ACUTE ORGANOPHOSPHORUS INSECTICIDE POISONING

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Poisoning due to organophosphate insecticides is not infrequently fatal, as these highly toxic compounds produce irreversible inactivation of the cholinesterases. These compounds, developed during the last war, as potential chemical warfare agents, are extensively used for the extermination of insect pests. Accidental poisoning following a single or repeated exposure is a well recognised hazard among farmers and crop dusters (Rosen, 1960). Moreover, the popularity of some of these compounds as suicidal poisons, especially the highly toxic parathion, is on the increase. Wyckoff *et al* (1968) report that 48 per cent of the 50 deaths caused by O.P. insecticides over a period of 7½ years, were suicidal.

It is also claimed that the administration of atropine without the concurrent use of cholinesterase activators, such as pralidoxime, very often results in a fatal outcome in severe cases of poisoning by parathion (Quinby and Clappison 1961; Kopel *et al*, 1962; Quinby *et al*, 1963). The purpose of this paper is to report a case of acute parathion poisoning and a second asymptomatic case of poisoning due to Fitios B/77, both treated successfully with atropine alone.

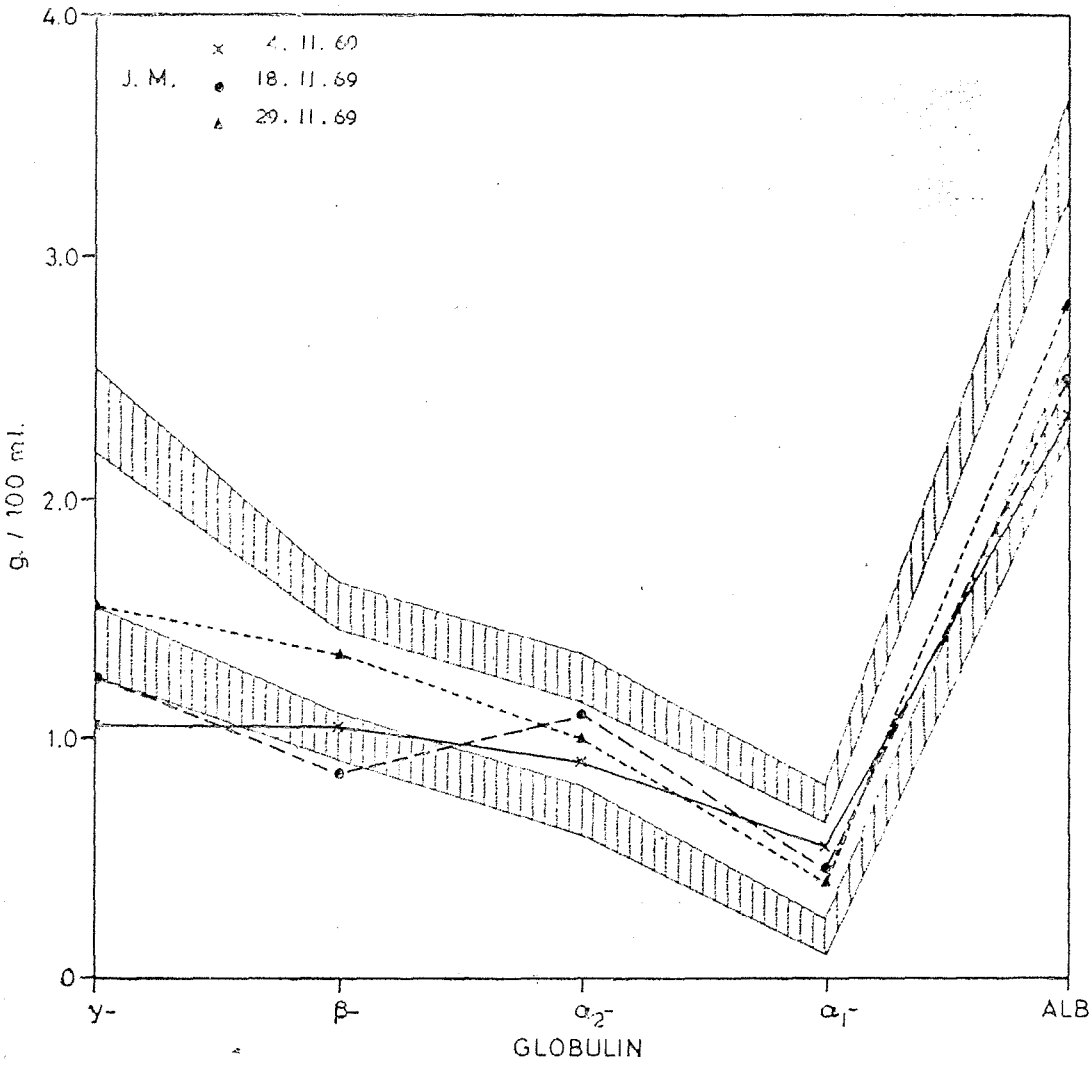

Fig. 1. Showing the changes in the serum electro-phoretic pattern in Case 1, with the upper and lower limits of normal, the shaded areas demarcating the limits of 2 S.D.

Report on Case I

L.C., male, 16 years, employed as a farm labourer for a month before hospitalisation, had been using parathion added to water for scrubbing the floor of henhouses. He wore no protective clothing and worked bare-footed. At about 5.00 p.m. on 12. 8. 68, after having used parathion, he drank water from the tap off his unwashed hands. At about 6.00 p.m. medical aid was sought because the boy was be-

having in a queer drunken manner, and by the time he was seen again by his doctor at 8.00 p.m. he was trembling, dyspnoeic and cyanotic.

On admission to hospital at 9.15 p.m., he was deeply comatose and very cyanosed. Respirations were laboured and noisy, and the R.R. was 34/min. There was marked sweating and salivation, and he was incontinent of urine and faeces. The jugular venous pressure was not raised; B.P. 160/60; pulse rate 84/min. regular and of good volume. The chest was full of coarse crepitations. The eyes were wandering; pupils pin-point and non-reactive to light. The boy was biting his lips most of the time and marked fasciculations were present. The reflexes were not elicited.

The liver and spleen were not palpable; bowel sounds were increased, and soon after admission the patient vomited.

Acute organophosphorus poisoning was diagnosed.

An intravenous infusion of 5% dextrose in normal saline was set up to facilitate the intravenous injection of atropine sulphate, 1.2 mg. at hourly intervals to attain adequate atropinisation. The criterion used to determine this effect was full dilatation of the pupils. The patient was washed thoroughly soon after admission and when the moist sounds present in the lungs had disappeared. At 1.05 a.m., the patient was still comatose and areflexic, but air entry was good with no adventitious sounds in the chest and the R.R. had dropped to 20/min. It was at this time that the pupils were noticed to be not as constricted as before. At 4.10 a.m., the pupils were fully dilated and the general condition had improved. During all this time he was receiving oxygen, but at no time did he require assisted respiration. At 5.30 a.m. he regained full consciousness and was co-operative, but his speech was rather slurred.

The patient was kept on a regime of hourly intravenous atropine, until at 11.30 p.m. of the second day in hospital, he became restless and hyperexcitable, with a very dry tongue and the pupils were still fully dilated. Hyperatropinisation was diagnosed; atropine was stopped but had to be re-started the next day when the pupils were becoming constricted again.

Laboratory Findings

E.S.R. 8 mm. in the 1st hour (Westergren); Hb 14.6 g/100 ml; WBC 7,800/ c.mm; differential count normal; blood urea 29 mg/100 ml. The urine had a pH of 5.5, contained glucose and a trace of protein, a slight excess of urobilin, no bilirubin, and no significant elements in the sediment.

The serum bilirubin was 1.0 mg/100 ml. The Van den Bergh reaction was indirect, and became negative only one month after presentation. Serum aspartate aminotransferase 15 i.u./l.; alanine aminotransferase 10 i.u./l.; alkaline phosphatase 10 (K-A) u/100 ml. The blood glucose on the day of admission was 140 mg./100 ml, and 80 mg./100 ml. the following morning. Serum electrolytes were normal; serum proteins 7.3 g/100 ml.; albumin 4.2 g/100 ml. The serum protein electrophoretic pattern was however, significantly different from the normal, and a reversal to a completely normal pattern was achieved only about 4 months later. (*Figure 1*).

The serum pseudo-cholinesterase (pChE) on admission was o u./ml. This, with the subsequent estimations are recorded in *Figure 2*.

Treatment

The dose of atropine administered in the first 24 hours was 26 mg. This was severely reduced in the subsequent 6 days according to the clinical improvement, and atropinisation was maintained using pupillary dilatation as the clinical guide. A total dose of 54 mg. was given over a period of 7 days.

Clinical improvement was noticeable as soon as full atropinisation had been attained. Although progress was maintained from the beginning, the first 7 days were marked with episodic bouts of epigastric pain and vomiting. He was able to walk

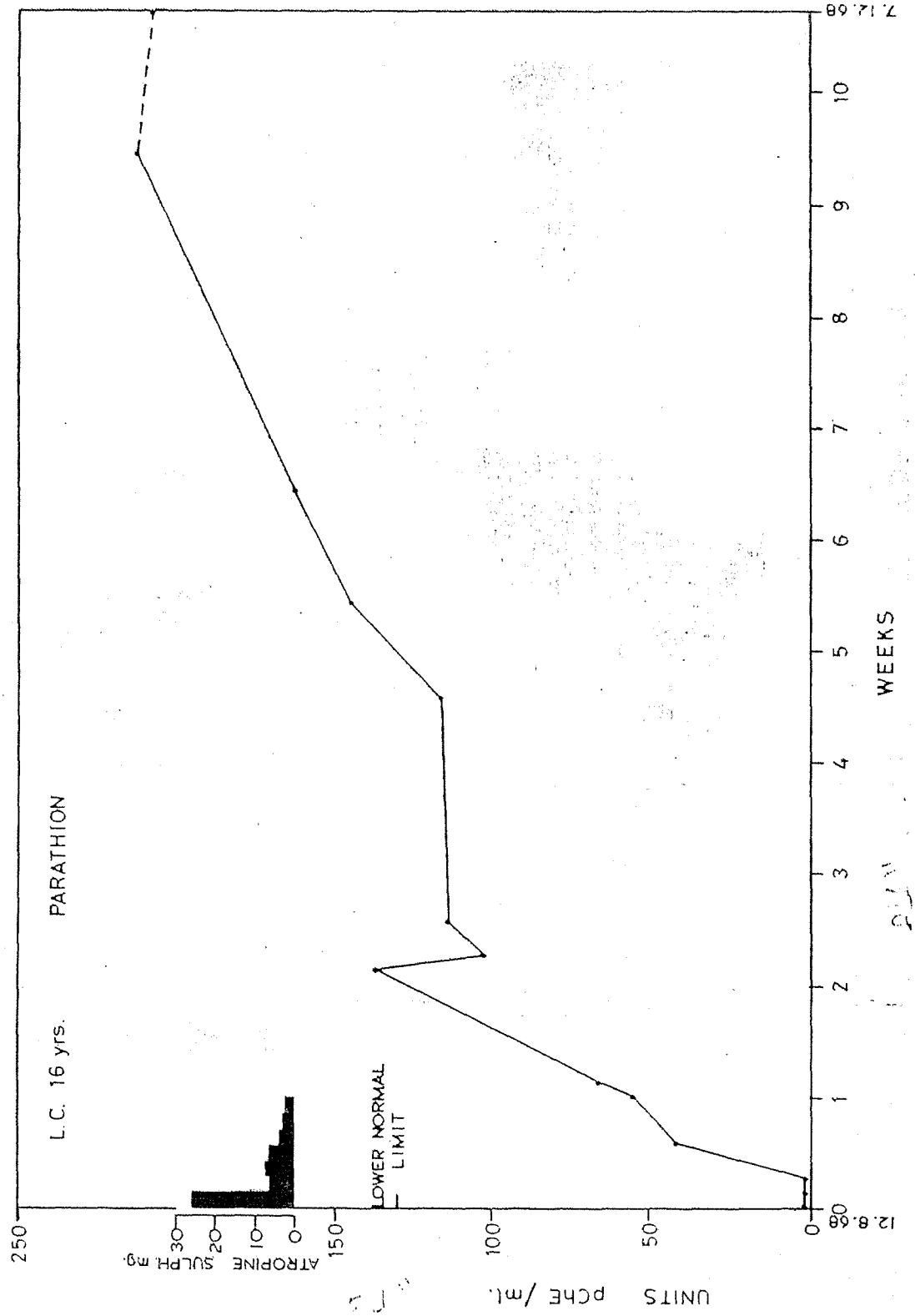

Fig. 2. Showing the limits of serum pChE and dosage of atropine sulphate in Case 1.

about on the 9th day and was discharged from hospital on the 18th day.

Report on Case 2

J.M., male, 48 years, a farmer who habitually handled Fitios B/77 (N-monoethylamide of 0.0-dimethyl dithiophosphorilacetic acid) was admitted on 21. 10. 69, half an hour after accidentally drinking about 3 ml. of a 20 per cent stock solution of this insecticide. He sought medical care not because he felt ill, but only because he realized that he had ingested a poison.

His past medical history was entirely negative, and on physical examination no abnormality was detected. Temp. 97°F, P.R. 76/min.; R.R. 20/min.; B.P. 120/75.

Laboratory Findings

The serum pseudocholinesterase (pChE) was 53 u./ml. on admission and on this basis he was treated for O.P. insecticide intoxication. Treatment with atropine sulphate was started, and serial estimations of pChE *(Figure 3)* confirmed the diagnosis.

Tests of liver function carried out during the period of observation showed only a slight rise in the serum aspartate aminotransferase to 30 i.u./l. 3 weeks after admission, while the serum alanine aminotransferase was normal throughout the period of observation. The serum bilirubin rose to 1.1 mg./100 ml. 2 months after admission.

Changes in the serum protein electrophoretic pattern were observed during this period *(Figure 4)*.

Atropine sulphate was administered i.m. for 11 days following hospitalisation, the dose being reduced progressively until the serum pChE level rose to the lower limit of normal. The total dose administered was 31.5 mg.

The patient felt well and presented no signs or symptoms whatever, except for an occasional rise in temperature up to 99.8°F. He was discharged home on the 24th day, and attended as an out-patient until he was finally discharged one month later. He continued to feel well, and on one occasion he remarked that in fact he was feeling even better than he had ever felt befort his admission to hospital. He attributer this to his having stopped handling the insecticide since hospitalisaton.

Discussion

The initial diagnosis of O.P. poisoning is usually a clincal one, and in the presence of a history of ingestion or occupational exposuer, this is not usually difficult. However, in the absence of a history of exposure and particularly in those cases affected by the highly toxic compounds, such as parathion, other conditions may be simulated. Gastro-enteritis, encephalopathy, as well as hypoglycaemic episodes may be erroneously diagnosed. The primary manifestations of O.P. poisoning arise from parasympathetic overactivity, so that excessive sweating and secretion of mucus, miosis, muscle twitchings, abdominal colic with diarrhoea, bladder contraction and bronchospasm become the principal symptoms. Though miosis is always specially emphasised, mydriasis has been observed in about 13 per cent of cases (Davies *et al*, 1967).

A hypoglycaemic episode can mimic O.P. poisoning, but hypoglycaemia has not been observed as a major clinical sign in cases of O.P. poisoning in adults. It has however been reported in an 8½ month old girl (Hruban *et al*, 1963), and the authors suggested that as pancreatic islet secretion is under parasympathetic control, over-stimulation of the pancreas may have resulted from O.P. poisoning in a child with labile control of blood glucose. As a matter of fact, ingestion of parathion by experimental animals leads to lowering of the blood glucose (Hruban *et al* 1963). However, Arterberry *et al*, (1961) and Wyckoff *et al* (1968) have reported that their patients suffering from parathion poisoning presented hyperglycaemia. In both cases here recorded, the blood glucose levels were within normal limits.

There is some evidence to suggest that other fundamental metabolic distur-

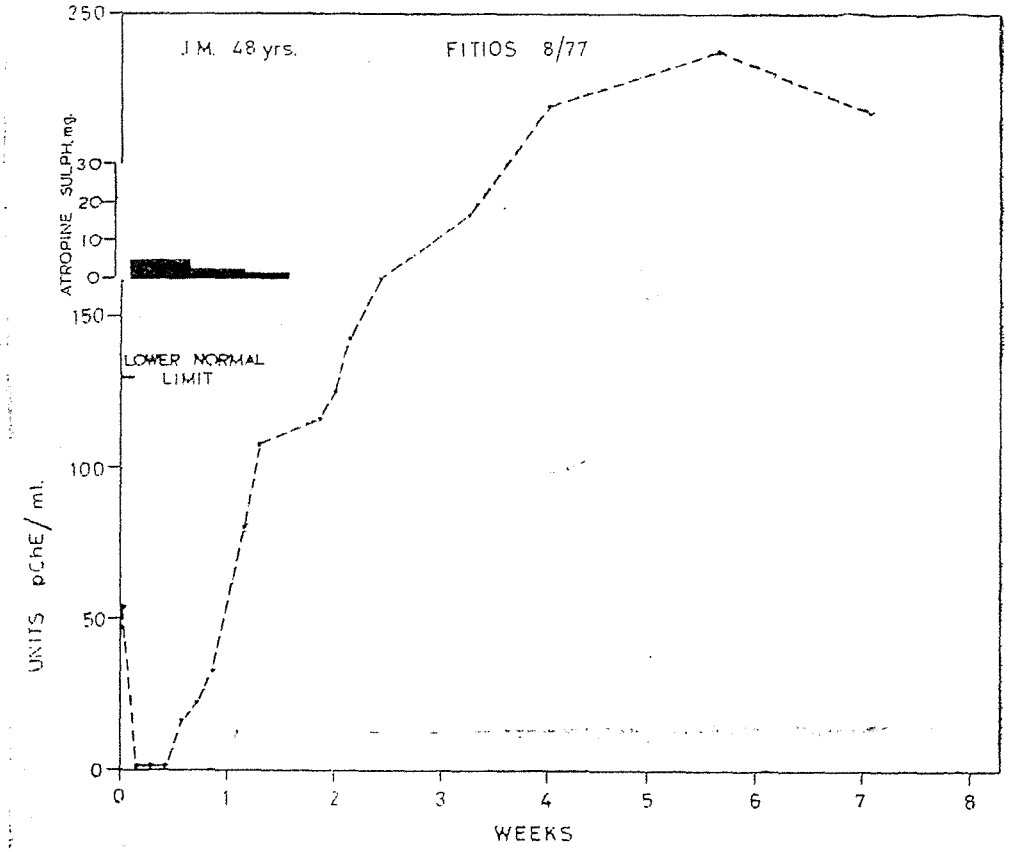

Fig. 3. Showing the limits of serum pChE and dosage of atropine sulphate in Case 2.

bances do occur in association with poisoning with O.P. compounds. Abnormal amino-acid excretion in the urine does occur (Comstock *et al*, 1967), and some degree of depression of serum enzymatic activity — alanine and aspartate aminotransferases and aldolase, besides cholinesterase — seems to become manifest following long term exposure to malathion (Grech, 1964).

The observations made on the changes in the serum protein electrophoretic pattern in our two cases are of interest. It is believed that the reduction in the beta- and gamma-globulin concentrations in the acute phase, and the gradual return to normal levels in both cases, is a true phenomenon. We are not aware that this observation has been previously recorded. It is tempting to propose that O.P. compounds might also exert an immuno-suppressant action, and if this is so their action is very rapid.

The O.P. compounds combine with the cholinesterases which become phosphorylated and therefore inactive against ace-

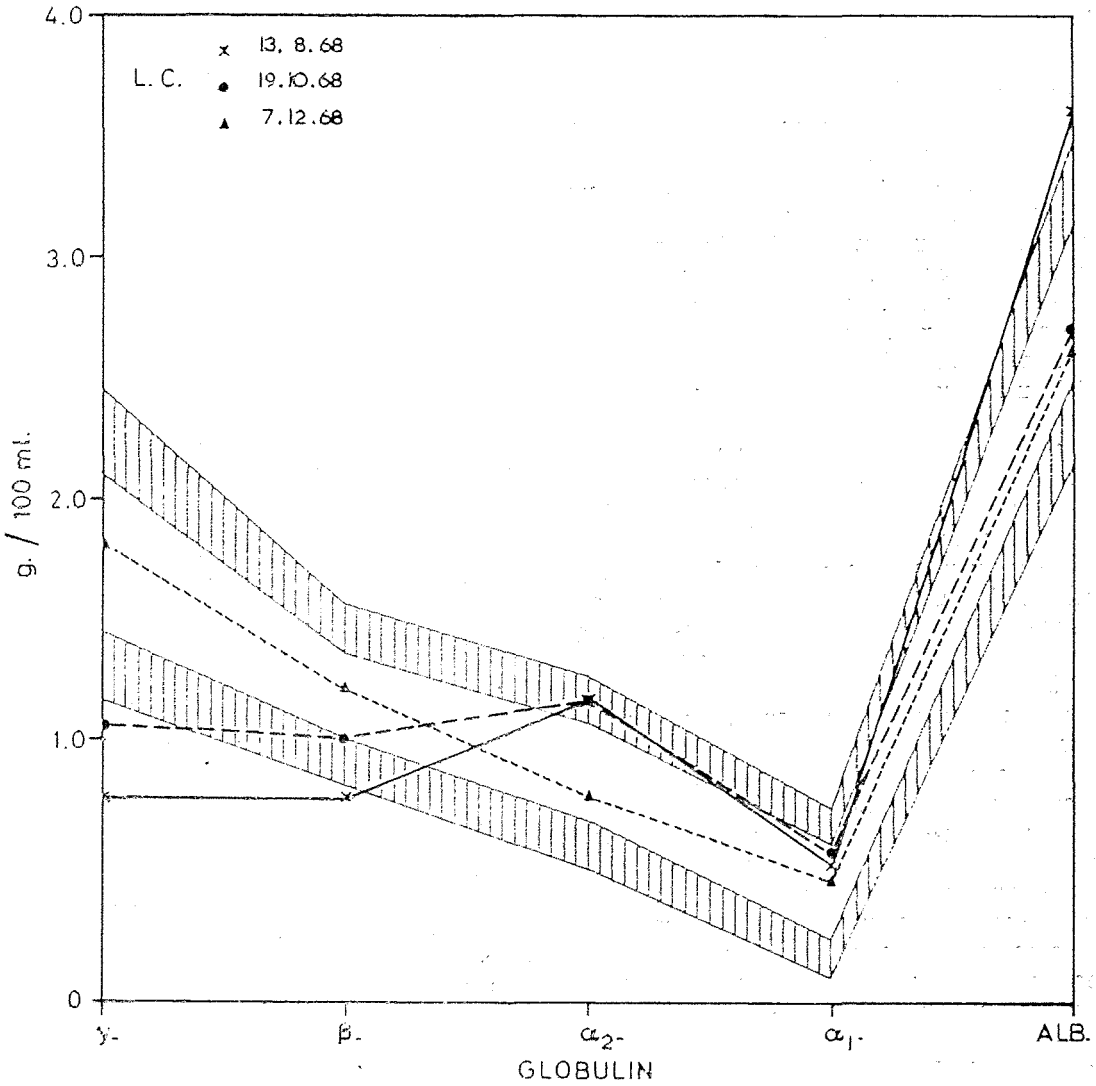

Fig. 4. Showing the changes in the serum electrophoretic pattern in Case 2, with the upper and lower limits of normal, the shaded area demarcating the limit of 2 S.D.

tylcholine, and the toxic symptoms result from the accumulation of acetylcholine at various sites. As a result of this irreversible inactivation of the cholinesterases, enzymatic activity will remain reduced until new cholinesterase is synthesised. It is claimed that non-specific cholinesterase is regenerated by the liver in about 2 weeks and at the rate of about 10% per day though it may take 12 weeks for this

to occur in the synapses and neuro-muscular junctions (Goth, 1968). In both of our cases the patient's normal level in the serum was reached before 12 weeks, rising rapidly in the first 2 weeks and more slowly afterwards.

Different O.P. insecticides vary in their toxic properties — parathion being 100 times more toxic than Fitios B/77 — the oral LD_{50} of parathion being 3 mg/kilo as compared to 340-350 mg/kilo for B/77 (Canniello, 1967). Though the degree of toxicity of these substances is different, the mode of action is the same. It appears that Fitios inactivates serum pChE much more rapidly than other cholinesterases in the body, because although no pChE activity was detected in the serum for 3 days after its ingestion, the patient remained free of symptoms.

It appears that there have been no fatalities from poisoning with Fitios (Canniello, 1969) and that this is the first case recorded in which evidence of poisoning by this insecticide has been found.

In the treatment of organo-phosphorus poisoning, the administration of atropine sulphate in full dosage, by blocking the peripheral muscarine effects and by protecting against the involvement of the central nervous system, is still the mainstay of therapy. However, as atropine exerts no protective action against skeletal muscle paralysis, as soon as signs of respiratory paralysis are evident, mechanical ventilation combined with tracheostomy, should be set-up. Naturally those drugs which potentiate the anticholinesterase effects of these insecticides such as theophylline, aminophylline and the phenothiazine derivatives are contraindicated (Arterberry *et al*, 1962). Pralidoxime and other reactivating agents may only hasten complete recovery.

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