The disease resembles a non-icteric form of Weil's disease and may prove to be caused by a leptospire. Its prevalence along river banks and estuaries in North Korea during autumn months, the presence of a suitable rodent carrier in vast numbers, and its general clinical course, with special emphasis upon renal involvement, are all suggestive of such an infection despite the absence of positive proof by laboratory demonstration. Weil's disease has a case mortality of 3% for the age group 16–30 (Broom, 1951), our mortality was 1 in 40 (2.5%), but diagnosis was possibly made more often in milder cases owing to its epidemic quality. All agglutination tests for leptospirosis were negative. As renal failure in this disease follows a period of hypotension it may be due to anoxia, which Darmady and his colleagues (1944) suggest is the causative mechanism in Weil's disease; the pathological picture of the kidney is one of cortical pallor and medullary hyperaemia, suggesting an alteration in the distribution of blood flow in the kidney which may short-circuit the glomeruli, as has been shown in rabbits by Trueta *et al.* (1947). Paralysis of the sympathetic nerves by high spinal anaesthesia was not attempted in our cases.

The hypothalamic and pituitary lesions possibly have far-reaching effects upon the hormonal control of urinary secretion and upon the autonomic control of the vascular system, and may be responsible in part for the tendency to inversion of sleep rhythm noted in some of our cases. Adrenal cortical damage may be responsible for the prostration and electrolyte imbalance seen early in the disease and for the delayed water excretion and apparent lack of concentrating power of the kidneys in the later phases.

Summary

An epidemic disease broke out among our troops stationed in Korea during the autumn months of 1951; a summary of its characteristic features as seen in 40 cases treated at the British Commonwealth General Hospital, Kure, Japan, has been presented, together with some of its complications. Its aetiology remains obscure; its similarity to anicteric forms of Weil's disease is noted. Chemotherapeutic and antibiotic agents have been proved of doubtful value in treatment.

My thanks are due to Lieutenant-Colonel K. P. Brown, R.A.M.C., officer in charge of medical division, for reading this paper and making helpful suggestions. Grateful acknowledgments are due to all those medical officers who have assisted with their case notes of the patients they have treated. For permission to publish this paper I am indebted to Colonel J. E. Snow and the Director-General, Army Medical Service.

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The first standard nomenclature in malariology (*Report on Terminology in Malaria*) was published by the Malaria Commission of the League of Nations in 1940. It has now been revised by a drafting committee (Professor N. H. Swellengrebel, Sir Gordon Covell, and Dr. P. F. Russell) appointed by the World Health Organization, and is issued as No. 13 in the W.H.O. Monograph series. Part 1 of *Malaria Terminology* is a commentary on the terms used by malariologists and falls into three sections, covering the parasites and the infections to which they give rise, the measurement of malaria in the community, and the vector itself. Part 2 is a comprehensive glossary. The price of this publication is 5s.

PARALYSIS FOLLOWING POISONING BY A NEW ORGANIC PHOSPHORUS INSECTICIDE (MIPAFOX)

REPORT ON TWO CASES

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The purpose of this paper is to report two cases of paralysis which developed in the third week after the onset of symptoms of acute organic phosphorus poisoning due to a new compound, *bis*-(mono-*iso*propylamino)-fluorophosphine oxide. The common name recommended for this substance by the British Standards Institution is mipafox. Like other organic phosphorus compounds used as insecticides, mipafox is an inhibitor of cholinesterase *in vitro* and *in vivo*. Preliminary tests had indicated that the new compound was effective as an insecticide, and that the oral toxicity to rabbits and guinea-pigs was only a twenty-sixth of that of "parathion" (*Nature*, 1951).

In August, 1951, three people employed in the manufacture of a small quantity of this substance by a pilot process developed the symptoms and signs characteristic of acute organic phosphorus poisoning, and two were admitted to hospital.

Case 1

The patient, a female research chemist aged 28, had been employed on the development of organic phosphorus compounds for 21 months before admission to hospital on August 15, 1951. During this time she had handled a number of substances in this group, and, although her exposure to them was mainly in the laboratory, she was concerned occasionally in the manufacture of small amounts of new compounds in pilot plants. She had experienced symptoms of mild organic phosphorus poisoning on at least three occasions during this time, and was away from contact with organic phosphorus compounds for two or three weeks in June, 1951, following one of these attacks.

At about 8 p.m. on August 15, when she had been working long hours on the pilot-scale production of mipafox for three days, she began to feel sick and tired. She attributed these symptoms to fatigue, and continued at work although the symptoms became gradually worse. She left the factory at 12 midnight and returned to lodgings, where she was quite alone. At about 2 a.m. on August 16 she began to suffer from vomiting and involuntary defaecation, and this continued at intervals of a few minutes until 3.30 p.m., when she was given 1/50 gr. (1.3 mg.) atropine by intramuscular injection and admitted to Addenbrooke's Hospital under the care of Dr. A. P. Dick. The vomiting and involuntary defaecation were accompanied by cramps in the muscles of the legs, and by 5 a.m. generalized muscular weakness was so great that she was unable to get out of bed to seek assistance.

The administration of atropine relieved the vomiting and diarrhoea within half an hour, but nausea and muscular twitchings persisted. On admission to hospital significant findings were suffusion of the conjunctivae, pin-point pupils, twitching of the facial and sterno-mastoid muscles, and

diminished tendon reflexes. On August 17 hypotonia of all muscles was still a striking feature. The gastro-intestinal symptoms were controlled by atropine, administered at frequent intervals, but this did not affect the muscular twitchings. The total amount of atropine administered was 0.9 gr. (58.5 mg.) given in the following doses: August 16: 1/50 gr. (1.3 mg.) × 7; August 17: 1/50 gr. (1.3 mg.) × 9; 1/100 gr. (0.65 mg.) × 4; August 18: 1/75 gr. (1 mg.) × 1; 1/30 gr. (2 mg.) × 1; 1/50 gr. (1.3 mg.) × 20; August 19: 1/50 gr. (1.3 mg.) × 4.

On August 19 the patient developed delusions and hallucinations which were attributed to overdosage with atropine. When the atropine was discontinued her mental state returned rapidly to normal. She was symptom-free after four days and was discharged from hospital on August 31, the sixteenth day after her illness began. For several days she had been out of bed and had walked about the ward, apparently well.

As she walked downstairs to leave hospital she noticed for the first time weakness and unsteadiness of her legs. During the next three or four days there was little change in her condition, which then began to deteriorate. The weakness in the legs increased, and she noticed weakness of the hands and arms. These symptoms became gradually worse, and she was readmitted to hospital on September 10. On examination she was found to have a flaccid paralysis of both legs and weakness of the muscles of the thighs. The knee-jerks were diminished and the ankle-jerks absent. There was no plantar response. Although the legs and feet were cold and the muscles tender to palpation, there was no change in cutaneous sensation to pin-prick or light touch. Weakness of the muscles of the right hand was present.

The paralysis progressed, and the patient was transferred to the London Hospital on September 15 under the care of Dr. Donald Hunter. At this time there was complete flaccid paralysis of the lower limbs. The knee-jerks and ankle-jerks were absent and the plantar reflexes could not be elicited. Tone and power in the arms, forearms, and hands were greatly reduced. The biceps-jerk was just present, but neither the supinator nor the triceps jerk could be elicited. The trunk muscles were also weaker than normal. Cranial nerves were normal, there were no signs of involvement of the central nervous system, and no disturbance of cutaneous sensation could be demonstrated. All muscles, particularly those of the calf, were tender to palpation, and muscle twitchings were observed in the deltoids, facial muscles, and muscles of the legs.

Power returned gradually over a period of weeks to the muscles of the thighs, arms, and forearms. On October 20 power and tone were normal in the arm muscles and the tendon reflexes were present and brisk. There was weakness of the long extensors of the fingers, and the lumbricals and interossei were wasted and completely paralysed. In the lower limbs power and tone had returned to some extent in the thigh muscles and flexors of the hip, but the muscles of the leg below the knee were still flaccid and completely paralysed. There was marked wasting of the small muscles of the feet. Although there was no spasticity, the knee jerks were exaggerated and patella clonus could be elicited without difficulty. The ankle-jerks were absent. Fasciculation was still present in the deltoids, facial muscles, and muscles of the legs, and the patient complained of cramp-like pains, affecting particularly the muscles of the lower limbs. Alternating vasodilatation and vasoconstriction resulted in subjective symptoms of burning and coldness in the hands and feet, and these were accompanied by flushing or pallor and cyanosis.

In the first week in November the clinical picture was complicated by subjective evidence of sensory changes of glove and stocking distribution. On repeated examination the distribution of these changes was not constant, and at times the pattern was bizarre. It is possible that these symptoms were functional in origin, and they disappeared completely within a few weeks.

Between November, 1951, and February, 1952, slow improvement continued in the groups of muscles which had already begun to regain their normal function, but the muscles of the legs and feet remained completely paralysed. The wasting of the small muscles of the hands became increasingly obvious (Fig. 1), and it seemed likely at this time that no recovery could be expected in these muscles or in the muscles of the legs and feet. From the first week in April, 1952, however, the small muscles

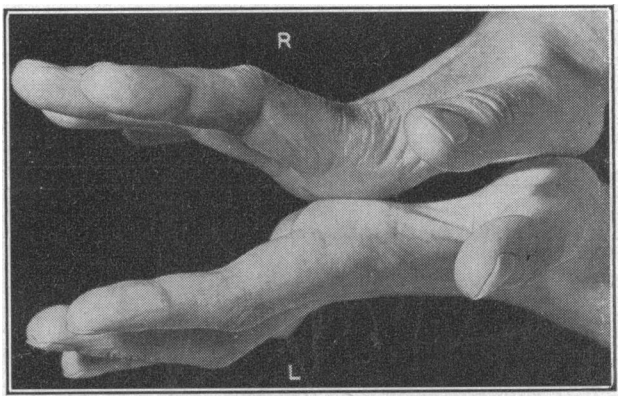

FIG. 1.—Wasting of small muscles of hands; Case 1, six months after mipafox poisoning.

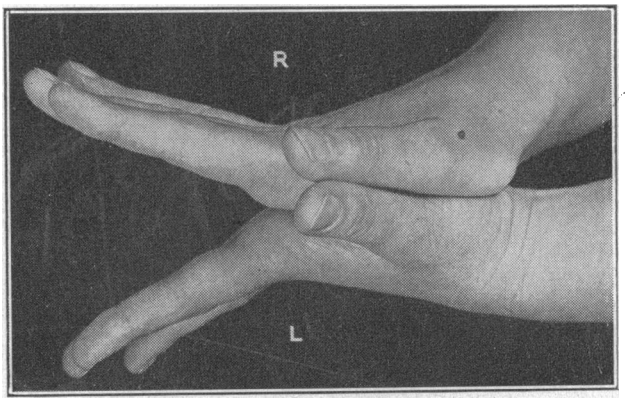

FIG. 2.—Case 1, recovery in hands five months later.

of the hands began to recover. Power returned slowly to the lumbricals, interossei, and opponens pollicis, and by July the wasting was much less (Fig. 2). In May the ankle-jerks were first elicited, and these were followed within a few days by the return of slight movement of the toes.

At the time of writing the upper limbs are normal. Power in the muscles of the thighs is almost normal, but is greater in the flexors than in the extensors. Although patella clonus can still be elicited it is much more difficult to demonstrate. Exaggerated ankle-jerks and ankle clonus are readily elicited and the plantar response is extensor on both sides. Movements of the toes are gradually increasing, and inversion and eversion at the ankle-joints are present but weak. Plantar flexion is strong, but there is little evidence of the return of power of dorsiflexion. For six months the patient has been able to go out in a wheel-chair, and is now able to stand with support.

Throughout the illness the right side has been more severely affected than the left in both upper and lower limbs, and is recovering more slowly. There has been a striking absence of trophic changes in the skin over the paralysed muscles. The cranial nerves have been unaffected at all stages of the illness, and no tremor or ataxia has been present at any stage.

Investigations

On August 17 the cholinesterase activity was as follows : Red blood cells (true cholinesterase), 9 units ; normal 75–142. Plasma (pseudo-cholinesterase) 1 unit ; normal 51–128 (Warburg technique). The results of subsequent estimations are shown in Fig. 3 and the Table. On September 19 lumbar puncture gave normal results. On September 20 the pyruvate tolerance test showed : 0 minutes, 0.92 mg. pyruvic acid/100 ml. blood ; at 60 minutes, nil ; at 90 minutes, 1.32 mg. pyruvic acid/100 ml. blood. (These results are within the normal range.) On October 5 visual fields were normal for white and blue objects. An electrocardiogram taken on October 10 showed physiological tracing.

Electromyographic Studies.—On September 19 the electromyogram showed a reduced interference pattern, but the individual motor units were normal. There was no activity at rest. Muscle stimulation showed complete reaction of degeneration in the lower limbs and partial reaction of degeneration in the thenar eminence. Further examination on September 21 showed the electrical responses to be equivocal and not definitely sluggish. Some polyphasic motor-unit potentials were found in the forearm extensors, but no fibrillation potentials. This is against a lesion producing lower-motor-neurone degeneration. On December 7 there was no response to 1 millisecond nerve stimulation, but a response to 100 millisecond stimulation, weakening on repetitive contraction ; spontaneous muscle-fibre activity ; motor-unit potentials were of short duration and all polyphasic. These findings are comparable with those found on the administration of a depolarizing drug such as decamethonium iodide, and suggest a state of neuromuscular block due to depolarization of the end-plate increasing on muscle contraction. On May 21, 1952, no decrease of muscle contraction on repetitive stimulation was demonstrable. Muscle fibrillation potentials were present, with definite evidence of lower-motor-neurone lesion. The picture was that of peripheral neuritis. There was probably some fibrosis of muscle, particularly in the gastrocnemius. Prognosis was now that for a peripheral neuritis.

Case 2

A chemical process worker, aged 39, was engaged with the research chemist (Case 1) in the manufacture of mipafox for five days before he became ill on August 16, 1951. He first noticed wheezing and tightness in the chest. This was followed by a sensation of pricking of the eyes accompanied by redness of the conjunctivae, constriction of the pupils, and difficulty in raising the upper eyelids. He gave up work and was given atropine sulphate 1/50 gr. (1.3 mg.) by intramuscular injection and sent home to rest in bed. Although the symptoms were relieved by the atropine they had recurred by next morning, when the patient was found to have bronchospasm, marked weakness and hypotonia of the muscles of the limbs, and constricted pupils which failed to react to light and accommodation. There was excessive sweating, particularly affecting the forearms.

He was admitted to Addenbrooke's Hospital under the care of Dr. A. P. Dick on August 17, with the symptoms and signs of organic phosphorus poisoning already described. He had experienced similar symptoms six months previously while working with a different organic phosphorus compound. On this occasion the symptoms subsided after he had been away from contact with the substance for two or three days.

Treatment with atropine sulphate 1/50 gr. (1.3 mg.) by intramuscular injection controlled the muscarinic symptoms as in Case 1, but attempts to reduce the dose resulted in a relapse on August 20. The doses of atropine given between August 17 and August 22 were as follows : August 17, 1/50 gr. × 5 ; August 18, 1/50 gr. × 22 ; August 19, 1/50 gr. × 11 ; August 20, 1/50 gr. × 7 ; August 21, 1/50 gr. × 17 ; August 22, 1/50 gr. × 8 ; making a total dose of 1.4 gr. (91 mg.). Mental disturbance suggestive of atropine poisoning occurred on two occasions, and disappeared when atropine was withheld. He was discharged from hospital, apparently well, on August 28.

Nine days later the patient became aware of weakness of the legs, associated with cramp-like pain in the muscles of the calves and feet. He first noticed these symptoms after riding a bicycle. The weakness of his legs progressed, and he was readmitted to hospital on September 11. There was weakness and loss of tone in the muscles of both lower limbs, particularly below the knee. The patient was unable to dorsiflex either foot ; the power of plantar flexion was absent in the right foot and weak in the left. The ankle-jerks were diminished and the plantar reflexes could not be elicited. Although the symptoms and signs of paralysis improved rapidly, he was transferred with Case 1 to the London Hospital on September 15 under the care of Dr. Donald Hunter. At this time there was lack of tone in the muscles of both lower limbs, and the upper limbs were also slightly affected. Power and movement in the left leg was diminished. On the right side dorsiflexion of the foot was very much impaired, and the power of plantar flexion was also diminished. Tendon reflexes were normal on the left side ; the ankle-jerk was diminished on the right. The plantar responses were flexor. The cranial nerves were normal. The affected muscles were tender to palpation, but no cutaneous sensory changes were present.

The patient's condition improved gradually, and he was discharged home on October 5 with bilateral foot-drop, more pronounced on the right side than on the left. There was wasting of the small muscles of the feet, particularly on the right side. Since his discharge from hospital there has been further improvement, but after six months he complained that he still became tired easily and could walk only two or three hundred yards before his feet, especially the right, became "floppy." There was at this time demonstrable weakness of both dorsiflexion and plantar flexion of the right foot, and, although the ankle-jerk on the right side could be elicited, it was less brisk than on the left.

At the time of writing the patient could walk two miles before he noticed any difficulty. Standing at his work, which he resumed ten months after the onset of the acute illness, causes low back pain, and it is at present necessary for him to have a sedentary job. He complains also of a dull aching pain in the right foot with exacerbations of cramp-like pain affecting the foot and calf muscles on the right. These occur most frequently at night, and are severe enough to wake him from sleep.

Investigations

On August 17 the cholinesterase activity recorded was : red blood cells (true cholinesterase), 15 units ; plasma (pseudo-cholinesterase), 10 units. The results of subsequent estimations are shown in Fig. 3 and the Table. On September 20 the pyruvate tolerance test read : at 0 minutes, 9.92 mg. pyruvic acid/100 ml. blood ; at 60 minutes, 1.28 mg. pyruvic acid/100 ml. blood ; at 90 minutes, 0.86 mg. pyruvic acid/100 ml. blood. (These results are within the normal range.) Lumbar puncture on September 21 showed nothing abnormal.

Electromyographic Studies.—On September 21 electrical stimulation showed a brisk response. Intensity duration curves were normal. An electromyogram showed a reduced interference pattern with normal motor-unit potentials and no spontaneous fibrillation potentials, suggesting that there was no lower-motor-neurone degeneration.

A Further Case.—Another man, working with Cases 1 and 2, developed acute symptoms, which were less severe than in those cases. Recovery was uneventful and no delayed effects developed. The results of cholinesterase estimations in this case are shown also in Fig. 3 and the Table.

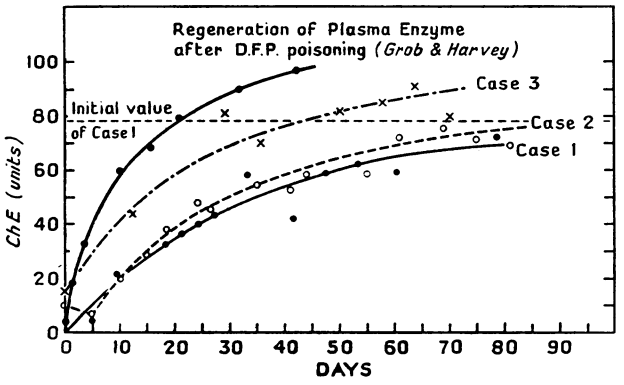

FIG. 3.—Rate of regeneration of plasma cholinesterase after mipafox poisoning compared with rate of regeneration following poisoning by D.F.P. (After Callaway, Davies, and Risley, 1952.)

Cholinesterase Activity (Warburg Units)

Days after Poisoning:		0	5	10	20	28	56	70
Case 1	R.B.C.	9	8	12	18	21	82	76
	Plasma	1	6	23	33	42	63	70
„ 2	R.B.C.	15	25	34	41	42	76	76
	Plasma	10	8	21	34	48	58	75
„ 3	R.B.C.	—	—	—	—	—	—	—
	Plasma	15	—	42	—	70	85	—

Treatment

Atropine, which is a specific antidote to the muscarinic and central-nervous-system effects of cholinesterase inhibition, was administered during the acute stages of poisoning. No antidote to the nicotinic effects is known and no treatment to counteract these was given either during the acute phase or after the onset of paralysis. Treatment of the paralysis included physiotherapy, which was limited because of the unusual fatigability of all muscles. This was particularly evident in the first patient. Ten weeks after the onset of paralysis, generalized muscular twitchings, clonic spasms affecting particularly the lower limbs, and a deterioration in her general condition were precipitated by an attempt to follow the routine of physiotherapy which would be usual for a patient affected to a similar degree by peripheral neuritis or anterior poliomyelitis. Occupational therapy was abandoned and physiotherapy was limited to passive movements, and from this time the patient made slow progress towards recovery, although the muscular twitchings recurred at intervals for four weeks. The administration of curare in small doses or of pseudocholinesterase preparations was considered, but, since the nature of the paralysis was so little understood, it was not thought justifiable to try either of these suggested methods of treatment.

Methods for the protection of persons handling organic phosphorus compounds in the manufacture, or in fields, orchards, or greenhouses, have already been described (Bidstrup, 1950). The need for regular estimations of blood cholinesterase activity in workers at risk was emphasized, and these cases illustrate the importance of making this test compulsory. Symptoms of poisoning may not develop until the cholinesterase activity is reduced to about 20% of normal, and removal from further exposure before this stage is reached may prevent serious illness and may save life.

Discussion

The use of organic phosphorus compounds such as hexaethyl tetraphosphate (H.E.T.P.), tetraethyl pyrophosphate (T.E.P.P.), and diethyl-*para*-nitrophenyl thiophosphate (parathion) as insecticides has resulted in many cases of acute poisoning (Grob, Garlick, and Harvey, 1950; Report to Committee on Pesticides, 1950). These substances, like the related compound di-*iso*propyl-fluorophosphonate (D.F.P.), inhibit the enzyme cholinesterase, and the symptoms and signs of poisoning have been attributed to the effects of inhibition of this enzyme. Although Abrams, Hamblin, and Marchand (1950) reported 30 fatal cases of poisoning among people engaged in the manufacture or use of these substances, no sequelae to acute poisoning were recorded among many patients who survived, and no chronic toxic effects were demonstrated in rats following prolonged administration of sublethal doses of these compounds (Barnes and Denz, 1951). Koelle and Gilman (1946) and Hunt and Riker (1947) had demonstrated persistent paralysis affecting particularly the hind limbs in dogs and cats following repeated sublethal doses of D.F.P., and A. Gilman (personal communication, 1950) suggested that the new organic phosphorus insecticides might be capable of causing in man a paralysis similar to the "ginger" paralysis described by Smith and Elvove in 1931.

"Ginger" paralysis was first observed in the days of prohibition in the United States of America in people who had been drinking Jamaica ginger contaminated with tri-*ortho*-cresyl phosphate (T.O.C.P.). Many such cases have since been described following accidental ingestion of T.O.C.P. (Sampson, 1942; Staehelin, 1941) or after exposure to T.O.C.P. during the manufacture of plasticizers (Hunter, Perry, and Evans, 1944). Hottinger and Bloch (1943) demonstrated that T.O.C.P. was an inhibitor of cholinesterase, and it was on this evidence that Gilman based his opinion that paralysis might follow repeated exposure to small amounts of the organic phosphorus insecticides. No such cases were reported until 1951, when Petry described paralysis in a man who had been using parathion in greenhouses in Germany and who had experienced symptoms of mild poisoning on several occasions. The onset of paralysis occurred almost three months after the last recorded exposure to parathion, but was preceded by severe "gastritis," and resembled closely in mode of onset and subsequent course the paralysis which follows poisoning by T.O.C.P.

R. H. S. Thompson (personal communication, 1951) has demonstrated that mipafox is an inhibitor of cholinesterase and has a selective action *in vitro* upon pseudocholinesterase occurring in white matter from the cerebral cortex. Barnes and Denz (1953) have produced paralysis in hens with mipafox, and also with D.F.P. and T.O.C.P., and have demonstrated demyelination in the peripheral nerves and spinal cord of the affected birds. Although Barnes and Denz were unable to produce permanent paralysis in rats and rabbits with mipafox, general weakness was observed and demyelination was found in the peripheral nerves and in the fasciculus gracilis in the cord. Tri-*ortho*-cresyl phosphate has a similar action to mipafox both on cholinesterase activity and in the ability to cause demyelination (Earl and Thompson, 1952a). The paralysis which developed in our patients is similar to that which follows poisoning by T.O.C.P.

There is nothing unusual in the manifestations of the acute stage of poisoning by an organic phosphorus compound in these two cases. Symptoms resulting from excessive stimulation of autonomic motor cells, from stimulation followed by paralysis of striate muscle, and from stimulation followed by depression in the central nervous system are characteristic of poisoning by substances which cause inhibition of the enzyme cholinesterase. The effects of different inhibitors vary at different sites of action, and in these patients there was little evidence of disturbance in the central nervous system. Mental changes occurred in both patients during the course of treatment with atropine. These may have been due to belladonna poisoning, but similar mental symptoms have been described in persons recovering from poisoning by other cholinesterase inhibitors.

The occurrence of paralysis in these two patients after a latent interval of approximately two weeks suggests a possible risk associated with repeated exposure to substances which irreversibly inhibit cholinesterase. In both these patients there is a history of previous mild poisoning by organic phosphorus compounds, and in the first patient,

who is more severely affected, three previous episodes are recorded. The third patient suffered relatively mild symptoms of acute poisoning, from which he recovered rapidly and completely. There is no evidence that he had previously experienced poisoning by organic phosphorus compounds. Koelle and Gilman (1946) were able to produce paralysis of the hind limbs in dogs following the administration of repeated sublethal doses of D.F.P., although recovery from a single dose appeared to be complete.

Recovery of normal cholinesterase activity after exposure to substances which inhibit the enzyme irreversibly depends upon regeneration of cholinesterase. After absorption of D.F.P. or T.E.P.P. the red-cell enzyme returns in linear fashion at approximately 1% per day, the plasma enzyme exponentially reaching normal after 40 days (Harvey, Lilienthal, Grob, and Jones, 1947). The rate of recovery of cholinesterase activity in our patients was studied by Callaway, Davies, and Risley (1952). They found that, although the rate of return of the red-cell-enzyme activity was similar to that following poisoning with T.E.P.P. or D.F.P., the plasma-enzyme activity returned more slowly. After D.F.P. poisoning the plasma enzyme had reached 60% of normal in ten days, whereas in these cases the recovery in this time was only 25%. After 40 days only 60% of the plasma-enzyme activity had returned in the mipafox cases, whereas, after D.F.P., recovery is complete in this time. Until normal activity is restored there is an unusual susceptibility to the effects of absorption of any anticholinesterase agent. The fact that both the patients who became paralysed were frequently working with such agents and had been affected by them in the months preceding the final acute episode may have contributed to the occurrence of the delayed effects.

The work of Earl and Thompson (1952b) suggests that lowering of the pseudo-cholinesterase may result in demyelination. They showed that the delayed paralysis in hens poisoned by T.O.C.P. is preceded by a marked lowering of the pseudo-cholinesterase activity of plasma, brain, and spinal cord which is present from the first to at least the tenth day after administration of T.O.C.P., and suggest that inhibition of pseudo-cholinesterase may be responsible for the demyelination which is the characteristic lesion in T.O.C.P. poisoning. Barnes and Denz (1953) conclude that the ability of mipafox, D.F.P., and T.O.C.P. to produce demyelination is not solely or directly related to the activity of these compounds as inhibitors of cholinesterase. Whatever may prove to be the explanation of these experimental findings, demyelination is the most likely cause of the symptoms and signs which persist in our patients, and these may be the result of the prolonged reduction of pseudo-cholinesterase activity which occurred in the early months of their illness.

In a review of the literature on anticholinesterase drugs Koelle and Gilman (1949) comment upon the similarity of the effects on muscular function produced by D.F.P. and T.E.P.P. (Harvey, Lilienthal, Grob, Jones, and Talbot, 1947) and the syndrome "ginger paralysis" which follows poisoning by T.O.C.P. They suggested that the "ginger paralysis" might be the result of the effects of the prolonged loss of cholinesterase at the neuromuscular junction. Three months after the onset of paralysis the clinical picture and electromyographic findings in Case 1 were comparable with those following the administration of decamethonium iodide, and suggested a state of neuromuscular block due to depolarization at the motor end-plate increasing on muscle contraction (A. T. Richardson, personal communication, 1951). Eight months after the onset of paralysis the changes in the electromyogram were those of a peripheral neuritis, and there was no evidence at this time of neuromuscular block. In our opinion prolonged failure of transmission of the impulse at the motor end-plate contributed to the paralysis in these cases in the early stages, and the onset of symptoms after moderate exertion in each case, at a time when the cholinesterase activity of the red blood cells and plasma was greatly reduced, lends support to this hypothesis.

Two of us (P. L. B. and J. A. B.) have more recently observed two men in whom hypotonia of voluntary muscles with diminished tendon reflexes persisted for at least two weeks after acute parathion poisoning, and in our opinion this clinical sign should be specially sought during convalescence from acute poisoning by organic phosphorus compounds. We are seeking confirmation of an impression gained from seeing a small number of people exposed to organic phosphorus compounds that hypotonia may be present without other symptoms or signs in persons in whom cholinesterase activity is below normal. This impression and our experience with the cases recorded in this paper suggest to us that patients who have had acute organic phosphorus poisoning should be kept at rest for a longer period after the acute symptoms have subsided, and that physical activity should be limited until a normal cholinesterase level is again established.

Summary and Conclusions

Two cases of paralysis beginning in the third week after poisoning by a new organic phosphorus compound *bis*-(mono-*iso*propylamino)-fluorophosphine oxide (mipafox) are described.

The clinical syndrome resembles closely that of poisoning by tri-*ortho*-cresyl phosphate ("ginger paralysis") and of paralysis in a German worker following the use of parathion, another organic phosphorus compound.

The cases are discussed in the light of recent work on inhibition of pseudo-cholinesterase, and of demyelination produced in hens by certain anticholinesterase agents.

Since it is now confirmed that certain organic phosphorus compounds which have the property of inhibiting cholinesterase may cause paralysis in man, substances in this group should not be recommended for use as insecticides or for other purposes until both acute and chronic toxicity has been studied in several species of animals.

The blood cholinesterase activity of workers at risk of absorbing organic phosphorus compounds should be estimated before and at frequent intervals during exposure to these compounds. No person in whom the blood cholinesterase activity is found to be reduced should be subjected to the risk of absorbing even small additional amounts of any cholinesterase inhibitor.

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