while *Micrococcus catarrhalis* ferments neither maltose nor glucose.

A rabbit and guinea-pig inoculated with cerebro-spinal fluid containing the organism showed no effect, though the guinea-pig died about a fortnight later. No pathological lesions were discovered, and cultures made from its brain and organs did not yield the organism in question.

Guinea-pigs inoculated with the patient's whole blood, with the plasma, and with cultures of the organism yielded similar negative results.

No agglutinating serums for meningococci could be obtained from various sources tried. A commercial polyvalent antimeningococcal serum did not agglutinate the organism even in low dilutions, but as it did not agglutinate the type strains of meningococcus I, II, III, and IV either, this observation was obviously not of much value.

A beginning was therefore made in the immunization of two rabbits with the diplococcus from the patient. The organism was first found in the patient's cerebro-spinal fluid on September 11th. It was present in films of the fluid only in small numbers, but growth was obtained, although with difficulty. As obtained from the spinal fluid, it did not grow nearly so profusely as it had when obtained from the blood stream. It behaved now, in short, as a meningococcus, and there was now no hesitation in labelling it as such. The patient died before the agglutinating serum from the rabbits was ready.

Four type strains of meningococcus (Lister Institute Collection) were tested with the serum along with the organism under examination (the "Murray coccus"). The emulsions were made in saline from growths on Thomson's medium, and the macroscopic method in a water-bath at 55° C. was used. Readings were made at intervals up to four hours. Both serum and saline controls were used. The test was not carried beyond 1 in 64 with Type III meningococcus.

Identification of Type of Meningococcus.

	Murray coccus serum: Dilutions, one in—									Controls.
	16	32	64	128	256	512	1,024	2,048	4,096	
Murray diplo-coccus	+++	+++	+++	++	++	++	+	+	Trace	—
Meningococcus Type I	±	Trace	—	—	—	—	—	—	—	—
Meningococcus Type II	+++	+++	++	++	+	±	±	Trace	—	—
Meningococcus Type III	++	±	Trace	—	—	—	—	—	—	—
Meningococcus Type IV	++	±	±	Trace	—	—	—	—	—	—

+++ represents complete clearing with sedimentation, and the other signs correspondingly smaller degrees of agglutination.

The organism could therefore be definitely labelled meningococcus Type II of Gordon's types.

Dock¹ has recently analysed sixty-eight reported cases of meningococcaemia, occurring in different parts of the world. In the case which he studied personally the organism was not agglutinated by the patient's serum or by polyvalent antimeningococcus serum at the second or third subculture, but at a later date was agglutinable in low dilutions both by antimeningococcus and antigenococcus serums. It was at first thought to be a gonococcus, but ultimately determined to be a meningococcus. The intermittent character of the fever, often with a definite malaria-like periodicity, was a salient feature of these cases.

Rolleston² also drew attention in his Lumleian Lectures on cerebro-spinal fever to these cases of meningococcaemia, which "may precede, follow, or occur without meningeal infection." He quotes some interesting observations by Netter and Dopfer. Dopfer's observation is that whereas before the war 96 per cent. of the cases of meningococcal meningitis were infected with the meningococcus Type A (Gordon's I and III types) a change has taken place, so that now the parameningococcus or Type B (Gordon's II and IV) is responsible for an equal, if not a larger, number of the cases. Netter³ comments that this observation may be correlated with an increased incidence of meningococcaemia, and meningococcal manifestations in the skin, joints, and eyes.

The organism in our case, a meningococcus of Type II (British classification) or Type B (French classification) certainly showed no particular affinity for the cerebro-spinal system, as it was more than four months before the

spinal fluid became infected. It is interesting that the organism disappeared from the blood stream before this terminal meningeal infection took place.

We shall not here embark on a discussion of the mutability or fixity to type of these bacteria beyond noting that the organism as obtained from the blood stream was a hardier, coarser-growing type than that obtained later from the cerebro-spinal fluid. Such a change might, of course, be merely a temporary or fluctuating variation due to environmental conditions, particularly as the hardier qualities were quickly lost on subculture.

The case emphasizes the necessity for bearing in mind the possibility of a change in the nature of meningococcal infections.

REFERENCES.

- ¹ Dock, William: Intermittent Fever of Seven Months' Duration due to Meningococcaemia, *Journ. Amer. Med. Assoc.*, vol. lxxxiii, No. 1, July 5th, 1924.
- ² Rolleston, Sir Humphry: Lumleian Lectures on Cerebro-spinal Fever, *Lancet*, April 5th and 12th, 1919.
- ³ Netter: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 3e série, vol. xli, 883, 1917.

THE CHEMOTHERAPY OF RECENT EXPERIMENTAL WOUND INFECTIONS:

WITH SPECIAL REFERENCE TO THE ACTION OF
ACRIFLAVINE.*

BY

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THE question whether localized infections can or cannot be treated effectively by means of antiseptics applied to the infected area appears still to be a subject for argument. Animal experiment might be expected to yield a decisive answer. But a difficulty, as most workers have found (for example, see Watson Cheyne, Bassett-Smith, and Edmunds⁶), is the tendency for infections in small animals to become generalized and so to escape beyond the range of action of the antiseptic. In the case of mice inoculated intraperitoneally with organisms so highly invasive as virulent pneumococci, we² have shown that it is possible to effect cure sometimes by means of intraperitoneal injections of various antiseptics; but this line of work has not been pursued owing to the difficulty in controlling the virulence of the infection. Recently, the infection of experimental wounds in guinea-pigs with a virulent culture of *B. diphtheriae* has been recommended as a test object for investigating the therapeutic properties of antiseptics (Braun,¹ Feiler⁴). In the first place, there is very little tendency for the infection to become generalized; and secondly, when a highly virulent culture is employed the results are decisive, since the unmodified infection is rapidly fatal.

METHODS.

Guinea-pigs of about 200 to 250 grams weight were used. An area of the skin of the abdomen was shaved. When the animal was under the influence of a general anaesthetic two parallel linear cuts, each measuring about 1.75 cm. and at a distance apart of 0.8 cm., were made through the skin in the direction of the long axis of the body, care being taken not to incise the deeper tissues. Then, by means of a stout wire bent into a loop, the strip of skin between the cuts and also the skin for about 1 cm. on either side of the incisions was raised from the deeper structures, so that pockets were produced; there was, of course, very little bleeding from the wound. About a quarter of a well grown forty-eight hours' agar slope culture of *B. diphtheriae* was then rubbed into the wound and the pockets. The animals were left for varying periods and were then treated. Treatment consisted in placing the animal on its back and pouring slowly into the wound 1 c.cm. of a watery solution of the substance the action of which was to be investigated, the wound and pockets being meanwhile swabbed out with a small

* Work done with the support of the Medical Research Council.

pledget of cotton-wool, like a throat swab, which had previously been soaked for several minutes in the same solution as that used to treat the wound. This procedure lasted for a minute and a quarter. At the end of this time any fluid which had not been absorbed by the tissues was allowed to drain away and the surrounding skin was swabbed dry. The wounds received no further treatment. (In the case of the experiments with bipp, as much of the undiluted mixture as would adhere to a swab was used to treat the surfaces of the wound and the pockets, any excess being wiped off the skin.)

The experiments were not considered as concluded until at least three weeks after the date of inoculation.

SERIES I.

Infection with highly virulent *B. diphtheriae* (strain A, recently isolated); designed to test whether effective treatment is possible. Twelve animals were inoculated. After intervals of 45, 75, and 120 minutes respectively two animals were treated with 1 per cent. watery solution of neutral acriflavine. At each period, by way of control, two animals were treated by washing the wounds similarly with 0.85 per cent. NaCl solution.

Results.—The animals treated with acriflavine (with one exception—treated after 1½ hours—which died eight days after inoculation without having shown signs of illness previously) remained alive and well. The six controls* treated with saline were all dead within forty-eight hours.

SERIES II.

Infection with highly virulent *B. diphtheriae* (strain A, recently isolated); in order to compare the therapeutic action of acriflavine and phenol and to ascertain the effect of treatment with 5 per cent. NaCl solution. The interval between inoculation and treatment was one hour.

Results.

Reagent used to Treat Wound.	No. of Animals treated.	Result.
Neutral acriflavine { 1 in 1,000 1 in 400 1 in 100	2 2 2	All survived.
Carbolic acid 1 in 20	2	
NaCl solution, 5 per cent. ...	2	
NaCl solution, 0.85 per cent. ...	2	Both* died within 48 hours.

SERIES III.

A distinctly less virulent diphtheria infection (strain A, some time after isolation) than that in Series I and II. Interval between inoculation and treatment, one hour.

Results.

Reagent used to Treat Wound.	No. of Animals treated.	Result.
Neutral acriflavine { 1 in 2,500 1 in 2,000 1 in 1,500 1 in 1,000 1 in 500 1 in 250	1 1 1 1 1 1	All survived.
Carbolic acid { 1 in 100 1 in 75 1 in 50	1 1 1	
Bipp	2	
NaCl solution, 5 per cent. ...	2	

SERIES IV.

A distinctly less virulent diphtheria infection (strain C) than that in Series III. Interval between inoculation and treatment, eighty minutes.

Results.

Reagent used to Treat Wound.	No. of Animals treated.	Result.
Neutral acriflavine { 1 in 5,000 1 in 2,500 1 in 1,000 1 in 500 1 in 200	1 1 1 1 1	All survived.
Carbolic acid { 1 in 80 1 in 40	1 1	
Bipp	1	
NaCl solution, 5 per cent. ...	1	
NaCl solution, 0.85 per cent. ...	1	

* Indicates that in these animals the suprarenal bodies were haemorrhagic, which is the most constant change found in death due to diphtheria infection.

There is little doubt that the late deaths were mainly the result of the infection, although the characteristic changes were absent at this stage, since most of these animals had been obviously ill for several days after inoculation.

The results show that in highly virulent infections (Series I and II) treatment of the wound with neutral acriflavine in dilutions down to 1 in 1,000 (the highest dilution tested) regularly caused survival (one animal only out of twelve died, after an interval of eight days). Treatment with 5 per cent. carbolic acid caused only a protraction of the infection. Treatment with 5 or 0.85 per cent. salt solution was entirely without effect under these conditions as the animals so treated died within forty-eight hours after inoculation.

In somewhat less virulent infections (Series III and IV) acriflavine in dilutions down to 1 in 2,500 caused survival. Carbolic acid solution had a distinct effect. Thus in Series III carbolic acid in a concentration of 1 in 50 led to survival, but animals treated with concentrations of 1 in 75 and 1 in 100 died acutely; in Series IV, which had the least virulent infection of the four, treatment with concentrations of 1 in 40 and 1 in 80 carbolic acid led to survival or marked protraction of the infection. Of three animals treated with bipp all died with typical *post-mortem* findings; in only one was the illness protracted. In the latter two series, out of four animals treated with saline, one (belonging to Series III, treated with 5 per cent. NaCl solution) died after fourteen days; the rest died acutely.

In still less virulent infections only a proportion of animals treated with saline die acutely in two to five days with typical *post-mortem* appearances; the rest may fail to become ill or may recover, some after being obviously ill; of the latter a proportion die after several weeks. Thus in addition to the above experiments several series were inoculated with the Park-Williams strain No. 8 of *B. diphtheriae*,† which, in spite of its high capacity for producing toxin *in vitro*, is of comparatively low virulence when young cultures are tested in animals. All of the nineteen guinea-pigs treated with acriflavine 1 in 100 at intervals of forty to ninety minutes after inoculation with this strain survived. Of the nineteen controls whose wounds were washed out at similar intervals with 0.85 per cent. saline eight died (42 per cent.). This result also is in support of the efficacy of treatment with the antiseptic as compared with mere washing of the wounds.

Of course, the results recorded here do not affect the question of appropriate operative procedures in the treatment of infected wounds, nor do they bear upon the need for antitoxin treatment in cases of diphtheria in man.

The efficacy of acriflavine (trypaflavine) in the therapy of experimental wound diphtheria has also been demonstrated by Feiler⁴ and by Reinhardt.⁵ It has been shown that this effect cannot be ascribed to destruction of diphtheria toxin present in the culture used for inoculation by neutral acriflavine, but is the result of destruction of the bacilli (Braun¹).

† For this culture we are indebted to Dr. R. A. O'Brien, Wellcome Research Laboratories.

CONCLUSIONS.

1. The results of treating recent experimental wounds opening into the subcutaneous tissue which have been infected with highly virulent diphtheria bacilli prove the efficiency of antiseptic therapy. Under the conditions investigated brief treatment with a suitable antiseptic (neutral acriflavine in concentrations of 1 in 100 to 1 in 1,000) has caused survival of practically 100 per cent. of the infected animals. On the other hand, salt solution (either 0.85 or 5 per cent. NaCl) similarly applied did not prevent in any instance the acute illness and fatal termination.

2. When acriflavine and carbolic acid are compared, it is found that the ratio of their therapeutic effectiveness exceeds 50 to 1. This conforms with estimates of their relative potency previously arrived at by us³ by other methods.

3. In less virulent infections the therapeutic action of carbolic acid is evident. But bipp showed practically no action even in the latter; it would appear that the therapeutic effect of this mixture, so frequently commented on by clinical observers, must depend on some property other than an antiseptic one.

REFERENCES.

- ¹ Braun: *Med. Klin.*, 1920, 16, p. 406; *Klin. Woch.*, 1922, 1, p. 761.
² Browning and Gulbransen: *Journ. Path. and Bact.*, 1919, 22, p. 265.
³ Browning, Gulbransen, Kennaway, and Thornton: *BRITISH MEDICAL JOURNAL*, 1917, i, p. 73; ii, p. 70; see also Browning's *Applied Bacteriology*, London, 1918, p. 65. ⁴ Feiler: *Deut. Zeit. f. Chir.*, 1921, 164, p. 379.
⁵ Reinhardt: *Zeit. f. Hyg. u. Inf.*, 1922, 95, p. 1. ⁶ Watson Cheyne, Bassett-Smith, and Edmunds; see Watson Cheyne, *Lancet*, February 27th, 1915.

THE DECLINE OF LITHOLAPAXY.

BY

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In the *Principles and Practice of Surgery* (1914), by Dr. A. P. C. Ashhurst, the following passage occurs:

"The operation of litholapaxy is not now in general use because the mortality of cutting operations is less than when Bigelow's operation was introduced, and because recurrence of stone formation is frequent (18 per cent.), either because all the fragments are not removed at first, or because urinary obstruction or vesical infection are not relieved. But the primary mortality is very low (5 per cent.), and the operation may be done under local anaesthesia in very debilitated subjects. It is best reserved for such patients, provided no cystitis is present."

The book is an American one, and, though presumably representative of practice in the United States, does not necessarily speak for British surgery. But this is, in any case, strange doctrine for the country of Bigelow, and there is reason to believe that the same view is gaining ground amongst British surgeons. A short time ago, for instance, I met a keen and highly qualified junior surgeon in charge of an Indian hospital, who was doing no crushing, and told me that the operation of litholapaxy was now regarded as obsolete at home. He had spent several years in resident appointments at well known English hospitals; and one is continually hearing the same view from men who have recently passed through British medical schools. It is for this reason that I have thought it worth while to write the following note.

Thirty years ago my old chief, Mr. F. A. Southam, was using lithotrites successfully in the Manchester Royal Infirmary, and there was no doubt in those days, so far as I remember, as to litholapaxy being the operation of choice for stone in the bladder. The chief arguments now brought against it appear to be that suprapubic lithotomy can be done with nearly as great safety, that litholapaxy is difficult to learn and dangerous when performed by inexperienced operators, and that there are more recurrences after it than after lithotomy.

A statistical comparison of the results of the two operations is hardly possible in India, where for the most part only the bad cases are dealt with by the cutting operation, and I have never seen an effective comparison of British figures, which might presumably be obtainable. The impression is widely prevalent in India, however, that litholapaxy in skilled hands is much the less dangerous opera-

tion, and our figures speak for themselves, and still more emphatically if it is admitted, as we all contend, that, contrary to the impression at home, our cases on the average are far less promising than those which come to the English hospitals. We have a very large proportion of large stones and septic bladders to deal with, and we consider, moreover, that the idea which seems to prevail at home that Indian patients in general bear operation better than Europeans is entirely erroneous. It remains to be said that suprapubic lithotomy is not without its dangers. A very little disturbance of the cave of Retzius may lead to disastrous consequences.

The frequency of recurrence after litholapaxy is much exaggerated. Under proper conditions recurrences should be very rare. Experience of my own and other people's work is that they are quite infrequent, though it is unfortunately impossible to put up figures in proof of this statement. A fair test of the general result of the operation is its reputation with the public. The Indian cultivator, who furnishes the great majority of our up-country patients, is an acute judge of the practical results of surgery, as shown, for instance, in his appreciation of Bassini's operation for hernia. As regards litholapaxy, he made up his mind long ago, and there is no surer way of emptying one's hospital than by reverting to a cutting operation where crushing has formerly been in vogue. There is not only the escape from the knife but the early discharge from hospital to be considered, and it is, of course, quite common for children who have been relieved of small stones by the lithotrite in the morning to be running about in the afternoon. It is, I think one may say, the opinion of an overwhelming majority of Indian surgeons that litholapaxy in proper hands has great advantages over any of the cutting operations in all but a small percentage of complicated cases, and it would be a very great pity if the contrary view were to be generally accepted and taught in the British schools, particularly in the case of men who are destined to practise in the East. I append a list of cases treated in four representative hospitals of this Presidency. Many more extensive series have appeared in the pages of the *BRITISH MEDICAL JOURNAL*, but they seem to have passed too readily into oblivion.

I.—Cases operated on by Lieut.-Colonel R. W. Anthony, F.R.C.S.E., during three years and three months in 1920-23 at the Civil Hospital at Hyderabad, Sind.

	Cases.	Deaths.
Litholapaxy (including 30 perineal litholapaxies)	1,253	7*
Suprapubic lithotomy	11	3
Perineal lithotomy	0	0

* Three others "discharged otherwise"—probably died.

This is the most noted centre for vesical calculus in this Presidency, and has dealt with an average of 464 cases a year during the last ten years. Colonel Anthony says that he looks on every case of stone as one for litholapaxy if it can be done, and that there are very few cases in which it cannot, given an experienced operator. If it is impossible to crush by the urethra in the ordinary way he performs perineal litholapaxy. He crushes stones up to about 6 ounces, and hardly ever gets one that he cannot deal with, either by the ordinary or perineal route, by means of a large lithotrite or a hammer. He apparently never does perineal lithotomy now, and only performs suprapubic lithotomy primarily from choice in patients with enlarged prostates. Thus, as he points out, his suprapubic cases must be taken largely as failed litholapaxies of a complicated nature—for example, cases in which the bladder has an hour-glass shape, or processes like the finger of a glove containing stone, or encysted stone; or those rare accidents where the lithotrite has jammed, or perforation of the bladder has accidentally occurred.

II.—Cases operated on by Lieut.-Colonel T. S. Novis, F.R.C.S., at the Jamssetjee Jeejeebhoy Hospital, Bombay, from June 14th, 1920, to December 31st, 1923.

	Cases.	Deaths.
Litholapaxy	114	1
Perineal litholapaxy	0	0
Suprapubic lithotomy	17	5
Perineal lithotomy	2	0

Note.—Of the deaths from suprapubic lithotomy, two were complicated with prostatectomy, and two developed pneumonia.

This is the chief general hospital in Bombay, and associated with the Grant Medical College. Here, also, litholapaxy is the routine operation, the contraindications quoted by Colonel Novis being very large or very hard stones, very soft putty-like stones, stricture, enlarged prostate, extensive kidney disease, and bladder growth of any considerable size. He lays stress on a routine cystoscopic examination of the bladder, both before operation, to exclude the possibility of encystment of the stone or other complications, and immediately after, or at any rate before discharge,