. John's series, 4 per cent.

4. Solomon and Aring's series, 1.7 per cent.

In a series of 42 new cases of coma studied by Joslin, Root, White, Marble, and Joslin (26) it was found that the average age in this series was 23.2 years. The oldest patient was 66.5 and the youngest was 2.4 years of age. Here also, as was pointed out in a previous article by these investigators, there was a preponderance of coma in females and this occurring in ages in which the preponderance of coma cases of diabetes is in males. Explanation for this preponderance of coma in females is as yet lacking. However, the above authors have put forth the theory that perhaps
there is a hyperactivity of the pituitary gland during catamenia or during pregnancy.

In Dillon and Dyer's (16) series of 268 cases of diabetic acidosis 81 were males and 187 females. Total mortality being 29.6 per cent for the males and 49.7 per cent for the females. They are unable to give any adequate explanation for the above figures. The incidence of acidosis was about two and one-half times as great in their colored patients. The mortality, however, was somewhat lower in the colored race, but this is mostly accounted for by the greater percentage of return calls.

B. Mortality:

The chief cause of death in diabetic patients, as listed by Joslin (Warren-58) in a study of 3575 cases, is coma. In the Naunyn era (1897-1914) diabetic coma was the cause of 63.7 per cent of all the cases. In the Allen era (1914-1922)--41.6 per cent. In the early (1922-1925), middle (1926-1929), and later (1930-1935) Banting era--21.5%, 10.8%, and 6.1% respectively. Cardio-renal-vascular diseases came second. The rest, listed in order of their frequency were: infections, cancer, tuberculosis, accidents, inanition, suicides, insulin reaction,
and other diseases. In Warren's own series of 486 diabetic autopsies, death due to coma was attributed to 26.1 per cent. The rest came in the following order of frequency; cardio-renal-vascular diseases, infections, cancer, hemochromatosis, pulmonary embolus, insulin reactions, accident, and other causes (Warren-52).

Lande (28) divides fatal cases of diabetic coma into four groups. Group one consists of cases not adequately treated. Group two consists of cases in which the coma was associated with conditions fatal in themselves. In this group he had a 33 per cent mortality rate. Group three consists of cases in which coma was the prime cause of death with associated conditions as contributing factors; 52 per cent. Group four consists of cases of uncomplicated diabetic coma; 2% per cent.

Lande (28) states that the death rate of diabetes has risen from 17.3 per hundred thousand in 1901 to 27.1 per hundred thousand in 1931. With the introduction of insulin in 1923 there was a slight recession in mortality rate, this however was lost and the diabetic death rate in the 35-44 year age period was increased, particularly in women. He studied 82 cases of diabetic coma from the adult
wards of the Mont Sinai Hospital for the insulin period (1923-1932); of this number 24 died, a mortality of 29 per cent. According to him the introduction of insulin has favorably affected the mortality of diabetes only in the group under the age of 35 years.

Joslin reported a negligible mortality in juvenile diabetic coma cases with Lande reporting only one death from this cause in the pediatric service at Mont Sinai Hospital in the last six years.

According to the reports of the Metropolitan Life Insurance Company in 1930, coma occurred in 37 per cent of fatal cases of diabetes (Allan-3).

The degree of hyperglycemia was thought at one time to have a great effect on mortality; however, Dillon and Dyer (16) believe that this misconception is probably due to other factors which are more likely to be present when there is a high blood sugar. The mortality for all their cases studied in which the blood sugar was above 700 was 57.7 per cent and in those cases with a blood sugar of 400 or below the mortality percentage was 29.1.
Lande (28) put forth two theories as to the mechanism of death in patients suffering from diabetic coma. The first and more probable theory is based on the idea of a vaso-motor collapse or shock basis. The second is based on a theory of hyperpyrexia whether it be of nervous origin or just a concomitant of dehydration.

ETIOLOGY

A. Primary Cause:

There is apparently no doubt in the minds of present day investigators and clinicians that the primary cause of diabetic coma is an insulin insufficiency whether it be of a qualitative or quantitative nature. The various theories as to the manner in which a person becomes a diabetic is not concerned with diabetic coma and hence the various phases as to the former's etiology will not be discussed here.

B. Precipitating Factors:

Only an outline form of the various precipitating factors, as given by John (22), Joslin (25), and Baker (8), will be considered here. In the order of greatest frequency they are as follows:

1. Dietary indiscretion and omission of insulin

Of Baker's series 37 per cent are placed
in this group. Joslin reports 32 cases of dietary indiscretions in a series of 42 cases; nearly one-half were children.

2. Infection.

Baker's series, 20 per cent. Respiratory infections are the most common with pyelonephritis coming second.

3. Operations.

Operative procedures on abscessed teeth and cholecystectomies head the list in a group of operative procedures which were followed by diabetic coma. Baker places 5 per cent of his cases in this group.

4. Ether and chloroform anesthesias.

This group, as is obvious, must be considered along with operative procedures.

5. Other causes.

Baker gives a percentage of 11 for glandular causes and 17 per cent for diabetic coma in which no precipitating factor or factors were in evidence.

Age, season of year, sex, and duration of the diabetes apparently are influencing factors in the precipitation of diabetic coma. Baker finds that the average age incidence in his series was 31.2
years, with diabetic coma occurring most frequently in young children and elderly persons.

Diabetic coma is especially prevalent during the months of August and October.

Sex, apparently predisposes to diabetic coma; Baker reporting a percentage of 43.5 in males and 56.5 in females.

In Joslin's series 23 per cent developed coma in the first year of the disease, while 58 per cent occurred within the first three years. Baker finds that 26 ½ months, on the average, elapse since the onset of diabetic symptoms before diabetic coma develops. Twenty-three and a half months elapse from the onset of glycosuria before coma develops.

PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY
A. Pathology.

Warren (52) divides the pathology of diabetes mellitus into four groups or categories. The first group consists of diabetes that show no significant pathologic changes. He found that in this group the islands of Langerhans were normal in number and appearance. The adrenals and pituitary were also normal. The second group, which made up 74 per cent of his own cases, consisted of diabetes
associated with insular insufficiency. Of this group one-fifth of his cases showed a decrease in the number of islands. The most frequent change was hyalinization of the isles with some fibrosis. Hydropic degeneration was rarely found except in the acute cases. Lymphocytic infiltration of the islands was especially prominent in children. It should also be stated here that in this group he found evidence of regeneration of the islands.

The third group which made up about 2 per cent of his necropsy patients and about 0.15 per cent of Joslin's series, consisted of diabetes associated with hemochromatosis. The fourth group consists of acromegalic diabetes. About 30 per cent acromegalics show glycosuria.

In this paper we will be concerned only with the pathology as indicated in the second group of Warren's series.

I. Essential (Pancreatic)

a. Macroscopic

Macroscopically the pancreas of a patient who has died of diabetes looks perfectly normal (Boyd-11).

b. Microscopic

The microscopic picture shows at
least one or more or all of the following pathological changes about to be described in persons who have died of diabetes melitius.

Hyaline Degeneration:

A specific type of hyaline degeneration in the islets of Langerhans, possibly identical with amyloid, was first described by Opie (38) in 1901. The material studied was taken from the pancreas of a diabetic girl 17 years old. Although his description was given 39 years ago there are at present many theories as to the exact nature of this type of degeneration and its relationship to diabetes. There are at the present time two views as to the exact origin of this material. The one view favors an epithelial-intracellular-origin, while the other view favors a mesoblastic-intercellular-origin.(Warren-52). Warren is apparently of the opinion that hyalinization of the isles is due to production of intercellular substance by fibroblasts and possibly by endothelial cells. When the process becomes sufficiently marked to destroy a number of the epithelial cells or to separate them from the blood stream by a practically impermeable membrane, diabetes will develop.

In his study of 300 cases of hyalinization of the
islands in diabetes he found that 97 per cent occurred in individuals over forty years of age. The hyaline material is not restricted to cases of diabetes alone but is also found in patients dying from other causes. However, Warren (51) states that these patients may have developed diabetes if they would have lived. As to whether hyalinization is a primary or secondary factor in diabetes Warren (52) believes that the former hypothesis is true, because as the frequency of hyalinization increases the severity of diabetes also increases.

Hydropic Degeneration:

Hydropic degeneration as first observed by Langerhans and later described in human cases by Weichaelbaum and Stangl, bears no microscopic resemblance to hyaline, colloid or amyloid degeneration (1;52). Homann, in his work on experimental and human diabetes, proved that the process is limited to the beta cells (Allan-1).

In hydropic degeneration there is a disappearance of the granules of the beta cells in the islets of Langerhans with a replacement by fluid so as to give a vacuolated appearance to the cells. Allan (1) regards the above two changes as evidence of exhaustion of the islets which break down under
undue strain; an internal secretory stimulus. This may be an adequate explanation, for in deaths from diabetic coma there is a much greater chance of finding hydropic cells. This type of pathology is also found in the severe diabetes of childhood (Boyd-11).

The striking feature, according to some investigators (1;11;51), of hydropic degeneration, is that it appears to be the result of injury by an excessive functional strain with vacuolation being reversible only in its slighter degree, but, once established, leads to atrophy and disappearance of the cell involved.

In a series of diabetic pancreases Warren (52) noticed the frequent appearance of changes suggestive of hydropic degeneration in many of the islet cells of those pancreases removed over three hours postmortem, and the comparative rarity of this finding in pancreases removed one hour or less postmortem. Allan (1) believes that hydropic degeneration is present only when the diabetes has been sufficiently intense and prolonged and he emphasizes the importance of fresh tissue for its demonstration. Warren (52) has seen the most striking cases of hydropic degeneration in fulminating cases of diabetes of relatively short
duration. He noticed that this was especially true in the study of a pancreas presented to him by Dr. John R. Williams of a case of only three weeks duration. The absence of a predominance of hydropic degeneration in Warren's series (51) is explained, by him, as possibly being due to insulin treated cases on the theory that insulin, by reducing functional strain, reduced the frequency of the lesion. But he goes on to state that the changes is nearly as rare in his cases not given insulin as in those treated with insulin.

According to Warren (51) in all the above changes described, there is no significant difference in the degree of involvement of the alpha end of the beta cells. He believes that the hydropic degenerative changes of the insular epithelium as described by Weichselbaum are simply a postmortem change. This view is directly opposed to Boyd's (11) point of view in which he lists hyalinization and fibrosis as those pathological changes of least significance. He says that in the acute diabetes of young people the islets may appear normal (no hyalinization or fibrosis), but if the tissue is fresh and well fixed, hydropic degeneration may be seen, while if specific granule stains are used, the granules will be found to have disappeared from
the beta cells. He especially stresses the use of special fixatives and stains to be used within one or two hours after death.

Fibrosis:

While hyalinization occurs more frequently in older persons, fibrosis which is laid down, without leukocytic action or evidence of necrosis, in much the same site as the hyaline, occurs more frequently in children and young adult diabetics. Of a total of 129 pancreases of diabetic persons studied by Warren (51), twenty-seven per cent showed slight fibrosis. Thus there is a tendency for slight fibrosis to be more frequent than marked, just the reverse of the frequency of hyalinization. According to Boyd (11) in severe diabetes of childhood there is neither hyaline changes nor fibrosis but usually a marked hydropic degeneration.

Lymphocytic Infiltration:

In children and young adults a lymphocytic infiltration of the islands is sometimes observed, which is characterized by a sharp restriction to the insular zones and a very appreciable disappearance of the epithelial elements of the island, (Warren-51). Warren (51;52) found the lesion in nine patients, seven of whom where under 30 years of age.
No constant change can be shown in the acinar tissue (Boyd-11).

II. Associated (Extra-Pancreatic)

a. Carbohydrate metabolic disturbances:

Warren (51) states that investigations in carbohydrate metabolic disturbances are concerned chiefly with glycogen because of the difficulty to detect sugars in tissues since they are so highly diffusible. In his studies he found that glycogen is laid down in the nuclei of liver cells and in the renal tubular epithelium especially Henle's loops. Boyd (11) also finds that these deposits are to be found chiefly in the cells of the loop of Henle, but adds that the convoluted tubules may also contain much glycogen.

The following three statements are given by Allan (1) as distinctions between the pancreatic changes and those in either the kidney or liver: 1. The former are strictly specific to diabetes while the latter are not; 2. The vacuoles in the pancreatic islands never contain either fat or glycogen; 3. The filling of kidney or liver cells with glycogen or fat apparently never leads to their destruction unless some other cause of injury is present, while the vacuolation of the Langerhans cells is part of a process which if continued destroys them.
b. Lipoid metabolic disturbances:

The blood lipid is usually high in diabetes mellitus and in some cases gives a milky plasma with a storage of lipids, chiefly cholesterol esters, in the reticulo-endothelial systems such as the spleen and liver. Yellow patches (xanthoma) may also occur in the aorta and skin. (Boyd-11).

One puzzling feature of a disordered fat metabolism in diabetes mellitus is that the lipid in the blood and that taken up by the cells of the reticulo-endothelial system show a variation in chemical constitution (Warren-52).

c. Cerebral lesions:

According to Warren (52) although diabetes mellitus is intimately connected with the central nervous system, he was able to demonstrate only changes that were almost entirely due to complications of the disease rather than to diabetes itself. In his own studies of brains taken from patients who died with diabetes mellitus he found no changes distinctive of diabetes other than the abnormal glycogen deposits in large amounts as droplets in the glia cells. He noticed this form of deposition in three diabetic brains, two from coma cases.

Several investigators have predicated a cerebral
factor in fatal cases of diabetic acidosis but Dillon, Riggs, and Dyer (15) have been unable to find any literature concerning demonstrable cerebral lesions or any explanation of its physiologic modus operandi. In their studies of eight cases of fatal diabetic acidosis, of which all were young enough to minimize the usual degenerative vascular changes and in which autopsies were performed at varying times within 24 hours after death, they made the following pathological summary of the brain findings. The brain shows lesions like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed, with the capillaries dilated and the endothelial cells showing degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema. As a result of the cerebral edema there is proliferation of neuroglia and acute degenerative changes in the ganglion cells. The degeneration of the ganglion cells is greatest in the third and fourth cortical layers, and in the extra-pyramidal system. These investigators state that there is no exact knowledge of the mechanism of production of the cerebral anoxia in diabetic acidosis. Their own theory is as follows: There is a cerebral anoxia, primarily based upon reduced blood volume with hemoconcentration; as the result, there
is marked reduction in the volume of circulating blood; a consequent reduction of blood pressure both systolic and diastolic; limitation of the amount of blood flowing to the head and resulting anoxia of the brain. The cerebral lesions, in turn, may further embarrass the cardiac function by paralysis of the vasomotor and other vegetative centers, and in consequence the patient may die as a result of collapse of the vasomotor system or failure of the respiratory function, even when chemical estimation of the degree of acidosis indicates an improvement.

Chornyak did some work for the U.S. Bureau of Mines relative to the effect of an atmosphere deficient in oxygen. He found that certain areas of the brain were more susceptible to oxygen insufficiency than other areas. Dillon, Riggs, and Dyer's work (15) showed their cases to present the greatest damage at these identical areas.

B. Pathological Physiology.

Since diabetic coma, as is the prevalent viewpoint today, is related to acidosis, it would be well at this time to give a resume of the mechanism leading up to coma and some of the normal mechanisms involved in the body in attempting to ward off such a catastrophe.

In the human body there is continuously being produced various organic and inorganic acids as end
products of protein, carbohydrate, and fat metabolism. Some of the various mineral acids or so-called inorganic acids which are produced are HCl, HS04, H3PO4, and H2CO3. The sulphur and phosphorus are derived from proteins. The organic acids are betahydroxybutyric acid, diacetic acid, acetone, and lactic acid. In relationship to the acids as produced in the human body one must not forget about our bodily source of alkalis. The source of alkali metals (Na, K, Ca, and Mg) for our blood come from the outside, that is in the food we take in, in the form of salts. The mechanism of how these alkalis are taken into our blood stream is explained by Ginsburg (18) in the following manner. The gastric secretion, as is well known, consists of acid (HCl). This acid is from the sodium chloride which reacts with H2CO3 or H2O in the following manner:

\[ \text{NaCl and } H_2CO_3 \text{ equals } HCl \text{ and } NaHCO_3 \]
\[ \text{NaCl and } H_2O \text{ equals } HCl \text{ and } NaOH \]

The following reaction may also be included.

\[ \text{NaOH and } CO_2 \text{ equals } NaHCO_3 \]

Hence alkalis are absorbed as NaOH, NaHCO3, and the -CO3.

According to Ginsburg (18) the following mechanism is given as to the regulation of the normal pH of the human blood.
$H_2C_6$ equals $H_2O$ and $CO_2$  
$HCl$ and $NaHCO_3$ equals $NaCl$ and $H_2CO_3$  
$H_2SO_4$ and $2NaHCO_3$ equals $Na_2SO_4$ and $2H_2CO_3$  
$H_3PO_4$ and $NaHCO_3$ equals $NaH_2PO_4$ and $H_2CO_3$  
$\text{Lactic acid and } NaHCO_3 \text{ equals Sodium lactate and } H_2CO_3$ (Best and Taylor-10).

Phosphates, sulfates, lactates, etc., are excreted in the urine; lactic acid is also removed to a large extent through its conversion to glycogen in the liver and muscles. The reaction of the urine is acid and usually lies between a pH of 5.0 and 7.0. This acidity is due chiefly to the proportion of di-basic (alkaline) and mono-basic (acid) phosphates present. Since the blood supply to the kidney is of a pH around 7.40, it is readily seen that the kidney plays an important role in the regulation of the acid-base balance of the body fluids. The mechanism for this change is described by Best and Taylor (10) as follows:

$Na_2HPO_4$ and $H_2CO_3$ equals $NaH_2PO_4$ and $NaHCO_3$

The bicarbonate is thought to be re-absorbed by the epithelium of the tubules, hence we have here an important means of conservation of base chiefly $Na$, but also $K$, $Mg$, and $Ca$ by the body. $Na_2HPO_4$ is the di-basic phosphate and $NaH_2PO_4$ is the mono-basic phosphate.

In the lungs $2NaHCO_3$ gives off one $CO_2$ and one
H2O leaving one molecule of Na2CO3. This latter compound goes back to take up one molecule of H2CO3 or a molecule of each of CO2 and H2O and carries it again to the lungs in the form of 2NaHCO3. Hence the sodium molecule is not lost and acts as a carrier for carbon dioxide from tissues to lungs to be eliminated. (Ginsburg-13).

After the alkalies have neutralized all the non-volatile acids there is still enough of them left to take care of the carbon dioxide and other acids that might arise, and it is this excess of the alkalies, which is left after all the non-volatile acids have been neutralized that is spoken of as the alkali reserve of the body. It is measured by the amount of carbon dioxide that the alkalies in 100cc. of plasma will combine with. Normally this carbon dioxide binding power of the blood varies between 59 and 75cc. per 100cc. of plasma. (Ginsburg-13).

Sellards (45), 1917, summarizes the mechanism of the normal equilibrium between acids and bases as it occurs in health in the following manner:

1. Intake of fixed bases in the food.

2. Elimination;

   (a) of carbon dioxide by the lungs,

   (b) of acid by the kidney.
Neutralization of acid in the body by ammonia.

Helms emphasizes the importance of preliminary oxidation of acids before a normal mechanism of elimination of the acids formed can be acquired.

It would be well to recall at this time that through the process of deamination of the amino-acids in the liver ammonia is formed. Ammonia and carbonic acid through various intermediary reactions unite to form urea. The urea is carried to the kidneys and here when needed ammonia is re-formed. (Best and Taylor-10).

Helms (20) gives the following steps in which the alkali of the blood is used up.

1. Neutralization by buffers.

Bicarbonate, carbonate, and phosphate which are the first to come into play and are instantaneous, their action being a simple chemical double decomposition of an acid and a base with the formation of a neutral salt. The buffers of the blood can handle 1000cc. of normal acid before fatal acidosis occurs.

2. Respiration.

This is the second mechanism to assert its effect and is also rapid in action and is chiefly for the purpose of lowering the HCO₃⁻ of the blood by added acid. The respiration does this by getting rid of formed HCO₃⁻, while permitting 80 per cent of the buffer-
ed salt to be neutralized before the pH falls to 7.0.

Neither of the above two mechanisms act to do anything to restore the body's alkali reserve to normal, that is to say, they do not bolster the depleted store of alkali.

3. The kidney's excretion of free buffer acids.

Free acids on entering the blood react to form alkali salts, thus causing a primary alkali deficit. In response to this the body excretes some of its phosphate which is transformed in the kidney to the acid form. As each molecule is transformed, it leaves one equivalent of alkali, which remains and reacts with the \( \text{H}_2\text{CO}_3 \) to form bicarbonate and builds up alkali reserve. This action therefore is one of replenishment while the neutralization by buffers and release by respiration is merely one of protection. However, it operates much more slowly than the buffers and respiration.

4. Removal of chlorine ion from the blood.

In some unknown manner, the chloride is removed from the blood leaving the sodium free to neutralize acids.

5. Combustion of organic acids, such as oxidation of lactic acid after exercise.

Various schools of thought on diabetic acidosis:

1. According to von Noorden (23), 1910, a variety
of morbid phenomena were attributed to autointoxication by the medical folklore of long ago. It was not until Bouchard and his pupils published their investigations on the subject that this theory attained the dignity of a scientific doctrine. German physicians at this time however were slow to accept the above theory.

2. Von Jacksch in 1895 attributed the cause of symptoms as found in intoxication to the appearance of acetone in the urine.

3. Bunge in 1901 attributed the cause of death to an intoxication with sulphuric acid.

4. Von Norden (49) in 1910 states that a perversion of oxidation leads to a formation of acetone bodies with a resulting decreased alkelescence of the blood followed by symptoms of acidosis.

5. Naunyn school 1906.

Acidosis is essentially an impoverishment of the body alkalies. He described it under the term hypalkalitait.


2. Defective elimination of the mineral acids.


1. Excessive production of acid in the body.

2. Defective elimination of acids normally
produced.

7. Ingestion of acids.

Here we are concerned chiefly with a defective oxidation of organic acids and an excessive production of acid in the human body. In diabetic acidosis there is an increased production of organic acids (Ginsburg-54). These acids are betahydroxybutric acid, aceto-acetic acid (diacetic acid), and acetone. According to Sellards (45) however it would be more correct to say that there is neither an increased production nor an increased accumulation of acid but that in health the acid is removed by oxidation and eliminated as carbon dioxide from the lungs, whereas in diabetic acidosis, it is removed by neutralization and elimination from the kidneys. The three acids mentioned above are intermediary products of fat metabolism and make their presence in abnormal amounts in the blood when there is a faulty utilization or metabolism of carbohydrates.

\[
\begin{align*}
\text{CH}_3\text{-CH}_2\text{-CH}_2\text{COOH} & \quad \text{Butyric acid} \\
\text{CH}_3\text{-C-CH}_2\text{-COOH} & \quad \text{Betahydroxybutric acid} \\
\text{CH}_3\text{-C-COOH} & \quad \text{Aceto-acetic acid} \\
\text{CH}_3 & \quad \text{Acetone}
\end{align*}
\]

Ketone bodies (Acetone Bodies).
As the acetone bodies are formed, some are excreted as such in the urine others are neutralized by the body alkali. The body attempts to save these alkalis hence it uses ammonia to neutralize the acetone bodies. If the diabetes is at all severe the extra alkali ammonia does not suffice. The alkaline metals are used up. The blood cannot carry the carbon dioxide from the tissue sufficiently well. The carbon dioxide stimulates the respiratory center; hyperpnea results but no cyanosis is in evidence because there is no increase in carbon dioxide in the blood for it is greatly diminished. The individual is able to secure plenty of oxygen but it cannot get into the tissues because of the presence of excessive amounts of carbon dioxide, therefore the brain suffers from a lack of adequate nourishment and these individuals subsequently go into coma. (Ginsburg-18). The above description given in 1933 is also given in almost the same manner by Sellards (45) as early as 1917.

Schneider and Droller (44) found that when aceto-acetic acid and its sodium salt were administered by continuous intravenous infusion into rabbits ears, there was produced a state resembling diabetic coma with normal or relatively high alkali reserves. They also found that betahydroxybutyric acid did not produce coma even at low alkali reserves. They concluded from their ex-
periments that diabetic coma was due, in the main, to a specific intoxication by the aceto-acetic anion. However, according to Dods and Robertson (17) a study of (a) the aceto-acetic acid and (b) the alkali reserve content of the blood in patients in diabetic coma failed to support the theories of ketosis and acidosis respectively as a cause of this condition. Thus, in many cases studied by the two, non-comatose diabetic patients were found to have higher aceto-acetic acid content than the comatose patients, and it was found impossible to correlate the blood analyses with the clinical condition of the patient.

Allan and Wishart (4) showed that coma is not due to a mere intoxication with acetone bodies or of poisoning with acid but due to some metabolic derangement of which the chemical signs are only a superficial and variable expression.

Although there is a relative increase of some substances in the blood due to the hemococoncentration, Peters, Bulgar, Eisenman, and Lee (29) have shown that in profound diabetic toxemia the salt (NaCl) content of the blood and probably that of the tissues is seriously depleted. This low level of plasma chlorides in diabetes, according to these investigators, may be an osmotic compensation for the hyperglycemia, or it may be just a
means of maintaining a balanced electrolytic concentration. In any event it makes available more base to combine with the organic acids and thus tends to conserve the NaHCO₃. However, it must be stated that low chlorides are often observed in diabetic patients without ketosis and in the presence of a normal alkaline reserve. Some of the plasma chloride is thought to go into the tissues where it must unite with base.

Some investigators believe that a high blood sugar causes coma, however, John (22) shows by recording blood sugar levels at the onset of coma in 82 cases that such is not the case.

**Blood Sugar**

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
<th>800</th>
<th>900</th>
<th>1000</th>
<th>1100</th>
<th>1600</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1</td>
<td>3</td>
<td>17</td>
<td>29</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

With a high glucose and low chloride concentration of blood there may be some indication as to a relationship between these two compounds, however, Williams (55) in studying the blood chloride and sugar of diabetic individuals was unable to find any consistent relationship between the level of glucose and the level of chloride in the whole blood, corpuscles, or serum.

The question may be asked if fats are poorly digested
and a resulting lipemia occurs, what then is the relationship between acidosis and the lipemia?

The blood fat is definitely increased in diabetic persons as is shown in chart form by Macleod (32).

In experimental reproduction of lipemia Curtis, Sheldon, and Eckstein (13) showed a relationship to exist between the degree of lipemia and the degree of acidosis as measured by either the acetone of the blood or urine or carbon dioxide capacity of the blood plasma. The lipemia, as they observed it, seemed to be in proportion to the acidosis throughout their entire study of the human cases, disappearing with a return of the acid-base equilibrium to normal and reappearing with the event of acidosis. They also observed that although the lipemia was attended by an intense glycosuria and hyperglycemia there was a lack of parallelism between them, as the disturbances of sugar metabolism may occur without the lipemia.
DIAGNOSIS

In attempting to diagnose diabetic coma one should secure a history of the onset, notice the appearance of the patient, the odor of the breath, make tests for sugar and acetone bodies, and finally determine the carbon dioxide combining power of the blood plasma.

A. Symptoms.

The cardinal symptoms as found in diabetic coma are Kussmaul breathing, nausea, vomiting, pain in the epigastrium, drowsiness and coma (8;47). Usually the symptoms follow a definite course as listed by Allen (3), that is, first a loss of strength, frequent excessive urination, and increased thirst; later a loss of appetite, nausea, vomiting, pains and aches in various parts of the body. There may be headache, backache, agonizing pains in the extremities, abdomen, and thorax. Drowsiness, stupor, and finally unconsciousness are usually found in the final stages.

B. Physical findings.

The usual physical findings that are in evidence according to Allan (3) and Smink (47) are as follows:

Acetone or fruity odor to the breath.

Dehydration as evidenced by a dry skin, glistening, throat, mouth, tongue, and lips.

Parached tongue.
Soft eyeball due to the decreased intra-ocular tension.

Shortness of breath which usually follows the vomiting.

Flushed cheeks.

Red lips.

Difficult breathing, in the absence of cyanosis.

Extremities are cold, bluish and mottled.

Temperature is sub-normal.

Decreasing blood pressure.

Heart beat is rapid.

Patellar reflexes disappear.

Pupils constricted, or may alternately constrict and dilate.

Superficial tissues are flabby.

I. Respiration.

The characteristic feature of respiration in diabetic coma is the so-called "Kussmaul breathing" which was described by Kussmaul of Strasburg in 1874 as the grosse Athmung (8). This type of breathing is characterized by deep, slow, and prolonged inspirations and short expirations with short pauses between. It is as if the patient had some great load on his chest which he was trying to throw off (Allen and Wishart-3). According to Joslin (22) this is the most significant
finding in diabetic coma. It was present in 29 of his 30 cases. Occasionally a patient with a blood carbon dioxide under 20 volumes per cent did not show this type of breathing. In the early stages it is normally present, but as weakness of the patient develops, the respiratory excursions grow less. Even when the carbon dioxide is markedly low, it may be absent. Wisliski attributes this to asthenia and circulatory failure particularly in the muscles (25).

II. Pain in the epigastrium.

Gastric symptoms are usually constant and consist of abdominal pain which is usually spastic in character. The abdominal tenderness and muscular spasms are usually accompanied by nausea and vomiting. Various suggestions have been made from time to time as to the cause of the abdominal symptoms and apparently they are all theories; however, the consensus of opinion seems to be that due to the muscular spasm of the abdomen a local ischemia is produced and hence pain is evidenced by the patient.

Walker (50) had a case in which the abdominal symptoms were severe and which cleared up after treatment with 1,000cc. normal saline and 50 units of insulin. He says a similarity exists in heat cramps, gastric tetany, and diabetic coma; in all three of which there
is a loss of sodium chloride and in which all three are apparently relieved by the administration of sodium chloride.

III. Eyes

The soft eyeballs as found in diabetic coma patients are due to the decreased intra-ocular tension which in turn is due to the dehydration. The eyeballs grow progressively more soft as the coma deepens. Lawrence (29) has seen cases in which the intra-ocular tension was so low and the eyeball so flat that he had to lift the eyelid to make sure the eyeball had not previously been removed.

The Loewi reaction which is said to be pathogramonic for pancreatic deficiency consists of the injection of epinephrine into the conjunctival sac. If the reaction is positive the pupils will dilate (23).

IV. Temperature

Temperature is usually subnormal and rises in the preagonal stage or if an infection occurs (23).

V. Circulation and hemoconcentration.

In some experimental work done by Peters and his co-workers (40) it was found that in severe acidosis the serum proteins are usually within or above the normal level. The initial high level seems to be due to hemoconcentration, the subsequent fall to restoration
of normal serum volume. This work has been substantiated by a large group of other investigators.

Joslin and his co-workers (25) found that circulatory collapse occurred in 5 patients of their present series; of these two died.

A poor peripheral circulation characterizes nearly all advanced cases of diabetic acidosis. Low blood pressure and tachycardia are common. In 65 per cent of a group of patients (Joslin-23) the pulse rate was 130 or above. Clinical signs of cardiac dilatation such as temporary extension of the borders beyond normal limits with murmurs and irregularities were not infrequent.

In Joslin and his co-workers' (23) former series they reported 21 cases, and of these the blood pressure was below 100 in 6, between 100 and 120 in 6 more, and between 120 and 154 in the remaining 9 patients. The systolic blood pressure in coma under present methods or treatment is therefore not so low as often reported.

VI. Dehydration.

The reason for dehydration in diabetic coma patients is many and varied; however, a brief summary of some of the ideas put forth by various authors will be presented here.

Lande (28) states that the breakdown of carbohydrate metabolism causes a greatly increased water excretion
and an equally pronounced excretion of electrolytes normally present in the intracellular (K) and extracellular (Na) fluids. He however makes no attempt to explain the reasons for such action. He also states that with the onset of acidosis, the excretion of ketones greatly augments the loss of water and electrolytes. As a result of the rapid loss of water, sodium and potassium, there develops a depletion of base in the body sufficient to cause dehydration of tissue (the mechanism for this is also omitted by Lande), the alkali deficit becomes more marked and hyperventilation ensues with its tendency to depress the blood pressure and increase the loss of water by evaporation from the lungs. There develops, according to Lande at the same time an increased permeability of the capillary walls with the tendency of fluids to pass from the vessels into the tissue spaces. In mild forms the transudate is relatively free from proteins, but in severe grades of acidosis permeability is so altered that proteins pass with the fluids from the blood stream. The diminished blood volume, lowered blood pressure, capillary stasis and escape of fluids from the blood stream combine to produce the syndrome of shock. Hence according to this author the depletion of plasma fluid is due to diuresis, vomiting, hyperventilation, and loss of fluid through
the capillary walls. Ketosis and alkali deficit play an indirect role by producing diuresis and overventilation.

VII. Anhydremia and anuria.

In relationship to dehydration as found in diabetic coma one must keep in mind the possibilities of very severe grades of dehydration and its immediate complications. The profound dehydration of patients in diabetic coma results in two serious complications; anhydremia and anuria (7;43;41;42;43).

Skinner (46) cites a commencing case of anuria and states that he considers this a sign that death is almost certain. He lost three old diabetics from coma immediately following an attack. Without exception they were all anuric for about 24 hours before death.

Ralli and Waterhouse (42) point out that in three of their four fatal cases the diastolic blood pressure was persistently low and in all four the systolic pressure was low for the age of the patients, never reaching more than 120mm. According to them this is an important factor in increasing the tendency toward anuria. They go as far as to say that only until dehydration and anhydremia supervene, the patient is not comatose.

VIII. Mental state.

Dillon and Dyer (10) in their study of 263
cases in acidosis divided them into a conscious and unconscious grouping, according to whether it was possible to arouse them sufficiently to answer "yes" or "no" to some simple question. Total unconsciousness characterized one sixth of the patients on admission to the hospital; another one sixth were nearly unconscious but could be roused. The remainder of the group of 29 were conscious although usually drowsy with an anxious expression (45).

Only four out of 42 coma patients studied by Joslin and his associates (86) were totally unconscious.

In a study of 200 cases by Joslin, Root, and White (23) they found coma to be present in 6 cases. Two others could be roused in spite of the fact that the carbon dioxide was below 0 volumes per cent.

C. Laboratory findings.

I. Hyperglycemia and acetonemia.

The blood sugar in diabetic coma is usually raised. See page 30.

For acetonemia see pages 38 and 29. It may be well to mention here that Lende (22) found no correlation between the concentration of ketones in the blood and the profundity of coma.

II. Glycosuria and ketonuria.

According to Joslin (24) the earliest re-
ports or hints of a knowledge of diabetes appeared in India and Rome; later Thomas Willis, born the year after the Pilgrims landed at Plymouth, observed that the urine of a diabetic tasted sweet. It was not until 1775, however, that Matthew Dobson proved that the sweet taste of such urine was due to sugar by actually fermenting the urine. The relationship of pancreas to sugar in the urine was apparently not appreciated until 1889, at which time von Mering and Minkowski observed that the urine of depancreatized dogs attracted insects on the laboratory floor; on examination of the urine these investigators found that it contained sugar, thereby discovering that their depancreatized dogs were glycosuric (Warren-51; Joslin-24). However, it was not until 1901 and 1902 that Opie in America and Sobolew, in Russia, showed that the cause of the glycosuria was due to the absence of the Langerhans islands and not due to the rest of the pancreas (Joslin-24).

In 1850 Boussingault made the discovery that large amounts of ammonia frequently appeared in the urine of diabetic patients. In 1880 Hallervorden confirmed Boussingault's work, and in 1888 Stadelmann, in attempting to search for acid radicals to account for the presence of these ammonium salts in acid urine found one of the ketone bodies, namely oxybutyric acid (Sell-
According to von Noorden (49), Petters was the first to find acetone bodies in the urine of diabetic patients. Stadelmann isolated crotonic acid from diabetic urine and later Minkowski and Kulz succeeded in isolating beta-oxybutyric acid itself from diabetic urine.

As early as 1910 it was noted by von Noorden (49) that beta-oxybutyric acid, dicetic acid, and acetone were derived from the same mother substance and represented merely different stages of oxidation. Even at this time it was assumed that the presence of these acetone bodies in the urine indicated some perversion of oxidation.

Glycosuria and ketonuria have been attributed, by most individuals, to give an indication of diabetes mellitus; however, true this may be, it is being brought forward in the literature today that the converse does not hold in its entirety. Only a few of the apparently enormous number of cases cited in the literature today as regards the latter statement will be presented here.

As early as 1910 von Noorden (49) reported cases on record of diabetic coma in which no acetone was excreted.

Joslin, Root, and White (23) reporting on a series of diabetic coma patients found that glycosuria, when
present, was not excessive. In this same series only two cases showed no acetone or diacetic acid in the urine. Absence of diacetic acid occasionally occurs in coma, especially when failing renal function results in a retention of ketone bodies in the blood stream (26).

Allan and Wishart (4) give a list of cases and references of coma without ketonuria or ketonemia.

III. Plasma carbon dioxide.

Dillon and Dyer (16) in a series of 263 cases found a carbon dioxide combining power of 29 or below in 109 cases. Of these 109 cases 47 deaths occurred, in seven no other cause of death was found. They found no values lower than six.

Dillon (14) in a study of 16 cases in diabetic coma on admission found that three had carbon dioxide combining powers of over 20.

In their studies of 42 new cases of diabetic coma patients Joslin, Root, White, Marble, and Joslin (26) found that the average carbon dioxide combining power of the plasma was eleven volumes per cent. In 11 patients the carbon dioxide combining power of the plasma at the time of the patients admission to the hospital was less than 5 volumes per cent; ten of these cases recovered.
IV. Leukocytosis.

According to Joslin and his associates (23) leukocytosis is the rule in coma. In five of their patients in which there were no apparent signs of infection or hemorrhage the white count varied from 15,000 to 44,000.

In 863 cases, studied by Dillon and Dyer (16), admitted in diabetic coma, and of whom 191 had a white count taken, it was found that all but 16 had a count above 10,000.

In a study of five cases of diabetic coma Allan (2) came to the conclusion that one must be careful in the interpretation of such white counts that ranged from 16,000 to 28,000 without any demonstrable infection, for such conditions may simulate an appendicitis.

According to Smink (47) the high white counts are due to the dehydration.

Anderson (5), in a review of the literature, concluded that the white count is usually higher in children than in adults.

V. Renal impairment.

Here, as is also apparent in studies on circulatory changes in diabetic-coma-patients, many theories are expounded as to the exact physiologic pathology of the kidneys.
McCance and Lawrence (34) in their excellent study and review on the literature as pertaining to kidney function and diabetic coma have been unable to put forth any complete explanation of the causes of disordered renal function but have at least made it clear that many suggested hypotheses are untenable.

Some of the chief causes of kidney dysfunction according to prevalent viewpoints today are:

A. Dehydration

McCance and Lawerence (34) state that increase of plasma proteins to more than one and a half times the normal amount has never been recorded and therefore dehydration alone cannot explain any increase of blood urea above this. Moreover, the plasma proteins have been normal or low in their cases of post-coma oliguria and nitrogen retention. According to them anhydremia has been absent and therefore cannot explain the dysfunction.

B. Failing circulation and low blood-pressure.

Failing circulation and low blood pressure are known to cause nitrogen retention but in McCance and Lawerence's (34) series they have been absent in most of the comatose and all of the post-coma cases.

In a series of cases studied by Joslin and his co-workers (34) they found that out of 25 cases 14 showed
a rise of above 40mg. non-protein nitrogen in the blood. The N.P.N. did not fall in proportion to the degree of recovery. In general the severer the case and the more prolonged the coma, the higher the non-protein nitrogen. In another series of cases they found that the non-protein nitrogen content of the blood when the patient was admitted to the hospital was more than 40mg. per hundred cubic centimeters of blood for 12 of the 12 patients in whom the test was performed, and 70mg. per hundred cc. or more in three. (26). In a third series of 42 cases they found that there was a notable lack of patients with significant kidney disease. In only 3 cases was the blood N.P.N. appreciably elevated (25).

Peters and his co-workers (42) found that the non-protein nitrogen fell as diuresis was established.

McCance and Weddowson (35) in a study of the kidney filtration function found that in diabetic coma, due to fall in blood pressure and dehydration, there was a fall in the glomerular filtration rate as measured by inulin clearance, which is a measure of glomerular filtration rate itself. The ratio of creatinine and inulin in normal persons is 1.4. In patients who are in deep coma and dangerously ill this ratio is usually below 1.0.

According to Bulgar (12) kidney damage is not
permanent and there is recovery of kidney function after adequate treatment.

C. Overproduction of urea.

According to Fullerton, Legall, and Davidson (25) who reported on six cases of diabetic coma, there were four deaths in which the blood urea was over 100mg. per cent and only one death among 13 cases in which the urea was below this level.

The overproduction of urea following the excessive catabolism of protein in intense diabetes must sometimes contribute to the high blood urea (34).

If kidney damage is so great as to cause retention the patient may have a high blood sugar and retention of ketones in the blood and die of uremia without being free from ketones or without attaining a normal blood sugar (Moore-36).

D. Insulin

Analysis of 63 cases by Joslin and his coworkers (33) showed that in general the more insulin the patients received the greater were the N.P.N. values. Recovery of kidney function, after adequate treatment was instituted, was so rapid that these investigators were unable to ascribe the temporary disorder to an acute nephritis. They wondered if this apparent kidney dysfunction was not due to insulin edema.
McCance and Lawrence (34) found that insulin had no direct action on the kidney itself and if it does it must cause retention of urea indirectly by the sudden restoration of carbohydrate metabolism which demands the retention of a large volume of water.

E. Ketone bodies.

Action of acetone bodies directly on the kidney is doubted by McCance and Lawrence (34). They list five reasons in their article for so believing and give one reason for the lack of experimental proof that the bodies are toxic to the kidney, because if they were one would expect to find definite and uniform pathological changes in the kidney; of this there is no evidence.

According to Warren, (52) not only is the kidney taxed to its uttermost in elimination of the excess ketone bodies produced by the organism but there is also a tubular nephritis due to toxic injury of the epithelial cells. Both these factors tend to impair renal function and to further the development of a vicious circle. This tubular nephritis is the cause of the showers of casts in the urine, so frequently associated with acidosis (36;42).

F. Chloride deficiency.

It has been shown by Hi (1936) and Meyer-
Bisch, and his associates (1934, 1936, 1937) that a fall in chlorides is followed by a rise in blood urea in an attempt to maintain a normal osmotic pressure. McCance and Lawrence (34) say that such is not the case and go on to cite references upholding their viewpoint.

VI. Cholesteremia.

Joslin found, in a study of 14 patients in coma, three cases with cholesterol values within the normal range (144-164mg. per 100cc.). The remaining 11 cases had high values of 238-297mg. per 100cc; in general these tended to decrease as the condition of the patient improved. His findings in these series tend to substantiate his findings of a year ago. It is his opinion that the findings of a normal or even low plasma cholesterol in cases of diabetic coma suggest that the coma is either essentially mild or of short duration or both.

VII. Lipemia.

See pages 304-31.

DIFFERENTIAL DIAGNOSIS

In making a differential diagnosis one must consider insulin reactions (hypoglycemia), uremic coma (nitrogen retention or nephritis), meningitis, cerebral hemorrhage, brain tumor, starvation, and the acute abdomen. Only some of the more essential differential
The differentiating points in hypoglycemia are as follows:

1. Onset is rapid.
2. Symptoms consist of hunger, weakness, trembling, sweating, and double vision.
3. Pulse rate is normal or slow and irregular.
4. Skin is moist.
5. Convulsions may be present.
7. Blood sugar is below 0.06.
8. Glycosuria and acetonuria usually absent.
9. Few casts or none in the urine.

The differentiating points in nitrogen retention are as follows:

1. Slow onset.
2. Symptoms consist of headache, nausea, vomiting, and labored breathing.
3. Pulse is full and bounding.
4. Skin is dry.
5. Convulsions are irregular.
6. Blood pressure is increased.
7. Retinitis of nephritis.
8. M.P.U. and creatinine are high.
9. Glycosuria and acetonuria are usually absent.
test of the urine for sugar is the deciding point (7). If there is doubt the blood sugar may be checked.

Joslin (17) cites one case which simulated diphtheria of the larynx. Ikaria of the lungs with rales and dulness lead Joslin and his associates to make a tentative diagnosis of pneumonia in four cases of 20 studied. X-ray examination refuted their diagnoses.

Acute abdomen;

Abdominal signs and symptoms are a great problem to the physician especially in children where there may be doubt as to the possibilities of appendicitis or a diabetic condition. To operate on a patient suffering from diabetic acidosis is an unnecessary hazard, but not to operate upon a gangrenous appendix is just as bad.

Baker (8) cites a case in which acidosis occurred and in which there was some doubt as to the acidosis being due to a probable appendicitis or to a diabetic condition. Conservative treatment was instituted, the patient got well, and was found to be a diabetic. However, he cites another case of a boy giving similar symptoms that was not a diabetic but who had a ruptured appendix with peritonitis. In a study of 108 cases Baker (8) found that 74 had abdominal pain and that of these 19 were due to the coma alone. Nausea and
vomiting occurred in 67 per cent of these 85 cases.

Bathe and Beardwood (3) in a study of a series of 1,260 cases of diabetic acidosis or coma, as to the evaluation of the abdominal symptoms, have made such a conclusive and complete study of it that it would be well to give an extensive summary of their work. They feel that a threatening case of diabetic coma or acidosis should be recognized before the deep sighing respirations, increasing drowsiness merging eventually into deep coma, are present. They refer to the early abdominal symptoms; namely, nausea, vomiting and abdominal pain and tenderness which are usually associated with fever and leukocytosis. These are present in the vast majority of cases of acidosis before the comatose symptoms develop.

Diabetic acidosis seldom comes on suddenly but usually develops over a period of 24 or 48 hours; while the abdominal symptoms usually are of a sudden onset. The early symptoms of polyuria and polydipsia may not be of sufficient severity to have attracted the attention of the patient.

In their series of 1,260 cases of diabetes, of which 136 were in acidosis, ninety-six (74 per cent) showed as the predominating symptoms, either nausea, or vomiting or abdominal pain, whereas 40 or 36 per cent
showed the central nervous system symptoms of drowsiness and coma. In those cases with abdominal symptoms 85 per cent showed leukocytosis (over 11,000) and 90 per cent had a fever (over 99 degrees F.).

The clinical appearance of patients suffering from diabetic acidosis is frequently not unlike that of acute intestinal obstruction in that they are toxic, markedly dehydrated, have abdominal symptoms, pain, nausea, vomiting, and obstipation.

**Prognosis**

Much to the assessment of this student there is apparently a great deal of literature on prognosis as related to diabetic coma and because of this only some of the more modern ideas as to prognosis will be presented.

A. Blood pressure.

When the blood pressure is very low at admission or falls during the course of treatment, this is of a very serious nature (16,42).

According to Peters and his co-workers (40) low blood pressure and signs of circulatory failure similar to shock are in evidence when hemoconcentration and hypoproteinemia fail to respond to treatment.

B. Urea

A high urea retention is not an indication for a poor prognosis unless the blood urea is found initially
to be very high (McCance and Lawrence-34). However, if uremic develops in the course of diabetic coma, it is usually associated with anuria and the prognosis is most grave (35).

C. Blood sugar.

A high blood sugar is not necessarily very prejudicial to recovery from coma, but the usual association of nitrogen retention and a high plasma cholesterol indicates a serious condition (35).

Bertram regards blood sugar values of 0.7 to 0.8 per cent or more as bad prognostic signs (36).

D. White cells.

There is no correlation between the degree of leukocytosis and the mortality rate in diabetic coma. More important is the fact that the degrees of leukocytosis seem to be about the same for the uncomplicated cases and for those in which complications are present (Lillon and Dyer-16).

Bertram occasionally finds a lymphopenia in some cases and in these regards the outlook as doubtful (36).

E. Mental state.

According to Dillon and Dyer (16) the importance of the mental state in the prognosis is very great. The total mortality for the conscious patients in their
series was 88.0 per cent and for the unconscious patients 81.0 per cent. A conscious patient is about four times as likely to recover from acidosis as an unconscious one.

According to Joslin (16) the longer a patient is unconscious before the institution of treatment is undertaken the worse the prognosis. However Joslin (25) in 1933 states that consciousness is not always an indication of a favorable prognosis. As evidence, he cites two conscious cases out of 29 fatal cases of coma which recovered chemically from acidosis but died from complications.

F. Carbon dioxide.

In 9 out of 91 patients in coma Joslin and his co-workers (16) found that those patients with a plasma carbon dioxide combining power of between 16 and 20 volumes per cent inclusive, died.

Bertram regards a carbon dioxide value of less than 10 as a bad prognostic sign. The reason for this is that at such a low level there are frequently associated severe complications, especially in the aged.

G. Hours in acidosis.

This is apparently a difficult thing to determine, however, Dillon and Dyer (16) have taken as beginning
signs of acidosis the onset of nausea and vomiting or the statement that the patient becomes definitely drowsy. They found in their series of cases a rapidly increasing mortality rate with the duration of the acidosis.

B. Age

The increase in mortality with advancing years is very striking as is shown by the series studied by Dillon and Dyer (16) in 1937. They found that the total mortality for patients up to 30 years was 16.4 per cent while those for over 50 years the mortality was 74.7 per cent. The average of all 268 cases was 37.8 years.

I. Dehydration.

Lande (18) in 1931 cited cases in which the blood protein figures were a more accurate reflection of the clinical picture than either the blood sugar or the blood carbon dioxide. He believes that the degree of dehydration is more unfavorable prognostically than either the degree or the duration of coma.

J. Response to treatment.

Obviously of greatest prognostic importance is the rapidity with which the patient responds to treatment.

As a summary to the above prognostic remarks it would be well to give Dillon and Dyer's (16) viewpoint.
In a study of 268 cases admitted in acidosis they concluded that a much more accurate prognosis can be given from the clinical data than from the laboratory data. They state that in estimating the prognosis of a given patient or in comparing the mortality of one series of comas with some other series, it is far more important to know the complications present, the mental state, the age of the patient, and duration of the acidosis, than it is to know the blood sugar, the carbon dioxide and the urea nitrogen values.

TREATMENT

A. Primary measures.

The object in the use of insulin is to bring about adequate combustion of sugars in order to burn the ketone bodies. With the complete oxidation of fats there is no excessive production of these bodies and hence base is thus kept free from uniting with the acetone bodies.

Baker (8) gives about 30 to 100 units as the first dose in diabetic coma patients; using on an average about 40 units. If no improvement occurs in 30 minutes the dosage is repeated and subsequent doses are diminished thereafter.

Joslin feels that an unconscious case requires 200 units in the first two hours. Urine test for sugar
are then ordered every one to two hours and insulin prescribed varying with the degree of reduction of Benedict's solution: 15 units for a red test, 10 for a yellow, and 5 for a green reaction. (Joslin-25;26).

It should be mentioned that there is no universal rule for the administration of insulin in coma and that insulin must be given according to the severity of the coma, as determined by clinical or chemical means, the age of the patient, the body weight, the duration of the diabetes as well as of the coma, and the preceding treatment particularly with insulin (8;26). Joslin (26) believes that no one can predict the course of diabetic coma for six hours in advance and hence disapproves of an endeavor to give a single dose of insulin and no other until the end of that period. He also advises the development of so called "coma-drills" just as much as a "fire-drill" and that no matter how clear cut the case may be, treatment should always be given under the direction of the hospital house officers or the internes superiors.

B. Accessory measures.

Usually patients in coma are in various degrees of shock due to the excessive loss of fluids from the body and treatment should be directed toward this end. "Treat the shock so insulin can act", Joslin (23).
If the blood pressure falls during the course of treatment and anuria ensues ("medical shock") transfusions may be of great value.


Joslin and Baker believe that alkali administration is of little value and even dangerous in the treatment of coma. It may be well to remember that before insulin, alkali was used and found to be of no value. Joslin (23) in showing the fallacy of alkali treatment, cites a case which developed alkalosis after recovery from coma without being given alkali in the treatment!

6. Blankets and heaters are used to combat the low temperature.

7. Glucose, orange juice, ginger ale or other forms of carbohydrates are given by mouth during the first few hours of treatment of coma (23). Unless 50 grams of soluble carbohydrate or more is taken the first 12 hours and again in the second 12 hours, dextrose intravenously or subcutaneously should be given (26).
BIBLIOGRAPHY


32. Macleod: Physiology in Modern Medicine, St. Louis, The C. V. Mosby Company, 1925


