1. Are there gradients of streptomycin concentration or antibiotic activity within the lung? If so, do these favour the development of resistant strains?

2. Is there in the tuberculous patient a competition for survival between sensitive and insensitive organisms? In the absence of streptomycin treatment have the sensitive strains any advantage?

3. Do the sensitive bacilli isolated from the sputum in the early stages of a course of streptomycin represent a population actively increasing? If growth has ceased, do the viable bacilli in the sputum represent dormant organisms coughed up owing to physical factors such as the disintegration of caseous masses? What proportion of bacilli seen in a sputum smear are actually viable at different phases of treatment?

4. What is the proportion of resistant tubercle bacilli in the sputum when resistance shows in our tests? What is the proportion of bacilli resistant at the end of treatment, and does this correlate with clinical progress?

5. What is the distribution curve of resistance in the pre-treatment population of tubercle bacilli? Does this vary from case to case, and how does it change during the course of treatment?

The clinical significance of the development of resistance is still uncertain. In only two of our cases was there a clear change for the worse coinciding with the isolation of resistant organisms, whereas resistant strains were obtained from three cases in which cultures subsequently became negative. Other cases continued to improve in spite of the isolation of streptomycin-resistant organisms. In the main M.R.C. series, of which our cases formed a part, a considerable proportion of the treated cases continued to improve after the second month, the mean date of emergence of resistance being the 53rd day. This continued improvement might be due to the streptomycin continuing to act on a residuum of sensitive organisms or to the patient's defences taking over when the streptomycin ceased to be effective.

Summary

Increased resistance to streptomycin was observed in strains of tubercle bacilli isolated from 12 out of 13 cases of severe bilateral pulmonary tuberculosis treated with 2 g. of streptomycin a day for four months or more.

The rise in resistance varied from 4 to over 4,000 times that of the control strain H37Rv. Resistant strains were isolated from the 42nd day of treatment onwards. In the individual case resistance usually rose fairly rapidly to a plateau and then remained at about the same level.

When bacilli persisted in the sputum the numbers at first fell but after resistance had developed tended to rise again.

Streptomycin-resistant strains were isolated from three cases which subsequently became sputum-negative.

The time at which resistance developed and the degree of resistance attained were related to clinical progress before, but not after, resistant strains had been found. In cases which did poorly at first resistant strains were usually isolated early and attained a higher degree of resistance.

The higher the degree of resistance the more rapidly did it appear.

Only two cases showed any great change in clinical course coinciding with the time when resistant strains were first found.

The bearing of these results on the problem of the mechanism of development of streptomycin resistance and its clinical significance is discussed.

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REFERENCES

- Barski, G. (1948). *Ann. Inst. Pasteur*, **74**, 1.
 Canada, R. O. (1947). *Amer. Rev. Tuberc.*, **56**, 508.
 Dubos, R. J., and Davis, B. B. (1946). *J. exp. Med.*, **83**, 409.
 Feldman, W. H., Karlson, A. G., and Hinshaw, H. C. (1947). *Amer. Rev. Tuberc.*, **56**, 346.
 ——— (1948). *Ibid.*, **57**, 162.
 Fisher, M. W. (1948). *Ibid.*, **57**, 53.
 Garrod, L. P. (1948). *British Medical Journal*, **1**, 382.
 Hinshaw, H. C., and Feldman, W. H. (1947). *Amer. Rev. Tuberc.*, **56**, 385.
 Karlson, A. G., Feldman, W. H., and Hinshaw, H. C. (1947). *Proc. Soc. exp. Biol., N.Y.*, **64**, 6.
 Kendall, M. G. (1943). *The Advanced Theory of Statistics*, 1st ed., p. 401. Griffin, London.
 Luria, S. E. (1947). *Bact. Rev.*, **11**, 1.
 Medical Research Council (1948a). *British Medical Journal*, **2**, 769.
 ——— (1948b). *Lancet*, **1**, 582.
 ——— (1948c). *Ibid.*, **2**, 862.
 Middlebrook, G., and Yegian, D. (1946). *Amer. Rev. Tuberc.*, **54**, 553.
 Pyle, M. M. (1947). *Proc. Mayo Clin.*, **22**, 465.
 Report to Council on Pharmacy and Chemistry from the Veterans Administration, Army and Navy (1947). *J. Amer. med. Ass.*, **135**, 634.
 Sadusk, J. F., and Swift, W. E. (1948). *J. clin. Invest.*, **27**, 278.
 Schwabacher, H. (1948). *Nature*, **162**, 339.
 Smith, H. V., Vollum, R. L., and Cairns, H. (1948). *Lancet*, **1**, 627.
 Steenken, W., D'Esopo, N. D., and Wolinsky, E. (1947). *Amer. Rev. Tuberc.*, **56**, 403.
 Youmans, G. P., and Feldman, W. H. (1946). *J. Bact.*, **51**, 608.
 ——— Williston, E. H., Feldman, W. H., and Hinshaw, H. C. (1946). *Proc. Mayo Clin.*, **21**, 126.

STREPTOMYCIN IN GONORRHOEA

WITH ITS EFFECTS UPON DARK-FIELD POSITIVE LESIONS OF SYPHILIS

BY

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In the field of venereology streptomycin has great potentialities which have yet to be adequately explored. It apparently has some action against syphilis, but venereologists hope that this will prove slight, for streptomycin will then assume many of the present indications for sulphonamides in the treatment of venereal diseases in which syphilis is suspect but not proved (Willcox, 1948). Moore (1947) considers that the drug is unlikely to be clinically useful in syphilis, and points to the work of Dunham and Rake (1946), who found that the antisiphilic effect of penicillin G was 3,000 times greater than that of streptomycin, though Herrell and Nichols (1945) treated four cases of early syphilis with doses of 1.2–10 g. of streptomycin and obtained a temporary absence of treponemata from the dark-field. Herrell (1947) later believed these results to be inconclusive and considered that so far there was no indication that the drug should be used in the treatment of this disease. Fiske and Gruhzt (1946) gave rabbits 1,000–3,000 subtilis units of streptomycin in three divided doses daily for 13–20 days and found no evidence whatever of any antispirochaetal action.

These observations are of considerable interest, for all reports indicate that streptomycin is particularly effective against gonorrhoea. This disease is at present being well controlled by penicillin and there is no clinical evidence of the development of penicillin resistance by the gonococcus on any substantial scale: many of the suspected cases so far reported have proved on investigation to be due not to the gonococcus itself but to a simultaneously acquired non-specific urethritis (Parkhurst *et al.*, 1947). The possibility that penicillin treatment of gonorrhoea might modify or mask an incubating syphilitic infection has been prominent in the minds of clinicians for some years, and indeed has been responsible for prolonging the period of

surveillance after treatment of gonorrhoea in this country. Such delayed syphilis is not often seen. This matter has been well discussed by Leeming (1947), though Cronin (1947) found little evidence to support this concept.

However, even though the masking of syphilis by penicillin should prove only a minor problem, if streptomycin will cure gonorrhoea in a single dose and at the same time leave the dark-field positive lesions of syphilis untouched it will still have a very definite place in the treatment of gonorrhoea. Especially will this be so in those cases with undiagnosed genital lesions or suspected false positive blood tests, in those persons with gonorrhoea who are known to have had recent intercourse with a syphilitic person, in the re-treatment of relapsing patients who showed Herxheimer-like reactions after the first treatment with penicillin, and in fact in all cases of gonorrhoea in which the risk of existing but undiagnosed concomitant syphilis is greater than the average. It may also be of value in cases in which it is desired that the period of subsequent surveillance should not exceed three months.

Streptomycin is effective against chancroid both in the experimental (Mortara and Saito, 1947) and in the human infection (Hirsch and Taggart, 1948a). In addition, most striking cures have been obtained in granuloma inguinale (Greenblatt *et al.*, 1947a, 1947b; Kupperman *et al.*, 1948; Marshak and Rodriguez, 1948; Hirsch and Taggart, 1948b; Barton *et al.*, 1947; Zimmerman and Smith, 1948). First reports of its action on non-specific urethritis are hopeful but equivocal (Pulaski, 1947; Kane and Foley, 1947), and my own experience will be the subject of a further paper. The drug has also been widely used in the treatment of urinary infections by Wilson (1948), Schwarz and Lazarus (1947), Keefer *et al.* (1946b), and Finland *et al.* (1946) with upwards of 50% success. In all cases failure seems to be due to a resistance which is very rapidly acquired; but better results, both experimentally and clinically, are obtained in an alkaline medium (Knop, 1946; Kane and Foley, 1947).

Resistance to streptomycin, once acquired, seems to be permanent. Murray *et al.* (1947) found that it continued through more than 100 transfers in a streptomycin-free broth, and Miller and Bohnhoff (1947) noted that two or three transfers in media containing increasing concentrations of streptomycin sufficed to permit the meningococcus to grow in a concentration of 50,000 μ g. of streptomycin per ml., whereas no fewer than 147 such subcultures were required for the same organism to grow in a concentration of only 5,000 units per ml. of penicillin.

One injection of streptomycin may cure gonorrhoea, and provided the dose is adequate the question of resistance does not arise, though streptomycin-resistant strains of the gonococcus may well appear in the same way as with the sulphonamides. Chinn *et al.* (1947) had all of 25 cases of gonorrhoea cured by a single injection of 0.5 g. of streptomycin, all of 10 with 0.4 g., and 15 others with 0.3 g. Though three out of five failed with doses of 0.1 g. there were only two failures out of 22 treated with single injections of 0.2 g., and toxic reactions were negligible throughout. It is noteworthy that two of these patients developed Herxheimer-like reactions at the time of treatment, and both were later shown to have syphilis. Pulaski (1947) treated nine cases of apparently penicillin-resistant gonorrhoea, and had complete success in seven. The two failures were improved clinically, but the complications of prostatitis and epididymitis were not resolved.

After a single injection of 0.5 g. of streptomycin the peak level in the blood is reached within an hour (Molitor, 1947), and effective levels are still present at eight hours.

For continued administration Loewe and Altire-Werber (1947) consider that six-hourly injections should suffice. The drug is excreted in the bile and urine, and may be recovered from the latter (Lamensans *et al.*, 1947).

The toxic effects of streptomycin include histamine-like reactions, headache, flushing of the skin, neurological disturbance, vertigo, paraesthesiae, and hypersensitive skin reactions; and there may be an eosinophilia (Keefer *et al.*, 1946a). There may also be renal impairment with cylindruria, which is possibly prevented by alkalis. These reactions are not usual after single injections of the drug, and, even with more prolonged administration, McDermott (1947) considers 3 g. the maximum safe daily dose. Skin sensitization, developing in a few months in those handling the drug, has also been reported (Strauss and Warring, 1947).

Streptomycin is given intramuscularly in aqueous solution. Preliminary tests have shown no advantages in a peanut-oil-beeswax suspension as with penicillin (Kolmer *et al.*, 1946); neither is the action of the drug satisfactory if it is administered orally. However, up to 0.1 g. in aqueous solution has been successfully given by the hypospray (jet injection) (Hirsch *et al.*, 1948).

Case Histories

The following case records confirm the claim that a single dose of streptomycin in aqueous solution is capable of curing gonorrhoea as effectively as penicillin—possibly more effectively—and that the same dose will not adversely influence the dark-field positive lesions of syphilis.

Syphilis

Case A.—The patient, a white man aged 23, had a typical penile chancre of two weeks' duration. Characteristic left inguinal adenitis was also present, and the Wassermann and Kahn reactions of the blood were strongly positive. The first dark-field examination was disappointingly negative, but two days later *Treponema pallidum* was visualized without difficulty. He was then given a single intramuscular injection of 0.6 g. of streptomycin in 6 ml. of isotonic saline; 24 hours later the sore had not altered in appearance and the responsible organism was still readily recoverable.

Case 1. Acute Gonorrhoea in the Male

A white man aged 27, the husband of Case 2, was first seen on Sept. 11, 1948, with a purulent urethral discharge of three days' duration. Gonococci were observed in the smear and the urine was hazy only in the first glass. He denied other than marital intercourse, which last took place four days previously. The only treatment given was a single intramuscular injection of 0.6 g. of streptomycin in 2 ml. of normal saline. Two days later the discharge had vanished, smears and cultures from the urethra were negative for the gonococcus, and the urine was quite clear. No gross upset was noted from the injection, though he did comment that when driving his car home from the clinic after the injection he had experienced an odd sensation as if objects were flying past at an abnormal speed.

The following day, however, the discharge recurred, though he denied further exposure or the taking of alcohol. His wife (Case 2) was also infected, and both consistently denied any extramarital relations, but the possibility of reinfection cannot be entirely excluded. A week after the first visit the discharge was as profuse as before and gonococci were once again present in the smear. A second dose of 0.6 g. of streptomycin (this time in 6 ml. of normal saline) was given intramuscularly. No untoward disturbance was noted on this occasion, apart from a transient headache four hours afterwards. The discharge again disappeared within 24 hours. At 48 hours the urine had completely cleared and gonococci were not obtained in urethral smear or culture.

A week after the second injection the findings were still negative and no abnormalities were detectable in the prostatic

bead or prostatic culture. Two days later he was allowed alcohol and protected intercourse with his wife (Case 2), who had also been treated with streptomycin. Actually, unprotected intercourse began the following night, but one, three, and eight weeks later no ill effects were reported by either partner.

Case 2. Acute Gonorrhoea in the Female

A white woman aged 27, the wife of Case 1, denied other than marital intercourse, which last took place six days previous to her attendance as a contact, she being quite symptom-free. On examination, however, a pronounced urethritis and a cervicitis were found, though erosion was not present. Smears of the discharges showed gonococci in both the cervix and the urethra. She was given a single intramuscular injection of 0.6 g. of streptomycin in 2 ml. of isotonic saline. Two days later no visible discharge was apparent in either cervix or urethra and, though some pus was still evident microscopically in smears from both sites, no gonococci were observed and none were found on culture.

The patient reported that she had slight pain at the injection site on the day of the injection, and that she had experienced symptoms of influenza two days later. Serum tests for syphilis, however, remained negative in both husband and wife. One week and two weeks later the urethral and cervical smears and cultures were completely free from pus and gonococci, and, as a test of cure for both partners, protected intercourse with her husband was urged. In actual fact unprotected intercourse took place the following night, and this was succeeded immediately by a menstrual period. When seen at the conclusion of this, three weeks after treatment, and again one and six weeks later, the smears and cultures from both urethra and cervix were still negative.

Case 3. Penicillin Relapse

This patient, a white man aged 28, was first seen on Sept. 6, 1948, when he presented an acute gonococcal urethritis of two days' duration which was treated with a single intramuscular injection of 300,000 units of penicillin in oil-beeswax. Five days later there was no discharge and the urine was clear, but on Sept. 20 the discharge, which contained an abundance of gonococci, was again profuse, having relapsed four days previously. No history of fresh exposure or alcoholic excess was admitted. He was then given a single intramuscular injection of 0.2 g. of streptomycin in 2 ml. of normal saline and the discharge disappeared within 24 hours. Nine days later he continued well, the urine was entirely clear, and no gonococci were found in urethral or prostatic smears and cultures. Further prostatic smears and cultures taken two weeks after treatment were also negative.

Case 4. Gonorrhoea of Long Standing

The patient, a white man aged 23, developed an acute urethral discharge on July 8, 1948, and gonococci were isolated in the smear. Surprisingly, he left for the Continent the next day without receiving any treatment, and remained untreated until Sept. 24, when the discharge was as profuse as ever and many gonococci could be seen in the smear. No complications had developed. He then received a single intramuscular injection of 0.3 g. of streptomycin in 3 ml. of normal saline. Two days later there was no discharge, and the urine, previously hazy, was now quite clear. The urethral smear showed a trace of pus but no gonococci, and the culture was also negative. Eight days later prostatic smears and cultures gave entirely satisfactory results. He then moved elsewhere, but seven weeks after treatment wrote saying he was well.

Case 5. Gonorrhoea: Sulphonamide Relapse

This patient, a white man aged 23, was first seen on July 17, 1948, having received 36 g. of sulphapyridine over 12 days from his own doctor for a urethral discharge the aetiology of which was never determined. Apart from some dampness of the urethra there was no discharge and the urine was clear. No treatment was advised, but he was kept under observation until Aug. 28, when he was still symptom-free, the urine being clear and the prostatic secretion free from pus. On Sept. 27 he attended with a slight mucopurulent discharge of one day's

duration. He denied fresh contact, yet gonococci were observed in the smear. The urine was still clear, but there were many threads in the first glass. He received a single intramuscular injection of 0.4 g. of streptomycin in 4 ml. of normal saline. One, two, and seven weeks later there was no discharge and the urine was clear and free from threads; urethral and prostatic smears and cultures were also entirely negative.

Case 6. Complicated Gonorrhoea: Cowperitis

A negro man aged 30 was successfully treated for gonorrhoea in 1945, in August, 1947, and in September, 1947, when he was given 200,000 units of penicillin. On the last-mentioned occasion he relapsed two days later, developing an abscess of the left Cowper's gland which ruptured exteriorly. On July 29, 1948, he again developed an acute gonorrhoea, which was successfully treated with a single injection of 300,000 units of penicillin in oil-beeswax; but five days later the left Cowper's gland was palpable as a small tender nodule and he was given a course of sulphadiazine in addition.

He defaulted from observation, but returned on Sept. 29 with yet another apparently fresh attack of gonorrhoea. Gonococci were present in the smear, and the urine was grossly hazy with threads. The left Cowper's gland was just palpable and was acutely tender. It was decided to treat him with streptomycin, though the very small dose of 0.2 g. in 2 ml. of normal saline was the only amount available. This was given intramuscularly, and when seen 24 hours later the discharge had gone though there was still some urethral dampness, a smear of which showed a moderate amount of pus cells but no gonococci. The urethral culture was also negative, the urine was clear and contained a few threads in the first glass only, and a rectal examination revealed no perineal tenderness.

Though the initial success of even this small dose was truly spectacular, not surprisingly it proved insufficient, for two days later the discharge again recurred, and when he attended a week after treatment there was a gross urethral discharge with gonococci present in the smear and a fluctuant left perineal abscess the size of an olive. This was aspirated, some 3 ml. of yellow pus being removed, and he was then given eight daily injections of 600,000 units of penicillin in oil-beeswax. Improvement was immediate, steady, and complete, and has been maintained.

Case 7. Uncomplicated Gonorrhoea

This patient, a white man aged 43, had a profuse urethral discharge of three days' duration when first seen. Gonococci were present in the smear, and the urine was hazy only in the first glass. Twenty-four hours after a single injection of 0.2 g. of streptomycin in 2 ml. of normal saline the urethral discharge had entirely disappeared. At 48 hours only epithelial cells were recoverable from the smear, and the urethral culture was also negative. The urine, too, was quite clear and free from threads. After one, two, and five weeks his condition continued to be satisfactory; the prostatic bead was free from pus and no gonococci were obtained in smear or culture.

The gonorrhoea cases, none of which showed any clinical or serological evidence of syphilis, are summarized in the following Table.

No.	Type	Sex	Dose	Initial Result	Later Events	Final Result
1	Simple	M	0.6 g.	Success	Recurrence after 3 days; re-treated with streptomycin	Success 56 days
2	"	F	0.6 g.	"	—	Success 63 days
3	Penicillin relapse	M	0.2 g.	"	—	Success 14 days
4	Protracted gonorrhoea	M	0.3 g.	"	—	Success 49 days
5	Sulphonamide relapse	M	0.4 g.	"	—	Success 49 days
6	Complicated Cowperitis	M	0.2 g.	"	Relapsed after 2 days; re-treated with penicillin	—
7	Simple	M	0.2 g.	"	—	Success 35 days

Summary

Seven cases of gonorrhoea (six males and one female), of which six were uncomplicated and one was complicated by Cowperitis, have been treated with single intramuscular injections of 0.2–0.6 g. of streptomycin in an aqueous medium. In all cases the initial response was at least as dramatic as treatment with penicillin in watery or oil-wax media. One patient, given 0.6 g., apparently relapsed after three days, but was successfully re-treated with the same dose of the drug. Another, complicated by Cowperitis, received only 0.2 g., and after a satisfactory initial response relapsed two days later with abscess formation in the gland and was then treated successfully with penicillin.

One patient with dark-field positive primary syphilis was given a single intramuscular injection of 0.6 g. of streptomycin, and twenty-four hours later *T. pallidum* was still recoverable without difficulty from the dark-field.

Apart from possible mild cerebral effects in Case 1, and mild pain at the site of injection in Case 2, no toxic effects were recorded.

It is concluded that streptomycin will be of the greatest value in venereology for all cases of gonorrhoea in which syphilis is more than usually suspect. As it appears that its use may not mask an incubating syphilitic infection, it is probable that only a three-months post-treatment period of surveillance to exclude syphilis will prove necessary for gonorrhoea treated with streptomycin, as compared with the six months usual after treatment with penicillin.

REFERENCES

- Barton, R. L., Craig, R. M., Schwemlein, G. X., and Bauer, T. J. (1947). *Arch. Derm. Syph., Chicago*, **56**, 1.
 Chinn, B. D., Putnam, L. E., Taggart, S. R., and Herwick, R. P. (1947). *Amer. J. Syph.*, **31**, 268.
 Cronin, E. (1947). *Brit. J. vener. Dis.*, **23**, 15.
 Dunham, W. B., and Rake, G. (1946). *Science*, **103**, 365.
 Finland, M., Murray, R., Harris, H. W., Kilham, L., and Meads, M. (1946). *J. Amer. med. Ass.*, **132**, 16.
 Fiskens, R. A., and Gruhitz, O. M. (1946). *Amer. J. Syph.*, **30**, 581.
 Greenblatt, R. B., Kupperman, H. S., and Dienst, R. B. (1947a). *Proc. Soc. exp. Biol., N.Y.*, **64**, 389.
 ——— (1947b). *J. vener. Dis. Inform.*, **28**, 183.
 Herrell, W. E. (1947). *J. Indiana med. Ass.*, **40**, 627.
 ——— and Nichols, D. R. (1945). *Proc. Mayo Clin.*, **20**, 449.
 Hirsh, H. L., and Taggart, S. R. (1948a). *J. vener. Dis. Inform.*, **29**, 47.
 ——— (1948b). *Amer. J. Syph.*, **32**, 159.
 Welch, H., Milloff, B., and Kaiz, S. (1948). *J. Lab. clin. Med.*, **33**, 805.
 Kane, L. W., and Foley, G. E. (1947). *New. Engl. J. Med.*, **237**, 531.
 Keefer, C. S., Blake, F. G., Lockwood, J. S., Long, P. H., Marshall, E. K., and Wood, W. B. (1946a). *J. Amer. med. Ass.*, **132**, 70.
 ——— Weinstein, L., and Hewitt, W. L. (1946b). *Med. Clin. N. Amer.*, **30**, 985.
 Knop, C. Q. (1946). *Proc. Mayo Clin.*, **21**, 273.
 Kolmer, J. A., Bondi, A., Warner, H. F., and Dietz, C. C. (1946). *Science*, **104**, 315.
 Kupperman, H. S., Greenblatt, R. B., and Dienst, R. B. (1948). *J. Amer. med. Ass.*, **136**, 84.
 Lamensans, A., Boyer, F., and Grehier, Mlle. (1947). *Ann. Inst. Pasteur*, **73**, 608.
 Leeming, J. A. L. (1947). *Brit. J. vener. Dis.*, **23**, 155.
 Loewe, L., and Altire-Werber, E. (1947). *Bull. N.Y. Acad. Med.*, **23**, 589.
 McDermott, W. (1947). *Amer. J. Med.*, **2**, 491.
 Marshak, L. C., and Rodriguez, J. (1948). *J. Amer. med. Ass.*, **137**, 1293.
 Miller, C. P., and Bohnhoff, M. (1947). *J. Bact.*, **54**, 467.
 Molitor, H. (1947). *Bull. N.Y. Acad. Med.*, **23**, 196.
 Moore, J. E. (1947). *Penicillin in Syphilis*, p. 283. C. C. Thomas, Springfield, Ill.
 Mortara, F., and Saito, M. T. (1947). *Amer. J. Syph.*, **31**, 20.
 Murray, R., Wilcox, C., and Finland, M. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 133.
 Parkhurst, G. E., Harb, F. W., and Cannefax, G. R. (1947). *J. vener. Dis. Inform.*, **28**, 211.
 Pulaski, E. J. (1947). *Ibid.*, **28**, 1.
 Schwarz, L. H., and Lazarus, J. A. (1947). *J. Bact.*, **53**, 128.
 Strauss, M. J., and Warring, F. G. (1947). *J. invest. Derm.*, **9**, 99.
 Wilcox, R. R. (1948). *Practitioner*, **160**, 380.
 Wilson, C. (1948). *British Medical Journal*, **2**, 552.
 Zimmerman, R. J., and Smith, G. C. (1948). *J. S.C. med. Ass.*, **44**, 267.

LARYNGEAL PARALYSIS ASSOCIATED
WITH CARDIAC HYPERTROPHY

REPORT OF FOUR CASES

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The association of laryngeal paralysis with aneurysm of the aortic arch is well known. That the left recurrent laryngeal nerve may be damaged in cases of cardiac enlargement is, however, less well recognized. The paralysis usually occurs in association with mitral stenosis, but recently some instances have been recorded of vocal-cord palsy in cases of hypertension with cardiac failure. The present communication is based on four cases of laryngeal paralysis attributable to a coexisting cardiac lesion.

Case Reports

Case 1.—A woman aged 26 was examined in consultation with Dr. James Richard on account of huskiness of a few months' duration. Laryngoscopy revealed complete abductor paralysis of the left vocal cord. The physical signs in the chest were those of cardiac enlargement and mitral stenosis with incompetence. The apex beat was 4 in. (10 cm.) from the midline, and the right border of dullness was at the right border of the sternum. There was slight oedema of the ankles. Her compensation was fairly good for a quiet life but failed on any exertion. Since the age of 19 she had been troubled with dyspnoea on exertion, palpitations, and oedema of the ankles. At the age of 7 she had had chorea followed by subacute rheumatism, at 10 peliosis rheumatica, at 14 tonsillitis, and at 19 subacute rheumatism.

Case 2.—A woman aged 51 was admitted to Dr. George Allan's wards in the Western Infirmary complaining of breathlessness and insomnia for three weeks and also of pain in the left leg and foot. During the previous two years her health had been poor—she was easily fatigued and had slight breathlessness. There was no history of rheumatism or other major illness. The lips and cheeks were cyanosed and there was considerable dyspnoea, which was increased even by speaking. The voice was hoarse. Both ankles were oedematous, the left one being tense and tender. The cardiac rhythm was regular at 150 and the pulse was of poor volume and tension. The blood pressure was 135/100. The arteries were not palpable. The apex beat was diffuse and visible and most forcible to palpation in the sixth interspace at 5½ in. (13.3 cm.) from the mid-sternal line. The borders of cardiac dullness were at the third rib, the mid-sternal line, and 5½ in. from the mid-sternal line. A loud musical murmur replaced the first cardiac sound and was conducted all over the praecordium and into the axilla. The second pulmonic sound was markedly accentuated. Laryngoscopy revealed complete paralysis of the left vocal cord. Examination of the fundi revealed slight arteriosclerotic changes. The patient died three weeks after admission. Permission for necropsy was not obtained.

Case 3.—A married woman aged 53 was admitted on May 19, 1933, to the Western Infirmary suffering from severe abdominal and left thoracic pain, tachycardia, and slight jaundice. She had had cholecystectomy for gall-stones in June, 1932, but had had recurrent attacks of jaundice during the following winter. The tachycardia was ascribed to auricular flutter, which with digitalis changed to auricular fibrillation and ultimately to regular rhythm. There was no material improvement, pain persisted, and she succumbed to hypostatic pneumonia on July 9. Paralysis of the left vocal cord was observed on laryngoscopy on June 27. The necropsy findings were as follows. The heart weighed 12 oz. (340 g.). The pericardium was healthy and the left ventricle was of normal size. The left auricle was markedly dilated, as were to a lesser extent both chambers of the right heart. The mitral valve was stenosed, being 7/10 in. (1.78 cm.) in diameter. The tricuspid