SEVERE CUTANEOUS ERUPTIONS CAUSED BY THIACETAZONE USED TO TREAT TUBERCULOSIS IN RIO GRANDE DO SUL, BRAZIL[1]

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The results of a Brazilian survey show that thiacetazone, a drug widely used for tuberculosis treatment, can produce severe and occasionally fatal cutaneous reactions in some patients. These results have led health authorities in the state where the survey was conducted to consider thiacetazone unacceptable for use in routine treatment of tuberculosis.

Introduction

Drug-related cutaneous reactions are among the most common dermatoses of our time. These undesirable effects, the mechanisms of which are not always clear, may occur even though great care has been taken to ensure that a given therapeutic agent is being properly administered. The skin eruptions, for the most part mild and transitory, generally occur alone but may be accompanied by systemic manifestations of varying intensity that are sometimes serious or even fatal. Drugs responsible for the reactions may be taken into the system via the most diverse routes—by ingestion, inhalation, inoculation, or absorption through the skin or mucosa; in mother's milk; or across the placenta (*3*). The responsible drug can be hard to identify; for while some drugs customarily provoke the same type of readily recognizable reaction, others produce extremely varied manifestations.

Today, 1 to 5 per cent of all patients in general hospitals suffer undesirable effects from drugs (*2*); the frequency of these reactions, among them the cutaneous reactions, is alarming. In fact, according to some authors, nearly everybody in the world today has at some time showed signs of intolerance to one kind of medication or another. The increasing number of drugs in use, the possible side effects that are unknown in many cases, multiple drug administration, and long-term treatment are all factors that contribute to the rising incidence of cutaneous drug reactions (*1*).

Among the most serious cutaneous reactions are those involved with the Stevens-Johnson syndrome and Lyell's disease—syndromes which are often fatal because of the extensive mucocutaneous and visceral involvement. The tissue loss caused by bullous lesions and/or epidermal necrolysis gives rise to clinical pictures resembling those of severe burns.

These two syndromes, produced by a wide variety of sometimes hard-to-trace causes, are usually triggered by such agents as barbitu-

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rates, penicillin, phenolphthalein, phenylhydantoin and related drugs, pyrazolon and its derivatives, and sulfa drugs. Other reported causes include allopurinol, benzothiadiazides, codeine, nitrofurantoin, phenacetin, phenylcarbazine, propranolol, tetracyclines, and thiacetazone (*12*).

Thiacetazone has been widely used in recent years for antituberculosis treatment. In fact, the eighth report of the WHO Expert Committee on Tuberculosis, published in 1964 (*13*), recommended thiacetazone as a cheap, effective drug for routine treatment of new tuberculosis cases; however, the committee also stressed the need for further toxicity studies employing a representative sample of cases. The committee's ninth report, published in 1974 (*14*), reaffirmed the drug's advantages—efficacy and low cost—and indicated that its toxicity level had been found acceptable in many communities. However, serious side effects were reported in studies from Recife, Brazil (*9*), Morocco (*5*), and the island of Trinidad (*8*) around this time; and, as a result of the two latter studies, the drug was not introduced into Morocco or Trinidad and Tobago.

Methodology

Rio Grande do Sul, Brazil's southernmost state, has an area of approximately 282,000 km^2 and a population of about 8,000,000 inhabitants. The incidence of tuberculosis in Rio Grande do Sul has declined in recent years, there being 7,223 cases (94.6 per 100,000 inhabitants) in 1976, and 6,110 cases (78.3 per 100,000) in 1977 (*11*). The State Health Department's Tuberculosis Unit is exclusively responsible for the area's control program.

A new therapeutic regimen, adopted for treatment of the disease in Rio Grande do Sul on 1 June 1975, called for 150 mg per day of thiacetazone and 420 mg per day of isoniazid for 12 months, plus 1 g per day of streptomycin, administered intramuscularly, during the first month. This "IST" regimen replaced the previous isoniazid, streptomycin, and PAS regimen in both inpatient and outpatient treatment.

Nevertheless, in view of the reports on thiacetazone's toxic effects—particularly erythroderma (*2*) and the Stevens-Johnson syndrome (*12*)—a prospective survey was conducted to assess the frequency of these effects. For this purpose cases were observed at the *Hospital Sanatório Partenon,* a tuberculosis hospital, taking advantage of a specialized dermatology unit attached to the hospital. The following patients were included in the study:

1) Those who began IST treatment after admission to the hospital.

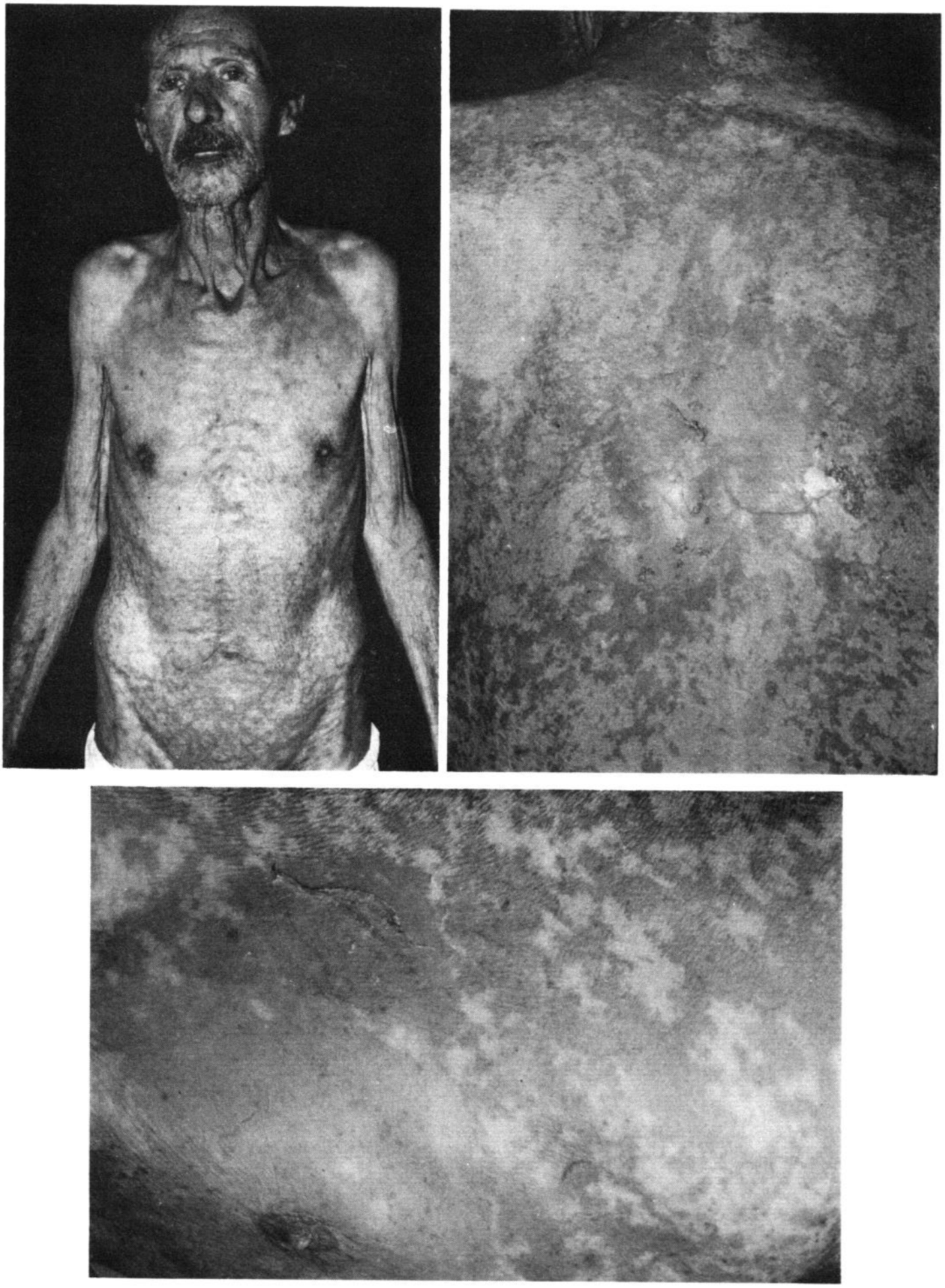
2) Those who first received IST ambulatory treatment and who were free of skin eruptions or other signs of toxic drug reaction upon subsequent admission to the hospital.

Results

The survey, concluded on 31 August 1977, included 1,890 patients, distributed by sex and age as shown in Table 1. The total number of patients admitted to the *Hospital Sanatório Partenon* and treated with IST from 1 June 1975 to 31 August 1977 was 1,926, but 36 of these were excluded from the study because the reason for their admission was serious drug intolerance during ambulatory treatment. (Thirty-four of these 36 patients

Table 1. Patients treated at the *Hospital Sanatório Partenon* during the period 1 June 1975-31 August 1977 who were included in the study, by age group and sex.

Age group (in years)	Males	Females	Total
0-9	—	—	—
10-19	91	85	176
20-29	243	210	453
30-39	283	126	409
40-49	288	81	369
50-59	200	50	250
60-69	118	41	159
≥ 70	48	26	74
Total	1,271	619	1,890



J.A.R., male, 63 years of age. This patient was treated with IST at *Hospital Sanatório Partenon* beginning on 9 October 1975. Lyell's disease was diagnosed on 3 November. Though hydrocortisone therapy improved regression of skin lesions, the patient died on 23 November 1975 from pneumonia.

had skin eruptions and the other two had hepatitis symptoms.) These cases were not included in our calculations because they were really part of the population receiving ambulatory treatment. However, they were registered and included in the projections for the entire IST-treated population in the state.

Seventy-one cases of drug-related cutaneous reactions were found in the 1,890 subjects studied, yielding a coefficient of 37.6 cases per 1,000 subjects. There were 48 male cases and 23 female cases; but because more male subjects were studied, the incidence coefficients (37.8 cases per 1,000 males, 37.2 cases per 1,000 females) were very similar. With respect to age, although the coefficients were high for all groups, they appeared highest among the older patients (see Table 2).

All the observed skin reactions appeared between two and 92 days after initiation of treatment (the average was 27.3 days); 52 cases (73.2 per cent) occurred during the first 30 days of treatment.

The various skin eruptions were classified by severity and type (see Table 3) as mild (uncomplicated pruritis, acneform eruption, morbilliform erythema, and suspected but unspecified reactions); moderate (extensive maculoerythematous eruption, urticaria, and purpura); or severe (erythroderma, erythema multiforme, Stevens-Johnson syndrome, and Lyell's disease). In terms of severity, the 71 cases were distributed as follows: mild, 34 (18.0 cases per 1,000); moderate, 19 (10.1 cases per 1,000); and severe, 18 (9.5 cases per 1,000). These reactions were deemed responsible for five deaths (deaths from uncertain causes being excluded), so that overall mortality from these reactions within the sample was 2.6 deaths per 1,000 subjects. This mortality is very similar to the overall mortality observed among subjects in other IST studies (see Table 4); these latter studies included 2,955 subjects treated with IST and reported a total of seven deaths; so even though the reported mortality varied considerably from study to study, overall mortality came to 2.4 deaths per 1,000 subjects.

Projections and Observed Reactions in Rio Grande do Sul

A total of 12,434 tuberculous patients received the IST regimen in Rio Grande do Sul between 1 June 1975 and 31 August 1977. If cutaneous reactions and reaction-related deaths occurred at the same frequency among these patients as among the patients studied at the *Hospital Sanatório Partenon,* then the numbers of mild, moderate, and severe cases

Table 2. The number and rate per 1,000 of drug-related skin eruptions among the study subjects, by age group and sex.

Age group (in years)[a]	Males		Females		Total	
	No. with skin reactions	Rate per 1,000 patients	No. with skin reactions	Rate per 1,000 patients	No. with skin reactions	Rate per 1,000 patients
10-19	2	22.0	2	23.5	4	22.7
20-29	4	16.5	4	19.0	8	17.7
30-39	9	31.8	5	35.6	14	34.2
40-49	12	41.7	5	61.7	17	46.1
50-59	8	40.0	3	60.0	11	44.0
60-69	11	93.2	1	24.4	12	75.5
≥ 70	2	41.7	3	115.4	5	67.6
Total	48	37.8	23	37.2	71	37.6

[a]No patients 0-9 years old were represented in the study population; in fact, there were only 19 study patients below 15 years of age (6 boys and 13 girls), and no drug-related cutaneous reactions were observed among them.

Table 3. Types of skin reactions observed among study subjects, showing the number of reactions of each type and the number of deaths among patients with each type of reaction.

Type of reaction	Cases	Deaths
Not specified[a]	17	1[b]
Pruritis	3	—
Acneform eruptions[c]	2	—
Morbilliform erythema	12	1[b]
Extensive maculoerythematous eruptions	8	1[b]
Urticaria	6	—
Purpura	5	1[b]
Erythroderma	6	1
Erythema multiforme	2	—
Stevens-Johnson syndrome	7	1
Lyell's disease	3	3
Total	71	9(4[b] + 5)

[a]Patients with residual lesions who were not seen by a dermatologist until remission; the reactions involved were generally mild.

[b]Cause of death uncertain. These deaths befell patients who had other serious complications preceding the cutaneous reaction—such as severe cardiopathy or severe cardiac insufficiency; these deaths were not included in the total mortality figure for this reason.

[c]Probably caused by isoniazid.

and deaths in Rio Grande do Sul State during this period would have been as follows:

Cutaneous reactions:

Mild	224 cases
Moderate	126 cases
Severe	118 cases
Total	468 cases
Deaths	32

A retrospective survey based on information supplied by health units throughout the state and by regional tuberculosis program supervisors revealed 128 cases of drug-related eruptions in patients receiving ambulatory treatment during the period. These cases included the 34 previously mentioned that were admitted to the *Hospital Sanatório Partenon.* Overall, 37 of the 128 cases were classified as mild, 17 as moderate, and 74 as severe. Seven deaths also occurred, five of them among the patients admitted to the *Hospital Sanatório Partenon.* However, these mortality figures are incomplete, follow-up not having been possible in most of the reported cases (see Table 5).

Since notification of ambulatory cases was incomplete (many health units not having reported drug-related eruptions), the disparity between the relatively large number of severe cases and the relatively small numbers of mild and moderate ones is understandable. Severe cases being more evident than mild or moderate ones, they are more easily observed and reported. This suggests that the figure for severe skin eruptions (74) should be the most accurate of the three. Overall, the 74 severe cases found among ambulatory patients and the 18 found among *Hospital Sanatório Partenon* inpatients yield a total of 92 severe cases statewide.

This amounts to 26 fewer than the 118 projected on the basis of the hospital study. That difference can be accounted for not only by the incompleteness of the ambulatory case data, but also by the fact that no data were available on 8 per cent of the 12,434 ambulatory patients who failed to terminate the course of treatment. In this regard, it is logical to suppose that in some cases severe drug-related reactions were responsible for premature termination of treatment.

All of this suggests that the incidence coefficients derived from the hospital study were probably quite close to the actual statewide coefficients. This conclusion would appear to justify considering the IST combination's toxicity level to be unacceptably high for routine treatment of tuberculosis. It also appears that the observed reactions were attributable to thiacetazone, since no similar toxic reactions except acneform lesions were detected during the state's extensive earlier experience with streptomycin and isoniazid used in combination with PAS. Therefore, on these grounds it was decided to exclude thiacetazone from primary and secondary tuberculosis treatment regimens in the state of Rio Grande do Sul.

Table 4. Toxic reactions and deaths found in other studies of thiacetazone treatment in various countries.

Country	Number of tuberculosis cases observed	% of subjects with toxic reactions		No. of deaths reported	Reference
		Total reactions	Cutaneous reactions		
Africa and Asia:					
East Africa (first study)	425	1.1	0.7	1	*Tubercle* 47: 1, 1966.
East Africa (second study)	360	5.0	1.6	—	*Tubercle* 47:315, 1966.
India (Bangalore)	127	18.1	11.0	—	*Indian J Tuberc* 14:41, 1966.
India (Madras)	75	12.0	7.0	—	*Bull WHO* 34:483, 1966.
Mali	57	28.5	12.2	—	*Bull Int Union Tuberc* 49(2):149, 1974.
Morocco	81	unknown	4.3	2	*Bull WHO* 39:731, 1968.
Rhodesia	69	10.1	9.0	1	*Tubercle* 49:48, 1968.
Singapore	72	72.0	42.0	—	*Tubercle* 52:88, 1971.
Western Hemisphere:					
Bolivia	1,214	12.0	1.8	—	*Prensa Médica* (La Paz) 21:80, 1969.
Bolivia	62	4.5	3.3	—	Medeiros, S. (*7*), 1972.
Brazil (Recife)	95	66.3	36.8	3	*Revista da Divisão Nacional de Tuberculose* 17:294, 1973.
Chile	101	18.7	9.4	—	Busel, I. et al. *(4)*, 1975.
Paraguay	30	6.6	3.3	—	Mallorquin, C. A., et al. *(6)*, 1971.
Peru	102	22.0	9.8	—	Romo Mayuri, M., et al. *(10)*, 1970.
Trinidad	85	61.2	42.4	—	*Bull WHO* 47:211, 1972.
Total reactions and deaths	2,955			7	

Source: Antonio Pio, Pan American Health Organization, personal communication.

Table 5. Drug-related cutaneous reactions and drug-related deaths reported among ambulatory tuberculosis patients treated with IST in the state of Rio Grande do Sul between 1 June 1975 and 31 August 1977.

Type of reaction	Ambulatory cases admitted to the *Hospital Sanatório Partenon*	Ambulatory cases reported but not referred to the hospital	Total ambulatory cases reported	Known deaths[a]
Not specified	5	1	6	—
Pruritis	—	19	19	—
Acneform eruptions	—	1	1	—
Morbilliform erythema	4	9	13	1
Extensive maculoerythematous eruptions	2	—	2	—
Urticaria	—	8	8	—
Purpura	—	5	5	—
Erythroderma	7	30	37	1
Erythema multiforme	1	9	10	—
Stevens-Johnson syndrome	11	7	18	3[b]
Lyell's disease	4	5	9	2[b]
Total	34	94	128	7

[a]Data incomplete; reliable information lacking concerning the outcome of severe reactions.
[b]Deaths occurring in the *Hospital Sanatório Partenon.*

Table 6. Severe reactions to IST treatment observed at the *Hospital Sanatório Partenon* by type of reaction and whether the reaction began in the hospital.

Type of reaction	Reactions among hospitalized patients	Reactions among ambulatory patients who were later hospitalized	No. of severe reactions	No. of deaths
Erythroderma	6	7	13	1
Erythema multiforme	2	1	3	—
Stevens-Johnson syndrome	7	11	18	4
Lyell syndrome	3	4	7	5
Toxic hepatitis	2	2	4	1[a]
Total	20	25	45	11[a]

[a]The death from toxic hepatitis was excluded from the hospital study's drug-related mortality figures because the patient's general condition was already very poor when hepatitis symptoms appeared.

Other Observed Signs of Toxicity

Besides skin eruptions, other toxic symptoms (especially of the digestive tract) were observed among the inpatients treated with IST. Specifically, three cases of gastric intolerance (severe nausea and vomiting) and one case of "uncontrollable dizziness" among the 1,890 *Hospital Sanatório Partenon* patients made it necessary to substitute second-line drugs. In addition, two of the patients developed hepatitis (probably toxipathic hepatitis) and one died. This death was excluded from the hospital study's mortality data because the patient's general condition was very poor to begin with, and so death could not be definitely attributed to thiacetazone-prompted toxipathic hepatitis. Overall, treatment had to be discontinued for 69 (3.65 per cent) of the 1,890 study subjects because of gastric intolerance (in three subjects), toxic hepatitis (in two), uncontrollable dizziness (in one), and skin eruptions (in 63).

Information about other toxic effects among ambulatory patients is incomplete, but 26 cases were reported in which treatment had to be discontinued because of gastric intolerance. In addition, two patients with symptoms of toxic hepatitis were referred to the *Hospital Sanatório Partenon,* and one of these subsequently died.

Counting both direct admissions and referrals from the outpatient service, a total of 45 patients with severe toxic reactions were seen at the *Hospital Sanatório Partenon* (Table 6), and 11 patients in this group died.

SUMMARY

The State Health Department of Rio Grande do Sul, Brazil's southernmost state, began treating tuberculosis patients with a regimen of isoniazid, streptomycin, and thiacetazone (IST) on 1 June 1975. However, reports of thiacetazone's possible toxic effects prompted a long-term study of 1,890 patients who received this regimen at the state's *Hospital Sanatório Partenon,* a tuberculosis hospital, between 1 June 1975 and 31 August 1977. That study revealed 71 cases of drug-related cutaneous reactions; 18 of these reactions were judged severe and 5 were fatal. No similar toxic reactions except acneform lesions had been detected during the state's previous extensive experience with isoniazid and streptomycin.

Although outpatient data are incomplete, there are grounds for believing that the incidence of toxic effects among all 12,424 patients receiving the IST regimen was similar to that observed among the 1,890 hospital inpatients. Because of the high incidence of toxic reactions and deaths apparently attributable to thiacetazone, health authorities in Rio Grande do Sul have classified this drug as unacceptable for use in routine treatment of tuberculosis.

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PREVENTION OF NEONATAL TETANUS

Tetanus claims at least a million human lives a year around the world, about half being those of newborn infants; and in many countries such neonatal tetanus kills about 85 per cent of those afflicted. Infants typically contract the disease at birth, when delivered in non-aseptic conditions—especially when the umbilical cord is cut with unclean instruments (ritual knives, pieces of glass, and so forth) or when the umbilical stump is dressed with ashes, soil, or cow dung.

Tetanus is best prevented by immunization. The immunity resulting from two injections of tetanus toxoid is highly effective and lasts for several years. Although newborns cannot themselves be immunized in time to prevent tetanus acquired at birth, immunity lasting several weeks can be transferred to the baby if the mother is immunized during pregnancy or if she already has a high level of immunity at the time she becomes pregnant.

Other measures that help prevent tetanus are introduction of hygienic principles into ritual cutting of the umbilical cord and "traditional" dressing of the stump. The presence of a health worker or medical staff member during childbirth is advised. [*Source:* WHO, In Point of Fact, No. 15, 1981.]