hospitals in rural districts (and in some urban areas), in annexes or wards of general hospitals in large towns and cities.

The hospital services are greatly helped, and the continuing education of general practitioners is advanced, when they work in wards or out-patient departments of larger hospitals as "clinical assistants" for not more than one or two sessions a week under the supervision of consultants. More of these appointments are needed. Senior and junior grades of clinical assistantships should be officially recognized and introduced into specialist teams with different rates of pay and differing degrees of responsibility. The senior grade should be long-term appointments, perhaps for several years, in which general practitioners with special interests and experience could play a really useful part in the work of hospitals, in a more important and responsible role than that of clinical assistants at present. The junior grade could be short-term appointments for those learning to develop special interests or striving to maintain their continuing education.

These measures should go far towards closing any "rifts" or "gaps," where they exist, between family doctors and consultants and between general practice and hospital work; and it should lead to better and much-needed integration, and happier co-operation, between these two great branches of our profession.

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NEUROPATHY AFTER INTAKE OF THALIDOMIDE (DISTAVAL)

BY

PAMELA M. FULLERTON, M.A., B.M., M.R.C.P.

Registrar, Department for Nervous Diseases,
Middlesex Hospital, London

AND

MICHAEL KREMER, M.D., B.Sc., F.R.C.P.

Physician, Department for Nervous Diseases,
Middlesex Hospital, London

There have been recent reports of cases of peripheral neuritis attributed to a toxic effect of thalidomide ("distaval") (Florence, 1960; Burley, 1961; and Kuenssberg et al., 1961). This paper is based on 13 patients who developed neurological disturbances while taking this drug as a hypnotic. The neuropathy is interesting, with some evidence that abnormalities are not confined to the peripheral nervous system.

Clinical Features

Details of the cases are shown in the Table. The ages of the patients ranged from 37 to 76 years. All had taken thalidomide regularly for 2 to 18 months before the onset of symptoms. In most cases the dose had been the usual one of 100 mg. each night, although a few had taken higher doses (up to 400 mg. nightly) and one had had only 50 mg. nightly.

The earliest symptoms were paraesthesiae and numbness in the feet followed by similar symptoms in the hands, usually a few months later. These disorders of sensation were the most prominent feature in all cases, and weakness of the limbs was a minor complaint in five and of major importance in only one. Seven patients complained of cramps in the legs as one of their most distressing symptoms.

All patients were carefully cross-examined for evidence of other neurotoxic exposure. Only one (Case 9) gave a history of excess alcohol consumption, after the onset of a depressive illness. He had taken a bottle of spirits daily for 16 months before the onset of symptoms. However, in this patient, many features, such as proximal weakness in the limbs, increased reflexes, and equivocal plantar responses, indicated that he was not suffering from an alcoholic peripheral neuritis. No other aetiological factors could be elicited from the history of the remaining patients.

Neurological examination showed altered superficial sensation of varying extent in the distal parts of the limbs in all patients. Eleven showed depression of all

forms of superficial sensation in a stocking-and-glove distribution, light touch being the most severely affected. In two there was marked overreaction to pin-prick and touch in a similar distribution. Vibration sensation was impaired in four of the more severely affected patients and position sense in one. Weakness of the limbs was present in seven—in two peripherally, in three involving proximal muscle groups, and in two there was mild diffuse weakness of the legs. Tendon reflexes were increased in eight patients, normal in two, and generally depressed in three. Complete abolition of a pair of reflexes occurred in three cases, as symmetrical absence of the ankle-jerks, but in only one of these was there depression of the other reflexes. The plantar responses were flexor in seven patients, equivocal in five, and extensor in one.

General examination revealed two other abnormal features in some patients. Redness of the palms, similar to that commonly associated with liver disease, was present in four, and three had brittle and broken fingernails and toenails, which had developed since the onset of their neurological symptoms. Both these manifestations were of early occurrence.

Two cases are described in detail to illustrate the features that we have come to accept as typical of the natural history of this condition.

Case 6

A married woman aged 54 began taking 100 mg. of thalidomide nightly in August, 1958. In June, 1959, numbness and paraesthesiae developed in the feet, and a month later similar symptoms developed in the hands. At the same time she noticed redness of the palms. The symptoms gradually spread to involve the whole of both lower limbs up to the groins. In September, 1960, she began to have frequent and severe cramps in the legs.

On examination in February, 1961, the only abnormality in the motor system was constant fasciculation in the calves and occasional fasciculation in the quadriceps muscles. There was no weakness. Tendon reflexes were normal, except the ankle-jerks, which were depressed; the plantar responses were flexor. Impairment of superficial sensation over the hands extended up to the wrists, and there was hypersensitivity to touch and pin-prick over the whole of both lower limbs up to the mid-thighs. Her palms were red and she had broken fingernails and toenails. Two months after stopping thalidomide there had been no change in her symptoms or signs.

Case 2

A spinster aged 50, the most severely affected patient, took 100 mg. of thalidomide about four times a week from December, 1957, to August, 1959, and from that time until December, 1960, she took 300 mg. about four times a week.

Clinical Features and Investigations

Case No.	Age and Sex	Nightly Dose (mg.)	Time before Symptoms (Months)	Duration of Symptoms before Examination (Months)	Motor Signs	Reflexes	Extent of Altered Superficial Sensation	Other Features	C.S.F. Protein (mg./100 ml.)	Nerve-conduction Tests
1	56 F	100	9	8	None	Increased. PI ? ?	To wrists and mid-calves	Numbness right side face	—	
2	50 F	100-300	8	24	Severe wasting proximal leg muscles. Proximal arm weakness. Severe leg weakness proximal > distal	Increased. AJ — — PI ↑ ↑	Fingers. Up to groins	Vibration depressed legs. Position defective toes	70	Right lateral popliteal motor velocity normal. Left median sensory potential reduced
3	75 F	100	Few	18	Mild weakness, feet	Depressed. PI ↓	Fingers and feet	—	25	Left median sensory potential reduced
4	37 M	100	12	16	None	Increased. AJ ± ± PI ↓ ↓	Fingers and toes	Leg cramps. Nails breaking	110	Right median sensory potential reduced. Right ulnar sensory potential absent
5	56 F	100	4	31	Wasting hands. Diffuse leg weakness proximal > distal	Increased arms. KJ ± ± AJ — — PI ↓ ↓	To wrists and mid-calves	Leg cramps. Nails breaking	60	Right lateral popliteal motor velocity normal. Right lateral popliteal sensory potential absent
6	54 F	100-200	10	20	Fasciculation calves	Normal. PI ↓ ↓	To wrists and mid-thighs	Red palms. Leg cramps. Nails breaking	60	Right median motor velocity normal. Right median sensory potential absent
7	48 F	100	8	5	None	Increased. PI ↓ ↓	Feet	Leg cramps	—	Left median sensory potential normal. Left lateral popliteal sensory potential absent
8	49 F	100	11	14	Mild diffuse leg weakness	Increased. PI ? ?	„	Reduced vibration sensation feet. Leg cramps	—	
9	57 M	100	16	8	Mild proximal weakness arms and legs	Increased. PI ? ?	Fingers and toes	Red palms. One bottle of spirits a day	40	Right median sensory potential absent. Left lateral popliteal sensory potential reduced
10	76 M	100	7	14	Moderate wasting and weakness hands	Depressed. PI ↓ ↓	To knees	Vibration sensation absent to iliac crests. Red palms	30	
11	68 F	200	18	18	Mild wasting hands. Mild proximal arm weakness	Depressed. AJ — — PI ? ↓	Fingers and to mid-calves	—	—	Right median motor velocity normal. Left lateral popliteal motor velocity normal. Right median sensory potential absent
12	69 M	100-400	2	24	None	Normal. PI ↓ ↓	Hands and to groins	Vibration sensation impaired to iliac crests. Leg cramps	70	Right median motor velocity normal. Right median sensory potential absent
13	54 M	50	9	11	„	Increased. PI ? ↓	Hands and to mid-shin	Red palms. Leg cramps	45	

PI = Plantar responses. AJ = Ankle-jerks. KJ = Knee-jerks.

In September, 1958, mild paraesthesiae and tenderness in the legs developed, but these symptoms did not become severe until March, 1959. In June, 1959, she had difficulty in climbing stairs, and subsequently the weakness in the legs gradually increased. In June, 1960, paraesthesiae in the hands developed.

When first seen (August, 1960) she had slight wasting of the small muscles of the hands and mild proximal weakness in the upper limbs. There was noticeable wasting and weakness of the muscles of the lower limbs, affecting particularly the glutei and thigh muscles. All reflexes were increased, except the ankle-jerks, which were absent. Abdominal responses were normal and plantar responses equivocal. There was impairment of superficial sensation over the fingers and in the lower limbs up to the knees. Vibration and position senses were normal in the upper limbs. Vibration sense was absent in the feet and there was a gross defect in position sense in the toes. Over the next six months her condition deteriorated and she was unable to raise either leg off the bed. The plantar responses became extensor. Thalidomide was stopped in December, 1960, and rapid improvement in power began immediately. Three months later she was walking well and had no weakness in the upper limbs. The hip flexors had regained 80% of their power and there was a corresponding increase in power in the other muscle groups. There had been little change in the sensory symptoms and signs.

Investigations

Haemoglobin values, blood-sugar levels, and liver-function tests were normal in all patients; one (Case 9) had an eosinophilia of 14%, but he was a known asthmatic. The cerebrospinal fluid was examined in nine patients, and was normal except for the protein content, which ranged from 25 to 110 mg./100 ml. and was over 50 mg. in five cases. Pyruvate-tolerance tests on five patients gave values within the normal range. Radioactive iodine studies were carried out on four, with normal results in three. One patient with no evidence of myxoedema had a reduced 24-hour uptake of radioactive iodine (16%), a finding which has been previously described during thalidomide medication (Murdoch and Campbell, 1958).

Muscle biopsies were performed on two patients (Cases 2 and 6), and both showed changes characteristic of denervation. One of them had noticeable wasting and weakness of the biopsied muscle (quadriceps) and the other had no clinical motor abnormality except fasciculation in the calves (the biopsy was taken from the tibialis anterior).

Studies of nerve conduction were carried out on nine patients. Velocity of motor conduction was estimated by the technique described by Thomas *et al.*, (1959). Sensory conduction in the upper limb was studied by the technique described by Gilliatt and Sears (1958) and in the lower limb by the technique described by Gilliatt (1961). In chronic peripheral neuritis the velocity of motor conduction may be much slower than normal and sensory potentials may be reduced in amplitude or absent (Gilliatt and Sears, 1958). The velocity of motor conduction was measured in five patients, in three of them on nerves supplying muscles which were clinically weak. All gave values within the normal range. Estimation of motor velocity depends upon conduction in the fastest surviving motor fibres, and normal results of the sort obtained here are not incompatible with moderate involvement of motor nerves.

Sensory-nerve conduction was abnormal in the distal segment of the median nerve in seven of the eight patients in whom this was tested and in the lateral

popliteal nerves of the three patients examined. There is therefore unequivocal electrical evidence of involvement of peripheral sensory-nerve fibres.

Discussion

As a large number of people now take thalidomide regularly, and as peripheral neuritis of unknown aetiology is a not uncommon disorder, it is at first a little difficult to be sure of the significance of this association. Our patients developed symptoms from 2 to 18 months after starting regular medication, which is suggestive of an aetiological relation, and this is supported by many of the unusual clinical features that were common to the group. A careful study of our cases has shown that only one patient had taken any substance other than thalidomide to which neuronal damage could be attributed. In this case the intake of alcohol had been for a relatively short time and the signs were very different from those commonly found in alcoholic peripheral neuritis. It seemed reasonable, therefore, to attribute the neuropathy here described to thalidomide.

This suggestion would be strongly supported if recovery occurred on withdrawal of the toxic substance. While we have seen a spectacular recovery of power in the one patient with severe motor affection the changes in the sensory symptoms and signs have so far been slight, though those that have occurred have all been in the direction of improvement and none have continued to deteriorate after withdrawal of thalidomide. It is unfortunately true that slow and variable improvement after withdrawal of toxic substances is well known in peripheral neuritis; therefore it is not surprising to find this disparity between motor and sensory recovery and the great delay on the sensory side. Our longest follow-up after withdrawal has been six months, and this period is far too short to determine whether irreversible changes have taken place. We have heard of mild cases that have recovered completely a few weeks after withdrawal (D. Burley, 1961, personal communication), but have not seen any ourselves.

The sensory symptoms and signs in these patients are characteristic of peripheral neuritis, and electrical studies have confirmed that conduction in peripheral nerve fibres may be abnormal. Our two biopsy studies showed that the lower motor pathway was involved, even though in one case there was no clinical evidence to suggest this. It is, however, not possible to determine the site of the lesion by this means. The clinical findings show that damage is not confined to peripheral nerves. Although peripheral paraesthesiae may increase the deep reflexes in a non-specific fashion, such increase in the presence of peripheral nerve involvement with equivocal plantar responses (frankly extensor in one) indicates that the upper motor neurone pathways may be affected. The predominance of proximal muscle weakness in some cases also suggests that the syndrome is not a simple peripheral neuritis.

We have not found any reason why few patients succumb to thalidomide when the population at risk is relatively large. So far the onset seems to be haphazard. The wife of one of our more severely affected patients took thalidomide in the same dose and for the same time as the patient, but did not develop any neurological symptoms other than fleeting peripheral paraesthesiae. Some psychiatric patients have had very large doses without developing obvious neurological disorder.

However, in our patients it was those who had taken the drug for the longest time who were the most severely affected. None of our patients had any blood relations taking thalidomide, so we cannot speculate on the possibility of susceptibility to thalidomide being on a genetic basis.

Little is yet known about the metabolism of thalidomide in the body after absorption. Its mode of action in producing both the desirable sedative and the undesirable toxic effects is unknown. Our investigations have not thrown any light on the mechanism of this neuropathy. There is no evidence as yet to suggest any interference with carbohydrate metabolism or other known enzyme mechanisms, though further study along these lines will be made if any new cases are seen. It is interesting that similar toxic effects have not been reported in patients taking glutethimide ("doriden"), which is chemically very similar. It is also interesting that several observers suggested, when seeing some of these patients before thalidomide toxicity was suspected, that the clinical features resembled those of neuropathy associated with malignant disease.

Two further articles have recently appeared in the German literature (Raffauf, 1961; Scheid *et al.*, 1961) in which 14 and 9 cases with neurological abnormalities attributed to thalidomide toxicity have been reported. The clinical features of these cases are similar to those reported here.

Summary

The neurotoxic effects of thalidomide in 13 patients are described.

Symptoms developed in from 2 to 18 months after starting regular medication, in doses varying from 50 to 400 mg. nightly.

The disorder was predominantly a sensory peripheral neuritis, but there was evidence of more widespread effects on the nervous system.

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The Derbyshire village of Eyam recently held its Plague Commemoration Service in the same spot where their forefathers met for church services nearly 300 years ago when plague killed hundreds of villagers. Tradition has it that the disease was brought to the village in a box of clothing that came from London in 1665 after London's great plague. The address was given from the rock platform once used by Rector William Mompesson, who was the village leader at the time. He had closed the church because of the risk of infection. Many of the plague victims lie buried in the fields near the spot where the service was held. (*Northern Whig*, August 28.)

VENEREAL DISEASE IN ADOLESCENTS

BY

LESLIE WATT, M.D.

Consultant Venereologist, St. Luke's Clinic, Manchester

Recently attention has been focused on reports of increasing promiscuity among adolescents. As an index of this promiscuity much has been made, both here and in America, of the "increasing incidence of venereal disease" in the younger age-groups. King and Wisdom (1960) have discussed adolescents who attended for diagnosis at a venereal disease clinic in London in 1958 and 1959.

The *Concise Oxford Dictionary* defines an adolescent as "a person growing up between childhood and manhood (14-25) or womanhood (12-21)." Common usage restricts the top limit of the age-groups to the twentieth year.

The present factual study was planned because of the widespread concern over published reports and because of the absence in Britain of any recent comparative survey of venereal disease involving the younger age-groups. No attempt has been made to analyse the reasons underlying any increase shown, apart from drawing attention to some of the factors that have influenced the general trends of venereal disease during the period under review. The study was undertaken in Manchester and Salford, where, until 1954, two venereal disease clinics served a large part of the area. These were amalgamated in 1954 at St. Luke's Clinic, which now serves the same area. The age-group chosen was 15-19 years in both sexes. Accurate statistics are not available, but Table I shows the estimated adolescent population in Manchester and Salford in the years studied. It will be noted that a considerable decrease in the numbers at risk has occurred.

The records of patients attending the two clinics in 1938, 1939, 1949, and 1950, and St. Luke's Clinic in 1959 and 1960 have been studied. The years 1938 and 1939 were preferred to 1939 and 1940 because of the increasing influence of wartime conditions in the latter year. Only new patients who had had no previous treatment were included.

There are now suggestions that many genital infections formerly classified as non-venereal should be included among venereal diseases. Whether this is desirable is a moot point, since the lay mind tends to dwell too much on the venery and not enough on the disease. In a significant proportion of cases many such conditions, although genital and perhaps sexually acquired, are not associated with promiscuity. To make a true comparison over the years under review, only cases of early infectious acquired syphilis and acute gonorrhoea were included. The number of infections in each year was used, not the number of individuals involved.

TABLE I.—Estimated Adolescent Population (15 to 19 Years), Manchester and Salford

Year	Manchester		Salford		Totals	
	Males	Females	Males	Females	Males	Females
1938	31,565	33,517	8,100	8,100	39,665	41,617
1939	31,401	33,210	8,000	8,100	39,401	41,310
1949	22,580	23,314	5,850	5,900	28,430	29,214
1950	22,784	23,431	4,450	5,600	28,234	29,031
1959	21,963	22,140	5,400	5,400	27,363	27,540
1960	21,788	21,875	5,600	5,600	27,388	27,475