NEUROLOGICAL CHANGES ASSOCIATED WITH P.A.S. AND I.N.A.H. THERAPY

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and

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SHORTLY after isoniazid (I.N.A.H.) was first used in the treatment of tuberculosis, it became apparent that side-effects were not uncommon. Thompson (1952) lists euphoria, hyperreflexia, vertigo, muscular twitching, insomnia, paraesthesiae and transient loss of memory among the reactions observed. These were noted to be mild and reversible but did suggest involvement of the nervous system.

That peripheral neuritis can be caused by I.N.A.H. is now well recognized. Gammon, Burge and King (1953) reported the findings in 46 cases drawing attention to the relation between the rapidity of onset of the peripheral neuritis and the size of the dose. Biehl and Vilter (1954) pointed out that rapid regression of symptoms occurs if the drug is promptly withdrawn but that residual defects may persist for up to a year if administration of the drug is continued. Polyneuritis was also described by Mollaret and Dupont (1959) who emphasized a gradual onset with paraesthesiae and occasionally the subsequent development of paralysis of the lower motor-neurone type. Neuropathological studies are rare but Ott, Rabinowicz and Morand (1959) report one case and describe demyelination of the peripheral nerves with relatively few changes in the central nervous system.

However, functional changes in the activity of the central nervous system have been found following the administration of isoniazid. Reilly *et al.* (1953) obtained evidence that large doses of isoniazid lower the seizure threshold to photic stimulation in man. In addition psychiatric abnormalities have been described. The commonest such disturbance would appear to be the development of mental states in which euphoria is a main symptom (Hunter, 1952). It is not uncommon for other disturbances to occur. Jackson (1957), for example, described five cases each differing in their main psychiatric symptom; one presented as an hysterical reaction, one as a mania, one with anxiety and paranoid ideas, one with a "schizoid reaction" and one with depression. Hare (1958) described two cases whose illness in many ways resembled schizophrenia. Complete recovery usually occurs following cessation of the therapy, although in the two cases described by Hare, the symptoms persisted six months and two years after withdrawal of the drug. Further evidence that the central nervous system may be involved comes from a case reported by Biehl and Vilter (1954). Their patient was treated with 20 mg./kg. of I.N.A.H. per day, developed convulsions and died. Death was considered to be due to a toxic encephalopathy.

More recently isoniazid has been implicated in another syndrome, that of spastic paraplegia. Money (1960) has described three cases occurring in patients treated for between three and eighteen months on conventional doses 2 to 4 mg./Kg./day). Psychiatric abnormalities were not mentioned and there was no

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evidence of peripheral neuritis. They recovered rapidly when administration of the drug was stopped and treatment with pyridoxin was commenced.

The two case reports that follow describe the main clinical features of two patients receiving treatment with isoniazid and para-amino salicylic acid, who developed definite disturbances in the central nervous system. In addition, both patients developed symptoms of an affective disorder.

Case 1

The patient (Miss L.) was born in 1909. The family history is not significant except that her brother has had two depressive illnesses treated in hospital. The patient took a B.A. degree in French and German when aged twenty and then taught these languages until 1939, when she became a censor of mail. Later she worked in Austria and in 1953 obtained a post as a research assistant in a National library.

Her previous health record was good and the only illness of note was an attack of depression lasting three months in 1950. This illness was associated with her father's terminal illness but she was not admitted to hospital for treatment.

Her friends and relatives described her as a quiet, studious person, fond of books and music. She was not a worrier and not subject to frequent mood changes. Her employers considered her a most able worker.

The patient was well in October, 1955, when she had a routine X-ray of the chest. This showed a small shadow in the right lung, but no tubercle bacilli were found in the sputum. She was treated with P.A.S. 10 Gm. a day, plus I.N.A.H. 200 mg. a day. There was a little diarrhoea, but she remained well for three weeks. Twenty-three days after starting the medication she developed general malaise and a widespread urticarial rash. The drugs were stopped a few days later. She developed a fever, she became confused and was admitted to Southfields Hospital, Edinburgh, under the care of Dr. F. W. A. Turnbull. On admission, there was a widespread urticarial rash, generalized lymph node enlargement and slight jaundice. Her temperature was 103·6° F., and she was disorientated in time and place. Two days later there was a sudden deterioration in her condition. She became comatose and was incontinent of faeces and urine, her arms were flexed and her legs were extended. She remained in this state for three weeks. Cerebro-spinal fluid examination was normal. Thereafter there was a slow and gradual improvement, associated with periods of disorientation. She found that she had difficulty in using common objects and could read and write only slowly. After six weeks it was possible for her to leave hospital but a few weeks later, because of depressive symptoms, she was admitted to the Maudsley Hospital under the care of Dr. Brian Ackner.

On admission, the only abnormal physical signs were to be found in the C.N.S. She walked stiffly and her movements were clumsy. Although right-handed, she tended to use her left hand when making fine movements. There was no evidence of sensory impairment. All limb reflexes were brisk; the abdominal and plantar reflexes were normal. There was no evidence of dysphasia; her knowledge of French and German was unimpaired. There was a right inferior quadrantanopia, constructional apraxia (block design), right-left disorientation and poor scores with simple mental arithmetic. These abnormalities suggested the presence of a left parietal lobe lesion. The EEG showed a minimal asymmetry, being of lower amplitude in the left parietal regions. Minimal slow activity was also present in the left posterior temporal areas.

She was a solitary woman, who often cried, and was very irritable. She slept poorly and there was early morning waking. She was severely depressed and contemplating suicide. Subjectively she experienced impairment of memory and there was a complete amnesia for January, 1956. More detailed psychological testing revealed a now average intelligence, whereas from her past academic record a superior level would be expected. Manual abilities showed evidence of definite impairment. (The Wechsler-Bellevue Verbal Scale—119; Performance Scale—89.)

She remained in hospital for five months, during which time a rehabilitation programme was arranged, aimed at improving her writing, typing and walking. Supportive psychotherapy was given, as were mild stimulant drugs. There was a slow general improvement and three months after admission depressive symptoms became less severe and improvement continued until she was well enough to leave hospital.

At home she remained fairly well for a few weeks, then there was a gradual return of the depressive symptoms. Suicidal ideas were particularly prominent in the mental state, and she was re-admitted to hospital after five months at home. On this occasion the physical signs were unchanged, and there was again evidence of a severe depressive illness. She was given 12 E.C.T.s, during the course of which there was a marked improvement in her condition, though she remained hypochondriacal and despairing about her disabilities. On this occasion she was able to leave hospital seven months after admission and was referred for a rehabilitation course which she was unable to complete. Follow-up five years after the initial illness showed that she was still not working, the main symptoms being inability to concentrate, slowness, and emotional lability.

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Case 2

The second patient (Mrs. C.) was born in 1934, the eldest of five. There is no history of mental ill-health in the family. She attended primary school, where she was described as average, left school at fifteen and had a succession of office jobs. She married in 1955 and has one child, born in 1959.

Her previous mental and physical health was good apart from enuresis till the age of six. She is described as being a happy, sociable girl with few outside interests apart from dancing and the cinema. There were no episodes suggesting transient neurological disturbances.

In June, 1959, a routine antenatal chest X-ray revealed an opacity at the apex of the right lower lobe. Her E.S.R. was 36 and she was treated with isoniazid 300 mg. and P.A.S. 16 Gm. daily. She persisted with the treatment in spite of nausea and vomiting lasting several months. In April, 1960, she complained of weakness of the legs, but no abnormality was noted. She became depressed and irritable and attempted suicide with sedatives and was then admitted to Bethlem Royal Hospital under the care of Dr. E. H. Hare.

Physical examination on admission in July, 1960, revealed no abnormality apart from brisk but equal tendon reflexes, the jaw jerk was not exaggerated. Mentally she was depressed, retarded, unable to concentrate, but she was correctly orientated and there was no dysmnesia. No improvement was obtained with 6 E.C.T.s. Gradually her condition deteriorated and she became withdrawn, incontinent of urine and faeces, and episodes of sweating and tachycardia without fever were noted. The patient then gradually developed hypertonicity of the legs, and left ankle clonus with an extensor plantar response were noted. There was no abnormality of the arms and no sensory impairment.

Special investigations: Hb. 83 per cent. E.S.R. 10. C.S.F. and Lange normal. Chest, skull and spine radiographs were normal. The EEG showed no significant abnormality.

In October, 1960, P.A.S. and I.N.A.H. were withdrawn and an injection of a multiple vitamin preparation (Parentrovite) given daily along with 100 mg. of pyridoxin orally.

Over the next two weeks her mental state improved so that she was able to co-operate more fully. Examination revealed disorientation in time and space, impairment of memory, more especially for recent events, and complete amnesia for the period since her admission. She was able to perform simple mental arithmetic. The cranial nerves were normal, as were the arms. There was no sensory impairment. Spastic paraplegia was present. Physiotherapy was commenced with gradually increasing co-operation of the patient. By the middle of December, 1960, slight movement was noticed in the left hamstrings, quadriceps and extensors of the toes. By January, 1961, her mental state was normal apart from amnesia for most of her hospital admission. Movements were present now in most muscle groups of both legs. There has been uninterrupted recovery until the present time, when the patient is attempting to walk.

There was at no time evidence of a dissemination of the lesion suggestive of multiple sclerosis, although this cannot be excluded with certainty. Likewise, at no time was any sensory impairment observed although this again may have been present as a transient disturbance when the patient was unco-operative.

Discussion

Both these patients while receiving isoniazid and P.A.S. in normally accepted doses, developed illnesses in which there was definite involvement of the central nervous system. In the first patient it is evident that the main damage was suffered by the parietal cortex; this occurred in the setting of a generalized toxic reaction. The second patient showed signs of an upper motor neurone lesion though the site of this must remain in doubt. The spastic paraplegia would indicate a level below the cervical enlargement; the briskness of the deep reflexes in the upper limbs would suggest a higher level, but the absence of an exaggerated jaw reflex makes it likely that the lesion occurred in the spinal cord.

Both patients showed an affective disorder with marked depressive features; in the first patient, the depressive features were persistent, but in the second patient seemed to occur as part of a toxic psychosis. It appears to us that these neurological changes were due to P.A.S. and I.N.A.H. acting either singly or in combination. Neurotoxicity to P.A.S. is rare (Mollaret and Dupont, 1959), although delirium has been recorded (Alenquer, 1958) also polyneuritis (Brun and Vialler, 1951). However, it is possible that it may cause anorexia and vomiting as in the second patient and thereby reduce the absorption of vitamins from the intestine.

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It is probable that the reactions that occurred in these two patients were due to I.N.A.H., although it must be emphasized that this cannot be proven. The similarity in structure between isoniazid and nicotinamide might suggest that it would block the action of this substance. Biehl and Vilter (1957) pointed out, however, that no case of pellagra had been observed following I.N.A.H. treatment. They could demonstrate no disturbance of nicotinic acid metabolites in the urine and a high urinary pyridoxin excretion was found in patients given large doses of I.N.A.H. These workers also noted the protective action of pyridoxin in preventing the peripheral neuritis frequently observed. The mechanism by which I.N.A.H. blocks the action of pyridoxin would seem to be by the formation of physiologically inactive compounds by the two substances (Greenfield, 1958).

It is of interest that in multiple vitamin deficiencies, pyridoxin specifically improved the insomnia, irritability, muscular weakness and difficulty in walking (Spies *et al.*, 1939). In experimental deprivation of the vitamin in a human subject, mental depression and confusion were noted by Hawkins and Barsky (1948). In monkeys, experimental deprivation of pyridoxin produced degenerative changes in the large pyramidal cells of the cortex and one animal showed loss of medullated fibres in both pyramidal tracts in the cord (Victor and Adams, 1956). Thus the similarity between the effects of pyridoxin deprivation and the toxicity of isoniazid is striking. Tower (1956) points out that pyridoxin is essential for the activity of a number of important enzyme systems in the metabolism of the brain and that it would also seem to be essential for the maintenance of the neural lipids in myelin.

It is of interest that both these patients developed severe depressive symptoms while receiving isoniazid though the chemically related iproniazid was the first of the compounds now known as the mono-amine oxidase inhibitors that have been shown to be of some value in relieving depressive states (Kline *et al.*, 1958; Robie, 1958).

Although rare and predominantly reversible, toxic reactions to isoniazid can be severe and perhaps permanent. The variety of their manifestations may well lead to their being misdiagnosed. In view of the experimental work mentioned above, treatment should include the administration of pyridoxin.

Summary

Case histories are presented of two patients who developed neurological changes whilst receiving isoniazid and P.A.S. The relevant literature is reviewed and the possible mode of action of the drugs in producing these changes are discussed.

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