The first figure to the right of the equation is a function purely of the number of cases in each group. The second figure is an estimate, in the form of a regression coefficient, of the logarithm of the rate of clearance of each particular group—a figure which varies from epidemic to epidemic. The difference between these two regression coefficients—0.01627—is an index of the difference in rate of clearance between the two groups. This figure can be shown to be highly significant statistically, its standard error being 0.003338, giving a “t” of 4.88 and a probability for 12 degrees of freedom which is less than 0.001. The figures compare favourably with the formula obtained by Hartley and Martin:

$$\text{Log}_{10} y = 2.6002 - 0.0218 x$$

The statistical methods were derived from Fisher (1944), and Yates's correction for continuity was used throughout in the estimation of χ^2 .

Discussion

This epidemic has been described because it is felt that it is comparatively unusual in four points—namely, the short duration before admission, the large serum doses used, the age group covered, and the use of penicillin pastilles.

The short duration of symptoms before admission demonstrates the value of brief educational talks during epidemic periods. From the figures, prompt administration of an adequate dosage of serum does not appear to play any great part in preventing the development of palatal paresis, although it may limit the neurological involvement. On the other hand, it is felt that the low incidence and comparative triviality of the circulatory changes may be the result of the treatment. With regard to factors operating in the development of neurological complications this series is not ideal for studying the effects of duration of symptoms prior to admission, as the majority were seen on the first or second day. The fact that we are dealing with an adult population, presumably partially immune, is reflected in the difficulty of diagnosis of early cases. The comparatively late development of membrane in the partially immune has been pointed out by Neubauer (1943), who also noticed that exudate was readily wiped off without bleeding. That a number of cases later progressed to membrane formation indicates that the appearance of follicular and confluent exudate is a stage in the development of membrane. Pallor of mucous membrane was of little diagnostic use in this epidemic, as 40% had a concomitant streptococcal infection.

The series receiving penicillin was small, but the results are statistically quite definite, and it can be assumed that penicillin pastilles are effective in increasing the rate of clearance. A number of late carriers were also treated with penicillin pastilles. The impression was formed that it was much less effective in this type of case, but the numbers treated were too small to be certain of this.

Summary

An epidemic of diphtheria in adults has been described, notable for the short duration of symptoms before admission. Difficulties of diagnosis have been discussed and the results of a short series of cases treated with penicillin have been given.

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PENICILLIN IN THE TREATMENT OF DIPHTHERIA

BY

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Diphtheria is one of the commonest causes of death among young children, and before the days of antitoxin serum it had a staggering mortality. Antitoxin has no doubt greatly reduced its mortality rate; nevertheless, it remains the most dangerous infectious disease to children. The sensitivity of *Corynebacterium diphtheriae* to penicillin is well known, but the therapeutic value of penicillin in diphtheria has not yet been ascertained.

Review of Literature

Christie and Preston (1946) reported two cases of malignant diphtheria with bull-neck treated with heavy doses of antitoxin serum and penicillin: one patient died and the other recovered. Richard J. Dodds (1946) reported 13 cases of diphtheria treated successfully with systemic penicillin in addition to normal doses of antitoxin. Ercoli, Lewis, and Moench (1945) reported experiments in which penicillin in a concentration of just over 1 unit per ml. inhibited *C. diphtheriae* *in vitro*. They induced experimental bacteraemia in mice by intraperitoneal injection of *C. diphtheriae* mixed with mucin. Subsequent injections of penicillin or sulphadiazine overcame the bacteraemia. However, when toxin was injected subcutaneously into rabbits or guinea-pigs it could not be counteracted by penicillin. A small inoculum of bacilli injected into guinea-pigs produced a local lesion with toxæmia just like human infection. In such cases they found that penicillin had negligible action. These observers concluded that penicillin might be of slight benefit in the prophylaxis of exposed contacts but that it could have no appreciable value in the treatment of patients suffering from clinical diphtheria, for which antitoxin should be given without any delay.

Penicillin in the treatment of diphtheria carriers appears to have been tried successfully by Berman and Spitz (1945). They treated 10 diphtheria carriers with penicillin solution containing 500 units per ml. four times daily: 1 ml. of this solution was instilled into each nostril and 1 ml. was sprayed into the throat with an atomizer. Within five days all reverted to a non-carrier state, whereas with a control group this took five to seven weeks. These observers believe that penicillin offers a quick and simple solution to the problem of diphtheria carriers. The fact that the organisms disappear quickly from the nasopharynx indicates that penicillin may be used as an adjunct in the treatment of clinical diphtheria. The replacement of antitoxin by penicillin, however, is not advocated.

It will be seen that there is no report of the use of penicillin without antitoxin serum in the treatment of clinical diphtheria. A trial of this nature is no doubt fraught with risk, as penicillin, although effective against *C. diphtheriae*, has no action on its toxin. The present study was undertaken with a view to ascertaining whether the drug can be used alone in place of the serum. The risk has been minimized by selecting early cases, under the assumption that

the child can destroy and/or eliminate a certain amount of diphtheria toxin. A few moderately severe cases have also been treated, but we kept a very close watch on them for development of bad symptoms.

The following facts should be kept in mind when conducting a clinical trial of penicillin in diphtheria: (1) That the main cause of death in diphtheria is the injurious action of the powerful exotoxin secreted by *C. diphtheriae* on the circulatory and nervous systems, and that the therapeutic value of antitoxic serum is due to its ability to neutralize this exotoxin, on which penicillin has no direct effect. (2) That there are cases of diphtheria in which death is due to asphyxia caused by mechanical obstruction of the air passage by the diphtheritic pseudomembrane. Penicillin by exerting its lethal effect on *C. diphtheriae* may be able to check further formation and spread of such membranes when it is used early enough. (3) That the role of secondary respiratory infections in increasing the mortality in diphtheria is not insignificant, and penicillin may be a valuable therapeutic agent against such infections.

Method

For the sake of convenience the series was divided into four groups. Only penicillin was given in each case, the mode of administration in all cases being as follows:

A solution of a sodium salt of penicillin containing 100,000 units in 20 ml. of sterile normal saline was used. Of this solution 2 ml. (containing 10,000 units) was injected intramuscularly every three hours, using a 2-ml. syringe that had been sterilized by boiling, the penicillin solution being kept in a refrigerator. The time for stopping the penicillin injections was determined by the following factors: (1) the fall of temperature and pulse rate to normal level, (2) the disappearance of the pseudomembrane, and (3) three consecutive negative swab cultures taken daily. The minimum period of treatment with penicillin was four days and the maximum period seventeen days. It will be evident from the case reports that the injections of penicillin were continued longer than necessary. In many of the earlier cases penicillin was given even when the patch had disappeared and the throat swab had become bacteriologically negative. This was due to our ignorance about the dose necessarily effective in diphtheria. We were trying to cover a new field of clinical investigation, which we were afraid might be injurious to the patients. Hence, when treatment with penicillin was first started in August, 1945, the drug was given for a period probably longer than necessary; this was just to be on the safe side. Later it was found that there was no need to continue penicillin when the patch cleared up and the swab became negative.

Classification into Groups

Group I: Early Cases, Bacteriologically Positive.—There were 12 cases (8 females and 4 males); 11 were Hindus and 1 a Muslim; their ages varied from 8 months to 11 years. They had had fever and sore throat for two to six days. The temperature ranged from 99° to 104° F. (37.2°–40° C.), and the general condition was good. They had either a small patch on one or both tonsils or a moderate-sized patch on one tonsil. Before starting penicillin injections throat and nasal swabs were taken and inoculated immediately on the spot into Dorset's egg medium or Loeffler's serum medium. Within 48 hours the temperature dropped to normal in seven cases and within three to six days in the rest. The patches cleared up completely within two to five days. The throat swabs became negative in three to seven days after treatment was started, the total dose of penicillin required varying from 390,000 to 510,000 units. The patients were kept in hospital for one to four weeks but had no complications, so were discharged as cured, and parents were asked to report every week if any complication occurred. One of the patients had an attack of non-diphtheritic sore throat about a week after discharge.

This was successfully treated with sulphonamides, and tonsillectomy was advised. No bad report was received from the remaining cases.

Group II: Early Cases, Bacteriologically Negative but Clinically Diagnosed as Classical Diphtheria.—There were eight such cases—all Hindu boys aged from 10 months to 6½ years. They came with a history of slight fever and cough of one to four days' duration. They had a small patch on one or both tonsils, a moderate-sized patch on one tonsil, or a small patch on one tonsil and another small patch on the uvula. The patches had all the characteristics of diphtheritic membrane, and so they were diagnosed as classical diphtheria. Their rectal temperature varied from 99° to 102° F. (37.2° to 38.9° C.) and their general condition was good. Before starting treatment throat and nasal swabs were inoculated into culture media. Within 72 hours the temperature dropped to normal except in one case where the temperature fell to normal on the sixth day. Within two to three days the patches cleared up completely. The throat and nasal swabs were negative from the beginning. Two patients who had received 480,000 and 560,000 units of penicillin were discharged at the request of their parents after a week's stay in hospital, and the parents were instructed to report if complications occurred at home. Another patient had had 480,000 units of penicillin when his parents took him away on risk bond. At the time of discharge he was doing well and there was no trace of a patch in the throat. The remaining cases had 320,000 and 400,000 units of penicillin and were discharged after two to four weeks.

Group III: Moderately Severe Cases, Bacteriologically Positive.—There were four of these cases—two Hindu boys aged 3 and 4 years and two Muslim girls aged 3. They had had a fever and sore throat for six or seven days; one had slight suction. Three had large patches on both tonsils and a small one on the uvula; one had small patches on both tonsils, with bleeding from the nose and enlarged cervical and maxillary lymph nodes. Two were slightly toxic. After taking nasal and throat swabs penicillin was started. Within three to six days the temperature fell to normal, with improvement of the pulse rate and disappearance of the patch. Throat swabs were negative in three days in two cases, in five days in one, and in six days in the other. They received 400,000, 480,000, 720,000, and 1,190,000 units of penicillin. They were kept under observation for four weeks without there being any complication and were then discharged as cured. No report of any complication has been received.

Group IV: Moderately Severe Cases, Bacteriologically Negative but Clinically Diagnosed as Classical Diphtheria.—In this group there were three cases—two boys and one girl; all were Hindus, their ages being 1, 2½, and 3 years. They came with a history of fever and sore throat of three to seven days' duration. They were slightly toxic, the temperature varying from 99° to 101° F. (37.2° to 38.3° C.). One had a moderate-sized patch on each tonsil; the second had a moderate-sized patch on the tonsils and uvula, hoarseness of voice, and slight difficulty in breathing; and the third had one moderate-sized patch on the left tonsil and another in the pharynx. The patches had all the typical characteristics of diphtheritic membranes. Throat and nasal swabs were inoculated before any treatment was started. Within one to three days the temperature came down to normal. The patches cleared up in two to three days. Suction and hoarseness of voice disappeared next day. The patients received 360,000, 365,000, and 400,000 units of penicillin. Two of them were kept in the hospital for four and five weeks without any complication and were then discharged as cured. The third stayed for

two weeks, and was reported to be keeping well a fortnight after discharge from hospital.

Case Reports

Case 1.—A female Hindu child aged 4 was admitted on Sept. 5, 1945, with a history of fever and sore throat for six days. General condition fair. Temperature 99° F. (37.2° C.), pulse 120, respirations 24. Small patch on left tonsil and another on tip of uvula. Throat swab positive. Temperature fell to normal within 48 hours; patch cleared up within five days; swab became negative in seven days. Total dose of penicillin, 960,000 units. No complications. Discharged on Sept. 17 at request of parents. No bad report received.

Case 2.—A female Hindu child aged 1 was admitted on Sept. 10, 1945, with a history of fever and sore throat for four days. General condition fair. Temperature 99° F., pulse 125, respirations 24. Tonsils congested and enlarged; patch on both tonsils. Throat swab positive. Temperature dropped to normal within 48 hours; patch cleared up in three days; swab became negative in five days. Total dose of penicillin, 560,000 units. No complications. Discharged on risk bond on Sept. 17. No bad report received since.

Case 3.—A male Hindu child aged 2½ was admitted on Sept. 10, 1945, with a history of fever and sore throat for five days. General condition fair. Temperature 99° F., pulse 110, respirations 24. Tonsils enlarged; patch on left tonsil. Throat swab positive. Temperature fell to normal in 24 hours; patch cleared up in two days; swab became negative in three days. Penicillin was stopped on Sept. 19. Total dose, 720,000 units. No complications. Discharged on Sept. 21. Had an attack of non-diphtheritic sore throat; treated successfully with a sulphonamide and was advised to have tonsillectomy afterwards.

Case 4.—A female Hindu child aged 10 was admitted on Nov. 14, 1945, with history of fever and sore throat for two days. General condition fair. Temperature 102° F. (38.9° C.); pulse 135, respirations 32. Tonsils enlarged; patch on both tonsils. Throat swab positive. Temperature fell to normal within 36 hours; patch cleared up in two days; swab became negative in three days. Penicillin stopped on Nov. 22. Total dose, 640,000 units. No complications. Discharged on Nov. 23. No bad report received since.

Case 5.—A female Muslim child aged 3 was admitted on March 27, 1946, with a history of fever and sore throat for six days and otorrhoea for two days. General condition fair. Temperature 102° F., pulse 126, respirations 30. Tonsils much enlarged; patch on both tonsils. Nose blocked with dry blood clot at the nares. Small furuncles in left external ear, which was discharging pus. Cervical lymph nodes enlarged. Throat swab positive; ear and nasal swabs negative. Temperature dropped to normal within three days; patch cleared up in four days; swab became negative in five days. Bleeding from nose stopped in two days. Penicillin was stopped on April 2. Total dose, 480,000 units. No complications. Discharged on April 24. Everything normal except slight discharge from left ear.

Case 6.—A male Hindu child aged 10 months was admitted on Sept. 10, 1945, with a history of fever and sore throat for two days. General condition fair. Temperature 100° F. (37.8° C.), pulse 130, respirations 30. Tonsils enlarged; one small patch on left tonsil and another on uvula. Throat swab negative. Temperature dropped to normal in 72 hours; patch cleared up in two days. On Sept. 15, the day of discharge, his throat was clear. Total dose of penicillin, 480,000 units.

Case 7.—A male Hindu child aged 6 was admitted on Sept. 12, 1945, with a history of fever and sore throat for two days. General condition fair. Temperature 100° F., pulse 112, respirations 24. Tonsils enlarged, small patch on left tonsil. Throat swab negative. Temperature fell to normal within 72 hours; patch cleared up in three days. Penicillin stopped on Sept. 19. Total dose, 560,000 units. No complications. Discharged on Sept. 21 at request of parents. No bad report received since discharge.

Case 8.—A male Hindu child aged 1½ was admitted on Nov. 21, 1945, with a history of fever and sore throat for one day. General condition fair. Temperature 100° F., pulse

134, respirations 32. Tonsils enlarged; small patch on both tonsils. Throat swab negative. Temperature fell to normal within three days; patch cleared up in two days. Penicillin stopped on Nov. 27. Total dose, 480,000 units. No complications. Discharged on Nov. 28 at request of parents. No bad report received since discharge.

Case 9.—A male Hindu child aged 6½ was admitted on April 22, 1946, with a history of fever and sore throat for one day. General condition fair. Temperature 102° F., pulse 120, respirations 26. Small patch on both tonsils. A few rhonchi in lungs. Throat swab negative. Temperature dropped to normal in three days; patch cleared up in three days. Penicillin stopped on April 27. Total dose, 400,000 units. No complications. Discharged on May 4. No bad reports received since.

Case 10.—A male Hindu child aged 1 year was admitted on April 24, 1946, with a history of fever and sore throat for four days. General condition fair. Temperature 100° F., pulse 135, respirations 30. Patch on left tonsil. Throat swab negative. Temperature dropped to normal within three days; patch cleared up in three days. Penicillin stopped on April 28. Total dose, 320,000 units. No complications. Discharged on May 5. No bad report received since.

Case 11.—A male Hindu child aged 3 was admitted on Aug. 6, 1945, with a history of fever and sore throat for seven days. Slightly toxic. Temperature 103° F. (39.4° C.), pulse 140, respirations 28. Moderate-sized patch on tonsils and uvula. Throat swab positive. Submaxillary lymph glands enlarged and tender. Temperature fell to normal within 72 hours; patch cleared up in three days; swab became negative after five days; the glands subsided in five days. Penicillin stopped on Aug. 15. Total dose, 720,000 units. No complications. Discharged on Aug. 30. Reported to be keeping well a fortnight later.

Case 12.—A female Muslim child aged 2 was admitted on Aug. 22, 1945, with a history of fever and sore throat for seven days. Slightly toxic. Temperature 102° F. (38.9° C.), pulse 150, respirations 32. Slight suction. Moderate-sized patch on tonsils and uvula. Throat swab positive. Temperature dropped to normal within three days; patch cleared up in four days; swab became negative after six days. On Aug. 25 penicillin had to be stopped owing to lack of supply. The temperature again shot up. Penicillin restarted on Aug. 27 and temperature fell to normal on Sept. 5. After this she had an uneventful recovery. Penicillin stopped on Sept. 11. Total dose, 1,190,000 units. Discharged on Sept. 25. No bad report received since.

Case 13.—A male Hindu child aged 3 was admitted on Aug. 10, 1945, with a history of fever and sore throat for seven days. Slightly toxic. Temperature 99° F. (37.2° C.), pulse 125, respirations 28. Moderate-sized patch on both tonsils. Throat swab negative. Temperature dropped to normal within 24 hours; patch cleared up in two days. Penicillin stopped on Aug. 14. Total dose, 365,000 units. No complications. Discharged on Sept. 17. No bad report received.

Case 14.—A female Hindu child aged 2½ was admitted on April 7, 1946, with a history of fever and sore throat for three days. Temperature 100° F. (37.8° C.), pulse 140, respirations 35. Slightly toxic. Voice hoarse. Slight suction present; cervical lymph glands enlarged. Moderate-sized patch on tonsils and uvula. Throat swab negative. Temperature dropped to normal within 48 hours; patches cleared up within three days. The suction and hoarseness of voice disappeared on the fourth day and the glands subsided within five days. On April 24 she developed slight pyrexia (99°–100° F. (37.2°–37.8° C.)), which continued intermittently till April 30. No local signs could be detected to account for fever. She was discharged on risk bond on May 2. Penicillin was stopped on April 12. Total dose, 400,000 units. No bad report received since discharge from hospital.

Case 15.—A male Hindu child aged 1 year was admitted on April 15, 1946, with a history of fever and sore throat for four days. Temperature 100° F., pulse 130, respirations 38. Slightly toxic. Moderate-sized patch on left tonsil and another on pharynx. Throat swab negative. Temperature fell to normal within three days; the patch cleared up in three days. On April 22 he developed slight pyrexia, which continued

intermittently for about a week. No local sign could be found to account for fever. Temperature normal on May 2. He was discharged on risk bond on May 3. Penicillin was stopped on April 19. Total dose, 360,000 units. Reported to be keeping fit a fortnight after discharge.

Case 16.—A Hindu female child aged 7 was admitted on Sept. 25, 1946, with history of fever for two days, pain in throat, and difficulty in deglutition. Anaemia present. Neck glands enlarged both sides. Tonsils enlarged, with moderate-sized patches. Throat swab positive. Temperature 99.6° F. (37.55° C.), pulse 124, respirations 32. Temperature dropped to normal within 48 hours. Patch cleared up within five days. Total dose of penicillin, 485,000 units. Discharged on Oct. 31. No complications.

Case 17.—A Hindu male child aged 11 was admitted on Sept. 4, 1946, with history of painful throat and difficulty in deglutition for two to three days. No history of fever. General condition fair. Temperature 98.4° F. (36.9° C.), pulse 88, respirations 24. Moderate-sized patch on both tonsils. Throat swab positive. Patches disappeared on fourth day. Throat swab negative after two days. Total dose of penicillin, 390,000 units. No complications. Discharged on Sept. 26.

Case 18.—A Hindu female child aged 10 was admitted on Aug. 2, 1946, with a history of fever for four days, difficulty in deglutition for two days, and painful throat. General condition fair. Moderate-sized patch on right tonsil and small one on left tonsil. Temperature 99° F. (37.2° C.), pulse 110, respirations 26. Cervical lymph nodes enlarged and tender. Throat swab positive. Temperature fell to normal on third day. Patch disappeared on fourth day. Throat swab negative on third day. Total dose of penicillin, 430,000 units. No complications. Discharged on Aug. 27.

Case 19.—A Hindu male child aged 6 was admitted on July 31, 1946, with history of fever and sore throat for seven days. General condition fair. Moderate-sized patch on both tonsils. Temperature 104° F. (40° C.), pulse 134, respirations 32. Throat swab positive. Temperature reached normal level on fifth day. No patch detected on fourth day. Throat swab negative on third day. Total dose of penicillin, 510,000 units. No complications. Discharged on Aug. 27.

Case 20.—A Hindu female child aged 7 was admitted on Sept. 2, 1946, with a history of fever and sore throat for one day. Moderate-sized patch on left tonsil and small one on the right. General condition good. Throat swab positive. Temperature 103° F. (39.4° C.), pulse 140, respirations 32. Temperature fell to normal on seventh day. Patch disappeared on fifth day. Throat swab negative on second day. Total dose of penicillin, 460,000 units. No complications. Discharged on Sept. 26.

Case 21.—A Hindu male child aged 8 months was admitted on July 17, 1946, with a history of fever and cough for eight days and reluctance to feed for the last three days. General condition fair. Small patch on left tonsil. Temperature 100° F., pulse 122, respirations 24. There was also extensive impetigo. Throat swab positive. Temperature came down to normal on fifth day. Patch disappeared on fourth day and throat swab negative on third day. Total dose of penicillin, 470,000 units. No complications. Discharged on Aug. 23.

Case 22.—A Muslim female child aged 3 was admitted on March 7, 1946, with a history of fever for six days, difficulty in breathing for four days, and difficulty in deglutition and painful throat for four days. Tonsils very much enlarged and covered with several small thin patches. Cervical and submaxillary lymph glands of both sides were enlarged. Temperature 103.8° F. (39.9° C.), pulse 122, respirations 32. Throat swab positive. Temperature reached normal level on third day. Patch disappeared on fifth day and throat swab became negative on third day. Total dose of penicillin, 480,000 units. No complications. Discharged on April 24.

Case 23.—A Hindu male child aged 4 was admitted on Nov. 1, 1946, with history of fever and cough for two days and slight difficulty in breathing. General condition fair. Tonsils enlarged. Moderate-sized patch on right tonsil, extending down towards the larynx, a small crescentic patch on left tonsil, and a small patch on the uvula. Temperature 100° F., pulse 110, respirations 36. Throat swab positive.

Temperature reached normal level on sixth day; patch disappeared on fifth day. Throat swab negative on third day. Total dose of penicillin, 400,000 units. Discharged on Dec. 4.

Case 24.—A Hindu child aged 8 months was admitted on Aug. 2, 1946, with a history of fever for one day, with excessive salivation. General condition fair. Small patch on right tonsil. Temperature 100° F., pulse 130, respirations 30. Throat swab positive. Temperature fell to normal on fourth day. No patch on throat on third day. Throat swab negative after second day. Total dose of penicillin, 390,000 units. No complications. Discharged on Aug. 22.

Case 25.—A Hindu male child aged 6½ was admitted on April 22, 1946, with a history of fever and painful throat for one day. General condition good. Small patch on both tonsils. Temperature 102° F. (38.9° C.), pulse 140, respirations 20. Throat swab negative. Temperature fell to normal on third day. Patch disappeared on third day. Total dose of penicillin, 400,000 units. No complications. Discharged on May 4.

Case 26.—A Hindu male child aged 1 year was admitted on April 24, 1946, with history of cough and fever for four days. General condition fair. Small patch on both tonsils. Glands of neck enlarged. Temperature 101.4° F. (38.55° C.), pulse 120, respirations 30. Throat swab negative. Temperature fell to normal on sixth day. Patch disappeared on third day. Total dose of penicillin, 400,000 units. No complications. Discharged on May 2 on request.

Case 27.—A male Hindu child aged 2½ was admitted on June 27, 1946, with a history of fever, cough, and excessive salivation for two days. A 1¼-in. (6-mm.) circular patch was seen on right tonsil. General condition fair. Temperature 102° F., pulse 134, respirations 26. Throat swab negative. Temperature fell to normal within 72 hours. No patch was seen next morning, but a raw ulcer area was found on right tonsil, persisting up to fourth day. Total dose of penicillin 210,000 units. No complications. Discharged on July 13.

Discussion

As only 27 cases were treated with penicillin it would be unsafe to draw any definite conclusion from the results of treatment. Still, it would not be out of place to discuss a few points regarding the merits and demerits of such treatment. As no antitoxic serum was used, only early cases or moderately severe cases with slight toxæmia were selected, for obvious reasons. Of the 27 cases 16 were bacteriologically positive, and the remaining 11, though bacteriologically negative, were clinically diagnosed as diphtheria. In the majority the temperature dropped to normal within one to three days. In diphtheria treated with antitoxic serum the temperature usually takes longer to fall to normal; this may, of course, be due to the fact that when large quantities of antitoxic serum (animal serum) are injected, the serum itself prolongs the raised temperature. In all cases the general condition greatly improved within three days, and in those cases in which this was good at the start of treatment it never deteriorated with the progress of the disease. Even the extensive patches affecting the tonsils, uvula, pharynx, and larynx disappeared within five days and the small patches within one to two days. Treatment with antitoxic serum does not heal the patch so quickly; usually it takes a week or more to clear an extensive patch. The bacteriostatic (and probably bactericidal) effect of penicillin may help to clear the patch and thereby quickly remove the source of exotoxin formation. This factor may have a definite influence on the ultimate prognosis of the disease. In all the 16 cases which were bacteriologically positive the swab became negative within six days. This is rather quick compared with the results in antitoxin therapy, where it takes more than a week, sometimes weeks, before the swabs become negative. Extension of the patch after starting the treatment was never noticed. In the present series of cases complications were singularly absent. The circulatory and nervous complications which are the

direct effect of diphtheritic toxin were absent, and so were the respiratory complications which are mainly due to secondary organisms. Tracheotomy was not necessary in any of the cases, though two of them were admitted with slight suction; of course such a result could be obtained with antitoxic serum. Not a single death occurred in the present series.

The mortality rate for diphtheria at the Medical College Hospitals, Calcutta, during the five-year period from 1941 to 1945 varied from 20 to 36%. The lowest (20.3%) occurred in 1941 and 1945, and the highest (36.5%) in 1944. The average mortality was 25.6%—total admissions, 1,429; deaths, 366. In the present series the mortality was nil, but we must keep in mind that of the 27 cases 20 were mild and 7 moderately advanced. From such a small number of cases we cannot assess the value of penicillin in the treatment of diphtheria, but we feel that the subject requires further study. Penicillin cannot replace antitoxic serum in severe cases of diphtheria where immediate neutralization of toxin is imperative, but is it possible to treat early cases with penicillin alone? Diphtheria confers a good deal of immunity to the sufferers who survive. For the production of active immunity we often have recourse to injections of modified toxin such as T.A.F. and T.A.M. or A.P.T. Now if an early case of diphtheria is treated with penicillin alone the infection may be checked, and at the same time the amount of toxin absorbed in the system will be partly destroyed and partly used up as an antigen. Can this toxin act as a stimulus for the production of a better type of immunity? The answer should be "yes," as we know that the best way to acquire immunity is to suffer from the disease in a mild non-fatal form. Incidentally, it may be mentioned that prophylactic immunization is practically not done in India as a routine.

The disadvantage to a child of three-hourly injections of penicillin should be kept in mind. It is distressing to the patient, and the parents will often object. Whether this disadvantage will be overcome by the discovery of a preparation such as penicillin in beeswax and peanut oil or by the injection of a single large dose of penicillin, as has been tried successfully in some cases of gonorrhoea, is still a matter of speculation, but such possibilities cannot be disregarded. Whether penicillin in conjunction with antitoxic serum can reduce the mortality rate and the incidence of complications in severe cases of diphtheria is also a subject that needs intensive study.

The financial aspect must also be considered. We have shown that the average curative dose of penicillin is within the limit of 500,000 units. In this institution an average curative dose of antidiphtheritic serum for a similar group of cases was 50,000 to 60,000 units. When we started to use penicillin therapeutically in the middle of 1945, the drug was scarce and the price varied from Rs.20 to Rs.15 (£1 10s. to £1 2s. 6d.) for each phial of 100,000 units. At the end of 1946 the price was Rs.3/8 (5s. 3d.) for 200,000 units, and the supply was ample. The price of antidiphtheritic serum in the middle of 1945 was between Rs.6 and Rs.7 (9s. and 10s. 6d.) for 10,000 units. The present price is Rs. 7 (10s. 6d.) for 10,000 units. Thus the cost for each case treated with penicillin is Rs.8/8 (12s. 9d.) and for each case treated with antidiphtheritic serum Rs.35 to Rs.42 (£2 12s. 6d. to £3 3s.). We expect the price of penicillin to fall still further. This reduction in cost is at present possible only in an institution where there is a whole-time staff and nurses to attend to the patients. In private practice the patient will have to bear the additional cost of continuous medical attendance for three-hourly injections, careful nursing, and the storage of penicillin, particularly in tropical climates.

Summary

Twenty-seven cases of diphtheria treated with penicillin alone are reported: 16 were bacteriologically positive and 11, though bacteriologically negative, were clinically typical cases of diphtheria. Twenty were early and seven moderately severe.

All the cases recovered without developing any complications; the temperature was normal within three days, the throat swabs became negative within three to seven days, and the patches disappeared within two to five days.

The merits and demerits of penicillin in diphtheria and the possibility of future improvement are discussed. Penicillin treatment is undoubtedly more economical.

Typing of the particular strain was not ascertained. Only the clinical aspect of the cases is mentioned.

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A CASE OF MESENTERIC THROMBOSIS COMPLICATING MULTIPLE WOUNDS RECOVERY FOLLOWING MASSIVE RESECTION

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Mesenteric thrombosis is a catastrophe that seldom occurs in men of military age. The following case history has an added interest because its aetiology is difficult to dissociate from the consequence of severe shell wounds sustained nearly four months previously.

Case Report

A trooper of the Royal Tank Corps aged 32 had enjoyed excellent health until he was wounded in action on Jan. 31, 1944. Severe injuries to both lower limbs necessitated transfusion and prolonged resuscitation before wound toilet was performed on Feb. 2. Secondary haemorrhage arose from an extensive infected wound in the left thigh on Feb. 12, and was controlled by ligation of the femoral artery in Hunter's canal. He then progressed satisfactorily until March 1, when a wound in the neighbourhood of the right knee-joint was found to have caused suppurative arthritis. This demanded wide incisions and splinting with strapping extension.

The patient first came under my care at the 67th British General Hospital on May 5, 1944. His general condition was very satisfactory and no disease of heart or lungs was noted. Temperature, pulse, and respirations remained normal. The plasters were changed. The wounds of the left thigh and leg were healed and a fracture of the left tibia had united. The right knee-joint was still slightly swollen and the drainage incisions were granulating. Quadriceps exercises were performed daily.

Occurrence of Thrombosis.—At 4 a.m. on May 27 the patient was awakened by abdominal pain, and after expressing a desire to defaecate, he attempted unsuccessfully to use a bed-pan. Vomiting then occurred, and collapse was evidenced by sweating, subnormal temperature, and a rapid thready pulse. The abdomen moved with respiration and tenderness was limited to a circular area 6 in. (15 cm.) in diameter around the umbilicus. Morphine, 1/4 gr. (16 mg.), was administered, and a plasma drip was started. At 8 a.m., although the degree of