

The Classic

Sulfonamides in the Treatment of Chronic Osteomyelitis*

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Abstract This Classic article is a reprint of the original work by John Albert Key, Sulfonamides in the Treatment of Chronic Osteomyelitis. An accompanying biographical sketch on John Albert Key, MD, is available at DOI [10.1007/s11999-009-0798-6](https://doi.org/10.1007/s11999-009-0798-6). The Classic Article is ©1944 by The Journal of Bone and Joint Surgery, Inc. and is reprinted with permission from Key JA. Sulfonamides in the Treatment of Chronic Osteomyelitis. *J Bone Joint Surg Am.* 1944;26:63–70.

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In the earlier days of sulfonamide therapy, the results of the treatment of bone infections were disappointing because sulfanilamide and sulfapyridine were the drugs in general use, and these have relatively little effect upon staphylococcal infections. The introduction of sulfathiazole and sulfadiazine has altered the picture, because the growth of both streptococci and staphylococci is inhibited by concentrations of these drugs, which may be maintained in the blood stream with relative safety.

Bacteria which are free in the blood stream are especially vulnerable to the drug, when it is administered systemically. Organisms in the tissues, in areas of inflammation, and in abscess cavities are less vulnerable to the sulfonamides for several reasons:

1. Actual contact of the drug with the bacteria is necessary, and the effectiveness of the drug varies directly with its concentration. The concentration in the tissues is less than that present in the blood stream (about one-half), and it is probable that many bacteria in inflamed areas are so well walled off from the blood stream that very little of the drug reaches them.

2. The action of the sulfonamides is inhibited by products of tissue destruction (peptones). The drugs are less effective if large numbers of bacteria are present.
3. In low concentrations, the drugs do not kill bacteria, but merely inhibit their growth, and they are then destroyed by the defense mechanisms of the host. However, inhibited but still living organisms may remain in the tissues, escape destruction, and later become active.

It is thus evident that the sulfonamides in the blood stream cannot exert their maximum effect upon bacteria in localized areas of disease; this is especially true in chronic osteomyelitis where some of the bacteria may be thoroughly isolated from the blood stream, and located in areas where the leukocytes cannot reach and destroy them, even if their growth is inhibited. On the other hand, we now have sufficient clinical evidence to warrant the conclusion that the systemic administration of sulfadiazine, and especially of sulfathiazole, to patients with acute osteomyelitis or an acute exacerbation of chronic osteomyelitis, usually has a beneficial effect, not

only upon the septicaemia, but also upon the local disease.

There is, however, considerable difference of opinion as to how much reliance is to be placed upon the drug in the treatment of the local disease. Some surgeons (Hoyt, Davis, and Van Buren) believe that most cases of acute osteomyelitis can be cured by the systemic administration of sulfathiazole, and that operation is rarely necessary. Others, of whom the author is one, believe that sulfathiazole is a valuable adjunct in the treatment of this disease, but that the focus in the bone should be drained and the limb immobilized as soon after the onset of the disease as the patient can stand the relatively minor operative procedure. Failure to do this may result in increased destruction of bone.

In chronic osteomyelitis, continuous administration of the drug over a long period will lessen the amount of discharge, but it will not cure the disease, because it cannot sterilize dead bone or cavities with necrotic contents and rigid walls. Here the problem is largely a mechanical one of removing the dead and infected bone, of eliminating the dead spaces, and of covering the remaining living bone with soft tissue that has an adequate blood supply to permit healing. In the Orr treatment, the operation was performed in an effort to obtain these results, the wound was packed loosely with vaseline gauze, left wide open, and permitted to heal by granulation. For several years the author has been partially closing such wounds, leaving in small vaseline wicks for drainage. This has resulted in quicker healing and in better scars. He has also used various chemicals in the wounds, and, at the American College of Surgeons in St. Louis in 1932, he showed cases in which the wounds had been almost completely closed and drained by wicks of gauze impregnated with merthiolate ointment. A review of these experiments indicated that neither the merthiolate ointment nor any other of the antiseptics used was any more effective than plain vaseline.

In 1941, Dickson, Diveley, and Kiene reported a series of twenty-two cases of chronic osteomyelitis in which the infected soft tissue and bone had been meticulously excised, the wound dusted with sulfathiazole powder and closed in layers, and the extremity immobilized in a plaster cast. The patients were given sulfathiazole by mouth for five days before the operation and for about fifteen days after the operation. Healing by primary intention occurred in 82 per cent. of the patients.

The author began using their method in 1940, after Dr. Dickson told him of their first success, and he has used it in operating upon 101 consecutive patients with chronic pyogenic infection of bone. Four patients were operated upon twice, two were operated upon three times, and one was operated upon four times. Of the 101 patients, the infection was in the tibia in thirty-three, in the femur in

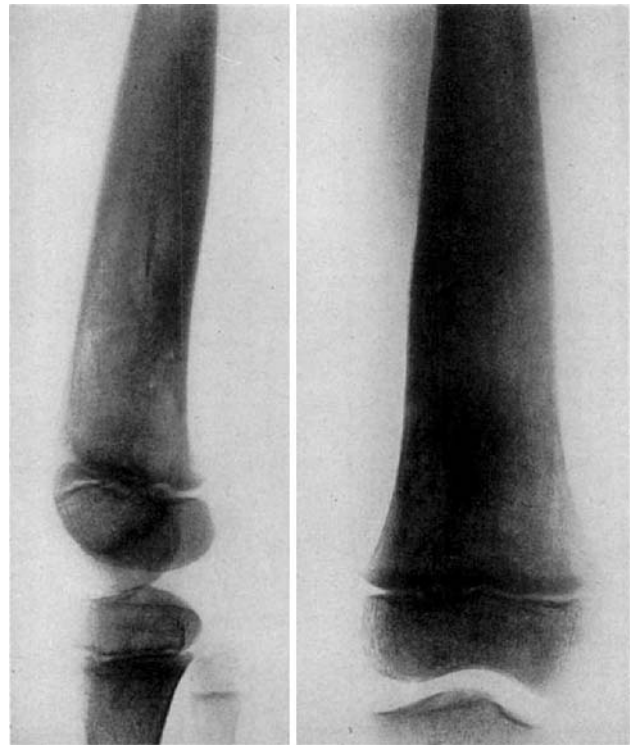


Fig. 1 Medium-sized cavity, with sequestrum and sinus, was excised after eighteen months. Healing by primary intention followed closure.

twenty-four, and in other bones in forty-four. In four patients, at the first operation, an acute abscess of an old chronic osteomyelitis was incised and drained, and no attempt was made to close the wound. In one of these, amputation became necessary later, and in the others healing has now taken place. The remaining ninety-seven patients were all operated upon while the disease was relatively quiescent,—that is, the patient was afebrile, and there were no general toxic symptoms and no evidence of acute infection in the local lesion. In these patients, an attempt was made to close the wound at the primary operation. This was not always possible, because of lack of soft tissue to cover the bone.

The technique followed was similar to that used by Dickson, Diveley, and Kiene, except that the excision of the infected scar tissue and sinuses was not carried out so meticulously, and, in several instances, extensive subfascial and deep abscesses were curetted and collapsed rather than excised. The usual saucerization operation was performed on the abscess cavities in the bone, and an effort was made to remove all sequestra and to eliminate dead spaces. However, no effort was made to remove all eburnated bone, which we believe is chronically infected and may contain minute abscess cavities which are not visible in the roentgenogram. As few vessels as possible were ligated, and these with fine silk, and no deep sutures were used. The skin and subcutaneous tissue were closed in one

layer, usually with a continuous suture of silkworm gut, after the wound had been sprinkled liberally with sulfathiazole powder. Then a pressure dressing was applied, and usually the limb was immobilized in a plaster cast.

Stainless-steel wire or screws were used in four instances, and in each instance the wound healed; but later a small sinus developed, and the offending wire or screws were removed.

In reviewing the results obtained in these patients, it is evident that each chronic pyogenic lesion in bone presents an individual problem which must be solved by surgical principles, and cannot be solved by chemotherapy. On the other hand, the use of chemotherapy has considerably increased the safety of our surgical procedures and has enabled us to close a large percentage of the wounds after a radical operation for the cure of chronic bone infection.

In this connection, it is well to consider the dangers of chemotherapy. In this series, the adult patients were given sulfathiazole in doses of from one gram every six hours to one gram every four hours on the day before the operation or earlier, and this was continued for about a week after the operation. Children were given the drug in smaller doses according to their body weight. In addition, from two to five or even more grams of the drug was placed in the wound before it was sutured. Routine blood levels of the drug were not determined, but the fluid intake and output were watched, and fluids were forced to a moderate degree. One patient with severe renal damage was not given the drug by mouth because he could not tolerate it. However, about five grams of sulfathiazole was sprinkled in the wound when his hip was disarticulated, and he made an uneventful recovery. The generalized oedema subsided promptly, and his condition improved after the infected femur had been removed.

Other than postoperative fever, which may or may not have been due to the drug and which in no instance was alarming, toxic reactions occurred in only six patients. These included suppression of urine in one, hematuria in one, and skin rashes in four. All subsided promptly when the drug by mouth was stopped and fluids were forced. It is believed that these were due to the drug administered by mouth, because in over 600 consecutive clean operations in which sulfanilamide or sulfathiazole powder or a mixture of the two drugs was implanted in the wounds there were no toxic reactions other than fever, and only two mild infections following operation (one from a lymph accumulation and one from a hematoma).

In only one instance in this series was it necessary to open the wound on account of an abscess after the operation. This was in an arthrodesis of an old tuberculous hip which was secondarily infected. Bony union was obtained, but the sinuses are still draining. In two other cases in this series, tuberculosis was present and was complicated by



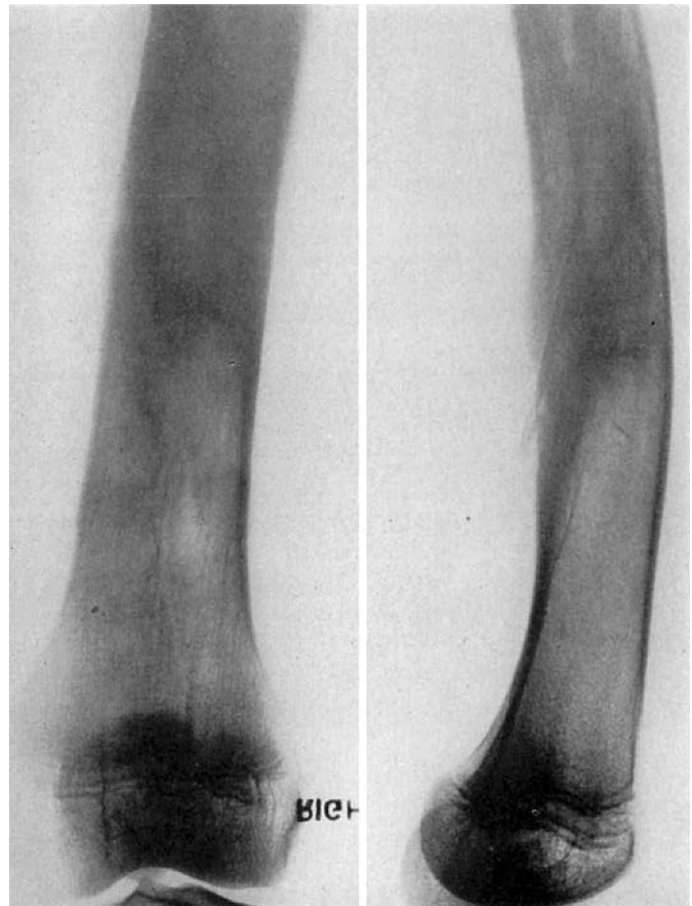
Fig. 2 Excision of third metatarsal shaft and part of tarsal bones, after three months, was followed by primary healing.

severe pyogenic infection. One knee with extensive abscesses in the popliteal space and posterior thigh was fused, and the sinuses were healed when the cast was removed twelve weeks after the operation. In the other case, the disease involved the first metacarpal and adjacent areas of the hand and wrist. Extensive excision, with amputation of the thumb and partial closure, resulted in a granulating wound which is healing slowly. It has been the author's experience that the sulfonamides have no influence upon tuberculous infection, but they are useful in a mixed infection.

There was one death in the series. This patient was a woman, eighty-seven years old, who had fractured a hip about a year before. The hip had been nailed, but the head of the femur was dead, the neck had been absorbed, and the distal fragment had slipped up on the nail. She returned to the Hospital with an ulcer and abscess over the projecting head of the nail, the infection extending into the hip joint. The nail and dead head were removed, but the patient gradually became weaker and died about two weeks later.

The series includes eleven amputations of one lower extremity; all were in adults, with infection so extensive that excision was considered impractical, as the patient would be left with a foot and ankle which were worthless

Fig. 3 Sequestrum and medium-sized cavity, present for ten years, were treated by excision and closure. Healing was by primary intention.



from a functional standpoint. Five had non-union, and two had old compound fractures at the ankle with extensive chronic infection. The author performed astragalectomies on these two and they did very well after the operation. However, when the casts were removed, it was obvious that amputation was necessary, and this was done without wasting any more time. In all of the amputations, the wounds were closed without drainage, and healed by primary intention.

Including the eleven amputations, sixty of the wounds healed by primary intention, but sinuses later developed in four of those which contained metal, and the metal had to be removed. Amputation was necessary in one of these cases; while in the other three healing occurred. In almost all of the other cases healing has taken place. The tuberculous hip is still draining after one year, and a femur with a large dead space is still draining after six months. Another femur in which amputation was advised is still draining, and infected bone surrounded by extensive scar tissue is exposed on two tibiae.

All of the failures have been in adults. This is largely because children's bones have more regenerative capacity than do adult bones, and it is possible to perform a more radical operation for a given area of infection and still

obtain a useful extremity. Also, in children, if the main focus is fairly well excised, the adjacent bone which is mildly infected will frequently heal, and dead bone which is not sequestered will be absorbed and replaced by living bone through creeping replacement. This is especially true in young children and in cancellous bone.

It is evident that the percentage of primary healing in this series is less than that obtained by Dickson, Diveley, and Kiene. However, their series apparently represents a selected group of cases in which it was possible to perform a satisfactory excision of the focus and then close the wound. The author's series represents every case of chronic bone infection that he has operated upon in the past two and one-half years,—and he has operated upon every patient who applied for treatment and did not refuse the operation. This series includes three patients who refused amputation. One of these is still disabled, one returned a year later and died of uraemia a few days after admission, and one has not returned. We are probably too slow in advising amputation in these old incurable infections of the bones of the lower extremities in adults.

The question arises, does the method of Dickson, Diveley, and Kiene for the treatment of chronic osteomyelitis have any advantage over the Orr method, which the

Fig. 4A–B (A) Showing large and medium-sized cavities with sinuses of seven years duration. (B) Healing was by primary intention after excision and closure.

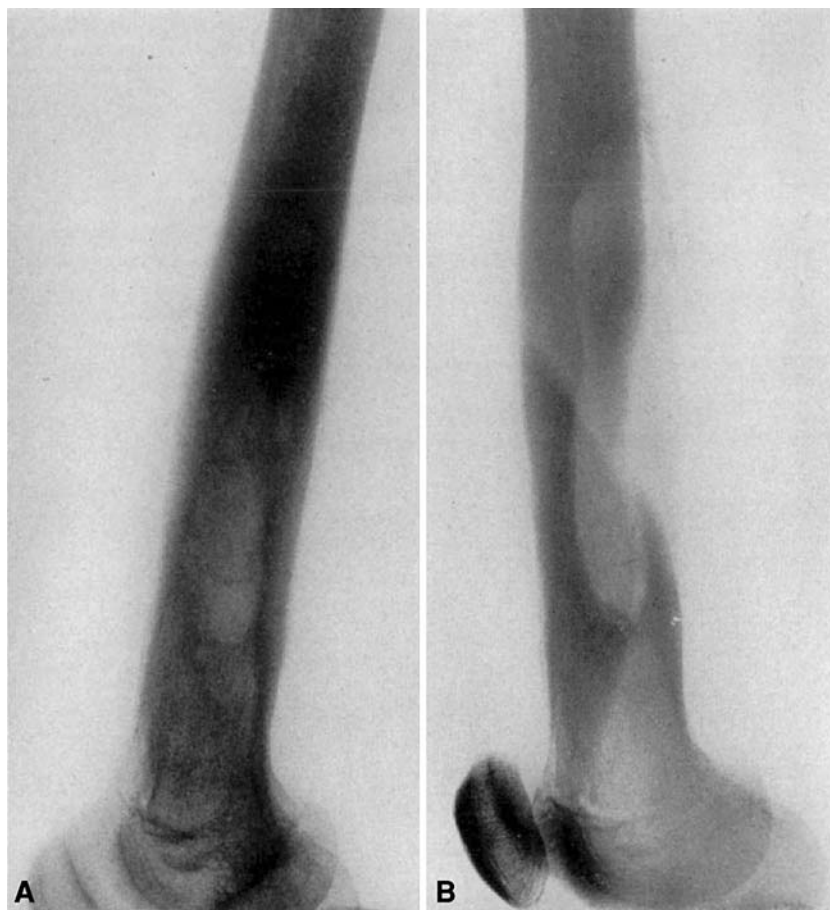
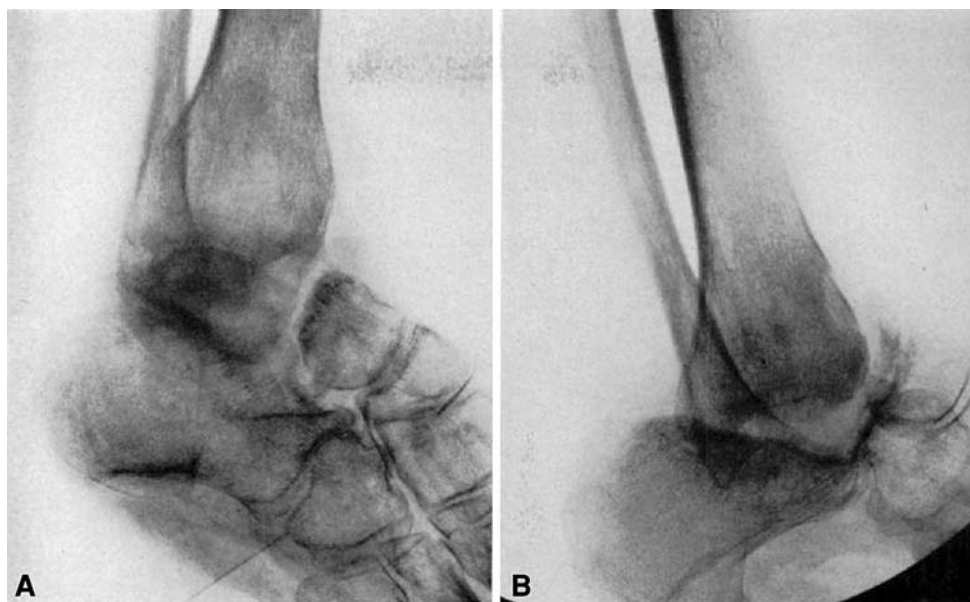


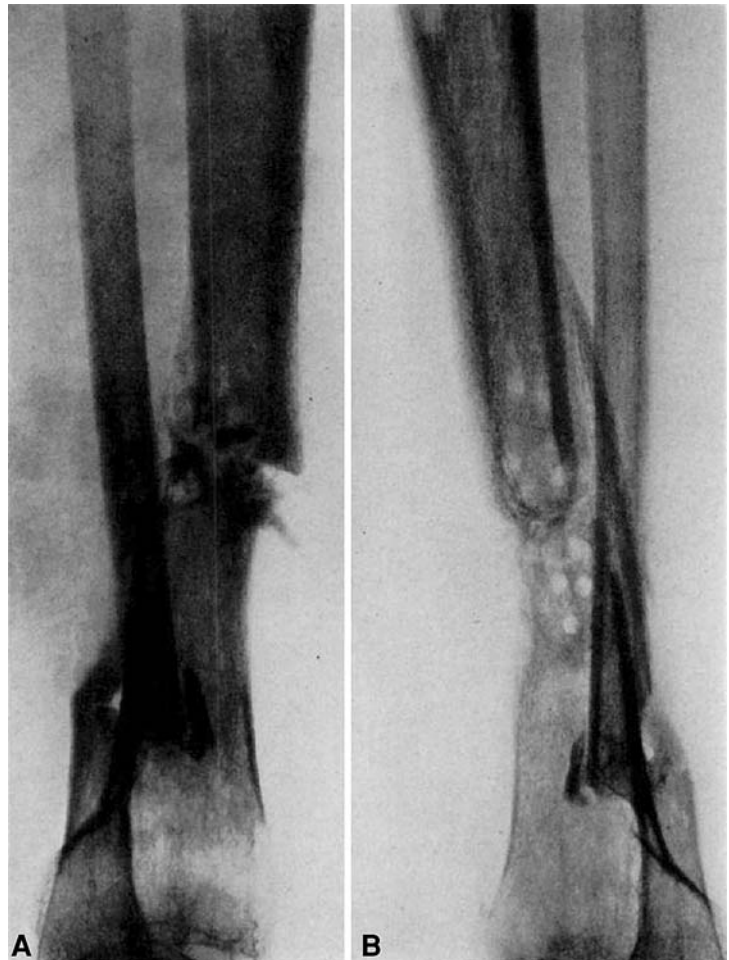
Fig. 5A–B (A) Old compound fracture with severe infection of one year's duration. (B) Astragalectomy with closure failed, and amputation was necessary.



author believes is the next best method? It does, because, in about 40 per cent. of the cases, the wounds may be closed and will heal by primary intention, if a satisfactory operation is performed. In adults, about 15 per cent. of the

affected lower extremities should be amputated; the stumps may then be closed without drainage and will heal. In about 10 per cent., the patient will appear during an acute exacerbation of the infection; this can be relieved by

Fig. 6A–B (A) Compound, comminuted fracture with infection and comminution of seven months' duration. (B) Excision and closure, with bone graft and multiple drilling, were followed by primary healing. Wound is now healed and fracture is united.



sulfathiazole and drainage, and a radical operation which can be done later, if necessary. In the remaining 35 per cent. of the cases, most wounds may be almost completely closed and will heal within a few weeks or months. There will be a few instances, probably 10 per cent., where amputation is not advisable and where healing does not follow surgery plus chemotherapy. We are anxious to know whether or nor penicillin will solve the problem presented by these.

It is probable that most of the cases which can be cured by the method of excision and primary closure can also be cured by the Orr method, but only after a longer interval and considerable unpleasantness. On the other hand, the closed method with chemotherapy is not dangerous and enables the surgeon to swing flaps, cover bones, and eliminate large areas of scarring in a manner which is not possible by any other method with which the author is familiar. The fact should be emphasized that this method is elastic and should be used in all cases of chronic pyogenic infection of bone, because a failure to obtain a complete success still represents an advance over older forms of treatment. This advance is measured by the degree of

closure obtained and the consequent reduction in the area which must be covered by secondary healing. If acute infection is present and the bacteria are actively invading the tissues, the sulfathiazole should be used locally and systemically, and the focus should be drained. A radical operation with excision and closure can be done at a later date if necessary.

Discussion

DR. H. W. ORR, LINCOLN, NEBRASKA: Dr. Key says that the wounds in this War are being treated better because we are substituting sulfa drugs for Dakin's solution. Dr. Key has shown that patients have recovered after sulfa drugs by some such equation as this: an infected wound plus drainage plus sulfa drugs plus something else—and you get a recovery. What Dr. Key has shown this morning, and more nearly so than ever before, is what the patient does toward his own recovery. He has apparently not observed that this same program, with the sulfa drugs left out, will give us a high percentage of recoveries even if they take

longer. It has been my feeling for a long time that, while a percentage of wounds may be closed primarily, another large percentage cannot be closed primarily and safely without risk to the patient. Many patients have recovered without credit to the doctor. The patient often has something in his system that allows closure without infection. What the sulfa drugs have to do with it, we do not know. We may continue to hope that some drug will be found sometime that will kill the staphylococcus without harm to the patient.

One of the questions I was asked to answer is: What are we to do about the odor in soiled dressings? My answer is that soiled dressings, or dressings with a "stench", represent the same thing in a dressing that infection does in a wound. It reflects a certain degree of discredit upon the surgeon. It has been our policy for a long time to dress these wounds with rather voluminous sterile dressings and with padding under the cast because we depend upon the pins embedded in the cast for immobilization. If moisture leaks through the sterile portion of a dressing to any outward surface which is not sterile, you have a culture medium extending all the way from the surface down to the wound. This is a fine field for the development not only of staphylococci or other infection, but for saprophytes that produce odor in the dressings. Prevention of contamination makes for prevention of infection and odor. If we prepare the wound and the cast so that no secretion exudes to the outside, odor will be prevented. That cannot be done at all times, but with a sufficiently sterile dressing, and with adequate disinfection chemically at the time of operation, the patient can be protected against that sort of thing. If complications occur in a wound, the surgeon will know how to protect the wound. If complications do occur, we may use heat about the wound area, just as we use heat for the wound itself.

DR. FRANK D. DICKSON, KANSAS CITY, MISSOURI: I am particularly pleased to discuss Dr. Key's paper, because our own interest in the local use of sulfonamides in osteomyelitis was stimulated by one of Dr. Key's original communications on the local use of these drugs. I would like to discuss this paper in an abstract way, avoiding controversial comparisons.

Dr. Key called attention to the fact that, if sulfonamides are going to be of value in local infection, three factors are important: first, the concentration of the drug in the immediate environment of the bacteria to be acted upon; second, the degree of concentration of sulfonamide-inhibitor substances present; and third, the effectiveness of the natural defense mechanism of the body. All investigation seems to indicate that a higher degree of concentration of the drug in the immediate environment of the bacteria is secured by the use of the sulfonamides locally than can be obtained by any known safe method of systemic administration. This strongly suggests that, if the

sulfonamides have any value, their local use is the most effective method of utilizing them. However, it is equally true that no matter how high a concentration of the drug is present in the environment of the bacteria, unless the introduction of the sulfonamides has been preceded by a thorough surgical clean-up of both bone and soft parts to eliminate or reduce to a minimum the sulfonamide-inhibitor substances (pus and necrotic tissue), you are not going to get results, since their action will be nullified. In other words, the primary factor of success is adequate surgery.

What does an adequate clean-up do when you are dealing with an osteomyelitic focus? It should do two things. First, it should reduce to a minimum the sulfonamide-inhibitor substances by removal of the source of these substances, which is pus and debris in the wound. Second, it should mechanically remove large quantities of bacteria. When these two purposes have been accomplished, the sulfonamides should be able to take care of what remains in the way of infecting bacteria, by inhibiting their growth, and to allow healing to take place by normal tissue repair.

As to primary closure, I am glad Dr. Key emphasized this fact, which we tried to emphasize when we originally reported our cases. If you are going to close a wound primarily, you must dissect away all scar tissue so as to bring the denuded bone into contact with healthy tissue with a good blood supply. I am convinced that bringing sclerotic scar tissue into contact with denuded bone is unphysiological. Certainly, its blood supply is poor and its lack of plasticity does not permit it to lie in close contact with the bone and so eliminate dead space, which is one of the primary factors in securing healing. So Dr. Key was quite right when he emphasized that this method of treatment was not advisable unless you could bring about a satisfactory closure. In about 80 per cent. of our cases of subacute and chronic osteomyelitis, in which the sulfonamides were used locally and systemically and primary closure was carried out, primary healing took place within three to four weeks. I believe our failures in the other 20 per cent. have been due to a poor selection of cases,—that is, we selected cases in which we were not able to get the proper tissue to cover the denuded bone. In but three or four of the failures has there been any extensive breaking down. There is usually a small area which does not heal, suggesting the existence of a dead space. If this method has any advantages, and we feel it has, there are two. In the first place, it gives rapid healing in three to four weeks. In the second, healing occurs with a minimum of scar-tissue formation. This is a very definite advantage if future reconstructive work is to be carried on. We have found it particularly useful in infected compound fractures, since the absence of extensive scar tissue enables us safely to apply a bone graft in eight to twelve weeks following healing.

DR. J. ALBERT KEY, ST. LOUIS, MISSOURI (closing): I did not realize that I had given the impression that the patient did not have something to do with healing. Sulfonamides do nothing but inhibit the growth of bacteria. By so doing, the wounds can be closed with a good margin of safety, 99+ per cent. In 101 cases we had only one abscess that required opening. However, some wounds could not be closed completely and from others there was drainage between the sutures.

I think that Dr. Dickson is wrong when he says that a meticulous operation is necessary. On several occasions where there were deep abscesses extending up beneath the fascia, I simply curetted them, wiped them out with gauze, removed most of the infection, put in sulfanilamide powder, and immobilized the limb under a pressure dressing in a plaster cast. We used this method in every case, but were not always able to do a complete operation. It is a great

advance over what we were able to do before the advent of the sulfonamides.

With his method, Dr. Orr may be able to keep the wounds dry, but I cannot. I do not like pin fixation with the Orr treatment, because pus may develop around the pin, and sometimes this leads to a diffuse infection of the bone.

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