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THE EFFECT OF NICOTINE ON SPINOCEREBELLAR ATAXIA*

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"Each synapse is an apparatus for co-ordination."
SHERRINGTON.

Ataxia resulting from disturbance of spinocerebellar mechanisms is a characteristic feature of disseminated sclerosis and the spinocerebellar degenerations. The latter are a group of disorders characterized by progressive incoordination, of which the pathological basis is degeneration of the cerebellum and associated tracts in the brain stem and spinal cord. Hereditary transmission is common, but the tendency varies and sporadic cases also occur.

Greenfield (1954) proposes the following classification:

A. *Predominantly Spinal Forms:*

1. Friedreich's ataxia (and allied syndromes)
2. Hereditary spastic ataxia

B. *Spinocerebellar Forms:*

1. Menzel type
2. Subacute spinocerebellar degeneration (carcinogenic and sporadic)

C. *Predominantly Cerebellar Forms:*

1. Holmes type
2. Diffuse atrophy of Purkinje cells (toxic and carcinogenic)
3. Olivo-ponto-cerebellar atrophy (Dejerine, André-Thomas)
4. Dentato-rubral atrophy (Ramsay Hunt)

Friedreich's ataxia is probably the commonest and best-known example of these disorders. It appears before the age of 20 years, and in one form or another recognition is not difficult.

Familial cerebellar degeneration falls into two main groups. In the type described by Menzel (1891) the disease process tends to be cerebello-petal in type and shows considerable variation. There is degeneration of the middle cerebellar peduncle, the pontine nuclei, the medullary olives, the cerebellar white matter, and cortex in that order of constancy. In the spinal cord one or more of the long tracts—that is, dorsal columns, spinocerebellar tracts, and pyramidal tracts—are degenerated in most of the recorded cases. It is apparently the same disorder as that described in sporadic cases by Dejerine and André-Thomas (1900), which they called olivo-ponto-cerebellar atrophy because of the noticeable atrophy of the olivary eminences and the pons. In the second type, described by Holmes (1907), where there is

less variation, the degeneration is of a cerebello-fugal type. The disease predominantly affects the cerebellar cortex and vermis and those parts of the olives which are related anatomically to the degenerated area of the cerebellar cortex. In this type also there are sporadic cases which generally resemble those described by Marie *et al.* (1922) as late cortical cerebellar atrophy.

Greenfield reiterates that no differential diagnosis is possible during life between these two forms of spinocerebellar degeneration. In the Holmes type the disease tends to begin later (average age at onset is 45 years), to last rather longer, and to result eventually in some degree of dementia. The Menzel type begins on an average ten years earlier. In both types there is slow and usually progressive disturbance in walking; dysarthria and clumsiness of hand movements follow later. Nystagmus is inconstant; urinary incontinence may occur. The clinical picture in different members of a family may vary considerably, but the pathological picture tends to remain the same.

Nothing is known of the causation of these disorders. The hereditary tendency, though strong in some cases, should not discourage search for other contributory factors. A knowledge of what aggravates a disease process in the nervous system may provide a clue to its origin or to the way in which it deranges nervous mechanisms. In this report I wish to describe the influence of nicotine on three patients with spinocerebellar degeneration and one patient with disseminated sclerosis.

Case 1

The patient is a man aged 65. When first seen in June, 1949, he was 60 and complained of increasing unsteadiness of gait of some six years' duration. He had injured his pelvis in an accident thirty years previously, but otherwise had enjoyed good health. He had no complaint except the unsteadiness of his gait. My notes at the time state: "He is emphatic that this unsteadiness is provoked by smoking." He was a coarse, garrulous type of man who had "knocked about a bit." There was no history of alcoholism, but he had had gonorrhoea several times. I suspected some deterioration of personality.

On examination the main abnormalities consisted of ataxia of the lower limbs without weakness or sensory loss and some ankylosis of the right hip-joint. Pupils were normal, there was no nystagmus, speech was slightly slurred, and movements of the upper limbs were a trifle incoordinate. Knee- and ankle-jerks were exaggerated; plantar reflexes were flexor. The abdominal reflexes were absent. He walked

*A communication in the form of a ciné film and voice recording was presented to a meeting of the Association of Physicians in Manchester, May 27, 1955.

unsteadily with his feet planted wide apart. He faltered or stumbled when he turned and held his arms away from his body. He could not walk heel-toe fashion, and when lying down the heel-knee-shin test was poorly performed. It was clear that his unsteadiness was not wholly due to his injured pelvis, and a tentative diagnosis of spinocerebellar degeneration was made.

I advised admission to hospital, but he declined, and I did not see him again until November, 1951. He had obviously deteriorated. His speech was now definitely affected, being slurred and jerky, his gait was grossly ataxic, and the upper limbs were more involved. There was no nystagmus, all deep reflexes were grossly exaggerated, and there were bilateral extensor plantar reflexes. There was no sensory loss. X-ray examination showed evidence of osteoarthritis of the right hip and lumbosacral spine; the spinal fluid was normal; the Wassermann reaction was negative in blood and spinal fluid.

Once again he affirmed that smoking aggravated his trouble. On this occasion, when accompanied on a ward round with my house-physician (Dr. A. Parry Jones), we decided to subject him to a test. We observed his gait, noted the degree of cerebellar ataxia of the upper limbs, trunk, and lower limbs, and listened carefully to his speech. Our notes made at the time state: "January 5, 1951: 10.35 a.m., walked unsteadily across the room, speech slurred, but spoke rapidly and could be easily understood. 10.40 a.m., started to smoke a cigarette. 10.45 a.m., speech much slower, slurring more obvious. 10.50 a.m., started second cigarette, *speech now incomprehensible*. 10.55 a.m., *he can now scarcely walk*; would have fallen several times unless caught. By 11.40 a.m. his speech and gait had returned to their state before testing."

The effect was quite striking. There was no doubt that his speech and gait abruptly deteriorated when he smoked. He himself began to feel unsteady when he had smoked only half a cigarette; when he had finished it there was no difficulty in recognizing the profound worsening of his ataxia. Thereafter, on three or four occasions, I repeated the test, recording his voice on a disk and making a ciné film of his ataxia before and immediately after smoking. None of my colleagues who have seen the film and heard the recording have expressed any doubt about the evidence. The patient himself was somewhat disturbed by these tests. He had restricted his smoking before I first saw him in 1949; and after a test in which he smoked a cheroot and was unable to get out of bed owing to profound ataxia he refused to co-operate further and left hospital. He would not allow me to make an intravenous injection of nicotine, but the evidence clearly showed that a "strong" cigarette had more effect than a "mild" one, and a cheroot or cigar had more effect still. Two ounces (57 ml.) of brandy had no effect on his disability.

He was a garage proprietor, and as his disease progressed he sold his business. He became demented for some months in 1954 and was in a mental hospital. He has periodic urinary incontinence, and spends his days sitting in a chair in his bedroom. Recently he allowed me to make an intravenous injection of 2 mg. of nicotine acid tartrate. He became hopelessly ataxic; his speech, scarcely comprehensible before injection, became completely so in a minute.

The injection caused him to void urine involuntarily. He cannot smoke half a cigarette without experiencing an intensification of his ataxia. He says, "My head goes round and round, and I cannot do anything." The cigarette has to be thrown away; he cannot stub it out, so clumsy are his hand movements. He knows of no other agent which influences his disability in this way.

There is no family history of any nervous disorder. He had always smoked about 30 cigarettes a day; he did not smoke a pipe. He thinks he first noticed the unusual effects of tobacco-smoking two years before I first saw him—that is, four years after the appearance of the first symptoms of his illness.

Case 2

A man aged 53 was first seen in February, 1955, and complained of the "staggers." Until two years previously he had enjoyed good health, but then began to have trouble in walking. At first symptoms were intermittent, but they had worsened steadily in the previous six months. He found that he could not walk in a straight line; he tended to stumble to one or other side. His toes caught on steps or kerbstones, and turning, bending, and getting up from a chair or couch induced sudden ataxia. He frequently toppled over at his work, and was finally forced to give up working a few weeks before I saw him. Clumsiness of hand and arm movements was occasionally experienced, and his speech also suffered at times. He felt that there was some fluctuation of his symptoms, but it was less evident now than formerly. Fatigue, overexertion, and prolonged standing aggravated his ataxia. With some effort, he could walk to work in the morning, but returning home at night was a trial.

He had noticed that after sitting down for a long time his gait would be noticeably "drunken" for the first few hundred yards; it would then improve. All these symptoms had, of course, led to allegations of drunkenness from time to time. He rarely drank alcohol and had not noticed that it affected him in any unusual way. When fatigue, a long walk, or a long period of sitting down aggravated his ataxia he noticed that his speech might also deteriorate. Sometimes, however, his speech would become slurred and difficult without any noticeable increase of his ataxia. He recalled two occasions when ataxia of gait and speech overwhelmed him; on both occasions he was doing heavy labouring. His speech became unintelligible, and he would have fallen if he had not been supported. His legs felt "rubbery" and turning his head caused objects to appear "out of focus."

An elder brother (Case 3) also suffered from this disease, and on a visit to Case 2, when these symptoms were developing, suggested that he restricted his smoking. Case 3 had found that tobacco seriously worsened his disability. Case 2 had smoked a pipe since the age of 18 years—4 oz. (113 g.) of strong tobacco each week (12 pipefuls daily). He soon found that his brother was right, and two years ago cut down his smoking to 2 oz. (57 g.) of mild tobacco weekly (six pipefuls daily). He found that one pipeful had no effect, but if he smoked two pipefuls consecutively his gait and/or his speech would be temporarily upset. The effect would usually appear while he was smoking the second pipeful, and would last until ten minutes after he had finished. Others had noticed these effects, and on several occasions he had tried to give up smoking altogether. Tea, coffee, or alcohol did not upset him; a cup of tea or sucking a sweet perhaps helped to restore his speech at times. *Tobacco was not constant in its adverse effects*; he had "good" days and "bad" days. Sometimes he would get up in the morning and soon realize that his unsteadiness was such that if he smoked too freely he would regret it. At other times the effect of smoking would be noticeable on a day when he felt "better." He appeared to be quite definite that his symptoms fluctuated apparently spontaneously, that tobacco often had an adverse effect, and that fatigue sometimes provoked temporary exacerbation of his symptoms. Concerning different brands of tobacco, he said that "strong" tobacco had a "stronger" effect. One particular brand which he said was "greasy" nearly always made him stagger.

On examination the only abnormal signs were found in the nervous system. There was horizontal nystagmus to right and left, slight incoordination of voluntary movements of the upper limbs, and an ataxic gait. He swayed and sometimes stumbled to right and left; he held his feet apart and would make shuffling steps on turning. He could not walk more than a few steps without deviation and could not walk heel-to-toe. He could not stand on one leg for more than a few seconds. His trunk swayed sometimes when sitting on a

couch. The heel-knee-shin test demonstrated the incoordination of his lower limbs. When first seen his speech was normal; he spoke rapidly and fluently. Later, during investigation in hospital, there were times when his speech was slurred and slower. There was no abnormality of sensation; power in the arms was good, in the lower limbs it was slightly reduced. All deep reflexes were exaggerated; there were a few beats of clonus at the knees; the right plantar reflex was extensor; left probably extensor. The abdominal reflexes were absent in all four quadrants. When he had not smoked for 24 hours the electroencephalogram showed low-voltage alpha rhythm at 10–11 c./s. arising in the occipital lobes. Scattered fast activity, also of low voltage, appeared in all leads. There were long runs of 5–6 c./s. theta waves in all leads after one minute of hyperventilation. There was no significant difference after smoking.

The effect of smoking was closely observed over a period of two weeks in hospital. He rarely went a day without smoking at all. There was never any abrupt deterioration on smoking. He always felt steadier and said his legs were "under better control" when he had not smoked for several hours. After smoking two strong pipefuls of tobacco an aggravation of his ataxic gait was observed on several occasions; it had no effect on his speech or on the ataxia of his upper limbs, or on the nystagmus. A ciné film clearly demonstrated, however, the increased unsteadiness on walking. There were days when this effect was more noticeable than on others. On three occasions 3 mg. of nicotine acid tartrate was injected intravenously. On the first and second occasions his speech was not affected, but he felt unsteady, and his gait was more ataxic for ten to twenty minutes. On the third occasion there was a noticeable and rapid deterioration in his speech, which was recorded on a disk. He also became grossly ataxic and could not walk unsupported. The effect passed off in 15 minutes. It is of interest that on this occasion he had said that on waking in the morning he had realized he was "in for a bad day." He felt unsteady, thought his speech was slurred, and said he had to walk more carefully. A recording of his speech immediately before the injection, when compared with that recorded the following day, demonstrated that it was in fact slurred and drawling. Nicotine had a noticeable and immediate effect. Alcohol—2 oz. (57 ml.) of brandy—had no effect.

Case 3

This patient, aged 58, was the brother of Case 2. He kindly consented to enter hospital in February, 1955. He is an intelligent person and was most co-operative. He knew of no other member of the family who had suffered any form of nervous disease. He became affected when he was 53, first noticing a tendency to bump into people when walking; he sometimes staggered. There had been slow progression, and two years ago he had consulted his doctor. He was forced to give up riding a cycle after experiencing sudden loss of balance. When walking he noticed that his feet would strike the ground with varying intensity; he tripped over small obstacles and had to take care on stairs, in passages, and in crowded streets. As in the case of his brother, he appreciated that his symptoms fluctuated, and he thought that fatigue, a long walk, and sitting down for some hours tended to aggravate his ataxia. Occasionally there was fleeting diplopia, and he found that his speech suffered. On two occasions when he had walked two or three miles, after a meal, he experienced a sudden deterioration in gait and speech. He was with a friend on one occasion and his brother (Case 2) on the second. These individuals were alarmed at his condition. He said his speech became practically unintelligible. He had to rest for some time before returning home. He felt quite well when he had set out for these walks, and recalls that they took place immediately after a midday meal. He thinks he was smoking during these walks, but cannot be quite certain about this. On reaching his office in the morning after a fifteen-minute walk he said his handwriting is "often jerky, angular, and almost illegible."

He first noticed the adverse effect of tobacco-smoking three years ago. At first he was not quite certain about it, as the effects were not constant. With increasing experience, however, he became sure of it, and warned his brother when he learned that he too was becoming ataxic. He found that smoking affected his legs; they felt "weak," and he described a sensation of "tension" in them. He was never a heavy smoker like Cases 1 and 2. He used to smoke some ten to twenty cigarettes a day. He now smokes five; he finds that if he smokes more his gait, handwriting, and speech become disturbed.

On examination the only abnormal signs were to be found in the nervous system. There was fine horizontal nystagmus to left and right, slight incoordination of voluntary movements of the upper limbs, moderate incoordination of the lower limbs, with brisk deep reflexes, retained abdominal reflexes, and flexor plantar responses. There was no muscular weakness or sensory loss. The Romberg test was positive, and there were slight swaying movements of the trunk when he was sitting. When walking he looked at the ground, deviated periodically to right and left, stumbled when trying to walk heel-to-toe fashion, and always held the seat of a chair when he sat down or stood up. When lying down the heel-knee-shin test was positive. His speech was sometimes normal; more frequently it was slightly slurred. An electroencephalogram was normal and unaffected by smoking.

The effect of cigarette-smoking was studied over a period of two weeks. He was well able to do without cigarettes for 24 hours at a time. At such times he was aware of an improvement in his balance, walking, handwriting, turning, stooping, speech, and the general execution of voluntary movements. But I myself could never be sure of this. A test was then arranged. He abstained from smoking for 24 hours. His voice was recorded immediately before starting to smoke, and again immediately after smoking three cigarettes in 30 minutes. He felt unsteadier, there was a noticeable increase in his ataxia, but his speech was only slightly affected. He was sent to walk around the hospital corridors, and half an hour later he came hurrying back to my room as best he could. His speech was grossly affected—slurred and drawling and jerky—and it was immediately recorded on a disk. His ataxia had increased still further. The effect on speech and gait began to pass off in 15 minutes and was back to its state before smoking in 30 minutes.

In similar tests he could always appreciate the deleterious effect of smoking on speech and/or gait, but it was not always readily apparent to me. One could never be certain that the symptoms were fluctuating independently of smoking. Pedalling for 20 minutes on a stationary cycle did not affect him. It was decided, therefore, with his permission, to give him an intravenous injection of nicotine acid tartrate. 3 mg. was injected and there was an immediate and striking effect on speech and gait. Immediately before the injection his voice was recorded as he read from a script, but when the injection was completed he was unable to speak at all for some two minutes. He made jerky, drawling, and unintelligible sounds. Blurring of sight probably added to the difficulty of reading from a script; but it soon passed, and re-reading demonstrated the profound increase of his dysarthria. The effect on his voice passed off in 15 minutes. During this time he sat in a chair and could not stand unsupported; he swayed about drunkenly and his arms were grossly ataxic.

This effect was as striking as in Case 1, so he was persuaded to allow me to repeat the test with a view to recording the ataxia of gait on a ciné film. This again showed the same sequence of events. The injection of nicotine produced immediate and striking ataxia, and a ciné film was made showing the gait immediately before and immediately after the injection. His gait returned to normal in 12 minutes. His speech on this occasion was again grossly affected. On both occasions the effect started when only 1 mg. of the substance had been injected.

Case 4

A man aged 30 was first seen in October, 1950, when aged 26, for disturbance of gait. At the age of 18 he had been rejected for National Service because of some clumsiness of movement and gait. When he was 25 a diagnosis of disseminated sclerosis had been made on the basis of nystagmus, intention tremor, spastic-ataxic gait, pyramidal signs, and a paretic type of colloidal gold curve in the cerebrospinal fluid.

He said that he first became aware of some difficulty in walking when he was 17, but until he was in his early twenties it gave him little trouble. However, walking had become slower and progressively more laboured; he tended to sway about as if drunk, he tired rapidly, and his legs felt more and more "stiff." He experienced no paraesthesias and does not recall having had any diplopia or blurring of vision. There were no urinary symptoms. Action tremor and clumsiness of the arms appeared when he was 26. Slight slurring of speech was first noticed (by his parents) during the past year. There have been no remissions or exacerbations; the course of the disease has been steadily progressive. There is no family history of neuropathy.

He is small (5 ft. 1 in.—155 cm.), sturdy, and has a short neck with a low hair-line. Several of his toes are webbed. There was temporal pallor of the optic disks, fine horizontal nystagmus to right and left, and vertical nystagmus on upward gaze. Speech is slightly slurred and scanning, and he has bilateral intention tremor, absent abdominal reflexes, slight weakness of the lower limbs with exaggerated knee-jerks, bilateral ankle clonus, and bilateral extensor plantar reflexes. Superficial sensation is unaffected and vibration sensation is only slightly affected in the legs; postural sensation is normal. There is no dissociated type of sensory loss. His gait is more spastic than ataxic.

Because of the short neck, the early onset of disability, and the progressive course, x-ray examination of the skull base and cervical spine was carried out. Two anomalies were revealed. Tomography clearly showed that there was basilar invagination with the tip of the odontoid 1 cm. above MacGregor's line, and an unfused posterior arch of the atlas. Lumbar air encephalography, vertebral arteriography, and opaque myelography have been carried out at different times during the past five years, and have all yielded normal results. There is no indication of any anomaly of the brain stem or cerebellum such as the Arnold-Chiari deformity. The bony abnormalities could not of themselves produce the neurological disability. A recent lumbar puncture has for the second time yielded a spinal fluid which gave a paretic type of colloidal gold curve. A diagnosis of disseminated sclerosis seems unavoidable.

He first noticed the unsteady effects of smoking four or five years ago. He began to smoke cigarettes when he was 18, and until four years ago averaged twenty cigarettes daily. He has had to restrict them to five a day because of the effect on his disability. At first he found that walking and movement generally were disturbed only if he chain-smoked, but in more recent years sensitivity to nicotine has increased remarkably. For some time he has found that when he is only halfway through his first cigarette "I get a queer, unpleasant rubbery sensation beginning in my legs and coming up all over me." By the time he has finished the cigarette co-ordinate movements of the arms and legs are more difficult to perform. He says, "This is nothing like the sensation you get when you start smoking as a youngster." He does not feel faint or giddy or nauseated. As he reaches the end of the cigarette his increasing clumsiness makes it difficult for him to get the cigarette into his mouth; he uses one hand to steady the other. He tries not to inhale and has learned to smoke slowly, and only one cigarette at a time, and never when he is standing or walking. The effect of one cigarette passes off in 15 to 20 minutes. His family knew of this influence of smoking and have encouraged him to give it up altogether. He drinks little alcohol and has not noticed any unusual effects from

it. A hot bath "makes me feel utterly useless and helpless." He is not aware that his speech is slurred, and did not think that smoking affected it.

Accordingly a smoking test and a nicotine test were arranged. His voice was recorded and a ciné film made of his movements and gait immediately before and after each test. It was found that before he had smoked half a cigarette he felt a curious sensation in his legs which spread up to his trunk, and as he continued to smoke his arms and head became tremulous and he had increasing difficulty in handling the cigarette. When he had smoked half of it writing was slower and halting, and his signature deteriorated. He could finish the cigarette only by using both hands to hold it steadily as he brought it to his lips. He swayed slightly in his chair; nystagmus was not altered and speech remained unchanged. His intention tremor increased and when he stood up to walk his steps were very faltering and difficult, and his progress was very much slower. His legs appeared to be more spastic and he had difficulty in lifting each foot from the ground. Smoking one cigarette undoubtedly increased his disability. There were no side-effects of a syncopal nature; he felt quite well in himself and the effect passed off in 20 minutes.

On another day he was given a slow intravenous injection of nicotine acid tartrate as he lay on a bed. When 1 mg. had been injected his legs started to tremble, then his arms and trunk. When 2 mg. had been injected he became pale, perspired, breathed heavily, and was frightened. The injection was stopped. Speech remained unchanged and power in the limbs was not reduced. Deep reflexes remained brisk. Intention tremor was markedly aggravated. He was able to sit on the edge of the bed seven minutes after the completion of the injection and he was obviously more disabled by the uncertainty of his movements. Two minutes later he was able to stand and to walk a few steps with great difficulty. He shuffled along, periodically swaying about, with his legs apparently rooted to the ground and with his arms held out from his body to help maintain balance. Fifteen minutes after the injection he began to improve again, and in another fifteen minutes he had practically returned to his initial status. The syncopal reaction complicated the test in this case, but it soon passed off, and did not seem to account for the overall neural disturbance.

In one respect his reaction appeared to differ from that of the other three patients. Their abnormality of gait was almost entirely cerebellar in character; the gait in Case 4 was much more spastic than ataxic. Nicotine increased the ataxic element of the gait in the former cases, but in Case 4, although the intention tremor was aggravated, it was the increase of the spastic disturbance of gait which struck one so forcibly. In each case the dominant disturbance of the gait appeared to suffer most.

Discussion

The first consideration is the diagnosis. Disseminated sclerosis is present in Case 4. The feature common to the first three cases is the onset of cerebellar ataxia in the fifties without previous nervous symptoms. All three showed progressive disturbance of gait, incoordination of the upper limbs, and characteristic cerebellar disorder of speech. Mental deterioration and periodic incontinence of urine occurred in Case 1; fleeting diplopia has been experienced in Case 3; there is nystagmus in Cases 2 and 3; exaggerated deep reflexes were present in all three patients and extensor plantar reflexes in Cases 1 and 2. In no one was there any subjective or objective disturbance of sensation, apart from slight impairment of vibration sense in the legs in Case 4. No other members of either family are known to have been affected by any type of nervous disorder.

Disseminated sclerosis sometimes develops in the fifties, but this is rare. Few neurologists would agree with the late Foster Kennedy (1950), who said it showed "an extraordinarily exact age incidence—16 to 45. Similarly appearing conditions should be viewed askance if they occur outside this most exact period—16 to 45."

McAlpine *et al.* (1955) say that "the diagnosis of multiple sclerosis must be made with considerable reserve when symptoms commence after the age of 50, particularly when they are progressive." Transient diplopia (Case 3) and periodic urinary incontinence (Case 1) are symptoms which have been recorded in cases of spinocerebellar degeneration confirmed by necropsy (Schut, 1950; Greenfield, 1954). It is known, of course, that there is a small familial incidence of disseminated sclerosis, which Pratt *et al.* (1951) estimated in a series of 310 cases to be 6.5%. The distinctive paraesthesiae and impairment of sensation of disseminated sclerosis are seldom met with in the spinocerebellar degenerations. The history in Cases 1, 2, and 3 was of a disorder of insidious onset beginning at the ages of 54, 52, and 53 years respectively. In Cases 2 and 3 symptoms were at first intermittent, but thereafter slowly progressive. In Case 1 symptoms were progressive from the onset. Intermittency of disability was noticed by Schut (1950) in the earlier stages of his series of cases of proved hereditary ataxias. In discussing the differential diagnosis of disseminated sclerosis and spinocerebellar degeneration Pratt *et al.* stress the late onset and the progressive course in the latter disease, but it is clear that the diseases may be confused. With these considerations in mind a diagnosis of progressive spinocerebellar degeneration was made in Cases 1, 2, and 3.

Effects of Tobacco

All four patients had already noticed aggravation of their ataxia and/or dysarthria by smoking. In Case 1 smoking two cigarettes had an effect on speech and gait that was striking; he was then scarcely able to walk or talk. Three years later, when he agreed to an intravenous injection of nicotine, his ataxia, now gross, became temporarily overwhelming, and his speech became incomprehensible. In Case 2 smoking two pipefuls of tobacco did not affect speech, but made walking unsteadier. Intravenous nicotine on one occasion greatly affected his speech, and, unsupported, he could not walk for about ten minutes. In Case 3 a striking and rapid deterioration in speech occurred half an hour after smoking three cigarettes. On two occasions when he was given an intravenous injection of nicotine he immediately became grossly dysarthric and ataxic. In Case 4 movement and gait were obviously disturbed by smoking one cigarette; speech was not affected. After an injection of 2 mg. of nicotine acid tartrate intravenously speech remained unchanged, but intention tremor was aggravated and walking became a great effort; he could progress only in short shuffling steps.

The alteration in speech and gait on smoking and after the injection of nicotine have been recorded on gramophone disks and ciné film. Ataxia of the trunk is noticeable before these patients stand up or try to walk. The effect on speech, when it occurs, is to make it slower, more drawling, slurred, and monotonous; the utterance as a whole becomes remarkably irregular and jerky. Both vowels and consonants are affected, and phonation as well as articulation is involved. An explosive tendency can sometimes be detected and respiration appears to be poorly integrated in the speech mechanism. Towards the end of a sentence the patient seems to run out of breath. Hiller (1929), in his studies of speech disorders in Friedreich's ataxia, particularly noticed this difficulty of subordinating respiration to the meaning and inner sense of speech. Holmes (1910) also comments on the ataxia of respiration which accompanies speech in Friedreich's ataxia and the "curious short inspiratory whoops." The irregularity of breath pressure in cerebellar speech has been mechanically recorded by Scripture (1930).

Apart from the urinary incontinence in Case 1 and transient blurring of vision in Case 3 no other significant effects of nicotine injection and tobacco-smoking were noted in these patients. There was no clouding of consciousness, no nausea or vomiting. They all perspired slightly and experienced a tingling sensation in the limbs, especially in the injected arm. Case 3 had slight substernal discomfort. Case 4 became pale and hyperventilated. Deep reflexes apparently remained unchanged.

When the effect of tobacco was observed and recorded on the first patient in 1951 inquiry of patients with disseminated sclerosis revealed no indication that tobacco influenced speech or ataxia. Several patients with gross dysarthria were inveterate smokers, and they or their relatives had not noticed any nicotine effect. The exception was one patient aged 58, a bank manager, with disseminated sclerosis of slight degree, whose symptoms of spastic-ataxia, paraesthesiae, and periodic urinary frequency had made their appearance 12 years previously. He had more than once mentioned to me that he thought smoking affected his unsteadiness, and recalled his surprise on observing the degree of his ataxia on a ciné film taken the year previously while on holiday. His wife had reassured him that the film was taken after he had just smoked a cigar. But Case 4 remains the only patient with disseminated sclerosis in whom I can say nicotine actually aggravates the disability.

Eight other patients with progressive spinocerebellar degeneration were studied, and in none was there any suggestion that tobacco-smoking exerted any harmful effect. The patients had not noticed any aggravation of symptoms on smoking, and nicotine injections proved harmless. Clinically these patients differed in no essential way from Cases 1, 2, and 3. Nicotine injections have also been harmless in some 20 different patients with various organic diseases of the brain and spinal cord. These included two cases of hereditary spastic paraplegia, four of disseminated sclerosis, four of striatal tremor, and three patients with cerebellar tremor and ataxia of the upper limbs, without other signs, first appearing in childhood.

Tobacco-smoking and Disseminated Sclerosis

I have not come across any reference to the effect of tobacco in the spinocerebellar degenerations, but there are some observations on record in disseminated sclerosis.

Franklin and Brickner (1947), during a study of 18 cases of disseminated sclerosis that showed constriction of retinal arterioles with scotomata which were said to be reduced by vasodilator drugs, mentioned that two patients said that intention tremor was aggravated by smoking cigarettes. One patient was tested, and it was found that his tremor was in fact increased by smoking one cigarette; his ability to draw horizontal lines on a sheet of paper was noticeably affected. Alcohol and papaverine seemingly inhibited this temporary effect of tobacco. No tests were carried out in the second patient. Franklin and Brickner also state that some of their patients with disseminated sclerosis have noted symptomatic improvement when they have stopped smoking. They were inclined to attribute the effects of tobacco to vasoconstriction. Brickner (1950) mentions another case with "an intention tremor regularly made transiently worse by smoking a cigarette" and a fourth patient who "invariably had transient blurring of vision and an increase in his leg weakness on smoking a cigarette."

McAlpine *et al.* (1955) also comment on the temporary effect of tobacco on the symptoms of disseminated sclerosis. They mention one patient (aged 27) who gave up smoking for some months, and on resuming the habit "then noticed that after starting a cigarette his legs felt heavy and dead for about a quarter of an hour." In discussing the differential diagnosis of disseminated sclerosis from progressive cerebellar degeneration these authors (p. 186) describe the case of a man who began to suffer from progressive cerebellar ataxia at the age of 51. A diagnosis of progressive cerebellar degeneration had already been made on this patient at a London teaching hospital before they had seen him. But he later became impotent and had urinary frequency, urgency, and occasional incontinence. His speech was not affected until "one evening his wife noticed that he could hardly speak and he was so unsteady that he had difficulty in getting upstairs. His speech remained indistinct." When "he had a couple of drinks or smoked, both his speech and walking at once worsened for a short time—a statement which was confirmed by his wife." McAlpine *et al.* considered that these observations pointed to a diagnosis of disseminated sclerosis rather than to a primary form of

cerebellar atrophy. The resemblance to my Cases 1, 2, and 3 is strong, and reasons have already been given for favouring a diagnosis of progressive spinocerebellar degeneration in these cases.

Pharmacological Properties of Nicotine

Few drugs possess more complicated pharmacological effects on the nervous system than nicotine. There are effects on muscular fibres and neuromuscular junctions, on autonomic ganglia, and also on the central nervous system. At each level, moreover, the effect depends on the concentration of the alkaloid and the degree of intoxication. The effects may be classified as stimulant and depressant, while the ultimate response of any one structure may thus represent the algebraic summation of the different effects of nicotine (Goodman and Gilman, 1941; Bovet *et al.*, 1947).

There are about 20 mg. of nicotine in a cigarette (Roth, 1951; von Ahn, 1954), but estimates of the amount absorbed into the blood stream vary considerably—from 0.4 to 3 mg. per cigarette (Ling and Parry, 1949; von Ahn, 1954).

At neuromuscular junctions nicotine first stimulates and then exerts a "curare-like" effect. Curare, however, is more active at neuromuscular junctions than at ganglia, and the reverse is true for nicotine. In my patients nicotine produced no peripheral paralysis; muscular power and reflex activity were unimpaired. In Case 3 a controlled injection of tubocurarine was followed by characteristic peripheral paresis without producing any effect like that of nicotine. A peripheral neuromuscular block is therefore unlikely to be the explanation for the phenomena described in these patients.

In the case of the ganglia of the autonomic system the effect of nicotine is again to excite, then to paralyse them. The pharmacology of the autonomic synapse appears to be essentially the same as that at the neuromuscular junction. At both sites acetylcholine is a major factor in the transmission of the excitatory state. In the ganglia nicotine does not interfere with the release of acetylcholine by impulses from the pre-ganglionic fibres, but renders the ganglionic cells more sensitive and then more resistant to the chemical mediator. The classical experiments of Langley and Dickinson (1889) showed that if a nerve pathway is blocked by applying nicotine to a ganglion it indicates the presence of a synapse in that ganglion. When nicotine is applied directly to a nerve fibre it interferes with conduction only when it is in high concentration. Intravenous tetraethylammonium bromide in Case 3 did not affect speech or ataxia.

Again, at higher levels of the nervous system nicotine has striking effects. It stimulates respiratory, vasomotor, and emetic centres in the medulla and can produce convulsions. These centres are depressed by larger doses of the drug, and death usually results from respiratory failure. The action of nicotine on respiration is particularly prominent; there are peripheral and central, stimulatory and inhibitory effects. Similarly, the circulatory effects of nicotine are marked and complex. There is at first slowing of the heart, peripheral vasoconstriction, and elevation of blood pressure. With increasing dosage opposite effects are produced and the manner in which they are brought about depends on the multiple sites of action of the alkaloid (von Ahn, 1954).

The actions which acetylcholine brings about at parasympathetic nerve endings were described by Dale as "muscarine-like," while those exerted at autonomic ganglia were "nicotine-like." One of the nicotine-like properties of acetylcholine is the liberation of the antidiuretic hormone of the pituitary gland by stimulating the supraoptic nucleus (Pickford, 1947). That nicotine itself possesses the same property was demonstrated by Burn *et al.* (1945). These authors concluded that stimulation of the supraoptic nucleus was one of the effects of smoking. In diabetes insipidus much larger amounts of nicotine are required to produce an antidiuretic action (Garrod and Cates, 1950). Burn (1951) points out that the antidiuretic hormone of the posterior

lobe of the pituitary gland is believed to be identical with the pressor hormone (vasopressin) which causes vasoconstriction. If the accentuation of symptoms by nicotine in my patients was due to vasoconstriction affecting the central nervous system we might have expected to see more evidence of cerebral ischaemia. But what was so impressive about the tests was the way in which the two outstanding symptoms—the dysarthria and the ataxia—were affected. Cerebral vasoconstriction, if it occurred, might conceivably have dire consequences on nervous mechanisms already deranged by disease, but if this were so we might also expect to see adverse effects of smoking in patients with cerebral arteriosclerosis. Everyday experience does not lend support to this argument, but little is known on the matter.

Eranko (1955) has demonstrated that nicotine also has a stimulant action on the adrenal glands. It causes a release of noradrenaline, the chemical transmitter of sympathetic nerve impulses, from cells of the adrenal medulla. Some of the pressor effect of nicotine may be due to this action.

Another way in which nicotine may accentuate the symptoms of spinocerebellar disorder must be considered. The best-known pharmacological effect of nicotine is the production of synaptic block in autonomic ganglia. Where there is no synapse, as in the sensory ganglia of the spinal nerve roots, nicotine does not block transmission of the nerve impulse. But neither does it seem to interfere with synaptic conduction in the spinal cord (van Harreveld and Feigen, 1948) nor in the cardio-inhibitory vagal mechanism (Heymans and van den Heuvel-Heymans, 1950). Chemical transmission of nerve impulses is not confined to the autonomic nervous system. Acetylcholine is a transmitter at neuromuscular junctions, where nicotine is also active, and possibly also at synapses within the central nervous system. The growth of the conception of chemical transmission in the nervous system has recently been summarized by Dale (1955), who postulates chemical mechanisms of transmission "at all the synapses in the immense complexity of the central grey matter." Is it not conceivable that the nicotine effect I have described in these cases is central in nature and concerned with synaptic transmission? Sherrington (1947) wrote that "each synapse is an apparatus for co-ordination." Certainly accentuation of existing inco-ordination was the phenomenon witnessed in these patients.

Heymans and de Vleeschhouwer (1948) and Heymans and Estable (1949) demonstrated that D.P.C.P.C. (diethylaminoethyl-1-phenylcyclopentane-1-carboxylate) and D.P.T. (N-diethylaminoethyl-phenothiazine), new synthetic drugs possessing therapeutic value in Parkinsonism, also possess powerful anti-nicotine properties. It was suggested that the therapeutic activity of some of the new drugs used in Parkinsonism might be related to the ganglion-blocking effect on the tonic centres of the extrapyramidal tracts or on cholinergic transmission (Bovet and Bovet-Nitte, 1948). Tripod (1949) investigated the relationship between the anti-nicotine effect and parasympathetic or autonomic activity of D.P.C.P.C. and D.P.T. He found that the anti-nicotine properties are related to the various sites of action of the alkaloid and not to a specific blocking of parasympathetic effects. The therapeutic activity of D.P.C.P.C. and D.P.T. in Parkinsonism does not appear to be related to its anti-nicotine activity.

Bovet and Longo (1951), however, found a parallelism between the antagonism of some drugs—d.ethazine hydrochloride ("diparcol"), caramiphen hydrochloride ("parpanit"), and benzhexol hydrochloride ("artane")—against the tremors induced by nicotine, and the clinical results obtained with these drugs in the symptomatic treatment by Parkinsonism. They considered their observations to be a new argument in favour of the development of a central action by cholinergic preparations. "It does not seem unreasonable, on this basis, to think that drugs effective in Parkinsonism block, at the level of the mesencephalic and bulbopontine centres, the effects of a cholinergic transmission no longer harmonically controlled by the superior centre, destroyed or deeply injured by disease."

I have not found that nicotine aggravates the symptoms of Parkinsonism. In Case 1 diethazine appeared to have no effect: in Cases 2 and 3 it aggravated the ataxia. Case 3 actually had to retire to bed for a few days with severe ataxia, and he considered that diethazine was more harmful than nicotine. Although nicotine has no known therapeutic value its usefulness as a pharmacological "tool" has long been appreciated. The observations here recorded suggest that the effects of the drug on the central nervous system in health and disease require further examination.

Summary

An account is given of four patients with spinocerebellar ataxia who complained of the adverse effect of tobacco-smoking on their disability. The diagnosis in the first three patients is one of progressive spinocerebellar degeneration; the fourth has disseminated sclerosis.

The correctness of their observations was confirmed. Tobacco-smoking had a striking effect on the dysarthria and on the ataxia of the lower limbs in Cases 1 and 3. In Cases 2 and 4 speech was not affected, but ataxia was noticeably increased.

These effects were also produced in each patient by the intravenous injection of nicotine acid tartrate.

It is suggested that they are brought about by some action of nicotine on the central nervous system which may involve disturbance of synaptic transmission of nerve impulses.

Tobacco-smoking and intravenous nicotine had no harmful effect in eight other patients with progressive spinocerebellar degeneration. They were also harmless in 20 patients suffering from various organic diseases of the brain and spinal cord.

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FORTY YEARS ON

A G.P.'s RETROSPECT AND REVIEW

BY

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With the lapse of forty years since qualification one is tempted to look back and try to assess the development of medical knowledge and practice in its impact on the general practitioner, and, at the same time, to attempt to see in proper perspective the progress and retrogressions in the various branches of medicine; for not all change is for the better, and occasionally it is definitely and demonstrably for the worse. Such a review must necessarily be incomplete, and even fragmentary; but it may be of interest, and just possibly of use.

It is perhaps a little obvious, but it is true, to claim that, in spite of certain regrettable tendencies, progress in the healing art has at least proceeded *pari passu* with, and has often excelled, that in other fields, and one remembers with gratitude that in spite of almost kaleidoscopic change the great fundamental principles taught in our student days remain unshaken, and as applicable now as they were then.

A Sound Medical Philosophy

When Sir Robert Hutchison (1928) wrote his matchless little trilogy of 50 pages—*The Principles of Diagnosis, Prognosis, and Treatment*—he provided the student and the practitioner for all time with a medical philosophy so sound that adherence to it would provide the means of avoiding many of the varied pitfalls of the practice of medicine. For in these days the enormous developments in the diagnostic field and the innumerable drugs which pour from the analytical laboratories put a strain on the judgment of the practitioner that has never been experienced before in such intensity.

To take one danger as an example—the temptation to a short-cut in diagnosis by ordering a roving inquiry into the blood, the urine, and the excretions generally, and perhaps elaborate x-ray investigations without a careful history, and without a thorough clinical examination. Probably we have all been guilty of this at times, and one or two lucky hits may lead us further astray; for, just as Sir Robert Hutchison says, "If you once get into the habit of guessing you are diagnostically damned"—so is the man who forms the habit of expecting the laboratory and the x-ray room to save him from those clinical observations and investigations that are an essential preliminary before any elaborate procedures can be justified.

I remember so well how a young woman whom I had attended for a difficult labour, complicated by hydrocephalus and hydramnios, fell into the hands of a pathologist (a relative) who, after the most involved laboratory investigations of almost every conceivable secretion and excretion but without proper clinical examination, issued a report with the diagnosis of intestinal toxæmia and endocrine insufficiency (these at the time were fashionable names for non-existent clinical conditions). What the patient was really suffering from was physical and mental exhaustion following a difficult labour, ending in a stillborn baby, and a mitral stenosis which was the only organic condition present, and this was omitted from the report.

X-ray investigations, though more and more reliable, can still be misleading, and experience seems to show that where the clinical indications point strongly in one direction and the x-ray result in another it is still generally safer to follow the former to a conclusion than to be overruled by the latter. Some years ago I was called to an old lady of 80 who had fallen down three stairs, at the foot of which