Mortality of Head Injury.—To set alongside these figures one should mention those patients with minor head injuries who were treated in the casualty department and then sent home, and also those who died before reaching hospital. Within the period under review at least as many cases were treated in the casualty department for minor head injuries and sent home as were admitted. With the kind help of the local authorities it has also been found that during this same period 12 patients died of head injury on the roads before they reached hospital. One estimates, therefore, that the mortality of cases of head injury severe enough to be admitted to hospital was certainly well below 10%.

It may be encouraging to note that whereas the gross mortality of the first 500 cases in this series was 11.4%, in the last 500 cases it was 6.6%, and this lower figure has been maintained to date. The series would have to be extended much further, however, before one could conclude that this apparent improvement was due to anything other than extraneous circumstances.

Summary and Conclusions

Attention is drawn to the frequency and mortality of head injuries, and it is suggested that in addition to the immediate effects of the brain injury there are other factors, some of which are preventable or amenable to treatment, which play an important part in the mortality rate. The paper is based on 1,000 consecutive cases of head injury admitted to an accident service in the last three and a quarter years.

Intracranial haematoma developed in 3.7% of an unselected series. The need for urgency in the evacuation of extradural haematoma, and the incidence of these clots in sites other than temporal, are stressed. The value of decompression in some cases of acute subdural haematoma and in certain other cases, and the possibilities of surgery in acute intracerebral haematoma, are discussed.

Chest complications are common in head injuries and account for many deaths. Their causes and treatment are outlined. The use of tracheotomy in selected cases is described.

Evidence is presented to show that metabolic disorders may develop in these patients. It is suggested that their management, and attention to the patient's fluid and electrolytic requirements in the light of the biochemical findings, may help in lowering the mortality rate.

Injuries to other parts occur in over 30% of cases. Their frequency and variety illustrate the advantages of treating head injuries within the framework of an accident service.

The overall mortality of the 1,000 cases was 9%. Among the 821 unselected cases there were 62 deaths, a mortality of 7.5%.

It is concluded that there are several ways by which the mortality rate of head injuries may be reduced. Although further attention to intracranial complications is required, it is believed that as much benefit will be derived from the prevention and treatment of some of the extracranial factors.

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STREPTOMYCIN RESISTANCE IN PATIENTS WITH PULMONARY TUBERCULOSIS PREVIOUSLY TREATED WITH P.A.S. ALONE

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In the treatment of pulmonary tuberculosis with streptomycin alone the emergence of strains of tubercle bacilli resistant to the drug is well known. That the same thing happens when isoniazid is used alone is now established (Medical Research Council, 1952a). But the possibility of resistant strains emerging when cases of pulmonary tuberculosis are treated with sodium or calcium *para*-aminosalicylate (P.A.S.) alone has received much less attention. This is perhaps partly because of the less rapid emergence of resistant organisms when an attempt is made to induce P.A.S. resistance *in vitro* (Steenken and Wolinsky, 1950) and partly because of the greater technical difficulty of the resistance tests. Nevertheless, the emergence of P.A.S.-resistant strains in a large proportion of treated cases has been reported in the literature. Some of these reports are summarized in Table I.

The results suggest that P.A.S.-resistant strains may emerge at a later period of treatment than is usual when streptomycin or isoniazid is used alone, but that, with prolonged treatment, they are isolated from a notable proportion of patients who remain sputum-positive. It is logical to imply that if these patients are later treated with streptomycin and P.A.S. in combination P.A.S. will no longer prevent the emergence of streptomycin-resistant tubercle bacilli. This probability has often been emphasized but is still ignored by many clinicians, partly perhaps because no direct evidence has, so far as we know, been provided. In addition it has been suggested that resistance to P.A.S. is transient and, by impli-

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TABLE I.—Some Previous Reports of the Emergence of P.A.S.-resistant Tubercle Bacilli in Cases Treated with P.A.S. Alone

Authors	Total No. of Cases	Percentage from which P.A.S.-resistant T.B. Isolated	Period of Treatment (Days)
Delaude <i>et al.</i> (1949) ..	5	100	157-251
Medical Research Council (1950)	37	32	< 84
Carstensen (1950) ..	79	13	184-435
Véran <i>et al.</i> (1950) ..	20	75	56-182
Veterans Administration (1951) ..	36	20	< 62
Espersen (1951) ..	11	73	40-354
Tempel <i>et al.</i> (1951) ..	37	51	< 120

cation, not of importance to later combined treatment (Tempel *et al.*, 1951). It is the purpose of this paper to provide evidence that P.A.S.-resistant organisms may be isolated from a high proportion of patients treated with the drug alone and whose sputum remains positive, that the resistant organisms may persist in the sputum for many months after treatment has ceased, and that streptomycin-resistant organisms may emerge rapidly if such cases are later treated with both streptomycin and P.A.S.

Material and Methods

The first group consists of nine patients with pulmonary tuberculosis who were treated with streptomycin, 1 g. daily, and P.A.S., 20 g. daily, for at least three months. (In one the daily dose of P.A.S. had to be reduced to 15 g. daily for five days a week at the end of two months, but her organisms were already streptomycin-resistant.) All had elsewhere had treatment with P.A.S. alone for periods varying from 6 weeks to 16 months, the exact daily dosage being in most cases unknown. The interval between the end of the course of P.A.S. alone and the beginning of the course of streptomycin and P.A.S. in combination varied from a few days to 39 months. Estimations of the drug sensitivity of the tubercle bacilli isolated from these patients, and the results of serial cultures and sensitivity tests while under treatment with streptomycin and P.A.S., were compared with similar results from a second group of five patients who began streptomycin and P.A.S. in the same doses about the same time, but who had not previously received P.A.S. alone. All the patients were initially included in the current chemotherapeutic trials organized by the Medical Research Council (1953).

Cultures of the sputum were obtained on Löwenstein-Jensen medium before the beginning of the course of streptomycin and P.A.S. in combination. Further cultures were made at least at monthly intervals for six months. Streptomycin- and P.A.S.-sensitivity tests were carried out in liquid medium according to accepted techniques (Medical

Research Council, 1948, 1950). Tubercle bacilli were regarded as drug-resistant if they were inhibited only by at least eight times the concentration which prevented growth of the sensitive control organism H37Rv; that is to say, if their "resistance ratio" was eight or above.

Comparability of the Two Groups.—The patients in the two groups were investigated with respect to factors in the pre-treatment state known to affect the emergence of resistant organisms. For this purpose we recorded the pre-treatment temperature and the extent of cavitation and confluence of shadows in the radiograph. The radiographic assessments were made by an independent panel unaware of the group to which the patient belonged, and the films were placed in previously defined categories. The results are recorded in Table II. It will be seen that the groups are roughly comparable, though in the first group gross cavitation was commoner.

Results (see Table III)

P.A.S. Resistance

It will be seen that in eight out of the nine patients who had previously been treated with P.A.S. alone tubercle bacilli isolated before beginning the combined streptomycin-P.A.S. course were P.A.S.-resistant, the resistance ratio varying from 16 to greater than 256 in different cases. In some cases there was a further substantial rise in the resistance ratio while on combined treatment. In the one patient, Case 9, whose bacilli were P.A.S.-sensitive before treatment, no P.A.S.-resistant organisms were subsequently isolated.

In three out of five of the patients who had not received previous P.A.S., bacilli isolated before the start of combined treatment were P.A.S.-sensitive. In the other two cases, for technical reasons, no pre-treatment culture was available for testing, but subsequent cultures were P.A.S.-sensitive. In none of these patients were P.A.S.-resistant bacilli isolated up to the end of the six months' observation period, though in three the sputum became negative.

It is clear, therefore, that P.A.S.-resistant tubercle bacilli emerged in a high proportion of those patients who had been treated with P.A.S. alone, and that the organisms might remain resistant for up to three years and more after stopping the drug.

Streptomycin Resistance

In 13 out of the 14 patients the tubercle bacilli were streptomycin-sensitive before the start of the combined course; in the thirteenth case (No. 10) the pre-treatment culture was contaminated but the bacilli were shown to be sensitive a month later.

Of those who had received previous P.A.S. alone, the one patient (Case 9) whose organisms were P.A.S.-sensitive before starting combined streptomycin and P.A.S. continued to excrete bacilli sensitive to both drugs up to the last available test, six months after starting the combined treatment. In all the eight other patients streptomycin-resistant organisms were isolated, in the first six cases within three months of starting treatment. In Case 7 the resistance ratio was 4, the upper limit of normal, after two and three months' treatment; at four months a culture slightly but definitely resistant (resistance ratio 8) was obtained for the first time, the ratio reaching 32 a few days later. In the remaining patient (Case 8) a resistance ratio of 4 was found at three months, the culture was contaminated at four months, and the first definitely resistant strain was isolated at five months. This last patient was the only one of the group whose bacilli attained only a low degree of streptomycin-resistance (resistance ratio 8); in the other seven the organisms became moderately or highly resistant.

Of the five patients who had not had previous P.A.S. alone, the sputum became negative in three (Cases 10, 12, and 14). In each case the last positive culture, on the 90th, 44th, and 31st days of treatment, remained streptomycin-sensitive throughout the six months' observation. In only one patient (Case 11) were slightly resistant organisms, with a resistance ratio of 8, isolated after five months' treatment.

TABLE II.—Pre-treatment Temperatures and Radiographic State

Case No.	Previous P.A.S. Alone	Pre-treatment Temperature*	Radiographic Classification, Pre-treatment	
			Cavitation†	Confluence‡
1	+	Moderate	+++	++
2	+	Afebrile	+++	++
3	+	"	+++	++
4	+	"	+++	+
5	+	Moderate	+++	++
6	+	Afebrile	++	+++
7	+	"	+++	++
8	+	Moderate	+++	+++
9	+	High	+++	+++
10	0	Afebrile	++	++
11	0	Moderate	+++	+++
12	0	Afebrile	++	++
13	0	Moderate	+++	+++
14	0	Afebrile	+	+

* Graded as follows: At least 1 reading in pre-treatment week over 101° F. (38.3° C.)—High, over 99° F. (37.2° C.)—Moderate, none over 99° F.—Afebrile.

† Total diameters of cavities present 5 cm. or above=+++; 2 to 4.9 cm.=++; less than 2 cm.=+.

‡ Shadows confluent over three-quarters or more of one zone=+++; one-quarter to three-quarters of one zone=++; less than one-quarter of one zone=+.

TABLE III.—Results

Case No.:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Previous P alone	Duration (months)	7	6	11	6	1½	16	4	3	9	0	0	0	0
	Interval before SP course (months)	4	10	4	14	39	8	16	0	0	—	—	—	—
SP course	S 1 g. daily (months)	3	4	3	3	3	3	4	3	3½	3	3½	3½	3½
	S 1 g. thrice weekly (months)	½	2	3	0	3	3	0	3	2½	3	2½	2½	1
	Preceding SP course	>256	64	16	16	>256	64	>256	>32	4	½*	½	2	1
P-resistance	Highest reached ..	>256	64	>512	>256	>256	64	>1,028	>256	4	4	1	2	1
	Time after starting SP (months)	Initial	Initial	6	6	Initial	Initial	5	6	Initial	3	Initial	Initial	Initial
S-resistance	Height of 1st resistant culture ..	32	8	256	128	32	>32	8	8	None	None	8	None	None
	Time after starting SP (months)	2	2	3	2	2	2	4	5	—	—	5	—	—
	Highest reached ..	256	128	512	256	32	>256	32	8	1	1	8	1	4
	Time after starting SP (months)	5	3	6	6	2	3	4½	5	Initial	3	5	1	6
Remarks	..										Sputum-negative after 90 days	Sputum-negative after 44 days	Sputum-negative after 31 days	

P=P.A.S., S=Streptomycin. Times are given in months. Resistance figures are resistance ratios (see text).

* No pre-treatment sensitivity test; figure for first subsequent culture.

† Pre-treatment sensitivity on solid medium only.

‡ Two days after first resistant culture.

Streptomycin-resistant tubercle bacilli, therefore, emerged in all of eight patients who had been previously treated with P.A.S. alone and whose organisms were P.A.S.-resistant before starting combined treatment with streptomycin and P.A.S. Of the six patients whose organisms were P.A.S.-sensitive before starting combined treatment, including one who had had previous P.A.S. alone, bacilli slightly resistant to streptomycin were isolated from only one, although in three the sputum became negative during the period of observation.

Discussion

The control group of patients who had not previously received P.A.S. alone was, of course, small. It was made smaller in the later stages of the investigation by a number of patients becoming sputum-negative. But a good deal of information is elsewhere available about the proportion of cases from which streptomycin-resistant organisms are likely to be isolated if streptomycin and P.A.S. are given in the same doses as in our patients. In the earlier Medical Research Council series the proportion did not exceed 10% (Medical Research Council, 1952b). In our group treated with previous P.A.S. alone the organisms were P.A.S.-resistant before combined treatment in eight out of nine, and in all of these streptomycin-resistant bacilli were isolated when they were later treated with streptomycin and P.A.S. in combination.

The implications of these findings are obvious. P.A.S., like streptomycin and isoniazid, should never be given alone to tuberculous patients. There is evidence that the use of streptomycin prevents or diminishes the emergence of P.A.S.-resistant organisms, just as P.A.S. prevents or diminishes the emergence of streptomycin-resistant organisms (Medical Research Council, 1950; Veterans Administration, 1951). If a patient is known to have had a long course, perhaps more than a month, of P.A.S. alone, it should be assumed, until the results of sensitivity tests become available, that his bacilli are P.A.S.-resistant. If chemotherapy is necessary he should be treated with streptomycin and isoniazid in combination. Finally, it is clear that tests for P.A.S. sensitivity are as important to the patient as those for sensitivity to streptomycin or isoniazid.

Summary

Tubercle bacilli from eight out of nine patients who had previously received sodium *para*-aminosalicylate (P.A.S.) alone for pulmonary tuberculosis were found to be resistant to the drug. The original course of treat-

ment lasted from 6 weeks to 16 months in different cases and the interval between the finish of the course and the resistance tests varied from a few days to 39 months.

When treated with daily streptomycin and P.A.S., streptomycin-resistant tubercle bacilli emerged in all the eight patients whose bacilli were P.A.S.-resistant before the start of the combined treatment. The streptomycin-resistant bacilli were obtained in six out of the eight cases within three months on combined treatment, in the seventh after four months, and in the eighth after five months.

By contrast a slightly streptomycin-resistant organism was isolated, after five months' treatment, from only one out of six similar cases whose organisms were P.A.S.-sensitive at the start of the combined course. Five of the cases had had no previous treatment with P.A.S. alone.

It is concluded that P.A.S.-resistant tubercle bacilli are likely to emerge if patients with pulmonary tuberculosis are treated with P.A.S. alone; that the resistant organisms may persist for long periods; and that, if the patients are later treated with P.A.S. and streptomycin, P.A.S. will then no longer prevent or diminish the emergence of streptomycin-resistant bacilli.

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