

A second international cooperative investigation into thioacetazone side effects *

2. Frequency and geographical distribution of side effects

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As part of a large-scale international cooperative investigation into the side effects of thioacetazone-containing regimens in the treatment of tuberculosis, an evaluation has been made of the variation in the frequency of side effects between different countries and between different centres in the same country and of the likely reasons for this variation. In 3 countries patients of different racial origin were under observation in the same hospital. Over a 12-week period of treatment there was considerable variation between the countries and centres in the overall frequency of side effects and of those leading to a major departure from prescribed treatment, the variation being similar for the two thioacetazone-containing regimens and for the streptomycin plus isoniazid control regimen, though at a lower level for the latter. In Malaysia, Singapore, and Trinidad, where different racial groups were under treatment, there was no clear indication that race was an important factor in explaining the differences between countries, except for cutaneous side effects in Trinidad and possibly in Malaysia.

It is concluded that the differences in the frequency of side effects to thioacetazone-containing regimens probably result from variation in the closeness of supervision of patients, in the recording and interpretation of side effects, and in environmental factors including the previous use of other medicaments or exposure to sensitizing substances.

It has been shown in a large-scale international cooperative investigation (Miller et al., 1970) that there was at most a slender and clinically unimportant benefit from the use of a vitamin and antihistamine supplement in preventing side effects to thioacetazone. Another important aspect of this investigation was the study of the frequency of side effects to thioacetazone in a number of countries, particularly in Asia and North Africa, that did not participate in the First International Co-operative Thiocetazone Side-Effect Investigation (Miller et al., 1966). This was desirable because the first investigation had shown the need for further study of geographical variations and their causes. A feature of

3 of the countries included in the present investigation was that patients of different racial origin were under study in the same hospital.

This report considers the geographical distribution of thioacetazone side effects and, in particular, the possible influence of the patients' racial origin. Another report gives the details of rashes reported during the investigation (Ferguson et al., 1971).

PLAN AND CONDUCT OF THE INVESTIGATION

Drug regimens

Full details of the plan and conduct of the study were given in the earlier report (Miller et al., 1970). In brief, patients were admitted to the cooperating centres and allocated at random to one of three regimens:

STH daily doses of 1 g of streptomycin intramuscularly, together with 150 mg of thioacetazone and 300 mg of isoniazid in a single tablet;

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- SH daily doses of 1 g of streptomycin intramuscularly, together with 300 mg of isoniazid in a single tablet; and
- TH daily doses of 150 mg of thioacetazone and 300 mg of isoniazid in a single tablet.

Within each regimen, by random allocation, half of the patients received an additive supplement of vitamins and an antihistamine and the remainder received a placebo supplement. Both were incorporated within the tablet of oral medicament as a yellow core. In view of the lack of any appreciable prophylactic effect of the additive supplement on side effects (Miller et al., 1970) the additive and placebo subgroups within each regimen have been amalgamated in this report.

The oral medicaments were specially made for this investigation and were similar in appearance and taste. The duration of chemotherapy was 12 weeks.

Selection of patients

The investigation was restricted to patients aged 15 years or over, with active pulmonary tuberculosis, who had had either no previous antituberculosis chemotherapy or chemotherapy for less than 2 weeks but not including thioacetazone or any other thiosemicarbazone preparation, and who were considered to be cooperative and likely to remain in hospital for 12 weeks.

Patients were ineligible if they were in very poor general condition, weighed less than 32 kg, had a haemoglobin level of less than 6 g/100 ml, were known to be pregnant, or had a nontuberculous disease that might contraindicate either the use of thioacetazone (for example, advanced liver disease) or injections of streptomycin (for example, advanced nephritis).

Investigations

The investigations both before and during treatment were kept to a minimum. In all centres a haemoglobin estimation, a total and differential white cell count, and a urine test for protein and sugar were carried out before treatment. At 12 weeks the urine test for protein and sugar was repeated. Some centres elected to perform a haemoglobin estimation, a total and differential white cell count, and a urine test for protein and sugar at 4, 8, and 12 weeks.

Definition of terms used in this report

Side effect. Any symptom or sign regarded by the physician as being due to the chemotherapy.

Treatment not interrupted. The regimen was given daily, as prescribed or in reduced dosage.

Treatment interrupted. Treatment with streptomycin or the oral medicament, or both, was interrupted for 1 or more days on account of a side effect, but was resumed before the end of the 12-week period. A course of desensitization to one or more of the drugs has also been regarded as an interruption.

Treatment stopped. Treatment with streptomycin or the oral medicament or both was stopped on account of side effects and not resumed before the end of the 12-week period of study.

Major departure from prescribed treatment. Treatment was either stopped or interrupted for 7 days or more on account of side effects.

RESULTS

A total of 4 210 patients were admitted to the investigation from 25 centres in 10 countries (see Table 3). Of these, 242 (79 STH, 79 SH, 84 TH) patients were excluded from the analyses for reasons given in the earlier report (Miller et al., 1970). After the exclusions, 3 968 patients remained for analysis, 1 396 on the STH regimen, 1 407 on the SH regimen, and 1 165 on the TH regimen.

Presentation of results

In view of the fact that when streptomycin was not allocated the physician knew that the patient was receiving the TH regimen, and because in Czechoslovakia and Morocco patients were not allocated to this regimen, a direct comparison should not be made of the frequency of side effects between the TH regimen on the one hand and the STH and SH regimens on the other.

The results are therefore presented in 3 sections:

1. Frequency and geographical distribution of side effects to the STH and SH regimens;
2. Frequency and geographical distribution of side effects to the TH regimen; and
3. Influence of race on the frequency of side effects to the thioacetazone-containing regimens.

1. Frequency and geographical distribution of side effects to the streptomycin-containing STH and SH regimens

Pretreatment comparisons. The condition of the patients on admission to treatment in each of the

Table 1. Frequency of side effects by symptom group in the streptomycin-containing regimens (based on 1 396 STH and 1 407 SH patients)

Symptom group	Regimen	Patients with side effects								Major departure from prescribed treatment	
		Total		Treatment not interrupted		Treatment interrupted		Treatment stopped			
		No.	%	No.	%	No.	%	No.	%	No.	%
gastric	STH	291	20.8	201	14.4	57	4.1	33	2.4	67	4.8
	SH	124	8.8	103	7.3	15	1.1	6	0.4	13	0.9
cutaneous	STH	318	22.8	149	10.7	107	7.7	62	4.4	138	9.9
	SH	166	11.8	128	9.1	26	1.8	12	0.9	32	2.3
vestibular	STH	445	31.9	264	18.8	108	7.7	73	5.2	154	11.0
	SH	220	15.6	155	11.0	53	3.8	12	0.9	49	3.5
neurological	STH	108	7.7	78	5.6	19	1.4	11	0.8	23	1.6
	SH	64	4.5	46	3.3	14	1.0	4	0.3	15	1.1
haematological	STH	4	0.3	2	0.1	1	0.1	1	0.1	2	0.1
	SH	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
miscellaneous	STH	139	10.0	83	5.9	38	2.7	18	1.3	44	3.2
	SH	82	5.8	63	4.5	15	1.1	4	0.3	15	1.1
total	STH	702	50.3	367	26.3	200	14.3	135	9.7	277	19.8
	SH	437	31.1	322	22.9	84	6.0	31	2.2	86	6.1

10 countries was set out in the earlier report (Miller et al., 1970). There was a preponderance of males in all countries, except Mongolia. Most of the patients were aged less than 45 years, the country with the highest average age being Trinidad, where 42% of 81 patients were aged 45 years or more; at the other extreme only 2% of 116 patients in Ethiopia were in this age group. The lightest patients on average were in India, their average weight being 41.2 kg and the heaviest were in Czechoslovakia where the average weight was 65.4 kg. There was, however, little difference between the regimens within each country for any of the pretreatment factors studied.

Deaths. During the 12-week period 16 (7 STH, 9 SH) patients died, 12 (3 STH, 9 SH) of tuberculosis. The details of the 4 (all STH) deaths not due to tuberculosis were given in the earlier report (Miller et al., 1970). Two were due to exfoliative dermatitis, 1 to an anaphylactoid reaction following the first dose of the oral medicament, and 1 to an unknown cause following acute abdominal pain.

Frequency of side effects. In total, 50.3% of the patients on the STH regimen had symptoms reported by the physician as side effects compared with 31.1% of those on the SH regimen (Table 1), a major departure from prescribed treatment occurring in

19.8% and 6.1% of the patients, respectively ($P \leq 0.001$ for both comparisons). In every symptom group there were more patients with side effects on the STH than on the SH regimen, the differences for the gastric, cutaneous, and vestibular side effects being statistically highly significant ($P \leq 0.001$ for each comparison). Haematological side effects occurred in only 4 (all STH) patients, 1 having leucopenia and 3 anaemia; no patient had agranulocytosis.

The differences between the regimens in the frequency of a major departure from prescribed treatment were significant for gastric, cutaneous, and vestibular side effects ($P \leq 0.001$ for each comparison).

In the gastric group of side effects (Table 2), nausea or abdominal discomfort occurred in 11.8% of the STH and 5.5% of the SH patients, leading to a major departure from the prescribed treatment in 1.7% and 0.2%, respectively. Vomiting occurred in 10.2% of the STH and 2.5% of the SH patients, leading to a major departure from the prescribed treatment in 2.9% and 0.6%, respectively. (All the differences are highly significant.) Jaundice or hepatitis occurred in only 5 of the STH and 2 of the SH patients.

Rashes occurred in 18.2% of the STH and 8.1% of the SH patients, leading to a major departure

Table 2. Frequency of various side effects in the streptomycin-containing regimens (based on 1 396 STH and 1 407 SH patients)

Side effect	Regimen	Patients with side effects								Major departure from prescribed treatment	
		Total		Treatment not interrupted		Treatment interrupted		Treatment stopped			
		No.	%	No.	%	No.	%	No.	%	No.	%
nausea and abdominal discomfort	STH	165	11.8	134	9.6	16	1.1	15	1.1	24	1.7
	SH	77	5.5	69	4.9	6	0.4	2	0.1	3	0.2
vomiting	STH	143	10.2	85	6.1	42	3.0	16	1.1	41	2.9
	SH	35	2.5	24	1.7	9	0.6	2	0.1	8	0.6
gastric diarrhoea	STH	12	0.9	12	0.9	0	0.0	0	0.0	0	0.0
	SH	22	1.6	21	1.5	1	0.1	0	0.0	0	0.0
constipation	STH	43	3.1	41	2.9	0	0.0	2	0.1	2	0.1
	SH	21	1.5	21	1.5	0	0.0	0	0.0	0	0.0
jaundice or hepatitis	STH	5	0.4	2	0.1	1	0.1	2	0.1	3	0.2
	SH	2	0.1	0	0.0	0	0.0	2	0.1	2	0.1
flushing, itching	STH	90	6.4	64	4.6	18	1.3	8	0.6	18	1.3
	SH	60	4.3	46	3.3	11	0.8	3	0.2	10	0.7
cutaneous rash	STH	254	18.2	109	7.8	91	6.5	54	3.9	120	8.6
	SH	114	8.1	89	6.3	16	1.1	9	0.6	22	1.6
dizziness, giddiness	STH	316	22.6	207	14.8	69	4.9	40	2.9	88	6.3
	SH	165	11.7	127	9.0	32	2.3	6	0.4	28	2.0
vestibular vertigo or ataxia	STH	142	10.2	67	4.8	43	3.1	32	2.3	67	4.8
	SH	57	4.1	32	2.3	19	1.4	6	0.4	20	1.4
tinnitus or deafness	STH	16	1.1	9	0.6	3	0.2	4	0.3	6	0.4
	SH	10	0.7	6	0.4	4	0.3	0	0.0	3	0.2

from prescribed treatment in 8.6% and 1.6%, respectively ($P \ll 0.001$ for both comparisons).

In the vestibular group of side effects, dizziness occurred in 22.6% of the STH and 11.7% of the SH patients, leading to a major departure from prescribed treatment in 6.3% and 2.0%, respectively, and vertigo or ataxia occurred in 10.2% of the STH and 4.1% of the SH patients ($P \ll 0.001$ for all 3 comparisons). Tinnitus or deafness was infrequent.

In summary, there were many more side effects in the STH series and many more major departures, especially as a result of gastric, cutaneous, and vestibular side effects.

Frequency of side effects according to country. The frequency of reported side effects (Table 3) varied considerably from country to country, ranging from 4% of 57 STH patients and 3% of 59 SH patients in Ethiopia to 78% of 101 STH and 44% of 101 SH patients in Malaysia. In every country, however,

the frequency of side effects in patients on the STH regimen exceeded that in those on the SH regimen, although in Algeria, Ethiopia, and Morocco the differences were small.

Because of large differences between countries in pretreatment factors, some of which were of prognostic importance, a direct comparison of the frequencies of side effects in the different countries could be biased. Multiple regression analyses were, therefore, carried out within each regimen in order to adjust the frequency of side effects in each country to allow for the pretreatment differences that were found to have a significant association with response. The pretreatment factors considered in all multiple regression analyses were: age; sex; weight; haemoglobin; neutrophil, eosinophil, lymphocyte, and monocyte counts; and protein and sugar in urine. Since, for example, light-weight patients had a greater frequency of side effects than heavy patients

Table 3. Frequency of side effects in patients on the streptomycin-containing regimens according to country

Country	Regimen	Total patients	Patients with side effects															
			Total frequency				Gastric				Cutaneous				Vestibular			
			No.	% ^a	Major departures % ^a	% ^a	No.	% ^a	Major departures % ^a	% ^a	No.	% ^a	Major departures % ^a	% ^a	No.	% ^a	Major departures % ^a	
Algeria	STH	115	36	33	9	17	24	(1)	25	(22)	(3)	9	13	2				
	SH	116	31	30	4	14	13	1	16	13	2	9	9	1				
Czechoslovakia	STH	101	26	35	32	5	8	(2)	9	(9)	(7)	16	33	25				
	SH	102	14	23	12	0	2	0	5	0	4	10	16	6				
Ethiopia	STH	57	2	(4)	(0)	1	(2)	(0)	1	(2)	(0)	0	(0)	(0)				
	SH	59	2	(3)	(0)	0	(0)	(0)	0	(0)	(0)	0	(0)	(0)				
India	STH	553	335	58	18	159	25	(6)	117	(21)	(8)	248	40	12				
	SH	568	216	36	4	75	12	1	66	13	0	122	20	4				
Malaysia	STH	101	78	78	38	32	33	(11)	37	(37)	(23)	56	55	21				
	SH	101	45	44	16	11	14	2	16	17	9	29	28	7				
Mongolia	STH	47	9	22	16	4	15	(2)	6	(13)	(9)	2	11	5				
	SH	45	4	11	6	1	4	3	4	10	5	0	-1	1				
Morocco	STH	79	12	17	15	2	7	(1)	5	(6)	(5)	5	12	7				
	SH	78	11	18	9	2	3	2	6	7	4	2	6	2				
Pakistan	STH	139	44	33	6	17	12	(0)	14	(10)	(2)	22	17	4				
	SH	141	25	19	1	8	7	0	7	6	0	11	7	0				
Singapore	STH	162	128	78	32	46	29	(10)	84	(52)	(25)	77	45	13				
	SH	158	75	43	8	12	6	1	39	23	4	33	20	5				
Trinidad	STH	42	32	75	39	8	16	(2)	20	(48)	(19)	10	24	17				
	SH	39	14	35	13	1	2	-1	7	15	4	4	9	7				

^a Percentages in brackets are standard percentages but all other percentages in this table have been adjusted for differences in factors of prognostic importance; hence some are negative.

there has been a corresponding increase in the adjusted frequency in those countries (notably Czechoslovakia) with the heavier patients. (Ethiopia was not included in this adjustment because there was a very low frequency of side effects and the pattern of association between pretreatment factors and their frequency was quite different from that of the other countries.) The frequencies, after adjustment, are presented in Table 3. Only for Czechoslovakia did the adjusted percentages for frequency or for major departures differ to any extent from the unadjusted percentages.

If an adjusted frequency of side effects of less than 30% is regarded as low, one of 30–59% as intermediate, and one of 60% or more as high, the countries fall into the following categories:

Frequency of side effects on SH regimen	Frequency of side effects on STH regimen		
	Low	Intermediate	High
Low	Ethiopia Mongolia Morocco	Czechoslovakia Pakistan	—
Intermediate	—	Algeria India	Malaysia Singapore Trinidad

It will be seen that the highest frequency of side effects occurred in Malaysia, Singapore, and Trinidad—namely, in 60% or more of patients on the STH regimen and in 30–59% on the SH regimen. Considering the frequency of side effects leading to a major departure from prescribed treatment (Table 3) a frequency of 20% or more on the STH regimen occurred in Czechoslovakia, Malaysia, Singapore, and Trinidad but not in any country on the SH regimen.

The adjusted frequency of gastric side effects on the STH regimen was 20% or more in Algeria, India, Malaysia, and Singapore; the frequency on the SH regimen was low everywhere. Few major departures from the prescribed treatment resulted with either regimen.

The frequency of cutaneous side effects was 20% or more on the STH regimen in Algeria, India, Malaysia, Singapore, and Trinidad, and on the SH regimen in Singapore; a major departure from the prescribed treatment occurred in 20% or more of patients on the STH regimen in Malaysia and Singapore but for the SH regimen, apart from Malaysia, major departures occurred in 5% or less of patients.

The adjusted frequency of vestibular side effects was 20% or more on the STH regimen in Czecho-

slovakia, India, Malaysia, Singapore, and Trinidad, and on the SH regimen in India, Malaysia, and Singapore; a major departure from the prescribed treatment occurred in 20% or more of the patients on the STH regimen in Czechoslovakia and Malaysia. In contrast the highest proportion of major departures in patients on the SH regimen was 7% in Malaysia and Trinidad.

Neurological, haematological, and miscellaneous side effects were infrequent in most countries (the findings are not tabulated here).

Thus the frequency of side effects and of major departures on both regimens varied considerably from country to country, but in every country they were almost without exception more frequent on the STH regimen.

Frequency of side effects in the Indian subcontinent. In all the centres in the Indian subcontinent (Table 4) there was a higher frequency of side effects on the STH than the SH regimen, except in Dacca, where no side effects on either regimen were reported. The adjusted frequency of side effects in the various centres can be classified as follows:

Frequency of side effects on the SH regimen	Frequency of side effects on the STH regimen		
	Low	Intermediate	High
Low	Dacca Quetta	Amritsar Bangalore Delhi Lahore	—
Intermediate	—	Amargadh Baroda Digri Gauhati Hyderabad	Bombay Tambaram Karachi
High	—	—	Coimbatore

The highest frequencies on both regimens occurred in Coimbatore in southern India (Fig. 1).

Analyses of the frequency of side effects in the Indian subcontinent were performed according to whether the patients were Hindu or Moslem. For the STH regimen in India side effects occurred in 60% of 464 Hindus and in 64% of 66 Moslems, the proportions with major departures being 22% and 17%, respectively. The corresponding proportions for the SH regimen were 38% of 476 Hindus and 45% of 67 Moslems, the proportions with major departures being 5% and 9%, respectively. Thus in India the frequency of side effects was very similar whether the patients were Hindu or Moslem. In Pakistan there were only 2 Hindus but there were

Table 4. Frequency of side effects in India and Pakistan in patients on the streptomycin-containing regimens

Centre	Regimen	Total patients	Patients with side effects											
			Total frequency			Gastric			Cutaneous			Vestibular		
			No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a
Amargadh	STH	32	13	40	25	3	9	4	(12)	7	7	9	28	16
	SH	29	9	33	7	1	5	1	(3)	(0)	7	25	7	
Amritsar	STH	42	23	56	7	10	25	4	(10)	7	13	33	3	
	SH	39	5	16	1	2	6	0	(0)	(0)	3	10	1	
Bangalore	STH	46	20	46	18	6	15	7	(15)	7	14	30	14	
	SH	45	6	14	2	2	6	4	(9)	(0)	1	1	0	
Baroda	STH	34	15	45	11	4	15	3	(9)	9	13	42	2	
	SH	39	15	37	3	0	1	1	(3)	(0)	11	24	4	
Bombay	STH	69	52	71	20	32	42	6	(43)	8	29	40	13	
	SH	69	33	43	2	19	24	0	(0)	(0)	6	9	1	
Coimbatore	STH	49	46	88	48	36	70	22	(45)	21	33	61	30	
	SH	49	34	62	17	19	34	9	(18)	(6)	9	17	4	
Delhi	STH	45	20	40	17	5	14	4	(9)	2	17	37	13	
	SH	46	8	18	-1	0	1	4	(9)	(0)	6	12	0	
Digri	STH	37	19	49	15	7	19	2	(5)	2	18	42	13	
	SH	38	15	38	11	3	9	1	(3)	(0)	14	34	12	
Gauhati	STH	67	37	57	8	10	13	11	(16)	3	31	46	3	
	SH	75	26	36	1	5	8	9	(12)	(0)	16	21	1	
Hyderabad	STH	73	40	54	17	20	27	13	(18)	12	31	46	7	
	SH	74	28	38	7	6	8	8	(11)	(1)	24	33	5	
Tambaram	STH	59	50	87	30	26	44	17	(29)	8	40	62	27	
	SH	65	37	55	6	18	28	7	(11)	(3)	25	36	5	
Dacca	STH	12	0	(0)	(0)	0	(0)	0	(0)	(0)	0	(0)	(0)	
	SH	9	0	(0)	(0)	0	(0)	0	(0)	(0)	0	(0)	(0)	
Karachi	STH	32	19	64	9	12	38	6	(19)	7	10	36	2	
	SH	35	14	40	4	6	16	5	(14)	(0)	5	16	0	
Lahore	STH	35	12	40	14	1	6	3	(9)	0	7	26	14	
	SH	36	2	11	1	0	3	0	(0)	(0)	2	8	2	
Quetta	STH	60	13	24	6	4	8	5	(8)	2	5	15	4	
	SH	61	9	21	2	2	4	2	(3)	(0)	4	12	2	

^a The percentages in brackets are standard percentages but all other percentages in this table have been adjusted for differences in factors of prognostic importance, hence some are negative.



Fig. 1. Centres in the Indian subcontinent.

137 Moslems on the STH regimen and 31% had side effects, major departures occurring in 5% compared with 17% and 1%, respectively, of 138 patients on the SH regimen.

Correlation of the frequency of side effects on the STH and SH regimens. The frequency of side effects on the STH regimen by country was closely correlated with the corresponding frequency of side effects on the SH regimen ($r=0.96$). A similar correlation was observed for side effects leading to a major departure from prescribed treatment, and for frequency of gastric, cutaneous, and vestibular side effects ($r=0.95, 0.78, 0.95$, and 0.98 , respectively). Corresponding analyses performed by centre also showed highly significant associations between the STH and SH regimens ($r=0.88, 0.80, 0.94, 0.88$, and 0.80 , respectively).

Thus when side effects were frequent on the STH regimen in a country or centre they were relatively frequent on the SH regimen also.

Results of routine investigations. A haemoglobin estimation was performed before treatment and at 12 weeks for patients in Algeria, Czechoslovakia, Malaysia, Morocco, and Singapore. The means of the haemoglobin levels of patients still on the STH and SH regimens at 12 weeks are shown in Table 5.

For patients on the STH regimen the mean haemoglobin level rose significantly during the 12 weeks in Algeria, remained the same in Morocco, and fell significantly in Czechoslovakia, Malaysia,

Table 5. Haemoglobin levels before treatment and at 12 weeks^a

Country	Week	STH			SH			P value for change weeks 0-12: STH versus SH	TH		
		Number of patients	Mean (g/100 ml)	P value for change weeks 0-12	Number of patients	Mean (g/100 ml)	P value for change weeks 0-12		Number of patients	Mean (g/100 ml)	P value for change weeks 0-12
Algeria	0	111	12.2	0.002	106	12.4	<0.001	<0.001	107	12.3	<0.001
	12	111	12.7		106	13.9			107	13.0	
Czechoslovakia	0	85	15.5	<0.001	97	15.4	N.S.	<0.001	0		
	12	85	14.2		97	15.2			0		
Malaysia	0	73	11.4	0.03	98	11.5	0.001	<0.001	79	11.0	N.S.
	12	73	10.8		98	12.2			79	10.7	
Morocco	0	68	12.6	N.S.	74	12.8	0.003	0.02	0		
	12	68	12.6		74	13.5			0		
Singapore	0	148	11.5	<0.001	152	11.5	<0.001	<0.001	119	11.2	N.S.
	12	148	10.7		152	12.8			119	11.0	

^a Patients were not allocated to the TH regimen in Czechoslovakia and Morocco. N.S. = not significant.

Table 6. Frequency of side effects in patients on the TH regimen according to country

Country	Total patients	Patients with side effects											
		Total frequency			Gastric			Cutaneous			Vestibular		
		No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a
Algeria	116	39	32	4	14	16	-2	25	19	2	6	5	(0)
Ethiopia	59	1	(2)	(0)	0	(0)	(0)	1	(2)	(0)	1	(2)	(0)
India	546	217	41	9	117	19	3	103	20	6	42	8	(1)
Malaysia	95	53	57	21	19	23	3	35	36	19	17	17	(0)
Mongolia	46	8	20	6	1	7	-2	7	14	6	1	2	(2)
Pakistan	134	25	20	4	14	12	1	4	4	2	6	5	(1)
Singapore	126	77	56	18	18	13	2	62	48	17	12	9	(0)
Trinidad	43	20	42	16	5	13	-1	16	33	12	1	0	(0)
All countries	1 165	440	(37.8)	(9.4)	188	(16.1)	(1.6)	253	(21.7)	(7.5)	86	(7.4)	(0.5)

^a Percentages in brackets are standard percentages but all other percentages in this table have been adjusted for differences in factors of prognostic importance; hence some are negative.

and Singapore, while in patients on the SH regimen the mean haemoglobin rose significantly in Algeria, Malaysia, Morocco, and Singapore but remained the same in Czechoslovakia. Comparing the changes in the haemoglobin levels over the 12-week period for the STH regimen and for the SH regimen, there was a significant difference in each country to the advantage of the SH regimen.

Patients in all centres had a urinalysis for protein and sugar before treatment and at 12 weeks. There were considerable differences in proteinuria between the countries, some of which may have been due to the use of different methods of testing.¹ Thus in Czechoslovakia, Ethiopia, Malaysia, Morocco, and Pakistan few if any patients on either regimen had proteinuria reported before treatment or at 12 weeks. In Algeria, India, Singapore, and Trinidad, however, a rise in the frequency of proteinuria was reported in patients on the STH regimen but not in those on the SH regimen over the 12-week period; the proportions with proteinuria in the STH regimen were 1% before treatment and 4% at 12 weeks for Algeria, 3% and 17% for India, 15% and 34% for Singapore, and 13% and 19% for Trinidad. In Mongolia a rise occurred in patients on both regimens.

There was also considerable variation between countries in the proportions of patients with sugar

reported in the urine (the findings are not tabulated here). However, in none of the 10 countries was the proportion at 12 weeks higher in either regimen.

2. Frequency and geographical distribution of side effects to the thioacetazone plus isoniazid regimen

Pretreatment status. Of the total of 1 165 TH patients in the analysis, 70.1% were male, 81.6% were aged less than 45 years, and 76.4% had a haemoglobin level of 10 g/100 ml or more; the average weight was 44.8 kg.

There were differences between the 8 centres in the condition of the patients on admission to treatment (Miller et al., 1970). Appropriate adjustments for these differences are made below. Only in Mongolia were the majority of the patients female. Only in Trinidad were the majority aged 45 years or more and the highest average weight, 52.2 kg, was also found in Trinidad.

Deaths. During the 12-week period 10 patients died, 9 of tuberculosis and 1 of agranulocytosis (see below).

Frequency of side effects. Side effects occurred in 37.8% of the 1 165 patients, the proportions ranging from 57% (after adjustment) in Malaysia to 2% in Ethiopia (Table 6). An intermediate frequency (30-59%) was observed in Algeria, India, Malaysia,

¹ The findings are not tabulated here.

Singapore, and Trinidad, and a low frequency (less than 30%) in Ethiopia, Mongolia, and Pakistan.

Side effects leading to a major departure from prescribed treatment occurred in 9.4% of the 1 165 patients. The range for the adjusted percentages was from 21% in Malaysia to 4% in Algeria and Pakistan.

Gastric side effects occurred in 16.1% of the 1 165 patients, the range for the countries (after adjustment) being from 23% in Malaysia to 7% in Mongolia. They rarely led to a major departure from prescribed treatment.

Cutaneous side effects occurred in 21.7% of the 1 165 patients, the range for the countries being from 48% (after adjustment) in Singapore to 2% in Ethiopia. They led to a major departure from prescribed treatment in 19% of patients in Malaysia, 17% in Singapore, and 12% in Trinidad, but infrequently elsewhere.

Vestibular side effects occurred in 7.4% of the

1 165 patients, the range for the countries (after adjustment) being from 17% in Malaysia to zero in Trinidad. They rarely led to a major departure from prescribed treatment. Neurological and haematological side effects were infrequent.

The frequencies of side effects in the centres in the Indian subcontinent are set out in Table 7. A high frequency occurred in Bombay and Coimbatore, an intermediate frequency in Bangalore, Baroda, Gauhati, Hyderabad, Tambaram, and Karachi, and a low frequency in Amargadh, Amritsar, Delhi, Digri, and Quetta. No side effects were reported from Dacca and Lahore. The frequency of side effects leading to a major departure from prescribed treatment (after adjustment) was 20% in Coimbatore and 12% in Gauhati, but less than 10% elsewhere.

The frequency of gastric side effects (after adjustment) ranged from 56% in Coimbatore to -3% (the negative value results from the adjustment) in Gauhati. They led to a major departure from pre-

Table 7. Frequency of side effects in the Indian subcontinent in patients on the TH regimen

Centre	Total patients	Patients with side effects											
		Total frequency			Gastric			Cutaneous			Vestibular		
		No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a
Amargadh	28	3	(11)	7	2	0	7	1	(4)	1	0	0	0
Amritsar	38	8	(21)	6	5	13	2	3	(8)	2	2	6	0
Bangalore	41	14	(34)	6	6	7	0	8	(20)	1	2	4	2
Baroda	37	13	(35)	9	3	3	-1	8	(22)	11	3	8	0
Bombay	67	43	(64)	5	18	22	0	30	(45)	5	1	2	0
Coimbatore	47	39	(83)	20	29	56	9	13	(28)	15	11	22	4
Delhi	46	9	(20)	9	5	13	0	7	(15)	9	1	1	0
Digri	40	7	(18)	5	3	12	1	1	(2)	4	3	8	2
Gauhati	63	20	(32)	12	7	-3	-1	9	(14)	7	3	6	0
Hyderabad	76	26	(34)	2	15	21	1	8	(11)	2	11	14	0
Tambaram	63	35	(56)	8	24	33	1	15	(24)	8	5	8	0
Dacca	8	0	(0)	(0)	0	(0)	(0)	0	(0)	(0)	0	(0)	(0)
Karachi	35	18	(51)	3	12	33	0	1	(3)	0	6	19	3
Lahore	35	0	(0)	(0)	0	(0)	(0)	0	(0)	(0)	0	(0)	(0)
Quetta	56	7	(12)	7	2	2	0	3	(5)	1	0	-1	1

^a The percentages in brackets are standard percentages but all other percentages in this table have been adjusted for differences in factors of prognostic importance; hence some are negative.

scribed treatment in 9% of patients in Coimbatore and 7% in Amargadh, but hardly at all elsewhere.

The frequency of cutaneous side effects ranged from 45% in Bombay to 0% in Dacca and Lahore. They led to a major departure from prescribed treatment (after adjustment) in 15% of patients in Coimbatore and 11% in Baroda but less than 10% elsewhere.

The frequency of vestibular side effects ranged from 22% in Coimbatore to -1% in Quetta, but rarely led to a major departure from prescribed treatment.

Agranulocytosis. Two (0.2%) of the total of 1 165 patients had agranulocytosis. One, a man of 50 in India, developed a perianal abscess in the fifth week. His condition deteriorated in spite of penicillin and he died after 16 days. A blood count on the day of death showed 3 200 white cells per mm³, all lymphocytes. A bone marrow specimen obtained *post mortem* showed acellular marrow with lymphocytes and normoblasts only. No sore throat had occurred and the study tablet had been continued up to his death. The other, a man of 41 in Algeria, had a blood count at 3 weeks that showed a total of 6 200 white cells per mm³; most of these were lymphocytes, no neutrophils being seen, and a bone marrow smear showed a reduction in the myeloid elements. The only complaint was of moderate weakness. The study tablet was stopped and the blood picture returned to normal after 11 days. Treatment was continued with streptomycin, 4-aminosalicylic acid, and isoniazid.

Results of routine investigations. A haemoglobin estimation was performed before treatment and at 12 weeks for patients in Algeria, Malaysia, and Singapore (Table 5). There was a significant rise in the mean haemoglobin level in Algeria and a slight fall in Malaysia and Singapore during the 12-week period.

Urinalysis for protein and sugar was carried out in all centres before treatment and at 12 weeks. There were considerable differences between the 8 countries in the proportion of patients with proteinuria, in 5 of them a rise in the proportion was reported at 12 weeks; the proportions with proteinuria were 0% before treatment and 7% at 12 weeks for Algeria, 4% and 16% for India, 0% and 11% for Mongolia, 18% and 28% for Singapore, and 17% and 31% for Trinidad. The proportion of patients reported with sugar in the urine also varied considerably, but in none of the 8 countries was an increase reported at 12 weeks.

3. Influence of race on the frequency of side effects to the thioacetazone-containing (STH and TH) regimens

In 3 countries—Malaysia, Singapore, and Trinidad—patients of different racial origin were under treatment in the same hospital (Chinese, Malays, and Indians in Malaysia and Singapore, and Africans and Indians in Trinidad).

Pretreatment status. Although there were differences between countries in some pretreatment factors, within each country there were no differences between the racial groups in the distribution of pretreatment factors for patients on the thioacetazone-containing regimens (the findings are not tabulated here).

Frequency of side effects. The frequency of side effects to the thioacetazone-containing regimens (the STH and TH regimens combined) was broadly similar in the different racial groups in each country (Table 8), but it will be appreciated that the numbers of Malays and Indians in the comparison were small. Thus the frequency (after adjustment, where appropriate) in Malaysia was 68% in the Chinese, 76% in the Malays, and 54% in the Indians ($P = 0.09$); in Singapore it was 71% in the Chinese, 71% in the Malays, and 74% in the Indians; in Trinidad, it was 56% in the Africans and 71% in the Indians ($P > 0.2$).

The frequency (after adjustment) of side effects leading to a major departure from prescribed treatment in Malaysia was 29% in the Chinese, 45% in the Malays, and 24% in the Indians ($P = 0.08$); in Singapore it was 29% in the Chinese, 25% in the Malays, and 30% in the Indians; in Trinidad it was 24% in the Africans and 41% in the Indians ($P = 0.1$).

The frequency of gastric side effects (after adjustment) in Malaysia was 34% in the Chinese, 15% in the Malays, and 14% in the Indians ($P = 0.02$ both for the Chinese *versus* Indian comparison and for the Chinese *versus* Malay comparison); these led to a major departure from prescribed treatment in 7%, 6%, and 6%, respectively. In Singapore, the frequency was 22% in the Chinese, 21% in the Malays, and 23% in the Indians, leading to a major departure from prescribed treatment in 5%, 8%, and 13%, respectively ($P > 0.1$). In Trinidad the frequency was 11% in the Africans and 23% in the Indians ($P > 0.1$).

The frequency (after adjustment) of cutaneous side effects (including itching, flushing, and mucous membrane involvement) in Malaysia was 33% in the

Table 8. Frequency of side effects according to race of patients on the thioacetazone-containing regimens

Country and race	Total patients	Patients with side effects											
		Total frequency			Gastric			Cutaneous			Vestibular		
		No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a	No.	% ^a	Major departures % ^a
<i>Malaysia</i>													
Chinese	117	79	68	29	39	34	7	38	33	19	43	37	8
Malays	40	30	76	45	7	15	6	22	57	36	16	41	20
Indians	39	22	54	24	5	14	6	12	28	11	14	34	16
<i>Singapore</i>													
Chinese	202	143	71	29	47	22	5	102	51	23	62	30	8
Malays	50	36	71	25	10	21	8	27	52	20	13	27	8
Indians	36	26	74	30	7	23	13	17	48	23	14	40	12
<i>Trinidad</i>													
Africans	54	30	(56)	24	7	11	(0)	19	33	(7)	7	14	11
Indians	31	22	(71)	41	6	23	(3)	17	58	(35)	4	11	6

^a Percentages in brackets are standard percentages but all other percentages in this table have been adjusted for differences in factors of prognostic importance.

Chinese, 57% in the Malays, and 28% in the Indians ($P < 0.01$ for the Chinese *versus* Malay comparison and $P = 0.01$ for the Malay *versus* Indian comparison), leading to a major departure from prescribed treatment in 19%, 36%, and 11%, respectively ($P = 0.02$ for the Chinese *versus* Malay comparison and $P < 0.01$ for the Malay *versus* Indian comparison). In Singapore the frequencies of cutaneous side effects and of those leading to a major departure from prescribed treatment were almost identical in the 3 races. In Trinidad the frequency was 33% in the Africans and 58% in the Indians ($P = 0.03$) leading to a major departure from prescribed treatment in 7% and 35%, respectively ($P = 0.003$).

The frequency of vestibular side effects (after adjustment) in Malaysia was 37% in the Chinese, 41% in the Malays, and 34% in the Indians, leading to a major departure from prescribed treatment in 8%, 20%, and 16%, respectively ($P > 0.1$). In Singapore it was 30% in the Chinese, 27% in the Malays, and 40% in the Indians ($P > 0.2$), leading to a major departure from prescribed treatment in 8%, 8%, and 12%, respectively. In Trinidad, the frequency was low and similar in the two races.

In summary, there was no evidence of differences in the frequency of side effects in the three races in Singapore but in Malaysia there were more cutaneous

side effects in Malays than in the other two races. These also led to a higher incidence of major departures from chemotherapy. In Trinidad there were more side effects in Indians, also largely due to a higher incidence of cutaneous side effects, which again led to a higher proportion of major departures from chemotherapy.

DISCUSSION

An earlier large-scale international cooperative investigation (Miller et al., 1966) in 13 countries showed that substantial differences existed between them in the frequency of side effects to two regimens—namely, streptomycin plus isoniazid plus thioacetazone and streptomycin plus isoniazid. Side effects were particularly frequent in Czechoslovakia and Hong Kong. A subsequent controlled clinical trial of thioacetazone plus isoniazid in comparison with 4-aminosalicylic acid plus isoniazid as therapy in Hong Kong (Hong Kong Anti-Tuberculosis Association and Government Tuberculosis Service/British Medical Research Council Thiacetazone Investigation, 1968) demonstrated an unexpected and surprisingly high frequency of side effects, particularly cutaneous side effects, raising the possibility that there was a special risk of toxicity in Chinese patients in Hong Kong. From Morocco, Papillon &

Berbich (1966) also reported a high frequency of side effects to thioacetazone in one area in contrast to the findings in two other areas of the country (Chicou et al., 1968).

It is possible that one or more of several factors contributes to the variation found between different areas:

1. There is closer supervision of the patients in centres that have adequate supervisory staff.
2. The classification into side effects and unassociated complaints inevitably differs in different areas.
3. Differences in the general environment such as the climate and exposure to sunlight.
4. Differences in the previous use of other medications or exposure to other agents that might make some members of the population more liable to develop side effects.
5. Racial differences, either with a genetic basis or based on differences in customs.

A particular feature of the present investigation was that in three of the countries patients of different racial origin were under observation in the same hospital, in Malaysia and in Singapore, Chinese, Malays, and Indians, and in Trinidad, Indians and Africans. In these countries the first three of the above five factors were the same for the different races, the previous exposure to other medicaments was likely to have been similar and thus the possible role of the patients' racial origin and associated customs could be investigated. In view of the reports from Morocco, centres in North Africa—Morocco itself, Ethiopia, and Algeria—were also included in the investigation. In addition, a number of centres in the Indian subcontinent were included because of evidence that, although the frequency of side effects to thioacetazone was acceptable, they might be more severe in South India (Gothi et al., 1966; Tuberculosis Chemotherapy Centre, Madras, 1966). In the present study, therefore, information has been obtained on the frequency of side effects in 10 countries over a wide geographical area.

An additional objective of this investigation was to determine whether a widely used and costly supplement, consisting of vitamins and an antihistamine, was an effective prophylactic of thioacetazone side effects as had been claimed (Patel, 1964; Patel et al., 1965). The supplement was found to have little or no prophylactic value in any country, centre, or racial group (Miller et al., 1970).

Three regimens were investigated: streptomycin plus thioacetazone plus isoniazid, streptomycin plus isoniazid, and thioacetazone plus isoniazid. The two streptomycin-containing regimens were those studied in the first International Thioacetazone Side-Effect Investigation (Miller et al., 1966) and, as in that investigation, they were given on a double-blind basis. The thioacetazone plus isoniazid regimen, studied in 8 of the 10 countries, could not be observed double-blind. Hence comparisons of the frequency of side effects on this regimen with the frequency with the streptomycin-containing regimens must be made with caution.

The reported frequency of side effects in the present study was inevitably much higher in all three regimens than would be experienced in routine practice, for the patients were seen daily and any symptom regarded by the physician in charge as being even possibly attributable to the chemotherapy has been included in the analysis. Thus a single mild episode, reported on only one day, was regarded as a side effect even if there was no interruption of chemotherapy. However, a better measure of the level of side effects of clinical importance is obtained by considering those that led to a major departure from prescribed treatment—that is, an interruption of chemotherapy of 7 days or more or the cessation of the regimen.

It is particularly noteworthy that the results in the 3 countries where patients of different racial origin were under study in the same hospitals suggest that racial origin is not a major factor in explaining the differences observed between countries. Nevertheless, evidence has been produced in Trinidad that cutaneous side effects are more frequent in patients of Indian origin than in subjects of African stock. Although there was also evidence in Malaysia that cutaneous side effects (including itching, flushing, and mucous membrane involvement) were more frequent in Malays than in Chinese and Indians, this is perhaps less likely to be an observation associated with the patient's racial origin since there was no difference between the occurrence of these side effects in Chinese, Malays, and Indians in Singapore. However, it might represent an increased exposure of Malays in Malaysia to skin sensitizing substances. It is known that the three racial groups in Singapore have similar thioacetazone blood curves after the standard 150 mg dose of the drug (G. Ellard, personal communication). The observation of increased frequency of cutaneous side effects in Indians compared with Africans in Trinidad fits in

with the widely reported safety of thioacetazone-containing regimens in Africa (East African/British Medical Research Council Investigation, 1960, 1963, 1966a, 1966b, 1969, 1970; Gordon, 1961, 1962a, 1962b; Miller et al., 1966) and the reports of higher rates of toxicity, especially major episodes of rashes, from India (Tuberculosis Chemotherapy Centre, Madras, 1966; Gothi et al., 1966).

Within the Indian subcontinent, and even within India, substantial variation between centres in the frequency of side effects occurred. There was, in fact, a suggestion of a trend of increasing frequency of side effects from the North to the South. Although the variation of major departures on the streptomycin plus isoniazid regimen was at a lower level, it was found that it also reflected the pattern on the streptomycin plus thioacetazone plus isoniazid regimen. Indeed there was a highly significant association between the frequency of side effects to the two regimens for the different centres, the frequency to both regimens either being high or low. This also applied when all the countries were considered, suggesting that thioacetazone itself is not responsible for the variation in the frequency of side effects between the centres or between the countries.

Factors that undoubtedly contribute to the major differences between countries are intensity of supervision and differences in reporting side effects. Furthermore, Sen (1970) has reported a seasonal variation in toxicity to thioacetazone in Madhya Pradesh in central India and suggested that climate may be an important factor, although the evidence presented is unsatisfactory. It seems very unlikely that climate could explain the wide differences in frequency of side effects observed in the present study between the many centres that lie in the tropics. Even so, further analysis of the data from the present investigation will consider the possible contribution of this factor. Another explanation that deserves consideration is that there are differences between countries in the exposure to substances that might sensitize patients to thioacetazone. In this respect it is of interest that 4 patients on the streptomycin plus isoniazid regimen who had rashes were shown to have hypersensitivity to thioacetazone (Ferguson et al., 1971) even though no patient with a history of treatment with thioacetazone or any other thiosemicarbazone drug was included in the investigation. Previous contact with a medicament related to thioacetazone or a chemical sensitizer present in the environment could explain this finding. It is relevant that Papillon & Berbich (1966) have suggested that

tattooing predisposes patients to thioacetazone hypersensitivity and suggest that previous exposure to substances with amines in the *para* position taken by mouth or introduced intradermally can sensitize to thioacetazone.

The present investigation has confirmed that the most frequent side effects to be expected from the use of thioacetazone-containing regimens are those grouped as gastric, cutaneous, and, when streptomycin is also used, vestibular. Vestibular side effects leading to a major departure from prescribed treatment were 3 times as frequent on the streptomycin plus thioacetazone plus isoniazid regimen (11.0%) as on the streptomycin plus isoniazid regimen (3.5%); major departures occurred occasionally on the thioacetazone plus isoniazid regimen without streptomycin (0.5%). This provides further evidence for the suggestion put forward by Miller et al. (1966) that thioacetazone potentiates streptomycin toxicity.

As in the previous investigation (Miller et al., 1966) agranulocytosis was very uncommon, occurring in only 2 of the 1 165 TH patients and none of the STH or SH patients. Changes in the haemoglobin level were studied in 5 countries in the present investigation and are of interest. In each country there was a significant difference between the streptomycin plus thioacetazone plus isoniazid regimen and the streptomycin plus isoniazid regimen in the change in the mean haemoglobin level. Thus in Algeria there was a rise on both regimens, but the rise was smaller in those on the thioacetazone-containing regimen; in Morocco there was no change in patients on the thioacetazone-containing regimen but there was a rise in those on the streptomycin plus isoniazid regimen; in Czechoslovakia there was a fall in patients on the former and no change in those on the latter and in Malaysia and Singapore there was a fall in patients on the former and a rise in those on the latter. The findings in Algeria and Morocco paralleled those previously reported from East Africa (East African/British Medical Research Council Thioacetazone/Diphenylthiourea Investigation, 1960) and Madras (Tuberculosis Chemotherapy Centre, Madras, 1966) while those in Czechoslovakia, Malaysia, and Singapore paralleled those previously reported from Hong Kong (Hong Kong Anti-Tuberculosis Association and Government Tuberculosis Service/British Medical Research Council Thioacetazone Investigation, 1968). All these observations suggest that thioacetazone-containing regimens depress haematopoiesis. Masei & Johnston (1968) from Australia reported haemolytic anaemia in a number

of patients on thioacetazone-containing regimens and they postulated a direct effect on the developing red cell.

Previous studies had suggested that the 12-week period of observation would be adequate to detect the most important side effects (Miller et al., 1966). This was largely confirmed in a recent extension of the present investigation in Singapore where patients received the regimens as allocated in this investigation for 6 months and then those who had had thioacetazone plus isoniazid with or without streptomycin continued on thioacetazone plus isoniazid, and those who had had streptomycin plus isoniazid continued on isoniazid alone, the comparison remaining double-blind for the whole year. Most of the gastric, cutaneous and vestibular side effects occurred in the first 3 months of treatment. However, jaundice appeared as frequently after 3 months, though to a similar extent on all 3 regimens (Singapore Tuberculosis Services/Brompton Hospital/British Medical Research Council Investigation, 1971). In Hong Kong (Hong Kong Anti-Tuberculosis Association and Government Tuberculosis Service/British Medical Research Council Thiacectazone Investigation, 1968) jaundice appeared after 3 months only on the thioacetazone plus isoniazid regimen but not on the 4-aminosalicylic acid plus isoniazid regimen studied concurrently.

In studies for a year in Hong Kong (Hong Kong Anti-Tuberculosis Association and Government Tuberculosis Service/British Medical Research Council Thiacectazone Investigation, 1968) and Singapore (Singapore Tuberculosis Services/Brompton Hospital/British Medical Research Council Investigation, 1971) the toxicity of thioacetazone plus isoniazid

with or without streptomycin was found to be too high to recommend their use in routine practice. Information was obtained at the end of 1970 from all except one of the centres that cooperated in this investigation. Confirmation has been obtained that thioacetazone-containing regimens are used in routine practice in Ethiopia, India, and Pakistan.

Algeria, Czechoslovakia, Malaysia, Morocco, and Trinidad, however, do not use thioacetazone-containing regimens routinely. Algeria now bases its approach to chemotherapy on supervised intermittent regimens and Morocco has for several years used ethionamide plus isoniazid as a primary regimen. Czechoslovakia, Malaysia, and Trinidad, as well as Hong Kong and Singapore, are countries with a high frequency of side effects to thioacetazone-containing regimens and also with the resources to purchase more expensive drugs.

Migrant populations are being increasingly used in epidemiological studies particularly of cancer and cardiovascular diseases. The interpretation of data from such studies presents many problems that have been discussed recently by Kagan (1970), Kmet (1970), and Stenhouse & McCall (1970). In the present investigation the study of different racial groups in the population avoids many of the problems met in migrant studies, because current events are being investigated rather than factors that first operated many years before, possibly in the country of origin of the migrants. The study of these migrant groups and the other populations in the various countries cooperating in this investigation has, therefore, helped cast further light on the geographical variation of side effects to thioacetazone and the possible causes of it.

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RÉSUMÉ

DEUXIÈME ENQUÊTE COLLECTIVE INTERNATIONALE SUR LES EFFETS SECONDAIRES DE LA THIOACÉTAZONE: 2. FRÉQUENCE ET RÉPARTITION GÉOGRAPHIQUE DES EFFETS SECONDAIRES

Au cours de cette enquête, 4210 malades, dans 10 pays, ont reçu par échantillonnage aléatoire l'une des trois associations thérapeutiques suivantes, pendant 12 semaines: 1 g de streptomycine par voie intramusculaire, ainsi que 150 mg de thioacétazone et 300 mg d'isoniazide en 1 comprimé, par jour (schéma STH); 1 g de streptomycine par voie intramusculaire et 300 mg d'isoniazide en 1 comprimé, par jour (schéma SH); 150 mg de thioacétazone et 300 mg d'isoniazide en 1 comprimé, par jour (schéma TH). Tous les comprimés étaient d'aspect identique et les deux schémas comportant l'administration de streptomycine ont été appliqués suivant la méthode du double anonymat. Les trois types de traitement ont été utilisés en Algérie, en Ethiopie, en Inde, en Malaisie, en Mongolie, au Pakistan, à Singapour et à la Trinité. Au Maroc et en Tchécoslovaquie, on n'a eu recours qu'aux schémas comportant des injections de streptomycine. Des sujets de race différente ont été traités dans un même hôpital: en Malaisie et à Singapour, des Chinois, des Malais et des Indiens; à la Trinité, des Africains et des Indiens. Après exclusion de l'étude, pour diverses raisons, de 242 malades, l'analyse a porté sur 3968 cas: 1396 STH, 1407 SH et 1165 TH.

Des effets secondaires ont été notés chez 50,3% des malades STH et 31,1% des malades SH; 19,8% des premiers et 6,1% des seconds ont dû interrompre le traitement définitivement ou pour une période de 7 jours ou

plus. Par pays, les pourcentages d'abandon de traitement ont été, pour les malades STH et SH respectivement, de: 9% et 4% en Algérie; 32% et 12% en Tchécoslovaquie; 0% et 0% en Ethiopie; 18% et 4% en Inde; 38% et 16% en Malaisie; 16% et 6% en Mongolie; 15% et 9% au Maroc; 6% et 1% au Pakistan; 32% et 8% à Singapour; 39% et 13% à la Trinité.

Dans les centres de traitement du sous-continent indien, on a relevé des variations considérables des taux d'abandon de traitement par les malades STH et SH: 48% et 17% à Coimbatore (Inde méridionale); 7% et 1% à Amritsar (Inde septentrionale); 0% et 0% à Dacca (Pakistan oriental).

Avec le traitement TH, la fréquence des effets secondaires a également varié dans une mesure très appréciable. La proportion des abandons de traitement a été de 21% en Malaisie et de 0% en Ethiopie. Dans le sous-continent indien, elle a été de 20% à Coimbatore et de 0% à Dacca et à Lahore.

En Malaisie, à Singapour et à la Trinité, où ont été traités des patients de diverses origines, on n'a pu mettre en évidence des facteurs raciaux susceptibles d'expliquer les différences d'incidence des effets secondaires entre pays, sauf en ce qui concerne les réactions cutanées à la Trinité et peut-être aussi en Malaisie.

On a constaté une corrélation étroite entre la fréquence des effets secondaires, par pays et par centre

de traitement, chez les malades STH et les malades SH.

Selon les auteurs, les variations de pays à pays de la fréquence des effets secondaires à la suite de l'administration de thioacétazone sont dues essentiellement à des

modalités différentes de surveillance des malades, d'enregistrement et d'interprétation des réactions, à des facteurs de milieu comme les habitudes alimentaires et le climat, à l'emploi antérieur d'autres médicaments ou à l'exposition à des substances sensibilisatrices.

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