THE RESULTS OF THE SYSTEMIC ADMINISTRATION OF THE ANTIOBIOTIC, BACITRACIN, IN SURGICAL INFECTIONS. A PRELIMINARY REPORT*

FRANK L. MELENEY, M.D., New York, N. Y.; WILLIAM A. ALTEMEIER, M.D., Cincinnati, Ohio; ALFRED B. LONGACRE, M.D., New Orleans, La.; EDWIN J. PULASKI, M.D., San Antonio, Texas, and HAROLD A. ZINTEL, M.D., Philadelphia, Pa.

BACITRACIN IS AN ANTIBIOTIC produced by the Tracey strain of *Bacillus subtilis*. It was isolated from the mixture of organisms found in the debrided tissues removed from a compound fracture of the tibia, while studying the prevention of infection in contaminated wounds by the use of sulfonamides.[1] Its commercial production has met with some difficulties similar to those encountered during the development of both penicillin and streptomycin.

During the early stages of the process of purification, bacitracin was used in the local treatment of various types of surgical infections and the first 100 cases were reported in March, 1947.[2] It yielded favorable results comparable to penicillin, and in many cases in which penicillin had failed. It was then taken up by the dermatologists, Miller and Slatkin, who reported success in the treatment of various types of pyodermias.[3] Similar encouraging reports were made in the field of ophthalmologic infections.[4]

During the past 20 months, purification and standardization have reached a point which has permitted the systemaic use of bacitracin. A number of groups are trying to evaluate this antibiotic in the systemic treatment of pneumonia, syphilis and various types of surgical infections. These studies are being carried out with the aid of funds provided by the Medical Research and Development Board of the Surgeon General's Office and the Antibiotics Study Section of the National Institute of Health. The leaders of these groups are co-authors in the presentation of this report.

The Surgeon General's Office called upon the Food and Drug Administration to set up specifications and tentative standards for bacitracin which would permit its systemic use under experimental conditions and which would safeguard the patients during the course of its clinical appraisal. Therefore, on January 20th of this year, Dr. Henry Welch called the manufacturers together and they subsequently agreed upon provisional specificiations regarding potency, solubility, stability, toxicity for mice, pyrogenic effects for rabbits, and vasopressor and vasodepressor effects on dogs. These minimum specifications must be met by all of the manufactured preparations before they can be applied in the treatment of human infections.

Bacitracin has a wide antibacterial spectrum, being effective against most strains of hemolytic streptococci, nonhemolytic streptococci, coagulase-

* Read before the American Surgical Association in Quebec, Canada, May 28, 1948.

positive staphylococci, pneumococci, gonococci, anerobic cocci in general, all of the gas gangrene group of organisms and the bacillus of tetanus, the diphtheria bacillus and diphtheroids, the spirochetes of syphilis and mouth spirochetes, the actinomycotic group of organisms, and among the protozoans, the Endamoeba histolytica. There is little or no action against the large group of aerobic Gram negative non-spore forming bacilli.

The chief advantages that bacitracin has over penicillin are (1) that it is not inhibited by the organisms which produce penicillinase and is, therefore, more likely to be effective in infections due to bacterial mixtures. (2) It is more slowly eliminated from the body and, therefore, can be given at longer intervals. (3) Its effectiveness against bacteria is in direct proportion to its concentration.[5] This has been brought out by Eagle in comparing the lethal action of penicillin and bacitracin against the spirochetes of syphilis. He has also demonstrated a significant synergistic action between penicillin and bacitracin in the treatment of experimental syphilis whereby small fractions of therapeutic doses of each, when combined, yield a therapeutic result.[6] (4) So far, bacitracin has shown less tendency to produce allergic or hypersensitive reactions but these may come with its more extended use. Certain strains of bacteria gradually build up a resistance to bacitracin but this is of a low order. As time goes on, more and more organisms belonging to groups susceptible to penicillin are proving to be resistant to it and in many instances these organisms are susceptible to bacitracin.

Its chief disadvantage, as compared with penicillin, is that it has not yet been obtained in a pure or crystalline form and, in the present state of its impurity, it produces, when injected systemically in man, certain evidence of nephrotoxicity which limits its dosage and the duration of treatment. This will be discussed more fully below.

Its chief advantages over streptomycin are its wider antibacterial spectrum, particularly with regard to the anaerobic organisms, and the low order of the development of resistance during the course of treatment. Its chief disadvantage with respect to streptomycin is its ineffectiveness against the Gram negative aerobic non-spore forming bacilli.

While bacitracin is not inactivated by gastric acidity or by the proteolytic ferments of the gastro-intestinal tract, it is not absorbed to any extent from the alimentary canal. However, while it cannot be given systemically as a mouth medication, it remains active and effective against the susceptible groups of intestinal organisms, particularly the *Clostridium welchii* and the intestinal streptococci, and it can be recovered from the feces in a concentration well above the lethal level for these organisms. It may, therefore, be combined with streptomycin or some of the relatively insoluble sulfonamides to minimize the activity of the intestinal flora before surgical procedures on the bowel. It has also been found effective in a few cases of intestinal infections, namely, in chronic ulcerative colitis

and regional ileitis. Furthermore, encouraging results are being obtained by mouth administration in both the acute and chronic stages of amebic dysentery.

The present report includes 105 cases of surgical infections observed in the units set up for the appraisal of bacitracin in New York, Cincinnati, New Orleans, San Antonio and Philadelphia. These studies are being carried on in a uniform manner and comparable data are being obtained in all cases. These data are being recorded on summary sheets especially prepared for this study, designed to bring out the essential features of these cases. In the course of the coming year, it is hoped that records will be obtained on approximately 1000 cases. Plans are going forward to analyze the results and determine their statistical significance so that at the end of that time, we may have a clearly defined knowledge of the indications for and limitations of this new antibiotic. These data will be collected and analyzed at the unit in New York.

The information which is being gathered with regard to various types of surgical infections includes diagnosis and duration (30 days having been set as the dividing line between acute and chronic infections); a record of the previous treatment, if any, both local and systemic; the general status of the patient as indicated by the blood count, sedimentation rate and kidney function, including the tests for nonprotein nitrogen or blood urea nitrogen, the clearance of phenolsulfonephthalein, and the presence of albumin, sugar, casts and cellular elements; the dosage of bacitracin, both systemic and local; the symptoms and signs of infection before and during treatment; the time relationship of any surgical procedure; the blood levels; the per cent of bacitracin excreted in the urine; a complete bacteriologic analysis of the infection before, during and after treatment and the results obtained.

It is understandable, since the advent of the sulfonamides and the antibiotics, particularly with the ready availability of penicillin and its low toxicity, that patients coming to any hospital with an infection are likely to have had some form of antibacterial therapy either self-administered or prescribed by the family doctor. This means that today relatively few patients are available for primary treatment with a new form of therapy. This is a handicap to the success of the new agent because it not only increases the proportion of cases which are resistant to all treatment but prolongs the duration of the illness before the institution of the new form of treatment. Until confidence can be built up in a new drug, doctors are not warranted in using it in the primary treatment of an infection. In view of these facts, the authors of this paper recognize that bacitracin will not be of any practical importance unless it can succeed where other forms of treatment have failed or unless it can demonstrate its clear-cut superiority over other forms of treatment so that it becomes the treatment of choice. As time goes on, however, if bacitracin demonstrates its effectiveness and

its safety and if the cases in which it is used are carefully studied and the indications for and the limitations of this treatment can be clearly defined, then it may be that certain conditions will indicate its use as the initial treatment.

During the preliminary stages of this investigation, the leaders of each group have proceeded cautiously with relatively small doses and a large proportion of the cases herewith reported include those which have failed to respond to other forms of treatment. Any statistical analysis of the results of such treatment must keep this in mind. It is exceedingly difficult to run parallel series of cases and to compare different forms of treatment with one another and, in any study of established infections, the controls must lie in the cases themselves and their response to previous forms of treatment.

Bacitracin has been used systemically in steadily increasing number of cases for the past year and a half. This number has been limited chiefly by production difficulties in obtaining a uniform product of consistent potency and low toxicity. More than 100 cases of syphilis have been treated by Eagle and his associates with bacitracin or a combination of bacitracin and penicillin. Reisner has treated over 25 cases of pneumonia. These will be reported elsewhere. A few other so called medical infections, such as malignant endocarditis, have been treated and others are being studied. This paper covers all of the cases of surgical infections so far treated systemically in the units set up especially for the appraisal of bacitracin and comprises 105 cases, the results of which are shown in the accompanying Table I.

TABLE I.—*Results Obtained in* 105 *Cases of Surgical Infections Treated by the Systemic Administration of Bacitracin*

DIAGNOSIS	Total Cases	RESULTS OF TREATMENT			
		Excellent	Good	Questionable	No Effect
Cellulitis	17	6	9	0	2
Deep abscess	15	0	10	2	3
Infected accidental wound	13	6	4	1	2
Chronic osteomyelitis	7	0	6	1	0
Operative wound infection	4	1	1	1	1
Multiple furuncles	4	0	2	1	1
Synergistic gangrene	3	3	0	0	0
Simple ulcer of skin	3	0	2	1	0
Ulcerative colitis	3	0	2	1	0
Thrombophlebitis	3	0	0	3	0
Brain abscess	3	0	0	0	3
Acute osteomyelitis	2	0	1	0	1
Undermining burrowing ulcer	2	0	2	0	0
Actinomycosis	2	0	1	1	0
Infected compound fracture	2	0	1	0	1
Meningitis	2	2	0	0	0
Human bite infection	2	2	0	0	0
Regional ileitis	2	0	2	0	0
Carbuncle	2	0	2	0	0
Miscellaneous*	14	2	5	3	4
TOTALS	105	22	50	15	18

Favorable results in 69% of cases.

* Includes one case each of septic abortion, breast abscess, calciled abscess, decubital ulcer. mediastinitis, acute suppurative tenosynovitis, bronchiectasis, cholangiitis, tuberculosis of glands of neck, strangulated hernia, pelvic thrombophlebitis, intestinal obstruction, ulcers of perineum and scrotum, tetanus with gangrene of foot.

The results of treatment are classified into four groups. They are called 'Excellent' if infection subsided rapidly and dramatically within 72 hours. They are called 'Good' if there was a definite response to the drug but the effect was more gradual during the course of a week or ten days. The benefit is 'Questionable' if the case might have done just as well without the drug, and the result is labeled 'No Effect' if the infection went on its course regardless of drug treatment.

The results which are called either 'Excellent' or 'Good' may be considered together as favorable results and the other two categories as unfavorable results, although, in the 'Questionable' group, there may be some cases in which the drug was of value. However, in order not to seem too optimistic, the doubtful cases are not put to the credit of bacitracin.

It will be seen that only three diagnostic groups include more than ten cases and the results in the smaller groups are not of statistical significance nor necessarily representative of what might be expected in those conditions. If we take the group as a whole, we find that the results were favorable in 69 per cent of the cases, whereas in the three categories having the largest number and almost one-half of the cases the results were favorable in 78 per cent. In the miscellaneous group including one case of each diagnosis, favorable results were obtained in only 50 per cent of the cases.

It is of interest that in three groups all of the results were 'Excellent,' namely, synergistic gangrene, meningitis, and human bite infection. These meningitis cases were associated with surgical conditions and, while this disease is not ordinarily considered a surgical infection, they are included in this report. It has been found that bacitracin does not penetrate well into the spinal fluid, only reaching a tenth of the level found in the blood [7] but in the presence of infection this penetration is increased.[8] However, if local application can be made by intrathecal injection or topical application, it is effective against susceptible organisms if it can reach the area involved, and it is not locally injurious to the meninges. In the cases of synergistic gangrene, these results are particularly significant because in every case this painful destructive process had spread over a large area of the body surface over a period of months, unchecked by many different forms of treatment including the sulfonamides and penicillin and in each instance the process came to a sudden halt within 72 hours, the necrotic skin was automatically loosened and subsequently separated from the necrobiotic zone, and the areas became covered with epithelium spontaneously without the necessity for any surgical procedure, even skin grafting. It will be remembered that this rare but distressing condition formerly required wide excision in order to effect a cure. Human bite infections may be particularly amenable to bacitracin therapy if given before extensive destruction of tissue has occurred because of the striking susceptibility of anaerobic streptococci and spirochetes.

The highest percentage of favorable results, 88 per cent, was obtained in the cases of cellulitis. This might be expected because organisms causing

these diffuse lesions are usually susceptible to bacitracin and because patent blood vessels permit the infiltration of any medication into the zone of infection. Furthermore the alarming nature of such a case often brings the patient to the doctor in the early stages of the disease.

It is perhaps of equal interest from a scientific point of view to point out those two groups in which the results were unfavorable, namely, throm-

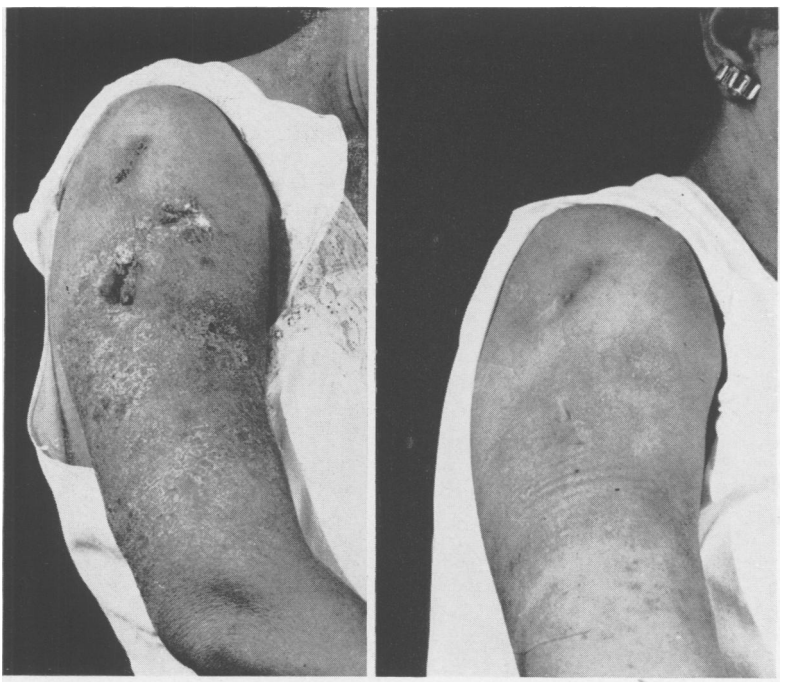

FIG. 1. FIG. 2.

FIG. 1.—Patient O.S.: Cellulitis of arm of four months' duration with seven sinus openings, two incisional and five spontaneous, before bacitracin treatment.

FIG. 2.—Patient O.C.: One month after bacitracin treatment. Sinuses all healed and surgery obviated.

bophlebitis and brain abscess. In the former group, the element of infection is probably secondary to physical and chemical changes in the blood, while in the cases of brain abscess there are other factors prejudicial to success which will be discussed later.

Although they were few in number, the encouraging results obtained in ulcerative colitis and regional ileitis suggest a thorough investigation of the value of bacitracin in these fields because of the fact that it may be administered by mouth for its local action on the bowel as well as systemically by muscular injection. Like streptomycin, as we have mentioned above, bacitracin is not absorbed to any extent from the alimentary tract, and comes through in the stool in a concentration well above the lethal level for susceptible organisms such as the streptococci and clostridia. Although the

causes of these diseases are not known, infection is of major importance and may be either primary or secondary.

In studying the results obtained in these cases, it seems to the authors to be particularly worthwhile to analyze the two extremes, namely, those yielding prompt, dramatic, almost immediate response to the drug treatment and those in which there is patently or obviously no effect whatsoever. In the

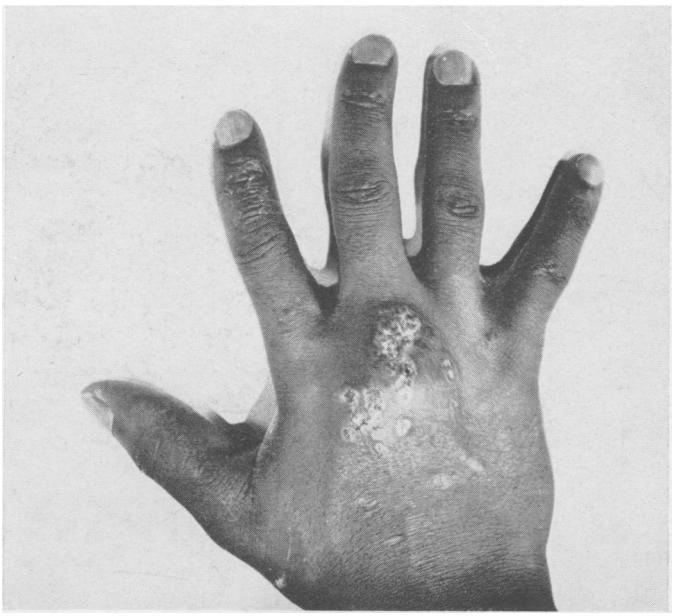

FIG. 3.—Patient E.W.: Actinomycosis of hand eleven months after human bite, before bacitracin treatment

'Excellent' group, there are 22 cases, three of which, namely, the synergistic gangrenes, have already been referred to. The two largest groups are those of cellulitis and infected accidental wounds. Cellulitis is one of the characteristic manifestations of hemolytic streptococcal infections and the more virulent strains of hemolytic *Staphylococcus aureus*. The hemolytic streptococci are particularly susceptible to bacitracin but they are also susceptible to the sulfonamides and penicillin. However, for one reason or another a number of these cases had not responded to these other agents and we find, in studying the bacteriology of these 'Excellent' results, that more than half yielded on culture streptococci, either hemolytic, nonhemolytic, microaerophilic or anaerobic varieties which seemed to play a dominant role in the infection. We also find among these cases four in which a hemolytic *Staphylococcus aureus* was the principal organism and proved to be resistant to penicillin but susceptible to bacitracin. In one case in which there was a combination of hemolytic streptococcus and hemolytic *Staphylococcus aureus,* it was found that both of these organisms were susceptible to both penicillin

and bacitracin and, although 2,100,000 units of penicillin within 24 hours failed to stop the infection, it responded within another 24 hours to 20,000 units of bacitracin given every six hours.

There were 18 cases in the group in which bacitracin had no effect on the course of the infection. One of these was a post-hysterectomy pelvic cellulitis with necrosis of the vaginal vault which had failed to respond to

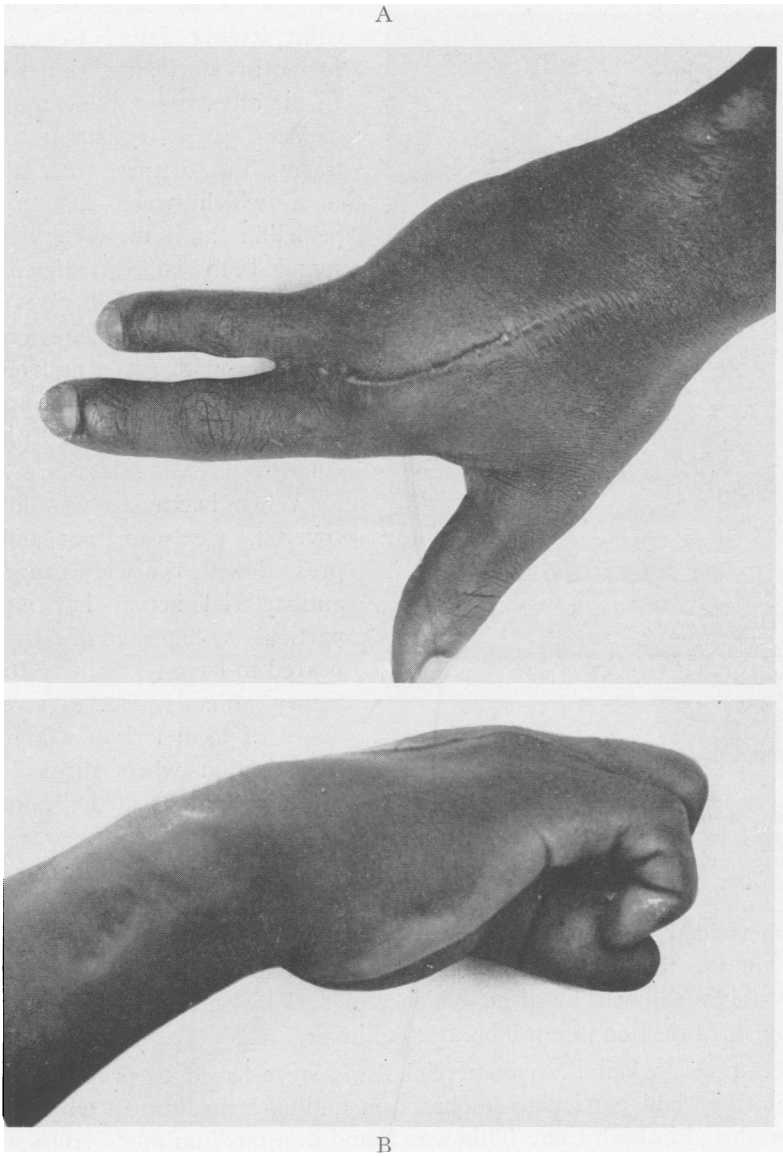

FIG. 4A.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full extension of fingers. B.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full flexion of fingers.

the sulfonamides, penicillin and streptomycin, and the patient was practically moribund when bacitracin was called for. Another case was a little girl of three who died from intestinal obstruction. This was caused by an abscess arising from a perforation of the tip of the appendix which was over on the left side and which surrounded and obstructed the sigmoid. Three patients with brain abscesses died without benefit of surgical drainage, bacitracin as well as the sulfonamides and penicillin having failed to reach the focus in sterilizing concentration. In the other cases, the causative organisms were resistant to bacitracin. Two of these were staphylococci which were susceptible to penicillin and these patients responded to later treatment with penicillin. The other cases had a multiplicity of organisms, one with four, one with seven and one with nine different species, the majority of which were resistant to bacitracin.

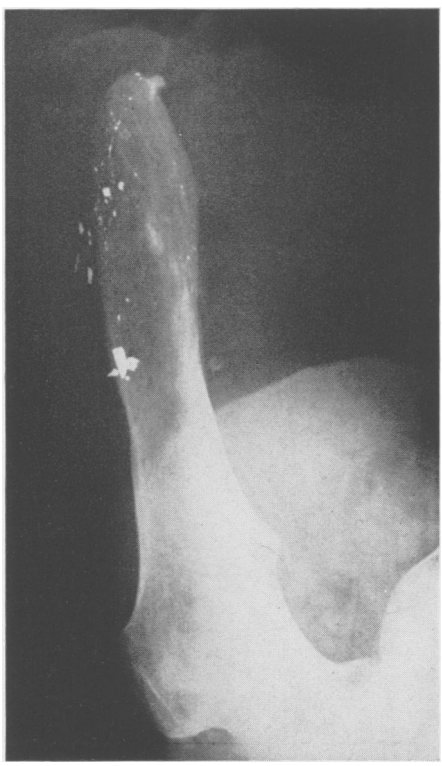

FIG. 5.—Patient V.H.: Osteomyelitis of stump of femur three years after receipt of battle wound, with two draining sinuses and three sequestra, before bacitracin treatment.

When bacitracin was first discovered, we were not only impressed with the wide range of its antibacterial action but we were particularly happy to find that it appeared to have no toxicity for laboratory animals and gave no evidence of local irritation at the site of injection when surgical infections were so treated. In order to get away from extraneous factors and to develop a uniform product, we utilized a synthetic medium which yielded from 6 to 12 units of bacitracin per cc. at the peak of production on the third day of incubation. The concentrated antibiotic obtained from this medium showed no evidence of toxicity on repeated and prolonged periods of injection in our laboratory animals.

However, when the commercial firms were asked to prepare this antibiotic, they laid particular emphasis on finding a medium in which it could be produced in high titer. This was found in a medium made from soy bean flour which was cheap and easy to prepare and which yielded five to ten times as many units per cc. as the synthetic medium. When that product was sent to us for clinical and experimental study, we began to see evidences of

toxicity, most important of which in human cases seemed to be the development of traces of albuminuria and occasionally nausea and vomiting. A careful study of this material by Scudi and his associates [7, 9, 10] demonstrated some nephrotoxicity for mice and to a lesser degree for monkeys but none

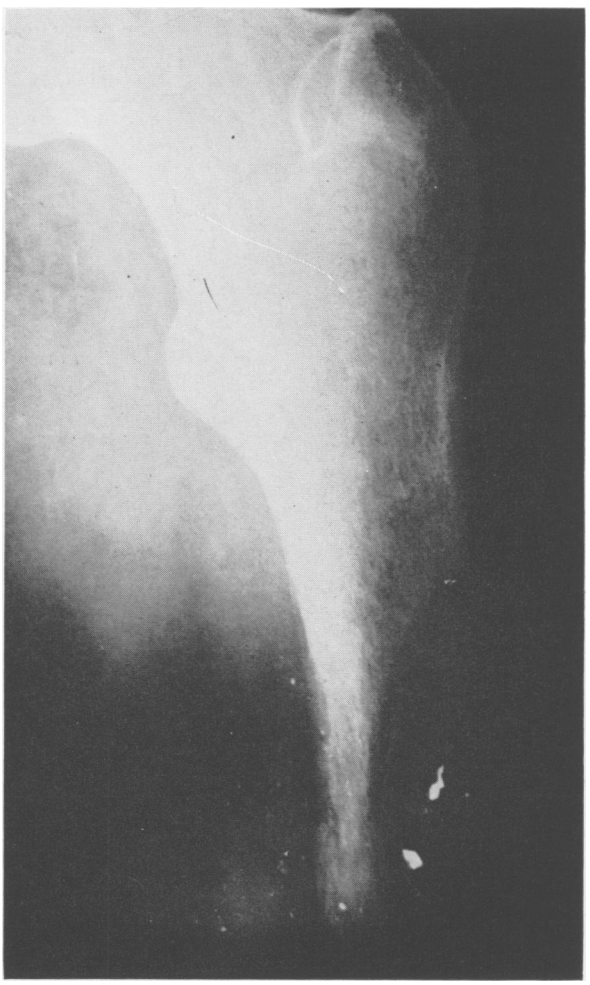

FIG. 6.—Patient V.H.: One month after excision of necrotic bone and removal of sequestra, with wound completely healed, after bacitracin treatment. Remaining foreign bodies in soft parts away from infected field.

at all for rabbits, rats and dogs. However, even in mice these kidney changes only occurred with very large doses well above the corresponding contemplated doses for man. Cautious use in human infections, produced a slight degree of albuminuria regularly, and occasionally abnormal cells and granular casts appeared in the urine, but we were happy to note that these abnormal

signs were transient and often disappeared during the course of treatment and that there was no appreciable rise in the nonprotein nitrogen or in the blood urea nitrogen. It was also observed that, if there was a persistance of any abnormality, it disappeared promptly after the termination of treatment.

TABLE II.—*Renal Excretion of Bacitracin—Patient V. H.*

Date	Specimen	Total Ml	Units Per Ml	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
1/29	24 hrs. ...	2050	13	26,650	...	...	7	0	0
1/31	24 hrs. ...	2300	30	69,000	132	52.3	6.5	st	0
2/1	18 hrs. ...	1270	30	38,100	99	37	6	ht	few
2/2	6 hrs. ...	800	60	48,000	...	...	7	t	few
2/3	6 hrs. ...	650	30	31,500	...	...	7	0	rare
2/4	24 hrs. ...	1900	20	38,000	132	28.7	7	0	0
2/5	24 hrs. ...	2100	40	84,000	132	63.6	7	spt	0
2/6	24 hrs. ...	1500	..	....	...	...	6.5	0	0
2/7	24 hrs. ...	1800	54	97,200	120	81	6.5	0	0
2/8	24 hrs. ...	1500	60	90,000	120	75	6.5	0	0
2/9	24 hrs. ...	1500	60	90,000	120	75	7	0	0
2/10	24 hrs. ...	1650	23	37,950	120	31.6	7	0	0
2/11	24 hrs. ...	1900	44	83,600	120	69.6	7.5	0	0
2/12	24 hrs. ...	2750	44	121,000	120	100	7.5	0	0
2/13	24 hrs. ...	2400	29	69,600	120	58	6	0	0
2/14	24 hrs. ...	2000	24	48,000	120	40	6.5	0	0
2/15	24 hrs. ...	1900	42	79,800	120	66	7	0	0
2/16	24 hrs. ...	2200	40	88,000	120	73 3	6	0	0
2/17	24 hrs. ...	1800	33	59,400	120	49.5	7.5	0	0
2/18	24 hrs. ...	1500	39	58,500	120	48	6.5	0	0
2/19	24 hrs. ...	2100	22	42,000	120	35	7.5	0	0
2/20	24 hrs. ...	2400	24	57,600	120	48	7.5	0	0
2/21	24 hrs. ...	2630	32	84,160	120	70.1	6	spt	0
2/22	24 hrs. ...	980	44	43,120	120	36	7.5	0	0
2/24	24 hrs. ...	2150	46	98,900	120	82.4	7.5	0	0
2/25	24 hrs. ...	2050	54	110,700	120	92.2	7.5	0	0
2/26	24 hrs. ...	1400	24	33,600	120	28	7	st	0
2/27	24 hrs. ...	2300	31	71,300	120	59.4	7.5	0	0
2/28	24 hrs. ...	2000	52	104,000	120	86.6	7.5	0	0
2/29	24 hrs. ...	1800	33	59,400	120	50	7.5	0	0

spt—Smallest possible trace.
st—Slight trace.
t—Trace.
ht—Heavy trace.

TABLE III.—*Renal Excretion of Bacitracin—Patient J. L*

Date	Specimen	Total Ml	Units Per Ml	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
2/16	Before ...	120	0	0	0	0	..	0	0
2/16	Dose 1 ...	170	21	3,570				spt	0
2/17	18 hrs. ...	600	37	22,200	80	27.75	6.5	st	rare
2/19	24 hrs. ...	1000	34	34,000	80	42.5	7	ht	occ.
2/20	24 hrs. ...	1300	34	44,200	80	55.2	5	ht	mod.
2/21	24 hrs. ...	1200	38	45,600	80	57	5	ht	mod.
2/22	24 hrs. ...	750	46	34,500	80	43.1	4.5	ht	occ.
2/24	24 hrs. ...	2050	40	82,000	80	102.5	4.5	ht	mod.
2/25	24 hrs. ...	995	54	53,730	80	67.1	4.5	ht	many
2/26	24 hrs. ...	1300	33	42,900	80	53.6	4.5	t	mod.
2/27	24 hrs. ...	1000	35	35,000	80	..	4.5	t	mod.
2/28	24 hrs. ...	1060	11	11,600	0	..	4.5	st	occ.
2/29	24 hrs. ...	1400	0	0	0	0	4.5	st	occ.
3/3	...	....	..	....	..	..	4.5	spt	0

spt—Smallest possible trace.
st—Slight trace.
t—Trace.
ht—Heavy trace.

This was the experience of all the units working with bacitracin and we began to have a sense of confidence in the safety of the drug, which we felt would permit effective clinical doses without any evidence of damage to the kidneys. Two illustrative cases are shown in the accompanying Tables II and III.

It was at this point that the Food and Drug Administration set up the temporary specifications of bacitracin, mentioned above, which were considered an adequate safeguard against injury to the patients.

About the first of the year, the methods of production and all of the material produced by surface growth in bottles by the Ben Venue Laboratories of Bedford, Ohio were taken over by the Commercial Solvents Corporation. The Ben Venue Laboratories had been furnishing us with our material and during the first two months of this year their stock-pile was gradually turned over to us by the Commercial Solvents Company in quantities as we needed it and it was used up on these patients. In February we

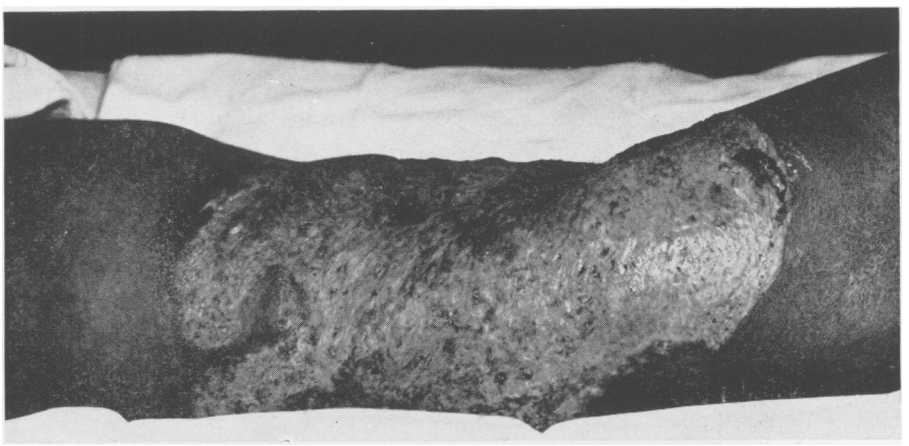

FIG. 7.—Patient A.W.: Bacterial synergistic gangrene of four months' duration, following hysterectomy, lesion involving lower half of abdomen and both thighs, before bacitracin treatment.

began to receive bacitracin made by the Commercial Solvents Corporation by the deep tank method, and then, for the first time, one of the units began to notice more pronounced evidences of nephrotoxicity than we had seen before with higher degrees of albuminuria and more cellular abnormalities, a higher rise in retained nitrogen and symptoms of lassitude on the part of the patient. Soon afterward these same results were observed in other units and in one case there was a temporary renal shut-down while in another there was an irreversible rise in blood urea nitrogen.

The case with the renal shut-down occurred in a patient with an extensive and rapidly spreading cellulitis of the neck which had not responded to penicillin. The causative organism was not obtained but the clinical activity of the organism indicated a hemolytic streptococcus. He was given double the usual primary dose of bacitracin and this was administered every four hours for the first 24 hours. The infection promptly came under control so that it is listed among the 'Excellent' results. However, after the cessation of treatment and after the patient returned home, he noticed a decrease in

the output of urine and a general lassitude which brought him back to the clinic. Here it was found that he had albumin in the urine and a rise in blood urea nitrogen and therefore he was admitted to the hospital for study. Gradually his urinary output rose to normal although the specific gravity remained low. His blood urea nitrogen came down to normal levels.

The toxicity of the presently available commercial product is under very close study. There are a number of facts which indicate that the toxic factors

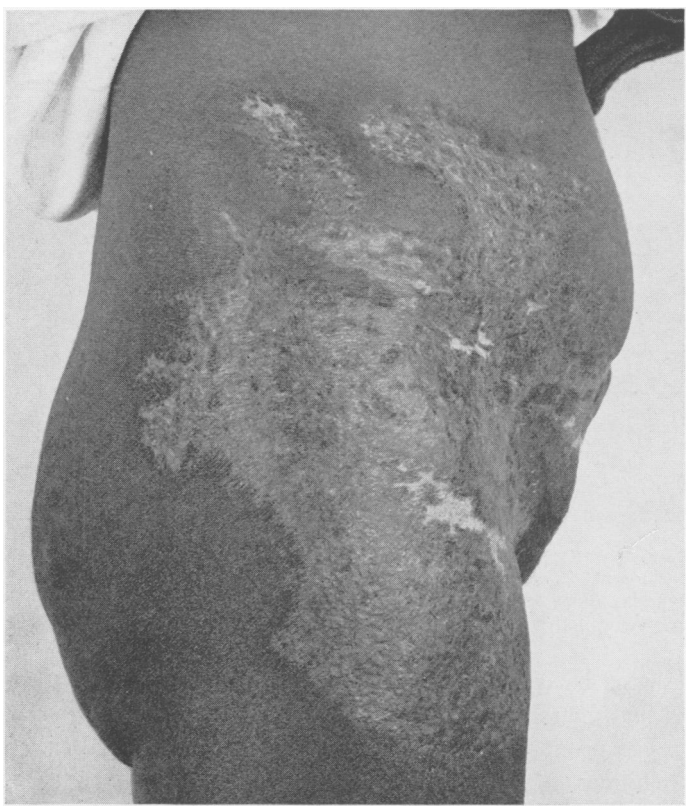

FIG. 8.—Patient A.W.: Synergistic gangrene wound completely epithelialized, seven weeks after starting bacitracin.

are by-products of manufacture, particularly of the deep tank method, and they appear in certain batches of the preparation but not in all. It is hoped and expected that they will be eliminated in the near future.

The exact chemical nature of bacitracin has not yet been determined although studies are being pursued in this direction in several different laboratories. We know that it is made up of a number of amino acids although it does not have the properties of a pure polypeptid. Some of these amino acids may be unnatural and thus give rise to nephrotoxicity, as is known to be the case with d-serine. It may be possible to eliminate these unnatural amino

acids without interfering with the antibiotic effect or it may be possible to neutralize their nephrotoxic action by some chemical means. For example, it has been demonstrated that a number of salts can greatly reduce the toxic action, among these are sodium chloride, sodium bicarbonate and sodium sulfate. In the administration of the antibiotic, therefore, for the time being

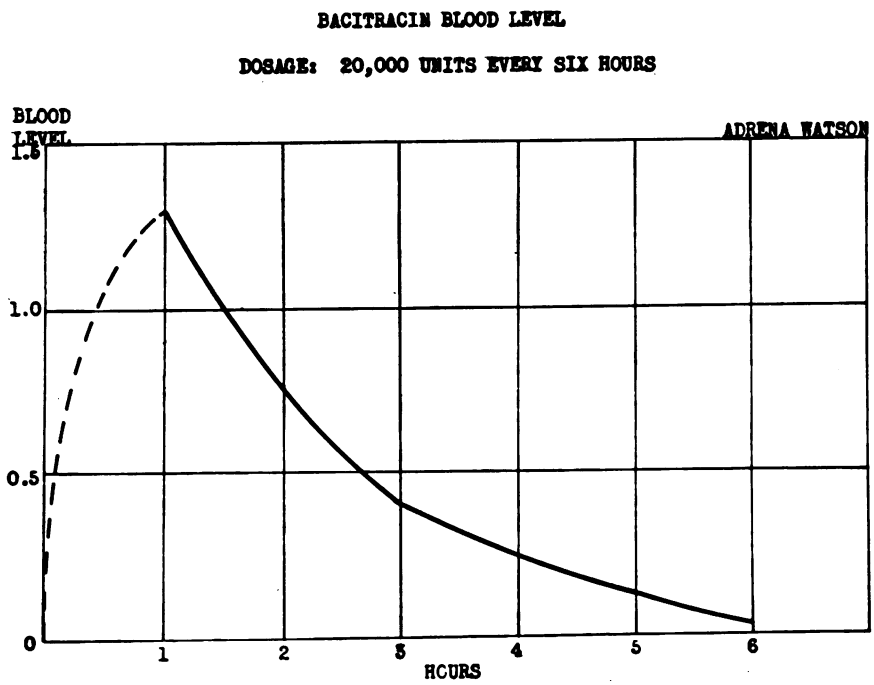

FIG. 9.—Patient A.W.: Bacitracin blood level after intramuscular injection of 20,000 Units.

the solvent should contain one or another of these salts. It is the present practice to dissolve the lyophilized product in 2 per cent novocaine made up in normal saline, and to alkalinize the patient so that the urine is always at a pH of 6 or more.

It is well known that individual animals and certainly individual human beings vary considerably in their reaction to all of these antibiotics and some persons may have an idiosyncrasy to them or develop an allergy to them. So far, these reactions have been minimal with bacitracin.

SUMMARY

1. The new antibiotic bacitracin may be used systemically as well as locally in the treatment of surgical infections.

2. Specifications have been set up by the Food and Drugs Administration to safeguard its use in clinical cases.

3. The results in 105 cases of surgical infections treated by the systemic

administration of the new antibiotic have been presented. These represent a wide diversity of conditions but for the most part they were cases which had failed to respond to the sulfonamides and to the other antibiotics.

4. There was an overall favorable response in about 70 per cent of these cases and, in about one-fifth of these, the results were dramatic.

5. Of particular interest were three cases of extensive progressive bacterial synergistic gangrene, all of whom responded within 72 hours and recovered without the necessity for surgical excision.

6. In the three largest groups, namely, "cellulitis", "deep abscess" and "infected accidental wound", favorable results were obtained in 78 per cent of the cases.

7. In the dramatic group, the causative organisms were for the most part in the staphylococcal and streptococcal groups. In the latter classification, were found hemolytic, nonhemolytic, microaerophilic and anaerobic streptococci. In a considerable number of staphylococcal strains, we found a resistance to penicillin and a susceptibility to bacitracin.

8. In 14 per cent the results were questionable and in a slightly higher percentage, the results were frankly nil. In most of these cases the causative organisms were resistant to bacitracin.

9. In the majority of the patients in the whole series there was a transient albuminuria which disappeared either during continued treatment or soon after treatment was discontinued.

10. Some of the later preparations of bacitracin made by the deep tank method have shown evidence of nephrotoxicity. New specifications will have to be drawn up to detect these toxic factors. When the presently available bacitracin is used systemically, there should be repeated tests of kidney function pathology and treatment should be discontinued if there is any indication of serious damage.

11. However, with doses which are not damaging to the kidneys, favorable and sometimes dramatic results may be expected in surgical infections caused by organisms which are susceptible to bacitracin. This covers a wide range of bacteria which are commonly found in surgical infections.

REFERENCES

[1] Johnson, B. A., H. Anker and F. L. Meleney: "Bacitracin: A new antibiotic produced by a member of the B. subtilis group." Science, **102:** 376-377, 1945.

[2] Meleney, F. L. and B. A. Johnson: "Bacitracin therapy. The first hundred cases of surgical infections treated locally with the antibiotic." J. A. M. A. **133:** 675-680, 1947.

[3] Miller, J. L., M. H. Slatkin and B. A. Johnson: "Local use of bacitracin." J. Invest. Dermatol. **10:** 179-188, 1948.

[4] Bellows, J. G.: "The use of antibiotics in ophthalmology." Presented at the New York Academy of Medicine, November 17, 1947. (to be published.)

[5] Eagle, H., A. D. Musselman and R. Fleischman: "The action of bacitracin and subtilin on T. pallidum in vitro and in vivo." J. Bacteriol., **55:** 347-358, 1948.

[6] Eagle, H. and R. Fleischman: "Therapeutic activity of bacitracin in rabbit syphilis, and its synergistic action with penicillin. A preliminary report." (to be published.)
[7] Scudi, J. V., M. E. Clift and R. A. Kreuger: "Some pharmacological characteristics of bacitracin. II. Absorption and excretion of bacitracin in the dog." Proc. Soc. Exp. Biol. & Med., **65**: 9-13, 1947.
[8] Teng, P.: Work in progress.
[9] Scudi, J. V. and W. Antopol: "Some pharmacological characteristics of bacitracin." Proc. Soc. Exp. Biol. & Med., **64**: 503-506, 1947.
[10] Scudi, J. V., I. A. Coret, and W. Antopol: "Some pharmacological characteristics of bacitracin. III. Chronic toxicity studies of commercial bacitracin in the dog and monkey." Proc. Soc. Exper. Biol. & Med., **66**: 558-561, 1947.

DISCUSSION.—DR. E. P. LEHMAN, Charlottesville, Va.: I want to report briefly on some work with bacitracin that is being carried on in our laboratories by Dr. William R. Sandusky under the guidance of Dr. Meleney. This work is concerned with the use of bacitracin in experimental clostriadial infections. The experiments were performed by exposing muscle in guinea pigs, crushing it, and closing the wound. After the would was closed, varying amounts of Clostridium Welchii were injected into the area of damaged muscle and a number of the animals were treated with varying doses of bacitracin.

There were 44 control animals, of which only 17 survived. I want to point out that 26 animals died of gas gangrene with the usual picture of an enormously swollen leg and the other phenomena with which we are all familiar. One died of other causes. In the 93 animals treated with bacitracin, none died of *C. Welchii* infection. There were 25 deaths from other causes—pneumonia, persistent diarrhea, and in one or two instances intestinal obstruction as the result of intussusception. The number surviving was 68. Counting in the deaths from other causes the mortality rate is 59 per cent in the controls and 27 per cent in the bacitracin treated animals, which presents a statistically significant difference. In those animals that died of other causes there was no evidence of *C. Welchii* infection at autopsy. Leaving out the animals that died of other causes, there is no mortality in the bacitracin treated series and a mortality of 59 per cent in the animals that had no bacitracin.

At the time these experiments were done there was a good deal of disease in the guinea pig colony and it is not possible to say that this relatively large number of deaths in the experimental series had anything to do with the drug itself. The fact that they did not occur in the other series might suggest that it was a toxic factor in the drug, but I should like to hear Dr. Meleney's comment on that. The results in any event appear to suggest strongly that bacitracin has a specific effect in the prevention of clostridial infection in the guinea pig.

DR. I. S. RAVDIN, Philadelphia: I should like to review a few impressions we have obtained with the use of bacitracin in the project under Dr. Meleney that Dr. Zintel is heading in our clinic. The clinical results of systemic administration of bacitracin have been encouraging but there can be no doubt, as Dr. Meleney said, and Dr. Lockwood re-emphasized, that bacitracin is nephrotoxic for man. Dr. James Mitchie of our Section in Urology has been studying the possibilities of renal injury with this substance. Four patients have been extensively studied for evidence of renal, hepatic and blood cytology toxicity and have uniformly shown moderately severe renal tubular injury.

One patient who received 3,744,000 units of bacitracin over a period of 13 days had a 66 per cent reduction in tubular function; one month later the tubular function was still 22 per cent below the premedication value. A second patient receiving 200,000 units of bacitracin daily for 10 days had an 85 per cent reduction in tubular function: