SULPHONAMIDE SENSITIVITY OF H. INFLUENZAE STRAINS

WITH SPECIAL REFERENCE TO THE COMBINED USE OF ANTIBACTERIAL DRUGS

BY

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It is now a commonly acknowledged therapeutic principle, as soon as treatment is begun, to use maximal doses of sulphonamides and of antibiotics to avoid, so far as is possible, the development of drug resistance in the infecting micro-organism. Nevertheless, the incidence of resistant strains has of late been commented upon and reported more frequently.

Haemophilus influenzae (Pfeiffer's bacillus) is sensitive to a comparatively wide range of sulphonamides and antibiotics, but it is also capable of developing strains resistant to the action of some of these drugs. It is therefore a suitable bacterium for the study of the antibacterial action of these preparations, and any theoretical and practical considerations arising from the study of its behaviour and of infections caused by it may be applicable to other pathogenic micro-organisms with a similar range of sensitivity.

Effects of Combination of Antibacterial Drugs

When two antibacterial drugs, each attacking bacterial populations in a different way, are allowed to act on the same bacterial culture the observed increase in the degree of sensitivity is exponential—that is, the effect of two or even more drugs is considerably greater than could be expected from the added values of the effects of each drug separately (Ungar, 1943; Thomas and Hayes, 1947; Mayr-Harting and Katscher, personal communication). This synergistic action is also well marked in strains resistant to penicillin when this antibiotic is combined with one of the sulphonamides (Chain and Duthie, 1945). Another principle involved, along with its bearing on clinical considerations with regard to the development of drug-resistant strains, has been stated very lucidly by Demerec (1948) as follows: "Theoretically, the most effective way of preventing the origin of resistant strains of bacteria is the use in clinical treatment of a mixture of two antibiotics, when such are available, that affect the same pathogen but are independent in their actions. The evidence of independence is that bacterial strains that have developed resistance to one antibiotic are still sensitive to the other, and vice versa. If such a mixture of two antibiotics is used, then only bacteria that are resistant to both can survive the treatment and form . . . resistant strains. Such bacteria would be exceedingly rare." It might be added that they would be rarer still if a third antibacterial drug with similar potency and mutation rate were employed.

Corresponding in vivo and Clinical Observations

American authors have produced *in vivo* experimental evidence showing that combination of the more effective sulphonamides with type-specific rabbit antiserum results not merely in an additive but in a synergistic effect (Pittman, 1942; Alexander and Leidy, 1943).

TABLE I.—*Clinical Results with Treatment of Various Combinations of Sulphonamides, Antiserum, and Antibiotics by Different Authors*

Author	Treatment				
	Sulphonamides	Serum	Penicillin	Streptomycin	Recovery Rate
Alexander *et al.* (1946b)	+	+	0	+	6/8
" "	0	+	0	+	3/3
" "	0	0	0	+	12/14
Zinnemann (1946)	+	0	+	0	8/15
Weinstein (1946)	0	0	0	+	7/9
Birmingham *et al.* (1946)	0	0	0	+	4/8
Logan and Herrell (1946)	+	+	0	+	3/4
Thomson *et al.* (1947)	+	0	+	0	3/4
Gottlieb *et al.* (1947)	+	0	+	0	3/4
Engbaek (1948)	+	+	0	+	6/7
Hoyne and Brown (1948)	+	0	0	+	26/28
Roscoe and Gleeson-White (1948)	0	0	0	+	3/4
Smythe (1948)	0	0	0	+	9/12
Kass (1948)	0	0	0	+	7/8
Braid and Meyer (1949)	+	0	+	0	8/11
" "	+	0	+	+	3/3
" "	+	0	0	+	1/1
Ounsted (1949)	+	0	0	+	12/13
Yampolsky and Jones (1949)	+	+	0	+	0/2
" "	+	0	0	+	19/20

Good therapeutic results have also been reported in larger series of cases treated with penicillin or streptomycin, either alone or in combination with sulphonamides or antiserum (see Table I).

The relapses frequently observed (Alexander, 1943; Zinnemann, 1946) after apparently successful treatment of *H. influenzae* meningitis seem to indicate not only survival of Pfeiffer's bacillus in inaccessible recesses of the cerebrospinal canal but possibly also the development of a strain of higher resistance to the particular form of treatment. Emergence of highly resistant strains in the case of streptomycin-treated patients has been demonstrated conclusively by a number of workers (Birmingham *et al.*, 1946; Alexander *et al.*, 1946b; Smythe, 1948; Roscoe and Gleeson-White, 1948).

At present we have at our disposal four clinically well tried substances attacking *H. influenzae*, each acting in a different way. These are: (1) Type-b-specific *H. influenzae* rabbit antiserum, which enters into an antigen–antibody reaction with the polysaccharides of the bacterial capsule. (2) Sulphonamides. It is claimed that they interfere with the intermediary metabolism of the bacterial cell by blocking the assimilation of para-aminobenzoic acid (Woods, 1940). (3) Penicillin, which acts on growing sensitive bacteria by preventing their multiplication (Garrod, 1945), possibly by blocking the passage of glutamic acid through the cell wall into the bacterial cell (Gale and Taylor, 1947). (4) Streptomycin, the mechanism of which is as yet little understood, but which has a rapid bactericidal action as distinct from the slower bacteriostatic and bactericidal effect of penicillin (Garrod, 1948; Alexander and Leidy, 1949). Another pointer to its possible mode of action is the interference of anaerobic conditions or of reducing agents with the antibacterial action of streptomycin (Bondi *et al.*, 1946). At a later date the newer antibiotics chloramphenicol and "aureomycin" may also be useful. These drugs are reported to evoke a pattern of development of resistance similar to that produced by penicillin (Alexander and Leidy, 1949; Demerec, 1949).

According to the foregoing considerations none of the earlier remedies successfully tried in severe *H. influenzae* infections has become obsolete in consequence of subsequent developments. There is every reason to suppose that the combination of therapeutic doses of sulphonamides, penicillin, and streptomycin—the first administered systemically and the other two both systemically and locally—is able to control any acute *H. influenzae* infection. It will, in the first instance, achieve speedy sterilization

of the affected organs or body fluids—a most useful characteristic of the action of streptomycin—while, secondly, it will at the same time prevent the high rate of drug-resistant strains observed in streptomycin-treated cases. If type-specific *H. influenzae* rabbit antiserum is also used its neutralizing action on the bacterial polysaccharide freely circulating in the blood and present in the cerebrospinal fluid will help the patient more rapidly to overcome a state of toxaemia, while the action of antiserum on the bacterial capsule is likely further to damage the invading micro-organisms. With regard to possible future developments, one has to keep in mind that a marked antagonistic action of some of the newer antibiotics on each other has been demonstrated recently when tested together against certain Gram-negative micro-organisms (Price *et al.*, 1949).

In practice three of the agents available—sulphadiazine, streptomycin, and penicillin or type-specific rabbit antiserum—have already been used simultaneously with good results as judged by the small number of cases (see Table I). Some experimental findings of Alexander and Leidy (1946) seemed to suggest that sulphonamides are incapable of enhancing the bactericidal effect of streptomycin. Potentiation of streptomycin by sulphonamides would not necessarily reveal itself under the experimental conditions used by these authors. This latter interpretation of their findings is supported by later papers recommending the combination of sulphadiazine, streptomycin, and type-specific rabbit antiserum in severe subacute cases and in children under 7 months of age (Alexander and Leidy, 1947, 1949).

Experimental Observations on Sulphonamide Sensitivity

It is likely, therefore, that for some time to come the sulphonamides will still have their value in the treatment of *H. influenzae* infections and in particular in *H. influenzae* meningitis. In view of a number of clinical reports mentioning resistance of some *H. influenzae* strains to one or the other sulphonamide (Pittman, 1942; McIntosh and Drysdale, 1945; Drysdale, McIntosh, and Brodie, 1946; Gottlieb, Forsyth, and Allott, 1947; Thomson, Bruce, and Green, 1947; Martin and Sureau, 1948) it seemed of practical importance to investigate this phenomenon *in vitro* in a greater number of strains than had been examined hitherto. Guyton (1940) had examined two strains for sulphonamide sensitivity, Pittman (1942) had noticed a variation in susceptibility to the same compound in some of six strains tested, and Alexander and Leidy (1943) in their inquiry into the synergistic effect of the various sulphonamides and rabbit antiserum had used only one strain.

Materials

Strains.—A collection of 50 capsulated and 50 non-capsulated strains of *H. influenzae* was investigated. The first group comprised 5 type a strains, 35 type b strains, one type c strain, three type d strains, one type e strain and three strains related to type e, and, finally, two type f strains. The majority of these strains had been isolated from cases of *H. influenzae* meningitis, some were originally found in the nasopharynx of children, the rarer types were stock strains kept for reference purposes, and four type b strains were obtained from the National Collection of Type Cultures. Twenty-four of the non-capsulated strains were isolated from pernasal swabs of children suspected of whooping-cough, two strains from the cerebrospinal fluid of cases of *H. influenzae* meningitis, two strains from antral washings, one from an eye swab, and the remainder from bronchial secretions and sputa.

Medium.—When choosing a nutrient medium in which to test sulphonamide sensitivity attention has to be paid to substances inhibiting the action of sulphonamides and known to be present in most media incorporating peptone. Neutralization of these inhibiting substances can be achieved by treatment with 5% horse blood (Harper and Cawston, 1945; Walker *et al.*, 1947). A Levinthal agar modified with this point in view was used. Ten per cent. oxalated horse blood was added to nutrient broth and incubated overnight at 37° C. On the next day this fresh horse-blood broth was used for making Pittman's (1931) modification of Levinthal agar, which was then poured into plates.

Technique.—The tests of sensitivity to the various sulphonamides were carried out on Levinthal-agar plates in two different ways. (1) By incorporating a suitable concentration of the sulphonamides into Levinthal-agar plates. Seven plates were necessary for each test, one for each sulphonamide, and a maximum of eight inoculations were placed on each plate. In this way seven *H. influenzae* strains and one other control culture—*Staphylococcus aureus* as a rule—could be tested in one experiment. (2) By the punch-plate method. Seven punch-holes in a single Levinthal-agar plate were filled with a solution of the seven different sulphonamides after the plate had been inoculated previously with a suitable dilution—1 in 100 or 1 in 1,000—of a 24-hour Levinthal broth culture of the *H. influenzae* strain under investigation.

The two techniques were applied to the same strains simultaneously, seven *H. influenzae* strains being tested against seven sulphonamides at a time.

The following sulphonamides were tested: sulphanilamide (henceforth abbreviated SA); sulphapyridine (SP); sulphathiazole (ST); sulphadiazine (SD); sulphadimidine, also known as "sulphamezathine" (SMZ); 2-(*p*-aminobenzenesulphamido)-4-methylpyrimidine, also known as sulphamerazine (SMR); and maphenide (MAPH) (4-aminomethylbenzenesulphonamide), also known as "marfanil" or "ambamide." The concentration tested was that corresponding approximately to the concentration obtained in the blood by the usually recommended dosages—that is, 10 mg. per 100 ml. This concentration was adopted for all seven sulphonamides. The readily soluble substances—SA and MAPH—were used as such to prepare solutions, while the more easily soluble sodium salts of the remaining five compounds were employed to make up stock solutions. All solutions were sterilized by filtration.

Results

Table II summarizes the results obtained with 50 capsulated strains tested by incorporating the sulphonamides in the medium. From 10 to 24% of the strains were completely inhibited. The majority of the strains were either markedly or slightly inhibited. One strain, the same in each instance, was resistant to 10 mg. per 100 ml. of

TABLE II.—*Capsulated Smooth H. influenzae Strains on Modified 10 mg. per 100 ml. Levinthal Agar*

Sulphonamide Tested	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
SA	13	32	5
SP	2	41	7
ST	0	38	12
SD	1	39	10
SMZ	1	41	8
SMR	1	41	8
MAPH	13	28	9

SA—sulphanilamide; SP—sulphapyridine; ST—sulphathiazole; SD—sulphadiazine; SMZ—sulphamezathine; SMR—sulphamerazine; MAPH—maphenide.

all sulphonamides except ST, by which it was inhibited to a marked degree. The considerable number of strains insensitive to both SA and MAPH is remarkable, though perhaps not altogether surprising. There can be no doubt that with this technique ST is the most effective drug.

TABLE III.—*Capsulated Smooth H. influenzae Strains on Modified Levinthal Agar, Punch-plate Method*

Sulphonamide Tested	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
SA	37	12	1
SP	6	37	7
ST	3	34	13
SD	4	36	10
SMZ	5	35	10
SMR	4	33	13
MAPH	32	18	0

Table III gives the results obtained with the same strains tested by the punch-plate method. When compared with Table II a general shift is noticeable from right to left. This is particularly evident with strains completely inhibited by SA and MAPH and less so with strains inhibited by the other sulphonamides. However, when the markedly inhibited and partially insensitive strains are considered the shift becomes more pronounced. The obvious interpretation of this shift is that the punch-plate method is less sensitive and therefore less accurate than the method incorporating sulphonamide compounds into the medium. In Table III, as in Table II, ST appears to be the most potent sulphonamide.

TABLE IV.—*Non-capsulated Rough H. influenzae Strains on Modified 10 mg. per 100 ml. Sulphonamide Levinthal Agar*

Sulphonamide Tested	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
SA	6	34	10
SP	2	31	17
ST	2	23	25
SD	1	34	15
SMZ	2	37	11
SMR	2	35	13
MAPH	5	32	13

TABLE V.—*Non-capsulated Rough H. influenzae Strains on Modified Levinthal Agar, Punch-plate Method*

Sulphonamide Tested	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
SA	32	16	2
SP	6	36	8
ST	3	32	15
SD	4	32	14
SMZ	5	32	13
SMR	5	33	12
MAPH	42	8	0

Tables IV and V show the results obtained when non-capsulated strains are tested with the same techniques. Here, too, ST is the most effective compound, although in this group of strains there are two which are completely insensitive to ST. On the whole, the figures for completely and partially inhibited strains are higher than those obtained with capsulated strains. In other words, more non-capsulated respiratory strains are effectively controlled by sulphonamides than capsulated strains. On clinical grounds it had been suspected earlier that differences in sulphonamide sensitivity might exist between capsulated and non-capsulated strains of *H. influenzae* (Gordon, Woodcock, and Zinnemann, 1944). This suggestion appears now to be confirmed by *in vitro* tests.

In these experiments the same strain was usually resistant to many or all sulphonamides, but occasionally a strain was found which was resistant to only one or two sulphonamides. This resistance, however, is relative in so far as in these tests sensitivity to only one concentration, the one easily attainable in the serum, has been investigated. With few exceptions resistant strains showed some degree of sensitivity to ST. It might seem, therefore, that ST should be the sulphonamide of choice in *H. influenzae* infections. Unfortunately, however, only a small fraction of ST as compared with other sulphonamides appears in the C.S.F. As Table VI shows, the level in the C.S.F. of the sulphonamide least effective with regard to *H. influenzae*—that is, SA—is equal to the blood level, while the level of the most effective sulphonamide *in vitro*—that is, ST—is lowest. In the case of SD, SMZ, and SMR, which are nearly as effective as ST, about half to three-quarters of the blood level is reached in the C.S.F.

TABLE VI.—*Concentrations of the Various Sulphonamides in the C.S.F. in Relation to the Blood Levels*

Sulphonamide	Sulphonamide in C.S.F. as Compared with Blood Level	Authors
SA	Approximately 100%	Marshall *et al.* (1937); Allott (1938)
SP	60–80%	Hobson and MacQuaide (1938); Long and Feinstone (1938)
ST	20–30%	Banks (1941); Andersen and Simesen (1943)
SD	50–80%	Long (1941)
SMZ	60–80%	Kremer *et al.* (1945); Rose *et al.* (1943); Macartney *et al.* (1942)
SMR	50–75%	Hageman *et al.* (1943); Murphy *et al.* (1943)

On the basis of the present investigations it would seem that ST is best suited for *H. influenzae* infections other than meningitis. However, ST should not be dismissed altogether from the treatment of *H. influenzae* meningitis, for this infection is often accompanied by septicaemia (Smith, Wilson, and Hodes, 1946).

When the above facts had become evident it was thought that a combination of the most effective sulphonamides should be tested against a similar series of *H. influenzae* strains. A combination of three sulphonamides is available as "sulphatriad" (S3), and includes 37% ST, 37% SD, and 26% SMR. The original recommendation of this or similar combinations by Frisk *et al.* (1947), Lehr (1947), and Martin and Sureau (1948) was made in order to obtain a higher total blood level and/or to avoid renal complications. As these considerations are of some importance in severe *H. influenzae* meningitis cases receiving maximal doses of sulphonamides over longer periods, the reasons for testing a mixture of sulphonamides seemed to be all the more compelling.

Accordingly a stock solution was made of the sodium salts of ST, SD, and SMR in the proportions in which they are present in commercial S3. The total of sulphonamides of the stock solutions was adjusted to give a final concentration of 10 mg. per 100 ml. This concentration was then tested in the same way and, so far as possible, with the same strains as the seven sulphonamides in the preceding experiments. Nine of the capsulated and eleven of the non-capsulated strains had to be replaced by others, as they had been lost accidentally.

TABLE VII.—*Sensitivity of Capsulated H. influenzae Strains to 10 mg. per 100 ml. of S3 on Modified Levinthal Agar*

Technique of Test	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
S3 incorporated in medium	0	27	23
Punch-plate method	3	19	28

TABLE VIII.—*Sensitivity of Non-capsulated Rough H. Influenzae Strains to 10 mg. per 100 ml. of S3 on Modified Levinthal Agar*

Technique of Test	Insensitive Strains	Partially Sensitive and Markedly Inhibited Strains	Completely Inhibited Strains
S3 incorporated in medium	0	23	27
Punch-plate method	0	35	15

The results for capsulated *H. influenzae* strains recorded in Table VII suggest that S3 is at least equal to if not more effective than the single sulphonamides which it contains. In this particular instance the punch-plate method seems a more sensitive test than incorporation of the drug in the medium. No explanation is offered for this phenomenon, which is the opposite of that observed in the preceding series and the one following. The behaviour of non-capsulated strains, as shown in Table VIII, indicates a high degree of sensitivity to S3, no insensitive strain having been encountered by either method of testing. Tables VII and VIII are not strictly comparable to Tables II–V, as not all strains in the two sets of tables are identical. Yet, judging by the width of the zones of inhibition in the series using the punch-plate technique the majority of *H. influenzae* strains, both capsulated and non-capsulated, seem to be more sensitive to S3 than to any of the sulphonamides singly. Here again more non-capsulated strains are sensitive to S3 than capsulated ones.

Discussion

On the one hand, these experiments establish on a broad basis the bactericidal and bacteriostatic action of sulphonamides on *H. influenzae*, thus indicating their usefulness in combined chemotherapy. On the other hand, strains occur which are not inhibited by the standard concentration of SD. In such cases the recommendations of Alexander and Leidy (1943) with regard to SD are not applicable. The results presented here point to the necessity for testing each individual strain isolated from a clinical case for its sensitivity to a standard concentration of 10 mg. per 100 ml. of at least the following sulphonamides: ST, SD, SMZ, SMR, S3, and possibly MAPH. The simplest method is the punch-plate technique. It can be employed quite efficiently for daily routine purposes so long as one keeps in mind that a strain completely insensitive by this method may yet show sensitivity when the sulphonamides are incorporated in the medium and that a repetition of the test with this more complicated technique may therefore be necessary. A further advantage of the punch-plate technique is the ease with which potentially resistant strains can be discovered. Such strains show single colonies of normal size in the area of inhibition surrounding the punch-hole. Subcultures from such colonies yield strains of comparatively high resistance to sulphonamides. This phenomenon has been noticed in several of the strains tested. The observation seems to confirm the theory of progressive selection of *H. influenzae* strains resistant to sulphonamides.

The preparation of modified Levinthal agar may be somewhat difficult in certain circumstances. For this reason chocolate-agar plates prepared for routine purposes with oxalated horse blood were used in parallel with Levinthal-agar plates in all experiments described above in which the punch-plate technique was employed. The readings were as a rule less sensitive than those with the punch-hole technique on Levinthal-agar plates.

Summary

The recent literature on resistance to antibacterial drugs and on the combined use of these drugs has been reviewed.

The sensitivity to the various sulphonamides of 50 capsulated and an equal number of non-capsulated *H. influenzae* strains was tested with two different techniques on modified Levinthal agar.

In a concentration of 10 mg. per 100 ml. sulphathiazole is the most effective drug *in vitro*, almost equalled by sulphadiazine, sulphadimidine, and sulphamerazine. Sulphatriad seems to be more effective than any of its constituent sulphonamides alone.

Non-capsulated strains of *H. influenzae* show a higher *in vitro* sensitivity to sulphonamides than capsulated strains.

Individual strains of *H. influenzae* may be sensitive to the standard concentration of one sulphonamide and resistant to that of others. Strains may occur which are insensitive to the standard concentration of sulphadiazine. It is necessary, therefore, to test each strain from individual clinical cases for sulphonamide sensitivities.

Advantages and disadvantages of the bacteriological techniques employed are discussed and recommendations are made.

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CHRONIC ADHESIVE SPINAL MENINGITIS ASSOCIATED WITH LUMBAR NAEVUS AND DIMPLE

BY

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Chronic meningitis confined to the spinal theca has been described frequently during the last fifty years ; it has been known by various synonyms—arachnitis adhesiva circumscripta, arachnoïdite cloisonnée, arachnoid cysts, circumscribed serous spinal meningitis, and chronic spinal meningitis.

The aetiology of the condition is obscure in most cases : Ford (1945) states that it may follow various types of meningitis, spinal analgesia, and, in the opinion of most authorities, trauma to the spine. The reason for this obscurity seems to be that chronic spinal meningitis is usually the end-result of a previously unrecognized inflammatory process, and there is a clearly defined picture in the later stages only, either clinically or at operation or necropsy.

The subject has been reviewed by Horsley (1909), Mauss and Krüger (1918), Elkington (1936), and Rocovich (1947) ; but these authors do not mention congenital dermal sinuses as an important cause of chronic spinal meningitis. Mallory (1892) described coccygeal sinuses and cysts without meningeal or spinal cord involvement, and discussed their pathogenesis, with particular reference to abnormal foetal development.

Moise (1926) states that the sacro-lumbar region is a common site for developmental anomalies, among which are included congenital dimples, sinuses, cysts, and tumours. These cysts and tumours may be dermoid or epidermoid (List, 1941). There is only occasionally a connexion between the spinal canal and the skin surface. Also there may be instances of spina bifida, with all gradations from an unnoticed spina bifida occulta with no evidence of an external defect to a fusion of the spinal cord with the integument. The cases showing a connexion between the spinal canal and the exterior do not as a rule survive infancy. Moise was the first to report a case of meningitis (*Staphylococcus albus*) secondary to a congenital dermal sinus ; there were no symptoms until the age of 18 ; there was spina bifida and a direct connexion between the skin and the spinal cord, and the patient recovered after laminectomy with drainage.

Ripley and Thompson (1928) described a case of *Staph. albus* meningitis in which a pilonidal sinus was the route of infection. Walker and Bucy (1934) reported seven cases in which a congenital dermal sinus, appearing externally as a small dimple in the midline of the back, had become infected (two with *Staph. albus*) ; all the cases but one were associated with spina bifida occulta.

Other cases have been recorded by Stammers (1938), Boldrey and Elvidge (1939), List (1941), and Tizard (1950). O'Connell's case (1942), that of a child aged 4, had a lumbosacral port-wine stain and a small central pit extruding sebaceous material on pressure ; this was complicated by recurring attacks of meningitis (coliform organisms) from the age of 8 months ; the sinus was traced through a lumbar spina bifida to a large intradural abscess lying among the roots of the cauda equina.

Intramedullary abscess of the spinal cord complicating congenital dermal sinuses has been recorded by Kooistra (1942) and Shenkin and others (1944). Mount (1949) has been the first to describe a case with intracranial abscess as a similar complication.

The following case is reported because the causation of the condition and the route of infection raise some interesting problems, and because in several features it resembles previously reported cases, especially that of O'Connell.

Case Report

A girl aged 9 had backache for two weeks in 1947. In February, 1948, she again had severe backache, low in position, with delirium and pyrexia for one week, and was admitted to a hospital near her home.

Her own and her family history revealed nothing relevant. She was pale and thin ; the posterior cervical and inguinal lymph nodes were enlarged ; and flexion of the left hip with straight leg raising was limited. The white cells numbered 5,000 per c.mm. (neutrophils 39%), the E.S.R. (Wintrobe) was 7 mm. in one hour, and the Mantoux test (1 in 1,000) was negative. Her temperature and pulse became normal within three weeks ; she received only sedatives.

In March, 1948, recrudescence of pain in the back and fever led to her readmission to the local hospital. There was limited mobility of the lumbar spine with spasm of the erector spinae. Swelling of joints, nodules, and skin rashes were absent ; the white cells numbered 9,000 per c.mm. (neutrophils 50%), the E.S.R. (Wintrobe) was 19 mm. in one hour, the blood Wassermann reaction was negative, and blood culture was negative. Radiography showed spina bifida of the eleventh thoracic, fourth and fifth lumbar, and first sacral vertebrae. A tentative diagnosis of rheumatic fever was then made. She was kept flat in bed for four months and was in hospital for eight months ; she was given salicylates and phenobarbitone.

In December, 1948, pain in the back and right lower limb and pyrexia reappeared.

In March, 1949, she was admitted to Great Ormond Street. She was miserable and wasted generally ; there was a circular brown pigmented naevus about 2.5 cm. in diameter with a shallow dimple or pit about 3 mm. in diameter over the lumbar spine. Walking was painful and difficult. Sitting with her knees fully flexed was the position she adopted in bed. There was no neck rigidity. In the upper and lower limbs muscular development, tone, and power were poor and impaired equally with the rest of the body and on the two sides. There was no localized wasting ; co-ordination was normal. The biceps, supinator, and triceps jerks were absent on the right and present on the left. The abdominal reflexes were present and equal. There was still gross limitation of straight leg raising—to 45 degrees. The right knee-jerk was exaggerated and the left