ABSTRACT OF THESIS

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Title of Thesis: The Heredo - Familial Acrodystrophic Neuropathies.

Two kindreds are described containing subjects with sensory loss of the extremities, and plantar ulcers (acrodystrophic neuropathy), inherited as a dominant trait.

In the "X" Family there were 18 certainly, or probably, affected, (3 autopsies), and 261 unaffected members, in 6 generations. The disorder conformed to the classical pattern of Hereditary Sensory Neuropathy, the clinical, radiological, electrophysiological, pathological and genetic features of which are reviewed.

In severe cases the feet became shortened and mutilated through extrusion, and absorption of bone, but full development of the "elephants foot" deformity depended upon backward subluxation of the tarsus at the ankle. Neurological signs antedated electrophysiological abnormalities, so that the latter were of no predictive diagnostic value. Histologically the most striking observation was the contrast between severely degenerated posterior roots, and healthy anterior roots. On average, affected individuals lived as long as the unaffected.

The "Z" Family presented a more unusual trait, with greater motor involvement, and lower penetrance of the mutant gene. One heterozygote appeared completely unaffected, both clinically and electrophysiologicaly.

There are a number of other inherited acrodystrophic neuropathies, apart from disorders in which acrodystrophic change is only an occasional event. At least six of the former are recessively determined.

Phenocopies occur through the agency of various chronic, acquired, sensory neuropathies, a proportion of which are identifiable.
Original plantar ulceration of propositus of the "X" Family (IV 37), in January 1952. The shape and dimensions of the feet are, as yet, unaffected.
THE HEREDO-FAMILIAL ACRODYSTROPHIC

NEUROPATHIES

D. J. Ellison, M.B. Ch.B. M.R.C.P.E.

M.D.
University of Edinburgh
August, 1974.
"... there is still scope for lone workers, particularly family doctors with large practices which are sure to include a few patients with unusual conditions. We know far too little of what the end result is in such cases, and what is required is more information about the final history of patients with rare diseases and their families. What in fact becomes of patients with tylosis, the Ehlers-Danlos syndrome, peroneal muscular atrophy, and many other similar conditions? A study of the natural history of such disorders would be most informative and needs no apparatus - only the use of the five senses - and a pen".

C.A. CLARKE

"Genetics for the Clinician", 1964.
"...... in the meantime there is a great need for clinical data, simply obtained .........

The Clinician can now perform a most valuable, if humble, role by collecting unselected series of patients, and submitting simple data of this sort to analysis. As the biochemical lesions are gradually uncovered, a series of patients classified in homogeneous sub-categories will then be available for the precise biochemical analysis that will provide the final classification".

R.T.C. PRATT

The Scientific Basis of Medicine Annual Reviews

(1971)
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April, 1974.
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Phenocopies occur through the agency of various chronic, acquired, sensory neuropathies, a proportion of which are identifiable.
Patients affected by an inherited disorder characterised by painless ulceration and mutilation of the feet, have existed in our practice for over a century.

It seems likely that for most of this time the complaint was accepted as an inevitable familial evil by patients and doctors alike, and that little speculation took place concerning its nosology.

However in 1951, Denny Brown reported the clinical and pathological findings in a member of a London family, designated "R", which had been originally described by Hicks in 1922. Affected members of this kindred resemble ours in presenting plantar ulceration complicating distal sensory loss in the legs, but differed through being afflicted also by shooting pains, and by progressive deafness.

Denny Brown identified changes in the posterior root ganglia which he rightly regarded as fundamental, and named the disease Hereditary Sensory Radicular Neuropathy (H.S.R.N.).
three qualifying adjectives used in this designation the third may be regarded as the least important, as it reflected the author's preoccupation with a radicular explanation of the sensory dissociation which is so characteristically present.

Within a few months of the publication of this major contribution, two of our patients, a father and son, were referred by my predecessor in practice to Dr. A.M.C. Campbell in Bristol. Recognising the essential similarity between these patients, and Denny Brown's case, he had no hesitation in diagnosing H.S.R.N.

Twelve years later this family was to form part of a report by Dr. Campbell and Dr. Lovell Hoffman (Campbell and Hoffman, 1964). They named it the "X" family, a designation to which I have adhered throughout the present study. The object of their paper was to demonstrate the existence of a continuum of phenotypic expression, as between the "purely sensory" form of H.S.R.N. typified by the "X" family on the one hand, and "purely motor" peroneal muscular atrophy on the other.

As intermediate forms they described a small family from Bath, now extinct, (the "Y" family), and an isolated case from Bristol ("Z"). One member of the "Y" family and "Z" family presented considerable and progressive muscular weakness and wasting as well as peripheral sensory loss and trophic ulcers.

Campbell and Hoffman made no pretensions towards undertaking a full genetic survey of the "Y" family. The pedigree they constructed is made up of 21 subjects (3 of whom they examined), whereas the
kinship in fact contained well over 200 members distributed over six
generations. Among the inevitable omissions, was a young man who has
subsequently developed marked muscular wasting. Indeed when seeking
genetic counselling elsewhere at a time when he was free from plantar
ulceration, he was diagnosed as suffering from peroneal muscular
atrophy. One of his sisters presents similar amyotrophy, with slowing
of motor nerve conduction, but no ulceration to date. This sibship at
least is not "purely sensory" in presentation.

In recent years other members of this generation have
expressed concern that they might become affected, and worse still trans¬
mit the trait to their children. The present study was partly moti¬
vated by their interest and concern.

It was begun in 1969 and forms the major part of this thesis.
It is essentially a clinical report, supported by the findings at three
autopsies. The biochemical investigation has been only of the most
routine kind, because it is generally considered pointless to look for
enzyme deficiencies in dominantly inherited traits (McKusick (1968),
Raine (1972)). H.S.R.N. is not an inborn error of metabolism in the
sense defined by Garrod. Nor have linkage studies been undertaken
because, although this is the largest reported British stock, the
number of living affected subjects is too small for these to have any
prospect of providing rewarding results.

Reference has already been made to a patient designated Z,
who is briefly described in the report of Campbell and Hoffmen in 1964.
A family history has subsequently been uncovered in his case, and in
1969 Dr. Campbell suggested that I should undertake a genetic survey of
this family. This forms a subsidiary part of this thesis.
There are pronounced differences in the clinical features of the affected members of the "X" and "Z" families.

The trait present in the "X" family is identical with that encountered in most stocks of H.S.R.N. There is distal, initially entirely dissociated sensory loss, usually not subjectively recognised in the early stages; variable, often severe ulceration and mutilation of the feet, with virtual sparing of the hands; usually slight, rarely severe muscular weakness and wasting; and sparing of the deep reflexes apart from the ankle jerk. Shooting pains are rare, deafness does not form an integral component of the syndrome, while appreciable ataxia and visceral and sphincteric disturbances do not occur. Inheritance is X dominant with high penetrance, particularly in males.

Besides evidently being more rare, the disease present in the "Z" family differs from this typical phenotype of H.S.R.N., since with the passage of time motor symptoms and signs have quite overshadowed those of the sensory neuropathy. Both living affected members have developed severe flaccid paralysis, and amyotrophy affecting all four limbs. The resulting incapacity has so spared their feet from trauma, that trophic lesions originally present have healed, although they still occur to lesser degrees in the hands, which have so far retained much of their power.

There is also a clear cut genetic distinction. The mutant gene present in the "Z" family appears to be dominant only in some heterozygotes, while it appears to be recessive, or almost completely so, in others. This sporadic dominant behaviour is at variance with that of the mutant gene present in the "X" family, and in H.S.R.N. in general.
Where the pattern of inheritance of two phenotypically similar traits is so different, they must, ipso facto, represent examples of different disorders. There are therefore genetic, as well as clinical reasons for regarding the two disorders as quite separate. These differences introduce problems of nosological classification which are discussed, in their historical as well as their contemporary context, in the chapter which follows. They are the main reason for selecting the generic term Heredo - Familial Acrodystrophic Neuropathy (H.F.A.N.) as the title for this thesis.
The "X" family has been traced back to Elisabeth Butler née Goddard (II in pedigree), who must have been a contemporary of the first familial case reported under the title "Affection Singulière des os du pied", (Nélaton, 1852).

It has been pointed out that credit for this first report should in fact be given to an anonymous writer of case notes at the Hôpital Des Cliniques in Paris, rather than to Nélaton who was one of the surgeons who from time to time treated this patient (Spillane & Wells, 1969). The identity of this contributor is unknown, whereas the later stage of the career of Nélaton has been described (Swain, 1970). He was to become the organiser of the French Aid Society, the forerunner of the French Red Cross. He accompanied the ill-fated Louis Napoleon throughout his disastrous campaigns in the Franco/Prussian war and was presumably present at the disasters at Sudan and Metz.

Speculation about the nosology of H.S.R.N. did not in fact begin until half a century after Nélaton's patient was described.
It immediately centred on the cardinal neurological feature, which was dissociated sensory loss in the extremities, particularly the lower limbs. Sensory dissociation was so suggestive of involvement of the central grey matter of the cord that it was immediately attributed to a lesion at this site in the lumbar cord. Thus arose the myth of familial lumbo-sacral syringomyelia (F.L.S.), a diagnostic invention which was to dominate the study of this disorder throughout much of the first half of the 20th century. F.L.S. apparently derived its original inspiration from a report of a family which included three siblings affected by a syringomyelic syndrome of the upper limbs. In two of these there were also sensory and motor signs in the legs. A single necropsy revealed a small fissure in the grey matter in the spinal cord which was interpreted as a syringomyelic cavity (Verhoogen & Vandervelde, 1904).

H.S.R.N. was not alone in being wrongly assigned a cord pathology at this time. Lesions in the cord rather than peripheral nerve were believed to be responsible for neurological signs encountered in alcoholism, diphtheria, diabetes and poisoning with lead and arsenic, (Favey, 1904). Charcot-Marie-Tooth disease was also often not distinguished from progressive spinal muscular atrophy (England & Denny Brown, 1952).

Over the years, numerous writers subscribed to the concept of F.L.S. (Bruns (1903), Clark & Groves (1909), Schulze (1917), Guillaum & Thévenard (1929), Wagner (1932), Thévenard & Coate (1935), Barraquer & De Cisapert (1936), Van Epps & Kerr (1937, 1940), Alajouanine & Mozziconacci (1940), Van Bogaert (1940), Mulvey & Riely (1942), Mueller & Suger (1943, Barré (1945), Jackson (1949), Feudell (1959), Logatchev (1964)).
Some inconclusive evidence has been presented which suggests that F.L.S. may indeed occur. (Barraquer-Ferre & Barraquer-Bordes, (1953)). In 1942, death occurred of an affected member of a Majorcan stock which contained several subjects suffering from trophic lesions complicating dissociated sensory loss in the legs (Barraquer & De Gispert (1936)). At autopsy there was macroscopic evidence of a large cavity in the lumbar expansion of the cord, around which the medullary tissue was reduced to a thin layer. A specimen was taken to the University of Barcelona and left in the Pathological Laboratory there, at a time when the Professorial Chair was vacant and the department apparently disorganised. The specimen was mislaid and so the naked eye appearances were never confirmed histologically.

It may be remarked that while the trait in this family resembled H.E.R.N. in its sensory and seeral trophic syndrome, it differed through the presence of considerable muscular wasting with steppage gait and loss of reflexes, gastro-intestinal disturbances, impotence or loss of sphincter control, impotence, and a relatively short course to a fatal outcome. These clinical features are highly suggestive of familial amyloid neuropathy of the type to be described 16 years later and not far away in Northern Portugal (Andrade (1952)).

Other authors were content to postulate lesser malformations than syringomyelia. To do so they invoked the hypothetical concept of myelodysplasia (Fuchs (1909)), the neural counterpart of spinal dysraphism, which in turn was held to form part of a wider spectrum of midline abnormalities (status dysraphicus). According to this theory, closure of the neural tube, before becoming complete, may have proceeded
imperfectly so as to lead to inclusion within the substance of the cord of "rests" of primitive medullary epithelium. Such rests were then assumed to undergo different degrees of degeneration, either simple gliosis, or necrosis with cavity formation, (syringomyelia), or even neoplastic change (Jackson 1949).

It therefore became possible to assign the clinical features to abnormalities within the cord of lesser degree than syringomyelia, and this solution was adopted by several authors. (Price (1915), Riley (1930), Kienböck (1930), Enderlé (1933), Tocantins & Reimann (1939)).

There is obviously a good deal of overlapping between these two groups, as myelodysplasia was regarded as a spectrum of abnormality of which syringomyelia was the most extreme expression.

Many of the affected subjects described in these two groups of reports presented midline and other abnormalities such as anomalies of the teeth and palate and xiphisternum, funnel chest, asymmetrical breasts, an excess of span over height, syndactyly of the 2nd and 3rd toes, camptodactyly, and anomalies of the spine including kyphosis, scoliosis, and spine bifida occult. These are the stigmata of so-called status dysraphicus, then regarded as the substrate for abnormalities occurring within the spinal cord itself.

The development of the concept of status dysraphicus, its inherent weaknesses, and the confusion caused by associating it with H.S.R.N. and syringomyelia, have been reviewed (Pratt 1967). 17% of normal individuals may exhibit some of its features.
A small group of German authors described families of H.S.R.N. under the title "Trophoneurosis" (Göbell & Runge (1914), Weitz (1921), Beiglbock (1939). This term did not disguise their inclinations towards F.L.S. as the aetiological basis of the disorder, but it indicated some reservations which were based mainly on its hereditary character. Another misleading concept was that of Morvan's Syndrome, which has been reviewed in detail elsewhere (Heller & Robb (1955), Spillane & Wells (1969). This owed its origins to a series of papers written by a French physician of that name between 1883 and 1889, in which he described the occurrence of a classical syringomyelic syndrome, limited to the upper limbs, of a small number of Breton peasants of both sexes. Confusion arose as the result of differences of opinion as to the presence or absence of syringomyelia in the first of these patients to come to autopsy, and the relative contributions of such cavitation (if present), and of peripheral neuropathy in the causation of the sensory and trophic changes in the hands.

Morvan's Syndrome is not genetically determined however, and the dorsal root ganglia are not affected (Pratt 1967).

Its only significance in the present context is that it has been used as a title to describe a number of familial cases in which similar symptoms and signs have occurred in the lower limbs (Gat & Riou (1936), Ogryzio (1946), Fisher (1950), Lessard & Poulriot (1953). By using this eponym these authors avoid committing themselves outright to the concept of F.L.S. but clearly they left their options open.

A minority of authors throughout the years have more
deliberately avoided subscribing to the interrelated concepts of
dysraphism, myelodysplasia and F.L.S.

Thus Hicks (1922), when a House Physician at St. Bartholomew's
Hospital, reported a most significant family in a paper entitled
"Hereditary perforating ulcer of the foot". He prudently settled for
this title because, although he considered that the signs and symptoms
bore "some resemblance to syringomyelia", he could "find no description
of syringomyelia which exactly corresponds with them". He emphasised
that its aetiology could only be determined by post-mortem examination.
14 years later a member of this family died, and at autopsy Greenfield
found neither syringomyelia, myelodysplasia nor dysraphism. Instead
there were degenerative changes in the dorsal root ganglia, the central
parts of their axons in the dorsal roots and their peripheral extensions
in the nerves of the limbs. (Denny Brown (1951), Greenfield (1958).

This family was important for a second reason, because it
showed for the first time, unmistakeable evidence of mendelian dominant
inheritance of H.R.H.N. with manifestation in both sexes. All previous
families had contained the disorder limited to a single sibship, with
the solitary exception of a dominant stock in which only males were
affected (Gobell & Runge (1914).

Other authors, impressed by the striking trophic destruction
of the bones in the feet and toes seen on x-ray, entitled their papers
"Familial Osseous Atrophy" (Smith (1934), Cooper et al (1947),
"Familial Neurogenic Osseous Atrophy" (Ciacca (1951), and "Arthropathies
Mutilantes Symétrique des Extrémités Inférieurs" (Van Bogaert (1940),
and in doing so reverted by almost a century to the terminology of
Nélaton (1852) and his "maladie "des os du pied". It is clear from the
text of these publications however, that these authors also subscribed,
if to varying extents, to the concepts of myelodysplasia and F.L.S.

In 1942 André Thévenard reported three families of N.C.R.N.
and reviewed the literature up to that time (Thévenard (1942)). The
main importance of this report lies in the accompanying discussion in
which the whole hypothetical edifice of F.L.S. and spinal dysraphism
was systematically undermined, even although the writer had no patho-
logical support for his theories.

Thévenard had described two of these families previously under
the title of F.L.S. (Guillain & Thévenard (1929), Thévenard & Coste (1935)).
He had done so, by his own admission, through the influence of earlier
writers, exclusion of other aetiological causes (especially syphilis and
leprosy) and because of the evidence that classical cervico-dorsal
syringomyelia could occasionally present as a familial disease, (although
only Van Sogaert (1934) provided conclusive pathological proof of this).

In a study of the literature of lumbo-sacral syringomyelia
identified at post mortem examination he found that this was never
familial, and only occurred as a complication of some other form of
acquired pathological process (intramedullary tumour, gross congenital
abnormality, or as the caudal extension of a cervico-dorsal cavity).
Furthermore, its clinical features, of which paraplegia and incontinence
were the most common, were extremely variable and almost without
exception totally different from those of the hereditary disorder with
which he was concerned.
Conversely, familial cervico-dorsal syringomyelia, when it made its rare appearance, differed in no particular way to the disease occurring in its usual sporadic form.

Thévenard was equally sceptical about status dysraphicus and its alleged predisposition to malformation of the posterior raphe during embryogenesis of the cord. Not only was pathological proof entirely lacking, but many patients with H.S.R.N. presented none of the stigmata of this syndrome. Of these he thought that the only really relevant one was spina bifida occulta, and he was unable to accept even that this minor abnormality, limited to one or two lumbar vertebrae, was necessarily associated with subjacent cord pathology.

In conclusion he advocated the abandonment of all the old ill-founded preconceptions and proposed the aetologically non-committal, purely descriptive terminology "Acropathie ulcero-mutilante familiale" (A.U.M.F.) until such time as a precise explanation of the disorder could be demonstrated at post mortem examination.

Ironically he was himself deprived of this satisfaction, as the upheavals of the war and the German occupation separated him from his affected patients, at least one of whom died during this time.

Eleven years later he was able to claim that his arguments had been largely accepted (Thévenard 1953). The impact of his earlier paper is reflected in the fact that out of 14 new families reported between 1942 and 1952, no fewer than 9 have been described as examples of A.U.M.F. and only 2 as F.L.S.
Furthermore since 1951 his views have been corroborated by the findings of Denny Brown.

The following sentences extracted from his second report could be looked upon as the epitaph of F.L.S. "Cette maladie en devenant familiale perdait sa topographie .......... et modifiait son tableau clinique". (Thévenard (1953)).

One can only wonder at the amount of effort that would have been conserved, and the hours of speculation, most of it arid and unproductive, avoided, had Greenfield's discoveries at autopsy in 1936 been promptly reported in the medical literature. These findings were in fact discussed at a meeting of the Association of British Neurologists in 1937, but publication was deferred pending a clinical survey of the entire kindred and this was never completed. They were then disclosed to a gathering of allied neurologists which included Van Bogaert in 1940. At long last in 1951 they were eventually published. Meanwhile a member of the stock described by Van Bogaert in 1940 died in 1947, and broadly similar conclusions were drawn from this necropsy. Publication of this report was withheld until Denny Brown's paper appeared, (Van Bogaert (1953)), an act of courtesy which itself caused a delay of 5 years.

In the event both authors were anticipated by another necropsy account which appeared under the title "Familiale Neuro-vasculaire Dystrophie", (Jügheen et al (1949), Wadulla (1949)).

This described a woman who like her father and one sister suffered from distal associated sensory loss in the legs, accompanied
by trophic changes, beginning late in the second decade. Some of the so-called stigmata of status dysraphicus were also present. The patient herself showed acrocyanosis, anomalies of the fingers, teeth and palate, and a curious flat, pallid facies. Her hair was everywhere sparse and her skin contained numerous scattered pigmented naevi. Her father had acrocyanosis, a funnel chest, kyphoscoliosis and camptodactyly.

The propositus presented originally with a spontaneous fracture involving the right leg. Painless indolent ulceration of the feet first arose as a consequence of pressure from a plaster cast. She died subsequently after caesarean section. The post mortem examination ruled out syringomyelia (indeed the central canal was obliterated), but a dysontogenic astiology akin to myelodysplasia, was assumed to account for the abnormalities which were identified (capillary telangiectasia with focal haemorrhages, gliosis, perivascular neuromata and degeneration of the posterior columns).

There were also changes in peripheral nerve in the form of demyelination, Schwann cell proliferation and oblitative changes in the vasa nervorum.

It seems likely that these findings might well have led to resurgence of the old concepts of myelodysplasia set in a background of status dysraphicus had they not been superseded over the space of the next four years by other comprehensive post mortem examinations which led to entirely different conclusions. (Denny Brown (1951), Blackwood (1952), Van Bogaert (1953)).
The history and findings in this case had been presented in some detail because of the close resemblance of the sensory trophic syndrome to that encountered in families with proven H.S.R.N. It seems likely that the most significant lesions of all would have been identified in the dorsal roots and ganglia had these been examined. Indeed it has been suggested that some of the abnormalities described in the report of this case were merely the expression of attempts at regeneration by dorsal root fibres, as similar appearances occur in association with protrusion of intervertebral discs. (Greenfield (1958)).

Nevertheless, the concept of neurovascular dystrophy had some impact for a time, (Jacob et al (1955), Brandt (1956), Van Bogaert (1957)).

Further evidence that the primary lesions occurred in the dorsal root ganglia rather than in the neighbourhood of the median raphe has been provided by later autopsy reports of familial (Campbell & Hoffman (1964), Wallace (1970)), and sporadic cases with similar clinical features (Vignon et al (1956), Geschwind & Segarra (1969), Spillane & Wells (1969)).

Kinships of H.S.R.N. have also been studied electrophysiologically, or with the aid of biopsy techniques more refined than those available to earlier authors (Kuroiwa & Murai (1946), Turkington & Stieffel (1965), Spillane & Wells (1969), Lassmann & Pertach (1970), Dyck & Lambert (1971)).

As a result, H.S.R.N. is now so well documented that it has come to be regarded as the sole explanation of the old concepts of F.L.S., myelodysplasia, familial Norvan's disease and A.U.M.F.
This has led to quite different diseases (in terms of age of onset, type of sensory loss and mode of inheritance), being designated as H.S.R.N. (Heller & Robb (1955), Schoene et al (1970), Dyck et al (1971) and to criticism where this has clearly not been possible (Ogden et al (1959), Greigner (1960), Nadia & Dastur (1960), Passis & Schneeweiss (1960), Spillane & Wells (1961).

Many families reported under the old titles differ from classical H.S.R.N. because the sensory-trophic syndrome is accompanied either by cortico-spinal tract involvement (see Chapter 22) or by pronounced muscle wasting, even flaccid paralysis, as in the "Z" family, (see Chapter 20). These additional physical signs cannot be explained on the basis of Denny Brown's findings.

This is also true of kindreds which combined histories of trophic disturbances with muscular weakness and wasting, and severe gastrointestinal and sphincteric disturbances. These clinical features suggest familial amyloid neuropathy, (see Chapter 22), and raise the possibility that this is one more trait which from time to time in the past has been reported under the old titles.

Furthermore, almost half the families reported under the old names and several reported since, have contained affected members limited to a single sibship, with parents not only apparently unaffected but occasionally consanguinely related. In some of these, symptoms had begun in early childhood and there may be differences in the qualities of sensory and reflex loss. These characteristics indicate traits distinct from H.S.R.N. which are apparently recessively inherited (see Chapter 16).

In fact, as delineated in later sections of this thesis, there are at least ten inherited disorders characterised by distal sensory loss and regularly expressed trophic lesions which can be
differentiated from each other on clinical and genetic grounds, quite apart from those in which trophic lesions may occasionally occur.


The defect of A.U.M.F. as a descriptive term lies in its omission of any reference to its neuropathic basis, which Grainger (1960) attempted to circumvent with her "Sensory Neuropathy with Ulcerating Mutilating Acropathy".

Spillane & Wells (1969) concluded that "a phrase was needed which would describe the hallmarks of the syndrome, irrespective of the aetiology and genetic background of an individual case; acrodystrophic neuropathy seems to meet these requirements and at the same time to leave open the degree of motor and sensory involvement".

Like A.U.M.F. this phrase also recognises the "trophic lesions which are so clamant a part of the syndrome".

It has been adopted as the title of this thesis and the prefix "Heredo-Familial" has been preferred to "Hereditary" because of the letters connotations with dominant inheritance (Fraser Roberts (1970)), since this is clearly not the only mode of transmission which is involved. Heredo-Familial Acrodystrophic Neuropathy (H.F.A.N.) is a generic term permitting the grouping together of the recessively determined cases,
H.S.R.N. itself and those cases in which a sensory and trophic syndrome occurs in combination with other hereditary degenerations of the C.N.S. either as a sporadic occurrence in otherwise typical stocks, or as part of a regularly expressed combined phenotype.

So far as this classification is concerned, the "X" family is presented as an example of a kindred which contains members affected by classical H.S.R.N.

The mutant gene occurring in the "Z" family is by contrast more pleiotrophic and the degree of muscle wasting and flaccid paralysis indicates a trait which cannot be compressed within the narrow confines of classical H.S.R.N. and which, in the absence of pathological data, requires the wider classification.
1. METHOD

The collection of pedigree data in the "X" and "Z" families followed the usual lines, with interviewing and examination radiating from the index cases, through their first degree relatives, to more distant kinsfolk.

This was carried out during 1969 for the "X" family and part of 1970 for the "Z" family. Children below the age of six were not examined in the "X" family, partly because sensory testing is inaccurate in very young children, and partly because the trait is usually not manifested before early adult life. In the "Z" family the arbitrary age of twelve was imposed for the second of these reasons, although some younger children were in fact examined. Details of the ascertainment of the "Z" family are provided in a later part of this thesis.

So far as the "X" family is concerned, 180 of its members were seen, of whom 150 were examined, 2 refused and 28 were below the
Of the 40 members of the kindred who had died prior to 1969, 8 had been known to the writer, of which two (111 13, IV 35) were affected and six unaffected. Of the remaining 32, four (11 1, 11 2, 11 3, 111 17) were stated by their descendants to have been affected, and as three of these had affected children, there seems little reason to doubt this amnestic testimony, particularly as it was corroborated by my still living predecessor, Dr. Ivan Keir, who had been in practice here for over fifty years until his retirement in 1958.

Similar evidence suggested that the remaining 32 were unaffected, although little information was available regarding some childless members of the third and fourth generations, and it is possible that one or two of these may have been affected.

Except in one instance, to be described later, scrutiny of death certificates proved quite unrewarding. This merely confirms the non-lethal character of the trait, and in this context it is of interest that H.S.R.N. did not appear even on the death certificate of
IV 36 in whom its presence had been duly demonstrated at post mortem examination.

It is also likely in times past, that no reference was made to this disorder on death certificates because the doctors concerned were unable to put a name to it, or they may not have been consulted about it. This is in keeping with the conclusions of Bell & Carmichael (1939) who found that death certificates were of little help in the study of rare hereditary disorders. They considered that affected subjects sought help early in the course of the disease, and finding that none could be provided, did not mention it again. Pratt (1967) considers also that there is a "tendency for affected families not to seek advice for the condition when their experience has led them to expect no relief". It seems possible that a form of silent conspiracy may have developed between patient and doctor alike, and that this extended as far as the eventual death certificate.

This is evidently not true nowadays so far as more lethal inherited traits are concerned as Hewer (1966), in a study of fatal cases of Friedreich's ataxia, concluded that this disease had if anything been over-diagnosed on death certificates in recent years.

2. THE INTERVIEW AND EXAMINATION

150 members of the "X" family were available for personal interview and examination. 28 were below the age of six in 1969 and 2 older subjects refused to cooperate, one because he was self-conscious about his generalised psoriasis, while the other was mentally subnormal. The interview and examination of the remaining 150 subjects took the following form. Initially, enquiries were made as to general health,
and in particular as regards the existence at any time of symptoms or signs affecting the limbs. (Ulceration, numbness, paraesthesiae, pains, weakness, unsteadiness or deformity).

Except in the case of affected subjects, neurological examination was restricted to make it acceptable to individuals who were, for the most part, strangers invaded in the privacy of their own homes.

It was limited to examination of cranial nerves, and detailed examination of all four limbs from shoulder and mid-thigh level downward after removal of top clothes, shoes, socks and stockings. The limbs were inspected and palpated for trophic change, wasting, deformity and enlargement of joints.

Power, coordination, tendon jerks, plantar responses and the sensations of pain, hot, cold, light touch, deep pressure, position and vibration sense were all tested, using conventional clinical methods. The gait was observed and the presence or absence of Romberg's sign determined.

One new affected subject was found as a result, $V_{52}$.

The underlining of Arabic numerals in the pedigree of the "$y$" family indicates that the subject so identified was examined personally.

3. **FOLLOW UP.**

Affected subjects were examined at intervals of about a year, but were usually seen much more often than this because they required
treatment. The whole family was reviewed in 1973, with neurological examination of all available first degree relatives of affected subjects, and ascertainment by enquiry of the remainder. Two new affected subjects were identified (V 55, V 56).

During this interval, there had been additions by birth to the 6th generation, and the formation for the same reason of a small 7th generation. These have not been added to the pedigree, which remains numerically as it was since 1969. It has, however, been amended by appropriate changes in relative symbols where the status of existing members has changed either through death or because they have become clinically affected.

4. ORIGIN OF THE "X" FAMILY.

It has been remarked that perusal of death certificates was helpful in only one instance. This was in the case of Elizabeth Butler, née Goddard, I 1, who was certified as dying from "gangrene of the feet and legs" in 1894, at the age of 67. As her three children are all reported as affected, it is clear that either this woman or her husband, Charles Butler, I 2, must have transmitted the trait. (He had predeceased her in 1878 from "pulmonary tuberculosis with haemoptysis").

Ischaemic arterial disease is the commonest cause of acral ulceration and mutilation, at least in temperate zones, and several historical precedents exist in which H.S.R.N. has been diagnosed as gangrene.

Among all these was case 1 of the "R" family (Hicks 1922), who was certified as dying from "gangrene and embolism" in 1874. His children
assured Hicks, that he had suffered from perforating ulcers of the soles of the feet, pains in the limbs and deafness, and had thus exhibited in full the pleiotropic effects of the mutant gene rampant in that family over several generations.

"Gangrene of the feet" was recorded as the cause of death in affected members of other families (Tocantins & Reimann (1939), Mulvey & Riely (1942)), while two members of another kinship underwent amputation of the legs for so-called gangrene, before the neurological basis of the disorder was recognised, (Mueller & Sugar (1943)). Three affected members of the New South Wales stock were also mis-diagnosed as suffering from some form of peripheral arterial disease (Wallace 1970).

An early German account of H.F.A.N. was written under the title "Familiäler Symmetrischer Gangrän Und Arthropathie An Den Füssen", (Bruns (1903)). Ischaemic gangrene was not intended by this title, however, as it had been recognised that the disorder was neurologically determined.

From all these considerations it seems reasonable to infer that Elizabeth Coddard was probably affected by H.S.R.N. and responsible for its introduction into the "X" family.

In fact, there is only one well documented case of true ischaemic gangrene complicating H.S.R.N. and causing death. This was an 84 year old man who had suffered from plantar ulceration for 40 years, with amputation of several toes. Finally he disliked the look of his left little toe to such an extent that he himself cut it off. Subsequently the foot became gangrenous, the left leg was amputated
at mid-thigh, and he died 10 days later". (Campbell & Hoffman, (1964)).

Elizabeth Goddard was a contemporary of Jane Moreing, who lived on the other side of the world in the Goulburn district of New South Wales. The latter is known to have had some form of foot trouble for which she wore old felt slippers, and she was the progenitor of a large kindred of over 400 members containing 42 subjects affected by H.S.R.N. (Wallace (1970)).

It is just possible that these two women were related and that the trait they both bore was of common origin, because Jane Moreing's mother, Hannah Blair, had been born in Salisbury in Wiltshire, just 30 miles from the small town where Elizabeth Goddard lived after her marriage to Charles Butler.
KEY.

Affected male, deceased.

Affected female, living.

Unaffected male, living.

(11) Female, stated to have died from "Gangrene of feet and legs".

(25) Male, living, with signs due to unrelated C.N.S. disorder.

Indicates Propositus.

Underlined arabic numerals indicate subjects who were personally examined.
"X" FAMILY: CLINICAL FEATURES OF PROPOSITUS, IV, 37.

Born 1921.
Maintenance Engineer at Rubber Factory.
Married; 2 children.
Died 1971.

HISTORY

One day in 1947, when he was 26, this man felt some discomfort in his right foot. He found he was unable to take his shoe off, as it was transfixed to the foot by a nail. A scab formed over the wound and persisted for 4 years.

In 1951 he was working on a surface composed of steel plates forming a roof over a trench into which boiling water was discharged. A blister formed on his left foot. This broke open, and at about the same time the scab came off his right sole (see frontispiece).

He now presented bilateral plantar ulceration, with which he was ultimately seen at the Bristol Royal Infirmary by Dr. A.M.G. Campbell, who elicited neurological signs in the legs. Pain and temperature
sensation was lost over the feet and calves and light touch impaired over the feet. Vibration sense, position sense and deep pressure sense were all intact. There was no muscular weakness, nor wasting, and the tendon jerks were present, equal and fairly brisk. The plantar responses were flexor. The Wassermann reaction was negative.

Knowing the patient's father to be similarly affected, and aware of the recent publication of Denny Brown (1951), Dr. Campbell had no hesitation in making a diagnosis of "Hereditary Posterior Ganglionic Degeneration." He commented on the slowly progressive nature of the disorder, and that it had not affected the hands, either in this patient or his father. He contemplated sympathectomy only to reject it as the circulation in the feet was good. Surgical boots with rubber insoles were provided.

During this period in hospital both ulcers became closed in with hard callus, and they remained in this state for several years.

Nevertheless the patient became increasingly aware of the sensory deficit in his legs.

Thus on one occasion after he had been repairing his childrens' shoes he walked round in his stockinged feet and that night found that he was unable to remove one of his socks. It was stuck to his foot by 3 tacks, which were so firmly embedded that he had to use pliers and considerable force to remove them.

At often times he was unaware that he was wearing slippers and would try to put shoes on over them, or find himself in bed still wearing them.
One day he limped all day, and found on removing his shoes that night that there was a glass marble in the heel of one of them, under its insole.

He often unwittingly stood on other peoples' feet, and would not know this until they cried out.

He often put his legs in hot water which was far too hot, jumping out after trying to sit down.

He believed that the degree of sensory loss varied, and that his feet and legs were more "dead" some times than at others.

His general health remained good until 1956 when, during a period of bed rest to help his feet, he acquired left basal consolidation with pleuritic pain, but without fever or haemoptysis. This resolved so slowly, and the appearances at the left hilum were so suspicious that he was subjected to bronchoscopy. Neoplasm was excluded. Thereafter, resolution progressed and became complete.

Soon afterwards he complained of substernal pain but an ECG was normal, and a barium meal negative.

In 1959 and again in 1961, bilateral planter ulceration needed long periods of bed rest to promote healing.

An x-ray of the left foot in May 1961 showed osteolytic destruction confined to the 3rd left metatarsal, (Plate 1). At this time it was noted that his ankle jerks had disappeared.
X-ray of left forefoot, April 1961.

Concentric atrophy of the third metatarsal has progressed to a stage where its head has become severed from its tapering shaft.

Other changes include patchy osteoporosis contrasting with areas of dense calcification and osteophyte formation. Developing sequestra are also visible.
In November 1961 after being laid up at home for ten weeks on account of his feet, he experienced severe pain in the chest and was admitted to hospital. ECG revealed anterior infarction.

Further ulceration in 1962 progressed, until the head of the left metatarsal was exposed. This together with the base of the proximal phalanx of the big toe, was excised for "osteomyelitis". For this operation the patient needed neither anaesthetic, nor post-operative medication.

Relapse rapidly followed this operation and within six months bilateral ulceration was again established.

The radiological appearances in 1963 are reproduced (Plate 2).

From this time until his death open ulceration had been present for almost all the time with the left foot the more troublesome, until 1969 - 1970 when the right foot became the more seriously affected.

Periods of rest have achieved less healing, more slowly, and relapse has followed more rapidly. Mutilation of the foot has progressed particularly on the left side. The appearances in 1966 are illustrated (Plate 3).

At about this time he first became aware of a discrete area above his right internal malleolus, about twice the area of a tenpence piece, where profuse sweating and erythema were evident.

Examination July 1968

The subject was a heavy man, with a splay footed, broad based,
X-ray of left forefoot in February 1963, one year after excision of head of first metatarsal. The head of the second metatarsal and the base of the adjacent phalanx have now disintegrated. Note free lying sequestra.
Appearance of soles in May, 1966.

Note shortening of left foot, and retraction of left hallux, which have developed since the operation in 1962.
somewhat stamping gait. The appearances of the feet at this time are shown (Plates 4 and 5).

They show an open ulcer on the left sole, dense callus on the right and twisting and distortion of most of the toes. The extensor tendons appear shortened and thickened.

Shortening of the inner margin of the left foot was conspicuous. Thus the distance from the tip of the left big toe to the base of the heel was 7 cm. shorter than the corresponding dimension of the right foot, and 2 cm. less than the length of the outer margin of the left foot (from the tip of the little toe to the back of the heel).

On neurological examination there was no weakness nor wasting, and the tendon jerks were all preserved except for the ankle jerks which were lost. The plantar responses were unobtainable. There was no ataxia. There was no palpable thickening of accessiblenerve trunks.

Pain and temperature sense were lost in both legs distal to the right knee and left mid-thigh and in both upper limbs distal to the right wrist and left mid-forearm. In addition, up to the waist and the shoulders encroaching on the chest, there was inconsistent recognition of painful stimuli, some of which were interpreted as touch or pressure.

Light touch was lost from both mid-calves downwards and over the palmar aspect of the fingers.

Vibration sense was diminished at the ankles where deep pressure sense was reduced. Position sense, even in the toes, was unaffected.
PLATE 4

Planter aspect of feet in July, 1968, showing further shortening of left foot and trophic changes in soles and nails.
Both feet were warm and moist with full pulses.

General physical examination revealed no abnormalities.

B/P 160/90.

X-rays of the left foot in 1963 (Plate 6) showed remarkably little deterioration since 1963. The right foot was now more seriously affected (Plate 7) although it is noteworthy, in view of future events, that the first metatarsal and the phalanges of the big toe remained intact.

X-rays of the left tibia and fibula (Plate 8) showed an osteoporotic area near the lower articular surface of the latter and some irregular periosteal reaction of the shafts of these bones.

Subsequent Progress

He did not work throughout most of 1969 because of the large ulcer of the left sole. Incongruously, during this period of rest, the ulcer on the right foot re-opened. He was, therefore, advised to rest up completely.

In November 1969, however, during this period of bed rest, he sustained a second major myocardial infarct, and was admitted to hospital in profound shock. ECG on this occasion showed posterior location of this infarct. He progressed well and went home after a month, with his plantar ulcers unchanged.

Examination during this period of convalescence indicated some proximal extension of sensory loss.

There has been little deterioration since 1963.
The third metatarsal is again the most severely affected.
Note robust and healthy appearance of first metatarsal.
X-rays of left tibia and fibula in July, 1968, showing coarse periosteal reaction.
As he resumed activity he became breathless and experienced angina. Bilateral basal crepitations were present. An ECG now showed left bundle branch block. Frusemide was administered, basal lung congestion eliminated and his breathing improved. He never worked again, however. Resumption of activity was also immediately harmful to his feet.

Both ulcers enlarged and the right first and second toes became inflamed and doubled in size. (Plate 9).

X-ray of the right foot in February 1970 (Plate 10) showed that the head of the first metatarsal had disintegrated. Some surgical emphysema is also visible.

During the next three months numerous pieces of bone were extruded from the right foot through the ulcer. A dozen of these were quite large (Plate 11).

Following this process the inflammation and gross swelling of the first and second toes subsided, although the ulcer remained unchanged (Plate 12).

X-ray in June 1970 (Plate 13) showed that the head of the right first metatarsal, together with the distal half of the second metatarsal, and the bases of the proximal phalanges of the first and second toes had disappeared. Clearly after disintegration these had been expelled as sequestra.

Throughout the second half of 1970, and until his death in August 1971, his general condition remained much the same with exertion
Appearance of right sole in February, 1970, showing extensive ulceration and swelling of toes, particularly the big toe.
X-ray of right foot in February, 1970, taken at the same time as Plate 9. The main change from Plate 7 affects the head of the first metatarsal which has disintegrated.
Photograph of some of the sequestra extruded from right foot during the spring of 1970. (Scale in inches).
IV 37. Plantar aspects in May 1970, following extrusion of sequestra from right foot. Swelling of the toes has diminished, and the ulcer is less extensive.
X-ray of right forefoot in June 1970. The head of the first metatarsal and base of corresponding proximal phalanx have been extruded as sequestra.
(Compare plates 10 and 11).
inducing angina more easily than breathlessness.

Occasional sequestra were dislodged from the right foot, where the ulcer extended slowly laterally. As the skeletal structure of the forefoot had virtually disappeared, the toes now remained attached to the foot by the thickness of soft tissues only. Surprisingly he remained able to flex and extend his toes. The appearance of the feet in July 1971 is shown (Plate 14).

On 21st August he began to experience further substernal pain at rest. This was severe but not persistent, about 20 attacks occurring over the next five days. He was eventually admitted to hospital with pain which was both more severe and more prolonged. Increasing left ventricular failure supervened with rapid, bubbly respirations. E.C.G.s showed left bundle branch block, and ventricular extrasystoles.

On 27th August he became moribund and was thought to have ventricular fibrillation. Defibrillation was effective for a short time, but the patient slowly became weaker, more breathless and more confused, dying on 28th August.

Investigations.

This man underwent numerous investigations throughout his life, apart from x-rays and E.C.G.s reported in the foregoing text. Many of these were only relevant to intercurrent illnesses or to the bacteriological status of his ulcers prevailing at that particular time, and these are not, therefore, reproduced here.

The following are the results of biochemical investigations.
Appearances of feet in July 1971, one month before death, showing extensive bilateral ulceration and shortening of both feet.
during the last two months of his life.

Haemoglobin 13.2 g/100ml. P.C.V. 44%. R.B.C. 5.0 million/cu.mm.
M.C.V. 91 c. J. M.C.H. 28 μg. M.C.H.C. 30%. W.B.C. 7500 (70% neutrophil polymorphs, 30% lymphocytes), slight anisocytosis. Blood urea 24 mg/100ml. Fasting blood glucose 76mg/100ml. Sodium 139 mEq/litre.
Potassium 5.3 mEq/litre. Chloride 96 mEq/litre. CO₂ content 25 mEq/litre. Protein 7.6 g/100ml (albumin 4.3, globulin 3.3). Electrophoretic pattern showed increased gamma and alpha 2 globulins.
Calcium 9.8 mg/100ml. Phosphate 4.9 mg/100ml. Alkaline phosphatase 10 units/100ml. Acid phosphatase 2.5 units/100ml. Vitamin B₁₂ 392 pg/ml. Serum aspartate aminotransferase (S.G.O.T.) 11 i.u/litre.
Lactic dehydrogenase 220 i.u/litre. Creatine phosphokinase 0.25 μmoles/ml/hr.

E.M.G. (Dr. Graham Wakefield, June 1971).

No electrical activity could be demonstrated below the knees.
In the right arm there was no recognisable loss of motor activity in the anterior pollicis brevis.

Motor nerve conduction velocity in the right median nerve was 40 metres/second.

No sensory action potentials could be obtained at the wrists on stimulating the right median and ulnar nerves at the fingers.

Post Mortem Examination.

This confirmed myocardial infarction as the cause of death.
The left ventricle was dilated, and its wall extensively and diffusely
replaced by scar tissue. Surviving muscle was discoloured by recent infarction. There was a recent thrombus in the right coronary artery, and old disease of the other coronary vessels.

Neuropathological examination was carried out by Dr. Betty Brownell at Frenchay Hospital, who reported as follows:

"Weight of brain 1,220 grams.

Hindbrain 275 grams.

External appearance.

At the vertex, the leptomeninges and pial veins show moderate congestion, and both hemispheres appear somewhat swollen. At the base, the vessels of the Circle of Willis are healthy on the whole, with no significant atheromatous change. The cranial nerves look normal and there are no internal hernias.

Cerebral slices.

These show a symmetrical cerebrum with moderately severe swelling of both hemispheres causing compression of the ventricular system. There is severe vascular congestion throughout, affecting the grey matter particularly, and there is at least one area of recent haemorrhagic infarction involving perietal cortex and immediately underlying white matter in the region of the Rolando sulcus. This lesion, which would appear to be about 24 hours or so old, is not a territorial infarct, but is suggestive either of embolic occlusion or of a watershed infarct. There is no evidence of any older vascular lesions in the cerebrum.

Brainstem and cerebellum.

These look normal to the naked eye.
Spinal cord.

The dura is normal, and the leptomeninges also look normal apart from some vascular congestion. The spinal nerve roots in the cervical region appear normal, but in the lumbosacral enlargement the roots appear rather thinner and browner than normal, and this applies to both anterior and posterior roots. Transverse cuts across the cord at various levels show vascular congestion of the grey matter, but otherwise no naked eye lesions.

Histology.

The following sections have been taken:
Right parietal lobe
Left cerebellar hemisphere
Midbrain, pons, medulla (2 levels)
Spinal cord at C4, C6, C8, T3, T9, L2, L3, L4 and sacral levels.
Lumbar anterior spinal nerve root.
Lumbar posterior spinal nerve root.

The softening in the right parietal lobe shows the typical changes of acute infarction. No occluded vessels are seen.

In the cerebellum, several areas of acute cortical infarction are present, probably the same age as the lesion in the cerebrum.

The midbrain, pons and medulla show no significant microscopical changes.

In the spinal cord loss of myelinated fibres is seen in the posterior nerve roots (Plates 37 - 41). The finding is present at all levels, but is much more severe in the lumbosacral levels, than
at cervical and thoracic levels. Degeneration is also present in the posterior columns of the spinal cord, and this is also more severe in the lumbar cord; the spinothalamic tract is more severely affected than is the cuneate. The anterior nerve roots appear normal, and the anterolateral white matter of the cord is also normal.

**Conclusion:**

1) Cerebral infarction.

2) Hereditary sensory radicular neuropathy.
CHAPTER 5

"X" FAMILY: CLINICAL FEATURES OF OTHER MEMBERS

1.1 Elizabeth B

Born 1827, Died 1894, age 67.
Certified Cause of Death: "Gangrene of Feet and Legs".

1.2 Charles B

Born 1826, Died 1878.
Certified Cause of Death: "Phthisis with Haemoptysis".

11.1 Mary E-C

Reported Affected

Born in 1840, she died in 1923 from "Interstitial Nephritis, Bronchitis and Heart Failure".
She is described as always having worn a slipper on one foot "cut all to pieces", but would not disclose why, and would not expose her foot to anyone.
Her nephew, 11.1.13, propositus of Campbell & Hoffman (1964) reported her as definitely affected, and his testimony was accepted by these authors.

11.2 Richard B

Reported Affected

Born in 1856, this man was regarded as affected by his nephew 11.1.13,
and therefore by Campbell & Hoffman (1964).

He committed suicide by drowning on 25th August 1917, because he was de-
pressed as the result of ill health. His sight was failing and he awaited cataract extraction. No abnormality of the feet was mentioned at the
inquest.

11 3 Elizabeth C  
Reported Affected

Born in 1855, this woman died in 1903 from "Gastric Ulcer 10 days, 
Apoplexy 2 days". She was the mother of 111 13 and grandmother of 
IV 37, so that their statements that she was affected can be accepted 
with some confidence.

111 1, 111 3, 111 6, 111 5, 111 6, 111 8.  
Reported Unaffected

Born between 1872 and 1882, these subjects died between 1913 and 1947. 
Not all their death certificates could be traced, but from available 
accounts they were free from lesions of their feet.

111 2 Frederick E  
Unaffected

Known to me for the last ten years of his life, this man was certainly 
unaffected. He died from Cerebral Infarction. He had total heart block 
for five years.

111 7 Sarah B  
Reported Affected

There are no medical records relating to this woman, who avoided doctors. 
Her surviving children (IV 27, IV 28, IV 29) are unanimous in assuming 
that she had severe mutilation of the feet.

This began with planter ulceration ("holes in the feet") which first made
their appearance during her fourth pregnancy. This progressed until, in later years, "she had no feet at all". She could scarcely walk, but cycled more easily. She spent most of her time lying on a couch. She was certified as dying of "Cerebral Thrombosis and Otitis Media" in 1947 at the age of 60.

Reported Unaffected

Born between 1879 and 1891, none of these 4 sibs survived beyond 1945. From the accounts of their relatives they were unaffected.

Ernest C
Born in 1882. Killed in action in 1915. It is not known if his feet were affected at the time of his death, but according to his wife they had appeared normal the previous year. He was the father of an affected son (IV 32).

Unaffected

Elsie C
Born 1873. This lady is the only survivor of this generation. There were no signs on examination in September 1968, nor subsequently on enquiry.

Affected

Oliver C
Born 1889. Died 1960. This man was the oldest affected member of the kindred concerning whom detailed medical records exist. He was also the first in whose case a formal diagnosis of H.S.R.H. was made. He was under my care during the last six years of his life. Plate 15 illustrates the state of his feet at the time of his death. No x-ray films survive.
Ulceration of the left foot began in 1918, when he was 29. His left big toe was amputated in 1923. In 1927 a sequestrum was removed from an ulcer of the right sole, at which time his W.R. was negative. In 1930 bilateral perifemoral sympathectomy was performed in Bristol. His urine did not contain sugar at that time.

By 1943 the soles of both feet were deeply perforated. His W.R. was again negative and the knee and ankle jerks were present. However, as "his pupils did not react" he was given some potassium iodide, and two injections of an organic arsenical compound.

Ulceration of the feet continued and now became complicated by bouts of secondary infection. Fever, swelling of the legs and enlargement and tenderness of the inguinal lymph glands occurred. Chiefly because of such episodes, he was admitted to the local hospital on seventeen occasions between 1930 and 1950. These periods in hospital during this time aggregated 50 weeks.

In 1950 he was referred to the surgical Professorial Unit at Bristol. By this time both feet were shortened, mutilated and deeply ulcerated. There was wholesale destruction of phalanges and metatarsals. The first diagnosis to be entertained was that of chronic cutaneous fungus infection, with secondary infection causing osteomyelitis. This could not be confirmed, and soon afterwards he was referred for a neurological opinion.

Examination by Dr. A.M.G. Campbell in 1952 revealed peripheral loss to pain and temperature in the legs and hands, and the ankle jerks were very sluggish. Dr. Campbell elicited the family history and diagnosed H.C.R.W. Later the same year arterial haemorrhage occurred from the ulcer of the right sole and was controlled with difficulty.

From 1954 onwards his general health failed and other symptoms overshadowed the condition of his feet, although these remained troublesome.
He became increasingly wheezy and cyanosed. He was so breathless that a strangulated right inguinal hernia was repaired under local anaesthesia in 1957.

In 1959 he developed severe epigastric pains, and a barium meal demonstrated a large ulcer of the lesser curve. Twice during 1960 he required admission to hospital in Bath with haematemesis and melena. On neither occasion was he fit for surgery. On the second occasion bleeding persisted and he died on 30th November 1960, despite repeated transfusions.

A general post mortem was carried out by Dr. R.B. Bston. The findings were "Haematemesis, chronic benign gastric ulceration, recent coronary thrombosis and pulmonary embolism, besides the evidence of familial neuropathy involving the feet and leading to disappearance of much of the foreparts of both".

The brain and cord were removed by a technician and sent to the late Dr. A.P. Normen at Frenchay Hospital for histological examination. Regrettably the material received by Dr. Normen did not contain a single dorsal root ganglion. For this reason he did not draw any definite conclusions, but reported as follows:-

"The Brain weighed 1300g, of which the cerebellum and brain stem accounted for 157g. The external appearances were normal and the blood vessels were free from atheromatous change. Celloidin and frozen representative sections were prepared from the cerebral hemispheres, basal ganglia, cerebellum, brain stem, spinal cord and peripheral nerve and were stained by standard methods for nerve cells, axis cylinders, myelin, fibrous neuroglia and lipid. In the central nervous system abnormalities were confined to the spinal cord. There was a slight diffuse loss of myelinated axons throughout
State of feet shortly before death.
the fasciculus gracilis, most marked in the lumbosacral region, but clearly visible in the cervical region. Lissauer's tract was affected, but there was no special involvement of Flechsig's posterior root zone. The ocommissural zone had not escaped but was slightly better preserved.

In the lower part of the cord there was also a well-marked pallor of myelin in the peripheral part of the antero-lateral white matter. In the more affected segments the posterior roots showed some loss of axons associated with connective tissue overgrowth. The anterior roots and horn cells were normal. The posterior root ganglia were not available for examination.

The posterior tibial nerve was severely atrophied and contained only a few isolated nerve fibres.

\[TW\] 1 - 24. 

All unaffected

10 of these 24 members of four sibships had died prior to the commencement of this investigation and are so represented in the Pedigree. Of these 10, three (\[TW\] 4, \[TW\] 8, \[TW\] 13) were patients of the writer and were certainly unaffected. The others were unaffected on enquiry.

Two others (\[TW\] 23, \[TW\] 24) had left the district and nothing was known about them. They may or may not have had children.

The remaining 13 subjects were examined and presented no evidence of involvement.

\[TW\] 25 Henry J.B. 

Affected


Occupation - Foundry worker.

In March 1928, when he was 22, this man was involved in a motor-cycle accident, following which his right big toe became red and swollen, and
subsequently ulcerated. 6 months later the ulcer was still active and the toe was x-rayed. This revealed necrosis in the proximal phalanx and erosion of the M.P. joint.

Necrotic bone fragments were removed on 3-4 occasions thereafter, and after a year the ulcer appeared to have healed.

One year later it recurred, and in November 1930 this toe was amputated. In 1931 a perforating ulcer appeared on the heel of the right foot. This never healed and troubled him for the rest of his life.

By 1951 both feet were ulcerated, mutilated and shortened. Secondary infection often occurred for which antibiotics were given, but for most of the time he attended to his feet himself.

A nephew (V 47) paints a gruesome picture of visiting his uncle to find him at the end of a day's work, extracting fragments of bone from his ulcers with a steel knitting needle. V 47 was impressed by the evident painlessness of this proceeding. X-rays of the feet in 1955 (Plate 16) showed on the right side, virtual disappearance of the bone framework of the toes, (although the latter survived as attenuated soft tissue appendages). Phalangeal remnants, metatarsals and tarsal bones distal to talus were fused together in solid masses, demarcated from each other by greatly narrowed, but still recognisable, metatarsophalangeal and tarsometatarsal joint spaces.

These was less destruction on the left side where concentric atrophy of metatarsals was the most conspicuous abnormality. Also visible on this side was a linear opacity embedded in the tarsus. This is probably the broken off point of a knitting needle. When further x-rays were taken in 1961 (Plate 17) there was little change in the left foot. In the right foot, however, tarsal, metatarsal and phalangeal bones had become fused into a single mass of bone, and the joint spaces by this time had disappeared.
X-rays of feet in September 1955, showing gross destruction affecting metatarsals and phalanges. These bones are fused into a solid mass on the right side, but the tarso-metatarsal and metatarso-phalangeal joint spaces can still be discerned.
X-ray of right foot in May 1961, showing further fusion of bone remnants and obliteration of T-M and M-P joint spaces.
Lateral views in 1961 (Plate 18) illustrated these trophic changes still further and showed posterior dislocation of the os callois at the right ankle and a probable similar disturbance beginning on the left. The x-rays taken in 1961 were obtained during a period when he was an in-patient in hospital. At this time it was stated that various toes were missing on both feet. He had a large sloughing purulent ulcer on the right sole and a smaller one on the left. The former contained sequestrating bone, and was surrounded by erythema. Both heels appeared to be elongated. Neurologically there was loss of pain sensation distal to the right mid-calf and over the foot. Temperature sensation was impaired over both feet but appeared normal on the legs. Touch sensation was preserved. Vibration sense was impaired at the right ankle. Only the ankle jerks were sluggish, all the other deep reflexes remaining brisk. There was no sensory loss nor other abnormality in the arms.

General physical examination was normal except for albuminuria, blood pressure 120/80, Hb. 68%, R.S.B. 104. Blood Wassermann and Kahn reactions were negative. A heavy growth of coagulase positive staphylococci was obtained on culture from the ulcers. Treatment with bed rest, Penicillin, Streptomycin and Eusol soaks led to progressive healing of the ulcers. This was well advanced by the time the patient took his own discharge after 5 weeks in hospital.

Thereafter he remained well for a time but within a year the familiar pattern of ulceration, mutilation, cellulitis and inguinal adenitis was again established. Such episodes responded to bed rest and antibiotics. This state of affairs persisted until 1964 at which time he must have decided that there was little point in seeking further medical aid.

Between 1964 and 1967 he made no further application to his doctor. In April 1967, however, he attended complaining of lassitude. His B.P. was now found to be 270/110 and there was heavy albuminuria. He was
Lateral x-rays of feet and ankles in May 1961, showing gross neuropathic destruction of bone and right ankle joint. The right os calcis is displaced backwards and upwards.

Note broken-off end of steel knitting needle (used by the patient to probe his ulcers) embedded in left foot.
anaemic, (Hb 60%) and ureemic (urea 150 mg%. A diagnosis of chronic nephritis was made and he was admitted to the local hospital.

He improved a little and was allowed home after four weeks, but finally died in uremic (urea 350 mg%) in September 1967.

No records exist regarding his neurological state at the end of his life, and autopsy was not performed.

IV 26 Olive B

Born in 1915, this girl died of pneumonia in 1922 at the age of 7 with an affected mother and 3 affected sibs. She may have inherited the mutant gene, but died long before the age of its manifestation.

IV 27 Grace H

This woman was examined in October 1969 and again in 1973. No neurological abnormality other than left external strabismus was found on either occasion. She was moderately hypertensive (S.P. 170/100).

IV 28 Ivan B

Affected

Born 1921. Foundry worker.

In 1947 when he was 26, when in a bath he discovered an ulcer on the sole of his left big toe. Hard callus formed over it. Later this came off and he tested it in a vice at work, finding it to be "harder than steel". The callus reformed, and reluctantly he agreed to enter hospital for surgery in 1966. He was in hospital for 2 days, during which the lesion, diagnosed as a "pigmented horny outgrowth" was excised. He did not
volunteer his family history and was not examined neurologically.
The surgical wound took 4 months to heal.
Prior to this in 1964, he had been found to be hypertensive (B.P. 240/150).
This presented with profuse epistaxis. Retinal changes and cardiac enlargement were identified, but there was no albuminuria. In the ECG the T waves in leads V4 and V5 were conspicuously inverted.
Since then his blood pressure has been well controlled medically.
He was examined annually in 1969, 1970, 1971 and 1972 and on each occasion there was dense hyperkeratosis over the plantar aspect of the left big toe (Plate 19). This was perforated by a central sinus from which purulent fluid could be expressed. Neurological examination in 1969 showed impairment of pain sensation in both soles, the dorsal aspects of both feet and the distal third of the left leg. Temperature sense was impaired over both soles and the lateral aspects of both feet. Light touch, vibration, position and deep pressure sense were intact. There has been no sign of muscle wasting and the tendon jerks were all brisk and equal. There were no abnormalities in the hands.
Some right lower facial weakness was present, apparently dating from a skull fracture sustained in 1956. X-ray of the left big toe in 1970 (Plate 20) shows early evidence of trophic involvement of the distal phalanx of the left big toe, represented by three small round translucencies in the substance of this bone, with more diffuse changes in the head of the proximal phalanx.
By 1972 the area of loss of pain sensation had extended proximally to the knees. Light touch was now lost distally on the soles, and over the plantar and lateral aspects of the toes. Thermal perception was lost over the same area as light touch with partial impairment up to the right knee and left mid-calf.
The external appearance of the trophic lesion however was unaltered.
Hyperkeratotic plaque of left hallux with sinus formation.

September, 1970.
X-ray of left big toe and first metatarsal in September 1970.
Translucent vacuoles are visible in the distal phalanx with more diffuse changes in the head of the proximal phalanx.
and there was no progression in the radiological appearances. The upper limbs remain unaffected.

**IV 29**  
Cynthia G.  
Affected

Born 1922. Housewife and part-time rubber worker.

In 1956 when she was 34, a hard irregular corn appeared on the under surface of the left big toe. Thereafter, from time to time this sloughed off, leaving either a briefly healed area or a small ulcer. The corn grew again quickly after each such occasion.

From about the same time she noticed that she did not feel pain in her feet. She has often walked home unaware of a stone in her shoe.

In 1963 the hyperkeratotic area became secondarily infected and an ulcer formed.

The toe itself was hot, red and swollen but quite painless. She was treated with bed rest and Penicillin injections. An x-ray showed destructive change in the proximal phalanx. An orthopaedic surgeon offered to amputate the toe but this she declined. Soon after a piece of bone was expelled through the ulcer, after which it healed.

Since 1968 she has experienced paresthesiae and some numbness in the fingers and hands. She has no difficulty in picking up small objects, nor in performing fine movements.

Ulceration of the left big toe recurred in 1969. It became inflamed again. This attack was less severe than that of 1963 but there was some discomfort and resolution was slow, with dressings and rest.

Examination in September 1969 showed an area of pale, soft, friable tissue, almost 3 square centimetres in area, occupying the ball of the left big toe (Plate 21) from which thin pus oozed. The whole toe was shrunken compared to its fellow (Plate 22), it was about 2 cm shorter,
Trophic lesion at base of shortened left hallux.

September 1969.
The left big toe is shortened and displaced. 

Note beads of sweat on its dorsal surface. 

September, 1969.
more pliable, the skin overlying it was puckered and sweated profusely. X-ray of the toe (Plate 23) showed gross shortening and deformity of the proximal phalanx with lesser changes near the base of the distal phalanx.

Neurological examination revealed loss of pain sensation in both feet, the distal two-thirds of the left leg, distal one-third of the right leg and all fingers of both hands. Thermal sensory loss was less extensive, being impaired only over the toes and distal third of the left foot, and over the right 1st and 2nd toes. Other sensory modalities were unaffected and there was no muscular weakness nor reflex change.

Re-examination in 1971, 1972 and 1973 indicated little or no progression in her neurological status, although infection in the soft tissue lesion has been troublesome on two occasions.

*1W 30  Roland C  Unaffected*

Born 1907.

This man presented no sign of neuropathy in 1968. He underwent partial gastrectomy in March 1960 for duodenal ulcer with pyloric stenosis, initially suspected as being carcinoma of stomach. He also suffers from recurrent cystitis for which no underlying cause has been demonstrated. He remains neurologically unaffected.
X-ray of left hallux, September 1969, showing shortening and deformity of proximal phalanx.
This woman showed no evidence of neuropathy in 1969. She was slightly deaf as the result of a large left-sided perforation, accompanied by deficient mastoid air cell development. From 1962 to 1966 she was treated intermittently with Carbimazole for a toxic thyroid adenoma and she came to subtotal thyroidectomy in February 1966, after which she complained of paraesthesias and cramps in all four limbs. This was associated with carpal pedal spasm and a positive Chvostek's and Trousseau's sign. She took oral calcium for two months, since when these symptoms and signs have not recurred. She was moderately hypertensive, (B.P. 190/100).

In December 1951, when he was 39, this man was referred to an orthopaedic surgeon with left hallux valgus, complicated by an infected bunion, and hammer deformity of the second toe. At that time it was noted that the soles of his feet were unduly calloused, and he admitted that this was of many years standing.

Later the same month the tip of the big toe became septic, and as ischaemic change was suspected, the intention to perform Keller's operation was abandoned.

In 1952 he experienced an episode of chest pain of two hours duration, accompanied by trembling and a rapid pulse. An ECG was not performed.

In 1954 both big toes became ulcerated and the inguinal glands on the right side were enlarged and tender. He also experienced abdominal pain and vomiting. He was treated with Penicillin injections with improvement.
Later in the year he was admitted to hospital. Despite the known family history his ulcers were ascribed to ischaemic changes, although his peripheral pulses were normal. He underwent bilateral lumbar sympathectomy. His urine, blood count, Wassermann and Kahn reactions were all normal.

In October 1955 he was referred to a neurologist who noted impairment of pinprick perception below the right knee and loss of light touch over both feet. His reflexes were present, brisk and equal. B.P. 190/120. Since 1954 the illness has pursued an indolent course. Excessive callus has formed continually on both soles. This has been kept pared down to a thin layer.

Beneath these hyperkeratotic plaques, ulceration has occurred with sinus formation, sloughing and infection, necessitating frequent dressings, courses of antibiotics and periods of absolute bed rest in hospital.

As time has passed, bed rest has been progressively slower in inducing healing.

Thus in July 1955 he was in hospital for only 9 days, but needed 12 days in February 1956 and 19 days in May 1960. From October 1964 he required 45 days and 43 days at the end of 1966. At the beginning of 1971 he was in hospital for 74 days.

In May 1960, hyperkeratotic tissue was radically excised from the right foot under general anaesthesia. This exposed the metatarsophalangeal joint of the third toe.

A Symes amputation of the right foot was contemplated, but postponed. Instead he was provided with surgical boots and an invalid car.

From 1964 onwards he has been troubled by chronic suppurative otitis media, with massive destruction of the drumhead on the left side.

In December 1969 he was referred to a physician with hypertension and
shortness of breath on exertion. ECG showed high voltage in all leads with ischaemic changes affecting the left ventricle.

In 1970 ulceration of the feet extended to involve the left heel.

In 1971, on separate occasions in January, May and August, sequestra have been extruded from an ulcer of the left forefoot. This has been accompanied by progressive shortening of the left foot between 1970 and 1973 which is well illustrated by a comparison of Plates 25 and 26.

Such episodes have always been painful. The pain has been of a squeezing or bursting character, subsiding rapidly after the bone fragments have been expelled.

There has been no measurable progression in neurological signs elicited at various times in 1968 and 1973. Surprisingly the areas of sensory loss have appeared to fluctuate and have been less extensive on some occasions than others.

His hands and feet are disproportionately small. The feet present a shrivelled atrophic appearance, seeming both shortened and narrowed (Plate 24). His toes are twisted and displaced. Dense hyperkeratosis involves most of the area of the balls of both feet and the left heel with visible sinuses at all three situations. (Plates 25 and 26).

The musculature of the hands and feet, and distal thirds of the legs (Plate 27) shows some wasting. There is no weakness.

The only neurological sign to progress has been impairment of the ankle jerks which, by 1973, had almost disappeared. All deep reflexes otherwise remain brisk.

The plantar responses have been unobtainable since the first examination in 1968.

Sensory examination has shown impaired pain and temperature sensation extending up to the knees and over all fingers. Light touch has been lost over both soles and the foreparts of the dorsum of the left foot.
Dorsal aspects of feet in September, 1970.
Soles of feet in September 1970, showing trophic changes. The right hallux is dorsiflexed and displaced laterally behind the 2nd and 3rd toes, and the left 2nd toe is also retracted and out of sight.
Appearance of legs and feet in May 1973, showing distal amyotrophy and foot deformities.
X-ray of left forefoot in September 1970, showing distal concentric metatarsal atrophy, and displacement and deformity of phalanges.
Kinesthetic sensation remains intact.
During periods of secondary infection, sensitivity to pain, both pin-prick and deep pressure, appear to have been temporarily enhanced, in the areas in which they were normally impaired.

Investigations.
X-ray changes are more marked in the left foot (Plate 28).
E.M.G. examination was refused.
Serological tests for syphilis were negative in 1954.
The urine has never contained albumin, glucose or excess porphyrin.
The following blood tests have also been within normal limits:

- Blood count
- Fasting glucose
- Total serum proteins
  - Albumin
  - Globulin
  - Bilirubin
  - S.G.P.T.
  - L.D.H.
- Alkaline phosphatase
- Creatine phosphokinase
- Cholesterol
- Total blood lipids
- Alpha and Beta lipoproteins

Arthur C

Born in 1911, this man left home when he was 20 and afterwards was only in desultory contact with his relatives. It is believed that he may have been killed in 1942 when serving in the Royal Navy.
34. **Gladys C.**

**Unaffected**

Born 1907.

This woman presented no evidence of neuropathy or other C.N.S. abnormality when examined in 1969, and has subsequently remained well. B.P. 170/100.

35. **Herbert C.**

**Affected**


In 1933, this man's left foot was transfixed by a nail. The ensuing lesion healed slowly and then broke down spontaneously. Thereafter it healed again and he was free of trouble for 5 years.

In 1938 iron pipes fell on to his left foot and after this, further ulceration of the left sole occurred. This healed sufficiently for him to be accepted for military service in 1939.

Ulceration quickly returned during his period of military training, and he was invalided out of the service after only three months.

During the following 2 years he underwent three operations for removal of sequestra from the left hallux. This left him with a sinus which discharged every few months.

An x-ray of the left big toe in March 1941 is reported as showing disappearance of the middle phalanx and deformity of the head of the 1st metatarsal, with some loose fragments of bone in its vicinity.

He declined amputation at this stage.

In 1945, the 1st metatarsal was visible in the floor of a large perforating ulcer of the left sole. The edge of this ulcer was excised together with the head of the 1st metatarsal.

X-ray now showed involvement of the 3rd and 4th metatarsals and...
and proximal phalanges.
In June 1949 there was no improvement and so he underwent below knee amputation of the left leg.
Following this he had no further trophic lesions other than a transient ulcer of the amputation stump in 1956 and apparently involvement of the right foot a month before his death in 1958.
In 1951 he began to experience spontaneous pain in his hands. The pain varied in intensity and when severe he likened it to having salt rubbed into a wound. At other times there was a stinging sensation in both hands. These pains were accompanied by subjective impairment of sensation in his hands of brief duration.
His hands also sweated profusely and propitiously at various times, and when this occurred the pain appeared to be relieved. When the hands were dry the pain often seemed more severe.
There were no pains in the legs.
In 1953 he was admitted to hospital in Bath for investigation of these upper limb pains. No objective signs were elicited in the arms, but pain and temperature perception were demonstrably deficient below the knees. Both knee jerks and the right ankle jerk were sluggish. Routine examination of urine, blood, C.P.F. and x-rays of the chest and cervical spine were all unrewarding.
From 1954 onwards he complained increasingly of angina of effort and in 1958 he collapsed and died during a severe attack.
Autopsy was not performed.

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<td>36 Oliver Frederick O.</td>
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This man stated that since the age of 7, the soles of his feet were always
calloused, and that for most of his life his left leg had felt numb from the thigh downwards. Both feet were often tender and hot, and because of this he never walked barefoot, even indoors. For the same reason he always wore sponge rubber insoles.

In 1939, when he was 17, he contracted rheumatic fever. Following recovery from the acute illness, it was noted that he had a systolic murmur. In 1950 he first complained of dyspepsia, and barium meals in 1954 and 1968 confirmed the presence of duodenal ulceration.

In 1939, on waking one morning, he stretched his arms prodigiously, and some of the transverse creases of both palms and fingers split open. This was attributed to "industrial hyperkeratosis". (He was making gas masks at the time.) The fissures became infected and healing was slow.

In March 1961 he was examined neurologically by the late Dr. Lovell Hoffman. Exuberant plantar hyperkeratosis was noted, and the toes of the right foot were thought to be hyper-extensible. There were no other c.n.s. signs. In particular there was no demonstrable sensory loss and the reflexes, including the ankle jerks, were present, brisk and equal, with flexor plantar responses.

It was considered that he had dealt with his tendency to the family disease very well, and that as a result there had been no ulceration. However, it was noted that he both drank and smoked to excess. An enlarged liver was discovered later the same year.

In 1963 he was referred to a general physician with substernal pain on effort and palpitation. The latter had been troublesome for 25 years but was now worse.

On examination the signs of mitral stenosis and aortic incompetence were present and the heart was enlarged, but there was no evidence of failure. B.P. 170/80. Propranolol was prescribed. Within three months, signs of congestive failure supervened and he had also developed intermittent
claudication of the left leg. The peripheral pulses could not be felt in the left foot. The liver was enlarged and tender.

In September 1968 he was in hospital for one week recovering from an alcoholic stupor.

In June 1968 and December 1968 he sustained attacks of myocardial infarction. At this time the signs in the heart were unchanged, but congestive failure required treatment with Digitalis, Fruseamide and Spironolactone. Notable physical signs at this time included liver enlargement 9 cms below the right costal margin, absent peripheral pulses on the left side and loss of both ankle jerks.

From these illnesses his exercise tolerance was further diminished by angina and he complained of impotence and loss of libido.

In September 1969 he presented with classical acute gout affecting the right 1st metatarsophalangeal joint. A second attack followed 14 months later. It was not possible to reduce the dose of diuretic.

Examination (March 1970)

This was the last of several occasions on which this man was personally examined.

The left ear, hand and foot were smaller than their fellows on the right side.

Dense callosities were present over the shafts of the 1st and 3rd metatarsal heads on both sides (Plate 29).

The hands appeared normal.

There was no muscle wasting nor weakness. Tendon jerks were brisk and equal, except for the ankle jerks which were sluggish. Plantar responses were flexor.

Pain sensation was lost over both soles and most of the dorsum of the left foot. It appeared to be slightly impaired up to mid-thigh level on both sides, and over both arms to the elbows.
IV 36: Plantar appearances in March, 1970.
Temperature sensation was lost over both soles and up to the knees, and over the fingers.
Light touch, position and vibration sense were unaffected.
In the other systems, the physical signs were those of mitral stenosis and aortic incompetence, with cardiac enlargement, some congestive failure and hepatomegaly.
Peripheral pulses were lost at the left ankle and impaired on the right side.
The urine contained a trace of albumen. B.P. 170/90.

Subsequent progress.
During the first of these there was an episode of transient left hemiparesis. This resolved rapidly, but he was always slightly ataxic thereafter.
In October 1970, a mid-line nodule was palpated in his liver. At this time the hilum of the left lung was noted to be prominent, and the possibility of carcinoma of the left lung with a secondary in the liver was entertained.
Tomograms of the left lung root were not carried out because his condition has deteriorated to such an extent.
Following the admission in May 1971, he went downhill rapidly. He became drowsy, confused, incontinent, and finally jaundiced. The urine contained albumin, and biochemical tests (see below) indicated combined renal and hepatic failure.
A remarkable terminal event was sloughing of the callosities of both feet, so that for the first time in his life, overt plantar ulceration occurred.
Investigations.

Blood:

October 1968  Haemoglobin 86%  
Cholesterol 230 mgm %
September 1969  Uric acid 10.3 mgm %
December 1969  Haemoglobin 77%  WBC 7000  Urea 60 mgs %  
Electrolytes normal. Plasma proteins 6.2 G %  
(Albumin 3.5  Globulin 2.7)  
Bilirubin less than 0.8 mg %
SGOT 42  LDH 542  Cholesterol 290
Total free fatty acids 670 mgm %

March 1970  Urea 50 mgm %  Sodium 135 mEq/l
Potassium 4.7  Chloride 96  Bicarbonate 27
June 1971  Haemoglobin 103%  ESR 18  WBC 10,000
Plasma proteins 7.8 G %  
(Albumin 4.6  Globulin 3.2)
Total bilirubin 2.4 mgm % Conjugated bilirubin present.  SGOT 205
Alkaline phosphatase 11

X-rays of the chest from 1960 onwards showed increasing cardiac enlargement. In summer 1968, there were confluent opacities over both lung fields consistent with pulmonary congestion. In April 1970, the appearances were those of consolidation and collapse at the left base. By October, this had largely resolved but the left hilum was unduly prominent.

Electrocardiograms:

May 1958  Sinus rhythm.  P-R interval 0.22 secs.
October 1967  Sinus rhythm. Broad bifid waves.
   P-R interval 0.24 secs.
September 1969  Sinus rhythm.  P-R interval 0.3 secs.
   T inversion in leads 2, 3, AVL.
   ST segments depressed in V5 and V6.
E.M.G. A normal action potential was recorded from the right median nerve at the wrist, after stimulation of this nerve at the right 2nd finger.

Sampling of the right abductor pollicis brevis gave normal results. No action potential was obtained from the lateral popliteal nerve at the neck of the right fibula, after stimulation of this nerve at the ankle. Motor nerve conduction velocity was 52 metres/second in the right median nerve, and 40 metres/second in the right lateral popliteal nerve.

Autopsy findings
After considerable discussion the relatives granted permission for an autopsy so long as the body was not moved to another hospital, and examination was restricted to pathological verification of the familial disorder. Accordingly the lumbar spine was extracted and taken to Dr. Betty Brownell, Consultant in Neuropathology at Frenchay Hospital. A length of sciatic nerve was also excised but was apparently lost in transit.

Neuropathological report
The specimen consists of the lumbar spine, with the spinal cord in situ. Posterior laminectomy was carried out, and the cord and posterior root ganglia removed.

On naked eye examination the spinal cord appears normal, but the posterior nerve roots of the cauda equina are grey and atrophic.

Histology
The lumbar cord has been sectioned at each segmental level and several sections have been taken of the cauda equina and posterior root ganglia. At all levels, the posterior nerve roots are grossly abnormal. Myelin
tubes are present, but these are scanty and stained palely compared with those of the anterior roots. (Plate 35).

Axon stains, however, show almost total absence of axons from all the posterior roots, the anterior roots being completely normal (Plate 36). Posterior root ganglia show degeneration and disappearance of nerve cells with proliferation of capsule cells, and a severe loss of intraganglionic axons.

Transverse sections of the lumber cord show degeneration of gracile tracts in the posterior columns, but this is surprisingly mild in view of the severe disorder affecting the posterior roots.

Comment

The changes are typically those described in cases of Hereditary Sensory Radicular Neuropathy, with the exception that in this case, posterior column degeneration seems disproportionately mild.

Propositus

Described in Chapter 4.

Unaffected

Born 1923. Housewife.

During her two pregnancies in 1943 and 1948, this woman developed deep vein thrombosis in both legs. In 1948 a massive pulmonary embolism proved almost fatal.

In recent years, both legs have ulcerated. These ulcers have been situated in the lower thirds of each leg and have spared the feet. They
had the appearance of varicose ulceration, and are often complicated by thrombophlebitis. At examination on three occasions between 1968 and 1973 she has been grossly obese at over 15-stone. Both legs have been the site of brawny swelling with scars from old varicose ulceration. No neurological signs have been elicited. E.M.G. examination was refused.

\[V 39\] Vivien C.   \text{ Unaffected} \\
Born 1926. Draughtsman.
This man suffered from repeated attacks of superficial phlebitis of the legs following tonsillitis between 1945 and 1957. The last of these attacks was the most severe with spread of thrombosis to deep veins in the calves and two episodes of pulmonary embolism, requiring emergency admissions to hospital and anticoagulant therapy. Since then his legs have remained swollen and have often ulcerated at the thigh and around the ankles.
When examined in 1969 he was grossly over-weight at 16-stones with swollen, scarred and pigmented legs, and prominent varicose veins. There were no trophic lesions in the feet themselves and no neurological signs.
Subsequently on reducing diets, he lost over 4-stone in weight. There was some improvement in the swelling and general appearance of his legs. On E.M.G. examination in 1970, digital action potentials were normal, but no compound action potential could be recorded from the right lateral popliteal nerve at the neck of the fibula after stimulation of this nerve at the ankle. Motor nerve conduction velocity in the right lateral popliteal nerve and its continuation anterior tibial was 45 metres per second.
4 of these 7 subjects had died prior to this study. One of these, \( \text{V} 41 \), was a patient of the writer.

He died in 1968 from cerebral infarction. Even after this event he presented no sensory signs in his legs.

All 3 living subjects were personally examined in 1969 and found free from C.N.S. and trophic signs.

\[
\begin{array}{c}
\text{V} 1 - \text{V} 11 \\
\hline
\text{All unaffected}
\end{array}
\]

Three, \( \text{V} 7, \text{V} 42 \) and \( \text{V} 43 \), had died in infancy. Of the 41 survivors, 36 were personally examined.

Three, \( \text{V} 9, \text{V} 22 \) and \( \text{V} 34 \), had left the district, while two, \( \text{V} 1 \) and \( \text{V} 17 \), were unwilling to be examined, for reasons already given.

Assuming an approximate mean age of onset of symptoms in affected members of 29 years, there were 12 subjects all in 1940 or later in whom this age of manifestation had therefore not been reached.

These were \( \text{V} 14, \text{V} 27, \text{V} 28, \text{V} 29, \text{V} 30, \text{V} 32, \text{V} 33, \text{V} 37, \text{V} 38, \text{V} 39, \text{V} 40 \) and \( \text{V} 41 \).

\[
\begin{array}{c}
\text{V} 25 \text{ Michael B.} \\
\hline
\text{Unaffected}
\end{array}
\]

Born 1933. Rubber worker.

During neurological screening of his kindred, some sensory impairment to all modalities was discovered in all four extremities. All tendon jerks were pathologically brisk, but the plantar responses were flexor and there was no clonus. His gait, however, was slightly spastic.
Enquiry revealed that in February 1954 he sustained a crush fracture of the 4th cervical vertebra in a motor accident. This had left him with a quadriplegia which had initially improved rapidly with traction. The signs seen in this man are clearly residual from this episode of trauma to the cervical cord.

Brian B

Born 1935, this son of an affected father died of pneumonia when he was two.

Doreen R.

Born in 1936, this woman emigrated to Canada with her three children in 1967. She has been mentioned in Chapter 3.

In May 1969 she was examined neurologically by Dr. Walker Fitzgerald of Toronto, who wrote stating that the patient herself had had no trouble with her feet. She had no trophic changes. She had not any significant callouses and had noticed no changes in the musculature of the legs or feet. She had no difficulties with balance and no difficulties with regard to feeling in her feet either pain, heat or cold. On examination he found her gait and stance to be perfectly normal. No abnormality of any kind was detected in the feet and legs. The texture of the skin of the feet was considered normal, and there was minimal callus consistent with a woman who wears high heeled shoes.

Specifically the examination of the feet and legs to light touch, pinprick, position, vibration, heat and cold was considered quite normal.
Deep tendon reflexes were normal.

The plantar responses were normally down-going and power, tone and coordination in the lower limbs was normal. He concluded that although she was the daughter of an affected man, there was no evidence of Hereditary Sensory Radicular Neuropathy, and no other neurological disability affecting her lower limbs. Accordingly he did not examine her children.

\[ V \text{ 47 Ronald L. } \text{ Unaffected} \]

This man was personally examined in 1969 when he was 31, and again in 1973.

The son of an affected mother, he himself presented no abnormal signs, and no trophic lesions had developed.

\[ V \text{ 48 Michael G. } \text{ Unaffected} \]

Born in 1947 to an affected mother, this man was examined on four occasions between 1968 and 1973.

He has high arched feet, and there are some errors of perception in hot and cold on the soles of the feet which are calloused. There are some patches of dry eczema over both insoles. There are no abnormalities in any sensory modality, power, coordination or reflexes, and no muscle wasting in all four limbs.

In 1970 he fractured his right tibia playing football with some consequent deformity. He wore a plaster cast for eight weeks but developed
no trophic lesions as a complication of this.

Onset of overt neuropathy was delayed in his mother until the age of 34, and in his two uncles until the ages of 25 and 28, so that he remains a candidate for the trait, although unaffected at his present age of 27. E.M.G. examination in 1970 provided normal findings.

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V 49 Roger C.  
**Unaffected**

Born in 1950, this man was personally examined in 1969, when he presented no signs of neuropathy. Trophic lesions had not appeared by 1972.

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V 50 and V 51

Born in 1937 and 1940 respectively, this brother and sister had left the district. Their unaffected mother reports that they remained free of symptoms in their legs.

---

V 52 Irene U.  
**Affected**


This young woman was examined by a physician in 1966 when 31 years old, together with her three sons then aged 9, 6 and 5. He reported that - "none have any complaints, the skin of their legs is healthy, and they all have brisk responses and no detectable sensory changes whatever,
while their foot musculature is strong. It would seem unlikely, therefore, that any of them have the disease.

She was not examined again until May 1970, during the course of this study, by which time she was 35. She denied symptoms but stated that she had a verruca of the left big toe. This was found to be a characteristic hyperkeratotic lesion.

Obvious muscle wasting was present below both knees, more marked on the left side. The circumference of the right calf 10 cms. below the tibial tuberosity was 30 cms.; that on the left 28.5 cms. Both ankle jerks were sluggish relative to the knee jerks, that on the right being more obviously reduced.

Sensory testing indicated blunting to pin prick over both surfaces of both feet, while thermal perception was impaired over both soles and the dorsal aspect of the right foot. Touch and position sense were preserved, but vibration sense was lost over the right big toe.

There was no sensory impairment, reflex impairment or muscle wasting in the upper limbs.

E.M.G. findings in May 1970 were in keeping with the clinical signs. Thus sampling of the right extensor digitorum brevis with a concentric needle electrode, revealed a much reduced interference pattern. There was no fibrillation and no giant units.

Motor nerve conduction velocity in the right anterior tibial nerve was 31 meters/second.

No compound action potential could be obtained from this nerve at the neck of the fibula after stimulation of the anterior tibial nerve at the ankle.

Normal sensory action potentials were evoked over the median nerve at the right wrist after stimulation of this nerve in the second finger.

She was re-examined by Dr. Graham Wakefield in March 1971, at which time
she presented the same plantar appearances and neurological findings.

V 53 Peter C.  
Affected

Born 1937, Draughtsman.

Early in 1958 this man first noticed a corn in the ball of his left foot. He treated this by abrading it with pumice stone. After playing football later in the same year, a blister formed alongside this corn. He consulted his doctor who diagnosed P.S.P.N. and instituted treatment with rest and bland dressings. Despite these prompt measures healing was delayed for almost two months.

In March 1959 he was unable to work because of pain and swelling in the left ankle. This had troubled him intermittently since a football injury in 1954. X-ray of the ankle showed no abnormalities and he returned to work after three weeks.

Thereafter, although hyperkeratosis persisted at the site of the original lesion, he remained free from serious symptoms for eight years. Overt ulceration occurred at the same site in 1966. This appeared to heal in the space of two months, but a further relapse followed almost immediately.

In January 1967 he was admitted to hospital in Bath under the care of the neurologist, Dr. Graham Wakefield.

Examination at this time showed him to be a tall, thin young man, with an ulcer of the left sole overlying the head of the second metatarsal. Both calves were wasted, and a lesser degree of wasting was present in both quadriceps. All deep reflexes were active. Pain and temperature sensation was lost in the feet, and impaired to
mid-calf level and over the fingers. The other modalities were intact.

There was a right orchidopexy scar. The left testicle was not palpable. The other systems were normal. P.P. 140/80.

Investigations revealed normal urine, blood count and E.S.R., liver function tests and glucose tolerance. The c.s.f. was also normal, (protein 33 mg%). X-rays of chest and feet showed no abnormality.

E.M.G. revealed reduced activity in the right extensor digitorum brevis, normal digital action potentials, but loss of the compound action potentials in the neck of the right fibula.

Motor nerve conduction velocity was reduced to 25 meters/second in the right lateral popliteal nerve.

He was discharged from hospital wearing cavus insoles and padded shoes, and thereafter remained for some time under the care of an orthopaedic surgeon.

The ulcer failed to heal, however, and in November 1967 it was excised, with the underlying head of the first metatarsal. No anaesthetio was required.

The resultant scar took two months to heal, but eventually became sound.

In December 1968, plantar ulceration recurred at the same site on the left sole, and there was dense callosity occupying a corresponding position on the right sole. (Plate 30). Wasting of the legs appeared to have increased. (Plate 31).

The ulcer persisted for more than one year on this occasion.

In August 1969 he was examined by the writer for the first time, as part of this study, the findings being as follows.
Appearance of feet in December, 1968, showing an open ulcer of the left sole and a dense callosity on the right.
Photograph in December, 1968, showing distal amyotrophy with swelling and valgus deformity of the left ankle.
Examination, August 1969

He appeared more preoccupied with his muscle wasting than the sensory and trophic changes.

The ulcer was about 2 cms square and overlying the second left metatarsal head. The left foot and ankle were hot and swollen, but painless. The left inguinal lymph glands were swollen and tender.

Distal amyopothy now affected all four limbs. It was conspicuous both below and above the knees, and also in the hands were the thenar and hypothenar eminences were flattened, more so on the right. There was some furrowing of the dorsal aspects of both hands between the metacarpal shafts.

Both ankle jerks were now lost, although the knee jerks and upper limb jerks remained brisk.

The area of sensory loss to pain and temperature had extended to above both knees, higher on the left, and above the wrists, higher on the right. The loss to temperature appeared greater than the loss to pinprick. Light touch and deep pressure sense were also affected as far up as the right mid-calf and just below the left knee, and also in both hands. Position sense was impaired over the left toes. Vibration sense was intact.

Subsequent progress.

The left sided plantar ulcer was again excised in October 1969 together with the head of the third metatarsal, and although it broke down subsequently, healing was eventually complete.

At this time the patient was seen by Dr. A. St.J. Dixon who provided seamless shoes of the type developed by him (Dixon & Franklin, 1968). Unfortunately the patient objected to their appearance and did not persist with their use.
When examined by Dr. Dixon in June 1970, the left foot had become very flat and there was an effusion into the left ankle. This was in valgus position, but could be corrected passively and painlessly. The skin of the soles was healthy apart from calloused areas over the second and third toes which were retracted dorsally.

X-ray of this ankle and foot showed a loose piece of bone, considered to represent a chip fracture of the talus.

For this a well padded walking plaster was applied which he wore for six weeks without ill effects to the skin surface.

In July 1970, when free from external trophic change, he attended a Genetic Counselling Clinic where it was concluded - "that we are dealing with a family that is showing dominantly inherited Charcot-Marie, Tooth disease".

Re-examination, May 1975

The soles of both feet now appeared healthy, apart from a scar from the original ulcer on the left side.

The left foot was much narrower than the right, with the result that the second and third toes were displaced dorsally and over-rove their fellows.

Muscle wasting was pronounced, particularly in the distal half of the legs (Plate 32), and in the hands where both thenar and hypothenar eminences were wasted, and there was some dorsal furrowing. (Plate 33). There was considerable weakness of ankle movements, particularly dorsiflexion, and in the fingers, particularly of abduction. He was quite unable to approximate his fingers when they were fully extended, and wrist dorsiflexion was also impaired.
Appearance of legs and feet in May 1973. New developments include narrowing of the left foot and over-riding of the 2nd and 3rd toes. Both changes are probably the outcome of surgical excision of metatarsal heads in 1967 and 1969.
Photograph of hands in May 1973 showing interosseous wasting.
He stated that his legs tired easily and that long walks were impossible, as they became "floppy" when he was tired.

Both ankle jerks and plantar responses were abolished, but the knee and upper limb jerks were present, brisk and equal.

Muscle tone was demonstrably diminished in all four limbs.

There was no incoordination in the finger/nose and heel/knee tests, and no Rombergism.

Sensory testing revealed loss of the ability to distinguish hot and cold up to the right mid-thigh and above the left knee. It was also impaired over both hands and to 1-inch proximal to the left wrist.

Loss to pain was more extensive and more symmetrical, reaching almost to groins and elbows.

Two point discrimination was impaired over both hands and both legs below the knees.

Light touch was preserved in the upper limbs, but lost in the legs up to both knees.

Vibration and position sense were both lost over the toes.

X-rays of the feet (Plate 34) showed evidence of previous excision of the 2nd and 3rd metatarsal heads. The left foot is narrower than the right, but the right ankle is broader, and there is a bit of loose fragment, probably derived from talus.

V 54 Christine C. Unaffected

Both in 1949, this girl who has psychiatric problems, was examined in 1969, 1973 and 1974, and no neurological abnormalities were identified
\[ V \] 53: X-ray of feet in May 1973, showing various abnormalities in the right foot which is narrower than the left foot. There is evidence of excision of the 2nd and 3rd metatarsal heads, concentric atrophy and, posteriorly, a loose fragment, probably derived from the talus.
Notoriously apprehensive and highly strung, she was unable to tolerate the discomfort of E.M.G. examination.

With an affected father and two affected sibs, her expectancy of developing the disorder remains 50/50, as she is well below the mean age of manifestation in female members of this stock.

\[ \text{V} \ 55 \text{ Marion S} \]

Affected

Born 1936. Housewife.

From 1967 onwards, this young woman has required regular chiropody for callosities overlying both 4th metatarsal heads, but there has been no ulceration.

She was considered to be affected by her father (IV 36) and is depicted as such in the pedigree of Campbell & Hoffman (1964) who did not however examine her.

When first examined in June 1969, dense hyperkeratosis was present in the situation described. Pain and thermal sensation were impaired over the soles of both feet and patchy over the dorsum of the right foot. The other modalities were unaffected and the upper limbs were normal to sensory examination. All deep reflexes were present, brisk and equal, and flexor plantar responses were obtained.

At E.M.G. examination in 1970, normal digital action potentials were obtained at the wrist after stimulation of the second finger, but a lateral popliteal compound potential at the neck of the fibula was not obtained.

When re-examined in December 1972, at the age of 36, she complained of
pain in the ball of the right foot, where two shallow ulcers were
located underlying the 4th and 5th metatarsal heads. The skin of the
left foot was intact, but calloused over the 4th left metatarsal head.
Objective evidence of sensory neuropathy was now more definite with
impairment of both pain and thermal perception over both soles, the
lateral margin of the right foot and the distal two-thirds of its dorsal
surface. Pain sensation appeared to be acutely increased over the ulcers
themselves and their margins.
The other sensory modalities were preserved and there was no wasting
or reflex change.

There was no evidence of neuropathy affecting the upper limbs.

V 56 Patricia H

Affected

Born 1939. Housewife.

When examined in 1968, this young woman was found to have marked hyper-
keratosis maximal over the metatarsal heads, and along the outer margins
of the feet. Sensory testing indicated some doubtful impairment of
thermal perception, and of pinprick on both soles and along the outer
margin of the left foot. There were no other neurological abnormalities.

At E.M.G. examination in 1970, normal sensory action potentials were
obtained at the wrist after stimulating the median nerve at the second
finger, and a compound evoked potential was obtained in the right
lateral popliteal nerve at the neck of the fibula after stimulation at
the ankle (amplitude 4 microvolts).

When re-examined in January 1973 at the age of 34, she was free from
ulceration and her dense plantar callosities were identical with those
found in other affected subjects; pain and temperature sensation were undoubtedly impaired over the foreparts of both soles, and in the toes. Light touch was lost over the inferior surface of the left big toe.

**V 57 Pamela S**

*Unaffected*

Born 1942.

When first examined in 1968, this young woman presented with a thyroidectomy scar dating from December 1969, when a large adenoparenchymatous goitre containing numerous cysts had been removed.

Small callusites overlay the 2nd metatarsal heads on both sides, but there were no neurological signs.

E.M.G. in 1970 revealed a normal digital action potential and a compound action potential from the right lateral popliteal nerve (amplitude 4 microvolts).

When re-examined in 1973, there was neither plantar ulceration nor signs of neuropathy.

**V 58 Margaret P**

*Unaffected*

Born 1943.

When first examined in 1968 she presented neither callus formation on the soles of the feet nor neurological abnormalities.

E.M.G. findings in 1970 were normal.

When re-examined in 1973 at the age of 30, the skin of the hands and feet was healthy and there was no evidence of neuropathy.
V 59  Beryl M  
Unaffected

Born 1945.

When first examined in 1968, small calluscities were present which overlay the 2nd metatarsal head on both sides, but there were no neurological signs.

She then left the district preventing E.M.G. studies and further neurological examination. Enquiry suggests that she remains free from subjective evidence of neuropathy.

V 60  Robert C  
Unaffected

Born 1946.

This man was first examined in 1968. His feet were calloused but there were no neurological abnormalities.

At E.M.G. his digital action potentials were not studied, but a normal right lateral popliteal compound action potential was demonstrated and motor nerve velocity in the legs was normal.

When re-examined in February 1973 at the age of 27, the appearances of the feet were unchanged, and he was free from signs of peripheral neuropathy.

V 61  Florence E.  
Unaffected

Born 1943.

This young woman was examined in October 1968, June 1970 and January 1973, and presented identical signs on each occasion. There was
considerable hyperkeratosis of both soles, especially the left, with some very questionable impairment of pinprick and temperature discrimination over both feet up to the ankles, but no other abnormality. At E.M.C. a normal digital sensory action potential was obtained at the wrist after stimulation at the right second finger.

No compound action potential was obtained from the right popliteal nerve however, after stimulation at the ankle. This was attributed to masking by background muscular activity, as she was unable to relax properly during the examination.

62 William O Unaffected

Born 1945.

When first examined in 1968, this man complained of aching feet. There was a thick area of densely calloused skin overlying the posterolateral part of his right heel.

There was some very doubtful reduction to pinprick over the soles, which was obviously maximal in the vicinity of this plaque.

Thermal perception, kinesthetic sensation, musculature and reflexes appeared normal.

At E.M.C. normal findings were obtained.

When re-examined in January 1973, there had been no extension of the areas of hyperkeratosis, and he remained free from definite signs of neuropathy.
V 63 Vivien B  Unaffected

Born 1943.

Examined 1970. No abnormalities.

V 64 Trevor P  Unaffected

Born 1949.

When examined in 1969 he gave an 18 month history of pain and slight swelling in both ankles. On examination he was very overweight.

There was no hyperkeratosis, ulceration of the feet or neurological abnormality.

V 65 Sheila C  Unaffected

Born 1947.

Examined 1968. This young woman exhibited dense hyperkeratotic plaques overlying the 1st, 3rd and 5th metatarsal heads of the left foot, but there was no neurological deficit.

She remains free from trophic lesions and subjective evidence of neuropathy.

V 66 Barry C  Unaffected

Born 1951.

Examined 1968. No abnormalities.
These 13 members of kindred were distributed in 5 sibships. All had unaffected parents and grandparents.

Four, (V 67, V 73, V 74, V 75) had left the district.

The remaining nine were examined during 1969 with negative results.

Only three however, ( V 72, V 73, V 76 ) had reached the age of 29, which is the mean age of onset of symptoms of the hereditary disorder in affected members of this kindred.

Four generations removed from an affected forebear, these 76 subjects are distributed in 24 sibships. The oldest of the group (VI 3) was only 23 when examined in 1969, six years below the mean age of onset of the trait in affected relatives.

52 were personally examined and presented no relevant abnormalities.

Of the remaining 24, four had left the district, nineteen were below six years of age and were not examined, while one (VI 18) had committed suicide by drowning in 1966 when 11 years old.

These three children had an affected grandfather. They were not personally examined as they had emigrated to Canada with their mother (IV 46). As the oldest member of this sibship was born in 1961, they remained well below the age of manifestation of the disorder in this kindred.
The older of these two children who was born in 1961 was examined in 1968, when she presented no abnormalities. They are three generations removed from an affected forebear.

These three children were not examined as they had left the district.

Living elsewhere, these three boys who were born in 1956, 1959 and 1962 respectively, were examined by a physician in 1967 when they were pronounced free from symptoms and signs of neuropathy. Enquiry of their General Practitioner indicated that they remain free from any disorders of their limbs.

VI 85 was examined by a Neurologist, Dr. Graham Wakefield in March 1974, when his findings were negative. Their mother (VI 52) is affected and so they each have a 1 - 1 expectation of developing this disorder. Unaffected at present, they are well below the mean age of onset of the trait in the "Y" family.
This girl was examined in 1969 at the age of 10. She presented no neurological abnormalities. She has an affected mother and therefore must remain a possible future candidate for the disorder.

These two girls were not examined because of their age.

The eldest of these children born in 1961 was examined in 1969, when there were no abnormal signs. All three remain well.

These two children were the only grandchildren of the propositus when the pedigree was constructed in 1969. They were born in 1961 and 1967 respectively. Neither presents any form of neurological abnormality.

These nine children of unaffected parents and grandparents included three who had left the district, and three who were aged 5 or less in
1965. The remaining three (VI 101, VI 102, VI 103) were personally examined with negative results.
CHAPTER 6

H.S.R.N.: THE SENSORY SYNDROME

1. SYMPTOMS

A. PRODROMAL

Although [IV 46] claimed that his feet were excessively sensitive from the age of seven, this experience was at variance with that of other members of the "X" family, all of whom denied symptoms and awareness of any sensory deficit prior to the onset of trophic ulceration.

In this respect, the "X" family appears to conform to the pattern most usually seen in H.S.R.N. Paraesthesiae, pains and numbness of the feet and legs may occur prior to the onset of ulceration, but they do so only in a minority of cases, apparently of the order of 30% (Thévenard (1953)).

Sensory prodromal symptoms have occurred frequently in some other families, (Gobell & Runge (1914), Weitz (1921), Beiglebock (1939), Mulvey & Riely (1942), Heller & Robb (1955), Wallace (1970).

In Wallace's large Australian "X" family in particular, paraesthesiae, subjective awareness of sensory loss and lightning pains,
preceded the onset of trophic lesions in many cases, sometimes by several years, most notably in the case of one man who was aware that his feet were anaesthetic for ten years before ulceration began, and sometimes such symptoms will be the only evidence of the trait and ulcers never appear (Wallace 1970).

Where sensory loss begins in childhood and is limited to siblings with unaffected parents, trophic ulceration may be preceded by sensory ataxia, and an inability to recognise objects by feel alone. These indicate a different trait and are considered separately elsewhere. (See Chapter 16).

**B. LATER STAGES**

In the "Y" family, patients became aware of their sensory deficit gradually, often not until months or years after the first appearance of trophic lesions. This slow evolution of subjective awareness of sensory loss has been described in some detail in the case protocol of propositus IV 37, who was a typical severely affected subject. The ulcers themselves were usually painless, or almost so, except in IV 32 where their development was attended by pain of a severe bursting or boring character, and exacerbations of these lesions were recognised more by the occurrence of such symptoms, then by any conspicuous change in their appearance. Lesser degrees of discomfort were experienced by other members, noticeably III 13, III 29 and V 55, but subjective disability was always less than might be expected from the nature of the lesions themselves.

In the Australian stock, however, the prodromal symptoms persisted in three-quarters of cases throughout life, and the ulcers
appeared to be no less painful than they might be expected to be if they occurred in normal subjects. They were as severe in octogenarians with thirty or more years of ulceration and mutilation, as they were in teenagers at the onset of the disorder. It is not surprising, therefore, that affected members of this kindred, suffering as much pain as they did, found it difficult to comprehend that their troubles were largely due to loss of sensation in the limbs (Wallace (1970).

C. LIGHTNING PAINS

In the "X" family, pains warranting this description were claimed only by IV 35, and took the form of intense pain in the hands which he likened to salt being rubbed into an open wound. They were of brief duration and accompanied by transient numbness in the arms. At times his hands became hot and sweaty, and this coincided with relief of these pains.

"Pains about the body" of a shooting quality, occurred in affected members of the London "R" family (Hicks (1922), Denny Brown (1951), and in some members of other stocks in which, however, they were limited to the limbs (Smith (1934), Van Epps & Kerr (1937), (1940), Van Bogaert (1940), Alajouanine & Mozzićonoci (1940), Thévenard (1942), Mendell & Smith (1960), Turkington & Stiefel (1965), Spilane & Wells, (1969).

They were a particularly dramatic feature of one member of an American kindred. He suffered from continual pain across the upper part of the back. This occasionally and briefly became so violent and intense as to cause circulatory collapse. Each episode was followed by an increase in sensory loss, and although this receded after a few days, it did so less completely with successive attacks (Roimann et al (1958)).
Lightning pains occurred in at least 8 of 41 members of the Australian stock both before and after the onset of trophic lesions, but never occurred elsewhere than in the limbs, (Wallace (1970)).

Lightning pains also occur in stocks distinguishable from H.S.R.N. by the severity and uniformity of muscular weakness and wasting.

Thus in 111 16 in the "Z" family, reviewed later, they have become a greater symptom of the disease in recent years, occurring in bouts lasting one or two days with intervals of freedom of 4 - 6 weeks duration.

In general, lightning pains also appear to be most severe and frequent in stocks combining acrodystrophic neuropathy with greater degrees of wasting and weakness than occur normally in classical H.S.R.N. (Halliday & Whiting (1909), Reimann (1930), Barraquer-Perré & Barraquer-Bordas (1953), Cossa et al (1957), Feudell (1959), Dyck et al (1965)).

Among the other H.F.A.Ns, shooting pains may occur in familial amyloid neuropathy and in the rare variant of familial spastic paraplegia with trophic ulceration (Ven Epps & Kerr (1940), Khalifey & Zellweger (1964)). These two traits are described in Chapter 22.

2. SIGNS

A. TOPOGRAPHY

Sensory loss in H.S.R.N. begins distally in the feet and slowly progresses proximally. It is usually extensive in the feet before it can be demonstrated in the hands, and the latter may be entirely spared. Sensory loss in all four limbs is uncommon, being present in
only 9 of 69 cases (Thévenard (1953)). Although its occurrence in the hands was foreshadowed by Nélaton’s patient, (Nélaton (1852)), who was fearful of unwittingly injuring them at work, it was apparently not found by earlier writers and not formally described until 90 years later (Tocantins & Reimann (1939)). Since then sensory loss in the hands has been frequently reported.

Sensory loss occurred in the hands of those members of the "X" family in whom the trait was sufficiently advanced, and in whom it was sought, but it was always much less definite than the loss in the feet and legs.

One patient in whom sensory loss occurred in the arms before the legs (Van Bogaert (1940)) was apparently unique. His case is perhaps analogous to uncommon examples of Charcot-Marie-Tooth disease in whom amyotrophy occurred in the hands and forearms before the legs (Bell (1935)).

The upper border of superficial sensory loss in the limbs is transverse and at right angles to their long axes. It is fading rather than abrupt, and below it sensory loss becomes denser as the extremity is approached.

H.S.R.N. does not materially differ in this respect from other neuropathies characterised by primary axonal degeneration in which this pattern is usual, (Simpson (1971)). It lacks the radicular distribution encountered in C.M.T.D. (Engeland & Denny Brown (1952), Wells (1965)).

Cutaneous loss may be very extensive. In 37 it reached the waist, and also extended on to the shoulders from the upper limbs.
Such extensive loss in H.S.R.N. has been exceeded among reported cases in only a few instances. Thus it has reached the xiphisternum (Thévenard (1942)), the clavicles (Denny Brown (1951)), the face (Reinemert et al (1953)) and appeared to be generalised all over the body surface (Ortiz de Zárate (1955)). In two members of the Australian "E" family, extensive anaesthesia over the trunk was accompanied by sensory loss of the tips of the ears (Wallace (1970)).

It does not occur on the trunk as a band of suspended anaesthesia with normal sensation below as well as above, (Thévenard (1953)). The extension of sensory loss on to the abdomen may be overlooked, through inadequate examination (De Leon (1969)).

In other kindreds, sensory loss has always remained acral in distribution, often confined to the immediate neighbourhood of severe trophic lesions, (Oehlecker (1939), Göbell & Runge (1914), Smith (1921), Cooper et al (1947).

Such marked differences are not likely to be due to individual vagaries of sensory testing, and probably reflect definite interfamilial differences. Stocks with H.S.R.N. also appear to differ in the extent of global sensory loss relative to the extent of dissociated loss. This ratio appears to have been higher in the "R" family (Denny Brown (1951)) than in the "Y" family and most other kindreds; as might be expected it is accompanied by more widespread impairment of the deep reflexes.

Sensory loss in H.S.R.N. is usually more symmetrical and less extensive than that encountered in other heredo-familial
acrodystrophic neuropathies, (see Chapter 16), in which global rather than dissociated anaesthesia is encountered.

**B. MODALITIES AFFECTED**

In a review of 69 cases of A.U.M.P. from the literature (Thévenard (1953)) it was shown that sensory loss conformed to three clinical types as follows.

(1) Loss of all modalities (global loss) over the entire territory affected (19 cases)

(2) Loss of pain and temperature sensation (dissociated loss) over the entire territory affected (23 cases)

(3) Distal global and proximal dissociated anaesthesia (21 cases).

This series, however, contains families in which H.P.A.N. is confined to members of single sibships, with unaffected parents, (consanguinously related in 3), and usually a much earlier age of onset (Bruns (1903), Price (1913), Schultze (1917), Wagner (1932), Enderle (1933), Barré (1945), Peron et al. (1949), Taleb (1950), Boudin & Djindjian (1961)).

If all these cases are extracted, together with 3 stocks of C.M.T.D. (Barraquer - Ferré & Barraquer - Bordas (1933), Alajouanine et al. (1946), England & Denny Brown (1952)), it is found that the first of these clinical types has been eliminated. The residue of cases conform to the pattern of classical H.P.A.N. and invariably exhibit dissociated loss with or without distal global loss.

There is further evidence that the second type evolves into
the third, and that they represent different stages of the same process.

This was certainly the experience in the "X" family. Loss of pain and temperature sensation appeared first and extended proximally and later other modalities, especially touch, became affected distally within the anaesthetic territory. This is also demonstrated in a patient in whom loss to touch appeared in an area which three years earlier had been insensitive only to pain and temperature (Göbell & Runge (1914)), and in another patient where distal loss to all modalities was found (Denny Brown (1951)), loss to pain alone having been present many years earlier (Hicks (1922)).

In other families, sensory loss may become less extensive, suggesting that the syndrome may occasionally remit (Reissner et al. (1959), Campbell & Hoffman (1964, Wallace (1970))).
CHAPTER 7

MOTOR, REFLEX, AND OTHER NEUROLOGICAL SIGNS

1. MUSCULAR WASTING AND WEAKNESS

Muscular wasting was inconspicuous in most affected members of the "X" family, but it was obvious in \( \overline{V} \) 52 and \( \overline{V} \) 53, and to a lesser extent in \( \overline{V} \) 32. Irregularly expressed atrophy, sometimes accompanied by some weakness, apparently distributed at random in kindreds with H.S.R.N., so that some affected subjects show it while the majority do not, appears to be characteristic and has occurred in many families, (Göbell & Runge (1914), Tocantins & Reimann (1939), Van Bogaert (1940), Alajouanine & Mozziconacci (1940), Thévenard (1955), Mulvey & Ricly (1942), Denny Brown (1951), Ortiz de Zárate (1955), Reimann et al (1956), Campbell & Hoffman (1964), Spillane & Wells (1969), Wallace (1970)).

\( \overline{V} \) 53 was almost unique in the "X" family, because of the considerable degree of weakness which could be demonstrated at the ankles, especially of extension of the foot, and in the hands where paresis of lumbricals was considerable, and extension of fingers also impaired.

Even greater degrees of muscular weakness than this appeared
in about 1 in 10 of the affected members of the Australian kindred, and were indistinguishable from that seen in C.M.T.D., with distal amyotrophy, steppage gait, a broad based walk and difficulty in maintaining a stationary, upright posture. These signs were most conspicuous in males (Wallace (1970)).

In other families, gross wasting and weakness may have been evoked by the intervention of other factors, themselves capable of causing neuropathy, such as diabetes (Ortiz de Zárate (1955)) and alcoholism (Campbell & Hoffmann (1964)).

Whether in fact neuropathies can summate in this way is questionable. Besides H.S.R.N., IV 36 of the "X" family was alcoholic, and suffered from liver disease, and terminally from uraemia, all of which are capable of inducing neuropathy. He remained conspicuously free from motor signs however.

Lesser degrees of amyotrophy may be overlooked or, in the feet and legs, they may be masked by inflammatory oedema and induration of the skin, extending proximally from trophic lesions of the feet.

When muscle has been examined histologically (see Chapter 14), it has usually shown signs of neurogenic atrophy, and it seems likely that muscle wasting always occurred but may usually remain subclinical.

Muscle wasting confined to the feet is not easily recognised when it is not severe (Christie (1961), Dyck & Lambert (1967)) and its recognition may depend on EMG studies (see Chapter 10).
2. THE REFLEXES

In the "X" family, the ankle jerks were preserved until the disease had been in progress for some years, but were ultimately lost in more severely affected subjects. The other tendon jerks remained unaffected.

Such modest loss of reflexes confined to the ankle jerk, appeared to be the most common pattern in H.S.R.N. (Göbell & Runge (1914), Weitz (1924), Tocantins & Reimann (1939), Van Epps & Kerr (1940), Van Bogaert (1940), Thévenard (1942), Jügbenn et al (1949), Reimann et al (1953), Pellis & Schneeweiss (1962), Campbell & Hoffman (1964)).

In the New South Wales stock, the ankle jerks were lost in only 6 of 41 affected members, all other reflexes remaining intact (Wallace (1970)).

In 4 families even the ankle jerks were not lost, although this may reflect assessment in an earlier stage of the disease (Mueller & Suger (1943), Cooper et al (1947), Jackson (1949), Mandell & Smith (1960)). More extensive reflex loss, however, involving knee and upper limb deep reflexes, has been reported in H.S.R.N. in otherwise typical stocks (Mulvey & Riely (1941), Benny Brown (1951), Ortiz de Zárate (1955), Kuroiwa & Mural (1964), Turkington & Stiefel (1965), Spillane & Wells (1969)).

Severe areflexia, however, when associated with sensory acro-dystrophy, is more likely to imply C.M.T.P., familial amyloid neuropathy
or the recessively determined forms, all of which are discussed elsewhere.

Acrodystrophic neuropathy may occur in kindreds who display exaggerated tendon jerks, sometimes with extensor planter responses. This association with hereditary spastic paraplegia clearly indicates a quite different disease. It may be dominantly or recessively inherited, and may occur with or without distal amyotrophy. (See Chapter 22).

Among cutaneous reflexes the plantar response is most often lost either through sensory impairment or because of trophic destruction of the forefoot.

3. Deafness

None of the affected members of the "I" family suffered from nerve deafness. The affected man IV 32 had impaired hearing from old inflammatory destruction of both ear drums, and otitis media was entered on the death certificate of the affected women III 7, as a subsidiary cause of death. 8 unaffected members of the "I" family also had impaired hearing for the same reason (IV 6, IV 31, IV 32, V 15, V 26, V 29, V 30 and V 71).

Severe nerve deafness, however, was a cardinal feature of the trait present in the "R" family (Hicks (1922), Benny Brown (1951)). It occurred early in the disease, usually at about the same time as lightening pains, and progressed until hearing was almost totally lost.

It has also been reported in other kindreds of H.S.R.N. (Van Bogaert (1940), Blackwood (1912), Turkington & Stieffel (1965), Hallpike (1967), Spillane & Wells 1969)), but in these stocks it has not necessarily occurred in every affected member.
Many members of the Australian "8" family were deaf from otosclerosis, but there was evidence in this family to show that the two traits, H.S.R.N., and otosclerosis, segregated independently (Wallace 1970).

Nerve deafness has been described in a patient combining C.M.T.D. with severe acrodystrophic change (Barraquer - Ferré & Barraquer - Bordes 1953), in congenital sensory neuropathy with trophic lesions (Ogden et al (1955), Munro (1956), Johnson & Spalding (1964)), and in sporadic acrodystrophic neuropathy of uncertain aetiology, probably non-genetic (Spillane & Wells (1969)).

In another sporadic case, severe vestibular involvement occurred, but hearing was not impaired (Reverdy et al (1970)).

4. Autonomic Disturbances

(a) Vasomotor

Cold feet and reduced sweating have been shown to be characteristic of C.M.T.D. (James (1972)), as indeed they are of neuropathies in general (Wilson & Bruce (1955)), and the phenotypic overlapping which occurs between the two traits, suggests that similar findings might be expected in H.S.R.N., in the absence of hyperaemia caused by secondary infection of the trophic lesions.

Evidence from the "X" family is conflicting; thus the feet of IV 29 and IV 37 in particular, were usually warm and moist, in contrast to those of IV 32 and IV 36 which were invariably dry and cool. Similar familial variations have been described in other stocks (Weitz (1924),
Thévenard (1953)).

Cold, clammy feet with dependent cyanosis were particularly noticeable in some affected members of some families with classical H.S.R.N. (Beiglbock (1938), Van Bogaert (1940), Mulvey & Riely (1942), Cooper et al (1947), Jüghenn et al (1949)).

Coldness of the feet has been sufficiently pronounced in several instances to have led to lumbar or perifemoral sympathectomy. This was performed in 2 members of the "X" family (111 13, IV 32), and in several reported cases (Weitz (1921), Thévenard & Coste (1935), Alajouanine & Mozziconocci (1940), Jackson (1949)). In most of these the neurological basis of the trait was recognised, and the operation was performed in the vain hope of improving this secondary effect on the cutaneous circulation.

Unlike diabetic neuropathy, there is certainly no tendency towards the development of true peripheral vascular disease. This was conspicuous by its absence in the New South Wales stock, although H.S.R.N. had been wrongly attributed to a vascular basis when its neurogenic origin had been overlooked (Wallace 1970).

Intermittent claudication was a late development in IV 36 of the "X" family, but he was over 60 when this first appeared. Another patient also experienced pain in the calves on exertion, relieved by rest, when he was only 33 (Alajouanine & Mozziconocci (1940)) and a woman of the same age is stated to have absent dorsalis pedis pulsation on one side (Mulvey & Riely (1942)). Such cases are exceptional and presumably indicate organic arterial disease rather than autonomic disturbance.

The circulation changes in H.S.R.N. appear to be less severe than they are in stocks which resemble C.M.T.D. more closely, because
of the inordinate degree of muscle wasting and weakness which is present. Thus, III 16 of the "Z" family (Chapter 20) always found that his feet were excessively cold both subjectively and to touch, and wore fur-lined boots even in mid-summer. There are a number of other stocks characterised by considerable muscle wasting in which abnormally cold feet have also been the general rule (Halliday & Whiting (1930), Enderlé (1933), Barraquer & De Gispert (1936), Gambier & LeFévre (1960), Plancherel (1964)).

(b) SUDOMOTOR

Significant hyperhydrosis may occur in some families with H.S.R.N. This was not particularly noticeable in the "X" family, although beads of sweat over the deformed big toe of IV 29 is well illustrated in Plate 22, while a local patch of hyperhydrosis occurred above one ankle of IV 37. In another member of the "X" family, IV 35, acute discomfort in the arms ceased when his hands suddenly began to sweat profusely.

One member of another stock normally had cold feet, which could suddenly and capriciously become hot and sweaty (Beiglböck (1938)). Even more striking evidence of hyperhydrosis occurred in other families. Members of one of these preferred to go barefoot because of the intolerable warmth and sweetness of their feet, and one subject could "wring water from her stockings" at the end of the day (Mulvey & Riely (1942)). Streams of sweat ran off the feet of members of another kinship, leaving wet patches on the floor (Jacob et al (1954)), while the shoes of a member of the New South Wales kindred became so full of sweat, that he literally "squelched" home from work (Wallace 1970).
The feet of another patient sweated so freely that he routinely bathed them in warm permanganate solution, on one occasion provoking a trophic lesion through a scald, (Spillane & Wells (1969)).

Less graphic descriptions of hyperhidrosis of the feet appear in accounts describing other stocks (Tocantins & Reimann (1939), Thévenard (1942), Peron et al (1949), Mandell & Smith (1960)).

(c) The Pupillary abnormalities

Pupillary abnormalities may complicate any longstanding genetically determined neuropathy (André - Van Leeuwen (1942, 1946)), but the proportion of cases affected in this way varies from trait to trait. It is particularly frequent, for example, in Hypertrophic Neuropathy, in which disorder more than a quarter of affected subjects may show abnormalities such as differences in size, irregular margins and sluggish responses, particularly to light (Austin 1956).

Among the Heredofamilial Acrodystrophic Neuropathies, pupillary abnormalities occur most often in Familial Amyloid Neuropathy (See Chapter 22), and are rare among other forms.

There are only three recorded instances in H.S.R.N. One of these was a member of the "Y" family, 111 13, whose pupils were unequal in size and reacted sluggishly to light. This finding, taken in conjunction with his perforating ulcers and absent ankle jerks, resulted in his being treated for neurosyphilis, although there was no serological support for this diagnosis.

The other cases were characterised by sluggish responses to accommodation, in the presence of a brisk reaction to light, (Göbell &
Runge (1914), and small irregular pupils with normal reactions to light and accommodation (Denny Brown (1951)).

(d) Visceral

Autonomic involvement of the viscera occurs in classical form in some cases of diabetic neuropathy, (Rundles (1965), Simpson (1962), R.M.J. (1972)). Thus impotence occurs in one half of all patients and there is also a high incidence of abdominal pain, anorexia, nausea and vomiting from gastric atony, with constipation or diarrhoea, sometimes steatorrhoea (Bergen et al (1936), Malins & French (1957)), from intestinal denervation. Detrusor paralysis of the bladder is reflected in hesitancy of micturition with straining, a large residual urine and liability to recurrent urinary infection. Incontinence may occur which may be faecal or urinary, or both. More recently observed abnormalities include oesophageal dysfunction sometimes producing symptoms (Mandelstam & Lieber (1967), Silber (1969)), facial sweating during or after eating (Watkins (1973)) and abolition of sinus arrhythmia, probably through vagal denervation of the heart (Wheeler & Watkins (1973)).

Such symptoms are due to parasympathetic blockade. Postural hypotension, a classical symptom of sympathetic blockade, may also occur and arises from interruption of baroreceptor reflexes, presumably in this instance mainly peripherally, so that there is failure of vasoconstriction on standing or after exertion, with the result that pooling of blood in the abdomen and legs is not prevented, as it is in health.

Visceral neuropathy of this order of severity never occurs
in families fulfilling the accepted clinical criteria of H.S.R.N.

Certainly in the "X" family there were none of the gastrointestinal, genito-urinary or sphincteric disturbances which have been described, and this is true of the great majority of the reported kindreds. IV 32 sometimes complained of abdominal pain and vomiting, but this seemed only to occur when there was constitutional upset from secondary infection of his trophic lesions, while the impotence of IV 36 occurred when he was in his sixties, and he experienced intermittent claudication at about the same time.

In the "R" family, however, (Hicks (1922), Denny Brown (1951)), recurrent diarrhoea affected at least 4 members, while the propositus of the Cél family (Guillain & Thévenard (1929), Thévenard (1942)), suffered from bouts of diarrhoea and passed up to 10 motions daily. Another patient described diarrhoea and impotence in early middle life, (Turkington & Stieffel (1965)).

Disturbances of autonomic control of visera is also unusual where inheritance of Acrodystrophic Neuropathy (A.N.) is by the recessive mode (Chapter 16), except in those extremely rare phenotypes in which considerable amyotrophy occurs as well (Poilici et al (1960), Jusics et al (1973)).

In the "Z" family which is described later, in which A.N. is combined with overt flaccid paralysis, the propositus IV 16 developed diarrhoea 3 years after the onset of plantar ulceration. 5 years later it became very troublesome and he was admitted to hospital for investigation. This proved negative and 2 years later his diarrhoea ceased spontaneously.

The propositus of another family which combined A.N. with muscle wasting and weakness affecting all members, also suffered from
persistent diarrhoea, and this was accompanied by difficulties of micturition (Bruns 1903).  

When A.N. and muscular weakness and wasting are accompanied by really severe visceral disturbances comparable with those which have been described in diabetic neuropathy, it is probable that the trait present is Familial Amyloid Neuropathy. This diagnosis will only be refuted if amyloid deposition cannot be found in biopsy material taken from several different tissues apart from nerve (Chapter 22).  

Stocks formerly described under the old title of F.L.S. (Barraquer & De Gispert (1936), Alajouanine & Mozzicamocci (1940), Feudell (1950)) and A.U.M.F. (Hermida et al (1964)) all suffered from severe gastro-intestinal and genito-urinary disturbances (as well as swallowing difficulties, hypotension and possible steatorrhoea in Feudell's kindred). With the wisdom of hind-sight, it seems likely that these were families with Familial Amyloid Neuropathy rather than H.S.R.N., as they have usually been classified.
CHAPTER 8

The Trophic Syndrome in H.S.N.N.

(1) Ulceration and Mutilation of the Feet

Almost without exception, it is the soles of the feet which are first affected by trophic changes in H.S.N.N., and lesions at this site always remain by far the most severe, and indeed are only infrequently accompanied by lesions elsewhere.

The first incrustation or ulcer usually forms in the neighbourhood of the first or second metatarsophalangeal joints of one or other foot.

Two factors presumably determine the particular vulnerability of this area. These are its distance from the neuraxis and the mechanical stresses and strains of walking and standing.

The precise localisation of the initial lesion within this area is probably determined by the structure of the patient's foot. Thus in the sibship IV 35, IV 36 and IV 37 and their father I11 13, who were rather flat footed, ulceration first appeared in the ball of the foot, whereas in the sibship I11 25, I11 28 and I11 29, who had
higher arches, it first affected the pad of the big toe. Pes cavus is seldom found in association with H.S.R.N., but where sensory loss is severe enough in C.M.T.D. to predispose to similar trophic lesions, these may first occur along the outer margin of the foot (Halliday & Whiting [1909], Rigley [1936], Hermida et al [1964]).

Characteristically painless, such lesions may come as a complete surprise to the affected subjects, as in the case of IV 28, who first discovered a plantar lesion when washing his feet. Such total lack of awareness is, however, unusual and has been described in only a few patients (Schultze [1917], Riley [1936], Endrélé [1933]). Another patient found an ulcer of one sole, only after first discovering swollen glands in his groin (Spillane & Wells [1969]).

Pain may, however, be severe as in IV 32, and this was the rule in the Australian stock (Wallace [1970]), while paradoxically a lesion which was painless at its inception may become painful when it recurs (Thévenard [1953]), a state of affairs also encountered in the "X" family in the woman IV 29.

In the Australian family, ulcers were always painful, and this contrasts with the propositus of the "X" family IV 37, who suffered only occasional discomfort during 30 years of plantar ulceration.

The original lesion usually heals with sufficient bed rest, but subsequent recurrence is the rule often within a few months, although it may be delayed for much longer periods. This was 5 years in the case of IV 35, and even longer intervals of freedom have been reported (Spillane & Wells [1969]).

Ulceration of one foot may be followed almost immediately by similar changes on the other side, as in the case of IV 37, but in other subjects it may be delayed for very many years. This is difficult to
explain as neurological involvement is usually symmetrical. In the case of \( \text{T} \ 35 \), ulceration did not become bilateral for 25 years, compared with the longest interval (19 years) reported in the literature (Thévenard 1953). In other members of the "X" family the condition has remained unilateral after 27 years in the case of \( \text{T} \ 28 \), and 13 years in \( \text{T} \ 29 \).

Rarely it may never recur on the side originally affected, even when later the opposite foot becomes ulcerated (Spillane & Wells, 1969)

Healing is progressively slower with these recurrent ulcers until eventually they are likely to become permanent unless some factor intervenes which involves greatly restricted activity. In the case of \( \text{T} \ 53 \) this was a degree of muscular weakness which greatly reduced walking. Spending the last years of life in a nursing home may have a similar effect (Wallace 1970). In \( \text{III} \ 16 \) of the "Z" family, overt flaccid paralysis of the legs afforded so much protection from trauma, that the original plantar ulcers healed and never recurred. Such degrees of weakness do not, however, occur in classical H.S.R.N.

The original trophic lesions may never significantly progress, as in the case of \( \text{T} \ 28 \). The appearances of this lesion have not materially altered over 26 years. Similar appearances on both feet of \( \text{T} \ 36 \) remained unchanged for 40 years, only to ulcerate, for the first time in his life, when he was on his death bed.

When deeply penetrating ulcers develop, however, these tend eventually to progress, partly because they indicate more severe expression of the trait, and partly because they permit secondary infection of deeper tissues, including bone.
Involvement of bone, mainly neuropathic, but partly osteomyelitic, is the factor which causes mutilation as opposed to ulceration of the feet. The extrusion of pieces of necrotic bone through the floor of ulcers is a particularly characteristic feature of H.S.R.M. and the allied traits, and is well illustrated by the sequence of events which occurred in the right foot of IV 37 (see Plates 10, 11 and 12). Shortening of the left foot of IV 32, consequent upon similar loss of bone fragments over the years 1970 - 1973, is well illustrated by comparing Plates 30 and 31.

By the time such changes occur, the overlying ulcer or ulcers will have become chronic and associated with changes in the surrounding skin and subcutaneous tissues. Such an ulcer will be of variable size and depth. It may exceptionally be very large and occupy most of the area of the sole (Thévenard 1942). Bone may be exposed in its floor, which is more usually composed of exuberant granulation tissue, and there is a variable degree of secondary infection. The ulcer is surrounded by a collar of hyperkeratotic skin which may be extremely dense and hard, or soft and friable. Small black or dark red patches in this callus indicate the sites of old localised bleeding, while in other places it is pale and avascular. The walls of the ulcer may be greatly undermined so that it appears smaller than it is in reality. A purely illusory appearance of healing may be caused by filling in of the ulcer crater with callus.

The remaining skin of the foot and perhaps the lower third of the leg is often abnormal in advanced cases. It is thickened, rough, scaly and discoloured by mottled brown pigmentation. Rarely there may be gross swelling of one or both legs (Wallace 1970), but this did not occur in the "Y" family.
toe in particular acquiring a volume at least twice normal, and presenting a grotesque appearance. This was accompanied by no more than slight discomfort.

Experience with these two patients suggests that these "poussées" are the external reflections of successive stages of bony involvement. In both cases they subsided after sequestrae were extruded.

Their effect is to produce further mutilation and progressive shortening of the foot.

"Pferdfüüs" (Bruns 1903), "Elefantfüüs" (Göbell & Runge (1914)), "un informe pilon" or misshapen pestle (Thévenard (1942)), are among the descriptions applied to the extraordinary hoof-like appearance that the residual stumps of the feet may eventually acquire in severe cases.

In the "X" family, these appearances were found in 1111 13 and 1111 25, and probably occurred also in 1111 7, who was reported as having "no feet" at the end of her life.

Loss of toes spontaneously or as the result of surgery, erosion of the foot itself, atrophy and fragmentation of phalanges, metatarsals and the anterior tarsal bones, with extrusion of numerous sequestrae, combine to produce these degrees of grotesque mutilation and shortening.

Another major contribution, less well recognised, to this hoof-like appearance, may be provided by backward and upward dislocation of the os calcis.

This event is well seen in the x-rays of 1111 25 of the "X" family, (Plate 18). It has been reported on a few occasions only, (Oehlerker (1906), Bruns (1909), Boudin & Djindjian (1951),
Barrera-Nordas et al (1955), Dyok et al (1965), and apparently did not occur in the Australian stock despite the severity of mutilation in this kindred (Wallace 1970). Assuming that the talus was also displaced or eroded, it may well explain the extraordinary case of the patient who walked on the exposed lower end of his tibia (Göbell & Runge (1917)).

This physical sign might well have been reported more often, but for the fact that legs approaching this degree of mutilation have usually been amputated.

It seems likely that such displacement of the os calcis might otherwise be part of the natural course of events in severe degrees of H.S.R.N. and the allied traits, for the following reasons.

The trophic process has never been described as extending so far back as to destroy the posterior part of the os calcis. A stage will be reached, therefore, when the attachments of all muscles and tendons to the feet have been eroded, but the achilles tendon and its insertion remain intact. Unopposed action of this tendon will tend therefore, to pull the os calcis up and behind the talus and the tibia. On the only recorded occasion when an attempt has been made to reduce this dislocation surgically (Schlecker (1906)), the achilles tendon was found to be shortened and thickened, and had to be divided.

In IV 25, backward dislocation of the calcaneum was not recognised during life. This is consistent with it being a gradual and silent process. It is likely also to be expressed as abnormal lateral mobility at the ankle joint (Bruns (1906)). Occasionally such dislocation may occur suddenly, (Boudin & Djindjian (1951), Brandt (1956)).

Clinically there will also be some elongation of the heel which corresponds with the amount of shortening of the forefoot
contributed by backward displacement of the os calcis. The heel of
IV 32 of the "X" family is currently thought to be abnormally long.
This may represent an early stage of this process in this subject.

2. Complications of planter ulceration

Apart from mutilation and deformity, the ulcers of H.S.R.N.
and the allied disorders frequently become infected, and septicaemic
episodes may occur and may endanger life (see Chapter 14).

Secondary amyloidosis is also an obvious possibility, although
it has only been documented in a single instance (Wallace 1970). It
may have been responsible for the terminal illness in IV 25 of the "X"
family. Rarely, erosion of a blood vessel by the ulcerative process
may induce severe bleeding.

Haemorrhage from one foot was severe and prolonged in III 13
of the "X" family and proved difficult to control.

In one of the Australian patients, brisk unrecognised bleeding
occurred and was only discovered when the patient demonstrated the con-
stitutional effects of severe haemorrhage (Wallace 1970).

A similar but less dramatic occurrence has been described in
a member of another family who one day found his shoe to be full of
blood (Smith 1934).

3. Ulceration of the legs

Ulceration proximal to the heel did not occur in the "X"
family, except transiently in the amputation stump of IV 35. Indeed
Ulceration of the legs is rare in H.S.R.N. generally, although it has been described complicating a plaster cast (Jüghenn et al. 1949).

Perhaps the most extensive area of ulceration ever described in H.S.R.N. was one which almost completely encircled one leg between knee and ankle (Pallis & Schneeweiss 1960).

Ulceration of the legs appears to occur more frequently in other forms of H.S.R.N.

Thus, unexplained ulceration of one knee occurred in 111/16 of the "Z" family and has also developed in other families with similar severe muscle wasting, either as the result of wearing a caliper, (Brunn 1903)) or a plaster cast (Riley(1930)), or after prolonged kneeling (Alajouanine & Mozsoconoci 1940)).

Ulceration of knees has also been described in childhood forms of H.S.R.N. (Dyck (1966), Hould & Verret (1967)), while in another sibling, one member experienced ulceration of one knee and one shin prior to the development of planter ulceration (Jusics et al 1973)).

Ulcers of the legs and knees appear usually to heal more rapidly than planter ulcers, perhaps because of their greater proximity to the neurexis (Thévenard 1953).

The relative invulnerability of the knees and legs, when compared with the soles of the feet, presumably explains the impunity with which some patients have been able to crawl about on well padded hands and knees, after mutilation of the feet has forced them to give up walking (Ogryzlo 1946, Cooper et al 1947, Dyck et al 1965)).

It is remarkable that ulceration of the dorsum of the feet should be so rare when one considers the severity of the assault on their planter aspects. It has not been described in H.S.R.N. and has
occurred only occasionally in the other forms of H.F.A.N. (Clarke & Groves (1909), Ogryzlo (1946), Jusics et al (1973)).

4. Trophic lesions of the hands

Although some sensory loss could be identified in the hands of all the severe affected members of the "X" family who were alive at the time of this survey, trophic lesions did not occur except transiently and rather inexplicably in the case of \( TV \) 36. In the Australian patients, painless injuries of the hands led to scarring but not to indolent ulceration or significant sepsis (Wallace (1970)).

Ulceration and mutilation of the hands, seldom severe, has been documented in H.S.R.N. and the allied dominantly inherited traits in only a few reports (Weitz (1924), Tocantins & Reimann (1939), Van Bogaert (1940), Thévenard (1942), Feudell (1959), Hermida et al (1964), Kuroiwa & Murai (1964), Turkington & Stieffel (1965)).

Usually it follows plantar ulceration by an interval of many years (Thevenard 1953)), except in the single remarkable exception where the hands were first affected (Van Bogaert (1940)).

Among the cases from South Wales, lesions of the hands occurred only in sporadic cases of A.N. and never in those with a family history (Spillane & Wells 1970).

By contrast, trophic lesions of the hands occurred more often and followed plantar ulceration much more rapidly in familial cases where onset was in childhood, and where the trait was limited to siblings with unaffected parents. In some of these families, ulceration also sometimes occurred in bizarre situations, although this is more
usual in sporadic cases with onset in infancy or early childhood, and in such cases the hands may also be affected before the feet. These presumably recessively inherited forms are considered in detail elsewhere. (See Chapter 16).

The predominantly upper limb form of Familial Amyloid may occasionally be complicated by trophic lesions affecting the hands or fingers. (See Chapter 22).

5. Neuropathic Joints

Plate 23 illustrates neuropathic destruction of an ankle joint in IV 25, and similar if less severe involvement expressed as painless swelling, affected IV 53. (See Plate 34).

Charcot joints proximal to the ankle are unheard of in H.S.R.N., but have occurred in the recessively determined A.W.'s, involving knees (Clarke & Groves (1909), Haddow et al (1970), Jusics et al (1973)), or even one hip where it was satisfactorily treated by total replacement (Murray 1973).

6. Spontaneous fractures

These did not occur in the "Y" family, and they are unusual in H.S.R.N. generally, except in small bones of the feet already undergoing neuropathic degeneration. There is only one recorded instance of unprovoked fracture of long bones, in this case tibia and fibula, in H.S.R.N. (Jüghern et al (1949)).
Bones such as the femur, patella or tibia and fibula have more often been reported as undergoing spontaneous fracture in other forms of H.F.A.N., either in association with gross muscle weakness and wasting (Riley (1930), Barraquer - Ferré & Berraquer - Bordes (1946)), or where the trait is apparently recessively determined (Clarke & Groves (1909), Ogryzlo (1946), Heller & Robb (1955), Dyck (1966), Houll & Verret (1967)).

The most striking sequence of spontaneous painless fractures of long bones (including one humerus) occurred in a sibship fulfilling both these criteria of recessive determination, and gross muscle weakness and wasting (Jusics et al (1973)).
R.P.R.R. is one of several inherited traits characterised not only by sensory loss and ulceration of the feet, but also by their mutilation due to neuropathic destruction of their skeletal framework.

These traits can be distinguished from each other on clinical or genetic grounds, or both, and are delineated in different parts of this thesis. Where a neurogenic osteoarthropathy occurs, however, it is essentially non-specific in character, and follows what appears to be an identical pattern in the different traits, although there may be some variation in its severity. It is for example, in general, more severe in the recessively determined traits than in those transmitted by the dominant mode. Nevertheless it is extremely severely expressed in H.S.R.N., as the x-ray plates of the "Y" family show.

The account which follows is a collective one which describes the radiological appearances as found not only in H.S.R.N., but also in some of the allied traits, and in this respect this chapter departs from the pattern which has been followed hitherto, in which
It has been limited mainly to an account of the physical signs as they classically occur in H.S.R.N. alone.

In the "Z" family, in contrast, the only radiological abnormality apart from evidence of surgical ablation of all digits in the propositus, was osteoporosis. This probably arose from disuse, as affected members developed a severe degree of flaccid paralysis presumably before the other abnormalities had time to develop. Similar diffuse osteoporosis, not necessarily severe, without other abnormalities has been the only feature in other families, most of whom have also been characterised by severe muscle weakness. (Riley (1930), Van Epps & Kerr (1940), Barraquer - Ferré & Barraquer Bordas (1953), Plancherel et al (1964)).

A neurogenic basis for the changes in bone that occur in H.S.R.N. and the allied disorders, is implicit in the nature of these disorders, the character and evolution of the osseous changes themselves, and the fact that these may precede trophic changes in the skin.

An example of the latter is provided by \( \bar{X} \) 25 of the "X" family, when atrophic changes in the articular surfaces of a metatarsophalangeal joint antedated plantar ulceration.

More striking examples of this phenomenon have been reported not only in H.S.R.N. (Oehlecker (1909), Heitz (1924), Beiglböck (1938), Van Bogaert (1940), Jackson (1949), Kuroiwa & Murai (1964)), but also in similar traits beginning early in childhood (Price (1913), Jusics et al (1973)).

In one case, overt ulceration did not occur until 27 years after changes in bone had been recognised. (Van Bogaert (1940)).

X-rays have been normal in less severely affected members of other stocks (Mulvey & Riely (1943), Ortiz de Zarrate (1955),...
Reimann et al (1953), Guaraldi (1962), Hermida et al (1964), although this may reflect investigation at an early stage of the disease. Repeat x-ray after an interval may demonstrate abnormalities (Thévenard (1953)).

Once overt ulceration occurs it appears that the changes in bone are accelerated, partly because the introduction of sepsis contributes to their development through osteomyelitis, but perhaps more importantly because of the loss of the cushioning and splinting effects provided by intact skin and subcutaneous tissue. The mechanical stresses and strains now act directly on the bones themselves, as these form the floor of the ulcers.

This is well illustrated by a comparison of the brothers IV 36 and IV 37. The former escaped overt ulceration until he was literally dying, and x-rays of his feet within six months of his death showed quite normal appearances. His brother, IV 37, had a history of 30 years of overt plantar ulceration, and this was accompanied by gross evidence of destruction of digits and metatarsals from an early stage of the disease. While there can be no doubt that IV 37 suffered from a more severe expression of the trait, (this was demonstrated at autopsy), this seems unlikely to be the sole explanation. The plantar ulceration itself probably contributed to the greater severity of the osteoarthropathy.

The changes in the "X" family included erosion of metatarsophalangeal and interphalangeal joints, loss of phalanges, narrowing and tapering and angulation of metatarsals, and in two instances, more severe lesions.

Once established, x-ray abnormalities may remain localised as in IV 29 of the "X" family, or they may steadily progress as illustrated by the serial x-rays of the feet of the propositus, IV 37, seen
The initial appearance is usually accepted as being a rounded translucency located in the head of a metatarsal, or in the base or head of a phalanx, (Weitz (1921), Thévenard (1942), Spillane & Wells (1969), Wallace (1970), Jusics et al (1973)). It is of interest that similar opacities have been described in phalanges in the fingers in Tangier Neuropathy (Kocen et al (1967)) and Familial Amyloid Neuropathy (Mahloudji et al (1969)).

The sites most often involved are in the neighbourhood of the first or second metatarsal-phalangeal joint, presumably for the same reasons that determine the localisation, at this site, of the early lesions in the skin.

Three such areas of translucency, limited to one phalanx, can be identified in the x-rays of BV 28. (Plate 20).

Enlargement and coalescence of these vacuoles is followed by erosion of the articular surfaces of this joint, which is more usually the first radiological sign. (Thévenard (1942, 1953)). Less often the tufts of distal phalanges disappear first (Spillane & Wells (1969)).

Similar erosion may occur into other M-P and I-P joints, although it is remarkable how localised the bony changes may be, with gross destruction in the neighbourhood of one joint, while its neighbours appear completely normal. (Wallace 1970)). This phenomenon is particularly well illustrated in Plate 2.

Patchy osteoporosis characteristically occurs distal to these joint changes.

Loss of a phalangeal or metatarsal head, either through the disease process itself as described, or through surgery, is quickly
followed by the characteristic change of concentric atrophy seen most characteristically in metatarsal shafts. A combination of these two processes, loss of the head of a metatarsal and concentric atrophy of its shaft, most marked distally, lead to the characteristic flame-shaped opacity demonstrated by these bones when the disease is well advanced.

Occasionally, this process may be more acutely disruptive, and fragmentation of phalanges or the heads of metatarsals, may occur with the formation of sequestrae, the extrusion of which is one of the most remarkable features of this group of diseases.

Such changes are dramatically shown by IV 37, (Plates 10, 11, 12). The head of this man's first left metatarsal virtually exploded into a number of free lying fragments. These were extruded over the next few weeks. X-ray later showed disappearance of the distal part of this bone, and of the sequestra.

In another patient, IV 29, the shaft of a phalanx was the source of a single large sequestrum, leaving this bone grossly narrowed and shortened, with preservation of both its head and base. (Plate 28). Similar preservation of articular surfaces in the presence of considerable atrophy of the intervening shaft has been regarded as a characteristic feature. (Giaccoi (1952)).

Narrowing of the shafts of metatarsals naturally also makes them liable to fracture, and this finding is commonplace in the literature.

Occasionally the converse happens and grotesque hypertrophy of a metatarsal may occur (Alajouanine & Mozziconacci (1940), Peron et al (1949)).
This is also unusual, however, and the general trend is towards dissolution and loss of phalanges and distal ends of metatarsals, such progression being often hastened by surgery.

Later, especially in the most severe and longstanding cases, necrosis may spread backwards and invade the tarsal bones, which may fracture easily as in IV 53 (Plate 41), and other cases (Heller & Robb (1955), Dyck (1966), Hould & Verret (1967)), while tarso-metatarsal dislocation may also occur (Wallace 1970).

Rarely, most of the tarsus may be eroded anteriorly, (Gobell & Runge (1918), Ogryalo (1946), Cooper et al (1947)) and even the os calcis may be attacked (Oehlecker (1906), Bruns (1909), Barraquer-Bordes et al (1958)), so that only its posterior aspect may survive (Enderlé (1933)). Pathological fracture of the os calcis may occur (Boudin & Djinájian (1951)).

More often the metatarsals and the tarsus become fused into solid masses so that it becomes impossible to identify constituent bones.

Plate 21, relating to IV 25, shows disappearance with preservation of a narrow tarsometatarsal space between fused masses of metatarsal and tarsal bones. Later this space was obliterated, (Plate 22).

Such ankylosis, together with the occurrence of osteophytes and bizarre hypertrophy of single bones, together with areas of dense calcification and of periosteal reaction, presumably reflect the effects of osteomyelitis playing a subsidiary role in the genesis of these changes. (Wallace 1970).

At a late stage, backward and upward displacement of the os calcis may occur. This has been described in the preceding section and is well illustrated by plate 23 obtained from the patient IV 25.
Changes in the tibia and fibula may eventually occur, but are usually limited to a periosteal reaction at their lower ends, which gives them an irregular and roughened outline. This is seen in Plate 8 relating to IV 37, and has also been reported in other patients, (Gehlecker (1906), Beiglböck (1938), Boudin & Djindjian (1951), Pallis & Schnoeeweiss (1961), Turkington & Stieffel (1963), Wallace (1970)).

Single reports describe tapering lower ends of the shafts of tibia and fibula with dissolution of malleoli (Bruns 1909), and paradoxical hypertrophy of a fibula to three times the girth of its fellow (Gehlecker (1906)). Such changes are rare, and obviously only occur in severe, longstanding cases.

In the vast majority of instances, the lesions are limited to necrosis of articular surfaces of the forefoot, some loss of phalanges for one reason or another, and concentric atrophy of metatarsals of varying degree.

Changes in the hands

Similar changes occur in the hands, but are extremely rare in H.S.R.N. and the other dominantly inherited A.N.s.

They are most often encountered in cases with onset in childhood and unaffected parents, and in such cases they may be severe.

A single account describes changes in the radial epiphysis (Boudin & Djindjian (1951)).
CHAPTER 10

E.M.G. FINDINGS IN THE "Y" FAMILY

1. Methods

13 members of the "Y" family underwent E.M.G. investigation during this study.

Dr. Graham Wakefield, Consultant Neurologist to the Bath Clinical Area, performed these examinations and I am grateful to him for his expertise, and for his comments and advice during these sessions.

The sample consists of 6 affected subjects and 7 of their unaffected first degree relatives.

Regrettably, 3 affected members (IV 23, IV 29, IV 32), declined investigation.

The techniques employed were those of Gilliatt & Sears (1958) for digital action potentials; Gilliatt et al (1961) for lateral popliteal action potentials; and the classical methods (see Leman & Ritchie (1970) and Campbell (1971)) for measuring motor nerve conduction velocity.

The range of normal values has also been derived from these sources.
2. **Results**

These are tabulated as follows:

<table>
<thead>
<tr>
<th>Column A</th>
<th>Designation of subject in Pedigree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column B</td>
<td>Amplitude of evoked potential in Right Median Nerve, after stimulation at second fingers. (Microvolts).</td>
</tr>
<tr>
<td>Column C</td>
<td>Latency of evoked potential in Right Median Nerve at wrist. (Milliseconds).</td>
</tr>
<tr>
<td>Column D</td>
<td>Amplitude of Compound Action Potential in Lateral Popliteal Nerve at neck of fibula, after stimulation at ankle. (Microvolts).</td>
</tr>
<tr>
<td>Column E</td>
<td>Motor Nerve Conduction Velocity in Right Lateral Popliteal (common peroneal) nerve. (Metres per second).</td>
</tr>
</tbody>
</table>
### Affected Subjects

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>36</td>
<td>45</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>52</td>
<td>45</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>55</td>
<td>60</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>56</td>
<td>45</td>
<td>2.0</td>
<td>4</td>
</tr>
</tbody>
</table>

### Unaffected Subjects

| V  | -  | -  | 0  | 45 |
| V  | 48 | 45 | 2.0 | 12 | 50 |
| V  | 57 | 30 | 2.0 | 4  | -  |
| V  | 58 | 60 | 2.0 | 7.5 | 52 |
| V  | 60 | -  | 0  | 7.8 | 51 |
| V  | 61 | 60 | 2.0 | 0 \(\times\) | -  |
| V  | 62 | 30 | 2.0 | 12 |

**Normal Range**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>9 - 45</td>
<td>4</td>
<td>2.0 - 15.5</td>
<td>42 - 61</td>
</tr>
</tbody>
</table>

**Mean** 52.

**Key:**

- 0 = Not obtained
- - = Not recorded
- \(\times\) = Masked by background activity
The right extensor digitorum brevis was sampled with a concentric needle electrode in most cases, but this was avoided in IV 37, in view of the severely inflamed condition of his foot at the time.

Significant abnormalities occurred only in the siblings V 52 and V 53, and took the form of increased insertional activity, and a reduced interference pattern from voluntary recruitment. There was fibrillation but no "giant" units.

3. DISCUSSION

A. Median Nerve Sensory Action Potentials

These were lost only in IV 37, the most severely affected man to be studied.

They were preserved in all the other affected subjects, even those with some superficial sensory loss of the hands including IV 36, who was to die within a year and presented dramatic evidence of degeneration of sensory neurones at autopsy.

Similar preservation of sensory action potentials in the upper limbs in the presence of advanced clinical involvement has been reported (Kuroiwa & Murai (1964), Spillane & Wells (1969)), but they have been lost in other cases (Alajouanine et al (1962), Turkington & Steffel (1965), Spillane & Wells (1969)).

In familial and congenital acrodystrophic neuropathies with childhood onset and probable recessive inheritance, digital sensory action potentials appear to be lost early (Dyck (1966), Haddow et al (1970), Schoene et al (1970), Murray (1973)).
They are also lost in some heredo-familial disorders in which sensory signs form only a subsidiary part of neurological syndromes, notably C.M.T.D. (Gilliatt & Sears (1958), Gilliatt et al (1961), Dyck & Lambert (1968), Spillane & Wells (1969)), Friedreich's Ataxia (Gilliatt et al (1961), Dyck & Lambert (1968), McLeod (1971)), and hereditary spastic paraplegia (Dyck & Lambert (1968).

A denominator common to all these traits, and which distinguishes them from H.S.R.N., is that vibration sense is lost relatively early. An apparent association exists between this modality and sensory action potentials in diabetic neuropathy (Gilliatt & Willison (1962)), so that both are either lost together or both preserved. Both presumably depend on synchronous conduction of a large number of volleys. temporal dispersion of which both abolishes the action potential and prevents vibration from being recognised.

Vibration sense is, of course, preserved until a very late stage of the disease process in H.S.R.N.


Loss of this compound action potential appears to be the earliest E.M.G. abnormality encountered in H.S.R.N., at least in the "X" family, and implies the occurrence of a combination of motor and sensory denervation in the feet or, undue liability to entrapment of the nerve at the neck of the fibula.

It was lost in 4 out of 6 affected subjects, may confidently be presumed to have been unobtainable in a 5th (the severely affected propositus, IV 37, in whom it was not sought), and was preserved only in IV 56, who was the youngest member to be investigated, and also the
most mildly affected.

L.P.N.A.P's have also been studied in 3 cases of H.S.R.N. from South Wales (Spillane & Wells (1969)). They were lost in two but preserved in one. They were also lost in a member of the Australian stock (Wallace (1970)).

Among unaffected members of the "Y" family, this evoked potential was not obtained in two. In one, $IV$ 61, this was because of excess background noise due to failure to relax the muscles. No such difficulty occurred in the other patient ($IV$ 39). This was a man of 46 who had suffered for 12 years from recurring attacks of both superficial and deep vein thrombosis in both legs (which remained brawny and swollen), complicated by two episodes of pulmonary embolism. In addition to these local abnormalities, he had recently induced a weight loss of 4 stones through strict dieting.

The lateral popliteal nerve is highly vulnerable to external trauma as it winds round the neck of the fibula. The most common form of trauma is compression of the nerve between the fibula and the opposite knee when the legs are crossed. This is particularly likely to occur in subjects who have lost much weight (Lerman & Ritchie (1970)).

Taking all these factors into account, it would have been surprising if this potential had been obtained in this man.

In subjects with generalised neuropathies, individual nerves are more liable to the effects of entrapment, or traction, than they are in normal individuals. This state of affairs has been demonstrated in diabetes (Mulder et al (1961)), Gilliat & Willson (1962)), in myxoedema (Simpeon (1962) and in familial neuropathies with liability to pressure palsies (Earl et al (1964), Roose & Thygesen (1972), Behse et al (1972)).
C. **Motor Nerve Conduction Velocity.**

Considerable slowing of M.N.C.V. was first described in H.S.R.N. in a Japanese kindred (Kuroiwa & Murai (1964)), and subsequently confirmed in 2 out of 3 of the patients from South Wales, (Spillane & Wells (1969)). A normal value was obtained in an American negro patient with the disease in advanced form (Turkington & Stieffel (1965)).

It nevertheless came as a surprise to find severe degrees of slowing in two members of the "X" family. These subjects also showed the greatest degrees of amyotrophy.

Reduction in M.N.C.V. of 40% or more, as found in V 52 and V 53, is regarded as signifying segmental demyelination, presumably with consequent abolition of saltatory conduction (Simpson (1964), Thomas & Lancelles (1965), Gilliatt (1966), Lerman & Ritchie (1970)).

4. **Conclusions**

The electrophysiological abnormalities demonstrated in affected members of the "X" family, comprised loss of the lateral poplitesal nerve action potential, muscle denervation and slowing of M.N.C.V. in subjects with appreciable muscle wasting, and preservation of digital sensory action potentials until a very advanced stage of the disease.

These signs do not contribute to the early diagnosis of the trait, because none of them precede the appearance of clinically demonstrable cutaneous sensory loss.

It was thought possible when this study was first begun, that
slowing of sensory nerve conduction might lead to the identification of heterozygotes in advance of obvious clinical involvement, in the same way that slowing of M.N.C.V. does in C.M.T.D. (Lambert (1956), Gilliatt & Thomas (1957), Dyck et al (1963), Myrianthopolous et al (1964)), and in metachromatic leukodystrophy (Pullerton (1964)).

The reason for this seems clear. Sensory action potentials provide no information about the smaller myelinated and "non-myelinated" axons (Gilliatt & Sears (1958), Gilliatt et al (1961)), which are believed to be the first to be affected in H.S.R.N.

It is of interest that although H.S.R.N. is predominantly a sensory disorder, the E.M.G. signs are predominantly motor. Even loss of the lateral popliteal nerve action potential implicates motor denervation, because it is compounded of orthodromic impulses in sensory fibres, and antidromic impulses in motor fibres, and its disappearance must therefore depend on impaired conduction in both.

The E.M.G. may, however, help in differentiating dominantly inherited H.S.R.N. from the recessively determined forms of H.F.A.N. (see Chapter 16), in those occasional cases where this cannot be decided on genetic grounds alone. In the recessive traits, digital action potentials are lost from the outset, but M.N.C.V. is normal (Dyck (1966), Haddow et al (1970), Schoene et al (1970), Murray (1973)), while a small L.P.N.A.P., presumably derived from intact motor fibres, may be retained (Dawson (1966)).
CHAPTER 11

PATHOLOGY OF H.S.R.N.

1. Introduction: Material from the "X" Family

Three members of the "X" family came to autopsy, and the findings in each case are reported in their individual case protocols in Chapters 4 and 5.

The neuropathological examination of III 13 was carried out by the late Dr. A.P. Norman, and of IV 36 and IV 37 by Dr. Betty Brownell, both of the Burden Neuropathological Laboratory at Frenchay Hospital. I am particularly indebted to the latter for her comments and advice, and for microphotographs of sections of anterior and posterior nerve roots from III 36 (Plates 35 and 36), and of posterior nerve roots from III 37, (Plates 37 - 41).

Unfortunately, a series of administrative mishaps prevented the presentation of the comprehensive account of the pathological findings which might be anticipated from such an abundance of material. These arose from the procedure followed. This entailed a routine postmorte
conducted in one city, at which the material was obtained, and sent on to another city for neuropathological examination.

In two cases, (IV 13 and IV 37), the cords were extracted from the spinal cavity in such a way that their dorsal root ganglia were avulsed, and were thus not available for histological examination. In the third case, (III 36), restrictions were placed by the relatives so that only the lumbar portion of the cord (in situ within the vertebral column) was made available. A section of posterior tibial nerve from III 13 was examined, but specimens of peripheral nerve and of muscle were either not obtained as in the case of IV 37, or were mislaid in transit as in the case of IV 36.

The account of the neuropathology of H.S.R.N. which follows includes the findings in these three members of the "X" family, but is from necessity heavily supplemented by data from the literature.

This literature consists of autopsy reports of familial examples of classical H.S.R.N. (Jughem et al (1949), Denney Brown (1951), Blackwood (1952), Van Bogaert (1953), Reimann et al (1953), Campbell & Hoffmann (1964), Wallace 1970), and mention of a sporadic case in which the evidence for genetic determination appears fairly strong (Geschwind & Segarra (1969)), and three other sporadic cases (Cirard et al (1953), Vignon et al (1956), Spillane & Wells (1969)) are excluded as there is no evidence that they were genetically determined, while another familial case (Giaccoi (1952) is also excluded because the recessive mode of inheritance involved implies a different trait.

The section on peripheral nerve is also supplemented by nerve biopsy reports from typical cases, but not from similar reports describing changes occurring in familial acrodyatrophic neuropathies shown elsewhere (see Chapter 16), to be entities distinct from H.S.R.N. (Boudin &

2. Brain

Areas of infarction were found in the brains of both 111 13 and 111 37. These must have occurred as late events in the general illness to which both succumbed, and there were no abnormalities which could be assigned to the hereditary disorder.

However, degeneration of cerebellar neurones and of inferior olivary nuclei has been described in one familial case (Blackwood (1952)), and in a sporadic case in which there was a family history of nerve deafness but not of neuropathy (Geschwind & Segarra (1969)).

3. Cranial nerves

In families in which deafness forms an apparently integral component of the clinical tableau of H.S.R.N., degenerative changes of differing degree have been described in the auditory and cochlear nerves and their peripheral sensory ganglia. (Denny Brown (1952), Blackwood (1952), Greenfield (1958), Hallpike (1963)).

As stated already, deafness did not occur in the "X" family.

4. Spinal Cord

The naked eye appearances of the cord in H.S.R.N. have usually been normal, with no sign of the slight atrophy seen, for example,
in C.M.T.D., except in the Australian cases where the dorsal columns appeared shrunken, especially in the lumbo-sacral region (Wallace (1970)). In IV 37 of the "X" family, however, there was vascular congestion of grey matter.

In a member of a family in which clinical signs very similar to classical H.S.R.N. were accompanied by pronounced muscular weakness and wasting in all cases, together with involvement of bladder and bowels (Barraquer & Be Gispert (1936)), a large syringomyelic cavity was visible to naked eye inspection (Barraquer - Ferré & Barraquer - Bordas (1955)), but the specimen was lost and not submitted for histological examination. This unusual and unconfirmed finding is scarcely relevant to H.S.R.N. as the trait appears to be quite different. It is mentioned again here for the sake of completeness.

The most consistent microscopical finding in the cord has been loss of myelinated fibres in the posterior columns, although this is mild when compared with the severity of degeneration seen in the posterior roots, and indeed it appeared to be absent in one case (Jüghenn et al (1949)). This discrepancy was otherwise most marked in IV 36. The changes in the posterior columns are present at all levels, but are most marked in the gracile tracts in the lumbo-sacral region. They are, however, evident also in the thoracic and cervical regions as in IV 13 and IV 37, and can be traced up to the medulla. The cuneate tracts are invariably less degenerated than the gracile, and may appear quite normal in upper cervical segments. (Denny Brown (1951)).

No especial involvement of the dorsal root zone (of Flechsig) was noted in the 3 members of the "X" family, and in another patient (Campbell & Hoffman (1964)). This is at variance with other accounts (Denny Brown (1951), Blackwood (1951), Van Bogeert (1953), Greenfield (1958)), and similar disagreement relates to the appearances of
Lissauers tract (seen to be affected in 111 13).

In 111 13, well marked pallor was discerned in the peripheral antero-lateral white matter. A similar appearance was demonstrated in two autopsies from the New South Wales kindred (Wallace (1970)).

This finding, may reflect a similar change to that seen in C.M.T.D. (Hughes & Brownell (1972)) in which a peripheral rim of myelin pallor occurred in association with fibrosis of the leptomeninges and was distinct from the spino-cerebellar tracts.

Long tract involvement, other than the posterior columns, has not otherwise been demonstrated in H.S.R.N.

The anterior horns of grey matter were normal in all three members of the "Y" family who were pathologically examined, and this has been the general experience. Exceptions are provided by a member of a large American kindred, who presented an unusual degree of distal amyotrophy, and by both autopsies from the Australian kindred. In the former patient, the anterior horn cells stained feebly and their nuclei were eccentric, while some showed central chromatolysis (Reimann et al (1958)). The significance of these findings is doubtful as they may apparently occur in control material (Hughes et al (1968)) and there appears to have been no outright loss of cells as occurs in C.M.T.D. (Hughes & Brownell (1972)). In the Australian cases (Wallace (1970)) there was diffuse loss of Nissl granules from the anterior horn cells, but again there is no mention of outright neuronal "fall-out".

Autopsy findings in the cord, construed as implicating a possible dysontogenic basis for H.S.R.N. (Jügemann et al (1949, Van Bogaert (1953)) have been discussed elsewhere (see Chapter 2), and will not be reconsidered here.
5. Nerve Roots

In all three members of the "X" family, the dorsal nerve roots appeared grey and atrophic to the naked eye at all levels, and this contrasted with the normal appearances of the ventral roots.

Ventral root involvement has, however, been noticed at one autopsy (Campbell & Hoffman (1964)). This patient had severe generalised muscular wasting and weakness. Only the eighth cervical anterior root was involved, and the abnormality was slight when compared with the corresponding posterior root.

Microscopically the contrast is even more striking, irrespective of whether sections are stained for myelin or for axons, (Plates 35 & 36). Indeed, there appears to be equal loss of these elements in the dorsal roots, whereas they are both intact in the ventral roots.

Although present at all levels, these changes in the "X" family, as in others, were more marked in the lumbar and sacral than in the thoracic and cervical segments. The first sacral dorsal root is probably the most often severely degenerated, followed in sequence by the lower 3 or 4 lumbar and 2 and 3 sacral, and then by the lower cervical and first thoracic, but even the most severely affected roots are not totally degenerated (Blackwood (1952), Greenfield (1959)).

The degree of degeneration affects the central and peripheral parts of the roots more or less equally.

Not surprisingly, the degree of neuropathological change is greater where the clinical course of the disease has been more severe. Thus, degeneration was more severe in 111 37 (See Plates 37 - 41), than in 111 36.
T.S. of Anterior (upper and lower left) and Posterior (upper and lower right), fifth lumbar nerve roots, stained luxol-fast blue and cresyl violet for myelin.

Magnifications: upper x 250; lower x 675.

Comment: Severe loss of myelin sheaths in posterior root, contrasts with normal appearance in anterior root.
T.S. of Anterior (upper and lower left) and Posterior (upper and lower right) fifth lumbar nerve roots stained with Holmes axon stain.

Magnifications: upper x 250; lower x 675.

Comment: Severe loss of axons in posterior root compared with normal appearances in anterior root.
Longitudinal section of first sacral dorsal nerve root x 310, stained with Holmes Axon Stain, showing severe depletion of axons.
Longitudinal section of first sacral dorsal nerve root x 750 (Holmes), showing severe loss of axons with irregularities in calibre of survivors.
Longitudinal section of first sacral dorsal nerve root (Loyez) x 310, showing severe depletion of myelinated fibres. Beaded appearance of survivors indicates degeneration.
Longitudinal section of first sacral dorsal nerve root x 750 (Loyez), showing greatly reduced number of myelinated fibres. "String of sausages" appearance of survivors indicates degeneration.
Transverse section of dorsal nerve root (4th lumbar) x 750 (Loyez).
Only a few myelinated fibres survive. The changes are more severe than in IV 36.
A generalised and variable degree of fibrosis of dorsal roots occurs. This was marked in 111 13 and 111 37 of the "y" family, and has been more marked in some subjects (Campbell & Hoffmen (1964)) than others (Denny Brown (1951)). Here again it is probably no more than might be expected from the degree of atrophy (Brownell (1973)), and therefore from the clinical severity of the disorder, as it affects different individuals.

6. **Dorsal Root Ganglia**

Posterior root ganglia were available for examination in the "x" family, only from 111 36, for the reasons already stated. These showed the abnormalities which typically occur in H.S.R.N.

Thus there was gross degeneration and disappearance of nerve cells, with proliferation of capsule cells and of fibrous tissue. The capsule cells occurred in clumps, presumably around degenerated neurones forming "residual Knötchen" as also seen, for example in Friedreich's ataxia, (Hughes et al 1968)) and in C.M.T.D. (Hughes & Brownell (1972)). There was also gross loss of intraganglionic fibres, but this did not selectively affect the larger myelinated fibres as in these other traits. There was also no sign of the proliferation of very fine unmyelinated fibres forming spherical tangles, such as occur in F.A. and C.M.T.D., although these have been noted in H.S.R.N. (Greenfield (1958)). This is considered to be a phenomenon associated with regeneration, and suggests that this process may be less in H.S.R.N. than the other diseases (Brownell (1973)).

The most severely affected ganglia naturally occur in relation
to the worst affected dorsal roots, and are therefore those of the lumbar and cervical enlargements of the cord, particularly the former, as already stated. There must also be variations between patients according to the severity with which the trait is expressed.

Capsule thickening and a diffuse increase in intraganglionic fibrous tissue are more marked in association with more severely degenerated ganglia, and have been more evident in some subjects (Blackwood (1952), Wallace (1970)) than in others, (Denny Brown (1951)).

As in other reports (Blackwood (1952), Campbell & Hoffman (1964), Wallace (1970)), there was no evidence of infiltration with hyaline material, whether resembling amyloid (Denny Brown (1951), Greenfield (1958)) or not, (Van Bogaert (1953)). When present, this material has taken the form of hyaline bodies containing pale, distorted nuclei, occurring between surviving neurones and in relation to capillaries, mainly under the capsule of the ganglion (Denny Brown (1951), Greenfield (1958)), or more widespread in proximal nerve fibres and at the periphery of the cord itself (Van Bogaert (1953)).

7. Peripheral Nerves

These, with a single exception (Case 2 of Pellis & Schneeveiss (1960)), invariably appear abnormally thin.

There is uniform agreement that the signs of Wallerian degeneration which are present in the nerve roots, both central and peripheral to the dorsal root ganglia, increase progressively as nerve trunks are followed to the periphery.

Thus, in one of the first patients to be exhaustively studied,
(Denny Brown (1951)), there was only patchy loss of axons and myelin in proximal nerve trunks, whereas the loss in the sciatic nerve at mid-thigh level amounted to fully \( \frac{1}{4} \) of fibres, and in the posterior tibial nerve at the knee, to about \( \frac{3}{4} \). It was even greater at the ankle where muscular nerves retained fewer than \( \frac{1}{4} \) of their complement of intact fibres.

The posterior tibial nerve of 111 13 was the only one examined in the "X" family. It was severely atrophied and contained only a few intact axons and sheaths. Similar changes in anterior tibial nerves have been reported in other subjects (Campbell & Hoffman (1964), Spillane & Wells (1969), Wallace (1970)).

More peripheral and subcutaneous nerves such as the sural and interdigital are the most severely affected, showing almost total loss of fibres (Blackwood (1952)), sclerosis of terminal twigs (Van Bogaert (1953)), Schwann cells and connective tissue overgrowth without surviving myelin or axons (Campbell & Hoffman (1964)), only a few normal nerve fibres (Turkington & Stieffel (1965)), almost total replacement by fibrous tissue (Spillane & Wells (1969)), total denervation of the skin (Lassmann & Paratsch (1970)) and loss affecting all fibre diameters, particularly small unmyelinated fibres (Dyck et al (1971)).

In spite of the severity of these lesions, signs of active degeneration are slight and represented only by occasional fragments of disintegrating axons, or by myelin droplets (Denny Brown (1951), Greenfield (1956)), or there may be no degradation products at all (Lassmann & Paratsch (1970), Dyck et al (1971)).

Such fibres as survive among densely packed columns of Schwann cells and increased fibrous tissue, appear to be healthy and intact (Denny Brown (1951), Van Bogaert (1953), Greenfield (1958),

The progressive loss of myelin which accompanies axonal degeneration is reported as being segmental in distribution (Jügenn et al (1949), Lassmann & P artsch (1970), Dyck et al (1971)).

8. Muscle

Histological evidence of neurogenic atrophy of varying degree has usually been found in H.S.R.N. when sought, but specified as being absent in other instances (Denny Brown (1951), Wallace (1970)).

9. Skin and Subcutaneous Tissue

The abnormalities occurring in these tissues in H.S.R.N. have been the subject of a recent study of amputation material (Lassmann & P artsch (1970)). In addition to evidence of inflammation, scarring, hyperkeratosis, old and recent haemorrhage and almost total cutaneous denervation, there were pronounced vascular changes. These took the form of a peripheral microangiopathy characterised by intimal proliferation of arterioles, swollen capillary cells and microangiomas.

Similar changes have been described less recently by other authors (Jügenn et al (1949), Pallis & Schneeweiss (1960)).
CHAPTER 12

PATHOGENESIS: Theoretical Considerations

Facts and theories concerning the H.S.R.N. trait itself and the physical signs which it causes, are discussed under the following headings.

(I) The H.S.R.N. trait itself
(II) The Sensory Syndrome
(III) Muscular wasting and weakness
(IV) Reflex impairment
(V) The Trophic Syndrome

(I) Pathogenesis of the H.S.R.N. trait itself

It is not a great theoretical venture to propose that the mutant gene which is expressed as H.S.R.N. does so by inducing some abnormality in the synthesis of a substance essential for the structure, or function, of certain first sensory neurones.

It is known that neurones are highly susceptible to oxygen and carbohydrate lack, but the gradual nature of the process makes it unlikely that the gene acts through simple prohibition of such vital nutrients.

It is also known that both the cytoplasm of the neurone and
the myelin sheath, are substantially composed of lipid substances, as well as proteins, and that cholesterol esters accumulate in nerve which is undergoing Wallerian degeneration (Cummings (1961)).

Neuropathy may be a prominent feature of at least five bizarre genetically determined syndromes due to disordered lipid metabolism (Wilson (1965), Cummings (1965), Simpson (1968)), three of which (Hofsaun's Syndrome, Metachromatic Leucodystrophy and Tangier Neuropathy) may persist into adult life.

These extremely rare traits differ from H.S.R.N. in such respects as recessive inheritance, early age of onset, complex abnormalities affecting tissues other than peripheral nerve, and primary segmental demyelination, rather than Wallerian degeneration, as the defect underlying the neuropathic components of the respective syndromes.

Primary segmental demyelination is usually ascribed to disease originating in Schwann cells (Gilliatt (1966), Simpson (1964, 1968, 1971), Gutrecht & Dyck (1966), Gutrecht et al (1968), Dyck et al (1971), Thomas (1971)), and there is no evidence for supposing that this is the primary event in H.S.R.N. Indeed, Schwann cell multiplication in this disease to form densely packed columns, reflects their normal behaviour, in Wallerian degeneration, and presumably represents their contribution towards attempts at regeneration (Malamud (1957), Greenfield (1958), Simpson (1968)). Their subsequent replacement by fibrous tissue is also a normal event when regeneration fails to materialise.

Disturbances of porphyrin metabolism which may be expressed as neuropathy (Goldberg 1959), Dean (1966), Ridley (1969)) do not occur in H.S.R.N. and the same is true of amyloidosis (See Chapters 22 and 23), although the evidence here is somewhat less convincing because of the pathological findings in one case with H.S.R.N. (Denny Brown (1951)) and
because of strong clinical similarities including dissociated sensory loss and trophic lesions.

For all these reasons, it seems virtually certain that the abnormality in H.S.R.N. resides in the abnormal formation of a protein, which is particularly vital to the structure or function of first sensory neurones.

At its simplest, a point mutation may be involved which takes the form of a single base substitution in the D.N.A. of a structural gene, as is the case in the abnormal haemoglobins (Lehmann & Carroll (1969)). As a result, an inappropriate amino-acid is coded and introduced into the amino-acid sequence of a polypeptide chain, which is, in consequence, defective. This defect is then conferred upon the protein molecule of which this polypeptide chain becomes a component.

Such proteins are either chemically less active, physically more unstable, synthesised inadequately, or affected indirectly through a repressor, or inhibitor, or in some other way (Harris (1968)).

Whatever the defect, its nature in H.S.R.N. must be such that its effects have the following characteristics:

(a) They are heterozygously expressed.

(b) They are most apparent among neurones of the lower lumbar, upper sacral, lower cervical and first thoracic dorsal root ganglia. These are the neurones which subservce sensation in the limbs, and must in consequence have the longest axons, and therefore presumably, the greatest metabolic requirements.

(c) They involve, more or less equally, or at least in rapid sequence, both the neurone and its myelin sheath, rather than predominantly one or the other, as is the case in other neuropathies, although the initial process is undoubtedly one of primary neuronal
failure and axonal decay.

(d) They are most pronounced, to begin with, at the extremities of these axons, but spread proximally towards the cell body as the disease progresses.

To explain all these characteristics satisfactorily, it is tempting, if speculative, to postulate that the mutation has an early, adverse effect upon the perineuronal cell membrane (axolemma). This intervenes between and is integrally related to both neurone and myelin throughout almost its entire length. It is essential to the neurone, and known to participate in the myelination process (Greenfield & Meyer (1963)).

A classical example of primary damage to cell membranes, occurs in the Thalassaemia, where the genetic defect is one of delayed synthesis of one or other of the globin chains, with consequent under-production of haemoglobin. The other globin chains are synthesised in normal amounts, but as they cannot be used, they are believed to be precipitated, and may damage the erythrocyte membrane mechanically (Weatherall (1969)).

There is no reason for believing that this type of defect is unique to the thalassaemias. It may illustrate a mechanism as widespread in nature as the simpler disturbance which accounts for the abnormal haemoglobins.

An analogous situation could occur in primary sensory neurones, with under-production of a neuroprotein, and accumulation of a similar toxic or traumatic deposit independently damaging the cell membrane, and through it, the myelin sheath. The dual effects of defective protein synthesis, and membrane and myelin destruction, eventually cause death of stricken neurones.

It is not necessary to look far among the hereditary neuropathies to find examples in which there is evidence of deposition of
spurious substances, which might have originated as the result of a process of this sort. Thus amyloid is found around neurones and their fibres in dorsal root ganglia and peripheral nerve in Familial Amyloid Neuropathy (see Chapter 22), while atypical findings in H.S.R.N. have included a similar distribution of a substance resembling amyloid, but lacking its staining properties (Denny Brown (1951)) and of a clear hyaline substance (Van Bogaert (1953)).

This concept is not invalidated by the observation that axonal degeneration is greatest peripherally in H.S.R.N. The existence of a centrifugal flow of axoplasm, from the perikaryon down the length of the axon, has been recognised since early experiments which showed swelling of axons proximal to constrictions (Weiss (1943)), and an outflow of axoplasm from their central ends when they are severed (Young (1945)). It is known that proteins synthesised in and around the nucleus, are conveyed along the axon to replace those catabolised distally, (Droz & Leblond (1963)), and a similar flow transporting exogenous toxins has also been demonstrated (Pleasure et al (1969)).

Surplus polypeptic chains could doubtless be moved in the same way. These would tend to become trapped as the axon tapered. Cell membrane damage would thus be greatest peripherally, where the effects of the associated protein deficiency would also be felt most acutely. Small neurones with narrow diameter axons would be particularly vulnerable.

Defective protein synthesis of this type is explained better by mutation occurring in a "controller" gene than in a structural gene (Weatherall (1969)).

Such a mutation may lead to the synthesis of an altered "repressor" substance, which abnormally, and more inflexibly, regresses structural genes responsible for the synthesis of a particular protein.
Being diffusible, this substance would affect both members of the relevant allelic gene pairs, so that the trait would be expressed in heterozygotes (Emery (1971)).

2. Pathogenesis of Sensory Dissociation

Since the eclipse of the old ideas involving lumbo-sacral syringomyelia and myelodysplasia, three theories have been put forward to explain the occurrence of sensory dissociation in H.S.R.N. These may be designated the Dimensional, Radicular and Environmental theories, and are considered in succession.

(A) The Dimensional Theory

According to this theory, the first sensory neurones to be affected in H.S.R.N. are those whose axons combine the dimensions of narrow diameter with the greatest length.

The latter characteristic determines the acral beginning of sensory loss, while the former is responsible for it being initially, at least, confined to the modalities of pain and temperature perception. According to simple orthodox theory, these forms of sensation are subserved by smaller neurones with fine diameter myelinated, or so-called unmyelinated fibres.

Quantitative estimates of depleted axons were not made in the "X" family, nor in any of the other reported necropsies (See Chapter 11) and until these have been carried out this theory rests on impression, and remains unproved.

Support for it is, however, provided by a study of biopsied sural nerve from a patient with H.S.R.N. (Dyck et al (1971)). A marked decrease was in fact found in all fibre populations, although the small
unmyelinated fibres were the most severely affected.

In discussing sensory dissociation in H,S.R.N, (Denny Brown (1951)) refers to the striking loss of small ganglion cells and fibres, but in the accompanying report of Greenfield's findings, which form the major contribution of this paper, there is little factual evidence in support of this observation, except in the posterior tibial nerve where it was evident that the surviving fibres appeared to be uniformly large.

Evidence from the "X" family to support the dimensional theory can be summarized as follows:

(1) In the dorsal root ganglion of T6 36, there was no sign of the relative increase in fine unmyelinated fibres seen in F.A. (Hughes et al 1968) and C.M.T.D. (Hughes & Brownell 1972). In these two traits there is selective loss of larger myelinated fibres, with preservation of smaller fibres, and the latter must therefore appear to be increased in number relative to the total fibre population.

(2) Posterior root degenerative in the "X" family was more severe than is seen in C.M.T.D. and probably approaches F.A. in severity. Posterior column degeneration, however, was considerably less severe than that encountered in these two diseases (Brownell 1973). Fibres ascending in the posterior columns on their way to synapses in the cuneate and gracile nuclei, which subserve proprioception, are known to possess the largest diameters of all sensory neurones (Melzack & Wall 1962), (Calne D.B. & Pallis C.A. 1966). Evidently most of the degenerated axons seen in the dorsal roots in the "X" family must have other destinations within the cord, these largest of all fibres being relatively spared.

(3) Digital nerve action potentials which provide information only about larger afferent fibres are preserved until a late stage of
disease, even in the presence of definite sensory impairment. As there must be loss of some afferent fibres to account for the latter, the inference must be that these are of small diameter. Circumstantial evidence supporting the fine fibre theory can also be derived from a study of the findings in other neuropathies. Thus, dissociated anaesthesia similar to that seen in H.S.R.N. is also seen in Amyloid Neuropathy. In this disorder there is nerve biopsy evidence of selective loss of fine diameter fibres (Dyck & Lambert (1969), Dyck et al (1971)).

A similar predominant loss of small fibres has also been shown to occur in a patient with childhood onset of a familial trait combining dissociated sensory loss and trophic lesions with liability to limb bone fractures and gross muscle wasting (Jusic et al (1973)).

The afferent pathways in Friedreich's Ataxia have been the subject of detailed study (Hughes et al (1968)) and the findings cast some light upon H.S.R.N. because of the striking contrasts which are involved. Thus, although superficial sensory loss in F.A. is usually slight, (Saunders (1913)), both vibration sense and position sense are severely impaired, reflex loss is greater and there is early loss of digital action potentials (Dyck & Lambert (1968)).

The afferent pathways in F.A. are characterised by selective depletion (up to 95%) of myelinated fibres, with preservation of those of smaller calibre (Greenfield (1958), Hughes et al (1968), McLeod (1971)).

Clearly different populations of sensory neurones degenerate in F.A. and H.S.R.N. and the dimension concerned is apparently that of size.

A recent study of C.M.T.D. (Hughes & Brownell (1972)) confirms that in this disease also, the afferent fibres chiefly affected are those of larger diameter, and this accords with the more usual sensory and reflex findings seen in this disease (see Chapter 18).
Why one neuropathy should affect larger diameter fibres and another those of lesser calibre is unexplained (Simpson (1968)).

It is unlikely that size alone is crucial. Sensory neurones resembling each other morphologically, probably also do so in other ways, such as metabolic requirements, membrane thickness and the rate at which they pump axoplasm centrifugally (Hughes et al (1968)).

The relative preservation of touch in all these disorders is probably due to the triple representation of this modality in fibres of large, medium and fine diameter (Dash (1968)).

It has been shown that all sensory modalities, all fibre sizes on biopsy, and all components of the compound nerve action potential are lost in a disorder designated Hereditary Sensory Neuropathy (Dyck et al (1971)). The trait investigated was, however, quite distinct from classical H.S.R.N. The patients concerned were members of a single French Canadian sibship (Dyck (1966), Hould & Verret (1967)), with unaffected parents, early age of onset and evident affinities with other sibships, some of whose parents were consanguineous. (Chapter 16).

Aware of these distinctions, this disorder has subsequently been renamed Hereditary Sensory Neuropathy Type II, to distinguish it from H.S.R.N. (Ohta et al (1973)).

If the dimensional theory of neurones is correct, the following sequence of events may be visualised as taking place in H.S.R.N.

The first neurones to be involved are the smaller ones with the longest axons, and are located in lower lumbar and upper sacral ganglia.

As a result, pain and temperature sensation become impaired in the toes and distal parts of the soles. This may not be clinically
recognisable at first because it is incomplete and patchy, but gradually becomes more obtrusive.

Later, more and more similar neurones successively succumb and, as these include those with progressively shorter axons, loss to these modalities spreads proximally and becomes more dense distally.

From analogy with C.M.T.D. (Christie (1961)), it may next be inferred that sensory loss will begin in the fingers, when it has reached mid-calf level in the legs, these areas being equidistant from the neuraxis. By the time anaesthesia is recognised in the fingers, however, loss in the legs will have extended still further proximally.

Perhaps by this time larger and less susceptible neurones in the lumbo-sacral ganglia are beginning to experience the effects of the metabolic defect, so that other modalities, especially touch, become impaired in the toes and forefoot. Perhaps at about this time also, motor fibres become involved, as well as large sensory neurones forming the afferent arcs of tendon jerks.

At some stage in this process a particular configuration of afferent nerve involvement develops with secondary effects on vessels, skin and subcutaneous tissue, so that not only does trauma go unrecognised, but it becomes translated into trophic lesions, and unless some form of protection is enforced, usually in the form of rest, normal healing will be prevented.

B. Radicular Theory

Denny Brown (1951) proposed the theory that H.S.R.N. is a progressive radicular disorder.
Severance of any single nerve root is known to produce an area of sensory loss which is greater for pain and temperature than it is for touch.

According to this theory, therefore, the earliest signs of H.S.R.N. are to be ascribed to destruction of the first sacral roots and ganglia. Later, as adjacent ganglia succumb, the degree of dissociation becomes progressively reduced, a state of affairs which he considered to be true of his "R" family.

Apart from the inherent improbability of such methodical and stepwise progression, the objection to this theory rests on the repeated observation that ganglion destruction never becomes complete, as some neurones always survive (Blackwood (1952), Van Bogaert (1953), Greenfield (1958)).

Furthermore, in the "X" family and most kindreds, notably the large Australian stock (Wallace (1970)), dissociated loss does not diminish relative to global sensory loss, but always remains much more extensive.

In H,F,A,N, of C,M,T, type as exemplified by the "Z" family, considered later, it is possible that the radicular element is more important. Sensory loss in C,M,T,D, tends to be radicular in distribution, in contrast to its glove and stocking topography in H.S.R.N. (England & Denny Brown (1952), Brodal et al (1953), Wells (1965)).

In both living affected members of the "Z" family, the total area of sensory loss has not materially increased over several years, although the loss to pain and temperature has become more dense, while within the anaesthetic area, the loss to other modalities has become greater and more extensive, so that sensory dissociation does appear, in fact, to have diminished.
C. Environmental Theory

Wallace (1970) has advanced a different theory to account for the regional distribution of sensory loss in H.S.R.N. and for its dissociated character, based on his observations in the large Australian "E" family.

In one member of this stock, a blow on any part of the body induced numbness at the site injured, and this lasted for several hours. A similar observation has been made in an American family (Van Epps & Kerr (1937, 1940)).

It was also found that the disease was more severely expressed in subjects living in colder parts of Australia, and in no fewer than 7 members, onset of the disease had followed exposure to intense cold. In 3 subjects the tips of the ears were anaesthetic. In another patient, a dairy farmer, extensive sensory loss had been found during the winter, but this had largely disappeared when he was re-examined in midsummer, and had entered a more sheltered occupation.

There are also several reports in the literature, discussed elsewhere, which indicate that frost bite, immersion foot and certain highly adverse social circumstances can generate almost exact phenocopies of this genetic trait (Chapter 23).

On the basis of these observations, Wallace has suggested that trauma in general, and cold in particular, contribute not only to the occurrence of trophic lesions, but also to the anaesthesia which underlies them.

The legs below the knees, and the hands, are among those parts of the human body which feel most the effects of cold, and this is held to be the factor which determines the main distribution of sensory loss.
in these areas in H.S.R.N.

It is also the surface of these parts which suffer most, and so the more superficially located nerve endings and end-organs, which subserve pain, temperature and touch, suffer more than the deeply placed receptors mediating other modalities.

Dissociated anaesthesia results.

Cold, and other forms of trauma, it is argued, damage nerve endings which are incapable of regeneration because of the inherited metabolic defect in the axon. Repeated damage leads to retrograde degeneration, first of the nerve trunks themselves, and eventually of the parent cells in the dorsal root ganglia.

An objection to this theory resides in the assumption that the distribution of the neurological deficit in H.S.R.N. is so unique as to warrant special explanation. In fact, this is not so, as a similar distribution is encountered in numerous neuropathies characterised by axonal "dying-back", where the metabolic or toxic defect is known to act on the parent neurone, rather than on peripheral nerve endings.

A similar special case is argued to explain the paramount loss of pain and temperature sensation. It is, however, not unusual to find selective loss of individual modalities of sensation in other familial disorders of the nervous system (Greenfield (1958)), and a similar trend can be discerned among certain acquired neuropathies (Simpson (1971)).

While it may seem easy to visualise environmental cold as a cause of superficial sensory loss in H.S.R.N., it is much more difficult to incriminate corresponding environmental influences capable of selectively affecting, for example, proprioceptive sensation in F.A. and C.M.T.D., or all modalities as in congenital sensory neuropathy.
Furthermore, it is doubtful whether climatic cold can have such a selective effect on pain and temperature. Even in the laboratory, cooling of the extremities can induce significant slowing of nerve conduction velocities, and the fibres which provide this information are those fast conducting, thickly myelinated ones of large calibre, which mediate other forms of sensation than pain and temperature, and which innervate muscle and form reflex arcs. Extreme cold would impair their function even more severely than this.

Indeed, it has been shown that nerve conduction in myelinated fibres ceases in temperatures as high at 7.6°C to 9.1°C (Paintal (1965)), and these may even be more vulnerable to cold than unmyelinated fibres (Sinclair (1955)).

Finally, even the observation that a blow anywhere on the body of affected persons can produce local numbness of several hours duration, may not have any particular relevance in this context. The same phenomenon has been noticed in Multiple Sclerosis (MoAlpine (1973)) where the peripheral efferent pathways are intact, and where the responsible lesion in the cord is even more remote, than the dorsal root ganglion cells, from the body surface and the sensory nerve endings.

Nevertheless, although this theory appears to overstate the case for climatic cold and other trauma in the genesis of sensory loss in H.S.R.N., it is important because it stresses the significance of environmental factors. These are so often neglected in studies of hereditary disease where attention may be focussed exclusively on the genetic contribution. In so doing it also directs attention towards measures which can and should be taken in the management of affected subjects.
3. Pathogenesis of Motor Wasting and Weakness

These signs, in variable degree, together with histological evidence of neurogenic muscle atrophy and electrophysiological evidence of muscle denervation and slowing of motor nerve conduction velocity, have already been shown to occur in H.S.R.N.

As the anterior horn cells and ventral roots have often appeared to be quite normal, different pathological processes are usually invoked to explain the sensory and motor components of the trait; namely, primary degeneration of sensory neurones with accompanying axon decay, and a peripheral motor neuropathy with minor and variable retrograde effects on motor neurones (Spillane & Wells (1969)).

It is even conceivable that an immune reaction against myelin and Schwann cells ensheathing motor fibres, might be generated by breakdown products from sensory fibres, analogous to the mechanism proposed to explain globular neuropathy (Dayan et al (1968)).

However, it seems unnecessarily complicated to propose different mechanisms to account for the motor and sensory findings in H.S.R.N.

Minor degrees of neurogenic atrophy can be detected when transverse sections of muscle are examined histologically, and this is a much more sensitive index of denervation than degeneration of anterior horns, since the latter requires about 50% of cell loss before it becomes recognisable (Brownell (1973)).

It seems, therefore, much more plausible to propose that the same mechanism, namely primary cell damage, affects both sensory and motor neurones, while recognising that the latter are much less susceptible, although perhaps not less so than certain of the larger
sensory neurones.

In any case, as already shown, minor changes have been described in anterior horn cells and in an anterior root (Chapter 11), and these observations favour the same conclusion.

It is of interest in this context that an hereditary neuropathy (dystonia musculorum) occurs in mice, (Duchen & Strich (1964), Janot (1972)). Degeneration first occurs in sensory roots and posterior columns, but later partial denervation of muscle can be detected. This is not accompanied by obvious anterior horn or ventral root abnormalities.

4. Pathogenesis of Reflex Loss

This was limited to the ankle jerk and plantar responses in the "X" family, and their outright loss was associated with evidence of impaired proprioceptive sensation over the feet and toes. Their loss appears, therefore, to depend upon degeneration of large fibres forming the afferent arcs of these reflexes.

Reflex loss was not greater in V 53, the patient with pronounced amyotrophy and some paresis, so the contribution from degeneration of the afferent arcs of these reflexes appears to be negligible, at least in this kindred.

Far greater degrees of muscle wasting and paresis were present in both affected members of the "Z" family (Chapter 20), and it is hardly therefore surprising that greater reflex loss was also present in the "Z" family.
5. Pathogenesis of Trophic Lesions

The mutation which produces H.S.R.N. affects the peripheral superficial sensory system so that it gradually ceases to be adapted to its environment. Planter ulcers and oral mutilation are the end results of this loss of adaptation.

While it is probable that a number of feed-back mechanisms are deranged, the most obvious one is that concerned with the recognition, and therefore the avoidance of painful injuries. Indeed, some authorities state categorically that no causal factors need be implicated over and above loss of perception to pain (Denny Brown (1951), Wallace (1970)). In support of this they cite the rapidity with which healing occurs once the feet are protected from continuation of the responsible trauma, through bed rest, or for other reasons.

Evidence is adduced elsewhere, however (Chapter 13) which suggests that, in fact, in this disease, healing is often abnormally prolonged. This was certainly the overall impression from experience with the "X" and "Z" families.

If this point is conceded it is necessary to look elsewhere for factors causing delayed healing. If they exist, it is a logical step to assume that they may also play some part in the generation of the trophic lesions in the first place.

The extremely rare trait, Congenital Indifference to Pain (Chapter 17), provides an opportunity of observing what happens in response to trauma, when only pain sensation is lost. In fact, gross injuries and loss of tissue may occur with deformities, contractures and scarring, but healing proceeds normally and the indolent, almost self-perpetuating lesions of H.S.R.N. do not appear to be encountered.
The disorder also tends to become less destructive with age, as affected subjects learn to avoid injury. In contrast, the trophic lesions of H.S.R.N., once established, are almost invariably slowly progressive, and extreme and unrealistic measures, such as permanent bed rest, would appear to be necessary if freedom from the characteristic trophic lesions is to be guaranteed.

Congenital indifference to pain differs from H.S.R.N. in a number of ways, of which the two most relevant in the present context are the preservation of temperature sense and normal cutaneous axon reflexes, as demonstrated by the "triple response" which is obtained following injection of Histamine (Ogden et al. 1959). That the latter are lost distally in the legs in H.S.R.N. has been known since an original account over 50 years ago (Mulvey & Riely 1942).

It is generally considered that loss of temperature sense is a less important source of trophic injuries than loss of pain sense, because thermal injuries, like scalds and burns, are normally avoided because they are primarily painful. An exception to this general rule is therefore provided by a member of the "Y" family from Bath, (Campbell & Hoffman 1964). Despite a considerable sensory deficit, this man experienced a trophic lesion only once during his life, and this was transient. It followed exposure to extreme cold during the Second World War. The adverse effects of climatic cold in the New South Wales stock have already been described.

It may well be that loss of temperature sensation is at least as important as loss of pain sensation, because it may exert important effects on cutaneous haemodynamics, in situations simultaneously rendered vulnerable to unrecognized trauma from loss of pain sensation.
Spinal thermo-regulatory reflexes probably exist which regulate local blood supply in relation to environmental temperature as recorded by thermal receptors in the skin (Johnson (1966)). Denervation of these receptors, as in M.S.R.N., presumably contribute to the circulatory abnormalities which may be found in this disease. These abnormalities are discussed elsewhere, (Chapter 7).

Intra-familial variations probably exist, and there are differences between individuals which probably depend on the stage the disease has reached, but it is possible to discern an overall pattern. This may be briefly summarised as indicating reduced superficial cutaneous blood flow, co-existing with an excellent blood supply to deeper tissues. Indeed some investigations in Acrodystrophic Neuropathies (Passouant et al (1951), Bureau et al (1953)) have suggested that the latter is so excellent relative to the former, that it may amount almost to an arterio-venous shunt, the whole situation in the skin being reminiscent of the preferential cortical ischaemia seen in some forms of renal disease.

There is also a considerable degree of correlation between deep skin temperature (which must be increased under these circumstances) and sweating (Kerslake (1955)), which might explain the hyperhidrosis so strikingly present in some stocks of M.S.R.N. (Chapter 7).

Vasodilation in the limbs may variously be attributed to parasympathetic dorsal root efferents, antidromic sensory nerve conduction, diminished sympathetic activity or axon reflexes, (Mitchell (1966)). Of these, the existence of the first is hypothetical, while the second has been demonstrated only experimentally (Chapman et al (1961)). To explain the opposite state of affairs, vasoconstriction, as it occurs in M.S.R.N., it is therefore necessary to postulate either
sympathetic over-activity, (which seems inherently improbable in a
trait characterised by loss of function or small unmyelinated fibres)
or loss of cutaneous axon reflexes. By exclusion, this loss remains
the most satisfactory explanation.

At some stage in the evolution of the neuropathy, these dis-
fuctional alterations in the smaller vessels are apparently succeeded
by actual structural changes. These have already been mentioned,
(Chapter 11), and may amount to an appreciable obliterative endarter-
itis. They have been variously incriminated in the causation of trophic
lesions (Jügheim et al (1949)), or as being merely the result of them
(Van Bogaert (1957)). The fact that they appear to be present in
tissues some distance from the site of ulceration or hyperkeratosis,
for example in otherwise unaffected bone (Lassmann & Fartasch (1970))
suggests that the former view is nearer the truth.

In another form of H.F.A.N., there was a severe obliterative
microangiopathy in the skin which suggested that neural control of
these blood vessels had been affected from the inception of the disease
(Jusin et al (1973)).

As axon length is again the crucial factor, such changes
must be most marked distally, so that the tissues most deprived of the
protective influence of pain sensation are also those least able to
withstand trauma because of localised ischaemia, small areas of infarction
and (through venous involvement), the accumulation of toxic sub-
stances released at the site of injury. The temperature of the skin
surface will also be lower than normal, and this effect will be increased
by excessive sweating, so that changes akin to "immersion foot" and
"trench foot" (Chapter 23) may develop at substantially higher environ-
mental temperatures than they usually do.
It has been suggested that trophic changes in bone may be initiated by small infarcts due to autonomic involvement of nutrient arteries (Spillane & Wells (1969)). This is clearly another manifestation of the same process.

Finally, once the skin has been breached, infection will enter with further destruction, and healing by fibrosis, so that the lesion tends to become indolent and self-perpetuating.
CHAPTER 13

MANAGEMENT AND TREATMENT OF H.S.R.N.

Many of the references cited in this chapter are derived from the literature of other forms of H.F.A.N. but they are included because they are also relevant to H.S.R.N.

As there is no way of altering the genetic constitution of patients with H.S.R.N. the only real prospect of making their disease less serious is to modify their environment to the extent that the onset of symptoms may be delayed, and their subsequent severity and rate of progression reduced. Such modifications in the environment should be made ideally in all patients at risk, and continued throughout life, or at least until it is clear that they are unaffected.

Once plantar lesions appear, their management should be predominantly conservative, with recourse to surgery only under special circumstances.

The management of H.S.R.N. may therefore be regarded as falling under three headings:

(1) The management and supervision of the pre-ulcerative neuropathy.

(2) The conservative medical treatment of the trophic lesion.

(3) Surgery.
A major objective of any genetic survey is to identify subjects at risk, and institute treatment which may at least lead to the avoidance of the worst manifestations of the trait concerned.

In some families with F.S.R.N. notably the "E" kindred from New South Wales (Wallace 1970), the identification of heterozygotes is made somewhat easier because of the high incidence of subjective prodromal symptoms in the form of pains, numbness and paresthesiae.

In the "X" family and the majority of other stocks, these prodromal symptoms do not usually occur, and the early recognition of heterozygotes depends upon the identification of the beginnings of objective sensory loss, with all its attendant shortcomings.

In both cases, however, heterozygotes can be identified at a stage when advice may be given, which may in the long term be of considerable value.

Many of the measures which can be recommended, however, seem trivial and mundane, but taken together they are likely to spare the patient some, if not a great deal of disability.

The advice that should be given to heterozygotes may be enumerated under the following headings,

A. Choose your shoes with great care

Shoes must be comfortable and well fitting with thick, soft soles. They should be ventilated to combat excessive sweating. They should preferably be made to measure, as a subject with a sensory deficit in his feet, is hardly likely to recognise comfort or discomfort in the shoes he tries on in a shop. Despite their ugly appearance,
seamless shoes of the type used in rheumatoid arthritis (Dixon & Franklin (1968)) are obviously ideal. Whatever shoes are worn, they must be kept properly repaired. Their interiors should be inspected on every occasion they are put on, to make sure that some foreign body, such as a fragment of coal or a glass marble has not been inadvertently dropped inside them.

B. Never Walk Barefoot

Stubbing the toe when walking barefoot was the commonest single precipitating cause of neuropathic ulceration in the Australian stock (Wallace (1970)). Almost equally common is the transfixing of an anaesthetic sole by a nail, tack or drawing pin. This happened to \( \overline{IV} \) 35 and \( \overline{IV} \) 37 of the "X" family, and has been reported as a causal event in other families (Smith (1934), Féron et al (1949), Jackson (1949), Mandell & Smith (1960), Wallace (1970)).

Walking barefoot out of doors poses even greater hazards, as in the case of a man who walked painlessly over hot ashes (Jackson (1949)), and a member of the Afrika Korps who burnt his feet on the hot sands of Libya (Feudell (1959)). A member of the French Foreign Legion experienced his first neuropathic ulcer after his foot had been pierced by a bamboo shoot (Pages (1952)).

C. Follow a Sedentary Occupation

The main causes of plantar ulceration are undoubtedly the summated effects of day to day walking, standing and weight bearing generally, and the most suitable occupations are those that reduce these activities to a minimum.
The beneficial effects of a sitting job compared with an active labouring one, is revealed by a comparison of the feet of the two brothers IV 36 and IV 37 towards the end of their lives. IV 36 was a draughtsman and sat at a desk most of the time. He presented callusities only (Plate 29), whereas his brother IV 37 followed a manual occupation and suffered from advanced ulceration and osteoarthropathy.

Apart from standing and walking, manual work involves other hazards, including exposure to cold, industrial burns, as sustained by IV 37, and industrial injuries. Thus the troubles of IV 35 began when iron pipes fell on his feet, and a similar history is provided by a member of another family (Ryck et al (1965)). In the earliest account of all, an affected man was fearful of unwittingly injuring his hands as he went about his work as a carpenter (Nélaton (1857)).

D. Avoid Combat Service

Of all the occupations affected subjects may be called upon to follow, this is the most hazardous with its combination of exposure, prolonged marching, ill-fitting boots and lack of rest, and it is remarkable how many observations relate the onset of trophic lesions with the obligations and disruptions imposed by war.

Thus IV 35 of the "X" family was discharged within three months of being called to the Colours, and 111 16 of the "Z" family within a year. A similar fate befell the military careers of other patients (Schulze (1917), Mueller & Suger (1945), Jacob et al (1954), Fendell (1959), Wallace 1970). German patients in 1914 are reported as developing the disorder when reaching military age (Göbell & Runge (1914)).
Successive wars may affect successive generations of the same family (Mueller & Sugar (1943)) and the wars themselves have spanned over a century from the American Civil War (Mueller & Sugar (1943)) to the last French Campaign in Indo-China (Pages (1952)).

E. Avoid climatic cold

Wallace (1970) has demonstrated the greater severity of H.S.R.N. in subjects living in colder parts of the Australian subcontinent, than in those living in warmer parts, and other patients have been more severely affected than normally when exposed to intense cold. (Mulvey & Riely (1943, Campbell & Hoffman (1964)).

Ideally, affected subjects would doubtless be better off if they could emigrate to warmer climates, but this will usually be a council of perfection (although it arose in connection with \( y \) 53 of the "y" family), and working in a warm indoor environment is the best available substitute.

Working indoors is not alone enough, however, because there are several reports of subjects still feeling the cold, and as a result burning their legs through sitting too near to fires and stoves, (Enderlé (1933), Barraquer & De Gispert (1936), Denny Brown (1951), Feudell (1959), Spillane & Wells (1969)). The addition of warm clothing is thus essential. This should include thick, full-length underwear, undarned woollen socks, thick trousers (in both sexes preferably) and warm shirts, sweaters and topcoat. Fur-lined boots were worn for preference by \( \frac{111}{16} \) of the "Z" family, even in high summer, and seem a good idea. Mittens indoors and gloves outdoors should also be recommended.
F. Have suitable hobbies and holidays

The adverse effects of prolonged walking are typified, in extreme form, in the enormous plantar ulcers that developed in patients making the long trek out of Paris, before the advancing German armies in 1940, (Boudin & Djindjian (1951), Thévenard (1953)).

Short walks need not be prohibited, but in summer at least cycling is to be preferred, as the part of the foot surface which is applied to the pedal is usually different from that which bears the brunt of standing and walking.

Competitive running has claimed its casualties (Riley (1931)) but on the other hand, some of the members of the New South Wales stock were athletes, and followed their various athletic pursuits without apparent ill effects, (Wallace 1970)).

So far as holidays are concerned, lying on a beach in the sun (so long as beach shoes are worn), must be preferable to hiking, skiing or mountaineering in the Northerly latitudes.

G. Own a car

Owning a conventional motor car (for which a grant may be obtained), or being allocated an invalid car, are obviously important because unnecessary walking will be reduced.

A motor cycle is much less satisfactory because of the risk to the feet and legs in even the most trivial accidents. Manifestation of H.S.R.N. in IV 25 followed a minor accident of this type.
H. Do not tamper with your feet yourself

One member of the "y" family, \( \text{V}^5 \), converted an initial plaque of hyperkeratosis into an ulcer by rubbing it with pumice stone, and similar injudicious paring of corns has led to equally adverse effects in other stocks (Göbell & Runge (1914), Pallis & Schneeweiss (1964)).

Even worse self-mutilation may be practised once ulceration is established. Thus, \( \text{V}^5 \) 25 used to probe his plantar lesion with a steel knitting needle. Eventually one of these broke, leaving its tip embedded in his foot.

Self-amputation of toes may also be practised at a late stage of the disease, and reference has already been made to a patient who caused his death in this way (Campbell & Hoffman (1964)).

I. Seek only fore-warned advice

Ideally, all identified heterozygotes, and younger subjects at risk, should carry with them information describing their liability to ulceration and mutilation of the feet, in case they should consult a chiropodist or another doctor.

It is evidently not enough for the patient alone to describe the trait, and give the family history. Thus \( \text{V}^5 \) 46, consulted one doctor who frankly disbelieved her in both, although she fared much better subsequently when armed with a suitable letter giving the same information.

J. Undergo surgical treatment of the feet and legs with extreme reluctance

Patients with H.S.R.N. who have never experienced trophic
lesions, should not undergo corrective procedures for bunions, hammer toes, claw toes or other structural deficits of their feet at this stage.

The classical example of failure to observe this precept is provided by two siblings who underwent corrective surgery for difficulties of gait (Gambier & LeFèvre (1960)). In both cases, immediate post-operative healing was satisfactory, but once normal activity was resumed, the scars broke down and were replaced by ulcers which did not heal.

In the event of fractures, plaster casts should be well padded and applied with extreme care. Their use should be avoided in lesser fractures such as those involving the shaft of the fibula without displacement, or the base of the 5th metatarsal, which should be treated with firm bandaging and rest only.

K. Avoid pregnancy

It is axiomatic that no affected parent should have children, when each one inherits a one to one expectation of developing a trait, which was originally described as "cette maladie terrible" (Nélaton (1952)), and 120 years later as being "quite as terrible as leprosy" in its effects on the extremities (Wallace 1970).

Genetic counselling based on these considerations has led to the decision by \( \frac{V}{53} \) to avoid procreation, and other members of the stock have, at least, restricted the size of their families.

H.S.R.N. is often not severely expressed, however, and it can also be shown not to shorten life (Chapter 14), so that the argument
is less strong than it would be, for example, in Huntington's Chorea.

The self-interest of affected women can, however, be enlisted in this context, because there is some evidence which suggests that the disease is aggravated by pregnancy. This is discussed further in the section on Biological Fitness in Chapter 15.

2. Conservative Treatment of Trophic Ulcers

Once an ulcer appears, the importance of all the foregoing measures is enhanced, but they are temporarily superseded by a period of absolute bed rest.

Healing of first ulcers usually proceeds quite rapidly, and a month in bed may be adequate.

The surface of the ulcer should be swabbed from time to time, and dressings applied according to the bacteriological findings. Dressings should always be cold as deterioration has followed applications which have been too hot, (Clarke & Groves (1909), Spillane & Wells (1969)).

If there is evidence of secondary infection sufficient to cause a purulent discharge, lymphangitis or lymphadenitis, the appropriate antibiotic should be administered.

If healing is unaccountably delayed, the foot should be x-rayed. If this indicates boney involvement, surgery may be indicated, unless there is a free-lying fragment which may be expected to make its own way out through the floor of the ulcer, after which healing usually
proceeds normally.

Sooner or later, perhaps very much later, ulceration will recur and further bed rest is required. If the ulcer has formed again at its original site, healing will take much longer, although some authors claim that it is always prompt (Denny Brown (1951), Turkington & Stieffel (1965), Wallace (1970)).

This, however, is at variance with the majority view and with personal experience with the "X" and "Z" families. Thus, planter ulcers took a year to heal in the case of both IV 25 and IV 35 of the "X" family, and two years for III 16 of the "Z" family. This man also developed, unaccountably, a shallow ulcer on one knee which took two months to heal, despite daily dressings and thick protective bandaging.

Clearly, it is impracticable to insist upon periods of bed rest of such duration, partly because otherwise healthy patients will not tolerate them and, more importantly, because of the hazards of prolonged recumbency.

Nevertheless even persistent, chronic ulcers will heal, if rest and freedom from weight bearing last long enough. This usually happens through the intervention of some other factor such as flaccid paresis of the legs in the case of III 16 of the "Z" family, while in other patients it has been brought about by ataxia and general debility (Denny Brown (1951)), major orthopaedic surgery (Spillane & Wells 1969)) and the semi-bed-ridden state of old age (Wallace 1970).

IV 37 was subjected to really prolonged periods of bed rest, in an effort to heal his ulcers, but during this period he sustained two myocardial infarcts, and a pulmonary embolism, and this policy was quickly discontinued.
When bed rest of reasonable duration has failed to induce healing, and the patient is ambulant again, he must continue to fulfill the measures enumerated in the first part of this chapter, and also attend at least once a week for local treatment. Daily dressings can be applied at home.

Such treatment takes the form of toilet to the ulcer with debridement of its surface, paring away the dense callus which surrounds it, and which must be harmful to underlying tissue because it is so hard and rigid. It may be continuous with moist, white, friable tissue that grows out and overlaps the edge of the ulcer. This is best trimmed away, because it probably makes the edges of the ulcer an even better nidus for infection than it is already, and because it certainly does not appear to contribute to healing.

From time to time there may be a sudden increase in the size of the ulcer with gross swelling of one or two adjacent toes. While this may be due to bacterial infection and should be treated with an antibiotic, it may also reflect sudden disintegration of underlying bone. If so, a sequestrum will tend to come towards the surface of the ulcer, and may be felt with a probe. Later it may be possible to lever it gently free, following which the ulcer may become quiescent again, and adjacent swelling diminish.

Such conservative treatment may be necessary for the rest of the patient's life, and this is acceptable when one considers that the only radical alternative is the undesirable one of major amputation.
"toute mutilation est contre-indiquées puisque les operations n'empéchant pas la récidive", Thus wrote Vésignié in 1852 and it is hardly less applicable today.

Certainly many unwary surgeons satisfied with the early results of excision of a neuropathic ulcer, have been dismayed by its prompt recurrence, and all too easily tempted towards repeating and extending the procedure. There are many examples in the literature of such stepwise progression of amputations, including Nelaton's patient, but none more dramatic than practiced on unfortunate members of a North American kindred (Tocantins & Reimann (1939)). One member of this stock underwent six successive ablative operations which eventually culminated in bilateral below-knee amputations.

Opinion among members of the "X" family is solidly against surgical treatment. Such family folklore is based on individual experiences in general, and the case of IV 35 in particular. This man underwent mid-calf amputation of the left leg for chronic plantar ulceration at the age of 28, and died of coronary thrombosis nine years later. His relatives connect these two events.

It seems clear that this operation was not, in fact, justified on the grounds of indolent plantar ulceration alone. Vigorous conservative treatment might well have been as effective in this man's case, as in that of his equally severely affected brother, IV 37.

There is no urgency in the surgical treatment of these ulcers as there is in those of diabetic neuropathy, in which generalised atherosclerosis and a lowered tissue resistance to infection predispose to ischaemic gangrene.
There is admittedly a local terminal micro-angiopathy in H.S.R.N. consequent upon a particular pattern of autonomic dysfunction, which predisposes to trophic lesions (see Chapters 11 and 12), but in general the peripheral vascular tree is healthy, perhaps better than average (Wallace (1970)), and there is no impairment of resistance to infection.

In the writer's view, the surgeon's armamentarium in the treatment of the trophic lesions of H.S.R.N. is limited to two procedures, one of which should be employed early, judiciously and reluctantly, while the second should be deferred until as late as possible.

The first of these is indicated where prolonged bed rest has failed to induce any evidence of healing, and where x-ray indicates localised involvement of underlying bone. The operation takes one of two forms. If the ulcer is located on a toe and there are trophic changes in the phalanges, the toe may be amputated. If the ulcer is located on the ball of the foot it should be excised together with the diseased underlying metatarsal, so long as the other metatarsals are intact.

The latter operation was performed in four members of the "X" family. It was ineffective in two (IV 35, IV 37), and successful in two (IV 25, V 53). It was also successful in III 16 of the "Z" family.

In the case of V 53 and III 16 there has been no recurrence of ulceration since, over the space of several years. This good result, however, is perhaps more easily explained by the increasing inactivity of these two patients, as the result of progressive muscular weakness, so that the factors promoting re-ulceration have been inhibited.
The failure of this operation in JV 37 is of particular interest, because there is every reason for supposing that the wrong metatarsal head was excised! Plate 1 shows the radiological appearance of his left forefoot in 1961. It reveals osteoarthropathy affecting the 3rd metatarsal and its distal joint only. The 1st metatarsal, by contrast, is thick, dense and robust in appearance.

Nevertheless, one year later, when his planter ulcer was excised, it was the head of this bone which was also removed. The disastrous result of this action is shown in an x-ray taken two years later (Plate 11). The remnant of the 1st metatarsal remains dense and apparently free from neuropathic change, but the appearance of the 3rd metatarsal and its phalanges indicates deterioration, while the 2nd metatarsal is now showing serious involvement, perhaps because it is no longer splinted by a healthy 1st metatarsal.

Re-xray in 1963 shows that there has been little further change. This suggests that unduly rapid deterioration took place between 1961 and 1963, which was the period during which this operation was performed.

For most of the remainder of his life this foot was to trouble him more than his right foot, and to have the more deformed appearance, and there seems little doubt that this was because healthy bone was removed and diseased bone left behind.

Nature makes no such mistakes. Seven years later the head of the 1st metatarsal of his right foot disintegrated into several fragments. These were extruded over the space of two months, following which his left planter ulcer became smaller and appeared less inflamed, although it did not heal.
It is possible that an operation devised for the treatment of planter ulcers complicating diabetic neuropathy (Catterell (1973)) may be preferable to the more localised excisions usually performed in H.S.R.N. and the allied traits.

This involves removal of the whole segment of metatarsal and toe, allowing the skin edges to fall together. These are not sutured in diabetes, although they probably should be in H.S.R.N.

Such a procedure should be carried out when only one metatarsal is involved. It cannot prevent subsequent involvement of other bones and indeed it may facilitate this, because of the reduction in the area of weight bearing bone, but it appears to be more definite and precise than the piecemeal and haphazard procedure with its high failure rate, which has been described.

It is to be hoped that such an operation will procure for the patient a long interval of freedom from trophic lesions, because obviously there are limitations on the number of times it can be repeated, as otherwise the whole forefoot will be progressively sacrificed, and the "elephants foot" deformity generated more rapidly, than if treatment had been wholly conservative.

In fact, such surgery is likely to be but a single event in the long term, otherwise conservative, management of these cases.

The second procedure in the surgeon's armamentarium in dealing with H.S.R.N. will only be needed in those severe cases in which mutilation and destruction have proceeded to the extent that shoes can no longer be worn, and the general health has become affected. When anaemia, and the effects of chronic sepsis and the risk of secondary amyloid appear, it is justifiable to proceed to major amputation.
This should be below the knee to retain flexion at that joint, but not so far below as to run the risk of serious trophic involvement of the amputation stump.


1. Introduction

The causes of, and ages at death, are known for eleven members of the "X" family, and the literature provides similar data about a further 26 subjects who were members of families enumerated elsewhere, as fulfilling exactly the diagnostic criteria of H.S.R.N. (Chapter 15).

A study of causes of death may reveal that a trait exerts some direct lethal effect (like ventilatory paralysis or pulmonary embolism in acute polyradiculo-neuropathy) or may possess some unexpected clinical association which only becomes evident in the last few months or years of life, (such as diabetes mellitus in Friedreich's ataxia).

A review based on only 37 subjects is, of course, unlikely to be rewarding unless either of these possibilities is a common event. Furthermore, a review relying so heavily on the literature of a rare disorder has obvious defects. In order to be as complete as possible, it must include reports from widely differing sources, published over a prolonged period of time. Differences in diagnostic fashion are therefore involved, as well as biased reporting. Deaths directly
attributable to the trait, such as septicaemia complicating trophic ulceration, are more likely to be recorded than apparently unconnected causes.

2. Fatal cases from the "Y" family

9 affected members of the "Y" family had died prior to the commencement of this study, and 2 more died while it was in progress.

The causes of death have already been recorded in the individual case protocols in earlier chapters, but they are also recapitulated below.

The quality of this information is very uneven. In 6 members it was derived from a scrutiny of death certificates only. In the remaining 5, detailed information was available from hospital and other records (and personal observation in 4 of these). 3 of the latter underwent postmortem examination.

This data is summarised below under the following headings:

A. Designation of patient in pedigree.
B. Year of death.
C. Age at death.
D. Cause of death.
E. Source of information relating to B, C, D and E.
3. **Effect on Life Expectancy in the "Y" Family**

The mean age at death of 11 affected members of the "Y" family was 55.7 (S.D. 10.1). There was no significant difference between the sexes (men 54.3, women 55.7).

The mean age at which trophic ulceration had appeared had been 28.8 years (S.D. 6.5). It was appreciably earlier in men (26 years) than women (34 years).

The duration of life from the onset of trophic ulceration until death, therefore, averaged 27 years (men 27\(\frac{3}{4}\) years, women 21\(\frac{3}{4}\) years).
In only 5 members were both the age of onset of trophic lesions and the age at death known precisely, however.

The duration of the disease in these individuals was 26 years (IV 7), 42 years (IV 13), 39 years (IV 25), 25 years (IV 35), and 24 years (IV 37), with a mean of 31 years.

It is evident, from this data, that H.S.R.N. in the "Y" family is a prolonged disorder. Starting in the 3rd or 4th decade, it pursues an indolent course and does not seem to shorten life appreciably.

A comparison with the ages at death of unaffected members of the "Y" family, suggests that it does not in fact shorten life at all, because affected members appear to live as long as the unaffected.

Thus the mean age at death of 16 unaffected members, who had survived past the mean age of onset of trophic ulceration in this kindred (28 years), and about whom accurate information was available, was 52.1 years (S.D. 20).

These are small numbers, but the evidence they provide suggests that H.S.R.N. in the "X" family, at least, is compatible with a normal life expectancy, when unaffected members are used as controls.

This accords with conclusions drawn from other families, (Cooper et al (1947), Murray & Jackson (1945), Wallace (1970)), and with the fact that patients with H.S.R.N. may live to a great age, as evidenced by reports of affected members living into the ninth decade, (Mulvey & Rieley (1942), Campbell & Hoffman (1964), Spillane & Wells (1969), Wallace (1970)).

The opposite view, that life was shortened by possession of the trait, has been expressed as applying to another kindred (Hicks (1922)), and examination of the data supplied supports this conclusion.
All 9 affected members of this kindred who had died, did so between the ages of 39 and 53 (mean 47.1 (S.D. 7.9)). Unaffected relatives, however, apart from those dying in infancy (each of whom it should be remembered, had a 1:1 expectation of inheriting the disorder), a young woman of 24 who died of tuberculosis, and a man dying of asthma, age unknown, were alive and well at the ages of 68, 75, 80, 56 and 52, (Denny Brown (1951)).

This "R" family differs from the "X" family and most other stocks in that all affected members suffered from both severe nerve deafness, and "shooting pains about the body". These features may occur in other kindreds, but when they do so they affect only one or two members, and do not appear to be an integral component of the clinical tableau.

These differences strongly suggest that the genes in the "R" and "X" families must be different, and this may explain differences in life expectancy also.

4. Fatal Cases from the Literature

These are known in respect of 26 cases of M.S.R.M., and the relevant data is reproduced below under the following headings:

A Cause of death
B Age at death
C Sex of subject
D Author and date of publication.

An asterisk denotes confirmation of the causes of death by postmortem examination.
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<th>A</th>
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<td>51</td>
<td>M</td>
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<tr>
<td>Tabes Mesenterica</td>
<td>46</td>
<td>M</td>
<td>Hicks (1922)</td>
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<td>46</td>
<td>F</td>
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<tr>
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<td>F</td>
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<td>20</td>
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<td>66</td>
<td>M</td>
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<td>50</td>
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<td>13</td>
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<td>32</td>
<td>F</td>
<td>Jügmann et al (1949)</td>
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<td>53</td>
<td>F</td>
<td>Denny Brown (1951)</td>
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<td>39</td>
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<td>At first sight, affected members of the &quot;Y&quot; family appear unduly prone to coronary artery disease.</td>
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Thus, a fresh infarct was found at necropsy in 111 13, while two of his sons, 1V 35 and 1V 37, both died from myocardial infarction. Another affected son, 1V 36, (who also had mitral stenosis and aortic incompetence), survived an episode of coronary thrombosis, only to die a year later from congestive cardiac failure. Their two unaffected siblings, 1V 38 and 1V 39, have remained free from cardiac symptoms and signs.

Two cousins have also suffered from both disorders. Of these, 1V 32 survived an infarct in 1952, while 1V 28 underwent E.C.G. examination in 1964, which revealed changes greater than might be expected from his hypertension alone, and these were transient.

Blood cholesterol, total lipids and lipoprotein fractions were measured in some of these subjects and were found to be within normal limits.
Coronary thrombosis is such a common disease that it is obviously likely to be found, from time to time, in association with almost any trait, however rare. Furthermore, first degree relatives of patients with early onset ischaemic heart disease, run a six-fold increased risk of dying from myocardial infarction themselves when compared with the general population (Black & Evans (1966)). Familial concentrations of coronary thrombosis are therefore to be expected.

It is therefore quite reasonable to suppose that it is no more than chance that has determined this association in the "X" family. It is certainly not found in R.S.N.H. as a general rule, as myocardial infarction has been recorded as being responsible for only three deaths in affected subjects in the literature (Van Bogaert (1955), Spillane & Wells (1969), Wallace (1970))

It is equally certain, however, that the heart may be involved in other neuropathies, either acquired or genetically determined. It is known to occur, for example, in Beri-Beri (Spillane (1955)), acute polyradiculoneuropathy (Haymaker & Kernohan (1949)), the severe sensorimotor form of rheumatoid neuropathy (Chamberlain & Bruckner (1970)), the neuropathy of intermittent porphyria (Ridley (1968)), in amyloid neuropathy, either sporadic (De Navasquez & Treble (1938)), Strich & Wade (1953), Chambers et al (1958), Munset & Poussaint (1962)), or hereditary (Jackson et al (1960), Schlesinger et al (1962), Mahloudji et al (1969)), in Friedreich's ataxia (Thoren (1964), Høver (1963)), Refsum's Syndrome (Gordon & Hudson (1955)) and Tangier Neuropathy (Frederickson (1966)).

Significant elevation of serum triglycerides is a biochemical abnormality which is shared by the two last named disorders (Frederickson (1966)), but was not present in the "X" family.
Conversely, patients with hypertrophic neuropathy do not exhibit cardiac involvement, except through chance association (Austin (1956)), and this appears to be true also of C.M.T.D. Dominantly inherited heart block has been described in kindreds with the latter (Smith (1958), Littler (1970)), but the two disorders have clearly segregated independently. Gross congenital heart disease has been described in association with the Roussy-Levy Syndrome (Lascelles et al (1970)), but occurred only in a single subject, who was the progeny of a consanguineous union between a neurologically affected man and an unaffected first cousin. The neurological trait itself was dominantly inherited.

Among other forms of H.P.A.N., there is a single report of congestive heart disease occurring in a woman who combined distal sensory loss, ulceration and mutilation of the feet, a spastic gait and distal amyotrophy (Enderle (1933)).

(b) Hypertension

Hypertensive disease followed an accelerated course in the affected man IV 25. His blood pressure had been normal in 1961, had risen steeply by 1965, and two years later he died in renal failure.

His brother, IV 28, and a cousin IV 32, both combined H.S.R.N. with severe hypertension.

This association must also be ascribed to chance, however, as no other affected members of the family have been hypertensive, so far as is known, and the combination of these two diseases, although it has occurred, has not been a frequent observation in other stocks.
Among other forms of H.F.A.N., the "Z" family contains many severely hypertensive subjects (see Chapter 21), all of whom, however, have escaped inheritance of the neuropathic trait.

Hypertension may, however, coexist with neuropathy in lead intoxication, neurofibromatosis (Bourke & Gatenby (1961)), and as a sequel to acute poly-radiculo-neuropathy (Haymaker & Kernohan (1949)). Its occurrence during the crises of porphyria has been ascribed to demyelination of inhibitory afferents from the aortic and carotid sinuses (Gibson & Goldberg (1956)). Hypertension may coexist with relative indifference to pain and Familial Dysautonomia (Riley et al (1949)).

(c) Renal Disease

"Interstitial nephritis" accompanied by heart failure, was the certified cause of death of IV 1 of the "Z" family, and her grandson IV 25 died of renal failure complicating hypertensive disease.

IV 36 was also uremic at death, but cardiac failure rather than renal failure seems a more likely explanation. Blood urea levels up to 200 mgs%, derived from metabolism of structural protein, may occur in congestive failure, even when the kidneys are healthy, and irrespective of diuretic therapy (Domenet & Evans (1969)).

Uraemia may cause neuropathy, a fact which has been recognised since observations by Charcot and Galar at the end of the last century (Lenoe (1966), Robson (1968)).

In this context it is perhaps remarkable that overt plantar ulceration appeared for the first time in IV 36 just before his death in ureaemia, even though he had been confined to bed for several weeks.

The two original and definitive postmortem examinations of patients with H.S.R.N., both demonstrated co-existing kidney disease.
In one, acute inflammation of the bladder with early abscess formation in the kidneys (Denny Brown (1951)) was found, while "cardiorenal sclerotic" was documented as the cause of death in the second, (Van Bogaert (1953)).

"Nephrosclerosis" is also listed as contributing to death in another man who came to autopsy (Reimann et al. (1959)) and contracted kidneys were found in one of the Australian cases (Wallace (1970)).

Although it is assumed that it was excluded, these observations certainly raise the possibility of secondary amyloid disease.

H.S.R.N. in late and severe form may be characterised by considerable chronic suppuration, so that secondary amyloidosis would not be an unexpected complication, and has definitely occurred in one instance (Wallace 1970). One of its component manifestations is, of course, renal failure.

Secondary amyloidosis is a serious possibility in the case of IV 25 of the "X" family who, as already mentioned, developed uraemia, albuminuria, and a rapidly rising blood pressure during the last 4 years of his life. Unfortunately, this man did not come to autopsy.

Renal damage from ascending infection and back pressure, must obviously be a serious hazard in those rare and bizarre stocks in which H.P.A.N. is complicated by bladder atony, retention of urine, overflow incontinence and the need for self catheterisation, (Barraquer & De Gispert (1936), Feudell (1959), Keonig & Spiro (1970)). Such severe degrees of autonomic involvement have not been described in H.S.R.N., but they occur in the Portuguese form of Familial Amyloid Neuropathy (see Chapter 22).

Primary amyloid involvement of the renal artery was the cause of several deaths from renal failure in the Iowa form of Familial
Amyloid Neuropathy (Van Allen et al. 1969).

Nephritis has been described in association with C.M.T.D. in two families (Lemieux & Neenah 1967, Henson et al 1970), probably as the result of chance.

(a) **Pulmonary Disease**

Death from asphyxia and pneumonia, consequent upon paralysis of respiratory muscles, may occur in predominantly motor neuropathies, such as acute poly-radiculoneuropathy (Haymaker & Kernohan 1949), and the neuropathies of the porphyrias (Ridley 1968, Dean 1960).

Pulmonary embolism may also cause death in chronic poly-neuropathies because of the liability to deep vein thrombosis in paralysed legs (Simpson 1968).

Such events are unlikely in H.S.R.N. where motor weakness is seldom more than moderate.

Terminal pulmonary embolism occurred in 111 of the "X" family, however, and has been described in sporadic cases (Vignon et al 1956, Spillane & Wells 1969).

113 of the "X" family probably sustained a pulmonary embolism in 1956, acquired during a period of bed rest enforced in an attempt to heal his plantar ulcers. This was diagnosed as pneumonia at the time, but slow resolution led to bronchoscopy to exclude an underlying bronchial carcinoma.

That the association of H.S.R.N. and pulmonary embolism in these two members of the "X" family is most probably due to chance, is suggested by the occurrence of more than one episode of pulmonary embolism in
two unaffected members of the kindred, IV 38 and IV 39.

(c) Gastro-Intestinal Disease

Both II 5 and her son III 13, members of the "X" family, died suddenly after a short illness due to gastric ulceration. Details of this are not known so far as II 5 is concerned. It may or may not have resembled the last illness of III 13, where terminal myocardial infarction and pulmonary embolism concluded a brief illness, the main feature of which had been torrential gastro-intestinal haemorrhage.

Death from haematemesis at the age of 42 occurred in a case from the literature (Pallis & Schneeewoss (1960)) and grave peptic ulceration has been associated with H.S.R.N. in other cases. (Thevenard (1942), De Leon (1960)). Carcinoma of the stomach accounted for one death (Velluz et al (1957)).

Achlorhydria occurred in at least 4 members of the "E" family, (Hicks (1922), Denny Brown (1951)), and in this kindred diarrhoea was also encountered, and may have contributed to the death of one member who was certified as dying from Tabes Mesenterica.

Although they are rare in H.S.R.N., autonomic disturbances expressed as diarrhoea, or constipation, or both, may occur in other forms of H.F.A.N., and particularly in familial amyloid neuropathy, where they may progress to haematemesis and melena, (Rukavina et al (1956), Jarnum (1965)).

Severe duodenal ulceration occurred in most of the affected members of the Iowa Kindred with Familial Amyloid Neuropathy (Van Allen et al (1960)).
(f) Diabetes Mellitus

The "Y" family did not contain a single diabetic among its affected or unaffected members, and the co-existence of diabetes and H.S.R.N. has only occasionally been reported (Tocantins & Reimann (1939), Jacob et al (1954), Ortiz de Zárate (1957), Wallace (1970)).

Where no family history is forthcoming, the presence of reducing substances in the urine will not unreasonably lead to a diagnosis of diabetic neuropathy. In two families, one with H.S.R.N. (Turkington & Stieffel (1965)), and one combining Acrodystrophic Neuropathy with corticospinal tract involvement (Khalifeh & Zellwegger (1963)), the subsequent discovery of an identical trait among non-diabetic relatives cast obvious doubt upon this original diagnosis.

Similarly, because of the clinical resemblance between the two disorders, relatively minor degrees of glucose intolerance will be assigned an importance that they may not merit (Boudin & Djindjian (1951), Alajouanine et al (1962), De Léon (1969)).

There is no evidence to suggest that any real relationship exists between diabetes and H.S.R.N. such as occurs in Friedreich's ataxia.

In this disease the incidence of diabetes has been reported as 22% (Thorén (1962)), 8% (Hewer & Robinson (1963)) and 23% (Hewer 1968).

It is of interest that this association was unknown 35 years ago. At that time, the duration of F.A. averaged 16 years from onset to death, which in two-thirds of cases was due to pneumonia or tuberculosis, (Bell & Carmichael (1939)). 30 years later, as the result of improved medical and social circumstances, the duration of F.A. had increased to 24 years, and an incidence of diabetes of 23% had been disclosed, usually recognised within the last three years of life (Hewer (1968)).
Clearly the elimination of tuberculosis and a great reduction in the incidence of fatal pneumonias, and the consequently increased life expectancy, has been responsible for this modern recognition of what must always have been a latent relationship.

Similar unexpected associations may be revealed in other genetically determined disorders, as modern treatment and conditions prolong life expectancy.

(g) Septicaemia and Chronic Sepsis

Clearly a disorder characterised by open ulceration of the feet must carry a considerable risk of bacterial invasion, and it is to be expected that occasionally this may proceed to frank septicaemia. Deaths from this cause, all occurring in the pre-antibiotic era, have been described in stocks of H.S.R.N. (Beigleböck (1938), Mandell & Smith (1960)), and of the allied traits (Bruna (1903), Riley (1930), Enderlé (1933), Heller & Robb (1954)).

Some of these deaths have occurred early in the course of the disease, while others have complicated amputation.

Yet other patients have been fortunate to survive severe septicaemic illnesses (Barraquer-Ferre & Barraquer Borde (1953), Jacob et al (1954)).

Such cases, however, are surprisingly few and there seems justification for the observation made long before the advent of antibiotics, that "there seems to be no special risk of septicaemia" (Hicks (1922)).

Frank septicaemia has not occurred in the "X" family, although local inflammatory episodes have been fairly frequent, particularly in 32 who often complained of malaise and tender, swollen inguinal
lymph nodes, without obvious alteration in the appearance of his plan-
ter ulcers.

Considering the nature of these lesions, this data suggests
the possible acquisition of considerable degrees of immunity to infections,
perhaps analogous to the rarity of acute, as opposed to subacute osteo-
myelitis among African natives. It has been suggested that the fre-
quent occurrence of cuts and abrasions of the feet of people who habitu-
ally go barefoot, leads to the development of high resistance to the
staphylococcus from an early age. (B.M.J. (1969)). Perhaps the trophic
ulcers of H.S.R.N. have a similar effect by constantly allowing small
numbers of organisms into the general circulation.

Between these extremes of overwhelming infection in a few cases,
and relative immunity in others, there exists a group of cases, which
perhaps all severely affected patients eventually join, whose health if
not their life expectancy, is impaired to a greater or lesser extent
through the effects of chronic sepsis.

The debilitating results of chronic suppuration as a cause of
death has been invoked in the case of patients who died of "exhaustion",
(Hicks (1922)), and "the anaemia and heart failure of chronic sepsis"
(Spillane & Wells (1969)).

That other well recognised complication of prolonged suppura-
tion, secondary amyloidosis, occurred in a member of the New South Wales
stock. Otherwise it was considered remarkable how well affected members
of this kindred stood up to the effects of secondary infection, despite
half a life time of chronic oozing suppuration (Wallace (1970)).
6. Conclusions.

H.S.R.N. does not appear to have shortened life in affected members of the "X" family. Their mean age at death was 55.7 years (S.D. 10.1), compared with a mean age at death of 52.1 years (S.D. 20) in unaffected members.

Overt manifestation of the disorder began late in the 3rd decade and lasted, on average, for more than 30 years.

In similar families possession of the trait is compatible with considerable longevity, affected subjects living even into the 9th decade.

Although septicaemia and the effects of chronic sepsis complicating trophic lesions accounted for some deaths in the pre-antibiotic era, these causes have probably now been eliminated, with advances in treatment, and no other deaths appear directly attributable to the inherited disorder, with the possible exception of the occasional case of secondary amyloidosis.

The possibility of this complication must always be remembered in H.S.R.N, and the other allied traits, and may dictate the need for amputation of a severely affected limb, wherever there is impairment of health in general, and renal function in particular.

Myocardial infarction occurred in several affected members of the "X" family, but this probably represents chance association of a common polygenetically determined tendency, in individuals who also happened to have inherited the mutant gene.

It seems possible that life expectancy was reduced in the "R" family (Hicks (1922), Denny Brown (1951)) in which all affected
members suffered not only from H.S.R.N., but also from severe nerve deafness and lightning pains. If this is so, it indicates still further the greater pleiotrophy of this gene as compared with that present in the "X" family, and most other stocks.


CHAPTER 15

GENETICS OF H.S.R.N.

This subject is reviewed under the following headings:

1. Dominant Inheritance
2. Mendelian Ratios
3. Age at Onset
4. Penetration
5. Expressivity
6. Sex Limitation
7. Genetical Heterogeneity
8. Fitness
9. Linkage Relationships

1. Dominant Inheritance

H.S.R.N. is by definition, dominantly inherited (Denny Brown (1951), Ortiz de Zarate (1955), Heller & Robb (1955), Pratt (1967)), and heterozygotes usually, but not invariably, manifest the trait.

Theoretically an identical clinical syndrome could be recessively determined, but the fundamental biochemical abnormality must be different, and in fact the similar recessive disorders have an
earlier age of onset, and usually differ in other respects (see Chapter 16).

The degree of dominance is unknown, because there is no recorded instance of marriage between two affected subjects, let alone of realisation of the 1:4 risk of an homozygous offspring from such a union.

It seems likely from analogy with other so-called dominant traits, that homozygotes would be more severely affected than heterozygotes (Fraser Roberts (1970)).

This means that the gene must more properly be regarded as intermediate in its effects, and this accounts for the fairly wide intrafamilial range of severity of the disorder and of the age of onset. These variations indicate selection against the gene, presumably through the accumulation of modifiers in the general population. Convergence of a large number of such modifiers is the probable explanation of the occurrence of individuals in whom the trait is almost completely suppressed.

When H.S.R.N. is considered as a separate clinical entity, it is necessary to exclude families in which all affected members demonstrate severe muscular weakness and wasting, or conspicuous evidence of visceral autonomic neuropathy, or corticospinal tract signs. These characteristics indicate different traits which are discussed elsewhere (Chapters 18 and 22).

When such families are excluded, the literature up to the beginning of 1974 is found to contain 19 kindreds classifiable as H.S.R.N., in which father to son transmission provides incontrovertible evidence of Mendelian dominant inheritance.
These 19 stocks have been reported by the following 20 authors or groups of authors:

Göbell & Runge (1944)
Hicks (1922)
Smith (1934)
Beiglböck (1938)
Tocantins & Reimann (1939)
Van Epps & Kerr (1940)
Mulvey & Riely (1941)
Thevenerd (1942, 1953)
Muller & Sugar (1943)
Cooper et al (1947)
Jackson (1949)
Denny Brown (1951)
Jacob et al (1954)
Ortiz De Zárate (1955)
Reimann et al (1958)
Mandell & Smith (1960)
Campbell & Hoffman (1964)
Spillane & Wells (1969)
Lassmann & Partsch (1970)
Wallace (1970)

Dominant inheritance is also probable in a number of other stocks which, however, lack the criterion of father to son transmission.

In these, the index cases were male with an affected mother, (Velluz et al (1955)), or affected paternal uncles (Brandt (1956), Campbell & Hoffman (1964), Eliseo & Zito (1968), Spillane & Wells (1969))
or affected half brothers (Thévenard & Coste (1935), Thévenard (1942), Turkington & Stieffel (1965)), or merely brothers whose disease appears exactly to conform to the pattern of H.S.R.N. (Pallis & Schneeweiss (1960)).

In other families, the index cases were female with affected fathers (Jükhenn et al (1949), Blackwood (1952), Alajouanine et al (1962)), or an affected mother (Kuroiwa & Murai (1964)).

Dominant transmission with limitation to the male sex is also probably involved in two kindreds in which X-linked recessive inheritance is a possibility (Weitz (1921), Van Epps & Kerr (1940)).

2. Mendelian Ratios

In the "X" family, all the affected subjects are distributed in 8 sibships.

There have been 17 affected individuals if 111 10 is included. He had an affected son, and had he lived he would presumably have manifested the trait.

There are 22 unaffected individuals if 111 8 and IV 33 are excluded. They both died in childhood, long before the age at which the disease first appears in this kindred.

The ratio 17 : 22 is a close enough realisation of the one to one expectation of Mendelian dominant inheritance, although it is less close than the corresponding figures of 40 : 39 found in the New South Wales stock, if 17 members are excluded because of insufficient data (Wallace (1970)).
Similar close fulfillment of the anticipated ratio has been recorded in the other large kindreds, which have been adequately ascertained (Denny Brown (1951), Laassmann & Partsch (1970)).

In practice, rather fewer affected than unaffected subjects would be expected, because penetrance is not quite complete.

An early genetic review (Ortiz de Zarate (1955)), identified 142 affected and 127 unaffected individuals in 52 sibships, mainly derived from the literature, which the author considered to have been ascertained in sufficient detail. This series clearly reflects a bias in favour of recording affected subjects, which is not surprising, as there was little attention to genetic detail in most of the earlier reports. Furthermore, the series is genetically heterogeneous as it includes families suffering from a variety of different disorders, including C.M.T.D. and familial spastic paraplegia as well as H.S.R.N., and in some the evidence of autosomal dominant inheritance is also lacking. As stated in another context (Gunther & Penrose (1955)), there is always a tendency to report families containing a high proportion of affected subjects, as these are more spectacular, and other cases are forgotten unless they are of exceptional clinical interest.

A special plea for the thorough ascertainment and recording of pedigrees has been entered (Pratt (1967)), and would be justified by their tantalising absence in so much of the literature of H.S.R.N. alone.

3. Age at onset

(a) Age at onset of neuropathy

Determination of the age of onset of hereditary disorders not manifest at birth, is always a matter of some difficulty (Bell (1955)). H.S.R.N. is no exception to this generalisation, because only
one third of affected subjects experience symptoms of the underlying neuropathy prior to the onset of trophic ulcers (Thévenard (1953)).

In most of the affected members of the "X" family, and in the majority of cases recorded in the literature, the first symptom of the disease has been the appearance of a trophic lesion, and the age at which this occurs has usually been regarded as the age of onset of the disease.

This is obviously incorrect, as the underlying neuropathy must have reached a fairly advanced stage before trophic changes developed. Its beginnings, however, must be so insidious, and its development so gradual, that the actual age at which it first appears remains vague and indefinite.

A case in point is provided by V 52 of the "X" family. When examined in 1970 at the age of 35, she was free from trophic lesions and certainly regarded herself as unaffected. However, she combined sensory loss over the feet with distal muscle wasting of the legs, and slowing of motor nerve conduction velocity.

An entirely different state of affairs obtained in the New South Wales Kindred in which evidence of neuropathy in the form of symptoms such as pains, numbness and paraesthesias, preceded the occurrence of trophic lesions by many months or years (Wallace (1970)). In this family, the existence of the trait could be ascertained on the basis of such symptoms alone, and plantar ulcers when they occurred, merely represented a later stage in the evolution of the disorder.

In this respect, this family resembles examples of acrodyntrophic neuropathy limited to siblings with unaffected parents and childhood onset (see Chapter 16), although in such cases the prodromal symptoms are different as they are usually the outcome of sensory
ataxia rather than cutaneous sensory loss.

There is insufficient data to determine whether interfamilial variations in the ages of onset may exceed intrafamilial variations, although one forms the impression that this may be so when the effects of sex limitation can be excluded. Thus a striking contrast exists between some families with ages at onset ranging from 8 to 12 in two half brothers (Thévenard & Coste (1935), Thévenard (1942)) up until the 4th and 5th decades among male members of other families (Vellus et al (1955), Campbell & Hoffman (1964)).

The phenomenon of anticipation suggesting "a process of progressive worsening of hereditary disease in succeeding generations" (Penrose (1948)), which is one of the pitfalls in the study of dominant pedigrees (Clarke et al (1968)), must be responsible for some of the wide interfamilial variations in age of onset encountered in the literature of H.S.R.N. Although not discernible in the "X" family, its occurrence was clearly demonstrated by Wallace among his Australian patients. Thus the mean age of onset in the 4th generation of this kindred was 49.5 years, in the 5th generation 38.5 years, in the 6th generation 29.0 years, while in the 7th generation it had fallen to 20.4 years.

Wallace concluded that this evidence for anticipation in his stock was partly at least due to the employment of different criteria in ascertainment. In the earlier generations, the age of onset was usually regarded as being the age at which trophic lesions first occurred. In later generations, larger proportions of affected subjects were personally examined, and the trait was increasingly recognised by the discovery of sensory symptoms and signs antedating the development of acrodytrophic lesions.
In most stocks, however, it seems doubtful whether the interval between the onset of objective evidence of sensory loss, and subsequently of trophic lesions, is sufficiently great for this to be other than a contributory factor.

More important explanations of anticipation include the probability that younger generations contain potential cases of late onset not yet manifest, and perhaps most important of all, the reticence of affected members of earlier generations, which led them to conceal mutilation and ulceration of which they had so often been ashamed.

(b) Age of onset of trophic lesions

Although it does not represent the first beginnings of the disorder, the age of onset of trophic ulceration has considerable significance because it is the age at which the patient's main disability begins, and it is one of the events in the course of the disorder which can be dated with considerable precision. It is an index of penetrance inasmuch as it is likely to occur at about the same age in subjects with similar neurological deficits and similar environmental backgrounds.

The age at which lesions first appeared on the feet is known with reasonable accuracy in 10 members of the "Y" family. It ranged from 21 to 39 with a mean of 28.8 (S.D. 6.5).

The literature of H.S.R.W., including all kindreds in which dominant inheritance was either certain or probable, provides a total of 104 cases in which the age of onset of trophic ulceration is fairly closely specified. In 70 of these, this was during the 2nd or 3rd decades. The findings in the "Y" family accord with this preponderance.

The age of onset of trophic ulceration is considered further
in the context of sex limitation, and when the age of onset in dominant pedigrees is compared with that in which a similar trait is first expressed in siblings with unaffected parents.

4. Penetrance

There is only one example of an allegedly unaffected member of the "X" family who had an affected child. This is 111 10 who was killed in action at the age of 37 in 1915. Nothing is known of his feet in his later years. Had he lived the trait might well have become manifest.

"Skips" have, however, occurred in six kindreds (Boiglbök (1938), Van Epps & Kerr (1940), Mueller & Sugar (1943), Campbell & Hoffman (1964), Spillane & Wells (1969)).

In the kindred from New South Wales, which contains 41 affected members and is easily the largest recorded, there were 5 members who had affected children, although they were themselves unaffected, (Wallace (1970)). This represents reduction in penetrance in this stock to less than 90%.

However, most other stocks have been ascertained by enquiry, rather than examination, and it has been the absence of trophic lesions rather than of neuropathy, which has led to the assumption that certain members were not affected.

Total loss of penetrance is rare, probably only occurring in otosclerosis and retinoblastoma (Bundy (1972)), some kindreds with spinal muscular atrophy (Becker (1966), Emery (1971), Zellweger et al (1972)) and apparently in the "Z" family, described later (Chapter 21).

IV 36 of the "X" family is an example of reduced penetrance.
He had neuropathy but no ulceration or deformity of his feet. The diagnosis of H.S.R.N. was confirmed at necropsy.

Other examples of H.S.R.N. with mild sensory neuropathy, but without acro-dystrophic change are reported (Tacantins & Reimann (1939), Ortiz de Zárate (1955), Reimann et al (1958)). If such cases had not been examined they would doubtless have been reported as unaffected.

In another family, an unaffected woman without either neurological or trophic abnormalities, was found to have electro-physiological abnormalities as severe as her clinically affected daughters, (Kuroiwa & Mural (1964)).

5. **Expressivity**

It is well known that the concepts of penetrance and expressivity largely overlap, both being indices of the severity of manifestation of a mutant gene.

In the present context, penetrance has been assigned a quantitative connotation, and has been measured in crude statistical terms (percentages and ages at onset). Expressivity is used in a more qualitative sense and relates to clinical variation in manifestation of the gene.

Expressivity is particularly well illustrated by the "X" family, after excluding subjects about whom there is inadequate data (I 1, \( \bar{I} 1 \), \( \bar{I} 2 \), \( \bar{I} 3 \), \( \bar{111} 10 \)), and others in whom the disorder is in its infancy and its ultimate course obviously unpredictable (\( \bar{V} 55 \), \( \bar{V} 56 \)). The remaining 12 affected members can be assigned to four fairly
distinct groups as follows:

**Group 1.**

The classical severely expressed disease, predominantly sensory, with gross ulceration and mutilation. III 7, III 13, IV 25, IV 32, IV 35 and the propositus IV 37 belong to this group.

**Group 2**

An arrested form of the disease with trophic ulcers limited to one big toe and without progression or mutilation after many years. The siblings IV 28 and IV 29 belong to this group.

**Group 3**

Sensory neuropathy without planter ulceration or bone changes, after many years. IV 36 conforms to this pattern.

**Group 4**

Patients with muscular wasting predominating over the sensory-trophic disturbances. The siblings V 52 and V 53 are of this type.

The occurrence of similar clinical patterns in siblings, suggests the possibility of genetic as well as environmental modification of the action of the main gene. On the other hand, the siblings IV 35, IV 36 and IV 37 exhibit between them both the most severe and the most mild clinical expressions of the mutant gene, and much of this variation must be environmental. IV 36, who escaped trophic lesions entirely, was more fortunate than his brothers in following a sedentary occupation, and he also took greater care of his feet in other ways.

The ability to assign members of the "Y" family to these four distinct groups is almost certainly an artefact due to the relatively small numbers of affected subjects. In the "B" family from New South Wales (Wallace (1970)), which contained rather more than twice as many affected members, a much more continuous spectrum of involvement was
evident, ranging from one patient in whom the only abnormality was recurrent blistering of the feet, to others with extensive sensory and motor involvement and severe ulceration and mutilation. In this family there also appeared to be a tendency for some siblings to manifest similar forms of involvement, either mild or severe, while all degrees of severity occurred in other sibships. About one subject in ten demonstrated conspicuous amyotrophy, which is a similar ratio to that found in the "X" family.

6. Sex Limitation

In the "X" family the sexes were affected in almost equal numbers (9 men and 8 women), and there were no examples of unaffected women having affected children. Some reduction of penetrance in women is, however, suggested by the observation that only one woman (111 7) is known to have presented a severe form of the disease, compared with 5 men. Furthermore, there appears to have been some postponement in the mean age of onset of trophic ulceration in women to 34 years, compared with 26 years in men.

Some at least of this difference is doubtless due to environmental factors, as the males were mainly engaged in heavy labouring work so that their feet were doubtless subjected to greater degrees of trauma than their female relatives.

In the New South Wales kindred (Wallace (1970)), there were 5 female but no male "skips", implying a reduction in penetrance to 50% in women. This was considered to be an under-estimate since some of these women at least might well have manifested neurological abnormalities had they been examined. A high value of over 90% was preferred.
because among the 14 women with affected children, who were personally examined, there was only one who had herself escaped almost all evidence of the trait.

In this family also, there was a greater divergence between the sexes in the mean age of first occurrence of plantar ulceration. In the case of men this was 29 years, compared with 42 years in women.

Other features such as the frequency of hand involvement, muscle wasting and the extent of sensory loss, were also greater on the whole among male members of this stock, than among the female members.

Although the data is insufficient to permit firm comparisons, one forms the impression that these Australian women may have fared somewhat better relative to their menfolk, than affected female members of the "X" family in Wiltshire. If so, it may not be unreasonable to assign this also to environmental differences, as the socio-economic background of the Australian stock appears to be distinctly higher than that of the "X" family.

Affected women in several other large stocks appear to have been even more fortunate, inasmuch as only men are alleged to have manifested the trait, although in each family the occurrence of an instance of father to son transmission excludes X-linked inheritance (Göbell & Runge (1914), Smith (1934), Van Epps & Kerr (1940), Mueller & Sugar, (1943), Cooper et al (1947)).

The existence of such kindreds is a major reason for H.S.R.N. being reported almost twice as often in men as in women (Ortiz de Zárate (1955), implying reduction in penetrance in the latter to below 60%. Many pedigrees have, however, been ascertained by enquiry alone and it is clear that the lowest values for penetrance in women, are
are associated with the more perfunctory investigations.

Inadequate ascertainment of pedigrees and the consequent overlooking of mild forms of the disease, are not the only explanations for falsely low penetrance values in this sex, however. A contributory factor is the delayed onset of the disease in women. This must mean that when a pedigree is ascertained at any single point in time, there will always be a larger number of women than men who have not yet reached the age at which symptoms and signs first appear.

**X Linkage**

The far greater number of affected men than women in the literature of H.S.R.N. raises the possibility of recessive X-linkage. Father to son transmission in at least one instance, effectively excludes this possibility in 20 stocks.

However, from analogy with C.M.T.D. (Allen (1939), Pratt (1967)) and F.A. (Bell & Carmichael (1939)), it is not unreasonable to speculate that a locus exists on the X chromosome, at which mutation could occur and be expressed phenotypically as H.S.R.N.

The possibility has been considered (Pratt (1967)) in a small kinship (Weitz (1924)) in which an affected man received the trait from an unaffected mother, one of whose brothers was affected. Sex limitation was considered more likely, however, and the family may be regarded in the context of others in which affected males have had unaffected parents, but a paternal uncle has manifested the trait (Brandt (1946), Campbell & Hoffman (1962), Eliseo & Zito (1968), Spillane & Wells (1969)).

There is, however, one pedigree of considerable interest, (Van Epps & Kerr (1940)). In this family, only males were affected. There were 6 of these and in each case both parents escaped the disorder.
Unfortunately the details of the pedigree are incomplete, and the sex of the parent who transmitted the trait is provided in only 3. In each case this was the mother.

However, even if the mothers had been responsible in all 6 instances, this pedigree could not prove the existence of X-linkage as it is too small, and inheritance can be explained on the basis of sex limitation.

There is no doubt that a large, well ascertained pedigree indicating this mode of transmission of H.S.R.N. would be of great interest.

7. *Genetical Heterogeneity in H.S.R.N.*

It is now generally realised that not only may different syndromes be determined by different mutations at the same locus, but clinically similar disorders may be due to mutations at different loci.

Genetical heterogeneity is in fact likely to be the rule, rather than the exception, although it may not always be readily discerned (Bundey & Carter (1972)). There are good reasons for believing that it exists in H.S.R.N., and may be suspected as the explanation of interfamilial variations in phenotypic expression.

Reference has already been made to the high incidence of prodromal sensory disturbances in the "E" family from New South Wales (Wallace (1970)), which are almost totally lacking in the "X" family. A different mutation is presumably responsible for this characteristic and there may also be differences between these two stocks in biological fitness, a subject which is discussed in the next section.

Although the "X" family appears to be similar to most other
stocks, the "R" family of Hicks and Denny Brown differs in a number of respects. Thus all its affected members developed severe nerve deafness, and most of them complained of severe spontaneous pains, while several members also had diarrhoea. There is also evidence that life expectancy was reduced in this kindred, although this is probably not true of the "X" family (see Chapter 14). Finally, there are histological differences in the form of an amyloid-like deposition in dorsal roots, ganglia and peripheral nerve; and the absence of neurogenic muscle atrophy, which has been identified in all other cases in which it has been sought (see Chapter 11). All these differences argue the operation of a different mutation.

The suggestion that a distinct and individual mutation is responsible for the trait in every reported family (Wallace 1970) appears to represent an extreme view, however.

Different genes may also account for differences in age of onset. This has been at the ages of 8 and 12 in two half-brothers (Thévenard & Coste 1935), Thévenard (1942), or delayed into middle life (Vellus et al. 1955), Campbell & Hoffman (1964), with the "X" family and most other stocks conforming to an intermediate group with age of onset in early adult life.

The trait described in a Canadian family (Heller & Robb 1955) under the title Hereditary Sensory Neuropathy is also clearly genetically distinct from classical H.S.R.N. as typified by the "X" family.

It was characterised by the appearance of acrodystrophic neuropathy in 5 members of two sibships who were distant cousins. There is no evidence that intermarriage had occurred and the authors favoured the explanation of sporadic dominant inheritance.

The disorder began in infancy in two cases, later in childhood in two, and between the ages of 18 and 20 in the 5th member.
Posterior column sensation was as severely involved as cutaneous loss, and all tendon jerks were abolished. Despite its severity, the trait did not appear to progress. One affected subject was not greatly disabled although he was 80 years old.

In another kindred (Toconscious & Reimann (1939), Reimann et al (1958)), H.S.R.N. was only one of several heritable disorders affecting various members. Anencephaly and meningocoele, hare-lip, cleft palate and epilepsy were also included. It has been suggested that in such families, the relevant gene may be distinct from others in which only the single trait is encountered (Roth (1948)). Chance association, however, remains the simplest explanation for this convergence of different disorders within one family, particularly as different modes of inheritance must be involved in the production of the different abnormalities.

3. Fitness

Wallace (1976) in his study of the much larger New South Wales kindred, found that 42 heterozygotes produced 117 children, whereas their 37 unaffected siblings produced 143 children. The corresponding mean family sizes of 3.9 and 4.8 respectively, represented a reduction in biological fitness of the mutant gene to 0.72.

In the smaller "X" family considered here, 17 affected members had 49 children, whereas 19 unaffected siblings produced only 43. The corresponding mean family size of 2.9 and 2.3 are at variance with Wallace's findings and lead to the conclusion that the reproductive ability of affected subjects may actually be increased, a state of affairs which recalls an opinion reached with regard to C.M.T.D. (Bell (1935)).
The data in the "X" family is, however, distorted by two factors. Thus the first two generations of the stock contained only affected members, so that there are no unaffected siblings with which their fertility may be compared, an important consideration when it is remembered that they lived at a time when larger families were the rule. However, even if these two generations are omitted, the evidence is still against reduced fitness, because it leaves 13 affected subjects, who produced 31 offspring, a mean family size of 2.4 which is not significantly different from the figure given above for unaffected subjects of 2.3.

The second factor distorting the data in the "X" family is the surprisingly large number of unaffected bachelors reaching reproductive age in the 3rd generation (11 4, 11 5, 11 9, 11 11). This failure to marry can be attributed to admission to mental institutions in two instances, and to death late in the 3rd decade in another. These four men are the least well ascertained members of the entire stock, and it is even possible that some of them may have had H.S.R.N.

In later generations, there is evidence of voluntary reduction in family size in affected branches of the family. The main motive for this may not have been altruistic. Thus the affected woman 11 7, developed her first plantar ulcer during her 4th pregnancy, and strongly advised her daughters 11 27 and 11 29 to limit the number of their pregnancies for this reason. Each contented themselves with a single child, as a result of this advice, and the disorder has died out in this branch of the family.

An adverse effect of pregnancy upon the evolution of H.S.R.N. has been reported (Jüghern et al (1949)), but it has not been generally observed, and indeed paradoxically, another affected woman appears actually to have improved during the course of pregnancy (Jacob et al (1954)).
Moreover, Wallace (1970) found that affected women tended to have as many children as affected men, which suggests that the former were not unduly disturbed by the effects of pregnancy upon the trait. This conclusion is supported by the limited data available from the "X" family. If the 5th generation is omitted on the grounds that many of its members have not yet completed their reproductive lives, it can be seen from the pedigree that 4 affected women had 24 children between them, compared with 8 affected men who had only 17.

In the "Z" family, on the other hand, which is considered later, there can be no doubt at all that a similar trait became much worse during the course of pregnancy, and it remitted subsequently.

There are also certain other heredo-familial neuropathies which appear actually to be provoked, or at least made worse, by pregnancy or the puerperium (Ungley (1933), Jacob et al (1960), Taylor (1960), Roos & Thygesen (1972)), while there is evidence that Refsum Syndrome may be adversely affected (Fryer et al (1971)).

Multiple sclerosis is the classical example of a neurological disorder which deteriorates during the course of pregnancy and the puerperium. However, even in this instance, the risk is insufficient and the results do not justify recommending termination (Schapira et al (1966)).

It would seem sensible to warn women affected with H.S.R.N. to restrict the number of their pregnancies, because in addition to the 1:1 risk of begetting affected offspring, there appears to be a possible additional risk to themselves.
9. **Linkage Relationships**

In the New South Wales stock, linkage studies suggested the possibility that the loci for the alleles responsible for the H.S.R.N. trait, and the P Blood Group, were within measurable distance of each other. No such relationship existed with the ABO or Rhesus blood groups (Wallace (1970)).

For reasons already given, linkage studies were not carried out in the "X" family.
CHAPTER 16

THE RECESSIVELY INHERITED ACRODYSTROPHIC NEUROPATHIES

There are good reasons for believing that several clinically distinct forms of H.F.A.N. exist which are recessively inherited.

The evidence for these conclusions is discussed in this chapter under the following headings:

1. Genetics of Sibships with Unaffected Parents
   (a) Classification of the Sibships: Theoretical possibility of recessive inheritance.
   (b) Age of onset of trait.
   (c) Parental consanguinity.

2. Clinical Features of Recessively Inherited Acrodystrophic Neuropathies
   (a) Type 1 Familial Acrodystrophic Neuropathy.
   (b) Type 2 Familial Acrodystrophic Neuropathy (Infantile and Juvenile Forms).
   (c) Progressive and Non-Progressive Sensory Neuropathies
   (d) Familial Acrodystrophic Neuropathy with Amyotrophy
   (e) Familial Acrodystrophic Neuropathy with Spastic Paraparesis
   (f) Congenital Sensory Neuropathy with Anhydrosis

3. Conclusions
1. Genetics of Sibships with Unaffected Parents

(a) Classification of the Sibships:

Theoretical possibility of Recessive Inheritance

In the previous chapter, it has been shown that the literature of H.F.A.N. includes 19 pedigrees of H.S.R.N., in which father to son transmission occurs in at least one instance, and 13 families in which this criterion is lacking, but dominant inheritance is probable.

There are also a number of other dominant pedigrees which differ clinically from H.S.R.N. through the uniform occurrence, either of considerable muscular weakness and wasting (see Chapters 18 - 22) or of cortico-spinal tract signs (see Chapter 22).

When all these pedigrees are extracted, there remain a total of 30 reports, some very scanty, which describe 26 families, under a number of different titles (see Chapter 2), in which acrodytrophic neuropathy is limited to two or more members of single sibships, with in each case, allegedly unaffected parents and no other family history.

These sibships are enumerated in chronological order in the list which follows, according to the names of the authors or groups of authors who described them. They are each designated by a number, and in later sections of this chapter are referred to by this numeral and not by the authors names.
<table>
<thead>
<tr>
<th>Sibship</th>
<th>Authors</th>
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<tbody>
<tr>
<td>1</td>
<td>Nélaton (1852)</td>
</tr>
<tr>
<td>2</td>
<td>Bramann (1889)</td>
</tr>
<tr>
<td>3</td>
<td>Oehlecker (1909)</td>
</tr>
<tr>
<td>4</td>
<td>Price (1913)</td>
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<tr>
<td>5</td>
<td>Schulze (1917)</td>
</tr>
<tr>
<td>6</td>
<td>Guillain &amp; Thévenard (1935), Thévenard (1942)</td>
</tr>
<tr>
<td>7</td>
<td>Wagner (1932)</td>
</tr>
<tr>
<td>8</td>
<td>Bériel et al (1934)</td>
</tr>
<tr>
<td>9</td>
<td>Gâte &amp; Riou (1936)</td>
</tr>
<tr>
<td>10</td>
<td>Van Bogaert (1940)</td>
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<tr>
<td>11</td>
<td>Barré (1945)</td>
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<tr>
<td>12</td>
<td>Ogryzko (1946)</td>
</tr>
<tr>
<td>13</td>
<td>Pérond et al (1949)</td>
</tr>
<tr>
<td>14</td>
<td>Taleb (1950), Ciaccal (1952)</td>
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<tr>
<td>15</td>
<td>Boudin &amp; Djindjian (1951)</td>
</tr>
<tr>
<td>16</td>
<td>Buziers et al (1952)</td>
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<tr>
<td>17</td>
<td>Lessard &amp; Poulion (1953)</td>
</tr>
<tr>
<td>18</td>
<td>Barraquer - Bordas et al (1955)</td>
</tr>
<tr>
<td>19</td>
<td>Fisher (1955)</td>
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<td>20</td>
<td>Pellis &amp; Schneeweiss (1960)</td>
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<td>21</td>
<td>Logatchev (1964)</td>
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<tr>
<td>25</td>
<td>Kozlowski et al (1971)</td>
</tr>
<tr>
<td>26</td>
<td>Murray (1973)</td>
</tr>
</tbody>
</table>
The existence of a disorder in siblings whose parents are unaffected does not alone indicate that it is recessively determined, as the same phenomenon may be due to sporadic dominant inheritance or, (if brothers only exhibit the trait), to X-linked recessive inheritance. There is also the academic possibility of somatic mutation occurring in a parental gonad.

Proof of recessive inheritance depends on other well known additional criteria.

Thus, the number of affected to unaffected siblings, where a large number of families are aggregated, should approximate to the 1:4 ratio of Mendelian recessive inheritance; while affected subjects should themselves have unaffected children, unless they are unfortunate enough to marry a heterozygote or another homozygote.

This information is not available in these families mainly because they have been reported for their clinical rather than genetic interest.

Formal proof of recessive inheritance is therefore lacking, although two further considerations make it probable. These are firstly the earlier age of onset of the trait in many of these sibships and secondly, the raised consanguinity rate among their parents.

(b) Age of Onset

The literature provides the precise age of onset of symptoms of acrodytrophic neuropathy (usually in the form of trophic ulceration) in 46 members of these sibships, and in 93 members from dominant pedigrees of N.S.R.N.
Their distribution is compared in the table below, where Column A is the age group, Column B the number of cases with unaffected parents, and Column C the number of members from dominant pedigrees.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
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<tbody>
<tr>
<td>0 - 5</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>6 - 10</td>
<td>11</td>
<td>1</td>
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<td>11 - 15</td>
<td>16</td>
<td>10</td>
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<tr>
<td>16 - 20</td>
<td>5</td>
<td>29</td>
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<tr>
<td>21 - 30</td>
<td>1</td>
<td>22</td>
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<tr>
<td>31 - 40</td>
<td>2</td>
<td>13</td>
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<tr>
<td>41 - 50</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>51 - 70</td>
<td>-</td>
<td>6</td>
</tr>
</tbody>
</table>

It is clear from all this data that the disorder tends to occur earlier where parents are unaffected, than in the dominant pedigrees. Indeed, onset in the first decade is almost synonymous with parents being unaffected. 80% of cases with unaffected parents first exhibit the trait before the age of 15, compared with fewer than 20% from dominant pedigrees. On the other hand, the disorder was first noticed after the age of 21 in only 7% of the former, compared with well over half the latter.

This predominant onset in childhood in individuals with unaffected parents is not a criteria of recessive inheritance, but is suggestive of it because, as a general rule, the age of onset of recessively determined disorders is earlier than that of the corresponding transmitted traits (Allen (1937), Fraser Roberts (1970), Fraser (1970)).
This has been shown to be true of a number of neurological heredo-degenerations, in which both modes of inheritance occur. Thus, in C.M.T.E., the mean age of onset was found to be 19 years where subjects had an affected parent, compared with 11 years where both parents were unaffected (Bell (1935)). Comparable figures were 20 years and 12 years in Friedreich's ataxia, 36 years and 15 years in spastic ataxia, and 19 years and 11 years in spastic paraplegia (Bell & Carmichael (1939)). Recessively determined forms also tend to occur earlier than dominant in the muscular dystrophies (Bell (1943), Walton (1969)), and in the spinal muscular atrophies (Emery (1971)). In Huntington's Chorea, where inheritance is uniformly dominant, the mean age of onset was 35 years (Pratt (1967)), although occasionally children may be affected in the first decade (Jervis (1963)). Where choreo-athetosis is recessively determined, however, early onset is invariable (Nutting et al (1969)). It is therefore not surprising that in practice, genetically determined neurological disorders occurring among children, are found to be almost always recessively determined (Wilson (1968)).

(c) Parental Consanguinity

7 of the 29 sibships were born to parents who were blood relatives and this provides powerful circumstantial evidence in favour of recessive inheritance.

In 4 instances, parents were first cousins (sibships 7, 17, 18, 26), and in a fifth, first cousins once removed (sibship 13).

In another family, not only were the parents first cousins, but there was a history of much inbreeding over previous generations.
This was an Arab stock from Beirut (sibship 14) in which first cousin marriages were apparently demanded by ancestral custom, and had occurred over several generations.

Consanguineous parentage has not always been sought, and indeed its significance would not have been realised in the earliest reports, so that it is possible that its incidence in this disorder is even higher than these figures suggest.

2. Clinical Features of Recessively Inherited Acródystrophic Neuropathy

The earlier age of onset and high incidence of parental consanguinity among these sibships can be correlated in many, but not all, instances with the appearance of clinical features which are distinct from those portrayed by dominantly inherited H.S.R.N. Only about half the sibships resemble H.S.R.N. clinically, with dissociated sensory loss and slight or moderate reflex impairment.

The other half differ because other sensory modalities are more severely affected and there is greater and more extensive reflex loss.

After discarding 5 sibships (numbers 1, 2, 3, 16, 21), which lack neurological detail, the remainder can be assigned with some confidence to one or other of the following syndromes.
9 sibships conform to this pattern.

6 are indistinguishable from H.S.R.N. with symptoms or signs appearing in the second or third decade (sibships 5, 6, 9, 10, 18, 20) and it seems likely that these are examples of H.S.R.N. in which the phenotype has been suppressed in the gene-bearing parent, and there has been a failure to identify any other relevant family history.

In 3 other sibships, however, (7, 11, 17,) onset has been during the first decade, and 3 of these (7, 17,) have been the progeny of consanguineous parentage.

This data suggests the existence of an extremely rare recessively determined variant of H.S.R.N., clinically distinguishable from H.S.R.N. only through its much earlier onset.

From one patient in this group (17), the extraordinary technique of biopsy of a 5th lumber sensory ganglion was performed (Desrochers (1955)). The histological appearances are stated to have been identical with those of dominantly inherited H.S.R.N. (Heller & Robb (1955)).

Sporadic examples of childhood A.N. have been reported which appear to conform to this pattern (Bousquet (1906), Bonnet & Goyet (1906), Munro (1956), Ogden et al (1956)). Although there can be no certainty that these were genetically determined, it is of interest that one was the offspring of parents who were first cousins.
(h) Type II: Familial Acrodystrophic Neuropathy;

(Impairment of all sensory modalities and greater reflex loss)

12 sibships belong to this group of which 2 (11, 26) are the product of consanguinous parentage.

Sensory loss is usually more extensive than in H.S.R.N., all four limbs being affected (sibships 4, 8, 12, 13, 19, 20, 22, 23, 24, 26), while in about a third there is also extensive loss over the trunk (sibships 15, 22, 24, 26).

Touch may be lost over an area as great or greater as that for pain and temperature (sibships 4, 8, 12, 13, 14, 15, 23, 24, 26), and proprioceptive loss may be severe (sibships 12, 13, 14, 22, 23).

Involvement of all sensory modalities prevents recognition of objects by touch and feel alone, visual inspection being necessary, while fine movements are performed clumsily, particularly if the eyes are shut (sibships 4, 12, 13, 15, 22, 24, 26). Such signs have often been observed prior to the onset of trophic lesions (sibships 4, 12, 13, 15, 22, 26). However, the degree of ataxia has only once been severe enough to cause Rombergism (22).

Lightning pains do not apparently occur in this form of A.N. and accessible nerve trunks have never been found palpably enlarged.

Trophic lesions of the hands may rapidly follow those appearing for the first time on the feet (sibships 14, 24, 25), or may even precede them (26).

Extension of sensory loss on to the trunk has not caused failures of diagnoses of abdominal catastrophies, although this is a hazard which has been recognised in sporadic cases (Taft (1971)).
Dense sensory loss over the limbs has led to delayed recognition of bone fractures (12, 13, 22, 24, 26), and to the development of neurogenic arthropathies affecting knees (24), or a hip (26).

These observations contrast with events in H.S.R.N, in which spontaneous fracture of a large bone in the leg has only once been recorded, while neurogenic involvement of joints proximal to the ankle apparently does not occur.

Tendon and cutaneous reflexes are much more severely affected than in H.S.R.N., being abolished or markedly depressed from the outset (4, 8, 12, 15, 22, 23, 24, 25, 26).

Muscular wasting and weakness are never clinically apparent, although E.M.G. findings in the most recent study of one of these sibships (22), implicate a minor degree of muscle denervation.

Visceral autonomic dysfunction is also unusual, but occurred in two sibships. In one of these (15) one member suffered from visceral crises which become increasingly dramatic as time passed. After 8 - 10 days of constipation, she developed rigors, fever, epigastric pain and vomiting. The pain then spread into the lower abdomen and violent diarrhoea ensued. In the second sibship (24) both affected siblings passed 3 or 4 loose motions daily for between 2 - 4 years. It then ceased. It was never explained. One child developed rectal prolapse which required surgical repair.

Retinitis pigmentosa has been described in 3 members of two sibships (8, 9).

As in H.S.R.N., C.S.F. examination has usually been unrewarding, although very low protein (24)and B,12 levels (25) have been reported.
There has been failure to evoke digital sensory nerve action potentials, although motor nerve conduction velocity has been normal, or only very slightly reduced (22, 23, 24, 26). This is in marked contrast to the "X" family (see Chapter 10).

Nerve biopsy findings have been characterised by gross depletion of both large and small myelinated fibres in cutaneous nerves, (22, 23, 24, 26), although this was less marked in more deeply placed nerves (22), and there is some loss of unmyelinated fibres also (22). There have, however, been no visible myelin breakdown products, nor other evidence of active degeneration (22, 23, 24, 26) except in the most recent study of one sibship (22) which has revealed some segmental demyelination and remyelination. The data provided was, however, insufficient to determine whether the process of degeneration began in neurones or in Schwann cells. More obvious evidence of demyelination was present in another sibship (15).

Other findings have included shrunken nerve trunks, subendoneurial distension by clear material, little abnormality in Schwann cell appearances with absence of "onion bulbs", and variable, usually slight, evidence of connective tissue increase.

The most recent study of the Quebec sibship (22) included estimations of phospholipids and glycolipids from liver biopsy material. These were normal, and this suggested that a specific defect in myelination could be excluded.

Sporadic examples of A.N. in children have been reported (often as cases of congenital indifference to pain), which appear to conform to this pattern. In some, symptoms and signs have appeared within the first year of life (Hend (1903), Ortiz de Zarate (1955), Sandell (1958), Ogden et al (1959), Wadia & Dastur (1960),

While there can be no proof that all of these are genetically determined, it is obvious that a disorder affecting two or more members of a sibship, must also sometimes occur in isolated individuals. Furthermore, several have been the progeny of consanguineous parentage, either first cousins (Parks & Staples (1945), Ogden et al (1959), Johnson & Spalding (1964)), or half-siblings (Johnson & Spalding (1964)).

In a unique Canadian kindred, a clinically identical trait was transmitted as a sporadic dominant with as many as 3 intervening generations who escaped its manifestations (Heller & Robb (1955)). Inheritance in this stock has been interpreted as possibly recessive, however, (McKusick (1964)), in which case almost half of the familial examples of this form of H.P.A.N. are found to be of East Canadian origin (the others being sibships 12, 19, 22, 24 and 26 ). This suggests a "founder effect" exerted by an early immigrant, presumably of French extraction, with spread of the gene which is presumably harmless in heterozygotes, facilitated by the population explosion known to have occurred in this region over the past two centuries. Hereditary tyrosinaemia is another illustration of the "founder effect" occurring in the same ethnic group (Harris (1970)).

A curious distinction between the familial and sporadic cases is provided by analysis of the sex incidence. This is equal in familial cases (17 males, 15 females, 1 unspecified), but there is a preponderance of males (10 cases) over females (3 cases) among sporadic cases. A possible explanation for this is that sporadic cases are less likely to
be reported than sibships containing two or more affected members, unless they are particularly severely affected. Such severe forms of involvement may occur more often in males, a state of affairs which has already been shown to be true of H.S.R.N.

X-linked recessive inheritance of a proportion of these cases is an alternative explanation.

(c) Progressive and Non-Progressive Sensory Neuropathies

The almost total absence of myelinated fibres in some of these cases, and also of myelin degradation products, was originally interpreted as indicating a primary failure of either myelin formation or out growth of myelinated nerve fibres from the neuraxis, probably the latter as the limbs are most affected (Dyck et al. 1966).

As the result of a more recent study of the same sibship (22), Dyck and his colleagues (Ohta et al. 1973) have revised this view because of the discovery of active degeneration and regeneration of myelinated fibres, and also of some depletion of unmyelinated fibres. This process must have begun extremely early, probably in utero, or at least soon after birth, because the total transverse fascicular areas of the nerves examined were reduced, indicating an attack upon them before development was complete.

The neurological deficit resulting from a congenital neuropathy of this type would be expected to be present, if not clinically apparent, at birth, or at least within the first year or so of life. Furthermore, as the original process was extensive and evidence of continuing degeneration slight, its clinical expression is likely to be severe, perhaps complete, from the outset.
This state of affairs correlates well with the concept of Non-Progressive Sensory Neuropathy (Ogden et al (1959)), of which the classical example is provided by a French patient who showed little deterioration over 22 years (Bonnet & Goyet (1906), Bonnet (1921), Barbier & Jaricot (1931)).

Such an explanation seems reasonable in those sibships in which the syndrome has been recognised within the first year or two of life (12, 22, 24, 25, 26 and several sporadic cases), but less so where symptoms have not appeared until later in childhood (4, 8, 13, 14, 15, 23 and other sporadic cases).

A juvenile sensory neuropathy of the latter type is more plausibly explained on the basis of a degenerative process beginning at a later date, and its progressive character is inherent in the very fact that it was not present at birth. This variety can be correlated with the concept of progressive sensory neuropathy (Ogden et al (1959), Johnson & Spalding (1964)). Eventually a deficit is acquired which may be almost as extensive as that present from the outset in Non-Progressive Sensory Neuropathy.

It has been suggested that children with Progressive Sensory Neuropathy are in reality sporadic, early appearing examples of H.S.R.N. (Ogden et al (1958)), or where this is not the case, they are examples of Non-Progressive Sensory Neuropathy in which a false impression of progression has been inferred, simply because the child has reached an age where he or she is able to cooperate more fully, and can recognise more subtle degrees of sensory impairment than was possible in infancy (Murray (1973)).

Modern concepts of genetic heterogeneity suggest that both these views represent over-simplifications.
(d) Familial Acrodystrophic Neuropathy with Amyotrophy

Reports from Bucharest of a sporadic case (Poilici et al (1960)) and from Zagreb of two siblings (Jusics et al (1973)), describe a severe A.N. beginning in the first decade, and accompanied by shooting pains and considerable muscle wasting.

These two features demarcate these cases sharply from the familial acrodystrophic neuropathies just described, in which both shooting pains and muscle atrophy are conspicuous by their absence.

In an American girl (Parks & Staples (1945)), A.N. was accompanied by muscle wasting but not by shooting pains. She was the offspring of a first cousin marriage. No mention is made of parental consanguinity in the Balkan reports.

The disorder began in the feet in all cases, with ulceration, extrusion of bone fragments and loss of toes, so that eventually an "elephants foot" deformity developed.

Spontaneous and painless fractures of long bones occurred in the Yugoslav cases, involving all the leg bones and the left humerus in the propositus, and one femur in his sister.

The muscles of the lower leg became thin, hypotonic and weak, with progressive loss of tendon jerks.

Trophic lesions and amyotrophy involved the hands within a few years of their appearance in the legs.

Symptoms of disturbed autonomic control occurred in the worst affected patients, with frequent vomiting bouts, (Poilici et al (1960)), and urinary difficulties and diarrhoea (Jusics et al (1973)).

Sensory loss affected pain, temperature and touch more or
less equally. It began distally in the limbs but eventually extended well up the trunk. Proprioceptive sensation was much less severely impaired.

The Yugoslav propositus was investigated by modern methods at the age of 14 (his sister had died of some "undefined abdominal distress", when 26 years old).

There was E.M.G. evidence of total denervation of the feet and partial denervation of the legs. Sensory action potentials could not be evoked at the wrist after digital stimulation of median and ulnar nerves in the fingers. Motor nerve conduction velocity was at the lower limit of normal in the arms, and just below normal in the legs.

Naked eye examination of nerves from an amputated leg showed these to be grossly atrophic, particularly distally.

Histologically there was severe loss of nerve fibres, especially those of narrower diameter. Both Schwann cells and endoneuritis were greatly proliferated with the formation of "onion bulbs" and resemblance in some sections to neurofibromatosis.

There was no tissue deposition resembling amyloid.

A severe obliterative angiospasm affected skin, nerve and bone.

The appearances in muscle were those of neurogenic atrophy.

This trait resembles that present in the "Z" family (Chapter 20), but differs in its much earlier age of onset, greater mutilation of the feet, less flaccid paralysis and the liability to spontaneous fracture.
(e) Familial Acrodytrophic Neuropathy with Spastic Paraparesis

There are a few instances in the literature which describe A.N. with ulceration and mutilation comparable to that seen in H.S.R.N, occurring among siblings who have also presented cortico-spinal tract involvement, in the form of some spasticity of the legs, exaggerated tendon jerks and extensor plantar responses.

A similar phenotype is also transmitted as a Mendelian dominant, and both forms are described together elsewhere (Chapter 22).

(f) Congenital Sensory Neuropathy with Anhydrosis

This extremely rare disorder is characterised by absence of sweating, dissociated sensory loss and trophic lesions, and affects both siblings and sporadic cases (Swanson (1963), Gillespie & Perucca (1960), Pinsky & Di George (1966), Vassella et al (1968)).

The sensory deficit is very extensive, so that ulceration of the tongue and fingers, from sucking and chewing, may appear in infancy. Later lesions include spontaneous fractures and dislocations.

The absence of sweating confers its own particular hazards. Trivial infections may provoke fever, and this may proceed to fatal hyperpyrexia, (Swanson et al (1963, 1965), Taft (1971)). The absence of pain sensation has been first recognised by the apparent painlessness of penicillin injections given for such fevers (Gillespie & Perucca (1960)).

Although tendon jerks and sensory nerve action potentials
are apparently preserved in some cases, the former have been diminished and accompanied by some degree of incoordination later in infancy, (Gillespie & Perucca (1960)).

Impaired thermal perception distinguishes this trait from congenital analgesia with anhidrosis, in which trait pain sensation is the only sensory modality which is lost (Brown & Podosin (1966)).

Sural nerve biopsy has shown normal numbers and appearances of myelinated nerve fibres (Pinsky & Di George (1966)), while a solitary post mortem examination revealed selective depletion of smaller sensory neurones with shrunken dorsal root ganglia (Swanson et al (1963, 1965)). A congenital failure of development of this population of neurones and their unmyelinated fibres, has been proposed as the explanation of the sensory loss.

Other striking abnormalities included absence of the dorsolateral fasciculus of Lissauer, subdural cavitation and thickened, adherent leptomeninges (Swanson et al (1963, 1965)).

3. Conclusions

When all the certainly or probably dominant pedigrees of H.S.F.W., and the allied phenotypes are extracted from the literature of F.L.S., myelodysplasia, Morvans Syndrome, trophoneuropsis, A.U.M.F., Hereditary (or Familial) Sensory Neuropathy and so on, there remains a residue of reports which describe subjects with acrodystrophic neuropathy with the following shared characteristics:

(1) They have at least one similarly affected sibling.

(2) Their parents are unaffected, and there is no other
family history.

(3) There is a high incidence of parental consanguinity.

(4) The disease begins much earlier (in infancy or childhood), then it does in the dominant pedigrees.

This combination of characteristics provides strong circumstantial evidence for recessive determination.

Clinically these traits may be subdivided into a minimum of six distinct clinical forms as follows:

(1) An infantile or congenital analogue of H.S.R.N. with dissociated sensory loss and preservation of tendon jerks except the ankle jerk. This form is exceedingly rare. To conform to the classification of the dominant trait, H.S.R.N. by the Mayo Clinic School (Ohta et al. (1973)) as Type 1 Hereditary Sensory Neuropathy, this disorder has been named Type 1 Familial Acrodystrophic Neuropathy.

(2) Congenital Non-Progressive Sensory Neuropathy with involvement of all sensory modalities and widespread areflexia.

(3) Juvenile progressive sensory neuropathy with involvement of all sensory modalities and widespread areflexia.

The latter two forms share the same neurological features, and have indeed been classified together as Type 11 Hereditary Sensory Neuropathy (Ohta et al. (1973)). In the writer's view, since recessive inheritance is involved, and because mutilation of the extremities distinguishes these cases from other chronic neuropathies of childhood, it would be better to describe them as Type 11 Familial Acrodystrophic Neuropathy, and at the same time to recognise that distinct congenital, non-progressive and juvenile, progressive varieties exist.

The purely sensory traits have often been confused with Congenital Indifference to Pain, which is discussed in the next chapter, (Chapter 17).
Three other distinct forms of Recessively Determined Acro-dystrophic Neuropathy of childhood also exist in which the sensory syndrome is accompanied either by distal muscular wasting and weakness, by cortico-spinal tract signs or by anhydrosis.

The latter named syndrome, Congenital Sensory Neuropathy with Anhydrosis, is classified by the Mayo Clinic workers as Type IV Hereditary Sensory Neuropathy.

Familial Dysautonomia (F.D.) is accorded the title of Type III Hereditary Sensory Neuropathy in this scheme. This trait is also described in the next chapter.

There are 4 other recessively inherited neuropathies, of which Hypertrophic Neuropathy has been the most frequently implicated, which may occasionally become complicated by ulceration of the extremities and erosion of bones, although usually not until adult life has been reached. These traits are described in the last part of Chapter 22.
CHAPTER 17

Familial Dysautonomia and Congenital

Innsensitivity to Pain

Familial Dysautonomia and Congenital Insensitivity to Pain are considered separately from the disorders described in the previous chapter, because their nosological status as sensory neuropathies remains debatable.

This is particularly true of congenital indifference to pain for which a central origin in brain or cord, at present unknown, is usually assumed.

So far as Familial Dysautonomia (F.D.) is concerned, a peripheral neuropathy has been identified in a minority of cases, and this has led to its recent classification as one of the Hereditary Sensory Neuropathies (Ohta et al. 1973). Histological reports to date, however, have been so conflicting that this classification appears to be premature, and the status of F.D. as an example of Hereditary Sensory Neuropathy must be regarded as remaining unsettled at present.
Relative indifference to pain is one of the essential clinical features of F.D. (Riley & Moore (1966)), and is accompanied by other neurological signs, notably absent or diminished tendon reflexes, poor motor coordination, and emotional disturbances (Riley et al (1949)), and less consistently by proprioceptive involvement including Rombergism and a broad based gait (Riley (1957)).

There is, in consequence, a failure to recognise injuries, so that fractures may only be diagnosed retrospectively, when unexplained bone swellings are x-rayed, while ulceration of the tongue and cornea reflect the generalised nature of impaired pain perception.

Ulceration and mutilation of the extremities of the limbs, as seen in the areodystrophic neuropathies is, however, apparently rare, and was not encountered among the dermatological abnormalities present in a series of 125 cases (Fellner (1964)), although it has been recorded in an atypical case (Riley & Moore (1966)). Charcot joints have been described (Brunt (1967)).

Furthermore, the indifference to pain is not true anaesthesia, as pinprick is readily identified and localised. It seems to be rather a lack of awareness of discomfort (Riley (1957)). On the other hand, stroking the scalp and soles of the feet may cause acute discomfort (Dancis & Smith (1966)).

These neurological abnormalities of F.D. are overshadowed by disturbances of autonomic function, notably diminished lachrymation, hyperhydrosis, transient skin blotching, an abnormal swallowing reflex, labile blood pressure and unstable temperature control.
A unique feature is the absence of lingual papillae (Smith et al. (1965)), so that inspection of the tongue is the simplest and possibly most reliable method of diagnosing the disease (Dancis & Smith (1966)).

Typically, F.D. involves Jewish children (Brunt & McKusick (1970)). There is a history of swallowing difficulty and fevers, (probably due to aspiration bronchopneumonia) from birth, (Riley & Moore (1966)). The other abnormalities become apparent within the next year or two of life, and are associated with delayed sitting, standing, walking and speech (Riley (1957)), and retardation of growth (Riley et al. (1954)).

The biochemical basis of the disease which is recessively determined (Pratt (1967), Brunt & McKusick (1970)), appears to be an in-born error of catecholamine metabolism. Urinary excretion of homovanillic acid (derived from Dopamine) is increased, relative to the degradation products of adrenaline and nor-adrenaline (Smith et al. (1963), Gitlow et al. (1970)). There is in consequence, an exaggerated response to infused nor-adrenaline (Smith & Dancis (1964)), while some of the signs of the trait may be reversed by infused methacholine (Smith et al. (1965)). The latter observation suggests an inadequate parasympathetic nervous system, and may be correlated with the observation that there is an excess of acetylcholinesterase in nerve plexuses around sweat glands (Hutchison & Hunter (1962)).

Examination of the eyes may be diagnostic, because of the association of corneal hypeaesthesia, absence of tear formation, exodeviation and an abnormal (miotic) response to dilute methacholine instilled into the conjunctival sac (Dancis & Smith (1966)).
Another diagnostic feature which supports the view that a peripheral sensory neuropathy exists, is the absence of a painful "flare" response to intradermal histamine (Smith & Dancis (1965)). This may occur in acrodystrophic neuropathies, but is limited to the peripheral territory of sensory loss, whereas it is generalised in Familial Dysautonomia.

Although there may be survival into adult life (Riley (1957), Yatsu & Zussman (1964)), death in childhood is probably the more usual outcome and results from the complications of autonomic dysfunction, notably hyperpyrexia, aspiration pneumonia and renal damage consequent upon hypertension (Riley (1957), Brown et al (1964)).

Autopsy findings are conflicting, suggesting that the observations may not be fundamental to the disease (Riley (1957), Dancis & Smith (1966), Smith & Hui (1973)), and usually appear to have wholly exonerated the peripheral nervous system (Brunt & McKusick (1970)). Even when there has been widespread demyelination within the cord, there has been only occasional loss of myelin sheaths in peripheral nerve (Brown et al (1964)), and indeed nerve biopsy may be totally unrewarding (Smith & Hui (1973)).

Recent studies of other typical cases have revealed considerable depletion of unmyelinated fibres in peripheral nerve however (Pearson et al (1970), Aguyoy et al (1971)), similar to that seen in familial amyloid neuropathy, and this has been accompanied by some reduction in the largest myelinated fibres (although signs of active degeneration have not been seen).

Such findings would explain loss of tendon jerks and sensory nerve action potentials, and slowing of motor nerve conduction velocity, all of which have been found, while the predominant loss of unmyelinated fibres in somatic nerve can be correlated with
widespread impairment of pain and temperature sense, and of corneal reflexes. If there is similar depletion of autonomic post-ganglionic fibres (which are invariably unmyelinated), both cholinergic and adrenergic, the whole range of autonomic disturbances so characteristic of the trait, can also easily be explained.

Taking all these factors into consideration, there appear to be good grounds for the Mayo Clinic classification of F.D. as one of the Hereditary Sensory Neuropathies, although the disturbance of nerve function is apparently primarily one of function, and only secondly one of structure.

Furthermore, the loss of pain perception at the extremities is no greater than over other parts of the body, and it is certainly much less in these situations than that occurring in the inherited sensory neuropathies described in the previous chapters. There is, as a result, no particular predisposition to ulceration and mutilation of the feet and hands, and F.D. cannot therefore be defined strictly as a form of Heredo-Familial Acrodystrophic Neuropathy.
Congenital Indifference to Pain

This trait has been well reviewed (Critchley (1956), Ogden et al (1959), Pratt (1967), Spillane & Wells (1969), Jewsbury (1970)), and it is outside the scope of this thesis to attempt more than a summary of its main features.

The sole consistent clinical characteristic, an inability to recognise painful stimuli, is present from birth and is generalised all over the body, with the result that if and when trophic lesions develop, they may be situated at any point which has been subjected to sufficient trauma. Typically, the first of these may be ulceration of the tongue or fingers from chewing during infancy, while later in life there may be deformity and invalidism from neglected fractures, degenerative changes in joints and loss of tissues such as fingers and toes with scarring and contractures. There may be blindness from corneal scarring. There is no particular predilection for acrodystrophic change as in H.S.R.N.

The disorder may be broadly heterogeneous in the sense that some cases are due to pathological loss of pain sensation, "pain unfelt", or to an extraordinary elevation of the pain threshold "pain unheeded", (Kunkle (1961)).

Although by classical definition there should be no other abnormality whatever, either sensory or reflex (Ogden et al (1959)), and while this is undoubtedly true in terms of major clinical signs, there may in fact be some impairment of taste, smell, the sensation of itching and the corneal reflexes (Critchley (1956)), auditory perception (Ounurookin et al (1968)), sweating (Brown & Podosin (1966)) and lachrymation (Thrush (1973)). There may also be evidence of abnormal
parasympathetic innervation of the pupil, sometimes accompanied by other signs of autonomic dysfunction (Osuntokun et al (1966), Thrush (1973)). The excretion of V, M, A., H, V, A., and the metanephrines is, however, normal (Thrush (1973)), or but slightly depressed (Brown & Podosin (1966)).

Such subsidiary signs are all overshadowed by the cardinal feature, namely loss of pain recognition, of which the subjective counterpart may be complete freedom throughout life from headache, earache, toothache, abdominal pain and colic (Ogden et al (1959) or labour pains (Ervin & Sternbach (1960)).

Essentially normal findings in the central nervous system have been obtained at necropsy (Baxter & Olczewski (1960), Magee (1960)) and there has certainly been no evidence of any of those gross lesions known to be capable of abolishing peripheral pain perception (Spillane & Wells (1969)).

Congenital indifference to pain has also been defined as a diagnosis which should not be made in the presence of mental deficiency (Ogden et al (1959)), although this view has been challenged (Kirmian & Bicknell (1968)). In fact, apparently genuine congenital indifference to pain has coexisted with mental defect in at least 24 recorded instances (Thrush (1973)). Self mutilation by subnormal children does not necessarily indicate loss of pain sensation.

Conversely, typical cases are often unusually intelligent, and this may account for the apparent improvement of the disorder with age, probably because affected subjects are so successful in avoiding serious trauma.

Another criterion which has been proposed for congenital indifference to pain is that there should be histological proof of normal
cutaneous innervation (Ogden et al. 1959). In two instances, however, modern techniques have revealed changes in biopsied sural nerve, namely loss of myelinated fibres, either those of the smallest calibre with an associated mosaic appearance in Schwann cells (Appenzeller & Kornfeld 1972), or those of the largest diameter with normal looking Schwann cells (Thrush 1973). In both instances, unmyelinated fibres were plentiful and appeared normal.

The disorders most likely to be confused with congenital indifference to pain are the group of congenital sensory neuropathies, both with and without anhidrosis, described in the previous chapter, particularly in those cases where the sensory defect extends over most of the body. These traits are, however, characterised by other forms of sensory loss, which becomes more dense as the periphery of the limbs is reached, and by loss of tendon jerks.

The genetics of congenital indifference suggest its determination by an extremely rare recessive gene, although the number of affected siblings is lower than might be expected. Males are affected half again as frequently as females, but there is no evidence for recessive sex linkage (Pratt 1967). Similar conclusions have been reached in a study limited to the familial cases (Thrush 1973). One third of the parents were consanguinely related, and a similar male preponderance was identified.

In another family, the trait affected members of two generations (Ervin & Sternbach 1960), while its presence in two half-siblings (Osuntokun et al. 1968), also raises the possibility of dominant inheritance. With a gene as rare as this, it is almost impossible to visualise a situation whereby a heterozygote would be so
unfortunate as to marry successively two other heterozygotes (unless these were themselves closely related).
 CHAPTER 18

Acrodystrophic Neuropathy in
Charcot-Marie-Tooth Disease

It has been shown that the neuropathy of H.S.R.N. is sensori-motor, rather than purely sensory, although in 9 out of 10 cases the motor element is muted.

Weakness and wasting of one member of the "X" family, $\overline{V}53$, are now so marked that since his ulcers have healed, he resembles more closely the phenotype of C.M.T.D. rather than that of H.S.R.N. Indeed, the former diagnosis was made when he attended a Genetic Counselling Clinic in 1972.

In C.M.T.D. there may be notable lesions in the afferent tracts (Hughes & Brownell (1972)), and indeed the presence of some sensory loss in this disease is one of the criteria by which it is distinguished from the spinal muscular atrophies (Emery (1971)).

It is surprising, however, how often the sensory degeneration of C.M.T.D. lacks a significant clinical counterpart.

Thus in a study of 100 cases from the literature, whose records were considered sufficiently adequate, cutaneous sensory loss was sought, but not found, in a single instance (Bell (1935)).
In other families it was present in only 2 out of 13 cases (England & Denny Brown (1952)), in 12 out of 14 (Brodell et al (1952)), in 3 out of 10 (Hierons (1956)).

In a large study (Dyck and Lambert (1968)), 67 cases of C.M.T.D. were examined from 21 kindreds. Sensory loss occurred later than motor loss, and joint position sense and vibration sense were impaired more often than cutaneous sensation.

C.M.T.D. is a potentially painful complaint, with deformities of the feet and toes, and cutaneous lesions resulting from these and from over-inversion at the ankles. Such lesions are mechanically induced and only indirectly neuropathic in origin (England & Denny Brown (1952)). The fact that patients so rarely complain about them may indicate some subjective loss of pain sensation (Bell (1935), Dyck & Lambert (1967)).

Rarely, however, pain, temperature and touch are severely impaired and predispose to a trophic syndrome which is indistinguishable from that which characterises H.S.R.N.

Usually this has occurred only in cases with severe forms of disease, and has been limited to one or two members of a kindred (Halliday & Whiting (1905), England & Denny Brown (1952), Barraquer-Ferré & Barraquer Bordes (1953), Cambier & Lefèvre (1960), Guaraldi (1962), Plancherel (1964), Spillane & Wells (1969)).

Even more rare and striking are kindreds of C.M.T.D. in which the majority of affected members have also developed acrodystrophic change (Dyck et al (1965)).

In other families severe motor wasting and acrodystrophic neuropathy have coexisted in every single affected member of the
kindred, (Bruns (1905), Riley (1930), Passouant et al (1951), Jusics et al (1975)). These are the "formes paréto - amytrophique de
l'acropathie ulcéro - mutilante familiale" of Thévenard (1942, 1953)).

Sometimes this combination has been accompanied by evidence of a severe visceral autonomic neuropathy and reduced life expectancy, suggesting the lower limb type of Familial Amyloid Neuropathy, (Barraquer & de Cispert (1956), Alajouanine & Mouziconocci (1960), Feudell (1959)).

Clearly there is a great deal of genetic heterogeneity within this group.

The "Z" family which is described in the following pages, contains at the time of writing, only 2 living affected members. In both, the disease presented with sensory loss and plantar ulcers. These features were subsequently superseded by a degree of muscle wasting and flaccid paralysis, which is altogether alien to H.S.R.N., although reconcilable with a diagnosis of C.M.T.D.

The trait present in the "Z" family is, as a result, of great interest, as it appears to combine the phenotypes of H.S.R.N. and C.M.T.D.

It is also of considerable genetic interest, as the phenotype appears to have been completely, or almost completely, suppressed in two members of the second generation.
CHAPTER 19

The "Z" Family

111 16 of the "Z" family was the subject of a brief report (Campbell & Hoffman (1964)), as a sporadic example of H.S.R.N. with an unusual degree of muscular wasting. A family history was not obtained at that time.

Within a year, however, a 16 year-old girl cousin (111 22) was referred to the late Dr. A.M.C. Campbell, with a planter ulcer which he recognised as being neuropathic in origin. Enquiry disclosed the relationship. It also led to the discovery that although the parents of neither patient were affected, one of their grandmothers, who had died in 1952, had suffered from ulcerated feet and difficulty in walking. Her former doctor, recollecting from memory 16 years after her death, described planter ulceration which he believed to have been of trophic origin, although glycosuria was not found and syphilis was excluded. His report and other anamnestic testimony is reproduced in Chapter 21.

No other members of the family were examined.

In 1970, Dr. Campbell, aware of my interest, suggested that I should make good this deficiency, and incorporate the results in this thesis.
A clinico-genetic survey of the kindred was accordingly undertaken during the winter of 1970, the method of ascertainment being similar to that employed in the "x" family (Chapter 3), and the pedigree was constructed (see Pedigree of the "Z" family).

Geographic and other reasons have prevented this study from being as detailed as that of the "y" family. However, all 26 members of the 2nd and 3rd generations who still lived in Bristol and North Somerset were personally examined, and the remaining four were ascertained by correspondence. Most of the 4th generation were below the age of 12 at that time, and only a few were personally examined.

Nerve conduction studies were limited to 111 16, his father 11 3, and his aunt 11 12, who was the mother of 111 22, the other severely affected patient.

Subsequent ascertainment has been by enquiry alone in 1973, (although 111 16 and 111 22 were re-examined). This procedure is unlike that followed in the "y" family in which all living affected subjects, and those at risk, were re-examined in 1973, after an interval of four years, and in several cases more frequently.

For all these reasons, this study of the "Z" family is included here in a subsidiary role only, its main importance resting on the similarities, and contrasts, which exist between its two affected members and those of the "y" family.

Although 111 16 was the first patient to manifest the trait, he was of little help in ascertainment, as he had little contact with his family. 111 22 on the other hand was full of information. For this reason they have been assigned equal status as propositi. The detailed results of this survey are described in Chapter 21.
The principal objective was the exclusion of significant manifestation of the trait in other members of the stock, and this was fulfilled, although signs suggesting a mild sensory neuropathy were identified in 5 other subjects.
CHAPTER 20

"Z" Family: Clinical Features of Index Cases

111 16: Brian T.

Unemployed labourer; married with 2 children.

Date of Birth August 1932.


History:

For a period in 1946, when he was 14, his feet were extremely tender. He was only comfortable lying on his bed with shoes and socks removed. He could not tolerate his feet being touched, and would cry out if anyone approached them too closely.

He joined the Navy in 1953, but was invalided after a few weeks with "flat feet". While serving he felt embarrassed because his legs were so "skinny".

In 1956 he was referred to a Plastic Surgeon with a "plantar wart". This overlay the head of the 3rd right metatarsal. It was excised, but healing failed and an ulcer persisted at the operation site (Plate 42). Skin grafting was unsuccessful (Plate 43) but
Original plantar ulcer following excision of "plantar wart" in June, 1956.
Recurrence of ulceration at site of skin grafting, January 1957.
healing occurred later after the ulcer was excised, together with the head of his right 3rd metatarsal.

Further ulceration now affected the right big toe (Plate A4) and led to his being referred to Dr. Campbell in June 1957. Pain and temperature sensation were found to be impaired over both feet, with preservation of the other modalities, and the deep reflexes. The legs were noticed to be wasted below the knees, and dorsiflexion at both ankles was weak.

H.S.R.N. was diagnosed.

Thereafter he remained under the care of an orthopaedic surgeon. His toes were clawed, as well as ulcerated. They were all amputated between June 1957 and May 1959. An ulcer of the left heel was grafted successfully in 1958. His feet were always cold and blue. He wore surgical boots at this time.

By May 1962, when he was nearly 30, his legs had become very weak and he could not control his feet. Callipers were provided but these caused ulceration of both malleoli, and were discarded.

Later in the same year, he noticed that his hands were becoming clumsy and were visibly wasted. He experienced difficulty in lacing his shoes, doing up buttons, identifying objects in his pockets and holding a knife and fork.

Re-examination by Dr. Campbell in 1963 showed amyotrophy of hands and below the knees. All hand and finger movements were weak except for abduction of the thumbs, which appeared normal. All ankle jerks were also weak. Extension at both knees was slightly impaired. Power at hips, wrists, elbows and knees was otherwise unaffected. The right ankle jerk was lost, and the left sluggish, but all other tendon
PLATE 44

Ulceration of right big toe, May 1957.
jerk.s were brisk and equal. Neither plantar response could be elicited. Sensory testing revealed dissociated anaesthesia distal to the elbows and mid-thigh level, with loss of light touch confined to the fingers and below the knees. Posterior column sensation appeared to be intact.

Thereafter he continued slowly to deteriorate, although power in the hands remained good as there had been a gratifying response to sublimis transfers carried out in 1966. In the legs deterioration progressed, so that by 1970 he was unable to walk (although he could stand unaided), and had to use a wheelchair.

Since 1959 he suffered from bouts of diarrhoea, These intensified in 1964 and for a time he passed as many as 10 motions daily, streaked with blood and mucus. He was admitted to hospital and investigated by a gastroenterologist. General examination, laboratory investigation of his stools, sigmoidoscopy and a barium enema were all unrewarding. Rectal biopsy was not performed. After a time the diarrhoea slackened, but he continued to pass 3 or 4 loose motions daily until 1971, after which normal bowel function returned.

This diarrhoea was not accompanied by incontinence nor by disturbance of micturition, loss of libido, impotence, or postural hypotension.

In 1969 he first began to experience shooting pains in both legs. These were brief, agonising and occurred in clusters, lasting several hours with intervals of freedom of several weeks. They were quite unrelieved by ordinary analgesics.

His feet and legs remained constantly cold. For this reason he wore soft leather fur-lined boots, even in midsummer.

In 1969 his left knee ulcerated. This was unexplained. He had not been kneeling. This ulcer took 3 weeks to heal, despite
daily dressings, and courses of antibiotics.

Examination by writer, March 1970

General physical examination revealed no abnormalities in systems other than the C.N.S. B.P. 130/75. In particular, there was no ichthyosis, hoarseness, nor orange discoloration of tonsils. The tongue was not increased in size and its papillae appeared normal. There was no enlargement of heart, liver, spleen or lymph glands, and no albuminuria nor glycosuria.

The cranial nerves were intact.

There were no vitreous, corneal, pupillary or retinal abnormalities, no nystagmus and no deafness.

All four limbs were thin, with obvious distal amyotrophy affecting hands and forearms (Plate 45) and below both knees. All toes had been amputated (Plate 46). The right pectoral muscles appeared to be reduced in bulk.

In the hands, both thenar and hypothenar eminences were noticeably flattened and there was some dorsal interosseous furrowing. Numerous small callosities and chronically inflamed areas were present on hands and fingers (Plate 45).

Scars of healed ulcers were visible on the left sole (Plate 47), the right ankle (Plate 48), and left knee (Plate 49).

There was bilateral foot drop, with paralysis of dorsiflexion and weakness of all other movements at the ankle, plantar flexion being affected least. Extension at both knees was weak.

The hand grip remained fairly strong, but all finger movements
Photograph of hands and forearms, showing muscle wasting and numerous small superficial lesions of traumatic origin. March, 1970.
Photograph of legs in March 1970, showing amputated toes and distal amyotrophy.
Appearance of feet in March 1970, showing scars of left sole due to healed ulcers, and absence of all toes.
Photograph of feet and ankles in March 1970, showing scar over right internal malleolus, resulting from healing of ulcer caused by former use of calipers.
Photograph of left knee in March, 1970, showing healed ulcer.
were weak. Extension at wrists, and to a lesser extent at the elbows, was impaired.

Proximal power (neck, shoulders, hips) appeared normal.

Upper limb tendon jerks were present, brisk and equal,

The right knee jerk was brisk, the left sluggish,

Both ankle jerks and plantar responses, and all four abdominal reflexes were lost.

There was no significant degree of incoordination.

Sensory testing demonstrated impairment to temperature recognition, distal to the waist and shoulders. Pain sensation was impaired from just below the shoulders and hips.

Light touch was lost distal to the mid thigh and elbow levels.

Vibration sense, deep pressure sense and position sense were lost at the fingers and ankles, but appeared to be normal more proximally.

None of the superficial nerve trunks could be palpated.

**Subsequent Progress**

Between 1970 and 1973 there was a gradual increase in paralysis, so that he was unable to stand unsupported. Feeding himself, any form of manipulation such as picking up small objects like coins or matches, had all become difficult. He was also conscious of progressively increasing density of sensory loss in the limbs.

Throughout 1972, the nail beds in the fingers of his right
The hand became successively inflamed. The nails became distorted, discoloured and friable, and several fell off. Infection spread to the distal phalanges of the right 2nd and 3rd fingers, necessitating partial amputation.

Shooting pains down both legs, which had first occurred in 1969, became more regular and severe. Each lasted for 60 - 90 seconds, with intervals of freedom of about 3 minutes. They occurred in clusters lasting 24 - 48 hours. Such bouts occurred every month or six weeks.

Between these attacks his legs ached frequently, but this was bearable and responded to ordinary analgesics.

In May 1973 he spilled boiling water over his left foot. This caused no sensation whatever, and he was only aware of it as he watched it happen. The scalded area was grafted a week later, skin for this purpose being taken from his left calf. No anaesthetic was required for this procedure, which was successful.

When re-examined in May 1973, his motor status had clearly deteriorated. The cranial nerves remained normal and movements of the trunk were powerful. Right pectoral wasting was no longer conspicuous, perhaps because he had gained weight.

Examination of the upper limbs, however, revealed bilateral "main en griffe" (Plate 50), with gross wasting of thenar, hypothenar and interosseous muscles. The only finger movement still present was flexion. The fingers could be straightened passively. The ability to abduct or adduct them was lost. Thumb movements remained fair, and he could still approximate his thumbs to individual fingers,
Appearance of hands in May 1970, showing inability to extend fingers, partial loss by amputation for chronic sepsis of right index and middle fingers, gross wasting of thenar and hypothenar eminences, and almost healed burn of left palm.
although these movements were easily overcome.

Uncontrollable twitching of the left thumb occurred from time to time during examination, and fasciculation of muscle was visible in both legs and forearms.

Forearm wasting had increased, and there was bilateral partial wrist drop, more marked on the left side. The ability to extend, abduct and adduct the wrist was lost, but flexion remained fairly vigorous.

Movements at the elbow were all weak, although flexion remained reasonably strong.

Shoulder movements were preserved.

In the lower limbs, wasting below the knee had increased to a "stork leg" appearance, and thigh wasting was now more obvious.

All movements at the ankle were totally paralysed. Movements at the knee were feeble, extension least of all. Power of most movements at the hip was also reduced.

The upper limb tendon jerks were all present except the supinators which were sluggish, while the finger jerks were lost.

Knee and ankle jerks were abolished.

Tone was remarkably reduced in all four limbs.

There was no incoordination in the upper limbs except with the eyes closed. Accessible nerve trunks remained impalpable.

Sensory examination revealed little or no increase in the total territory of sensory loss, but within this area of anaesthesia, there had been an increase in the density and extent of loss of touch and of kinaesthetic sense.
Light touch was now impaired almost to shoulders and hips, and although vibration sense and position sense were totally lost only in the legs and over the fingers, they were clearly impaired at elbows and shoulders.

**Investigations.**

Numerous investigations were carried out throughout the long course of his illness.

They all gave results which were within normal limits, except where specified.

**Blood:** Haemoglobin, red and white cell counts, absolute indices, sedimentation rate, glucose, urea, sodium, potassium, chloride, calcium, inorganic phosphate, proteins, liver function tests, acid and alkaline phosphatases, S.G.O.T., L.D.H., C.P.K., cholesterol, total lipids, alpha and beta-lipoproteins, B₁₂, folate.

Serological tests for syphilis.

Karyotype.

**Urine:** Albumin, glucose, microscopy, culture, aminoacids, porphyrins, creatinine (57 mgm%), ketosteroids.

**C.S.F:** Cells, protein (53 mgm%), glucose, chloride, dynamics.

**Stools:** Microscopy, culture, fat balance.

**X-rays of feet and legs:** Diffuse osteoporosis, maximal distally.
X-rays of hands: Diffuse osteoporosis distally. Ankylosis of interphalangeal joints of right thumb and left little finger.

Barium Enema: N A D.

E.M.Gs: 1963. A number of muscles were sampled at all 4 extremities. Fibrillation at rest was encountered in each case, with reduced interference patterns, and an increased proportion of large polyphasic units. These abnormalities were most marked in the right tibialis anterior.

1970. No electrical activity of any kind could be demonstrated on stimulation of the ulnar nerve in the right forearm, the median nerve at the right second finger, the lateral popliteal nerve at the neck of the right fibula, or the anterior tibial nerve at the right ankle.

Nerve Biopsy: 1962. (Professor Blackwood).

Normal appearances were found in an interdigital nerve from the right foot.
Date of Birth - June 1947. Housewife.
Married, with one child.

History

When 16, this girl developed an ulcer on the ball of the left foot. Because of this, and the presence of hammer toes, she was referred to an orthopaedic surgeon. He found sensory impairment of the feet, and concluded that the ulcer was of neuropathic origin. It healed with bed rest. Over the next four years there was repeated blistering and infection of the toes, commonly accompanied, or preceded by, fever.

When 19, and two months pregnant, she fell off a horse and injured her back. X-ray showed no bony injury. Two months later, pain and tenderness developed in the calves on walking, and a month after this, an ulcer appeared on the ball of the right foot (Plate 5ª). When six months pregnant she was found to have bilateral foot drop, with loss of knee and ankle jerks. Pain and temperature sensation were lost as far up as the knees, and light touch half way up both calves.

Delivery of a living, healthy male child was by forceps extraction for delay in the second stage, on 28th July, 1967.

After the puerperium the rate of deterioration slackened, and she thought that her walking improved. The plantar ulcer persisted until it was curetted in 1969. Thereafter she was fitted with "seamless" shoes and remained free from skin lesions for two years.
Ulcer of right sole in 1966.
Investigations

Blood count and E.S.R. were normal between episodes of secondary infection. No L.E. cells were found.

Blood urea, serum electrolytes, serum proteins, glucose tolerance, serum B12, serum folic acid, the phosphatases, L.D.H., S.G.O.T. and liver function tests, were all within normal limits.

Serological tests for syphilis were negative.


X-rays of chest and skull showed no abnormality. The cervical spine was normal except for rudimentary cervical ribs. The lumbar spine was also normal, without evidence of spina bifida occulta.

X-rays of the feet showed some haziness and irregularity of the 4th metatarsal head.

Examination by writer in March 1970

She was a pleasant, attractive and intelligent young woman of 23. General physical examination revealed no abnormalities. B.P. 110/70.

Neurological examination: The cranial nerves were intact. In the upper limbs there was some wasting of interossei and palmar eminences, and slight weakness of abduction and adduction of fingers. Tone, coordination and reflexes were normal. Thermal discrimination was impaired to the left wrist and over the right fingers, but pain sensation was lost only over the left index finger distally. The other modalities were unaffected. In the lower limbs there was bilateral foot drop, hammer toe deformity affecting all 10 toes, webbing of the 3rd and 4th toes on both sides, and a scar on the ball of the left foot.
There was marked muscle wasting of both legs below the knees, with hypotonia and weakness. The knee and ankle jerks and plantar responses were abolished. Power at knees and hips appeared normal but all movements, particularly dorsiflexion, were impaired at the ankles and toes.

There was no palpable enlargement of accessible nerve trunks.

Sensory testing revealed loss of pain and temperature sensation to mid-thigh level. The upper margin of sensory impairment was higher anteriorly and medially, than laterally and posteriorly. Light touch was lost over the feet and ankles, with a fading upper border over the lower third of both shins. Deep pressure sense and two-point discrimination were lost over the feet, but vibration sense and position sense were intact.

**Subsequent Progress**

She spent most of the winter in an orthopaedic hospital where she underwent tendon transplants to improve her gait. She was fitted with below-knee calipers.

E.M.G. studies at this time showed a greatly reduced interference pattern, diminished motor recruitment on voluntary contraction and very occasional enlarged motor unit action potentials.

Throughout 1971 and 1972 she again became subject to recurrent, indolent sores and blisters of the toes and feet. Their eruption was often preceded by fever.
Re-examination by writer in May 1973

Although the overall deterioration was slight, her gait was
by now more obviously flaccid, and the foot deformity had increased.

Both feet were narrow, atrophic, plantar flexed, abducted
and everted. There was clawing of all toes, which were calloused and
scarred, with a scattering of small septic areas.

All movements at the ankle were weak, particularly dorsiflexion, abduction and inversion, and there was some weakness of
extension at the knees.

There appeared to have been little or no increase in wasting
of the legs, and none at all of the thighs, but fasciculation was
present in the calf muscles. Hip movements were strong. The ankle
jerks were abolished, but weak knee jerks could now be elicited on
both sides. Plantar responses remained absent.

There had been no significant increase in the territory of
superficial sensory loss, but vibration sense and position sense were
now lost at the toes.

The neurological status of the upper limbs appeared
unchanged.

There were no cranial nerve abnormalities, ataxia nor
Rombergism, and superficial nerve trunks remained impalpable.
CHAPTER 21

"Z" Family: Results of Survey: Genetics:

Much of the data reported below about I 3, the apparently affected grandmother of the index cases, was already known before this study was undertaken, but it is included at this point because of the uncertainty of the diagnosis, and because additional information about her was obtained from relatives during the course of this survey.

Symptoms and signs suggesting mild neuropathy were elicited in 4 subjects, and a 5th wrote in answer to enquiry, describing some possibly relevant symptoms and signs. Letters to this patient's doctor have unfortunately remained unanswered.

Two other members of the family suffered from different neurological disorders. Five had bilateral soft tissue syndactyly affecting the 2nd and 3rd toes. Severe hypertensive disease affected some older members of the kindred.

I 3. Mrs. Elizabeth T.

Born 1875. Died 1952.

Certified cause of death - "Myocardial degeneration, arteriosclerosis, bronchitis".

This lady was reported as having suffered from ulceration of
both feet and difficulty in walking since middle life. The ulcers were located on the soles of the feet and not on the ankles or the lower part of the legs. Bone was exposed at times in the floor of these ulcers. Toes "rotted" and one was amputated in 1934 (no records could be obtained). The feet became mutilated, so that she became "too disgusted to look at them". Relatives did not notice any wasting or weakness of arms or legs.

Her family doctor responded to an enquiry in August 1968 with the following report:

"She had chronic ulceration of the soles of both feet with hyperkeratosis. These were surrounded by sodden epithelium which would reach a thickness of half an inch or more in a few weeks. This overlapped the ulcer by several inches. The actual ulcers were shallow and not punched out. They were treated by paring away, and by various dressings. She was otherwise normal to examination. There was no glycosuria. Her knee jerks were present, and the plantar responses flexor. The pupils were normal. There were no signs of syphilis. We supposed some trophic disturbance like syringomyelia, but she could feel heat with the feet".

No details were known about the London family from which she derived.
11 8. Robert T


Retired carpenter.

This 70 year old father of 111, 16 denied any disability.

On examination there was wasting of the right calf, its girth being about 1.5 cm less than the left calf, at a point 6 cm above the internal malleoli. Both feet were flat. There was no weakness. The knee and ankle jerks were present, equal and fairly brisk. No plantar responses could be elicited. Pain and temperature sensation were impaired from midcalf level downwards on both sides, and over the dorsum of all 10 fingers.

E.M.G. examination in November 1970 showed slowing of motor nerve conduction velocity in the right lateral popliteal nerve to 37 metres per second. The compound action potential at the right knee could not be obtained, but a digital action potential was evoked from the right median nerve which was of normal amplitude and latency.

On enquiry in May 1973, he stated that he was suffering from "shingles on the chest". There were no symptoms referable to the limbs.

11 12. Winifred B.


Housewife.

This 64 year old mother of 111, 22, denied symptoms affecting the limbs, and neurological examination was entirely normal.

E.M.G. examination later in the same year showed normal conduction velocity in the right lateral popliteal nerve (42 metres per second). A small compound action potential was obtained from this nerve
at the neck of the fibula (amplitude 3.0 microvolts). A digital action potential was evoked from the right median nerve after stimulation at the 2nd finger, (amplitude 9 millivolts, latency 0.3 metres per second).

Her condition was unchanged when she was seen again in May 1973.

111 8.


This pleasant, unintelligent labourer son of an unaffected father appeared unable to differentiate between sharp and blunt, and hot and cold stimuli applied to both feet and ankles, and both hands. There were no other abnormalities.

111 18.

Born 1945.

This 25 year old youngest brother of 111 16 who was a clerk, complained of extremely tender feet which he disliked having touched. Pain and thermal perception were impaired over both surfaces of both feet, and dorsiflexion at both ankles appeared weaker than normal.

Enquiry in 1973 indicated that he remained well.
111 20. Jacqueline C.

Born 1935.

This 35 year old woman wrote stating that she required treatment from time to time for excess callus formation of the soles of both feet. Her chiropodist told her that her feet were deformed. She complained of painful legs in the week before her menses. As a child she had suffered from an indolent ulcer of one foot.

Her doctor did not reply to letters of enquiry about her.

IV 18. Tony R.


This 16 year old engineering apprentice was a nephew of the index cases. His mother had died in 1954 from malignant melanoma at the age of 26. He volunteered the information that the backs of his feet always felt numb, and the soles extremely tender. The latter prevented him from walking barefoot on fine sand, a fact which his father and stepmother confirmed. On examination there were no motor or reflex abnormalities, but pain and temperature sensation appeared impaired on the dorsal aspects of both feet, although the soles appeared normal.
Other morbidity in the "Z" Family

Hypertension.

II 5, II 7 and II 10 had died from cerebral vascular accident complicating hypertension.

II 6 and II 15, both attend outpatient clinics for visual failure complicating hypertensive retinopathy.

II 3 and II 12 are treated for high blood pressure by their general practitioners.

Syndactyly.

One of the propositi, III 22, has webbed 2nd and 3rd toes on both sides. This involves soft tissue only, the phalanges remaining distinct.

A similar anomaly was seen in an uncle, II 15, a first cousin II 8, and two first-cousins once removed (IV 19, IV 20).

Genetics of the "Z" Family

The certain occurrence of this unusual trait in two members of a kindred, is likely to represent the effects of genetic determination, rather than random association of phenocopies. So far as the mothers of the propositi could recollect, they had not contracted rubella nor other infections during pregnancy, nor had they ingested any unusual drugs. They were unrelated, lived in different homes, saw little of each other, and there was an interval of 15 years between
the two pregnancies. Apparently identical syndromes are known to occur in circumstances which place their heredo-familial origin beyond dispute.

So far as the mode of inheritance is concerned, X-linked recessive inheritance is excluded by the equal severity of the disorder in members of opposite sexes (allowing for differences in age and the duration of the disease), and by the occurrence of father (11 8) to son(111 16) transmission in one instance. This also excludes X-linked dominant inheritance.

Autosomal recessive determination does not usually manifest itself in more than one sibship of a generation, unless the gene is common, as for example, mucoviscidosis, or unless multiple consanguineous marriages have taken place ancestrally (Zellweger et al (1972)).

The first of these possibilities can be discounted, because even if the trait present in 111 16 and 111 22 is no more unusual than recessively determined C.M.T.D. with chance association of severe sensory loss, this is itself rare. It is much less common that the dominantly transmitted mutation (Bell (1935)), and in a prospective study of distal amyotrophy was encountered in only four instances, compared with 67 of the dominant form (Beyck & Lambert (1968)).

So far as consanguinity is concerned, the father (11 8) of 111 16, and the mother (11 12) of 111 22 were, of course, brother and sister, but no blood relationship existed between them and their respective spouses, nor were the latter related to each other, even distantly. Intermarriage earlier in the kindred is precluded by the origin of 1 3 from a London family, whereas her husband came from West Country stock. There appears to have been no other contact between
the families.

Polygenic inheritance seems unlikely from analogy with similar traits such as C.M.T.D., H.S.R.N., F.A., Hypertrophic Neuropathy and Familial Amyloid Neuropathy, in all of which simple genetic mechanisms are involved. The same considerations exclude a chromosomal abnormality which is in any case, ruled out by the discovery of a normal karyotype in 111 16.

The remaining possibility, dominant transmission with reduced penetrance, appears to be the most probable explanation, even if the status of 1 3 as an affected subject is ignored.

Polygenic modification of penetrance as proposed for epilolia in a classical account (Gunther & Penrose (1935)), causes relatively minor variations in expression of phenotypes within individual families, and is unlikely to account for the sharp discontinuity seen in the "Z" family, whereby the trait is totally, or almost totally suppressed in some individuals, and present in flagrant form in others.

The simplest proposition to explain this state of affairs is a multiple allelic system similar to that which may occur in some forms of spinal muscular atrophy (Becker (1966), Emery (1971), Zellweger et al (1972)).

Adapted to the "Z" family, this theory implies that besides the main "normal" gene (A), and the mutant gene (M), there must arise from the same locus a third gene (B). The effects of A are dominant to M, but those of M are dominant to B. M becomes "activated" in the presence of B.

Individuals with the constitution BM, manifest the trait as in 111 16 and 111 22, whereas those with the constitution AM do not, and this genotype is proposed for 11 8 and 11 12. The genotypes
A B and B B are also assumed to be phenotypically normal, or almost so.

11 16 and 11 22 must have inherited M from 11 8 and 11 12, and B from their other parents.

11 8 and 11 derived M from their mother 1 3, and A from their father.

If 1 3 presented the same disorder as 111 16 and 111 22, she must also have the configuration B M, in which case she inherited B from one parent, and M from the other.

B must be much commoner than M therefore, because it entered the pedigree through at least 3 unrelated individuals, whereas M entered it only through 1 3.

Indeed, A and B probably exist as a polymorphism, either transient or balanced (Ford (1964)), which will have arisen either through natural selection, or through random genetic drift, probably the former (Harris (1971)).

Sporadic dominant inheritance of this type may account for the occurrence of a similar syndrome, combining muscle weakness and wasting and acrodistrophic neuropathy, both in familial form, (Bruns (1903)), or as sporadic cases, particularly in adults (Alajouanine et al (1962\(^\text{1}\), 1962\(^\text{2}\)), Spillane & Wells (1969)).

Modern genetic theory indicates that many more than three alleles may be generated at some loci, so that the foregoing explanation is almost certainly an over-simplification, (Harris (1968, 1969, 1970)).
Genetic Counselling.

If the trait is recessively determined, the risk to children must be negligible, as the gene is obviously very rare.

If, as seems likely, sporadic dominant inheritance of the type suggested is involved, the risk cannot be calculated in the absence of any knowledge of the relative frequency of the allelomorphs A and B. The prognosis is best if A is much commoner than B, because it increases the likelihood of the spouses of 111 16 and 111 22 possessing the genotype A A, in which case none of their children will develop the trait. If, however, the constitution of either or both of them is B B, the risk is the same as the 1 : 1 expectation of Mendelian dominant inheritance with high penetrance. The genotype A B, in an unaffected parent confers a risk of 1 : 4 to any progeny.
CHAPTER 22

Other forms of H.F.A.N.

Earlier sections have dealt with H.S.R.N., acrodystrophic forms of C.M.T.D., and with a group of recessively determined congenital and familial sensory neuropathies of childhood.

Plantar ulceration and other lesions of the extremities of neuropathic origin may also occur in Hereditary Amyloid Neuropathy; in association with a syndrome resembling familial spastic paraplegia in certain rare stocks; and as an occasional event in other genetically determined neuropathies.

These traits are the subject of the present chapter.

Tangier Neuropathy is described in more detail than its importance warrants, because the writer had the opportunity of examining the only reported British example of this disease in 1973.

1. Hereditary Amyloid Neuropathy

There are four principal types of Hereditary Amyloid Neuropathy, all sensorimotor in character, all dominantly inherited, and
all first causing symptoms in adult life.

Their main features are summarized below. Only the first type can be regarded as acrodystrophic insofar as sometimes it causes plantar ulceration and mutilation of the feet and it is the only one which will be described in greater detail later.

**Type 1:** The Portugese or Andrade type, which predominantly affects the lower limbs. It begins in early middle life and pursues a rapid downhill course.

**Type 2:** This is the upper limb type, often presenting with the carpal tunnel syndrome and following a more benign course, so that affected individuals have been known to survive for 40 years or more, although considerable terminal invalidism may occur. There are two main stocks, one from Indiana (Rukavina et al (1956), Jackson et al (1960)), and one from Maryland (Mahloudji et al (1969)). The legs may be entirely spared, particularly in women. Blisters, burns, small ulcers and superficial infections of the hands may occur, but chronic trophic lesions have been described in only one instance (Schlesinger et al (1962)).

**Type 3:** This form combines neuropathy with a high incidence of renal failure and duodenal ulceration, and has affected a single kindred originating in Iowa (Van Allen et al (1969)). Mean duration from onset of symptoms to death is 12 years. Acrodystrophic change has not been described, presumably because there appears to be much greater motor than sensory involvement.

**Type 4:** This variety combines a predominantly cranial neuropathy with lattice dystrophy of the cornea and has been described in three Finnish families (Meretoja (1969)). A spinal neuropathy occurs late in life and is apparently never severe enough to predispose
to trophic lesions.

**Type 1 Hereditary Amyloid Neuropathy** in its Portugese form was originally described in a classical account by Andrade in 1952.

In the fishing port of Povoa de Varzim and the surrounding district of Oporto in Northern Portugal, there had been known to exist, over many generations, a disorder of the feet known locally as "mal dos pesinhos" (disease of the feet). Andrade studied 74 cases, both familial and sporadic in origin, recognised their neuropathic basis, and identified amyloid infiltration of nerve roots and peripheral nerve as the cause of the neuropathy. Detailed observations "enabled us to get an idea of the incidence of the disease, and to realise the monotonous and constant nature of the clinical picture, the large number of cases in certain families and the inexorable course of the disease".

The trait superficially resembles H.S.R.N., but the responsible mutant gene is clearly both more pleiotrophic and lethal.

Onset in Andrade’s cases was in the 3rd and 4th decades usually, and the subsequent course was characterised by progressive loss of weight and strength, gastro-intestinal disturbances (abdominal distension followed by severe diarrhoea), genito-urinary disturbances (retention of urine and impotence), sphincteric disturbances, and the development of a severe sensorimotor peripheral neuropathy.

The latter presented with numbness or with severe paraesthesiae (tingling, pricking and burning sensations), and shooting pains. In some cases, touching the feet or legs caused acute discomfort and a gentle stimulus such as stroking the soles could cause pain, sometimes severe, not necessarily limited to the part stimulated.

Objectively, sensory loss began distally and spread proximally.
Temperature, pain, touch and deep sensibility were affected in that order, so that finally the limb came to demonstrate three zones of sensory loss - proximal and patchy, intermediate and dissociated, and distal and global.

Trophic lesions included hyperkeratosis, thickened, ridged nails and, in some cases, perforating ulcers. These could be either painful or painless, but usually healed readily with bed rest. Mutilation leading to mis-diagnosis as leprosy sometimes occurred.

Weakness and wasting followed sensory paralysis, and foot drop was a common sequel. "In Povoa de Varzim it is not unusual to see fishermen, once robust and full of vitality and now thin, weary and resigned looking, walking slowly and bending their knees excessively to compensate for their foot drop". The stretch reflexes were progressively lost, sweating was impaired in anaesthetic areas, and ocular signs (which are discussed later) also occurred. The peripheral nerves were not palpably enlarged. As in all forms of Hereditary Amyloid Neuropathy, the cerebro-spinal fluid protein was substantially increased. The Congo red test was positive in some instances.

The disease followed a rapid course with death supervening within 7 - 12 years.

Autopsy examination revealed diffuse deposition of amyloid in many organs. Nerves and kidneys were chiefly involved, then the pancreas, while lesser degrees of infiltration affected stomach, skin, heart, aorta, lungs and spleen.

In contrast to secondary amyloidosis (Briggs (1961)), the liver was remarkably spared.

Microscopically severe Wallerian degeneration of nerves
appeared to be maximal in relation to deposits of amyloid material. Lesser changes in the posterior columns and anterior horn cells probably reflected retrograde degeneration.

This trait is not restricted to Portugal, having been carried by emigration to both Northern and Southern America, other parts of the Mediterranean littoral and elsewhere (Andrade et al. (1969)).

Furthermore, there are now many reports of a closely similar, if not necessarily genetically identical trait, occurring in other ethnic groups, without any trace of Portuguese ancestry.

These predominantly lower limb types of Hereditary Amyloid Neuropathy, with similar clinical features, have been described in an American family (Shulman & Bartter (1956), Kaufman (1958), Kaufman & Thomas (1959)), in a Japanese kindred (Araki et al. (1968)), and in German (Delank (1965)) and British families (De Bruyn & Stern (1929), Zalin et al. (1974)).

Some of these kindreds have exhibited additional autonomic features such as postural hypotension (Shulman & Bartter (1956), Araki et al. (1968)).

It is inconceivable that this disease should have escaped notice prior to Andrade’s account, particularly as it must be one of the most common forms of H.F.A.N. Thus 732 affected subjects from 165 families were identified in less than 20 years (Canijo & Costa (1968)). Andrade himself drew attention to 2 cases reported from Brazil in 1939, who presented identical clinical features but were undiagnosed. They had emigrated from Northern Portugal. A British family was reported in 1929 under the apparent misnomer of progressive hypertrophic neuropathy (De Bruyn & Stern (1929)), while other cases were misdiagnosed as sprue, Beri Beri and leprosy (Andrade (1952)).
It is almost certain also that Hereditary Amyloid Neuropathy shares with H.S.R.N. and the other forms of H.F.A.N., a common heritage of being reported under the old title of familial lumbo-sacral syringomyelia. It may be suspected in such recorded stocks if these combine trophic lesions with severe subjective sensory disturbances, including shooting pains, and with muscle wasting and weakness, pupillary abnormalities and, above all, by prominent visceral symptoms of the kind already described, particularly if the life span is also reduced.

There are a number of families which conform to this pattern (Barraquer & De Gispert (1936), Alajouanine & Mozziconacci (1940), Feudell (1959)), while in an Argentinian kindred described under the title "la forme paréto-amyotrophique de l'acropathie ulcéro mutilante familiale", impotence and diarrhoea preceded the onset of acrodystrophic neuropathy in most instances (Hermida et al (1964)).

Retrospective diagnosis of Hereditary Amyloid Neuropathy must remain purely speculative in such instances. Even in contemporary cases the diagnosis is difficult, depending as it does on the discovery of amyloid deposition in biopsy material obtained, for example, from the rectum (Gafni & Sohar (1960)), and the kidney (Van Allen et al (1969)), using the latest staining and magnification techniques (Hobbs (1973)). Nerve biopsy alone is certainly inadequate.

There is evidence for supposing that plantar ulceration occurs less regularly in Hereditary Amyloid Neuropathy than it does in H.S.R.N. This is probably because of the greater restriction of activity imposed by flaccid paresis and the much shorter course of the disorder. Trophic ulceration occurred in every single member of only one family (Araki et al (1968)).
The neurogenic osteoarthropathy of foot bones, which is such a commonplace in H.S.R.N., appears to occur only very occasionally in Hereditary Amyloid Neuropathy, and is seldom severe. Diffuse osteoporosis of the extremities is the more usual finding.

Amyloid deposition in tissues other than peripheral nerve may never be obtrusive enough to help in the clinical diagnosis. When it occurs it may follow different patterns and be manifested for example as exophthalmos (Kanterjian & De Jong (1953)), vocal hoarseness (Araki et al (1968)), macroglossia and hepatosplenomegaly (Shulman & Bartter (1956)) and prominent cardiac involvement (Zalin et al (1974)). The two British stocks were also characterised by palpable enlargement of accessible nerve trunks, which is on the whole unusual in Hereditary Amyloid Neuropathy, by a significantly later age of onset and by the absence of sensory dissociation (De Bruyn & Stern (1929), Zalin et al (1974)).

When present, the vitreous opacity is pathognomonic (Pratt (1967)). It has been shown to be composed of amyloid tissue (Kaufman (1958)), and it may rarely cause total blindness (Shulman & Bartter (1956)).

Despite the clinical variations between families, the trait appears to carry a prognosis which is more or less equally severe. Thus death occurred within 3 years of onset (De Bruyn & Stern (1929)), 5 years (Shulman & Bartter (1956)), 6 years (Kanterjian & De Jong (1953)), 8 years (Zalin et al (1974)) and 7 - 12 years (Andrade (1952), (Araki et al (1968)).

Death is due more often to inanition and exhaustion consequent upon severe involvement of the nervous system, both somatic and autonomic, than to cardiac or renal failure which are the usual
causes of death in "secondary" amyloidosis (Briggs (1961)).

A symmetrical sensorimotor neuropathy of the type seen in Type 1 Hereditary Amyloid Neuropathy cannot readily be ascribed to occlusion or compression of vasa nervorum by amyloid as has been suggested (Strich & Wade (1953), Pruitt et al (1953)), nor to compression (De Nevasquez & Treble (1938)), or kinking of nerve fibres (Andrade (1952), Chambers et al (1953)), although all these phenomena doubtless occur. Such changes would cause discrete mononeuropathies (Simpson (1963)).

The intervention of some additional toxic or metabolic factor is necessary, and has been suggested by the application of modern techniques, to biopsied sural nerve from a patient with this form of amyloid neuropathy (Dyck & Lambert (1969)).

These have revealed gross selective degeneration of unmyelinated and to a lesser extent fine myelinated fibres, with a corresponding loss of C fibre action potentials and diminution of A delta potentials. The best explanation for such findings is selective degeneration of the population of smaller neurones, with secondary segmental demyelination. There is also evidence in the form of abnormally short and thinly myelinated internodes which suggests attempts at regeneration. Nerve conduction velocities are consistent with axonal decay rather than segmental demyelination (Araki et al (1968)).

These observations also correlate well with the predominant sensory deficits, which are to pain and temperature, producing dissociated sensory loss as in H.S.R.N., and predisposing affected subjects to similar plantar ulceration. Significantly, sensory loss is not dissociated in the other forms of Hereditary Amyloid Neuropathy in which trophic lesions are of most unusual occurrence.
Genetically it would seem that penetrance of the gene producing Type 1 Hereditary Amyloid Neuropathy is reduced, particularly in women. This reduction is of the order of one third. The mean age of onset in women at 44 years is also delayed relative to men in which it is 33 years (Becker et al. (1964)).

It has been argued, however, that suppression of the phenotype is never complete because all gene-carrying women eventually manifest its effects to some extent later in life (Andrade et al. (1960)). "Skipping" probably does occur, however, and may be responsible for the appearance of genetically determined cases as sporadic forms (Gafni et al. (1964)).

2. Familial Spastic Paraplegia (F.S.P.) with Acerodystrrophic Neuropathy.

Like peroneal muscular atrophy, Familial Spastic Paraplegia "is inappropriately described by its motor syndrome alone" (Wilson & Bruce (1954)). Degeneration of posterior columns and of dorsal root ganglia may in fact be as severe as that seen in the corticospinal tracts (Greenfield (1958)).

It has been suggested that the sensory findings in Friedreich's Ataxia (Saunders (1913)) can be extrapolated to F.S.P. because of the phenotype inter-relationships which exist between the two diseases (Bell & Carmichael (1959)).

If this was the case, however, severe involvement of the large sensory neurones and their fibres as seen in F.A. would interrupt afferent arcs and abolish the increased tendon jerks and muscle tone which are the clinical criteria upon which the diagnosis of F.S.P. is based.
Proprioceptive sensory loss has been demonstrated (Roe (1963), Silva (1966), Dyck & Lambert (1968)), but it has usually been slight, and occasionally overshadowed by superficial sensory loss (Mahloudji (1963)), although more often this also is negligible.

Occasionally, however, distal sensory loss to pain, temperature and touch may be severe, and lead to trophic lesions similar to those seen in E.S.R.N. Usually this has occurred in stocks in which the motor disability has been slight, or very slow and insidious in development. Severe disability and early invalidism are likely to protect against ulceration and mutilation, because they eliminate the trauma to the feet inherent in the activities of walking and standing.

Several families of this type have been described since an original account (Clarke & Groves (1969)). This described two siblings, living in Bristol, who suffered from a severe and longstanding disorder characterised by increased tone and reflexes in the legs, clonus at knees and ankles, extensor plantar responses, distal sensory loss, plantar ulcers and disintegration and dissolution of the bones of the feet with loss of toes and extrusion of sequestra.

Their parents were unaffected, and so also were those of two American sisters who presented a similar syndrome (Van Epps & Kerr (1940)), and those of an isolated case (Spillane & Wells (1969)).

Unaffected parentage does no more than raise the possibility of recessive inheritance, a mode of transmission which appears to be virtually certain in another kindred, of whom 9, all members of a single degeneration but distributed in more than one sibship, combined distal sensory loss with a spastic syndrome in the legs. 3 of these developed plantar ulcers. All affected subjects were the issue of first cousin marriages. They belonged to a Swiss isolate descended
from a common ancestor 5 generations back, with much intervening inter-
marrage (Jequié et al (1945, 1947)).

In another family, two brothers presented A.N., but cortico-
spinal tract involvement was evident in only one, who also presented
distal amyotrophy (Spillane & Wells (1969)). This combination of A.N.,
spasticity and muscle wasting also occurred in 3 sisters who were mem-
ers of an Italian genetic isolate (Enderlé (1933)), and 2 brothers who
in addition demonstrated a curious facies, mental defect, ichthyosis,
splenomegaly and an unidentified amino-acid complex in their urine
(Bruck et al (1964)).

Familial spastic paraplegia may also be dominantly inherited
(Pratt (1967)) and there are several pedigrees in which this trait,
combined with A.N., has undoubtedly been transmitted by the dominant
mode (Van Epps & Kerr (1940), Khalifeh & Zellwegger (1963), Friedman
et al (1968), Koenig & Sprio (1968)). In another stock, exaggerated
reflexes and extensor planter responses occurred in only a minority of
members who had been affected by A.N. since childhood (Lary et al
(1963)), while in another dominant pedigree A.N. accompanied a motor
syndrome compounded of spastic paraparesis and distal amyotrophy
(Hermida et al (1964)).

The association of familial spastic paraplegia with distal
muscle wasting is itself unusual, although well documented (Bell &
Carmichael (1939), Refsum & Skillcorn (1954), Roe (1963), Gilman &
Horenstein (1964), Silva (1966), Dyck & Lambert (1968)).

Clearly A.N. may occur in association with F.S.P., both with
and without distal amyotrophy, and there is obviously a great deal of
genetic heterogeneity within this group as a whole.

Conversely, extensor planter responses may occur occasionally
in stocks of undoubted C.M.T.D. (Bell (1935), Hierons (1956)).
Rarely this combination may also co-exist with A.N. (Plancherel (1964)).

3. Miscellaneous rare neuromathias occasionally liable to sarodystrophic change.

(a) The Roussy-Levy Syndrome.

A recent report (Oehlschlager et al (1971)) has gone far towards re-emphasising the independent status of this trait, about which there has been so much controversy (Pratt (1967)).

This report distinguishes the trait from F.A. because of its dominant inheritance, the absence of cerebellar signs, slow progression and the rarity of extensor planter responses; and from C.M.T.D. by the more widespread reflex loss, later onset of muscular wasting, (although weakness occurs early), and the absence of vasomotor disturbances.

Its chief characteristic, however, is the presence of a tremor. This is an integral component of the syndrome which is not independently inherited (Yudell et al (1965)).

Trophic lesions would not be anticipated in the Roussy-Levy Syndrome because sensory loss when it occurs, is slight and mainly restricted to proprioceptive sensation (Yudell et al (1965), Oehlschlager et al (1971)).

However, a unique report exists in which A.N. has been demonstrated in association with this disorder (Spillane & Wells (1969)). This was a man who combined a tremor of the head and upper
limbs with halting, tremulous speech, mild ataxia of all four limbs and Rombergism, bilateral nerve deafness, dissociated sensory loss in the legs and plantar ulceration. Only the ankle jerks were lost and there was no muscle atrophy.

The nosological difficulties are emphasised by the fact that although a nephew was similarly affected, he did not display any tremor, and resembled a case of C.M.T.D.

It would seem reasonable to suppose that stocks in which the C.M.T.D. and Roussy-Levy Syndrome phenotypes co-exist, are genetically distinct from those which generate either phenotype in isolation.

(b) The Hypertrophic Neuropathy (H.N.) of Déjerine & Sottas

Perforating ulcers have been described in association with H.N. on several occasions (Cornil et al. 1930), Leandikowski (1931), Thiébaut et al (1947), Bérgouignan & Seilhan (1957), Ritz (1961).

Classically H.N. begins in childhood and disability progresses inexorably so that affected subjects may be confined to a wheelchair by early adult life (Dyck & Lambert 1963).

Incapacity to this extent naturally protects against the development of serodystrophic complications other than decubitus ulcers and callosities associated with foot deformities. In other cases onset is delayed, however, even into the 6th decade (Austin 1956), and the more insidious course thus followed exposes the affected subject to the stresses and strains of walking, in the presence of a sensory deficit, and it is among this group that the foregoing cases tend to appear.
It has been suggested that such cases of H.N. with plantar ulceration may in reality have been sporadic examples of familial amyloid neuropathy (Shulman & Bartter (1956)). It is certainly true that both traits may present similar degrees of sensorimotor neuropathy with areflexia, pupillary changes, shooting pains, palpable nerve trunks and elevation of the C.S.F. protein, but in addition H.N. usually demonstrates changes such as ataxia, nystagmus, intention tremor, various foot deformities and kyphoscoliosis, which make its confusion with Friedreich's Ataxia more likely (Austin (1956), England & Denny Brown (1952), Dyck & Lambert (1963)), while conspicuous autonomic disturbances such as those seen in Hereditary Amyloid Neuropathy are most unusual (Austin (1956), Gathier & Bruyn (1970)).

Biopsy may, however, be the only sure means of differentiating the two disorders. Findings in nerve of which the "onion bulb" is characteristic but not specific, are distinctive in H.N. (Dyck (1966), Thomas & Lescelles (1967), Dyck et al (1971)), while biopsy of other tissues such as rectum and kidney, and appropriate staining techniques are necessary, as shown already, if amyloidosis is to be incriminated.

(c) Neuropathies resembling Rasmus's Syndrome.

Plantar ulceration and trophic changes in the bones of the feet, beginning at the age of 12, have been described in a woman who later developed retinitis pigmentosa, ataxia, vestibular disturbances (without deafness), and widespread reflex loss. Her neuropathy was predominantly sensory and ulceration and mutilation of the feet progressed to the appearances of "pied d'elephant classique" (Raverdy et al (1970)).
The resemblance of this woman's neuropathy to Heredopathia atactica polyneuritiformis (Refsum (1946)) led to estimation of her serum phytanic acid concentration. This was normal.

In another case believed to be an example of Refsum's Syndrome (Néhlin (1965), bone and joint changes in the feet were believed to be neurogenic in origin, and were accompanied by bilateral club foot, cubitus varus, ichthyosis, alopecia and deafness, but the neuropathy was almost exclusively motor and indeed there was neither sensory loss over the feet, nor external trophic lesions. Retinitis pigmentosa was not present. She was mildly diabetic. Serum phytanic acid levels were not estimated.

A scrutiny of the relatively circumscribed literature of Refsum's Syndrome indicates that, whatever may be true of such neuropathies as the foregoing which superficially resemble it, biochemically proven examples of the trait are not prone to acrodystrophic change. This is perhaps due to the "protective" effect of early incapacity from night blindness, cerebellar symptoms (Alexander (1966)), the severity of the motor component of the neuropathy and the shortened life expectancy from cardiac involvement (Gordon & Hudson (1959)).

Furthermore, only rarely does superficial sensory loss overshadow impairment of the other modalities (Fleming (1957)) and thus conform to the classic configuration which predisposes to trophic lesions.

Epiphysial dysplasia and shortening of digits and metatarsals may occur in Refsum's Syndrome (Reese & Bareta (1950), Rake & Saunders (1966), Campbell & Williams (1967), Fryer et al (1971)), but the radiological appearances are totally distinct from neurotrophic changes in bone as seen in H.S.R.N. and the allied disorders.
(d) Freidreichs Ataxia

Although ulceration of the feet and legs has been described in F.A. (Van Bogaert (1957)), the ulcers which occurred appear to have been decubitus ulcers, such as might occur with almost any paralytic disorder, as the result of enforced recumbency and inadequate nursing. Theoretically A.N. would not be expected as a complication of F.A. because in this disease, superficial sensation is but slightly affected (Saunders (1913)) and the rapid progression towards invalidism is likely to act protectively.

(e) Tangier Neuropathy

Tangier Disease (Frederickson et al (1961)), Frederickson (1966, 1972)), the basic defect of which is a gross reduction or absence or high density (alpha) lipoprotein, is sometimes complicated by neuropathy which may be of a mild, relapsing asymmetric type (Engel et al (1967)), or a more severe progressive form, as described in a 37 year old English patient from North Somerset (Kocen et al (1967)).

When this last case was first reported, pain and temperature sensation were lost over almost the entire body, except paradoxically, at the extremities, and there were many scars from healed burns on the arms and from other injuries around the mouth. There was also gross weakness and wasting of the muscles around the eyes and mouth, in the hands, and to a lesser extent below the knees.

Radiological evidence of acrodystrophic change was provided by the presence of cystic areas in the digits adjacent to some of the proximal interphalangeal joints, and absorption of the tip of the distal phalanx of the right ring finger.
The writer had the opportunity of re-examining this man at Frenchay Hospital in 1973, when there were some minor changes in his condition, including the presence of fasciculation in the wasted muscles around the eyes and the mouth. The hands presented a "main-en-griffe" deformity and were very weak. Acrondystrophic changes were present in the form of transverse ulcers in the dorsal skin creases overlying the flexed, proximal, interphalangeal joints of most of the fingers. There were no trophic lesions of the feet or legs, and indeed he appeared to be unduly sensitive to pain in these areas. Other modalities of sensation were intact. Ankle jerks which had been abolished in 1967 could be elicited, although they were sluggish. Possibly this was as the result of treatment with strict carbohydrate restriction and clofibrate.

These clinical features are thus entirely different from those of H.S.R.N., with trophic lesions of a minor character occurring only in the fingers, and complete sparing of the feet and legs.

There were also important extraneural differences in the form of yellowish deposits in the cornea and pharyngeal lymph follicles, and enlargement of the spleen.

Biochemically, besides the basic deficit, there is a combination of low plasma cholesterol and high triglycerides, which is virtually diagnostic (Kocen et al (1967)), while the histological characteristic is the "foam cell". These are cells of reticulo-endothelial origin packed with cholesterol esters, obtainable on marrow aspiration, and also found at nerve biopsy, where they accumulate around disintegrating myelin sheaths.
Sporadic Acrodystrophic Neuropathies

and their Differential Diagnosis

More than 100 unexplained, apparently non-familial examples of severe Acrodystrophic Neuropathy are recorded in the literature since an original account (Vézigné (1852)), many of them concentrated in two large series (Kienböck (1930), Spillane & Wells (1969)).

This total probably represents a minute fraction of their total incidence. Most sporadic cases lack sufficient interest to justify their being reported (Thevenard (1953)).

They tend to be less severe and to develop at a later age than familial cases (Van Bogaert (1953)).

The converse to this last observation is also probably true. The younger the patient and the more florid the acral lesions, the greater is the likelihood of genetic determination.

Such instances provide justification for the generalisation that H.S.R.N. is "a clinical entity which once seen is unlikely to be forgotten", (Pellis & Schmeewiss (1960)), and for occasionally making a firm diagnosis of H.S.R.N., even in the absence of any history of the trait in forebears and other relatives (Spillane & Wells (1969)).
A family history may not be obtained for a variety of reasons.

These include sporadic dominant inheritance as seen in the "Z" family, or recessive inheritance affecting only a single member of a sibship.

More prosaic explanations of failure to elicit a family history include inadequate enquiry, prolonged loss of contact between the patient and his relatives, as in the case of a Polish member of the French Foreign Legion in Indo China (Pages (1952)), and of a Greek convict in a French prison (Velluz et al (1955)), while in other families there may be outright hostility effectively preventing genetic investigation (Thévenard (1942), Cambier & Lefèvre (1960), Wallace (1970)).

Even if allowance is made for such failures, it seems likely that only a minority of sporadic cases of acrodystrophic neuropathy are genetically determined.

The majority appear to be due to some form or other of prolonged neuropathy, predominantly characterised by distal cutaneous sensory loss, and with sufficient preservation of motor power to circumvent the protective effects of inactivity.

The possible origins of such neuropathies are reviewed in this chapter. No attempt is made to review the neuropathies in general. Discussion is restricted to those neuropathies which can be demonstrated with various degrees of certainty, as capable of generating more or less exact phenocopies of the inherited traits.

In a given case of sporadic acrodystrophic neuropathy, however, after all these possible causes have been considered, it is likely that there will be a hard core of cases which remain unexplained.
This is not surprising because about 50% of all neuropathies are of unknown origin (Spillane (1959), Simpson (1971)) and this proportion may well be higher in children (Tasker & Chutorian (1969)).

There can be no reason for presupposing a higher level of diagnostic success in those forms of neuropathy which are complicated by acrodermatrophic change.

The first possible cause is considered briefly, if only to be dismissed immediately.

This is Peripheral Vascular Disease which must be the commonest cause of ulceration and necrosis of the toes and feet in temperate zones. These changes are not infrequently accompanied by sensory, motor and reflex change, as the blood supply to peripheral nerves and muscles is also compromised (Simpson (1962), Hutchinson (1970)). Nerves are relatively invulnerable to ischaemia, however, owing to the excellence of their normal blood supply (Asbury (1970)), and neurological abnormalities are rarely marked and often absent. If present, they are overshadowed by persistent ischaemic pain and by vascular changes in the form of lost pulses and coldness and discoloration of the skin. There may be a previous history of intermittent claudication or injury to a large artery, or the heart may be fibrillating.

While it has been shown elsewhere that H.S.R.N. has quite often been mistaken for gangrene, the converse mis-diagnosis is extremely unlikely.

Leprosy in its tuberculoid or neural form is the commonest worldwide cause of neuropathy (Simpson (1962)), and it is reasonable to infer that it is easily the most frequent cause of neuropathic ulceration and mutilation of the feet and hands.

The mycobacterium leprae particularly attacks cooler tissues
such as the skin, nose, pharynx, larynx and the anterior parts of the eyes. It has a predilection for nerves, to which it gains access through their cutaneous branches in the skin. Hence neural leprosy is asymmetrical, at least in its earlier stages (Granger (1966)), and nerves are often attacked in a particular sequence (Browne (1972)). The more superficial distribution of the receptors for pain and temperature leads to these sensory modalities being impaired first. Sensory loss is characteristically dissociated (Dastur (1955), with relative preservation of touch, presumably because of its triple representation in fibres of large, medium and small diameter (Dash (1968)). Touch is affected later, together with deep pressure, but joint position sense, vibration sense and the deep reflexes are rarely affected (Dale et al (1968)).

This configuration closely resembles that seen in H.F.A.N, and predisposes in these, and in leprosy, to destruction and mutilation of skin and bone at the extremities.

Leprosy is, in fact, the archetype of all acrodytrophic neuropathies. Indeed, in an attempt to convey an impression of the severity of trophic lesions in H.S.R.N., these have been described as being "quite as terribly as leprosy" (Wallace (1970)), while another patient was described as looking like a leper (Feudall (1959)).

Besides resembling each other in causing deep perforating ulcers of the soles, neural leprosy and the H.F.A.Ns also have similar effects on the bony framework of the extremities.

In leprosy, destructive changes tend to be most pronounced in the balls of the feet and the tips of the fingers, presumably because these areas are subjected to the greatest degrees of trauma (Faget & Mayoral (1944), Cooney & Crosby (1944)).
The hands may be much more severely affected than in H.S.R.N., but not necessarily more severely than in some of the recessively determined acrodistrophic neuropathies (Chapter 16).

Terminal phalanges develop fissures in the cortex of their distal ends which widen, producing a frayed appearance on x-ray. Later the tips disappear, so that affected phalanges have a "sliced-off" appearance. Dissolution progresses centripetally until only the base of these bones may persist as "collar-button" opacities, which later also disappear. Similar changes affect proximal phalanges. Bone literally "melts away" and whole digits may be lost, or else persist as squat appendages attached to feet which have been shortened through metatarsal involvement. The latter are similarly affected, but as in H.S.R.N. they develop tapering distal ends. They do not become "sliced off". Translucent vacuoles may appear in the shafts of any of these bones, and occasionally progress to a honeycomb appearance (Paterson (1955)). Concentric metatarsal atrophy is another characteristic finding. These bones may become "needle thin" and are then liable to spontaneous fracture. Concentric atrophy appears to be due initially to shrinkage of the medullary space as the cortex retains its normal thickness until a later stage (Barnetson (1950)). Concentric metatarsal atrophy may be curiously localised and cause an annular indentation rather than a diffuse narrowing (Paterson (1955)). Sequestrum formation and extrusion, periosteal reaction and osteosclerosis can all occur, and have been blamed on secondary infection through ulcerating skin lesions (Barnetson (1950)).

Metacarpals, carpel and tarsal bones are not often affected in leprosy; indeed the latter may be less severely attacked than in severe examples of the inherited traits.

Posterior subluxation at the ankle can however occur, and is
well illustrated by one x-ray plate (Cooney & Crosby (1944)), causing apparent elongation of the heel and increasing the shortening of the forefoot. An almost identical, rather more severe appearance, has been described in IV 25 of the "X" family.

The end result of all these processes is gross mutilation and deformity of the feet and hands.

However, by the time such gross lesions have developed in leprosy, there will almost certainly be evidence of this disease elsewhere in the body in the form of hypo-pigmented, hypaesthetic skin lesions and motor signs, such as claw-hand, foot-drop and facial palsy, (Browne (1963)). Indeed, motor nerves may be almost exclusively involved in a minority of patients (Faget & Mayoral (1944)). Accessible nerve trunks may be enlarged, nodular, hard and tender, although later they may become fibrosed and thinner than normal (Dale et al (1963)). There may also be bewildering evidence of systemic leprosy with such complications as orchitis, polyarthritis, hepatitis, nephritis, haemolytic anaemia, acute gynaecomastia and personality disorders (Browne (1972)).

Such a confusing picture may lead to the diagnosis of leprosy being overlooked for several years. The classical misdiagnoses include syringomyelia, allergy and fungal infection (Powell & McDougell (1974)).

The diagnosis is confirmed by isolating the M. Leprae from the active edge of an ulcer or nodule, the post-nasal space or biopsy material.

Gross slowing of motor nerve conduction velocities (Granger (1966)), implies segmental demyelination (Gilliatt (1966)). This process would also explain the transient nature and rapid reversibility with treatment of some nerve lesions. Axonal decay has usually been regarded as the principal histopathological lesion, however, until
recently when segmental demyelination has also been convincingly demonstrated (Dayan & Sandbank (1970)). The appearance of leprosy bacilli in Schwann cells suggest that these are attacked directly. Involvement of axons is presumably a more remote effect.

Many, but not all of the sporadic cases of acrodystrophic neuropathy in the literature have been studied carefully to exclude leprosy. In one case the distinction was never finally made with absolute certainty (Spillane & Wells (1969)).

The diagnosis of leprosy in this country is no longer academic in view of the large scale immigration from endemic areas, and indeed it has been correctly made in our practice area on two occasions since the last war (Haythornthwaite (1953)). The appearance of the feet in one patient was identical to that encountered in H.S.R.M.

Cases of H.F.A.N. have initially been diagnosed as leprosy in several instances (Endrile (1933), Gate & Riou (1936), Andrade (1952)).

It is likely that the reverse is true and that a few of the reported examples of sporadic A.N. have in reality been cases of leprosy.

Although Diabetic Neuropathy occurs frequently in known diabetics, when it often but not invariably follows a period of loss of stabilisation due to therapeutic neglect, intercurrent infection, or other stress, it may also be the presenting feature in maturity onset diabetes mellitus (Rundles (1945), Martin (1953), Pirart (1965)).

In this form of the disease ketosis does not occur, with the result that symptoms are so mild and develop so insidiously, that the patient is not aware that he is ill until neuropathy (or some other complication) supervenes. The neuropathy and its cause are then
diagnosed simultaneously. Few doctors will have lacked this experience.

The neuropathy may even become established before glycosuria appears, perhaps because of a high renal threshold for glucose (Thomas (1970)), or at a time when the glucose tolerance test is not significantly abnormal (Ellenberg (1958)).

Furthermore, in at least two-thirds of cases, the neuropathy itself will not cause symptoms, at least in the early stages (Pirart (1965)) with the result that it may have been present for some considerable time before its presence is recognised.

Although motor involvement is occasionally conspicuous, the neuropathy is more often almost exclusively sensory and prone to complication by trophic lesions of the feet.

It is therefore clear that diabetes can cause occasional instances of acrodystrophic neuropathy at a time before it, itself, becomes recognisable. A case in point is provided by a patient who presented a severe neuropathy, later to be complicated by trophic disorders, which antedated discovery of the causal diabetes by a full five years (Appelman (1964)).

It has been stated that this chronic sensory form of diabetic neuropathy mimics H.S.R.N. more closely than any other acquired disorder (Denny Brown (1951)) and indeed there is a close similarity between classical English language accounts of the two disorders (Pavy (1904), Hicks (1922)).

There are other similarities. These include a preponderance of male cases which is surprising as diabetes is more common among women (Martin (1953)).
There is also a characteristic foot deformity (Simpson (1962)), probably due to weakness of the intrinsic foot musculature. This may be the only evidence of motor weakness and recalls observations made elsewhere about H.S.R.N., that weakness and wasting may be restricted to the feet.

Rarely, however, diabetic neuropathy may be complicated by severe degrees of paralysis and wasting far greater than that ever seen in H.S.R.N. and comparable to that encountered occasionally in other forms of H.P.A.N., as for example in the "Z" family. Histological evidence of involvement of lower motor neurones in diabetic neuropathy is provided by the presence of neurogenic muscle atrophy and demyelination of peripheral motor nerves. In a minority of cases there may be outright loss of anterior horn cells (Greenbaum et al (1964)). Formerly such cases were classified separately, but the fundamental unity of diabetic neuropathy has been stressed by various writers (Gilliatt & Willison (1962), Greenbaum (1964), Pirart (1965)). Considerable, if less extreme variations in motor involvement do occur in H.S.R.N., but there can be no dispute that these occur within the framework of a single pathological entity. The same consideration applies to diabetic neuropathy.

Finally, neurogenic osteoarthropathy of the feet also occurs in diabetic neuropathy. In leprosy and H.S.R.N., a similar phenomenon has been shown primarily to affect the metatarsal heads and phalanges and the intervening joints. In tabes dorsalis and syringomyelia, large proximal joints are affected. There is some evidence to suggest that similar destructive changes in diabetic neuropathy show a predilection for intermediate joints, such as the tarso-metatarsal and ankle (Bailey & Root (1947)) and the knee (Jacobs (1958)), although more distal changes also occur. The appearances otherwise are identical
with those found in H.S.R.N., but extrusion of sequestra is not described, although they are formed and can, at x-ray, be seen lying free in the tissues. It is probably as a consequence of this that mutilation of the feet does not occur to the extent seen in H.S.R.N. In other cases the only radiological abnormality is diffuse osteoporosis without destructive changes (Martin (1953)). Bone changes are rare in diabetes mellitus as a whole, their incidence being variously reported as less than 0.1% (Bailey & Root (1947)), and 0.22% (Martin (1953)). A further index of their relative rarity is provided by the observation that they were first described less than 40 years ago (Jordan (1936)). A far higher percentage of patients with H.S.R.N. develop osteolytic changes in their feet.

H.S.R.N. and diabetic neuropathy differ in a number of respects of which the most fundamental, obviously, is the presence of glucose in the urine, and evidence of impaired glucose tolerance in the blood. Diabetic neuropathy is, of course, far more common and tends to make its first appearance in a much older age group. The incidence in patients over 50 has been variously described as 37% (Jordan (1936)), 53% (Rundles (1945)) and 70% (Martin (1953)). The inherited traits usually appear much earlier.

Other differences include a high incidence of prodromal symptoms, notably pains and distressing paraesthesiae in a minority of patients, and earlier and more widespread loss of posterior column sensation with ataxia, particularly in the dark (Simpson (1962)), while vibration sense is also lost earlier and over a much wider area (Rundles (1945)). Severe degrees of Rombergism are, however, unusual (Martin (1953)). Reflex loss is also greater with loss of knee jerks in a third (Martin (1953)) to one half of cases, and loss of one or more
upper limb reflexes in a third (Rundles (1945)). Loss of ankle jerks in 80% is less significant, because these are often lost in non-diabetic elderly people.

As described in detail elsewhere (Chapter 7), a severe visceral autonomic neuropathy may occur in diabetes mellitus with impotence, postural hypotension and gastro-intestinal and bladder disturbances. Such symptoms appear rarely, and never severely, in H.S.R.N., although they may occur in other forms of H.F.A.N., notably Hereditary Amyloid Neuropathy (Chapter 22).

Diabetic neuropathy may often be accompanied by retinopathy but this association is indirect, because neuropathy is related to the period of therapeutic neglect, or diagnostic delay, whereas retinopathy depends on the duration of diabetes from its inception, irrespective of the quality of treatment (Martin (1953)). This dichotomy is well illustrated by the fate of patients with retinopathy and neuropathy, once the underlying disease is brought under good control. The neuropathy becomes arrested and may even improve, whereas retinopathy progresses and may eventually cause blindness (Greenbaum (1964)).

E.M.G. abnormalities in diabetic neuropathy include marked slowing of motor nerve conduction velocity (Mulder et al (1961)), loss of digital sensory action potentials (Downie & Newell (1961)), and loss or reduction in amplitude of lateral popliteal action potentials (Gilliatt & Willison (1962)).

Some of these abnormalities may occur in diabetics without overt neuropathy. In the "Y" family at least, latent H.S.R.N. could not be discerned in this way.

Slowing of E.M.G. can occur in what appears to be a purely sensory diabetic neuropathy, whereas in the "Y" family, significant
slaving only occurred in those cases of H.S.R.N., accompanied by considerable amyotrophy.

Sensory action potentials are probably lost earlier in diabetic neuropathy than in H.S.R.N., an observation which can be correlated with the greater loss of vibration sense in the former (Gilliat & Willison (1962)).

There are also important histological differences. Thus in diabetic neuropathy the primary lesion is segmental demyelination suggesting a basic defect in Schwann cells (Thomas & Lascelles (1965)). Axonal decay is secondary to this and may be long delayed, whereas it is the initial event in H.S.R.N. Remyelination in diabetic neuropathy explains the substantial degrees of recovery possible, once the underlying metabolic disorder is closely controlled.

Such recovery in nerve function may not only be reflected in obvious clinical improvement, but also electrophysiologically. M.N.C.V.s increase but do not return fully to normal, although lost sensory potentials (which imply more severe neuropathic involvement) are never restored (Ward et al (1971)).

Alcoholic Neuropathy may cause distal sensory loss and predispose to plantar ulceration.

Plate 52 illustrates such a lesion in the sole of a 40 year-old alcoholic patient who was to die within two years from ruptured oesophageal varices. Hepatic coma was the mode of death in a similar case (De Léon (1969)).

It is probable that other stigmate of social deterioration besides alcoholism, particularly exposure and malnutrition, are necessary to provoke degrees of neuropathic ulceration and mutilation of the feet, comparable to that seen in H.S.R.N.
Patient J.H.  Alcoholic Neuropathy

Trophic ulceration of ball of left foot, present 3 months before death from ruptured oesophageal varices complicating cirrhosis of liver.
A large series of this type has been described in which these factors appear to have been combined in a group of impoverished peasants in the Loire basin (Bureau & Barrière (1955), Bureau et al (1957)).

One member of this series had been described in detail some years earlier (Devic et al (1943)), and eventually came to autopsy Vignon et al (1956). Pathological lesions in peripheral nerves, dorsal roots and ganglia and posterior columns, were broadly similar to those seen in H.S.R.N.

No especial mention was made of the liver in this patient, but abnormal liver function tests were commonplace in the series as a whole, and liver biopsy revealed changes of cirrhosis in two cases.

The primary histopathological event in peripheral nerve is axonal degeneration (Gilliat (1966), Dayan & Williams (1967), Thomas (1971)), with only mild secondary demyelination, so that the reduction in motor and sensory nerve conduction velocities rarely exceeds 30 % (Mawdsley & Mayer (1965)).

Peripheral neuropathy may also accompany liver disease. This may take the form of alcoholic neuropathy, or diabetic neuropathy may accompany haemochromatosis, while a purely sensory neuropathy has been shown to be due to xanthomatous deposition in peripheral nerve trunks in primary biliary cirrhosis (Thomas & Walker (1965)).

Peripheral neuropathy may, however, occur in association with various forms of liver disease, in the absence of any of these aetiological factors. It has been shown to be due to segmental demyelination (Dayan & Williams (1967), Knill-Jones et al (1972)), and there is corresponding slowing of M.N.C.V. (Davidson et al (1972), Knill-Jones et al (1972)), and increased latency or reduced amplitude
of median nerve sensory action potentials (Seneviratne & Pieris 1970). Electrophysiological evidence of peripheral neuropathy is encountered far more often than clinical evidence, while histopathological evidence is seen even more frequently (Knill-Jones et al 1972).

The incidence of peripheral neuropathy is highest in association with oesophageal varices, and in the presence of considerable collateral shunting. The latter observation raises the possibility that entero-genous toxins normally deactivated in the liver, are able to reach the brain (causing encephalopathy), and peripheral nerve (causing neuropathy).

Objective clinical evidence of peripheral neuropathy, when present, consists of loss of vibration sense and ankle jerks and, less often, loss of distal appreciation of pinprick and impairment or loss of knee jerks. Subjective awareness of peripheral neuropathy is not usual, and severe degrees of involvement are extremely rare. Thus, out of 70 patients with various liver diseases, 14 of whom had peripheral neuropathy, there was only one patient who was severely affected. He complained of numbness of the legs and fingers, and of an unsteady gait. Both knee and ankle jerks were lost and there was wasting and cutaneous anaesthesia below both knees. Vibration and position sense were greatly impaired in all 4 limbs (Knill-Jones et al 1972).

On the face of it therefore, the neuropathy of liver disease would appear to be an unlikely candidate for secondary acrodystrophic change.

There is, however, one report in the literature which suggests that it may occasionally occur (Jacob et al 1954). This was the case of a young woman with proven hepatic cirrhosis, who subsequently developed peripheral neuropathy with recurrent plantar ulceration and dense
hyperkeratosis. Symptoms of A.N. began when she was 15 and the liver disease had been present from an even earlier age, so that an alcoholic origin for both diseases seems highly improbable.

A.N. may undoubtedly occur as a late sequel to "Trench Foot" or its maritime equivalent "Immersion Foot".

These syndromes are produced by long exposure to temperatures ranging from just below freezing point to about 10 degrees above (Ungley & Blackwood (1942)). Such temperatures are insufficient to cause frost bite. The severity of Trench Foot and Immersion Foot are increased in proportion to the duration of exposure, by prolonged immobility of the limbs in the dependent position, by pre-existing peripheral vascular disease and, above all, by injudicious rapid warming of the legs subsequently; an item of mismanagement which has been recognised since the Napoleonic Wars (André & Goethals-Borin (1955)).

A short initial phase of vaso-constriction, commonly complicated by thrombus formation (Abbott (1970)), is replaced by hyperaemia, and the limbs become hot, red, painful and swollen. Actual tissue destruction may be negligible, or superficial gangrene may occur (Ungley & Blackwood (1942)).

Of all mammalian tissues, peripheral nerve is the one most sensitive to cold. It has been shown experimentally that axonal degeneration begins within two hours of such exposure (Ashbury (1970)), while in isolated nerves, conduction ceases in myelinated fibres at temperatures below 7 degrees centigrade (Paintal (1965)). In the E.M.C. laboratory, even, conduction in limb nerves is always slower distally than proximally, and this difference is invariably intensified by cold (Simpson (1956)).
Damage to peripheral nerve is reflected in sensory loss, motor weakness, and vasomotor and sudomotor paralysis, and the ultimate prognosis depends upon the degree of nerve regeneration, more than any other factor (Ungley & Blackwood (1942)).

Sensory loss in particular may last for months or even years (Abbott (1970)).

Late symptoms include pains, dysesthesiae, blister formation, cold sensitivity and disturbance of sweating and of the peripheral circulation. The latter may be so acute as to suggest sudden vascular occlusion (Ungley & Blackwood (1942)).

This combination of prolonged distal sensory loss, with an unstable circulation and possibly scar formation from former superficial gangrene, clearly constitutes an ideal background for the generation of almost exact phenocopies of H.S.R.W.

Detailed records in fact exist of patients who have developed plantar ulceration and neuropathic bone changes in the feet, complicating distal sensory loss and occurring several years after such exposure (Van Epps & Kerr (1940), André & Goethals-Borin (1953), Thévenard & Raverdy (1959)). In another case, the hands were affected with destruction of bone appearing one year after exposure (Bernl et al (1967)).

Such cases have usually been ascribed to frost bite. In this condition, however, actual freezing of tissue occurs with the formation of ice crystals. Gangrene is more widespread and penetrates more deeply, but the neurological deficit is localised to a narrow band around the area of tissue destruction, and prolonged neurological sequelae are correspondingly less likely (Asbury (1970)).

Trench Foot and Immersion Foot are much the more probable
antecedents of such cases.

Early lumbar sympathectomy is of value in relieving late effects of Trench Foot and Immersion Foot (Ungley & Blackwood (1942)). It proved helpful, although carried out at a much later stage, in one of the cases of A.N. already mentioned (André & Goethals-Borin (1953)), and in sporadic cases occurring among impoverished French peasants (Bureau et al (1957)) in whom exposure probably exaggerated the effects of alcoholic neuropathy.

This response of the occasional case of A.N. to sympathectomy (Engelbert et al (1951)) may provide a clue to its origin from exposure to intense climatic cold. Indeed it has been suggested that most sporadic cases originate in this way (Wallace (1970)).

A Rheumatoid Neuropathy of mild, mainly sensory type, and insidious onset, may occasionally predispose to trophic lesions of the lower limbs (Hart et al (1957)).

The main symptom is numbness, paraesthesiae being relatively rare (Pallis & Scott (1965)). The development of such symptoms is often not distinguished by the patient from the disability and pain of the associated arthritis.

Plate 53 illustrates an almost healed ulcer on the outer margin of the right foot of a man with seropositive rheumatoid arthritis, principally affecting his right ankle. All modalities of sensation, except position sense, were impaired over both feet and the ankle jerks could not be obtained. His signs remained static and did not progress.
Patient E.J.S.  **Neuropathy complicating rheumatoid arthritis.**

Photograph showing almost healed trophic ulcers of right heel and right ankle.
Usually sensory loss is limited to the toes and distal thirds of the feet and vibration sense is impaired more often than cutaneous sensation. There is a tendency to spontaneous recovery as evidenced by a reduction in subjective symptoms, and in the area of sensory loss. A previously absent lateral popliteal nerve action potential may be restored (Chamberlain & Bruckner (1970)).

Normally such cases are unlikely to present as A.Ns of unknown aetiology because of the prominence of arthritic manifestations which overshadow the neurological syndrome. In those extremely rare instances where neuropathy complicates monarticular rheumatoid, particularly if this affects one knee or ankle, as in patient E.J.S., it is possible that the joint disease might wrongly be assigned a neuropathic basis.

This benign sensory form of rheumatoid neuropathy is to be distinguished from compression neuropathies resulting from distortion of nerve trunks by swollen and deformed joints, from neuropathy due to coincidental disease such as amyloid or alcoholism, or due to drugs used in the treatment of the arthritis (Hart (1969)), and from a much more severe sensori-motor neuropathy (Pallis & Scott (1965), Pallis (1966), Chamberlain & Bruckner (1970)).

Ulceration of the legs is more likely to occur in the latter form, than in the benign sensory form, but this is due to the associated vasculitis. This is widespread throughout the body, and is responsible for the ominous prognosis which characterises this disorder, death often occurring within a year or two of its onset from coronary thrombosis, or some intra-abdominal vascular disaster.

This severe and fulminating sensori-motor neuropathy affects males more often than females, whereas the benign distal sensory form
mirrors the known higher incidence of rheumatoid arthritis in women.

The predominant histological abnormality in rheumatoid neuropathy is segmental demyelination (Weller et al. 1970), with axonal degeneration tending only to occur in association with vasculitis (Beckett & Dunn 1970). The former is reflected in the severe degrees of slowing and of nerve conduction which have been demonstrated (Chamberlain & Brucker 1970). This may affect more nerves than clinical examination would suggest, and may indicate considerable motor nerve involvement, even where the neuropathy appears to be exclusively sensory.

By the time painless, perforating ulcers on the soles of the feet occur in Tabes Dorsalis, the knee jerks will almost certainly have been lost, and posterior column involvement will be greater, and reflected in loss of position sense, vibration sense, ataxia and Rombergism. The pupils will be abnormal, and lightning pains and visceral crises may occur. Serological tests for syphilis will be positive.

Sporadic cases have commonly been mistaken for syphilis however, and this is true of familial cases also. Thus 11/13 of the "X" family received anti-syphilitic treatment, and other patients have fared similarly (Smith 1934), Thévenard & Coste 1935), Van Bogaert (1940), Mulvey & Riely (1942), Wallace (1970)).

Wallace believes that mis-diagnosing H.S.R.N. as neurosyphilis in earlier generations was responsible for the reticence, even hostility which he sometimes encountered during his ascertainment of the "E" family.
A predominantly sensory Carcinomatous Neuropathy is extremely rare, only eight instances being identifiable out of 162 patients with carcinomatous neuropathy (Croft & Wilkinson (1965)).

It may have a most dramatic onset with distressing paraesthesiae of the extremities, and marked loss to all sensory modalities, developing over the course of a few weeks, sometimes overnight. The patient may become too ataxic to stand unsupported and may exhibit slow, writhing movements of the limbs - so called "pseudo-athetosis", (Croft et al (1965)).

Such symptoms progress to their zenith and then become stationary or even remit, which makes it difficult to interpret the response to therapy even when this has involved removal of the responsible growth (Henson et al (1954)).

All these considerations demarcate carcinomatous sensory neuropathy sharply from the inherited traits.

Mixed motor and sensory neuropathies, which are less incapacitating, are much more common (Henson et al (1954), Croft & Wilkinson (1965), Croft et al (1967), Roberts (1970)), and distal sensory loss may also complicate other non-metastatic neurological syndromes due to carcinoma, particularly encephalomyelitis (Henson et al (1965)).

Although any type of neuropathy may apparently occur in association with any type of malignant disease, the relationship between carcinoma of the lung and the peripheral neuropathies is particularly close, and this relationship is most marked with the sensory neuropathies (Croft & Wilkinson (1965)). The "Oat-Cell" carcinoma is the histological type most often implicated (Dayan et al (1965)).
The responsible pathological lesions are located in dorsal root ganglia, peripheral nerve and posterior columns (Benny Brown (1948), Henson et al (1954), Croft et al (1967)).

Histologically, both axonal degeneration and segmental demyelination occur, but the latter is the more severe and widespread lesion (Croft et al (1967)). Its presence accounts for the gross slowing of M.N.C.V. which may be found (Gilliat (1966)), and as remyelination also occurs, for the remarkable fact that improvement in nerve function may sometimes occur.

Similar lesions can be found even when sensation appeared to be normal in life, as in both carcinomatous cerebellar degeneration (Brain & Wilkinson (1965), Vick et al (1970)), and carcinomatous motor neurone disease (Brain et al (1965)).

The appearances in the afferent tracts are qualitatively similar to those seen in H.S.R.N., although posterior column degeneration is undeniably more severe.

As a result, acrodystrophic lesions might occasionally be anticipated in those cases in which the course of the illness is sufficiently prolonged, and where incapacity from ataxia or muscular weakness does not seriously restrict normal activities.

A search of the literature of carcinomatous sensory neuropathy does not support this contention, although patients have been described as having sustained painless burns of both hands (Croft et al (1965), Croft & Wilkinson (1967)).

The literature of sporadic A.N., however, provides accounts of two patients who died from oesophageal cancer (Vésignié (1952), Girard et al (1953)).
The second of these cases came to autopsy, and although the sensory ganglia were not examined, there was severe loss of myelin and axons in sciatic nerve, dorsal roots and, to a lesser extent, dorsal columns. At that time a purely sensory carcinomatous neuropathy was not recognised, let alone one associated with oesophageal carcinoma, and because the anterior roots appeared normal, the authors decided against a diagnosis of carcinomatous neuromyopathy.

In the same year, however, it was shown that carcinoma of the oesophagus could indeed be accompanied by a predominantly sensory neuropathy (Dodgson & Hoffman (1953)).

The presence of a carcinoma does not necessarily mean that it is responsible for any co-existing A.N. An example of this truism is provided by the case of a woman with plantar ulcers who died of a gastric neoplasm. Later her son developed similar trophic lesions, thereby incriminating H.S.R.N. (Velluz et al (1955)).

Nevertheless, it seems possible that some of the sporadic cases of A.N. reported in the literature, may have been examples of carcinomatous neuromyopathy. The latter may occur in as high a proportion as 6% of all cases of malignant disease (Roberts (1970)), in perhaps one fifth of which sensation may be materially impaired.

Furthermore, the interval between the onset of neurological signs and the first appearance of the initial symptoms directly due to the neoplasm, may be as long as three years (Beathfield & Williams (1956)) or nearly four years (Croft et al (1967)). In other cases, the carcinoma may not be diagnosed at all during life (Croft et al (1965)).

In all instances of unexplained neuropathy developing during the second half of life, it is mandatory to exclude carcinoma, particularly carcinoma of the lung, using bronchoscopy if necessary.
There is no reason for exempting A.N. from this general rule, and one may be permitted to speculate on the possible findings, had all the sporadic changes reported in the literature come to necropsy.

Sporadic cases of *Idiopathic* or *Primary Amyloidosis* may present with neuropathy (De Nevasquez & Treble (1938), Strich & Wade (1953), Rukavina et al (1956), Chambers et al (1958), Munsat & Poussaint (1962), French et al (1965)). This is occasionally acrodystrophic.

Accessible nerve trunks may be palpably enlarged, a characteristic which amyloid neuropathy shares with leprosy and hypertrophic neuritis. Suggestive symptoms and signs which may co-exist with the neuropathy include diarrhoea, impotence, hoarseness, non-specific E.C.G. abnormalities, cardiac enlargement and failure, and ocular signs such as vitreous opacity and pupillary abnormalities. The C.S.F. examination reveals raised protein levels, a characteristic which amyloid neuropathy has in common with many cases of the Guillain-Barré syndrome and also with hypertrophic neuritis. The diagnosis is confirmed by biopsy, particularly rectal biopsy (Gafni & Sohar (1960)) and renal biopsy (Hobbs (1973)).

The incidence of neuropathy in non-familial cases is much lower than it is in hereditary amyloidosis however, 14% as against 97% (Kauffman & Thomas (1959)). This may be because a peri-collagen distribution of amyloid may be necessary to induce neuropathy, whereas many sporadic cases may be characterised by a peri-reticulin distribution. It is known that the former occurs in the Portuguese Type 1 (Hobbs (1973)), and the Iowa Type 3 (Van Allen et al (1969)), forms of familial amyloid neuropathy, and also in association with myelomatosis which may itself generate amyloid neuropathy (Campbell & Halford (1964), Davies-Jones & Esiri (1971)).
In an allied plasma-cell dyscrasia, Waldenstrom's macroglobulinaemia, a predominantly sensory amyloid neuropathy, led to the development of neuropathic joints at both knees and ankles (Scott et al. (1973)).

Clearly it is not enough to make a diagnosis of amyloid neuropathy, even though this is itself meritorious. A search must also be made for a causal myeloma or similar tumour. In a recent series of 40 cases of idiopathic amyloidosis, 33 such treatable growths were identified (Hobbs (1973)).

Acute Demyelinating Polyradiculoneuropathy may follow infectious illnesses, such as upper respiratory infections, herpes zoster, infective hepatitis and mumps, as well as inoculation procedures and surgery. The causal infection, for example glandular fever, may be so trivial as to escape notice (Groves & Faorino (1972)). The neuropathy may follow a recurrent and chronic relapsing course (Thomas et al. (1969)). It is usually regarded as a predominantly motor neuropathy, as death may occur in the acute stages from motor paralysis, either by respiratory failure or because of pulmonary embolism from thrombosed veins in paralysed legs (Haymaker & Kernohan (1949), Thomas et al. (1969)).

In fact, sensory loss may be considerable. It was present in the cases of the eponymous authors (Guillain-Barré & Strohl (1916)) and has been widely reported since (Spillane & Wells (1964), Wiederholt et al. (1969), Ravn (1967)). Occasionally it may be the main feature (Rosenblum et al. (1966), Jefferson (1967), Simpson (1968)).

At necropsy, demyelination of dorsal roots and ganglia may be as severe as that seen in anterior roots (Rosenblum et al. (1966),
When recovery occurs it may be incomplete, so that reflex loss and sensory impairment may persist for several months or years, even though physical activity has been resumed (Wiederholt et al (1964)).

This is an ideal background for the development of acrodystrophic lesions.

A scrutiny of the literature reveals two instances in which A.N. apparently developed in this way. In the first of these (Ionesco et al (1958)), a classical attack of polyradiculoneuropathy occurred one month after T.A.R. immunisation. This improved only slowly, with persistence of extensive sensory loss. Two years later, planter ulcers developed with destructive changes in the bones of the feet, and a spontaneous fracture of one femur. The disorder was ascribed to syringomyelia and benefit claimed for deep x-ray therapy.

In the second case (Spillane & Wells (1969)) pains in the back and down both legs developed one month after a second dose of poliomyelitis vaccine, administered in June 1959. These subsided after a month, but were succeeded by numbness and pains in the calves. Later he limped and became unsteady in the dark. He had also become impotent. In spite of these developments he was given his third dose of polio vaccine in January 1960. When first seen by the authors in May 1960, there was gross impairment of pain and temperature sensation over the root zones L.4 to S.5, and of the corresponding tendon jerks. The other modalities were but little affected and wasting was slight.

Deep plantar ulceration began 18 months later in December 1962, and was bilateral and severe by 1964.

Similar examples might be revealed by analysis of the
extensive French literature relating to acrodystrophic neuropathy which poured out in the form of Papers and Theses in the 3rd, 4th and 5th decades of this century (see Plancherel (1969) for references).

During the earlier part of this period, immunisation against rabies was widely performed in France, using an anti-serum which was notorious for its contamination by actual nerve tissue impurities, (a formula broadly similar to that used more recently to induce "allergic" neuropathy in experimental animals). Use of this vaccine is known to have generated a high incidence of acute radiculoneuropathy (Arneson & Asbury (1968)).

Nowadays, active immunisation against rabies using the Sempé Vaccine is more effective, but still carries a substantial risk of post-vaccinial neurological consequences (Kramer (1968)).

**Syringomyelia** is unlikely to cause confusion owing to its predilection for the cervical and upper thoracic parts of the cord. Thus dissociated anaesthesia and trophic lesions are limited to the hands which are also wasted. These signs are usually unilateral at first and even when they affect both sides, they rarely become truly symmetrical. The upper limb reflexes are lost.

If signs are present in the legs these are purely motor and ensue from cortico-spinal tract involvement with some weakness, increase of tone, exaggeration of tendon jerks and extensor planter responses.

Neuropathic joint involvement is likely to be proximal and limited to the upper limbs. Kyphoscoliosis is commonly present.

Ultimately spastic paraplegia of the legs may supervene, usually after a long interval. Ulceration of the feet and legs may
then occur, but these are decubitus, and not trophic ulcers.

Other lesions of the cord in the neck such as spondylarthrosis, tumor of the cord and hypertrophic neuropathy with intrathecal entrapment of grossly enlarged nerve roots (Symonds & Blackwood (1962)), may produce similar signs but sensory loss in the hands will not be dissociated.

Injuries to major nerve trunks may lead to neurogenic ulceration of the feet and to osteoarthropathy, as well as motor signs. These injuries may affect the cauda equina (Pommé (1931), Pommé et al (1931), André (1951), André-Van Leeuwen & André (1951), Barraquer-Serré & Barraquer-Bordas (1952), Kelly & Coventry (1953)), or they may be the result of injury more peripherally such as to the sciatic nerve (Hodgson et al (1948), Kelly & Coventry (1953)). Other evidence of such injuries is likely to be obvious, so that the acrodermatrophic lesions are easily explained.

Miscellaneous causes include spina bifida (Hodgson et al (1948), Lorber (1969). This is likely to become an increasingly important cause in view of the successes of specialised surgical techniques in this field. In such cases, however, the explanation will be obvious. Another possible explanation is yaws, while A.N. has been described as complicating herpes zoster on a single occasion (Kelly & Coventry (1953)).

In a unique case, a primary defect of skin and subcutaneous tissue was incriminated as the cause of trophic ulcers. This defect was believed to exert an effect on terminal nerve endings producing a light peripheral anaeesthesia without other neurological signs (Eyckmans et al (1951)).

Theoretical possible causes include the sensorimotor neuropathies which may complicate various diseases such as reticuloses
(Mawdsley (1968), Currie et al (1970), Currie & Henson (1971)), and the collagen disorders, particularly systemic lupus erythematosus (Johnson & Richardson (1968)).

Vitamin B₁₂ deficiency may cause a purely sensory neuropathy (Thomas (1970)) and will doubtless be looked for in most cases.

The neuropathies due to deficiencies of the other members of the B group of vitamins are not apparently complicated by acrodermatitis enteropathica (Spillane 1958), and the same is true of the neuropathies due to Industrial Chemicals, heavy metals and drugs. Among these, only Thalidomide causes a purely sensory neuropathy (Spalding (1969)).
AUTHOR INDEX

Amsterdam: Elsevier.


ALAJOUANINE, T. & MOZZICONACCI, P. (1946). "Un cas de syndrome syringomyélïque lombo-sacré familial avec spina bifida".
REV. NEUROL. 98, 693 - 4.

REV. NEUROL. 106, 433 - 52.


ALEXANDER, W.S. (1966). "Phytic Acid in Refsum's Syndrome".
J. NEUROL. NEUROSURG. PSYCHIAT. 29, 412 - 6.


ACTA NEUROL. PSYCHIAT. BELG. 51, 9 - 16.


BRAMANN, (1899). cit. BRUNS (1903).


BROWNEILL, Betty. (1973). PERSONAL COMMUNICATIONS.


Cit. BUREAU et al (1957).


CROCHET, PETGES & JOULIA (1920). "Un cas de maladie de Morvan chez un enfant de sept ans". BULL. MEM. SOC. MED. CHIR. BORDEAUX. 1920, 232 - 90.


HAYTHORNTHWAITE, F. (1953). "Leprosy at large". BRIT. MED. J. 2, 1053.


KANTARJIAN, A.D., & DE JONG, R.N. (1953). "Familial Primary Amyloidosis with nervous system involvement". NEUROLOGY (Minneapolis) 2, 399 - 409.


KUNKEL, C. (1961). "A pain unfelt or pain unheeded; A distinction with a difference". ARCH. NEUR. (Chic.) 5, 579.


LOGATCHEV, K.D. (1964). "Familial form of lumbo-sacral syringomyelia". ZE NEUROPATH. PSYCHIAT. KORSAKOV. 64/6 806 - 10. Abstracted from the RUSSIAN IN EXCERPTS NEUROLOGICA.


diagnosis of Amyloid Polyneuropathy: Report of 3 cases".
NEUROLOGY (Minneapolis) 12, 413 - 22.

MURRAY, T.J. (1975). "Congenital Sensory Neuropathy".
BRAIN, 98, 387 - 94.

"Nerve conduction & other studies in families with Charcot-Marie-Tooth 
Disease". BRAIN, 87, 589 - 605.

manifestations osseuses, cutanées et cardiaques".
PRESS MED. 23, 2031 - 4.

NELATON, (1852). "Affection singulière des os du pied".
GAZ. HOP. CITV. MILIT. (PARIS). 25, 13.

Generalised Amyloid Disease with involvement of the nerves".
BRAIN. 61, 116 - 23.

"Benign recessively inherited chorea-athetosis of early onset".
J. MED. GENET. 6, 403 - 10.

OEHLICKER, F. (1909). "Zur kassistik und zur behandlung neuropathischer 
gelenkr krankungen". BEITR. KLIN. CHIR. 45, 63 - 105.

"Rouaey-Levy Syndrome: Report of a kindred with discussion of the 
nosology". ACTA NEUROL. SCAND. 47, 80 - 90.

"Some sensory syndromes in children: indifference to pain & sensory 
neuropathy". J. NEUROL. NEUROCHIR. PSYCHIAT. 22, 267 - 76.

OGRYZLO, M.A. (1946) "A familial peripheral neuropathy of unknown 
origin, resembling Marvans Disease". CANAD. MED. ASSOC. J. 54, 547-53.

"Hereditary Sensory Neupathy, Type II: Clinical, electrophysiologic, 
histologic & biochemical studies of a Quebec sibship".
ARCH. NEUROL. (Chic.). 29, 23 - 37.


PARKS, R., & STAPLES, O.S. (1945). "Two cases of Morwans Syndrome of uncertain cause". ARCH. INTERN. MARR. 72, 75 - 81.


PRATT, R.T.C. (1967).

THE GENETICS OF NEUROLOGICAL DISORDERS. LONDON: O.U.P.


RILEY, R.J. (1930). "Syringomyelia or Myelodysplasia". J. NERV. MENT. DIS. 72, 1 - 27.


SCHULZE, F. (1917). "Familier auftretendes malum perforans der fusze (Familier lumbale syringomyelic ?)". DTSCH. MED. Wschr. 43, 545 - 7.


SLACK, J., & EVANS, K.A. (1966). "The increased risk of death from Ischaemic Heart Disease in first degree relatives of 121 men - 96 women with Ischaemic Heart Disease". J. MED. GENET. 3, 239 - 257.


PROC. RAY. SOC. MED. 62, 201 - 10.


DEVELOP, MED. & CHILD NEUROL. 13, 109 - 11.


Cited by Fewer (1968).


VAN BOGAERT, L. (1953). "Essai de classement et d'interprétation de quelques aéro-ostéolyse mutilantes et non-mutilantes actuellement connues".
ACTA NEUROL. PSYCHIAT. BELG. 52, 90 - 115.


ANN. MED. 56, 148 - 70.

ANN. SOC. ROY. SCI. MED. NAT. BRUX. 3, 267.
Cited by Thévenard (1942).


WLD. NEUROL. 1, 409 - 17.

WADULLA, M. (1949). "Familière neurovasculaire dystrophie".
DTSH. Z. NERVENHEILK. 160, 413 - 38.


WEITZ, (1921). "Kasuistisches zur familiären trophoneuroses an den füssen und handen". DtSCH. Z. NERVENHEILK. 82, 57 - 64.


