Summary

The aetiology and pathology of superior mesenteric arterial occlusion are discussed, and arterial "stupor" is suggested as being of importance.

The history, clinical findings, and course of a case of "spontaneous recovery" are detailed and the diagnosis and differential diagnosis noted.

The causation of shock is discussed and suggestions are made as to its treatment.

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CHEMOTHERAPY OF INFECTED URINES IN PARAPLEGIA

BY

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During the routine bacteriological examination of urines from patients with complete transverse lesions of the spinal cord and suffering from chronic cystitis it was noticed that a large percentage of the lactose-fermenting colonies grown, which on staining were seen to be composed of Gram-negative bacilli, were distinctly mucoid in appearance. They occasionally contained a bubble of gas trapped in the substance of the colony, which suggested that the organisms were *Bact. aerogenes* rather than *Bact. coli*. This observation, together with the increasing interest in the treatment of urinary infections with streptomycin and penicillin, prompted this investigation. Fifty strains of coliform organisms from the above-mentioned paraplegic patients were tested to determine the incidence of *Bact. aerogenes* and their sensitivity to penicillin, streptomycin, and sulphathiazole.

Materials and Methods

Fifty strains of these Gram-negative organisms, which produced acid and gas from a fluid medium containing 1% lactose, were primarily isolated from the routine litmus-lactose-agar plate cultures of paraplegic patients' urines. These were either the predominating or the only organisms grown. A single colony was picked off the plate, spread on a second plate, and reincubated; after incubation overnight at 37° C. a single colony was picked off the second plate and inoculated on a broth-agar slope in a cotton-wool-plugged centrifuge tube (4 in. × 5/8 in. —10.2 cm. × 1.6 cm.). After incubation overnight the slopes were covered with sterile liquid paraffin as described by Morton and Pulaski (1938), who showed that organisms kept under such conditions did not alter their characteristics. After six months at room temperature all cultures were viable. During this period the organisms were subcultured and subjected to biochemical tests for identification and tests for sensitivity to streptomycin, penicillin, and sulphathiazole.

The stock cultures were subcultured on to litmus-lactose plates to check purity. The following day one colony was picked off into peptone water. The peptone water was

then incubated at 37° C. for 4 to 6 hours, when subcultures were made into the following media: (1) Clark and Lubs's glucose phosphate medium, (2) Koser's citrate broth, (3) McConkey's broth. The first two were incubated at room temperature and the latter at 44° C. The peptone-water cultures were retained and incubated at 37° C.

Indole Test.—This was performed on the original peptone-water cultures with equal parts of culture and Ehrlich's reagent and one drop of saturated potassium persulphate. The test was performed at 3, 5, and 10 days. All positive reactions were obtained on the third day and remained positive on the fifth and tenth days.

Voges-Proskauer Reaction.—Glucose-phosphate medium was used and incubated at room temperature, and the α-naphthol test of Barritt (1936, 1943) was used. The test was performed at 48 hours.

Methyl-red Test.—Glucose-phosphate medium was used and incubated at room temperature. The test was performed at 3 days.

Growth in Citrate.—Koser's citrate was inoculated with a straight wire from the peptone-water culture and incubated at room temperature. The cultures were not discarded for 10 days, but if growth occurred it was evident in the first 48 hours.

Gas at 44° C.—McConkey's broth was inoculated after being warmed to 44° C. The cultures were incubated in a water-bath running at 44 ± 1° C.

In the case of four anomalous cultures the tests were repeated; the ability to grow in citrate was also tested at 37° C., with a normal as well as a large inoculum, all with the same results.

Penicillin and Streptomycin Sensitivity Tests.—The appropriate concentration of the drug was diluted in infusion broth and approximately 1 ml. of this solution transferred to sterile cotton-wool-plugged tubes, 3 in. × 1/2 in. (7.6 cm. × 1.25 cm.). These were inoculated with a drop of broth culture of the organisms under test and incubated overnight. The following morning the tubes were examined with the naked eye for growth.

Sulphathiazole Sensitivity Tests.—Poured-broth-agar plates were used with the appropriate concentration of sulphathiazole added and containing laked horse's blood to neutralize sulphonamide antagonizers, as described by Harper and Cawston (1945).

Results

Table I shows the incidence of the different types of organisms and their biochemical reactions. Table II shows the results of the sensitivity tests. Those organisms which were resistant to 500 units of penicillin per ml. were subjected to a further series of tests for sensitivity to penicillin; the results of these and of the tests for sensitivity to sulphathiazole are shown later.

The results of the streptomycin-sensitivity tests show that 9 out of 12 (75%) of the strains of *Bact. coli* are sensitive

TABLE I

Organism	No. of Strains in Each Group	Per cent Incidence	Gas at 44° C.	Methyl-red Test	Indole Production	Voges-Proskauer Test	Utilization of Citrate
<i>Bact. coli</i>	12	24	+	+	+	—	—
Irregular <i>Bact. coli</i> type 1* ..	2	4	—	—	—	—	—
<i>Bact. aerogenes</i>	32	64	—	—	—	+	+
Unclassified	4	8	—	—	—	+	+
Total	50	100					

* An atypical form of *Bact. coli* (Wilson and Miles, 1946).

TABLE II

Organism	No. of Strains in Each Group	μ g. of Streptomycin per ml. Inhibiting Growth				Units of Penicillin per ml. Inhibiting Growth				
		<1	1-8	8-16	16-32	50-75	75-100	100-200	200-500	>500
<i>Bact. coli</i> ..	12	4	5	0	3	1	9	0	2	0
Irregular <i>Bact. coli</i> type I ..	2	0	1	0	1	1	1	0	0	0
<i>Bact. aerogenes</i> ..	32	18	14	0	0	0	0	0	2	30
Unclassified ..	4	2	2	0	0	0	0	0	0	4
Total ..	50	24	22	0	4	2	10	0	4	34

to less than 8 μ g., and 3 out of 12 (25%) of the strains to between 16 and 32 μ g. of streptomycin per ml.; 46 out of 50 (92%) of all the organisms are sensitive to less than 8 μ g., and the remaining 8% to between 16 and 32 μ g. per ml. Out of 32 strains of *Bact. aerogenes* 30 (94%) will grow in a concentration of 500 units of penicillin per ml.; whereas 10 out of 12 (83%) of *Bact. coli* strains are inhibited by 100 units of penicillin per ml. Seventy-six per cent of all strains grow in 200, 68% grow in 500, and 24% are inhibited by 100 units of penicillin per ml.

Forty-six (92%) of the strains resisted 50 mg. of sulphathiazole per 100 ml.; 4 (8%) were sensitive to 1 mg. per 100 ml. Of the 4 that were sensitive 2 were *Bact. aerogenes* and 2 *Bact. coli*.

The 34 strains (30 *Bact. aerogenes* and 4 unclassified) which were resistant to 500 units of penicillin per ml. were tested in 11 higher concentrations to a maximum of 100,000 units per ml. Twenty-five were inhibited by concentrations of between 1,000 and 5,000 units per ml., but 6 were resistant to 50,000, and 1 strain to 100,000, units per ml.

Discussion

It is generally agreed that *Bact. aerogenes* is found most commonly in soil and on vegetation and when encountered in public-health work is not necessarily considered indicative of recent excretal contamination of water and food-stuffs. But Cruickshank (1931) states that it can be isolated from the stools of the majority of normal people if enrichment methods are used, and Gray (1932) found it in 37 out of 40 samples of faeces from 10 normal people. Other workers give figures from 0 to 26%.

However, *Bact. aerogenes* is not infrequently found in urinary infections. This organism has been reported as constituting 63% (Burke-Gaffney, 1932) and 52% (Burke-Gaffney, 1933) of urinary coliform organisms in Tanganyika territory, 50% of urinary Gram-negative bacilli (Hill *et al.*, 1929) in the U.S.A., and 39% of all urinary organisms from patients with "neurogenic" bladders (Petroff and Lucas, 1946) also in the U.S.A. The latter workers, however, do not mention *Bact. coli* in their list of percentage incidence of organism although it does appear in their tables, so it is impossible to calculate the proportion of *Bact. aerogenes* to *Bact. coli* in their series of 87 cases. It thus appears that the incidence of *Bact. aerogenes* in the series of patients reported in this paper is of the same order as that in groups of patients with urinary infections described by other workers.

The organism called "Irregular type I" resembles *Bact. coli* in its primarily intestinal origin and biochemical characteristics, differing only in that it does not produce gas from McConkey's lactose broth. It also resembles *Bact. coli* in being comparatively sensitive to penicillin (see Table II). The group labelled "unclassified" in the tables resembles *Bact. aerogenes* biochemically except that it does not utilize citrate. The resistance of this group to penicillin and streptomycin is of the same order as that of *Bact. aerogenes*.

It is clear from the results of the sensitivity tests (see Table II) that all the organisms examined here are fairly susceptible to streptomycin irrespective of their type. However, all the *Bact. aerogenes* and the unclassified organisms are sensitive to 8 μ g. or less per ml., whereas 3 out of 12 *Bact. coli* strains and 1 out of 2 of the related irregular types are insensitive to 16 μ g. but sensitive to 32 μ g. per ml. Thus perhaps *Bact. coli* is less sensitive to streptomycin than is *Bact. aerogenes*. In any event 46 (92%) of the strains of coliform organisms lie within, and the remaining 8% are doubtfully within, the therapeutic range of streptomycin.

It is difficult to foretell from these *in vitro* tests how successful streptomycin is likely to be in treatment, because the failures in these cases appear at times to be due to the rapid development of resistance by the organism to the drug. Despite this complication, however, Petroff and Lucas (1946) consider that their paraplegics with "neurogenic" bladders benefited from treatment with the drug, although their paper in some respects is not altogether conclusive. It may well be that streptomycin will become a valuable weapon in these infections, but from my experience it is obvious that as high dosages as possible should be tried. Starting the course with a dose considerably greater than the subsequent ones should be borne in mind. The purpose of these precautions is to ensure that the responsible organism is never subjected to a concentration of streptomycin below the bactericidal or bacteriostatic level—that is to say, to those conditions that are likely to increase its resistance to the drug. We are assuming that the development of resistance is the result of contact with the drug and not due to the presence of a small percentage of naturally resistant strains. This point has not been decided, and no convincing evidence exists for either view.

Since Peeney (1947) advocated the use of penicillin in Gram-negative bacillary infections of the urinary tract and Helmholz and Sung (1944) found that *Bact. aerogenes* was relatively insensitive to penicillin, it seemed important to determine here the incidence and resistance of that organism to penicillin, for a high incidence of penicillin-resistant organisms, either widespread or in any particular locality or group of patients, would be a contraindication to the routine use of the drug in treatment.

In this series penicillin divides the organisms into two fairly clearly defined groups: all but two strains of *Bact. coli* and the associated irregular *Bact. coli* are sensitive to 100 units of penicillin per ml., whereas the *Bact. aerogenes* and the associated unclassified organisms are resistant to 200 units per ml. of penicillin, above which level Peeney (1947) suggests that they are not likely to respond to penicillin therapy. Thus resistance to penicillin may be a characteristic of the *aerogenes* group of organisms, and the incorporation of penicillin in an appropriate concentration in a medium might be suitable for isolating *Bact. aerogenes*. In view, then, of the high incidence of *Bact. aerogenes* in this and other series of cases and the undoubted resistance of this organism to penicillin, it is obvious that this drug cannot be used for the routine treatment of urinary infections involving coliform organisms, especially if we accept Peeney's (1947) suggestions without reserve. Moreover, 76% of the total number of coliforms in this series are resistant to penicillin according to his criteria. Under the circumstances penicillin treatment would be only occasionally successful in these infections and then only under full bacteriological control.

It has been assumed that it is necessary to obtain only the concentration of penicillin in the urine which *in vitro* will be bactericidal to the organisms involved; this obviously is not the case, for the organisms must be causing

the mischief in the tissues of the urinary tract. This is evident from the polymorphonuclear leucocytosis that occurs, and it is generally accepted that these infections are blood-borne or spread by lymphatics (Walker, 1922, 1930). This worker and others have demonstrated organisms and cellular infiltration in the tissues of the urinary tract. Of course the mischief may not be very deep-seated and the concentration of penicillin in the tissues of the urinary tract may be higher than elsewhere owing to the diffusion of that substance from the urine, but even if this is the case the tissue concentration must be lower than the urinary, though it may be greater than the blood. Thus we see that it is impossible to relate directly the urinary level and the sensitivity of the organism to penicillin *in vitro* and in this way determine whether a urinary infection is likely to respond to treatment with a certain dosage of penicillin; this argument will apply to any other drug. The final court of appeal, as always in this particular type of problem, will be clinical trial and error of various dosage systems given under standard conditions and related to the *in vitro* drug sensitivity of the organisms.

With ordinary doses it is practicable to maintain an average level of 200 units per ml. of penicillin in the urine, but theoretically there is no reason why 2 or more million units of penicillin should not be injected every three hours, though even under the best conditions this dosage would be inadequate for one-quarter of the *Bact. aerogenes* and nearly one-fifth of all the organisms in this series (as indicated by the extended penicillin sensitivities listed in the results). When penicillin becomes cheaper and even more readily available it may be possible to treat most Gram-negative urinary infections with it. In any event, it is already useful for treating urinary infections associated with Gram-positive organisms.

Of the coliforms examined 46 out of 50 (92%) resist 50 mg. of sulphathiazole per 100 ml. using the method described above. This is in approximate agreement with the findings of Neter and Clark (1944) but not with Strauss and Finland (1941), who used a synthetic medium. There do not seem to have been any published reports of the correlation of *in vitro* sensitivities with clinical results, but the figure seems high. Bearing in mind the possible site of action of the drug, one must pause to consider how much value the sulphonamides are in urinary infections with Gram-negative bacilli. However, Nathan (1947) reports favourably on them for treating paraplegic patients with suprapubic cystostomy.

Summary

Of 50 strains of lactose-fermenting coliform organisms isolated from infected urines of paraplegic patients 32 were *Bact. aerogenes*, 12 were *Bact. coli*, 2 were irregular types of *Bact. coli*, and 4 were unclassified. The incidence of *Bact. aerogenes* in this group does not differ greatly from that in other patients with urinary infections.

All the organisms were sensitive to streptomycin, and all but 4 resistant to 50 mg. of sulphathiazole per 100 ml.

Bact. aerogenes and the unclassified organisms were relatively resistant, and *Bact. coli* and its irregular types relatively sensitive, to penicillin. The high incidence of *Bact. aerogenes* and its undoubted resistance to penicillin does not favour the use of the drug at present in the routine treatment of urinary infections by Gram-negative bacilli. In this series it was concluded that at least one-fifth of all the organisms were too resistant for penicillin treatment in high dosages and three-quarters too resistant for ordinary dosages.

The results are discussed and their impact on the treatment of urinary infection considered.

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CARDIAC MURMURS IN INFANCY

BY

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Much has been written about cardiac murmurs in older children, but relatively little work has been done on their incidence and manifestations in infant communities. Von Reuss (1929) states that any definite murmur heard in a child who is quiet should be regarded as evidence of congenital heart disease and that murmurs at this age are very rare. On the other hand Holt (1940) states that 50% of all children have a functional murmur at some time. Lyon and others (1940) examined 7,000 newborn infants in the obstetrical wards of a general hospital and found that 147 (1.9%) had apical systolic murmurs; two of these died of congenital heart disease, and in 14 of the 88 who were re-examined six months later the murmurs were still present.

Since the Child Health Survey of the Institute of Social Medicine was initiated at Oxford three years ago 630 children have been enrolled, and the oldest have now been under observation for three years; 520 children remain in the survey at present, the 110 defaulters belonging chiefly to families which have moved to other areas owing to the housing shortage. The defaulters were followed up for periods varying from six months to two and a half years. It should be emphasized that this is not a hospital series but a sample of ostensibly healthy children drawn from all social classes, whereas the authors quoted either employed a hospital population or have not stated how their samples were obtained. Of the 630 children, 32 (5%) have been noted as having a murmur at some time. It was thought that it would be interesting to investigate the time of development of these murmurs and their subsequent history so far as at present observed.

In the course of the main health survey a full physical examination is made at regular intervals; first at the age of 6 weeks or less, then at 3, 6, 9, and 12 months, with subsequent examinations at six-monthly intervals. It has not always been possible to adhere strictly to the exact intervals owing to illnesses or other difficulties. Three observers, working in succession but observing the same routine as closely as possible, have carried out examinations on children first seen at infant welfare centres or at mothercraft clinics. All the children have had their chests examined radiographically, first at the age of 6 months and