Henneman, P. H., Dempsey, E. F., Carroll, E. L., and Henneman, D. H. (1962). *Metabolism*, 11, 103.
 Jackson, W. P. U., and Linder, G. C. (1953). *Quart. J. Med.*, 22, 133.
 Leedham-Green, J. C., and Golding, F. C. (1937-8). *Brit. J. Surg.*, 25, 77.
 Linder, G. C., and Vadas, D. G. M. (1931). *Lancet*, 2, 1124.
 McCance, R. A. (1947). *Quart. J. Med.*, 16, 33.
 Michaelis, L. (1932). *Fortschr. Röntgenstr.*, 45, 187.
 Monier-Vinard, R. (1940). *Bull. Soc. méd. Hôp. Paris*, 56, 529.

Reifenstein, E. C., jun., Albright, F., and Wells, S. L. (1945). *J. clin. Endocr.*, 5, 367.
 Robertson, B. R., Harris, R. C., and McCune, D. J. (1942). *Amer. J. Dis. Child.*, 64, 948.
 Rose, G. A. (1956). *Brit. med. J.*, 2, 805.
 Segar, W. E., Iber, F. L., and Kyle, L. H. (1956). *New Engl. J. Med.*, 254, 1011.
 Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., and Burnett, C. H. (1958). *Medicine (Baltimore)*, 37, 97.

Prolonged Streptomycin and Isoniazid for Pulmonary Tuberculosis

R. N. JOHNSTON,* M.D., M.R.C.P., F.R.C.P.ED.; D. H. SMITH,* M.D.

R. T. RITCHIE,* M.B., M.R.C.P.ED.; W. LOCKHART,*† M.B.

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Streptomycin and isoniazid are the most effective drugs in the treatment of tuberculosis. There are many reports on isoniazid dosage from 200 to 1,000 mg. daily but few on the optimal dose of streptomycin.

A daily dose of 1 g. has become widely accepted, especially as toxicity is low in young patients receiving this drug for only three to six months. More recently, dissatisfaction with the self-administration of *para*-aminosalicylic acid (P.A.S.) and recourse to streptomycin and isoniazid for longer periods in elderly patients has shown that labyrinthine damage due to streptomycin is a troublesome and serious complication. The prolonged use of streptomycin and isoniazid made it desirable to explore methods for diminishing the incidence of labyrinthine damage without loss of therapeutic efficiency. Reduction of the dose of streptomycin to 0.75 g. daily appeared to be a reasonable compromise, and preliminary results have already been reported (Johnston *et al.*, 1961). Penman *et al.* (1957) found that pantothenic acid alleviated the vertigo of streptomycin. We were unable to trace any reports on the use of pantothenic acid to prevent labyrinthine damage due to streptomycin. We therefore decided to explore this possibility, to study 0.75 g. of streptomycin and high-dosage isoniazid. With this background we planned the following controlled clinical trial in 1958.

Method

All new patients over the age of 15 years admitted to hospital with active pulmonary tuberculosis were accepted with the following exclusions: previous antituberculous chemotherapy, primary tuberculosis, diabetes mellitus, pneumoconiosis, non-Europeans, and expectant mothers. From November 1958 to December 1959 138 patients were accepted. When a patient was admitted to the trial the name was forwarded to a central secretary, who chose a card at random from a series specifying one of the following three regimens:

- (1) S.I.=Streptomycin sulphate 1 g. daily plus isoniazid 1,000 mg. given in two divided doses with pyridoxine 50 mg. b.d. (After leaving hospital, isoniazid reduced to 600 mg. once daily plus pyridoxine 100 mg. once daily.)
- (2) S.P.=Streptomycin sulphate 1 g. daily with pantothenic acid 150 mg. orally daily at the same time plus isoniazid 100 mg. b.d. (After leaving hospital 200 mg. of isoniazid daily as a single dose.)
- (3) S.½=Streptomycin sulphate 0.75 g. as a single injection plus isoniazid 100 mg. b.d. (After leaving hospital 200 mg. of isoniazid daily as a single dose.)

In addition, each patient received P.A.S. 12 g. daily for the first six weeks. After leaving hospital streptomycin and isoniazid were given daily except Sundays to complete 18 months' chemotherapy. By 1960 we were satisfied that the S.½ regime merited further examination. During that year and 1961 we admitted a further 37 patients who fulfilled the same criteria except that they had to be sputum-positive initially. This latter group was not allocated by random selection, and is considered separately and styled the *late* S.½ group.

Initial examination in hospital included a radiograph of chest, tomography, and a minimum of three sputum specimens or laryngeal swabs. The former were stained for acid-fast bacilli and cultured on Loewenstein-Jensen media for *Mycobacterium tuberculosis*. Sensitivity tests were performed to streptomycin, P.A.S., and isoniazid on all positive cultures, using solid media, and all tests were performed against the standard H.37 Rv. strain. In the case of streptomycin and P.A.S. the organism was regarded as resistant if the test strain was four or more times resistant to the drug, compared with the H.37 Rv. culture. Resistance to isoniazid was shown by a growth of more than 20 colonies on the tube containing 0.2 µg of isoniazid per ml. In addition to routine ward tests the urine was examined in the central laboratory for protein together with microscopy of the deposit. Renal function was further assessed by the blood urea and measurements of the streptomycin serum levels at 1 hour and 24 hours after the streptomycin injection. These latter bio-assays were performed after the P.A.S. had been discontinued and using the same strain of *Klebsiella pneumoniae* known to be streptomycin-sensitive. The E.S.R. was measured by the Westergren method. Subsequently two sputum smears and cultures were examined every two weeks until discharge, with radiographs of chest and E.S.R. monthly.

At three-monthly intervals from the start of treatment, in addition to the above, clinical examination included the Romberg test, examination for nystagmus, and observations of the patient's gait. Later we reinforced the Romberg test by asking the patient to "about turn" with closed eyes and heels together. When a patient complained of dizziness or a tendency to stagger, these tests were repeated, and included the Hallpike caloric test (Hallpike, 1956). We assessed the degree of vertigo as follows: "doubtful," where the symptoms were very mild, unsupported by clinical examination and caloric tests, and where the patient's behaviour raised doubts; "slight," transient or intermittent dizziness/ataxia with or without nystagmus; "moderate," more persistent but less than "severe," obvious ataxia requiring support. Where we assessed the symptoms as doubtful we continued injections during a further few days. If symptoms continued even though they were then only mild and unsupported by objective evidence of labyrinthine damage

* Department of Tuberculosis, University of St. Andrews, and Chest Service, Dundee.

† Dr. Lockhart died on 27 May 1964.

we stopped treatment. Usually this meant substituting P.A.S. and isoniazid for streptomycin and isoniazid with the following exceptions: four patients receiving 1 g. were reduced to 0.75 g. and two changed to an equivalent dose of streptoduoicin ("dimycin"). The average duration of hospital treatment for the three treatment groups was as follows: S.I., 150 days; S.P., 129 days; S.½, 134 days.

Most of the patients attended the chest clinic subsequently for streptomycin and isoniazid. A daily register was kept of their attendance during the ensuing 12 to 15 months. Fourteen patients received their treatment at home from the district nurse, and 10 at a hospital close to their homes. In these 24 no register was kept. The nurses concerned reported those who failed to have their treatment. During their summer holidays most of the patients reverted to 12 g. of P.A.S. and 200 mg. of isoniazid daily in a combined cachet for two weeks, but a few patients preferred to continue their streptomycin and isoniazid. All patients were re-examined at three-monthly intervals, and examination included a radiograph, E.S.R., and two sputa or laryngeal swabs cultured for *M. tuberculosis*. Patients were encouraged to report any untoward symptoms. Chemotherapy was continued for 18 months in all except one patient (S.½ group) who received two and a half years' chemotherapy, with the last nine months on P.A.S. and isoniazid only. Thereafter, patients were seen at six-monthly intervals, with a special review two years after stopping treatment, and at that time caloric tests were arranged for all those who were willing to attend. The study now extends to five years' observation on the earliest patients.

Distribution of Patients

The figures in Table I show that the patients in each treatment group were moderately well matched except for the S.I. group, where the disease area was greater and the average cavity size larger. The youngest patient was 16 years and the oldest 85. The oldest to complete treatment was 70 (S.½).

TABLE I.—*Distribution of Patients*

	S.I.	S.P.	S.½	Late S.½
Total No. of patients	43	46	49	37
Males	30	29	31	27
Females	13	17	18	10
Average age	45	42	41	41
Pretreatment weight: average (lb.)	122	125	121	124
" E.S.R.:	48	30	30	38
Sputum smear positive	19	20	20	34
Culture positive	32 (74%)	35 (76%)	35 (71%)	37 (100%)
X-ray analysis:				
Minimal	17	12	21	6
Moderately advanced	14	24	20	22
Far advanced	12	10	8	9
Average disease area (sq. cm.)	76	47	49	66
Average cavity size (cm.) ..	2.47	1.95	1.92	2.21
No. with cavity	18	26	22	22

Withdrawals

There were 138 patients in the initial trial and 37 in the later stage—a total of 175. The reasons for withdrawal are shown in Table II.

TABLE II.—*Withdrawals*

	S.I.	S.P.	S.½	Late S.½
Total No. of patients	43	46	49	37
Withdrawals (individuals) ..	23	19	15	11
Death (cause)	1 (CO poisoning)	1 (A.P.T.)	1 (prostatectomy)	1 (A.P.T.)
Vertigo	15 (35%)	12 (26%)	3 (6%)	3 (8%)
Isoniazid psychosis	1	0	0	0
High-tone deafness	1	0	0	0
Drug rash (STM)	0	0	2	1
Drug resistance (pretreatment)	1	0	0	2
Diagnosis in doubt or error ..	0	2	3	0
Refusal of treatment	4	4	6	4

Deaths

Two of these were due to uncontrolled tuberculosis—one in the S.P. group and another in the late S.½ group. Both patients were acutely ill with far-advanced tuberculosis, and death occurred 18 days and 20 days after starting treatment. The only death in the S.I. group was due to carbon monoxide poisoning. This patient, who had previously shown no mental disturbance, committed suicide shortly after self-discharge from hospital. Necropsy was not performed. There is the possibility that the high dose of isoniazid precipitated an acute mental disturbance, but of this we have no proof. The fourth death was that of a man of 75 who died following a prostatectomy performed three months after the start of chemotherapy.

Vertigo

The assessment of the early stages of labyrinthine damage is difficult. Observation of gait and tests for nystagmus, the Romberg test, and the Hallpike caloric tests are all frequently normal or equivocal. We have found the reinforced Romberg test of more value, but there still remained patients in whom, despite a complaint of dizziness, no abnormal physical signs were apparent. We believe that this sensation precedes overt signs of labyrinthine damage. A more precise method of measuring early labyrinthine damage is required. (After our own investigations were well advanced we learned of the American "mattress test" but have no personal experience of this.)

A comparison of degrees of vertigo and related factors is shown in Table III. All these patients had normal blood-urea levels. When patients were finally reviewed two years after stopping treatment, we asked whether they were aware of any residual disability.

TABLE III.—*Analysis of Vertigo*

	S.I.	S.P.	S.½ + Late S.½
Total No. of patients	43	46	86
No. with vertigo	15	12	6
Doubtful	1	1	3
Slight	12	7	1
Moderate	2	0	1
Severe	0	4	1
Initial caloric tests:			
Normal	5	6	3
Abnormal	6	5	2
Not done	4	1	1
Average age	57	54	50
(Average age without vertigo) ..	40	36	39
Average weight and weight range (lb.)	128 (90–177)	124 (95–168)	99 (72–144)
(Average weight without vertigo) (lb.)	122 (93–169)	124 (92–168)	125 (84–178)
Average No. of days' treatment ..	172	127	279
2-year assessment (after cessation of treatment):			
Normal	12	7	4
Residual disability	1*	1	1
Died or defaulted	2	4	1†

* Later died. † Slight residual disability.

From Table III certain trends emerge. (1) Severe vertigo was seen mainly in the S.P. group. (2) There is a lower incidence of vertigo in the S.½ and late S.½ groups. (3) The average age of patients with vertigo is consistently higher compared with those who do not show this symptom: +17 years in the S.I.; +18 years in the S.P.; +11 years in the S.½. But vertigo developed in 7 (21%) patients below the age of 40 (four in S.I., one in S.P., and two in S.½). The youngest patient was 19 (S.I.). (4) The average weight of those in the S.½ group who develop vertigo is lower. Indeed, if the "doubtful" group is excluded the average weight of the remainder is only 84 lb. (38.1 kg.). Among these six patients there was only one of normal weight (144 lb.; 65.3 kg.), and her vertigo was assessed as "doubtful." (5) In the S.½ group vertigo developed at a later stage of treatment. (6) The majority of patients in all groups made a good functional recovery. Although the numbers are too small to permit more detailed comparison, the recovery evident at two

years showed a trend in favour of those in the S.I. group. There were more patients with a residual disability in the S.P. group. (7) The serum-streptomycin levels have been of little value (Table IV). Neither the "peak" (one-hour) values nor those at 24 hours have been of help in predicting which patients would develop vertigo. (All our patients had already been screened by the absence of proteinuria, the normal urinary deposit, and the blood-urea levels.)

TABLE IV.—Serum Streptomycin Levels ($\mu\text{g./ml.}$)

	Without Vertigo			Vertigo		
	S.I.	S.P.	S.‡	S.I.	S.P.	S.‡
<i>1-hour Levels</i>						
10–16 μ	2	6	24	0	1	0
17–32 μ	18	17	35	8	5	6
>32 μ	7	8	11	2	4	0
Not done	1	3	10	5	2	0
<i>24-hour Levels</i>						
<1.5 μ	22	26	56	10	7	5
1.5 μ or more ..	4	5	9	0	3	1
Not done	2	3	15	5	2	0

At the final review we arranged caloric tests for all the patients who were willing to attend, and 89 were examined. One patient showed an absent response and four a sluggish response, but none of these complained of any residual disability. One patient (S.I.) with no response had not had earlier caloric tests but had suffered vertigo and treatment was stopped. Of the other four, three had developed vertigo (two S.I. and one S.P.) and one (S.‡) had no record of previous vertigo. Thus there was only one instance of "silent" labyrinthine damage.

At the final review five patients showed a residual disability and had caloric tests which were abnormal in four. In two of these four the usual tests at 30° and 40° C. gave equivocal results, and evidence of labyrinthine damage was found only by repeating the test with water at 20° C.

Isoniazid Psychosis

Isoniazid psychosis developed in two patients in the S.I. group. (The second patient was withdrawn because of vestibular damage and therefore only one patient is shown in Table II.) Their mental symptoms resolved when the dose of isoniazid was reduced to 200 mg. daily.

High-tone Deafness

This was observed in only one patient—a man aged 33 (group S.I.) who complained of slight deafness three months after the start of treatment. Audiograms showed a marked high-tone deafness on both sides and caloric tests some disturbance of vestibular function. There were no signs of abnormal renal function and the blood-urea and serum-streptomycin levels were normal.

Diagnosis in Doubt or Error

Five patients were withdrawn because of doubt or error in diagnosis—one suffering from bronchial carcinoma, two with quiescent pulmonary tuberculosis, one with aspergillosis, and one with an atypical mycobacterial infection.

Refusal of Treatment

Eighteen patients refused treatment—one at eight months, 13 on discharge from hospital, and another four at one to five months after discharge from hospital. Most of these patients were intellectually backward. Other reasons for failure were resumption of work and travelling for treatment, especially in

winter (bus fares were refunded for those on National Health Insurance).

Results

There was no difference in the degree of clinical improvement observed in the three main groups as measured by the average gains in weight: S.I., 13.3 lb. (6 kg.); S.P., 13.6 lb. (6.2 kg.); S.‡, 15.1 lb. (6.8 kg.), and late S.‡, 18.1 lb. (8.2 kg.). The apparently better results in the late S.‡ group are related to the more acute disease present in this group.

Bacteriological

Excluding the two deaths due to uncontrolled tuberculosis, 100% sputum conversion was achieved in all groups by the end of six months' treatment. The rates of sputum conversion (culture results) are shown in Table V. Only two patients have relapsed with positive cultures for *M. tuberculosis*. One patient (S.‡) defaulted after four months and refused further treatment. The positive cultures obtained subsequently were sensitive to streptomycin, P.A.S., and isoniazid. Another patient (S.P.) defaulted at one year, refused further treatment, relapsed, and later was readmitted with an extensive spread; cultures positive for *M. tuberculosis* showed complete sensitivity to streptomycin, P.A.S., and isoniazid.

TABLE V.—Results. Sputum Conversion

	S.I.	S.P.	S.‡	Late S.‡
Total No. of patients	43	46	49	37
Positive initially	74%	76%	71%	100%
" at 1 month	30%	32%	31%	59%
" 3 months	7%	7%	9%	15%
" 6 months	0	0	0	0
Average No. of "negative cultures subsequently	13	12	14	11

(These percentages are expressed on those remaining in the trial at the intervals stated.)

None of the 72 patients with initially positive cultures treated with 0.75 g. of streptomycin has relapsed.

Radiological

The x-ray analysis was made by two of us. Each reported the films of those patients not under his personal care and whose treatment was unknown to him. The results were recorded on a special form.

The extent of disease was recorded according to the National Tuberculosis Association (1961) classification: the size of cavities was recorded in centimetres and when more than one was present the total diameters were added together. In addition, an independent assessment of the area of disease present on the postero-anterior film was made, using a transparent grid ruled in 1-cm. squares. The films taken 6, 12, and 18 months after the start of treatment were compared with the original, and also a film taken two years after the cessation of treatment. The degree of improvement was recorded as slight improvement (1+), moderate improvement (2+), considerable improvement (3+), and exceptional improvement (4+). The results in Table VI for the readings at 6, 12, and 18 months represent the average index of improvement obtained by summing these

TABLE VI.—Results. X-ray Improvement. Average Improvement Index

	S.I.	S.P.	S.‡	Late S.‡
6 months	2.11	1.71	1.78	1.94
12 "	2.32	2.13	2.22	2.18
18 "	2.32	2.32	2.39	2.38
Percentage area clearing at 18 months	67%	66%	65%	73%
Average decrease in cavity size	1.92 cm.	1.29 cm.	1.73 cm.	1.5 cm.
Closure of cavity	4/18 (22%)	12/26 (46%)	17/22 (77%)	11/20 (55%)

figures and dividing by the number of patients. In addition, the area of disease present at the time treatment was stopped (18 months) was again measured. The decrease in this disease area has been expressed as a percentage clearing of that present in the original film. Change in cavity size and cavity closure have also been recorded.

There is no appreciable difference in the degree and rate of clearing in the three treatment groups with the exception that in the S.I. group there was more rapid clearing in the first six months and less in the succeeding year.

Efficiency of Treatment after Discharge from Hospital

Attendance for injections and supervision of the isoniazid administration has meant that the regularity of treatment was precisely established for each patient. The results of the attendance register concerning 107 patients who completed treatment at the chest clinic were: "regular," 61 (57%); "acceptable," 21 (20%); "unreliable" 25 (23%).

We have classified those who have completed treatment as regular where attendance was near perfect (96% with absences amounting to not more than one week, six injections); acceptable (92% of the prescribed treatment) where only the equivalent of one month's treatment was lost; and unreliable (84% of the prescribed treatment) where failure to attend for treatment varied from one to three months.

A total of 25,612 injections was given at the chest clinic with only two complications, one being a mild and transient sciatic irritation, and the other a painful reaction in another patient who subsequently was unwilling to continue injections. (Among those treated elsewhere, one patient developed an abscess which required drainage but resolved promptly.) This regimen has proved acceptable to a majority of patients in this study, but there remained an important minority who attended irregularly for treatment. Of the 25 unreliable patients 17 were sputum-positive with moderately or far-advanced disease initially. Of these 17, 15 have completed their two-year post-treatment review and none of them has shown evidence of reactivation. The two missing patients have repeatedly defaulted. Both are known to be alive and one is well and working. None of the remaining eight sputum-negative patients has relapsed.

Discussion

We have shown that the lower dose of streptomycin is as effective in combination with isoniazid as the usual 1 g. dose, is less toxic, and prevents the emergence of isoniazid resistance.

In considering the place for prolonged streptomycin + isoniazid can it be shown (1) that this regime is clinically more effective than P.A.S. + isoniazid, and (2) that it is acceptable to the average patient?

During 1957–8 we treated 148 new patients with a positive culture for *M. tuberculosis*. Of this number 130 received streptomycin, or P.A.S. + isoniazid, or streptomycin + isoniazid while in hospital, and subsequently P.A.S. + isoniazid at home for an average of 18 months. The majority received streptomycin for three to six months. During the two years following cessation of treatment five of these patients relapsed. Eighteen patients received P.A.S. + isoniazid only and four of these relapsed. (Three of the four were known to have taken their treatment irregularly.) The problem of omitted P.A.S. + isoniazid has been emphasized by Simpson (1956), Dixon *et al.* (1957), and others. R. T. Ritchie (personal communication, 1958) confirmed these findings in 487 Dundee patients. All these reports are based on random urine tests which show that chemotherapy is sometimes omitted but does not define the frequency.

Livingston (1959) has reported a short-term (eight months) trial comparing all three drugs with regimens of streptomycin + isoniazid and isoniazid + P.A.S., and in this short period has shown no significant difference between these regimes. Fox (1963), in a recent further analysis of the Medical Research Council (1962) trial, has shown a significant advantage to those patients who received an initial six weeks of streptomycin in addition to P.A.S. + isoniazid, compared with those who received P.A.S. + isoniazid alone. He points out that the benefit may be due to daily streptomycin and daily isoniazid initially.

In the present report there has been no relapse among our patients who have completed treatment. It should be noted that those patients who attended irregularly have as yet fared no worse. The 25 "unreliable" patients attended for an average period of 11 months after discharge (total chemotherapy approximately 15 months). During the first six months of out-patient treatment these patients did not miss more than four treatments per month—that is, treatment became irregular only after the tenth month. These "unreliable" patients may eventually suffer, but it seems unlikely on the present evidence. Our findings suggest that beyond a year the need for daily streptomycin + isoniazid may not be essential. The recent report from the Tuberculosis Chemotherapy Centre, Madras (1963), on intermittent treatment of pulmonary tuberculosis showed that intermittent streptomycin + isoniazid merits further study but when employed initially falls short of 100% sputum conversion.

The incidence of vestibular disturbance depends on the dose of streptomycin, the frequency of administration, the duration of treatment, the age and weight of the patient, and the methods used to investigate this complication. Even with a dose of 1 g. of streptomycin daily the reported incidence of vestibular dysfunction varies between 6% (Kalinowski *et al.*, 1961), 12% (Medical Research Council, 1950), 14% (Penman *et al.*, 1957), 30% (Mahady *et al.*, 1953), and 60% (Sita Lumsden and Powell, 1953). These last authors, unlike the others, carried out caloric tests before and after treatment. Since pantothenic acid was of no value we have combined the results of the S.I. and S.P. groups to show the incidence of vertigo under the conditions of our trial with a daily dose of 1 g. of streptomycin—27 (30%) of 89 patients. With 0.75 g. of streptomycin daily the incidence fell to 6 (7%) of 86 patients. These results are statistically significant at the 0.1% level ($\chi^2=15.61$, $n=1$, $P<0.001$). Where the body weight is below 100 lb. (45.4 kg.) it may be desirable to reduce the dose of streptomycin further to 0.5 g.

Since the dose of streptomycin was known to the clinicians assessing labyrinthine damage and also to some of the patients, we must consider how far this knowledge may have influenced these results. Patients were under the separate charge of the four of us, each making his assessments independently. Moreover, patients were in four different wards in two widely separated hospitals over a two-year period. We consider it unlikely that bias in favour of one regimen should have influenced us all in the same direction. Further, if vertigo had been missed in, say, the S.3 regimen at the time of onset, it is likely that more residual disability (recorded also by other members of staff) would be apparent at the two-year post-treatment assessment.

As with P.A.S. and isoniazid, our present regimen is not acceptable to all patients. At the time of discharge from hospital there remained 125 patients, of whom 18 refused further streptomycin + isoniazid, leaving 107. This regimen has therefore been 86% successful, or, viewed more critically, 82/125 (64%)—that is, the "regular" plus "acceptable" attenders. Velu *et al.* (1961) have reported acceptability figures similar to our own for streptomycin + pyrazinamide. Stradling and Poole (1963) found only 38 (51%) patients from among 74 who completed 18 months streptomycin + isoniazid. Of these 38, 34 showed "quite regular attendance"—that is,

46% of the original group. The general acceptability of this regime may well vary in different localities.

Since the combination of streptomycin and isoniazid is more effective than P.A.S.+isoniazid it may be possible to reduce the length of treatment from the generally accepted period of 18 months. We are satisfied that the present results with daily streptomycin+daily isoniazid justify further trials to assess now the optimal duration of these drugs, including possibly an intermittent regime during the later stages of treatment.

Conclusions

Streptomycin 0.75 g. is an adequate dose and may represent the optimal dose in combination with isoniazid for the treatment of pulmonary tuberculosis.

This dose significantly reduces labyrinthine damage. Pantothenic acid has failed to prevent this complication.

High-dose isoniazid offers no advantage and is more toxic.

Summary

A total of 138 patients with active pulmonary tuberculosis were allotted by random selection to three regimes to examine the advantages of high-dose isoniazid, pantothenic acid to mitigate streptomycin-induced vestibular damage, and the effects of reduction of the daily dose of streptomycin from 1 to 0.75 g. A supplementary group of 37 patients who received the lower dose of streptomycin were added later. Patients were treated for 18 months and the results were analysed two years after stopping treatment.

Lowering of the daily dose of streptomycin to 0.75 g. reduced complicating vertigo from 30% to 7% without loss of therapeutic efficiency.

No long-term advantage was gained with high-dose isoniazid, which proved more toxic. Under the conditions of this trial pantothenic acid was of no value.

There is some evidence that daily streptomycin+isoniazid is not essential beyond a year, and an intermittent regime may be adequate in the later stages of treatment.

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REFERENCES

- Dixon, W. M., Stradling, P., and Wootton, I. D. P. (1957). *Lancet*, **2**, 871.
 Fox, W. (1963). *Bull. int. Un. Tuberc.*, **33**, 68.
 Hallpike, C. S. (1956). *J. Laryng.*, **70**, 15.
 Johnston, R. N., Smith, D. H., Lockhart, W., and Ritchie, R. T. (1961). *Brit. med. J.*, **1**, 105.
 Kalinowski, S. Z., Lloyd, T. W., and Moyes, E. N. (1961). *Amer. Rev. resp. Dis.*, **83**, 359.
 Livings, D. G. (1959). *Transactions of the 18th Conference on Chemotherapy of Tuberculosis*, p. 18.
 Mahady, S. C. F., Armstrong, F. L., Beck, F., Horton, R., and Lincoln, N. S. (1953). *Amer. Rev. Tuberc.*, **68**, 238.
 Medical Research Council (1950). *Brit. med. J.*, **2**, 1073.
 — (1962). *Tubercle (Lond.)*, **43**, 201.
 National Tuberculosis Association (1961). *Diagnostic Standards and Classification of Tubercle*, p. 39.
 Penman, A. C., Dickson, I., and Miller, J. S. (1957). *Tubercle (Lond.)*, **38**, 422.
 Simpson, J. McD. (1956). *Ibid.*, **37**, 333.
 Sita Lumsden, E. G., and Powell, R. J. (1953). *Tubercle (Lond.)*, **34**, 324.
 Stradling, P., and Poole, G. (1963). *Ibid.*, **44**, 71.
 Tuberculosis Chemotherapy Centre, Madras (1963). *Lancet*, **1**, 1078.
 Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Jacob, P. G., Nair, C. N., and Ramakrishnan, C. V. (1961). *Tubercle (Lond.)*, **42**, 136.

Circulating Cancer Cells

R. A. SELLWOOD,* F.R.C.S.; S. W. A. KUPER,† M.B., B.CH.; J. I. BURN,* F.R.C.S.
 ELSIE NOEL WALLACE,‡ M.B., B.S., D.M.R.T.

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Two decades of advance in surgical techniques and management have permitted the cancer surgeon to perform massive local resections of tissue and increasingly extensive block dissections of the lymphatic pathways. In addition, with a more enlightened general public and greater diagnostic facilities, early diagnosis of cancer is becoming increasingly common. Nevertheless, the overall mortality from cancer remains very much the same as it was 25 years ago, the patients continuing to die from distant metastases. There is therefore increasing interest in the mechanisms of tumour dissemination and the means of preventing it.

Circulating cancer cells were first described by Ashworth in 1869, and further observations were made by Loeper and Louste (1904), Schleip (1906), Ward (1913), Marcus (1917),

Quensel (1921), and Pool and Dunlop (1934). Pool and Dunlop examined samples of peripheral blood from 40 patients with advanced cancer and recorded the presence of cancer cells in 17 of them.

Engell's (1955) description of cancer cells in the blood of patients with carcinoma of the large bowel aroused great interest, particularly in the U.S.A., and workers from several centres have described their results with the use of various techniques. Moore *et al.* (1957) identified cancer cells in peripheral blood samples from 93 (52%) of 179 cases. Roberts *et al.* (1958) found malignant cells in 16.7% of "curable" patients and in 31.1% of "incurable" patients, while Pruitt *et al.* (1958) described an incidence of 39% and Salgado *et al.* (1959) one of 57%.

We have attempted to repeat this work as part of an investigation into the exfoliation of cancer cells from various sites and the mechanisms by which they produce metastases, but, like other workers (Spriggs, 1960; Kuper *et al.*, 1961), we have been unable to confirm this high incidence.

* Department of Surgery, Hammersmith Hospital and Postgraduate Medical School, London.

† Department of Pathology, Brompton Hospital, London; Part-time Consultant, Hammersmith Hospital.

‡ Department of Radiotherapy, Royal Marsden Hospital, London.