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Deterioration of Cycloserine in the Tropics*

K. V. NAGESWARA RAO,[1] L. EIDUS,[2] C. EVANS,[3] S. KAILASAM, S. RADHAKRISHNA, P. R. SOMASUNDARAM, H. STOTT,[4] S. SUBBAMMAL & S. P. TRIPATHY

Gross deterioration of cycloserine during transit and storage in the tropics is reported from the Tuberculosis Chemotherapy Centre, Madras. Laboratory experiments suggest that high humidity, rather than high temperature, is the main cause of the deterioration. Further investigations undertaken at the Centre indicate that deterioration can be prevented by storing the drug in tightly closed glass bottles in an air-conditioned room (18°C); if such facilities are not available, and the drug has to be stored at ambient temperature and humidity, the use of air-tight polyethylene bottles will serve to delay *the deterioration. The findings also suggest that, when cycloserine is dispensed to patients, individual doses should be heat-sealed in polyethylene strips and that not more than a week's supply should be given at any one time. The authors discuss various measures that could be employed by manufacturers and by shipping and clearing agents to minimize the possibility of deterioration.*

Cycloserine is frequently used in the re-treatment of patients with pulmonary tuberculosis who have failed to respond to standard chemotherapy, and cycloserine in combination with ethionamide is the basis of a valuable regimen (Brouet et al., 1959; Veran et al., 1959; British Tuberculosis Association, 1961; Schwartz, 1962; Salomon & Gold, 1963; Ramakrishnan et al., 1967). During a therapeutic study of the combination at this Centre, a major deficit in the stated content of cycloserine in tablets was detected. The present paper describes the discovery of this deficit, which was caused by deterioration of the drug, and the subsequent field and laboratory investigations undertaken to determine the rate at which deterioration occurred, its causes and ways in which it could be prevented or delayed.

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[1] Present address: University of Chicago, Chicago, Ill., USA.

[2] Present address: Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada.

[3] Present address: Department of Health, Brisbane, Australia.

[4] Present address: Tuberculosis and Chest Diseases Research Unit (Medical Research Council), London, England.

DISCOVERY OF CYCLOSERINE DEFICIT

Receipt, storage and dispensing of cycloserine at the Centre

Supplies of cycloserine arrived at the Centre either by air, taking 1–3 weeks after despatch from the factory, or by sea, usually taking 2–3 months. The cycloserine was supplied as 250-mg tablets or 250-mg capsules in amber-coloured screw-capped bottles, each containing 500. These bottles were kept in a store at ambient temperature and humidity, and issued to the outpatient clinic at approximately weekly intervals, according to requirements.

The cycloserine was administered under supervision to patients treated in sanatorium and to ambulatory patients who attended the Centre daily. For the other patients, who attended the Centre once weekly or twice weekly and self-administered the drug at home, a supply of cycloserine for a week, or for 3 or 4 days, was dispensed in paper envelopes.

Deterioration of cycloserine tablets stored in the Centre

Up to September 1964, only capsules of cycloserine were used at the Centre and no urine-testing for the drug was performed. At this stage, the use of tablets was introduced and, by coincidence, urine tests for cycloserine, using the method of Rao et al. (1965), were started for patients receiving the drug.

Until April 1965, the urine-test results for patients in the sanatorium (who received the cycloserine tablets daily under supervision) were almost always positive. However, towards the end of April, very many negative results were reported. This finding was so much at variance with the established reliability of the test (Rao et al., 1965) that, after preliminary investigations had excluded laboratory errors or inadequate supervision as possible causes, it was decided to assay the tablets in current use by the colorimetric method of Jones (1956), using pure cycloserine [1] as the standard. The tablets that were assayed were taken from a batch of 50 bottles, marked with an expiry date of April 1966, which had arrived at the Centre by air in October 1964. It was found that the screw caps of many of the 33 bottles remaining in the store from this batch were loose, and that the tablets smelt strongly of ammonia. Further, the tablets were discoloured yellow and were stuck to one another, as well as to the cotton packing in the bottles. From the 33 bottles, 7 were selected by a systematic sampling procedure, starting from the second and thereafter selecting every fifth bottle, and 1 tablet taken indiscriminately from each of these bottles was assayed. The cycloserine content ranged from 6 mg to 142 mg, the mean for the 7 bottles being 77 mg, that is, 31% of the stated content of 250 mg.

During the period of storage (October 1964–April 1965), the daily temperature [2] in Madras ranged from 23°C to 31°C (mean, 27°C). The daily relative humidity [2] ranged from 56% to 95% (mean, 76%) and the maximum at any time during the period was 100%. Thus, the tablets had been exposed to high temperatures and, especially those in bottles with loose caps, to high humidity also; it was subsequently realized that storage under such conditions was contrary to the recommendation that "cycloserine should be kept in a well-closed container, protected as far as possible from moisture, and stored at a temperature not exceeding 25°C" (*British Pharmacopoeia*, 1963). However, the only instruction on the labels of the bottles was "store in a cool place".

Potency of cycloserine tablets on arrival at the Centre

Sea freight. Two consignments of cycloserine tablets were received at the Centre by sea after the assays were started. The first, consisting of 50 bottles (each containing 500 tablets) with an expiry date of May 1966, took about 6 months in transit, from December 1964 to June 1965. On arrival, the caps of many of the bottles were loose, and the tablets smelt strongly of ammonia, were tacky and were discoloured yellow. Assay of single tablets, taken indiscriminately from each of the 50 bottles, showed that the cycloserine content ranged from 12 mg to 225 mg, the mean content for the sample being 130 mg, that is, 52% of the stated content of 250 mg. The tablets in the second consignment (60 bottles, each containing 500 tablets), which took about 2 months in transit between June and August 1965, had a satisfactory appearance on arrival and the mean cycloserine content of a sample of 24 tablets (2 from each of a random sample of 12 bottles) was found to be 257 mg. No consignment of capsules arrived by sea after assays were started.

Air freight. Two bottles of cycloserine tablets and 2 of capsules, each bottle containing 500, were received at the Centre by air in July 1965 for experimental purposes. Assays undertaken on 25 tablets and 25 capsules showed that the mean cycloserine content was 260 mg in tablets and 259 mg in capsules. In August 1965, a consignment of 30 bottles, each containing 500 capsules, arrived by air; the mean cycloserine content of 18 capsules (3 from each of a random sample of 6 bottles) was found to be 250 mg.

FIELD AND LABORATORY INVESTIGATIONS

Storage in the Centre under various conditions and in patients' homes

An investigation was undertaken to determine whether the cycloserine content of tablets and capsules was affected by storage and, if so, the relative importance of (1) storage conditions, (2) type of container used for storage, and (3) duration of storage. The tablets and capsules used in this and subsequent investigations were taken from the 4 bottles received by air for experimental purposes (see above), which were stored in the laboratory cold-room at a temperature of approximately 9°C and a relative humidity of approximately 75%.

A supply of tablets was placed in (1) an original (manufacturer's) glass bottle (screw-capped, tightly closed and with cotton packing inside) in an air-conditioned room (temperature 18°C, relative humidity 55%), (2) a tightly closed screw-capped poly-

[1] Pure cycloserine was supplied by the manufacturers in powder form in heat-sealed, amber-coloured ampoules. At the Centre, the ampoules were stored in a cold-room at a temperature of approximately 9°C.

[2] Mean of 24 readings, recorded at hourly intervals.

TABLE 1

DETERIORATION OF CYCLOSERINE DURING STORAGE IN THE CENTRE AND UNDER VARIOUS CONDITIONS IN PATIENTS' HOMES

Place of storage	Container	Mean cycloserine content (%) [a] in following no. of days: [b]								
		1	2	4	7	14	21	28	42	56
Tablets										
Air-conditioned room	Glass bottle	100	100	102	98	98	104	103	101	98
Clinic	Polyethylene bottle	102	100	100	100	99	102	97	*96*	99
Clinic	Glass bottle	101	100	101	97	100	*96*	*94*	(*83*)	(*61*)
Clinic	Paper envelopes	101	101	*95*	*94*	*91*	(*84*)	(*82*)	(*35*)	(*8*)
Patient's home (1)	Paper envelopes	98	100	97	(*83*)	(*33*)	—	—	—	—
Patient's home (2)	Paper envelopes	100	98	*93*	(*51*)	(*4*)	—	—	—	—
Capsules										
Air-conditioned room	Glass bottle	102	101	*96*	99	99	100	102	100	97
Clinic	Polyethylene bottle	103	100	97	100	99	99	101	*95*	*91*
Clinic	Glass bottle	102	98	*96*	*97*	*93*	(*81*)	(*76*)	(*42*)	(*5*)
Clinic	Paper envelopes	101	*95*	98	*91*	(*73*)	(*57*)	(*51*)	(*4*)	(*1*)
Patient's home (1)	Paper envelopes	101	*96*	*88*	(*64*)	(*15*)	—	—	—	—
Patient's home (2)	Paper envelopes	99	*92*	(*75*)	(*26*)	(*3*)	—	—	—	—

[a] Expressed as a percentage of the mean cycloserine content of the 36 control tablets (261.5 mg) or the 36 control capsules (259.2 mg) that were assayed, 4 on each of the 9 occasions.

[b] Parentheses indicate that the cycloserine content is less than the minimum B.P. limit of 231.25 mg for tablets and 225.0 mg for capsules. Italics indicate that the loss in cycloserine content is statistically significant at the 1 % level. As the variance of the cycloserine content of replicate tablets or capsules stored under identical conditions (container, temperature, and humidity), differed from one storage condition to another (data not presented here), the magnitude of the decrease required for statistical significance is not necessarily the same for the various storage conditions.

ethylene bottle (100 ml) in the clinic, (3) an original glass bottle (described in (1) above) in the clinic, (4) paper envelopes, each containing 4 tablets, in the clinic, and (5) paper envelopes, each containing 4 tablets, in the homes of 2 patients.

It was planned to assay 4 tablets from each container and, as a control on laboratory standards, from the stocks in the laboratory cold-room, 1, 2, 4, 7, 14, 21, 28, 42 and 56 days after storage. (As it happened, the cycloserine content in tablets stored in patients' homes was so low at 14 days (see Table 1) that subsequent assay of tablets from this source was discontinued.) On each of these days, all the tablets for assay were sent with code numbers and in a random order to the biochemist, thereby ensuring that he was unaware of the identity of any of the individual tablets or, indeed, which tablets had been stored under the same conditions. Identical procedures were employed for capsules. During the period of this investigation, the daily temperature in Madras ranged from 25°C to 31°C and the relative humidity from 74% to 98%, the means being 28°C and 85%; the maximum relative humidity was 90% or above on *all* days and 100% on as many as 23 days.

There was no evidence of changes in laboratory standards during the course of this, or any subsequent, investigation; thus, the variation, from one day to another, in mean cycloserine content of the 4 control tablets or capsules was no more than the variation in content between replicate tablets or capsules assayed on the same day. Consequently, in each investigation, the cycloserine content after a period of storage has been expressed as a percentage of the mean content of all the control tablets or capsules in the investigation—that is, the latter has been regarded as the initial content.

In this report, the earliest occurrence of a statistically significant decrease (at the 1% level) [1] in cyclo-

[1] Since the effect of storage could only be a loss in cycloserine content, one-tail tests of significance were employed.

serine content has been taken as the first indication of deterioration, except on occasions when there was a conflicting finding at the next assessment. A second criterion, namely, a fall in cycloserine content to below the B.P. limit, has also been employed; this limit, which is based on tolerances for manufacturing variations, is 92.5% (i.e., 231.25 mg) for tablets and 90.0% (i.e., 225.0 mg) for capsules (*British Pharmacopoeia*, 1963, 1966).

Tablets. No deterioration occurred in the tablets stored in the glass bottle in the air-conditioned room (Table 1). Considering the various containers at ambient temperature and humidity in the clinic, no deterioration was detected after storage in the polyethylene bottle but tablets stored in the glass bottle had deteriorated by 21 days and the mean content fell below the B.P. limit by 42 days; with paper envelopes, deterioration occurred by 4 days, and the mean content fell below the B.P. limit by 21 days and was as low as 8% at 56 days. However, the deterioration was greatest when the tablets were stored in paper envelopes in patients' homes: the cycloserine content fell below the B.P. limit by 7 days in both cases, and was only 33% and 4%, respectively, at 14 days.

Capsules. As with tablets, no deterioration occurred in the capsules stored in the glass bottle in the air-conditioned room. Capsules in the polyethylene bottle in the clinic showed deterioration at 42 days but the cycloserine content did not fall below the B.P. limit even at 56 days. The mean content of capsules in the glass bottle in the clinic fell below the B.P. limit by 21 days, the deterioration having first been detected at 4 days. Finally, as in tablets, the deterioration was swift and striking in capsules stored in paper envelopes, especially at patients' homes: deterioration was detected at 7 days in the clinic and in 2 days in both the homes, and the mean content fell below the B.P. limit by 14 and 7 days, respectively.

In summary, storage in tightly closed glass bottles in an air-conditioned room prevented the deterioration of cycloserine over a period of at least 56 days, in spite of the bottles having been opened on 9 occasions to take out tablets or capsules. Storage in a tightly closed polyethylene bottle at ambient temperature and humidity prevented the deterioration over a period of 28 days, Finally, storage in paper envelopes was very unsatisfactory: deterioration occurred within 48 hours and virtually no cycloserine remained at 14 days, in some cases.

TABLE 2
SUITABILITY OF UNIVERSAL CONTAINERS FOR STORAGE OF CYCLOSERINE IN PATIENTS' HOMES

Duration of storage (days)	Mean cycloserine content when stored in paper envelopes (%) [a]		Mean cycloserine content when stored in Universal containers (%) [a]	
	Tablets [b]	Capsules [b]	Tablets [b]	Capsules [b]
2	*95*	*94*	99	101
3	*95*	(*83*)	98	99
4	*94*	(*77*)	100	97
5	(*83*)	(*66*)	97	96
6	(*75*)	(*55*)	*95*	*95*
7	(*59*)	(*33*)	101	96
11	(*16*)	(*10*)	100	*95*
14	—	—	101	*92*
21	—	—	*96*	(*83*)
28	—	—	*97*	(*71*

[a] The mean content of the tablets or capsules stored in the homes of the 3 patients was computed, and is expressed as a percentage of the mean cycloserine content of the 40 control tablets (258.8 mg) or the 40 control capsules (262.8 mg) that were assayed, 4 on each of the 10 occasions.

[b] Italics indicate that the loss in cycloserine content is statistically significant at the 1% level. Parentheses indicate that the cycloserine content is less than the minimum B.P. limit of 231.25 mg for tablets and 225.0 mg for capsules.

Storage in different containers in patients' homes

In order to prevent, or at least delay, the deterioration of cycloserine when stored in patients' homes, the suitability of screw-capped Universal containers (which were more readily available at the Centre than polyethylene bottles) and heat-sealed polyethylene bags (prepared by nurses at the Centre) was investigated.

Universal containers. In each of 3 homes, a supply of tablets was placed in a screw-capped Universal container and, as a control to confirm the occurrence of deterioration, in paper envelopes (each containing 2 tablets). It was planned to assay, 2, 3, 4, 5, 6, 7, 11, 14, 21 and 28 days after storage, 2 tablets from each container in each home and, as a control on laboratory standards, 4 tablets from the stocks in the laboratory cold-room; in the event, however, the assay of tablets stored in paper envelopes was discontinued after 11 days since the cycloserine content had fallen below 20% by that time (see Table 2). Each day, all the tablets for assay were

TABLE 3
SUITABILITY OF POLYETHYLENE BAGS FOR STORAGE OF CYCLOSERINE IN PATIENTS' HOMES

Duration of storage (days)	Mean cycloserine content when stored in paper envelopes (%) [a]		Mean cycloserine content when stored in polyethylene bags (%) [a]	
	Tablets [b]	Capsules [b]	Tablets [b]	Capsules [b]
7	*(86)*	*(70)*	98	*97*
14	*(39)*	*(25)*	*92*	*87*

[a] The mean content of the tablets or capsules stored in the homes of the 6 patients was computed, and is expressed as a percentage of the mean cycloserine content of the 16 control tablets (258.0 mg) or the 16 control capsules (261.4 mg) that were assayed, 4 on each of the 2 occasions for the 2 sets of homes (see text).

[b] Italics indicate that the loss in cycloserine content is statistically significant at the 1% level. Parentheses indicate that the cycloserine content is less than the minimum B.P. limit of 231.25 mg for tablets and 225.0 mg for capsules.

sent under code numbers and in a random order to the biochemist. An identical experiment was concurrently undertaken with capsules. During the period of this investigation, the daily temperature in Madras ranged from 25°C to 28°C, and the relative humidity from 69% to 98%, the means being 27°C and 84%, respectively; the maximum relative humidity was 90% or above on all days.

The findings are set out in Table 2 and are based on the mean cycloserine content for the 3 homes. In the case of paper envelopes, deterioration was detected even at 2 days, both in tablets and in capsules; further, the mean content fell below the B.P. limit at 5 and 3 days for tablets and capsules respectively. In contrast, with Universal containers, deterioration was detected only at 21 days in tablets and 11 days in capsules; also, the mean content for tablets was above the B.P. limit even at 28 days while that for capsules fell below the B.P. limit by 21 days. Thus, the Universal containers succeeded in delaying, but not preventing, deterioration.

Polyethylene bags. In each of 6 homes, a supply of tablets was placed in heat-sealed polyethylene bags (each containing 2 tablets) and, as a control to confirm the occurrence of deterioration, in paper envelopes (each containing 2 tablets). At 7 and at 14 days after storage, 1 bag and 1 envelope were withdrawn, together with 4 control tablets from the stocks in the laboratory cold-room, and assays were undertaken after codification and randomization. (The investigation was commenced in 3 homes, and 6 days later 3 more homes were included.) An identical experiment was concurrently undertaken with capsules. During the period of this investigation, the daily temperature in Madras ranged from 24°C to 28°C and the relative humidity from 69% to 96%, the means being 26°C and 84%, respectively; the maximum relative humidity was 90% or above on all days.

The findings are set out in Table 3 and are based on the mean cycloserine content for the 6 homes. Considering first the paper envelopes, the mean content at 7 days showed a statistically significant decrease and was also lower than the B.P. limit, both for tablets and for capsules. In contrast, the mean content was 98% (range, 97%–101%) for the tablets and 97% (range, 94%–100%) for the capsules which were stored in polyethylene bags. This suggests that the polyethylene bags were largely successful in preventing deterioration up to 7 days. However, at 14 days, definite deterioration was detected, the mean content being 92% (range, 88%–97%) for tablets and 87% (range, 77%–96%) for capsules. Even so, an examination of the data for individual homes (not tabulated here) showed that the mean content had fallen below the B.P. limit in only 2 instances, and in both, only in capsules.

Summarizing the findings of both the investigations in patients' homes, there was clear evidence that the storage of cycloserine tablets, and to a lesser extent capsules, in tightly closed screw-capped Universal containers or heat-sealed polyethylene bags delayed, but did not prevent, deterioration of the drug.

Relative speed and magnitude of deterioration of tablets and capsules

A comparison of the speed and extent of deterioration of tablets and capsules, abstracted from the data in Tables 1 and 2, is given in Table 4.

Considering first the storage of cycloserine at ambient temperature and humidity in the clinic, the difference in mean content between tablets and capsules was highly significant at 2 days ($P=0.001$) and subsequently. Further, the mean content fell below the B.P. limit by 42 days for tablets and by 21 days for capsules. The mean content of cycloserine stored in homes was significantly higher at 3 days in tablets than in capsules ($P<0.01$); subsequently, it fell below the B.P. limit at 6 days for tablets compared with 5 days for capsules. These findings demonstrate that the deterioration of cycloserine capsules was more rapid and more substantial

TABLE 4

RELATIVE SPEED AND MAGNITUDE OF DETERIORATION OF CYCLOSERINE IN TABLETS AND CAPSULES

Container and place of storage	Form of cycloserine	Mean cycloserine content (%) in following no. of days: [a]												
		1	2	3	4	5	6	7	11	14	21	28	42	56
Polyethylene bottles, glass bottles and paper envelopes in clinic [b]	Tablets	102	100	—	99	—	—	97	—	97	94	91	(71)	(56)
	Capsules	102	98	—	97	—	—	96	—	88	(79)	(76)	(47)	(33)
Paper envelopes and Universal containers in patients' homes [c]	Tablets	—	97	97	97	90	(85)	(80)	(58)					
	Capsules	—	98	92	88	(82)	(75)	(65)	(53)					

[a] Parentheses indicate that the cycloserine content is less than the minimum B.P. limit of 231.25 mg for tablets and 225.0 mg for capsules. [b] Data from Table 1. [c] Data from Table 2.

than that of tablets, both in the clinic and in patients' homes.

Laboratory investigations of the effect of temperature and humidity

Investigations were undertaken in the laboratory to determine the roles of temperature and humidity in causing deterioration of cycloserine. A desiccant, phosphorous pentoxide, was placed at the bottom of each of 4 screw-capped honey-jars, and water in each of 4 others. A small beaker containing 4 tablets of cycloserine was placed in each of the 8 jars, and the screw caps of those containing the desiccant were sealed with wax while those of the jars containing water were left loose. All the jars were placed in an incubator at 39°C and it was planned to assay 1 tablet from each jar at 4, 15, 22 and 30 days after storage, together with 4 control tablets from the stocks in the laboratory cold-room. An identical investigation was undertaken concurrently with capsules.

No deterioration occurred over the 30-day period in tablets and capsules exposed to a temperature of 39°C in a dry atmosphere (Table 5); in contrast,

TABLE 5

LABORATORY INVESTIGATIONS OF THE EFFECT OF TEMPERATURE AND HUMIDITY ON CYCLOSERINE CONTENT OF TABLETS AND CAPSULES

Experiment	Packaging and storing conditions	Relative humidity	Temperature (°C)	Mean cycloserine content (%) [a] of tablets in following no. of days: [b]				Mean cycloserine content (%) [a] of capsules in following no. of days: [b]			
				4	15	22	30	4	15	22	30
1	Loose in presence of desiccant	Negligible	39	101	100	100	98	98	99	99	99
	Loose in presence of water	Approx. 100 %	39	*(3)*	—	—	—	*(2)*	—	—	—
2	Loose in presence of water	Approx. 100 %	25	*(4)*	—	—	—	*(3)*	—	—	—
3	Foil-packed in presence of desiccant	Negligible	39	102	102	104	103				
	Foil-packed in presence of water	Approx. 100 %	39	103	(89)	*(66)*	*(56)*				

[a] Expressed as a percentage of the mean cycloserine content of all the control tablets or all the control capsules that were assayed during the course of the experiment; the means were 266.4 mg, 268.8 mg and 254.7 mg for tablets in experiments 1, 2 and 3, respectively, and 259.8 mg and 260.2 mg for capsules in experiments 1 and 2, respectively.

[b] Italics indicate that the loss in cycloserine content is statistically significant at the 1% level. Parentheses indicate that the cycloserine content is less than the minimum B.P. limit of 231.25 mg for tablets and 225.0 mg for capsules.

virtually no cycloserine remained at 4 days (and consequently, no further assays were done) in tablets and capsules stored in saturated air at the same temperature (39°C) or indeed (as shown by the results of a second experiment), at a lower temperature (25°C). Finally, a third experiment, employing tablets sealed in aluminium foil strips by the manufacturer and stored at 39°C, showed that no deterioration occurred in a dry atmosphere, but in saturated air, deterioration occurred and the cycloserine content fell below the B.P. limit by 15 days. These results suggest that high humidity is a more important cause of deterioration of cycloserine than high temperature, and that the dispensing of cycloserine tablets in aluminium foil strips can delay, but not prevent, deterioration of the drug under tropical conditions.

DISCUSSION

This paper reports deterioration of cycloserine which occurred during transit and storage in the tropics, and has shown that loss in cycloserine content can occur if tablets or, more particularly, capsules of cycloserine are exposed to atmospheric conditions of high humidity and high temperature. Further, laboratory investigations suggest that high humidity plays a more important part in causing deterioration than high temperature.[1] Finally, it has been shown that it is possible (*a*) to *prevent* the deterioration of cycloserine by storing the tablets or capsules in tightly closed glass bottles in an air-conditioned store (18°C), and (*b*) to *delay* the deterioration by storing the drug in air-tight screw-capped polyethylene bottles in the clinic (at ambient temperature and humidity) or dispensing it to patients in screw-capped Universal containers or in heat-sealed polyethylene bags.

In view of the possibility of deterioration, manufacturers should label bottles of cycloserine prominently with the appropriate storage requirements.[2] However, as it is often difficult in developing countries in the tropics to conform to these requirements, it is important that manufacturers should provide suitable packing, especially to protect against high humidity. (The bottles should have tight-fitting sealed caps as a minimum requirement, and the addition of a desiccant would be advantageous.[2] Strip packs of polyethylene or aluminium foil, which in bulk should be packed in air-tight containers, would also afford some protection, but would increase the cost by about 5%.) It is also important to ensure that the drug is not exposed to adverse conditions in transit, and consignments of cycloserine should therefore be prominently marked to ensure storage in a dry and preferably cool place. Finally, it is necessary to treat consignments of cycloserine as perishable goods and avoid delay in docks or warehouses, or if delay is unavoidable, to ensure that the drug is stored under suitable conditions.

Despite all precautions taken by the manufacturer and the shipping and clearing agents, medical stores in the tropics should aim to provide suitable storage conditions and arrange that only limited supplies of the drug are issued at any one time to clinics and hospitals, unless they have suitable storage facilities.

In many tropical countries, it is usual for patients to receive antituberculosis drugs in a paper envelope or just wrapped in paper. Our investigations have shown that these methods are very unsatisfactory for dispensing cycloserine (for instance, when tablets and capsules were stored in paper envelopes in patients' homes, deterioration occurred in as short a period as 48 hours), and have suggested 2 better methods. One is to dispense no more than a week's supply at a time in air-tight containers; the effectiveness of this measure will, however, depend on the patient's remembering to close the container tightly after each dose. The other is to dispense the week's supply in moisture-proof strips of aluminium foil or polyethylene, in which the individual tablets or capsules are sealed in separate compartments. Such a measure, apart from being more workable, will save time in the dispensary. However, certain special precautions would have to be taken with aluminium foil strips since they are liable to crack if folded or handled roughly, leaving minute perforations through which moisture can be readily absorbed.

There is clearly a need for periodic verifications of the potency of cycloserine in tropical conditions. Ideally, assays of the drug content should be undertaken, both on receipt and at intervals thereafter. However, facilities for quantitative assay are often not available in developing countries in the tropics. In these circumstances, a simple qualitative test, capable of detecting a loss in drug content of about 15% or more (Rao, Kailasam & Nair, 1968) may be employed. If the deterioration is gross, it can be detected by simple inspection in the case of tablets

[1] This has been confirmed independently by the manufacturers of cycloserine capsules (Rice, personal communication).

[2] Since our findings were made known, bottles of cycloserine tablets arriving at the Centre have labels clearly specifying the storage requirements, contain a desiccant and have polyethylene snap-caps sealed with metal foil.

since they turn yellow (from white), become tacky and smell of ammonia. Lastly, it must be emphasized that although a high number of negative urine-test results in patients receiving cycloserine under supervision drew our attention to the possibility of cycloserine deterioration, urine-testing (employing the method of Rao et al., 1965) is unsuitable for monitoring potency as the urine test yields positive results at 24 hours even when the content of the tablets is about 80% (unpublished observations).

Our findings have shown that the deterioration of cycloserine is more rapid and more substantial in capsules than in tablets; this is presumably because the drug is pressed firmly with adjuvants in the case of tablets and thereby acquires some protection against humidity, while in capsules it is in powder form.

In conclusion, evidence is presented in this paper that loss in content of cycloserine tablets and capsules may occur in a tropical climate with high humidity and high temperature. Such an occurrence could have serious effects since the deteriorated product is inactive [1] and since cycloserine is a drug in which the margin between adequate and inadequate dosage is probably small (Canetti, 1964); furthermore, this drug is usually prescribed to patients who have been unsuccessfully treated with 1, or even 2, previous regimens of chemotherapy. It is therefore imperative that all possible precautions should be taken to prevent deterioration of cycloserine, both in transit and subsequently.

[1] Microbiological assays, using *Mycobacterium tuberculosis* H37Rv and *Staphylococcus aureus* as test organisms, were undertaken on tablets and capsules which were found to be deficient in content by the colorimetric method; they showed a corresponding loss in the inhibitory activity of cycloserine, indicating that the deteriorated product was inactive *in vitro*.

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RÉSUMÉ

Les auteurs rapportent les résultats de leurs recherches sur la détérioration de la cyclosérine pendant son transport et son stockage à Madras (Inde) où la température et l'humidité sont généralement élevées.

Une enquête, au cours de laquelle des comprimés et des capsules de cyclosérine ont été conservés dans diverses conditions pendant une période de 56 jours, a montré que: *a*) la conservation en flacons de verre hermétiquement fermés, dans une pièce climatisée, empêche la détérioration du produit pendant une période d'au moins 56 jours; *b*) la conservation en flacons de polyéthylène hermétiquement fermés, au dispensaire, dans les conditions de température et d'humidité ambiantes, prévient la détérioration du produit pendant une période de 28 jours; *c*) la conservation dans des enveloppes de papier aboutit à une détérioration rapide, en particulier au domicile des malades où la teneur moyenne en cyclosérine des comprimés et des capsules descend en 7 jours au-dessous des limites prescrites par la Pharmacopée britannique.

Lorsqu'ils sont gardés au domicile des malades dans des récipients hermétiquement fermés par des couvercles à vis, les comprimés ne subissent aucune altération pendant au moins 14 jours et les capsules pendant au moins 7 jours; en outre, la teneur moyenne en cyclosérine reste supérieure aux limites prescrites par la Pharmacopée britannique pendant 28 jours dans les comprimés et 14 jours dans les capsules. En conservant les comprimés et les capsules, au domicile des malades, dans des sachets de polyéthylène fermés à chaud, on réussit à empêcher la détérioration du produit pendant un maximum de 7 jours; au bout de 14 jours, bien que l'on puisse constater une nette altération des comprimés et des capsules, leur teneur moyenne en cyclosérine reste supérieure à la limite fixée par la Pharmacopée britannique. Les capsules se détériorent plus rapidement et plus fortement que les comprimés. D'après les données recueillies au laboratoire, il semble qu'un degré élevé d'humidité relative soit un facteur de détérioration plus important qu'une température élevée.

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