was a 22%, 15%, and 12% reduction in risk of coronary heart disease at eight weeks, eight months, and four years, respectively, using a multiple logistic function from the London Whitehall study. The reduction in the incidence of new electrocardiographic abnormalities at four years was greater than predicted. This may have been the result of chance variation, but it may suggest that relaxation affects pathways other than the established cardiac risk factors.

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Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial

BRITISH THORACIC SOCIETY RESEARCH COMMITTEE

Abstract

One hundred and fifty two patients with tuberculosis of lymph nodes were enrolled in a randomised trial of nine versus 18 months' chemotherapy. The regimens consisted of rifampicin plus isoniazid for nine or 18 months, supplemented initially by ethambutol for eight weeks. At 36 months data from 113 patients were available for analysis, of whom 56 had received the short course regimen. Progress during chemotherapy was uneventful in 84 of the 113 patients. Fresh nodes appeared in 13 patients and existing nodes increased in size in 13; these events occurred within the first eight months of treatment. In 10 patients residual nodes were palpable at the end of chemotherapy. Events including enlargement of nodes, appearance of new nodes, fluctuation, and formation of sinuses occurred in 12 patients after the end of chemotherapy. The incidence of these events was similar in both groups, and they did not result in an unfavourable outcome.

Nine months' treatment with rifampicin and isoniazid supplemented initially by ethambutol should be adequate for tuberculosis of lymph nodes, but confirmation must await a longer period of follow up.

Introduction

A survey of notifications of tuberculosis in England and Wales in 1978 showed that disease of the lymph nodes was the commonest form of non-respiratory tuberculosis.[1] The British Thoracic Association's first controlled trial of chemotherapy for tuberculosis of lymph nodes compared two 18 month regimens in 90 patients.[2 3] The regimens comprised either rifampicin plus isoniazid or ethambutol plus isoniazid, both supplemented with streptomycin for the first two months. A satisfactory response to chemotherapy was seen, and microbiological relapse did not occur when treatment was stopped. In a retrospective study of lymph node tuberculosis Summers and McNicol reported no relapse in 239 patients, some of whom were treated with nine month regimens incorporating rifampicin and isoniazid.[4]

Our study compares treatment with rifampicin and isoniazid given for either nine or 18 months, supplemented initially by eight weeks' treatment with ethambutol. We describe the state of patients 36 months after entry to the study.

The study was organised by a subcommittee of the research committee of the British Thoracic Society, whose members were: Dr I A Campbell (chairman), consultant in thoracic medicine, Llandough and Sully hospitals, Cardiff; Dr C R McGavin (coordinator and compiler of the report), chest physician, Plymouth Chest Clinic; Dr J A R Friend, consultant in thoracic medicine, City Hospital, Aberdeen; Dr R M Greenwood, member of scientific team, Division of Computing and Statistics, Clinical Research Centre, Harrow, Middlesex; Dr P A Jenkins, head of department, Mycobacterium Reference Unit, University Hospital of Wales, Cardiff; and Dr A R Somner, consultant physician, Chest Clinic, Wallsend, Tyne and Wear.

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Patients and methods

Patients aged between 15 and 80 with tuberculosis of the cervical, axillary, or inguinal lymph nodes were studied provided they had never received chemotherapy for tuberculosis. Pregnant women, patients with active pulmonary tuberculosis, and patients with important impairment of visual, hepatic, or renal function were not included.

Patients entering the study were divided into three groups according to the way in which they had been managed on presentation: those who had undergone surgical removal of all affected nodes (group 1); those who had undergone biopsy or needle aspiration of nodes for diagnostic purposes (group 2); and those in whom the initial diagnosis had been made clinically supported by a positive tuberculin test (Mantoux 10 tuberculin units, induration $\times 10$ mm, or Heaf grade 3 or 4) (group 3). Within each group sets of four patients were randomly allocated to receive either nine or 18 months' treatment with rifampicin and isoniazid. All patients received ethambutol (15 or 25 mg/kg body weight) for the first eight weeks. The dose of rifampicin was 600 mg orally for patients weighing 50 kg or more and 450 mg orally for those weighing less than 50 kg. The dose of isoniazid was 300 mg. All drugs were given once daily, and the patients were managed according to each doctor's usual practice. Patients were not given corticosteroids.

Before chemotherapy was started the positions of palpable lymph nodes and biopsy and resection scars were drawn on a diagram. Also recorded were diameters of node, lengths of scars, and the presence of fluctuation or a sinus. Histological and microbiological examinations were carried out at laboratories at local hospitals. Positive cultures were sent to the Mycobacterium Reference Unit in Cardiff for identification and sensitivity testing. The doctor assessed lymph nodes and scars and recorded fresh nodes and sinuses every month for three months after treatment was begun and thereafter at six, nine, 12, 15, 18, 24, and 36 months. Patients who received nine months' chemotherapy were reviewed three, six, nine, 15, and 27 months after the end of chemotherapy, whereas those who received 18 months' treatment were reviewed six and 18 months after the end of chemotherapy. A node was judged to have disappeared when its diameter was recorded as 5 mm or less and to have enlarged when an increase in diameter of 10 mm or more was recorded.

Results

One hundred and fifty two patients from 21 centres in Britain were accepted into the trial between December 1979 and June 1981. Thirty nine patients were withdrawn from the study before review at 36 months; table I shows their characteristics and reasons for their withdrawal. No important differences were seen between the patients who were taking the nine and 18 month regimens in terms of withdrawals, and those patients who were withdrawn did not differ in any important respect from the patients left in the trial. Of the two patients with drug resistant organisms, one was Asian and the other Europid.[5] Eight of the patients were withdrawn during follow up after chemotherapy, four from both regimens, and in these patients progress up to the end of chemotherapy was satisfactory.

Of the remaining 113 patients, 56 were receiving the nine month and 57 the 18 month regimen. Table II summarises their characteristics and their distribution between groups. Twenty three Europid patients and four patients of other and mixed racial origins were combined as non-Asians. The mean age of the Asian group was 33 years and of the non-Asian group 47 years. The infected nodes were cervical only in 98 patients, axillary only in seven, cervical and axillary in seven, and inguinal in one.

The diagnosis was confirmed by culture or histological examination, or both, in all 32 patients in group 1 and in 59 of the 62 patients in group 2 (table III). For the remaining three patients in group 2 no specimens were submitted for histological examination and the results of culture were negative. The specimens submitted for microbiological examination were pus in 19 cases, nodal tissue in 27, and unspecified in 14. Positive cultures were obtained from 13 specimens of pus and 16 specimens of nodal tissue; the difference was not significant. *Mycobacterium bovis* was isolated from a 60 year old non-Asian man; the other strains isolated were *M tuberculosis* sensitive to rifampicin, isoniazid, and ethambutol.

Table IV summarises the progress of patients during chemotherapy, which was entirely satisfactory in 84 of the 113 patients. Events marred the progress of 29 patients; all occurred during the first eight months' treatment. No important differences were seen between the two regimens. Fresh nodes appeared in 13 patients; in four of these fresh nodes were recorded twice. Eleven of the 17 fresh nodes appeared during the first three months of treatment. Enlargement of existing nodes was recorded in 13 patients; in seven the increase in diameter of the node was 10 mm, in four it was 20 mm, and in two it was 30 mm or more. Fluctuation of the nodes developed in eight patients, and further surgical procedures, including aspiration of pus, were done in 10. Nine months after the start of chemotherapy nodes were still palpable in seven patients given the nine month regimen and 15 taking the 18 month regimen. Residual lymph nodes were palpable at the end of chemotherapy in 10 patients.

TABLE I—*Characteristics of 39 patients withdrawn from trial and reasons for withdrawal*

	Duration of treatment		
	Nine months (n = 20)	18 months (n = 19)	Total (%) (n = 39)
Characteristics:			
Asian	14	13	27 (69)
Non-Asian	6	6	12 (31)
Male	11	7	18 (46)
Female	9	12	21 (54)
Mean age (years)	37	37	37
Reasons for withdrawal:			
Chemotherapeutic error	6	7	13
Non-attendance	8	5	13
Emigration	3	2	5
Diagnostic error	1	2	3
Drug resistant organism*	2		2
Non-tuberculous death		2	2
Hepatitis during treatment		1	1

**Mycobacterium tuberculosis* resistant to isoniazid in one case and to both streptomycin and isoniazid in the other.

TABLE II—*Characteristics of 113 patients in trial and number in each group*

	Duration of treatment					
	Nine months (n = 56)		18 months (n = 57)		Total (n = 113)	
	No	Mean age (years)	No	Mean age (years)	No (%)	Mean age (years)
Asian:						
Male	22	30	15	30	37 (33)	30
Female	23	40	24	38	47 (42)	36
Non-Asian:						
Male	2	65	5	41	7 (6)	48
Female	9	47	13	42	22 (19)	47
Group:						
1	18	35	14	48	32 (28)	40
2	30	37	32	37	62 (55)	37
3	8	32	11	30	19 (17)	31

TABLE III—*Microbiological and histological results for patients in groups 1 and 2*

	Microbiological culture				Histology			
	Positive	Negative	Not done	Total	Positive	Negative	Not done	Total
Group 1	11	6	15	32	30	1	1	32
Group 2	34	9	19	62	42	1	19	62

TABLE IV—*Progress during chemotherapy*

	Duration of treatment		
	Nine months (n = 56)	18 months (n = 57)	Total (%) (n = 113)
No of patients with uneventful progress	42	42	84 (74)
No of patients with events during chemotherapy	14	15	29 (26)
No of events during chemotherapy	21	28	49
No of patients with residual nodes at end of chemotherapy	7	3	10 (9)
Events:			
Fresh nodes	5	8	13 (12)
Increase in size of node	8	5	13 (12)
Fluctuation of nodes	4	4	8 (7)
Formation of sinuses		3	3 (3)
Breakdown of scars		2	2 (3)
Further surgical procedures	4	6	10 (9)

Table V shows the progress of the patients after chemotherapy. Progress was entirely satisfactory in 101 patients and events were recorded in 12, seven of whom received the nine month regimen and five the 18 month regimen. In 10 of these 12 patients no events were recorded more than six months after treatment. Two patients who received the short course of treatment and three who received the long course had residual nodes at 36 months. Further chemotherapy was given to two patients who had received the short course. In one patient nodes enlarged three months after treatment, which was restarted by the doctor without any specimens having been obtained. Of the nine other patients whose nodes enlarged, two underwent node biopsy.

TABLE V—*Progress after chemotherapy*

	Duration of treatment		
	Nine months (n = 56)	18 months (n = 57)	Total (%) (n = 113)
No of patients with uneventful progress	49	52	101 (89)
No of patients with events after chemotherapy	7	5	12 (11)
No of events after chemotherapy	10	5	15
No of patients with residual nodes at 36 months	2	3	5 (4)
Events:			
Appearance of fresh nodes	2		2
Increase in size of nodes	6	4	10 (9)
Fluctuation of nodes	1		1
Formation of sinuses			
Breakdown of scars			
Further surgical procedures	1	1	2

The tissues obtained were sterile but histologically showed caseating tuberculous adenitis. One of these two patients received further chemotherapy despite negative culture; the other was not retreated and remained well. No relapse was recorded on microbiological examination. Table VI summarises the timing of events during and after chemotherapy. No important differences in outcome were seen when the data were examined according to the way in which the patients were managed initially—that is, by group.

TABLE VI—*Timing of events during and after chemotherapy (figures are numbers of patients with events)**

Duration of chemotherapy	Month after treatment started									
	1	2	3	6	9	12	15	18	24	36
Nine months (n = 56)	6	4	3	3		6	1			
18 months (n = 57)	4	2	5	5	1				3	2

*Some patients had several events at one time and others had single events at different times.

Discussion

Tuberculosis of lymph nodes was reviewed by Campbell and Dyson, who described a prospective controlled trial of two 18 month regimens.[2] The population of the present study was similar to that described by Campbell and Dyson in terms of race (predominantly Asian) and sex distribution (predominantly women). The response of lymph nodes to the present regimen was similar to that observed by Campbell and Dyson, who used isoniazid and ethambutol or isoniazid and rifampicin, both regimens being supplemented with streptomycin for the first two months. In 2% of their patients, however, nodes enlarged during the last half of the regimens, a result that we did not observe. Of our patients receiving treatment for 18 months, 3 (5%) had residual nodes at the end of treatment compared with 13% in the previous study.

Short course regimens have been assessed prospectively in pulmonary tuberculosis but not tuberculosis of lymph nodes. All the events after chemotherapy in the patients who took the nine month course occurred within six months after the end of treatment, during which time the patients taking the 18 month course were still receiving treatment. During the subsequent 21 months' follow up no further events occurred in those who had taken the short course regimen. After treatment no relapse was recorded microbiologically in the 27 months' follow up of the 56 patients who had taken the nine month regimen or in the 18 months' follow up of the 57 patients who had taken the 18 month regimen. The one patient who was retreated without further histological or microbiological specimens being obtained may have had a true relapse, but results from this and previous studies show that nodes may enlarge and new nodes appear both during and after chemotherapy without indicating a failure of treatment or relapse. These nodes may show histological features characteristic of tuberculosis but be sterile on culture. The enlargement may be due to a reaction to tuberculoprotein. Our study provides no evidence that surgical removal of nodes is advantageous in the treatment of tuberculosis of lymph nodes. Furthermore, an operation is not necessarily indicated for nodes that enlarge after treatment because this enlargement is usually transient.

This report suggests that a nine month regimen comprising rifampicin and isoniazid is adequate treatment for tuberculosis of lymph nodes. A further report will be written when the five year follow up is complete.

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