PAPERS AND SHORT REPORTS

Respiratory impairment induced by smoking in children in secondary schools

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Abstract

A longitudinal study was carried out from 1975 to 1979 in a cohort of 405 secondary school children. At yearly intervals they underwent a series of tests of pulmonary function designed to monitor lung development; some of these tests are relatively sensitive indicators of early abnormalities. A self administered questionnaire provided details of smoking habits and respiratory symptoms. The prevalence of smoking increased with age; most of those smoking at 16 had already been smoking, at least experimentally, at 13. Taking up smoking was clearly associated with the early onset of cough, production of phlegm, and shortness of breath on exertion.

After two years of smoking more than a few cigarettes a day the children who smoked appeared considerably less healthy than their non-smoking peers and showed some evidence of early obstruction of the airways.

Introduction

Previous reports from this department have described the results from two cross sectional questionnaire surveys of smoking habits and respiratory symptoms in a secondary school population in 1975 and 1979.[1 3] The present report gives the results of a prospective study of a cohort of 405 children studied from 1975 to 1979, with yearly assessment of smoking habits, respiratory symptoms, and respiratory function. Our main objective was to document the natural history of smoking and the development of symptoms and pulmonary function during early adolescence and to see whether children who smoked were less healthy than children who did not smoke.

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Subjects and methods

We studied children attending two secondary schools in the outer London borough of Hounslow. Within these two coeducational schools all 628 children in the second school year were asked, via their parents, to participate in the study. Participation entailed four visits after school, at roughly yearly intervals, to a lung function laboratory. On each visit children completed a confidential questionnaire, based on that of the Medical Research Council for respiratory symptoms.[4] The questions on which the subsequent analysis was based were: (1) Do you usually cough first thing in the morning or during the day, in the summer or in the winter, or both? (2) Do you get short of breath when hurrying on the level or walking up a slight hill? (3) Do you bring up any phlegm from your chest first thing in the morning, during the day, or at night?

The children were classified according to smoking habit as non-smokers ("I have never smoked a cigarette); experimental smokers ("I have smoked the odd one or two cigarettes"); ex-smokers ("I used to smoke regularly but I do not at all now"); or regular smokers ("I smoke more than one cigarette every day").

A range of respiratory function tests, including several that are considered to be fairly sensitive indicators of early pulmonary abnormalities, were performed. These included forced expiratory flow volume curves,[5] single breath nitrogen washout,[6] multibreath nitrogen washout[7] to determine functional residual capacity, and standard spirometry, which, with the measurement of functional residual capacity, permitted derivation of all lung volume divisions. Standing height and weight were noted at each visit, and an estimate of recent exposure to cigarette smoke was obtained from a measurement of mixed expired carbon monoxide concentration.[8]

Statistical analysis—Descriptive analyses of all data were performed with the statistical package for the social sciences[9]; sex, visit number, and smoking habit were taken as the main selection variables. Quantitative data, if normally distributed, were recorded as means (SD), and qualitative data, such as symptoms, were recorded in the form of contingency tables. Groups were compared with paired t tests or χ^2 analysis, using McNemar's paired test as appropriate.[10] We took $p < 0.05$ as indicating significance in two tailed tests.

Representativeness of the schools was assessed by comparing the answers in the initial cross sectional questionnaire in 1975 given by

the children from the two schools[1 2] with those given by children in the same year from 13 out of the 15 other schools in the borough. The χ^2 test was used to analyse differences in sex distribution, prevalence of cough, production of phlegm, shortness of breath on mild exercise, ethnic origin, and smoking habit.

Representativeness of the study cohort—We identified the cross sectional questionnaires completed in 1975 by those children from the two selected schools and within the school year from which the study cohort was ultimately formed. The answers given by those within the cohort were compared with those given by the children not in the cohort because of refusal or inability to take part in the prospective study. Differences were analysed as above with the χ^2 test.

Results

There was no significant difference between children in the schools chosen for study and children in the other schools in the borough, or between children in the cohort and children not in the cohort but in the same year and school. The cohort was therefore considered to be representative.

DESCRIPTION OF COHORT AND ITS SMOKING HABITS

Table I shows the constitution of the cohort during the four years of the study. Follow up of the 92 children who failed to attend after at least two requests showed that in all but 27 cases the reason for non-attendance was not connected with the study. In the second, third, and fourth years of the study χ^2 analysis was used to compare those who had dropped out with the remainder of the cohort in terms of smoking category for the previous year; there were no significant differences.

As expected from the findings of the cross sectional studies in 1975[1 2] and 1979[3] the prevalence of regular smoking increased throughout the study and was roughly equivalent in the two sexes. Table II shows the prevalence of regular smoking and of non-smoking in children in the cohort and in children of an equivalent age in the two cross sectional studies. Although the longitudinal study started with fewer regular smokers and more non-smokers, these differences disappeared towards the end.

Table III shows the natural history of smoking habits in those children who attended each year and were either non-smokers at the start or regular smokers at the end of the study. Of those who smoked regularly at the age of 16, 19 (24%) had been non-smokers at the age of 13 and only four (5%) at 14. Conversely, of those who did not smoke at the age of 13, only 21 (13%) were smoking regularly at 16, with a further 43 (27%) classifying themselves as experimental smokers.

Table IV shows the reported daily cigarette consumption of the regular smokers. The intensity of smoking clearly increased throughout the study.

RESPIRATORY SYMPTOMS

Regular smokers

The relation between smoking habit and cough, production of phlegm, and shortness of breath on exertion (dyspnoea) was studied in the following way: at each of the four visits regular smokers were classified in terms of how long they had smoked (one, two, three, or four years) and their average daily cigarette consumption over that period classified as low (<7 cigarettes/day) or high (≥7 cigarettes/day).

At each visit regular smokers were matched with a non-smoking child of the same sex, and of as similar height and age as possible; height was more important than age. The two groups were compared for each symptom with McNemar's paired χ^2 analysis.[10] Matching was achieved in all but eight of the 195 instances in which regular smoking and symptomatology were reported. The adequacy of matching for age and height was shown by the small differences in the mean values for each group: height (cm): year 1, 0·2; year 2, 0·1; year 3, 0·1; year 4, 0·2; age (months): year 1, 0·1; year 2, 0·4; year 3, 0·4; year 4, 0·2). Paired *t* test analysis showed no significant differences.

Table V shows the results. Except in the nine children who had smoked for at least four years there was a significantly greater prevalence of all symptoms in regular smokers than matched non-smokers; dyspnoea and production of phlegm were more prevalent than cough in those who had smoked for one or two years. The effects of increased cigarette consumption appeared to be less sig-

TABLE II—*Number (%) of children in cohort not smoking and smoking regularly in successive years compared with number (%) in corresponding age group in each cross sectional study*[1 3]

	Year 1	Year 2	Year 3	Year 4
Regular smokers				
1975 cross sectional study	506 (10·8)*	649 (16·5)*	950 (21·4)	875 (27·5)
1979 cross sectional study	422 (8·5)*	627 (13·7)*	1063 (19·0)	868 (20·7)†
Present cohort	14 (3·5)	37 (10)	66 (19·2)	82 (26·2)
Non-smokers				
1975 cross sectional study	1898 (40·4)*	1353 (34·4)*	1398 (31·5)	922 (29·0)
1979 cross sectional study	2050 (41·3)*	1607 (35·1)*	1779 (31·8)	1333 (31·8)
Present cohort	199 (49·1)	168 (45·5)	124 (36·0)	102 (32·6)

Significance of difference between findings in the present cohort and in previous studies: *$p < 0.001$, †$p < 0.05$.

TABLE III—*Development of reported smoking habit in children who were non-smokers at start of study and in children who were regular smokers at end of study. Only children who attended in all four years are included*

	Year 1	Year 2	Year 3	Year 4
Regular smokers at fourth visit				
Non-smokers	20	4	1	
Experimental smokers	45	46	24	
Ex-smokers	8	4	3	
Regular smokers	7	26	52	80
Non-smokers at first visit				
Non-smokers	160	132	102	96
Experimental smokers		24	51	42
Ex-smokers			2	2
Regular smokers		4	5	20

TABLE IV—*Reported cigarette consumption each year. Data expressed as numbers (%) of regular smokers*

No of cigarettes/day	Year 1	Year 2	Year 3	Year 4
1-5	10 (71)	18 (49)	24 (36)	20 (24)
6-10	4 (29)	18 (49)	29 (44)	39 (48)
11-15		1 (2)	9 (14)	17 (21)
16-20			4 (6)	4 (5)
21-25				2 (2)

TABLE I—*Details of cohort and its smoking habits*

Year	No observed (%)			Mean (SD) age (months)	Mean (SD) height (m)		Smoking habit (No (%))							
							Non-smokers		Experimental smokers		Ex-smokers		Regular smokers	
	Total	Boys	Girls		Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1	405	206	199	156 (4·8)	1·55 (0·07)	1·55 (0·07)	92 (44·7)	107 (53·8)	86 (41·8)	74 (37·2)	19 (9·2)	13 (6·5)	9 (4·4)	5 (2·5)
2	369 (91)	193 (94)	176 (88)	168 (5·0)	1·62 (0·05)	1·59 (0·06)	87 (45·1)	81 (46·0)	76 (39·4)	69 (39·2)	12 (6·2)	7 (4·0)	18 (9·3)	19 (10·8)
3	344 (85)	178 (86)	166 (83)	180 (4·7)	1·68 (0·07)	1·61 (0·06)	61 (34·3)	63 (38·0)	77 (43·4)	63 (38·0)	6 (3·4)	8 (4·8)	34 (19·1)	32 (19·3)
4	313 (77)	159 (77)	154 (77)	189 (4·3)	1·72 (0·07)	1·62 (0·07)	50 (31·5)	52 (33·8)	62 (39·0)	50 (32·5)	7 (4·4)	10 (6·5)	40 (25·2)	42 (27·3)

TABLE V—*Symptoms in smokers (grouped according to whether they had a high (≥7 cigarettes/day) or a low (<7 cigarettes/day) consumption) and matched non-smokers*

Duration of smoking (years)	Consumption	n	No reporting presence of: Cough				Dyspnoea				Phlegm			
			Smokers	Non-smokers	p*	Odds ratio†	Smokers	Non-smokers	p*	Odds ratio†	Smokers	Non-smokers	p*	Odds ratio†
1	All	96	43	26	0·014	2·4	36	9	<0·001	7·8	34	12	<0·001	7·7
	High	43	24	12	0·015	14·0	16	5	0·009	8·0	17	7	0·038	4·5
	Low	53	19	14	0·70	1·4	20	4	0·002	7·7	17	5	0·009	14·0
2	All	54	27	13	0·012	3·3	24	7	<0·001	9·5	31	3	<0·001	29·0
	High	27	15	5	0·009	6·0	12	2	0·010	12·0	14	1	0·002	14·0
	Low	27	12	8	0·55	2·0	12	5	0·078	7·0	17	2	<0·001	3·8‡
3	All	28	16	4	0·003	13·0	12	4	0·042	5·0	18	5	<0·001	3·3‡
	High	15	9	2	0·024	1·8‡	6	2	0·24	5·0	12	3	0·003	2·3‡
	Low	13	7	2	0·13	7·0	6	2	0·13	5·0	6	2	0·13	1·0‡
4	All	9	5	1	0·13	1·0‡	2	0	0·49	0·5‡	4	1	0·25	0·8‡

*Based on McNemar's χ^2 analysis.
†Cornfield's odds ratio for paired data; point estimates are stated except where the value is infinity (‡), when the lower 95% confidence limit is given.
A table showing the 95% confidence limits for odds ratio is obtainable from Dr L Adams.

TABLE VI—*Pulmonary function* in smokers (grouped according to whether they had a high (≥7 cigarettes/day) or a low (<7 cigarettes/day) consumption) and matched non-smokers. Data expressed as means†*

Duration of smoking (years)	Consumption	n	Peak flow rate (l/s)			Forced expired volume in 1 s (l)			Forced vital capacity (l)			Expiratory flow at 50% vital capacity (l/s)			Slope of phase III of single breath nitrogen washout test (%/l)		
			Smokers	Non-smokers	p‡	Smokers	Non-smokers	p‡	Smokers	Non-smokers	p‡	Smokers	Non-smokers	p‡	Smokers	Non-smokers	p‡
1	All	96	6·88	6·92	0·82	3·04	3·01	0·46	3·64	3·47	0·007	4·14	4·18	0·70	1·31	1·28	0·67
	High	43	7·22	6·96	0·17	3·25	3·17	0·37	3·77	3·66	0·27	4·10	4·12	0·88	1·31	1·34	0·80
	Low	53	6·59	6·88	0·20	3·13	3·08	0·68	3·53	3·31	0·008	4·15	4·22	0·68	1·32	1·23	0·40
2	All	54	7·08	7·32	0·21	3·19	3·03	0·034	3·75	3·51	0·002	4·17	4·42	0·15	1·44	1·21	0·019
	High	27	7·15	7·21	0·90	3·34	3·10	0·023	3·86	3·60	0·004	4·13	4·56	0·008	1·51	1·16	0·006
	Low	27	7·01	7·43	0·17	3·17	3·11	0·60	3·64	3·42	0·11	4·20	4·29	0·72	1·35	1·27	0·50
3	All	28	6·80	7·41	0·015	3·16	3·09	0·48	3·69	3·57	0·30	4·05	4·12	0·31	1·37	1·31	0·80
	High	15	6·91	7·74	0·026	3·26	3·22	0·82	3·80	3·69	0·75	4·16	4·53	0·37	1·47	1·10	0·084
	Low	13	6·66	7·04	0·27	3·06	2·86	0·26	3·56	3·44	0·38	3·93	3·63	0·34	1·28	1·45	0·48
4	All	9	7·08	7·60	0·30	3·52	3·14	0·088	3·99	3·74	0·17	4·66	3·99	0·22	1·32	1·53	0·44

*Poorer function is indicated by lower values in all variables except the slope of phase III of the single breath nitrogen washout test, when it is indicated by higher values.
†In each test SDs for smokers and non-smokers were of a consistent magnitude.
‡Based on paired *t* test analysis.
A table showing the correlation coefficients r of the paired data from smokers and non-smokers is obtainable from Dr L Adams.

nificant because of the sizes of the groups; at each stage, however, cough was more prevalent in those with a high cigarette consumption, whereas there appeared to be no consistent trend for dyspnoea or phlegm production. The relative risk of a symptom developing as a result of smoking was assessed by Cornfield's odds ratio.[11] In general, the relative risk did not seem to increase with duration of smoking.

Experimental smokers

A two by two contingency table for each symptom was established separately for those who said that they had been experimental smokers for one, two, three, and four years respectively. The equivalent population of non-smokers served as a reference group. Analysis with the χ^2 test did not show any significant differences for any of the symptoms in those who had been experimental smokers for two, three, or four years. Those, however, who had smoked experimentally for one year showed a significantly higher prevalence of cough ($p<0·05$) and dyspnoea ($p<0·001$) but not of production of phlegm.

Ex-smokers

Analysis of the data for this group was difficult because of its small size and because many of those in it gave inconsistent information about their smoking habits over the years of the study. Analysis with the χ^2 test using the same classifications as for experimental smokers, showed no significant differences between ex-smokers and non-smokers.

RESPIRATORY FUNCTION

On the basis of a preliminary examination of those variables of lung function that were measured, seven were selected for comparison between the same smoking and matched non-smoking groups used for symptoms. These variables were functional residual capacity, residual volume, forced vital capacity, forced expired volume in one second, peak flow rate, expiratory flow at 50% vital capacity, and slope of phase III of the single breath nitrogen washout test. These measures include variables of lung size (functional residual capacity, residual volume, forced vital capacity), resistance of large airways (peak flow rate, forced expired volume in one second), and function of small airways (expiratory flow at 50% vital capacity, slope of phase III of the single breath nitrogen washout test).[12] Peak flow rate, forced vital capacity, and forced expired volume in one second have been widely quoted in research related to smoking,[4 12] and studies in our laboratory have suggested that expiratory flow at 50% vital capacity and the slope of phase III of the single breath nitrogen washout test provide the most sensitive indications of early abnormalities of the airways in adults (unpublished observations).

Regular smokers—Table VI summarises the results of tests in which differences were found. In all groups forced vital capacity was greater in smokers than non-smokers, and this difference was significant in those who had been smoking for up to two years; these differences were reflected in the measurements of forced expiratory volume in one second. In contrast, no significant differences were found for functional residual capacity and residual volume. The greatest differences were in expiratory flow at 50% vital capacity and the slope of phase III of the single breath nitrogen washout test, which indicated worse lung function after two and three years' smoking in children with a high cigarette consumption, but these differences were significant only after two years' smoking. Peak flow rate was lower in the smokers than the non-smokers in the second, third, and fourth years of smoking, but differences in peak flow rate were significant only in the third year, except in the group with a low cigarette consumption. The small number of children who smoked regularly for four years made the results for this group difficult to interpret.

Experimental smokers and ex-smokers—In view of the small differences between regular smokers and controls and the fact that

these differences occurred only with high cigarette consumption, no attempt was made to perform a similar analysis with experimental smokers or ex-smokers.

Discussion

Two cross sectional surveys of all secondary school children in the London borough of Hounslow, performed by this department in 1975[1,2] and 1979,[3] showed that four years of antismoking health education had had little impact on smoking behaviour. Moreover, a study carried out in 1982 of a sample of secondary school children throughout mainland Britain indicated that there had been little change in attitudes to smoking or in its prevalence and growth.[14]

Although the present cohort appeared to be representative of the whole secondary school population in Hounslow there was a significantly lower prevalence of smoking and a higher prevalence of non-smoking in children aged 13 and 14 in this longitudinal study than in the cross sectional studies. The fact that these differences disappeared later on makes it difficult to suggest an obvious explanation. Interestingly, however, these apparently discrepant observations in the cohort agree with those reported in the recent national study, in which the sample was similarly small.[14] Although we showed that those who dropped out of the cohort were representative of the group as a whole in terms of smoking behaviour at their last recorded visit, we could not be sure in many cases that the children's subsequent failure to attend was not influenced by the fact that they had started to smoke; however, the prevalence of smoking in the cohort in the fourth year of the study was similar to that reported in our previous surveys and in other surveys, which argues against this.[14-16]

Although prevalence of smoking increased appreciably with the age of the group, it did not differ between boys and girls; this supports recent evidence that the prevalence of smoking in girls has caught up with that in boys, in whom it had previously been much greater. For this reason, and because the cohort provided relatively small numbers of regular smokers, we analysed the development of smoking and its relation to respiratory problems in both sexes together.

Details of smoking habit recorded each year clearly showed an increase in regular smoking with age. By observing the trends in smoking habit in individual children over the four years, however, we found that subsequent behaviour patterns are to some extent established by the age of 13. Thus those who at 13 say that they do not smoke are much less likely to be smoking regularly at 16 than those who admit to having smoked the "odd one or two."

The increase in cigarette consumption at successive visits in those of the cohort reporting regular smoking was as expected from cross sectional surveys.[2,3,14] There is firm evidence that, in responding to a questionnaire, children tend to play down their smoking experiences[14] and that figures reported for both prevalence and intensity of smoking may be underestimates. In this study, however, the children were generally aware that one of the tests (measurement of expired carbon monoxide concentrations) could detect exposure to cigarette smoke and for this reason may have been more inclined to respond honestly. Indeed, an increased expired carbon monoxide concentration was hardly ever observed in those reporting themselves as non-smokers, experimental smokers, or ex-smokers.

In our examination of the development of respiratory symptoms and functional impairment related to smoking, data from any visit at which regular smoking was recorded were used independently and classified according to the duration of regular smoking and average cigarette consumption during that period. This approach allowed all data in smokers to be used to produce groups of sufficient size for meaningful analysis. Any differential effects of sex, age, and size should have been accounted for by the pairing of data from smokers with data from matched non-smokers; although factors such as time of year and ethnic origin were not considered, it is unlikely that finding the best match would result in consistent differences in such variables.

The effectiveness of the matching procedure allowed statistical tests (McNemar's, χ^2, and paired t tests) of considerable power to be used. Calculation of the correlation coefficient in paired t tests indicated that pairing was always effective in reducing subject variability for peak flow rate, forced expired volume in one second, and forced vital capacity and was sometimes effective, albeit less so, for expiratory flow at 50% vital capacity and the slope of phase III of the single breath nitrogen washout test. Pairing did not reduce the effectiveness of the t test on any occasion.

The results show that symptoms are more prevalent even after only one year of regular smoking and that such symptoms continue to be reported more often while smoking persists. Even those who experiment with smoking initially report more symptoms than non-smokers. In this study the children who did not smoke reported an extraordinarily high prevalence of relevant symptoms.

Our results did not show any effect of smoking on lung growth. Our finding that those who take up smoking have larger vital capacities was surprising, but this has been previously reported.[17] Despite this difference peak flow rate was consistently higher in non-smokers than smokers from the second year onwards. The data suggest that this resulted from a failure of peak flow rate in the smoking group to increase as the mean age increased. These differences became significant at three years in those with a high cigarette consumption. This may have been partially due to the relatively high peak flow rate in the matched non-smoking group, but when all smokers at three years were considered a significant difference was still observed without a relatively high peak flow rate in the non-smoking group. The significantly poorer function of the small airways at two years in those who smoked more was not observed at three years; the differences in mean expiratory flow at 50% vital capacity and the slope of phase III of the single breath nitrogen washout test were, however, maintained, and this loss of significance probably resulted from a decrease in the size of the group. The degree of impairment shown in the lung function tests was so small that if the results were taken individually they would not be considered to be abnormal.

The present study shows that the health of school children may be impaired by regular smoking.

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Comparison of regimens of treatment with sodium stibogluconate in kala-azar

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Abstract

One hundred and twenty six patients with kala-azar (visceral leishmaniasis) were allocated at random to one of two groups for treatment with sodium stibogluconate. One group was treated for 20 days; in the other group the patients were assessed after 20 days' treatment and treatment was continued if necessary. Both groups were followed up for six months. There was no significant difference in symptomatic outcome between the two groups at 20 days. At six months eight of the patients in the group treated for 20 days had relapsed and 54 were cured. Of the group given more than 20 days' treatment if necessary, 62 were cured and none had relapsed (12 required more than 20 days' treatment). This difference between the two groups was significant. One patient in each group did not respond to sodium stibogluconate, but both were cured with pentamidine. Altogether 104 patients were cured after 20 days' treatment; 20, including the eight who relapsed, were cured after more than 20 days' treatment. There was no significant difference between the two groups in the side effects of the drug, which were minor. The longer courses of treatment (50 days in one patient) were well tolerated.

It is suggested that the traditional six day course of treatment with sodium stibogluconate for kala-azar is grossly inadequate and that a longer course is required to prevent relapse.

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Introduction

In the 1970s Bihar province in India experienced a massive epidemic of kala-azar (visceral leishmaniasis), and the disease is still endemic in some areas. Out of the 400 000 new cases of leishmaniasis in the world in 1977,[1] a quarter occurred in Bihar.[2 3] Sodium stibogluconate was used as a first line drug during this epidemic. Manson-Bahr's regimen of six days' treatment with sodium stibogluconate,[4] still advocated in current editions of most textbooks,[5-8] was the standard treatment in India.

A committee of Indian experts suggested that two courses of sodium stibogluconate lasting for 10 days each and interrupted by a break of 10 days should be adequate to treat Indian kala-azar.[2] This was a modified version of Manson-Bahr's regimen of treatment for Kenyan kala-azar.[9] We had found Manson-Bahr's regimen for Indian kala-azar grossly inadequate, and even with the regimen suggested by the committee of Indian experts the incidence of relapse was high.[10 11] We started to give the drug continuously for 20 days, or even longer in some cases, and the incidence of relapse (0·5%) was almost negligible.[12] This encouraged us to compare in a randomised trial the efficacy, safety, and desirability of giving the drug for 20 days, or longer if necessary. We report the outcome of that trial.

Patients and methods

We undertook this trial to see whether treatment with antimony for 20 days, or longer if necessary, was effective and could be tolerated by Indian patients with kala-azar. A subsidiary aim was to confirm that it is not necessary to give an initial dose of 1 or 2 ml to test for hypersensitivity. On the basis of previous experience, assuming the incidences of drop out and of spontaneous cure to be 0% and the incidence of cure with the standard treatment to be 70%, and with the difference in the incidence of cure between the standard treatment and the new treatment expected to be 20%, we used a sample size of at least 60.[13]

The study was conducted from January 1981 to November 1982. All patients at this hospital with kala-azar, confirmed by the finding of amastigotes of leishmania (figure) in smears of bone marrow or spleen stained with Giemsa, were included in the study. Patients were excluded if they had haemoglobin concentrations below 3 g/dl; had complications such as pneumonia, jaundice, tuberculosis, or renal disease; or had received treatment with antimony or pentamidine for kala-azar before coming to this hospital. A total of 126 patients (104 men and 22 women (ratio 4·4:1)) were entered into the trial. Equal numbers of men and women were randomly allocated to two