given less often than eight-hourly. Pneumococci and staphylococci seem to reappear during long courses of treatment, but not to persist. In most cases, once the *H. influenzae* returns the other invading bacteria quickly die out. Mild and unilobar cases may remain symptom-free for many months after a course of two weeks' treatment (eight cases). Severe cases have always relapsed within 10 days of ceasing treatment, and sometimes the relapse is heralded by an acute febrile illness lasting one or two days. In every case another course of treatment has produced another remission. The question arises whether in severe cases the *H. influenzae* remains deep in the tissues of the bronchiectatic lung, ready to reappear in the sputum when the drug is stopped, or whether reinfection occurs. The larger doses that might reduce the risk of relapse on the first hypothesis have not been regarded as safe in these observations.

Unfortunately the possibly toxic effect of chloramphenicol on bone marrow, responsible for one death in the cases treated in this series, makes the prolonged use of the drug unwise. Some of the cases reported here have taken as much as 100 g. in six months without apparent ill effect, and repeated blood examinations might give warning of trouble in time for the drug to be stopped, before changes in the marrow become irreversible. *We do not, however, intend to persist with this treatment.* We feel that our results must be recorded to show that there is a place—if now vacant—in the medical treatment of bronchiectasis in children for an antibiotic sharing with chloramphenicol the power of rapidly reaching a high enough concentration in the respiratory tract to destroy *H. influenzae* without inducing resistance, so that recurrent infection may be successfully treated in the same way. Such a drug would combine safety with the power to dry up sputum and to make bacteriologically safe surgical procedures on lower respiratory tract or on upper respiratory tract, so often the site of disease causing persistence of symptoms; secondly, would be suitable for routine preventive treatment in severe bronchopneumonia in infancy, especially in association with pink disease and whooping-cough; thirdly, would keep the mild unilobar case free from recurrences following intercurrent influenza or other acute respiratory infections; and, fourthly, would give periods at least of freedom from endless cough and sputum in the severest cases where five lobes are diseased in early childhood, and where even the boldest thoracic surgeon must refuse surgical help. For those who believe that *H. influenzae* is responsible for the persistence of symptoms in the majority of cases of bronchiectasis, and that bronchiectasis is a disease with a tendency towards improvement and dying out of symptoms in time, the situation urgently demands a safe antibiotic with the remarkable powers of chloramphenicol. Our experience with aureomycin and terramycin, to which *H. influenzae* is also very sensitive, is so far too limited to justify any report.

### Summary

Of 36 cases of bronchiectasis in children a pure or almost pure infection by *H. influenzae* was present in 35.

Chloramphenicol, to which this organism is highly sensitive, invariably produced a remission while being given in adequate doses. After cessation of treatment, severe cases reverted to their original condition, but some milder ones appeared to have received more lasting benefit.

One patient died of aplastic anaemia, an occurrence which led to the abandonment of the treatment.

We are indebted to Miss Pamela M. Waterworth for skilled laboratory assistance, and to Miss Gosling and her staff at the Meath School of Recovery for collecting and personally conveying to London many specimens of sputum.

# THE IN-VITRO SENSITIVITY OF H. INFLUENZAE TO FIVE DIFFERENT ANTIBIOTICS

BY

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At times clinicians find it difficult to select and bacteriologists to suggest the antibiotic most effective in some of the less common bacterial infections until detailed sensitivity tests have been carried out, with the result that there is a delay of at least 24 hours in administering the one regarded as most suitable.

This situation occurs particularly often in infections due to *Haemophilus influenzae* (Mulder, 1952). This organism causes both acute infections—for example, meningitis, obstructive laryngo-tracheobronchitis, pneumonia, empyema (Rivers, 1922; Alexander, 1943; Zinnemann, 1947), and also chronic infections with acute exacerbations, such as otitis, sinusitis, and bronchiectasis (Hirsch, 1912; Mulder, 1940; Allison, J. Gordon, and Zinnemann, 1943; Bjuggren and Tunevall, 1952; Tunevall, 1952). It is sensitive in some degree to all antibiotics easily available in this country (M. Gordon and Zinnemann, 1945; Hewitt and Pittman, 1946; Alexander, Leidy, and Redman, 1949).

Few comparative assessments of the more recent antibiotic drugs against *H. influenzae* have been made, and these mostly on a small number of strains (Alexander *et al.*, 1949; Long *et al.*, 1950; McCrumb *et al.*, 1951; Schoenbach *et al.*, 1952). Recently two larger series have been published (Mulder *et al.*, 1952; Tunevall, 1951): see Table I. Mulder *et al.* recorded only the upper and lower limits of the minimal *in-vitro* inhibiting doses for *H. influenzae* as did all authors quoted above, with the exception of Tunevall, whose findings will be discussed in detail later. The results obtained have not led any of the authors to make specific recommendations for the choice of an antibiotic drug in *H. influenzae* infections. The figures of Mulder *et al.*, however, are slightly favourable to chloramphenicol, whereas those of Tunevall suggest aureomycin.

TABLE I.—*Minimum Inhibitory Concentrations of Antibiotics for H. influenzae, Expressed in μg. per ml. of Medium in vitro, as Determined by Various Authors*

| Authors | Penicillin | Streptomycin | Aureomycin | Chloramphenicol | Terramycin | Total No. of Strains Tested |
|---|---|---|---|---|---|---|
| Alexander *et al.* (1949) | N.T. | 1–3 | 0·5–1 | 1 | N.T. | ? |
| Long *et al.* (1950) | ,, | 1·25 | 0·625–2·5 | N.T. | 2·5 | 2 (C) |
| McCrumb *et al.* (1951) | 0·8–10 | 0·8–10 | 0·4–10 | 0·4–5 | 1·7–2·5 | 16 (C) |
| Schoenbach *et al.* (1952) | 0·156–10 | 1·56–3·1 | 0·156–2·5 | 0·156–5 | 0·156–5 | 22 (C) |
| Mulder *et al.* (1952) | 0·35–2·8* | 0·5–8 | N.T. | 0·25–3 | 5·8 | 14–187 (N) |
| Tunevall† (1952) | 0·35–2·8* | 0·25–4 | 0·063–0·5 | 0·063–0·5 | 0·063–0·5 | 21 (C) 42 (N) |

N.T. = Not tested. (C) = Capsulated strains. (N) = Non-capsulated strains.
* Figure arrived at by conversion of Oxford units to micrograms.
† Author records number of strains and percentages inhibited by serial twofold dilutions within the limits quoted in this table.

During our routine determinations of the sensitivity of *H. influenzae* strains to antibiotics the impression was

obtained that chloramphenicol was more effective than the rest. To confirm this impression capsulated and non-capsulated strains of *H. influenzae* isolated from pathological conditions during the period January 1, 1951, to October 30, 1952, and a number of strains of both varieties from similar routine material kindly forwarded by Dr. K. B. Rogers, of the Children's Hospital, Birmingham, were tested by the standard method described below, and the results analysed. The data were collected as strains became available.

*Technique.*—As soon as possible after isolation the strains were inoculated into Levinthal broth and incubated overnight. Four drops of a 1 in 1,000 nutrient-broth dilution of this culture were spread uniformly over the whole surface of each of three heated horse-blood (chocolate) agar plates. With a sterile cork-borer a number of holes were punched at regular intervals in the medium around the edge of the plates. The holes were filled to within about 1 mm. of the rim with the dilutions of the antibiotic drugs. Penicillin was tested by itself on the first plate; streptomycin was paired with aureomycin on the second, and chloramphenicol with terramycin on the third plate. The standard dilutions of antibiotics employed were 1 μg., 2 μg., 5 μg., and 10 μg., except for penicillin. Of the last-named drug 1, 2, 5, and 10 Oxford units (corresponding to 0.61, 1.22, 3.05, and 6.1 μg.) were used. After overnight incubation the plates were read and the results recorded.

*Definitions.*—Some investigators have based their readings on partial, others on complete inhibition (Jackson and Finland, 1951). Results of the two methods arrive at different values. To facilitate comparison with the findings of other workers the results for both methods of reading are given in Tables IV and V. In this investigation the term "partial inhibition" is not based on any measurements of the width of inhibition zones but indicates a marked zone of inhibition of growth around the punch-holes with slight growth still occurring inside the zones and right up to the edge of the punch-holes. The term "complete inhibition" indicates complete absence of growth within the whole or part of the inhibition zone.

## Results

A total of 34 capsulated and 50 non-capsulated strains of *H. influenzae* were investigated. All these strains were isolated from cases in which *H. influenzae* was present as the only or predominant bacterium and in which it appeared that the clinical conditions were related to or aggravated by this organism. Tables II and III give details of the sites from which the strains were isolated and the number of strains isolated from these sites. As was to be expected, the majority of capsulated *H. influenzae* strains were obtained from the cerebrospinal fluid of cases of meningitis in children, and all 21 strains from this site were of type b (Pittman). The possible sources of non-capsulated strains are fairly well represented by the 50 strains investigated. All strains may thus be regarded as unselected.

TABLE II.—*Distribution of 34 Capsulated H. influenzae Strains According to Types and to Sites from which Isolated*

| Site | No. of Type Strains Isolated | | | | | |
|---|---|---|---|---|---|---|
| | a | b | c | d | e | f |
| Cerebrospinal fluid .. | 0 | 21 | 0 | 0 | 0 | 0 |
| Blood culture .. .. | 0 | 2 | 0 | 0 | 0 | 0 |
| Bronchial secretion .. | 0 | 2 | 0 | 0 | 0 | 0 |
| Nasopharynx .. .. | 0 | 2 | 1 | 0 | 1 | 0 |
| Sputum .. .. .. | 0 | 0 | 0 | 1 | 0 | 0 |
| Trachea at necropsy .. | 0 | 0 | 0 | 0 | 2 | 0 |
| Ankle-joint .. .. | 0 | 1 | 0 | 0 | 0 | 0 |
| Conjunctival sac .. | 0 | 1 | 0 | 0 | 0 | 0 |
| Total .. .. | 0 | 29 | 1 | 1 | 3 | 0 |

TABLE III.—*Distribution of 50 Non-capsulated H. influenzae Strains According to Sites from which Isolated*

| Site | No. of Strains Isolated |
|---|---|
| Blood culture .. .. | 3 |
| Bronchial secretion .. | 9 |
| Sputum .. .. .. | 3 |
| Throat .. .. .. | 8 |
| Nose .. .. .. .. | 4 |
| Nasopharynx .. .. | 6 |
| Antrum .. .. .. | 6 |
| Ear .. .. .. .. | 3 |
| Conjunctival sac .. .. | 5 |
| Pleural cavity (empyema) .. | 3 |
| Total .. | 50 |

A more exacting test is the *in-vitro* determination of the concentration of any given antibiotic required to inhibit a micro-organism completely. Table IV shows that in such a test 1 unit per ml. of chloramphenicol inhibits completely one-quarter of the capsulated and two-fifths of the non-capsulated *H. influenzae* strains, while all other antibiotics tested inhibit only 6% or less of all the strains. At a concentration of 2 units per ml. chloramphenicol inhibits one-half of the capsulated and over four-fifths of the non-capsulated strains, while none of the other antibiotics inhibits completely more than roughly one-quarter of the capsulated and one-sixth of the non-capsulated strains. All of the capsulated strains, with one exception, and 100% of the non-capsulated strains are completely inhibited by 5 units per ml. of chloramphenicol, while the most effective of the other antibiotics inhibit only three-quarters of the strains at this concentration. The effective concentrations are naturally lower if partial inhibition is used as the basis to assess antibiotic activity (Table V).

Terramycin and penicillin follow chloramphenicol fairly closely in their *in-vitro* performance against *H. influenzae*, and it would be difficult, on the basis of the figures obtained, to decide which of these two drugs is more active. Streptomycin and aureomycin appear to be roughly equal but less inhibitory than terramycin and penicillin, particularly as judged by the partial inhibition test.

## Discussion

The superiority of chloramphenicol in inhibiting *H. influenzae in vitro* in these investigations is somewhat surprising in view of the absence of similar statements in the not inconsiderable literature on the drugs tested, although chloramphenicol and aureomycin have now been in use for five and terramycin for three years. Clinically, however, infections due to Gram-negative organisms have been reported to respond better to chloramphenicol (McCrumb *et al.*, 1951). Jackson and Finland (1951) drew attention to the fact that determinations of *in-vitro* sensitivity to antibiotics carried out with diverse methods and in the hands of different investigators cannot easily be compared and that the conclusions reached may differ. Such divergencies in tests on *H. influenzae* are shown in Table I. The argument does not seem entirely valid if used against the results reported in this communication, for the following reasons.

Table I, which summarizes the principal papers on the sensitivity of *H. influenzae* to antibiotics, shows that, with the exception of one (Tunevall), the authors have confined themselves to indicating the upper and lower limits of the minimal inhibiting doses of the antibiotics investigated. In the results here reported the figures have been analysed in such a way as to record the number of strains of *H. influenzae* inhibited at four concentrations of five different antibiotics. This method of tabulating results is better suited to stressing the superiority of one or the other of the drugs investigated. Results similar to the ones reported here have been obtained by an independent observer (W. Goldie, personal communication, 1952). However, Tunevall (1952) recorded his findings in a way closely resembling the one used in this communication. In his Table I there is a suggestion of a slight superiority of aureomycin over chloramphenicol, although in his conclusions the author regards the two drugs as equally effective. The explanation for the divergence between the two sets of experiments may perhaps be found in the different

techniques used, as Jackson and Finland (1951) suggested. Tunevall incorporated the antibiotics in serial twofold dilutions in a solid medium, which was then inoculated with the strains to be tested, while the present findings are based on the punch-plate technique.

As a rule determinations of sensitivity carried out in fluid media or with the antibiotic incorporated in a solid medium tend to give lower values than those obtained with the punch-plate method. It may be inferred from this fact that the actual inhibitory concentrations of all antibiotics tested in the way here described are lower than appears from the findings recorded. However, the order of effectiveness should not be influenced by lower readings.

Ease of administration favours the so-called broad spectrum antibiotics, but side-effects such as gastro-intestinal irritation may sometimes make their administration difficult if not impossible, quite apart from the uncertainty about the doses given if vomiting occurs. In practice, blood concentrations of penicillin high enough to inhibit most or all *H. influenzae* strains are difficult if not impossible to achieve and to maintain, although such concentrations can be obtained easily in the C.S.F. by intrathecal injection. On the other hand, therapeutically effective blood concentrations of the order of 5 to 10 μg. are the rule with usual oral doses of chloramphenicol, aureomycin, and terramycin, or with intramuscular doses of streptomycin (Zintel *et al.*, 1945; Ehrlich, 1947; Dowling *et al.*, 1948; Glazko *et al.*, 1949; Welch, 1950; Eads *et al.*, 1952). It is evident, therefore, that the quite impressive *in-vitro* performance of penicillin is not likely to be equalled by its performance in clinical infections due to *H. influenzae*, except in some conditions, such as meningitis (Zinnemann, 1946) or empyema, where a high concentration of the drug can be applied locally. This circumstance still further emphasizes the value of chloramphenicol in *H. influenzae* infections, with terramycin as a good second best. Aureomycin is a difficult drug to assess in *in-vitro* experiments, as up to 50% of its activity may be lost during incubation at 37° C. (Chandler and Bliss, 1948). It is possible, therefore, that the *in-vivo* activity of aureomycin against *H. influenzae* is greater than is suggested by the *in-vitro* results given in Tables IV and V. However, observations on patients with chronic infections due to *H. influenzae* (Allibone, 1953, personal communication) seem to agree well with the *in-vitro* results reported here, the order of *in-vivo* effectiveness being chloramphenicol, terramycin, and aureomycin. It must be stressed, though, that *in-vitro* sensitivities to antibiotics do not necessarily permit conclusions on the effectiveness of these drugs *in vivo* in spite of good agreement in this series.

In view of the greater inhibitory action of chloramphenicol on *H. influenzae* it is unfortunate that this drug is claimed to cause aplastic anaemia and related blood dyscrasias (Volini, *et al.*, 1950; Gill, 1950; Smiley *et al.*, 1952). Sturgeon, 1952; Rheingold *et al.*, 1952; Hawkins and Lederer, 1952; Wolman, 1952; Hargraves *et al.*, 1952). Probably no great harm will be done if chloramphenicol is used for one short course of a few days' duration. Repeated or prolonged administration seems to be the common feature of most of the cases of blood dyscrasias reported hitherto, though a few cases have been described with granulocytopenia following one short course of the drug (Gill, 1950; Volini *et al.*, 1950). Hargraves *et al.* (1952) attribute the deaths from aplastic anaemia of two of the cases reported by them to comparatively small doses of chloramphenicol, but there is an element of doubt in the history of administration of the drug.

Thus it would appear that the antibiotic having the best *in-vitro* and *in-vivo* inhibitory action against *H. influenzae* may have limitations in practical application. More evidence for or against the prolonged or intermittent administration of chloramphenicol is required to assess its value in the therapy of chronic infections due to *H. influenzae*.

## Summary

The *in-vitro* antibiotic action of penicillin, streptomycin, aureomycin, chloramphenicol, and terramycin on 34 capsulated and 50 non-capsulated *H. influenzae* strains has been tested at four concentrations. The punch-plate method was used for these sensitivity tests.

Chloramphenicol is the only one of the antibiotics tested which is capable of inhibiting 100% of the strains investigated at the comparatively low concentrations

TABLE IV: COMPLETE INHIBITION.—*In-vitro Sensitivity of H. influenzae Strains to Antibiotics. Punch-plate Method on Heated Blood (Chocolate) Agar Plates; Units/ml. = Oxford Units in the Case of Penicillin and μg. in the Case of All Other Antibiotics*

| Antibiotic Drug | Capsulated Strains | | | | | Non-capsulated Strains | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. and Percentage of Strains Inhibited by Units/ml. | | | | Total No. of Strains Tested | No. and Percentage of Strains Inhibited by Units/ml. | | | | Total No. of Strains Tested |
| | 1 | 2 | 5 | 10 | | 1 | 2 | 5 | 10 | |
| Penicillin .. | 0 | 8 (23·5%) | 17 (73·5%) | 9 (100%) | 34 | 3 (6%) | 3 (12%) | 29 (70%) | 14 (*1*) (98%) | 50 |
| Streptomycin .. | 1 (2·9%) | 3 (11·8%) | 16 (58·8%) | 11 (*3*) (91·1%) | | 1 (2%) | 7 (16%) | 26 (68%) | 10 (*6*) (88%) | |
| Aureomycin .. | 1 (2·9%) | 3 (11·8%) | 10 (41·2%) | 13 (*7*) (79·4%) | | 2 (4%) | 1 (6%) | 17 (40%) | 24 (*6*) (88%) | |
| Chloramphenicol | 8 (23·5%) | 9 (50·0%) | 16 (97·0%) | 1 (100%) | | 20 (40%) | 22 (84%) | 8 (100%) | — | |
| Terramycin .. | 0 | 1 (3·0%) | 23 (72·7%) | 7 (*2*) (93·9%) | 33 | 1 (2%) | 3 (8%) | 33 (74%) | 12 (*1*) (98%) | |

Figures in parentheses indicate number of strains not inhibited by 10 units/ml.
Plain figures indicate absolute number of strains inhibited by a particular concentration of a particular antibiotic; percentage figures indicate proportion of *all strains* inhibited by a particular concentration of antibiotic drug.

TABLE V: PARTIAL INHIBITION.—*In-vitro Sensitivity of H. influenzae Strains to Antibiotics. Punch-plate Method on Heated Blood (Chocolate) Agar Plates; Units/ml. = Oxford Units in the Case of Penicillin and μg. in the Case of All Other Antibiotics*

| Antibiotic Drug | Capsulated Strains | | | | | Non-capsulated Strains | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. and Percentage of Strains Inhibited by Units/ml. | | | | Total No. of Strains Tested | No. and Percentage of Strains Inhibited by Units/ml. | | | | Total No. of Strains Tested |
| | 1 | 2 | 5 | 10 | | 1 | 2 | 5 | 10 | |
| Penicillin .. | 8 (*3*) (23·5%) | 15 (76·5%) | 8 (100%) | — | 34 | 5 (*1*) [*3*] (10%) | 21 (*8*) (54%) | 13 (*1*) (96%) | 1 (100%) | 50 |
| Streptomycin | 3 [*1*] (8·8%) | 14 (*3*) (50.0%) | 10 (*1*) (79·4%) | 2 (97·0%) | | 5 (*3*) [*1*] (10%) | 21 (*5*) (58%) | 9 (*1*) (86%) | 3 (94%) | |
| Aureomycin | 4 (*1*) [*1*] (11·8%) | 9 (41·2%) | 13 (79·4%) | 5 (94·1%) | | 3 [*2*] (6%) | 17 (40%) | 24 (88%) | 5 (98%) | |
| Chloramphenicol .. | 17 [*8*] (50·0%) | 15 (*1*) (94·1%) | 1 (100%) | — | | 41 (*1*) [*20*] (82%) | 8 (100%) | — | — | |
| Terramycin.. | 2 [*1*] (6·1%) | 18 (*4*) (60·6%) | 7 (93·9%) | 2 (100%) | 33 | 4 [*1*] (8%) | 31 (*2*) (70%) | 12 (98%) | 1 (100%) | |

Figures in parentheses = number of strains partially not inhibited at given but completely inhibited at next higher concentration.
Figures in square brackets = number of strains not tested at < 1 unit/ml.
Plain figures indicate absolute number of strains inhibited by a particular concentration of a particular antibiotic; percentage figures indicate proportion of *all strains* inhibited by a particular concentration of antibiotic.

obtained with the usually recommended therapeutic doses. Terramycin comes next in order of effectiveness, followed by streptomycin and aureomycin. Penicillin *in vitro* is as effective as chloramphenicol and terramycin, or even better, on a weight-for-weight basis, but blood concentrations within the effective range are difficult to obtain and maintain.

Deterioration of aureomycin at 37° C. may be responsible for the comparatively low rating of the drug, but clinical impressions in chronic *H. influenzae* infections also suggest the superiority of chloramphenicol.

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The Home Office has recently issued the report of the Commissioners of Prisons for 1952 (Cmd. 8948). It deals with the administration of prisons; statistics of the prison population; the treatment, training, and after-care of prisoners; Borstal training; detention centres; and the health of prisoners. In spite of the serious overcrowding in the prisons, there was no epidemic of infectious disease last year, and even the usual outbreaks of influenza in the early months were conspicuously absent at most establishments. Indeed, the director of medical services notes, as an interesting observation, that during past influenza epidemics, where three men have shared a cell and one has developed the disease, the infection not infrequently has spread to men in neighbouring cells, while others in the original cell may escape it altogether. However, the potential risk to health consequent on overcrowding is constantly in the minds of the prison medical officers. In August, 1952, the first detention centre for boys of 14 to 17 years was opened, and the medical officer reports that the training there has had a beneficial effect on the physique and health of the boys admitted. The idea of the centre is to provide an alternative to prison for young offenders who do not need prolonged Borstal training yet are unlikely to respond to probation.

# THE PROGNOSIS AND ROLE OF SURGERY IN SPONTANEOUS INTRACRANIAL HAEMORRHAGE

BY

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A balanced understanding of the diagnosis and treatment at present available for spontaneous intracranial haemorrhage is extremely important, and this paper presents on the one hand our experience and on the other our considered opinion regarding the treatment of this condition. The term "spontaneous intracranial haemorrhage" is used rather than "subarachnoid haemorrhage," as the major portion of the bleeding may be at any site from the subdural space to the ventricle. Apoplexy in the elderly arteriosclerotic, so classical in its clinical manifestations, is not included.

## Prognosis

The prognosis in cases treated conservatively has been reviewed many times in the past few years, and there is no doubt that the initial mortality rate is about 50%, rising with recurrent episodes and in older patients. In our assessment our first consideration was a series of 100 consecutive cases managed conservatively by one of us from 1936 until 1951. Conservative care means rest in bed for at least one month, care of the bowels, sedation, and the judicious use of lumbar puncture. In these 100 cases, 53 female and 47 male, there were 43 deaths during the initial period in hospital. Although these 43 deaths occurred at any time up to six weeks after the onset of haemorrhage, one third (14 cases) occurred in the first 24 hours and another third (15 cases) in the second week. Excluding the first day there were only eight deaths in the first week, and six patients died in the second to sixth weeks. Fairly clear evidence of recurrent bleeding was present in half the patients dying during the first and second weeks and in all those dying after the close of the second week. All the 57 survivors have been traced. Eight of them have died from recurrence of intracranial haemorrhage and two others of intercurrent disease. Twenty of them have been left with some permanent neurological disability, although only seven are completely disabled by hemiplegia or intellectual loss. Of the eight late deaths from recurrence only two have been in the disabled group; the other six have occurred in those who had made a complete recovery from the initial haemorrhage. The deaths have occurred after an interval of time up to 12 years from the initial episode. Four died of a single recurrence, but four others of a second, third, or fourth haemorrhage. Before considering the way in which surgical investigation and treatment may improve both the mortality and