BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 13 1960

CERVICAL DISK LESIONS WITH NEUROLOGICAL DISORDER DIFFERENTIAL DIAGNOSIS, TREATMENT, AND PROGNOSIS

BY

A. M. G. CAMPBELL, D.M., F.R.C.P.

Neurologist, Bristol Royal Infirmary and Frenchay Hospital

AND

D. G. PHILLIPS, F.R.C.S.

Neurological Surgeon, Regional Neurosurgical Unit, Frenchay Hospital, Bristol

In spite of much work on cervical spondylosis in the past ten years, the published results of treatment, particularly in cases of myelopathy, remain disappointing. Opinions vary regarding the right policy, from marked conservatism to radical surgery.

Classification

Some confusion arises from failure to distinguish between the main types of lesion found in association with cervical spondylosis in assessing results. These may be classified under four headings.

1. *Cervical Spondylosis with Myelopathy.*—These cases, clearly distinguished from true prolapse of the nucleus pulposus by Brain (1948) and Brain *et al.* (1952), are the most difficult to treat and in which to assess results. Most authors state that conservative methods should be tried first, and operation performed if these fail. This may consist of laminectomy with division of the denticulate ligaments, or radical removal of the bony spurs in front of the spinal cord (Allen, 1952; Mayfield, 1955). The latter is not favoured in this country. O'Connell (1955, 1956) distinguishes "secondary spondylosis" at a single level after ruptured disk from "primary spondylosis" with generalized degenerative changes and osteophyte formation. He believes immobilization of the cervical spine is the rational treatment for the latter, and that indications for surgery are limited. Results of treatment in four published series, each of 40 to 50 cases, in this country showed improvement of varying degree in approximately half the cases (Brain *et al.*, 1952; Northfield, 1955; Clark and Robinson, 1956; Bradshaw, 1957). This figure included many cases with only slight improvement, and applied equally to conservative and operative treatment. Large American series of surgically treated "ruptured cervical disks" or "cervical disk lesions" consist almost entirely of cases of brachial neuritis (Scoville, 1954, 1958; Odom *et al.*, 1958; Cloward, 1958). It appears that in the few cases of spondylosis with myelopathy results have been poor.

2. *Cervical Spondylosis with Brachial Neuritis.*—In this condition excellent results have been reported in the large American series just quoted, and by Frykholm (1951), but good results also follow immobilization of the neck in a collar (Jefferson, 1951).

3. *Prolapsed Cervical Nucleus Pulposus.*—True prolapse of the disk interior may be traumatic or spontaneous, and should be distinguished from cervical spondylosis of degenerative aetiology (Brain *et al.*, 1952). Symptoms may be sudden in onset or appear gradually. There is "clear evidence of a segmental lesion at the level of the protrusion" (O'Connell, 1955). In many published series it is not clear what proportion of cases of myelopathy with disorder of the cervical disk belong to this category. O'Connell (1955) reports eight well-documented cases with good results from surgery. Scoville (1954) and Odom *et al.* (1958) report disappointing results in "central ruptured disks" or "medial soft disk protrusions" with cord involvement.

4. *Cervical Spondylosis with Myelopathy Due Partly or Wholly to Other Aetiology.*—It is well recognized that cervical spondylosis often exists without neurological complications (Pallis *et al.*, 1954). Many authors (Brain *et al.*, 1952; Clarke and Robinson, 1956; Bradshaw, 1957) have emphasized the importance of differential diagnosis in cases of myelopathy where cervical spondylosis is present. In the early stages of intrinsic—for example, demyelinating—disease of the cord differential diagnosis may be impossible. This clearly affects assessment of treatment, especially if the follow-up is limited. Russell (1956) expressed surprise at surgeons advocating operation in cervical spondylosis, and said, "If wearing a collar is not followed by some improvement the diagnosis should be reconsidered."

Present Series

The present series of 60 cases includes all those (with only such exceptions as mentioned below) treated between 1948 and 1958 in the South-western Regional Neurosurgical Unit for myelopathy or radiculitis associated with disorder of the cervical intervertebral disks, whether this presented as a spondylosis or as a true prolapse of the nuclear portion of the disk. It includes nine cases in which intrinsic disease of the cord or brain was later proved. With the exception of patients who died before that period, all have been followed up for a period of two years or more. Only four cases have had to be excluded because attempts at follow-up were unsuccessful.

Cervical Spondylosis with Myelopathy

To allow comparison with other series Tables I and II include only those cases in which diagnosis was confirmed by myelography or operation. (Of seven patients who did not have myelography, all had improvement sustained for over two years after treatment by a collar, and five remained at work.) The nine patients for whom an alternative diagnosis was proved are considered later. All had well-marked ridges formed by exostoses on the posterior margins of adjacent vertebral bodies at one or more levels. In only five cases was the ridge confined to a single level (the "focal spondylosis" of Bradshaw, or "secondary spondylosis" of O'Connell). Otherwise the distribution of the abnormalities was as recorded elsewhere, being maximal at the levels C 5-6, and C 6-7.

With the exception of one patient, in whom symptoms and signs were confined to the lower limbs, all had symptoms and signs of neurological disorder affecting upper and lower limbs, with varying degrees of spastic paraparesis.

The average age of the patients was 53 years, and the average duration of symptoms 17 months. The time off work before admission to hospital, where this was recorded, averaged six weeks.

Choice of treatment was at first somewhat arbitrary. In the earlier years operation was resorted to more readily, being done mainly in those cases considered more severe. Later few operations were done, because of the continued success of conservative treatment. The change in policy followed unexpected improvement in two patients with severe syndromes who were awaiting operation in hospital.

A man aged 60 had had numbness of the extremities, loss of fine hand movements, and increasing difficulty in walking for eight months. He had the greatest difficulty in walking up the aisle in church. Some improvement in walking occurred after bed rest in hospital, though he still had a shuffling gait. He had slight wasting and marked weakness of the intrinsic muscles of both hands, and spastic weakness of the lower limbs, more on the left. Tendon-jerks were exaggerated and the plantars extensor. There was hypalgesia of the ulnar border of the left hand, of a band about the waist, of the right leg below the knee, and the dorsum of the left foot. Myelography showed "large central disk protrusions at C 4-5, and C 5-6, with a smaller one at C 6-7." There were also protrusions at C 3-4, and C 7-T 1. Dysuria followed the myelography. Operation was deferred because of a coryza. After two weeks' complete rest in bed, in Fowler's position, with improvement, a Minerva plaster jacket was applied, and the patient was sent home. Three months later micturition was normal and walking had improved, though the gait was still halting and the left foot dragged if he hurried. The hands were weak but more agile. A short plastic collar was supplied. A year later he was able to walk a mile and did light work. Power of the hands and sensation of hands and feet were normal. Three years later there had been no relapse.

A woman aged 63 had two episodes of transient weakness and paraesthesia of the left arm. Two weeks later there was a sudden onset of weakness of the left limbs with pain in the left arm. Urinary retention followed. Some improvement in the power of the limbs occurred, though not in bladder function, during the next four weeks in hospital. On transfer to the neurosurgical ward a left Horner syndrome (ptosis and meiosis) was found. Hypertonia and slight wasting of the left arm and hand were present. Tendon-jerks were increased. The left leg was spastic and could barely be lifted from the bed. There was bilateral ankle clonus. Pain and temperature sensation

were impaired on the right side below T 2 level. Vibration sense was lost over the trunk and lower limbs. Myelography showed "postero-lateral bar formation at the levels C 5-6 and C 6-7, on the left side." With rest further improvement with recovery of bladder function occurred. Eleven days later a Minerva plaster collar was applied, this being retained for 10 weeks, and was followed by a plastic collar. After six months the patient did all her housework and could walk two miles. Some hypalgesia of the right trunk and lower limb remained. Two and a half years later her progress had been maintained.

A Minerva type of plaster collar (see Fig.) has remained the mainstay of conservative treatment in all but minor cases. It is retained for three months and followed by a short plastic collar for a variable period, usually from three to six months. Most of the operated cases had a collar after operation, and in five of these it was of a Minerva type.

In Table I the gradings of "much improved" and "slightly improved" are of course arbitrary. Table II indicates that in most cases the improvement has been enough to allow

A light Minerva collar as used for cervical spondylosis.

continued work, even though in a few cases the work has had to be modified.

The two deaths occurred three months and one year after operation in bedfast cases. In one there had been temporary slight improvement. The patient in whom the result in Table I is queried is not at work, though when seen 18 months after treatment there was no complaint of his limbs as previously. He was then in a mental hospital, and remained incapacitated because of his psychiatric condition.

Most patients returned to work within four months, though four took over a year to get back to work.

Perhaps the most striking finding in this group was the fact that of those who returned to work and have

TABLE I.—Results of Treatment After Two Years

	A	B	C	D
Myelopathy (26 cases*):				
Treated by rest or short collar ..	3	1	1	
.. .. Minerva collar ..	4	2	2	(?)
.. .. operation ..	3	4	3	2†
Brachial neuritis (12 cases) ..	9	2		1†
Prolapsed nucleus pulposus (6 cases) ..	5			1†
Altered diagnosis (9 cases) ..		3		6

* Excluding seven cases without myelography.

† Died.

A=much improved. B=slightly improved. C=unchanged. D=deteriorated.

TABLE II.—Working Capacity After Two Years

	Working	Not Working	Died
Myelopathy	20	4	2
Brachial neuritis	11	0	1
Prolapsed nucleus pulposus	5	0	1
Altered diagnosis	1	8	0

been followed up for long periods (treated by short collar, for 6, 2½, 2, and 2 years; by Minerva, for 6, 4, 3½, 3½, 3, 3, 2½**, and 2 years; by operation, for 7, 5, 5*, 4, 4, 4, 4*, and 3 years), only the two marked with an asterisk had ceased work because of progress of the disease, after five years and four years. One other (marked with two asterisks) ceased work because of intercurrent illness. Apart from the two who died, even those patients who did not return to work had not deteriorated further after periods of two to five years.

It was not found possible to compile a table relative to change in gait to compare with that of Bradshaw (1957), but in only two cases has the gait deteriorated, and that only five and four years after previous marked improvement. In all others the gait has remained at least as good as before, and in most there has been great improvement. This compares favourably with Bradshaw's findings, where improvement in gait was confined to cases of "focal spondylosis," and most cases of "generalized spondylosis" had deteriorated.

Where duration of symptoms was over one year, improvement was limited. Of four such cases treated with collars, there was slight improvement two years later in two and no change in two. Of eight such cases after operation, one had much improvement sustained at two years, though relapse occurred three years later; three were slightly improved and two unchanged two years after; while two had died less than a year after operation.

Cervical Spondylosis with Brachial Neuritis

All 12 patients had abnormal neurological signs in the upper limbs as well as subjective complaints, but no long-tract signs. Myelography was performed in four of the eight non-operated cases. The average age of these patients was 44 years, and the average duration of symptoms eight months, with an average of 2½ months off work. One patient with a history of over two years went back to work 18 months after treatment (by Minerva collar) but stopped work six months later. One patient with a history of 18 months maintained slight improvement three years after operation. Two others, with a history of 14 months before operation and 12 months before Minerva plaster, remained well ten years and five years later. One patient died of pulmonary embolism five weeks after operation. The rest have remained well after long periods (10, 7, 7, 4, 3, 2, and 2 years).

As with the previous group, selection of cases for operation had been somewhat arbitrary. Osteophytes had been chiselled away in three of the four operated cases. The satisfactory results of treatment by plaster immobilization led to operation being abandoned in this group.

Prolapsed Nucleus Pulposus

There were six patients with this condition; their average age was 46 years, and average duration of symptoms 4½ months. All had progressive well-marked syndromes of a segmental cord lesion at the cervical level with involvement of all four limbs and trunk, except in one case where there was brachial neuritis only.

Myelography in four cases showed a complete block in one case, gross defects at two levels in another (there were two prolapsed disks in this case), and partial blocks in the remaining two. The myelographic abnormalities were of a grosser degree than in the cases in the cervical spondylosis group. In the case with the complete block

on myelography, the C.S.F. had been normal two weeks earlier, with no block on Queckenstedt's test. There had been a complete block with this test in another case, the C.S.F. protein being 160 mg./100 ml., and partial blocks in three others, with C.S.F. protein of 150, 60, and 50 mg.

Operation was performed on all these patients. One was explored the day after a fall had produced complete quadriplegia and double incontinence. Prolapsed disk was not found, but at necropsy a month later a central prolapse anterior to the cord was seen.

The other five patients did well, though one required 3½ years' intensive rehabilitation before getting back to work, which he continued successfully three years later. The remaining four patients remained at work 10, 6, 6, and 4 years after operation, with minor disabilities.

Altered or Modified Diagnosis

In many cases of cervical spondylosis with myelopathy the diagnosis must at first be a provisional one. Confirmation will depend on response to treatment and observation of the case over a certain period of time. In seven of the nine cases in this group there was some intrinsic disease of the spinal cord; four of these were found eventually to be suffering from disseminated sclerosis. In two of them it was the first diagnosis considered, and only because of the accompanying spondylosis was a collar tried to see if it would relieve the symptoms. As 75% of people over the age of 50 years show some cervical spondylosis radiologically, it is not unusual that the two conditions can be associated, particularly as disseminated sclerosis is the commonest systemic disease of the nervous system.

Three of our cases were found to be cases of motor neurone disease where the early picture was predominantly damage to the upper motor neurone.

The development of dysarthria or an increased jaw-jerk was the earliest sign that the disease was not confined to a cervical origin. The dysarthria in certain cases did not show itself until from 18 months to four years after the symptoms of myelopathy had become evident.

One patient, 2½ years after operation for spondylosis, was found at necropsy to have cervical extradural round-cell sarcoma. Another developed a picture of diffuse cerebral degeneration two years after cervical laminectomy, and this was thought to be responsible for the early pyramidal signs.

Discussion

These results confirm the good results obtained by others in cases of prolapsed nucleus pulposus with cord compression which need operation (O'Connell, 1955) and in cases with brachial neuritis which do not (Jefferson, 1951).

Whether or not as the result of treatment, we have found the prognosis in cases of cervical spondylosis with myelopathy to be more favourable than have other authors.

The patients with myelopathy were no younger in this series than in others. The average age at onset was over 51 years. Brain *et al.* (1952) give this figure as 49 years, Clarke and Robinson (1956) as 50 years, and Bradshaw (1957) as 48 years.

On the other hand, the average duration of symptoms before treatment in this series (17 months) was less than

in others. Of 26 patients, 7 had a history of over two years and 6 others of over one year. Brain *et al.* (1952) had 20 out of 43 cases with a history of over two years. Northfield (1955) had 16 over two years and 8 others over one year out of 39 cases. Clarke and Robinson (1956) had a mean duration of symptoms of three years, and Bradshaw (1957) an average of two to three years. Earlier treatment might therefore account in part for less disability and better results in the present series.

Though severe disturbance with retention or incontinence was rare in any series, the incidence of bladder symptoms might be an index to the relative severity of cases. In this series of 26 cases bladder disturbance was noted in 10. Northfield (1955) recorded it in 14 out of 39 cases, Clarke and Robinson (1956) in 40% of all patients, and Bradshaw (1957) in 23 out of 55 cases. For what it is worth, this suggests that there was no great difference in the degree of neurological disorder.

In assessing prognosis and results of treatment it is essential to differentiate the various types of disorder associated with cervical intervertebral disk lesions.

Cases of brachial neuritis and of true disk prolapse with cord compression have a good prognosis, the first with conservative treatment, the second with surgery.

It is wise to stress again the importance of the differential diagnosis. The vast majority of errors in the diagnosis are due to confusion with disseminated sclerosis or motor-neurone disease involving particularly the upper motor neurone, in the presence of cervical spondylosis, which is shown either on the straight x-ray films or myelography. In our series this has proved the most confusing diagnostic problem. As Brain and Wilkinson (1957, 1958) have stressed, disseminated sclerosis and cervical spondylosis can exist in the same patient, and it is quite justifiable to try to relieve the cervical spondylosis by anything other than drastic operative treatment. It will soon be seen whether immobilization by a collar proves effective or not in relieving at least some of the symptoms; for, as Russell (1956) has said, improvement which results from treatment of cervical spondylosis with myelopathy becomes immediately apparent and is a therapeutic check on the correctness or otherwise of the diagnosis.

It must, however, be realized that in certain cases of disseminated sclerosis, having a natural tendency to remission, a spontaneous recovery may be attributed to a plaster collar when in reality it is related to a remission of the demyelinating condition. Perhaps it should be stressed once more that an inquiry into the history of the patient to ascertain whether there were any previous episodes suggesting demyelination, and particularly episodes of ocular disturbances, should be made with the greatest care.

The possibility of a cervical tumour should always be borne in mind. Two patients have recently attended our unit in whom a meningioma had been previously missed. One had been seen in another neurosurgical unit and diagnosed as a case of cervical spondylosis because abnormalities indicating this were shown on the straight x-ray film. In the second there was a history of trauma, which had been accepted by an eminent neurologist as the cause of the spastic weakness of the legs. If a myelography had been done earlier this confusion would not have arisen.

Vitamin-B₁₂ deficiency in the form of subacute combined or neurological complications of steatorrhoea rarely causes confusion, but where the symptoms of

vitamin-B₁₂ deficiency present with a mainly spastic weakness of the legs and very minor sensory changes, the diagnosis may be difficult, particularly if the blood count is normal. The diagnosis can be obtained only by sternal marrow puncture and vitamin-B₁₂ assay. Clarke (1958) has also drawn attention to the confusion which exists between peripheral neuritis and cervical spondylosis. Certainly some cases of cervical spondylosis present with sensory changes of a "glove and stocking" type, which initially suggest some peripheral nerve damage. These are probably due to involvement of the blood-supply to the posterior column from a compressing lesion. Usually the development of frank motor signs will clarify the picture.

It is not perhaps usually appreciated that cerebellar ataxia may be found in lesions in the neck, due to cervical spondylosis.

Lastly, disease of the brain should be considered, and Brain (personal communication, 1959) told one of us that he had recently seen a patient who had been diagnosed as a case of cervical spondylosis, with motor weakness in the lower limbs, and who in fact had a parasagittal meningioma compressing the motor areas of the brain.

The psychological disturbances produced by cervical spondylosis with neurological complications are those associated with any chronic nervous illness causing gross incapacity. Often the muscular weakness is exaggerated, as Miller (1956) has suggested, by the tension of the patient and the exaggerated effect on muscle tone. One of our patients, a highly intelligent man, commented on this, and said that when his tension state became better his movements became much easier.

It can be seen from this brief survey that the differential diagnosis between cervical spondylosis and other neurological conditions is not always easy and that any myelographic findings should be assessed in association with the clinical picture. A long follow-up in which the patient is seen regularly every few months is essential to avoid errors of diagnosis and to assess the results of treatment.

Allowing for some variation in the degree of the presenting disability and difference in classification, it seems that improved results in the cases with myelopathy described here can be attributed, at least in part, to methods of treatment.

It is generally agreed that milder degrees of myelopathy may become arrested spontaneously or by relatively simple measures. Nevertheless, poor results of conservative treatment in the past have led many to advocate surgery for this condition. Surgery has also proved disappointing.

Conservative measures are often inadequately applied. Most reliance is placed on short plastic collars. While not generally used for cervical spondylosis with myelopathy, a Minerva type of collar, including the head and the upper chest, has been advocated by Jefferson (1951) for brachial neuritis associated with prolapsed cervical disk. Such a collar can hardly fail to give better immobilization of the whole cervical spine than shorter models. It prevents rotation or lateral flexion of the head and allows movement of the lower jaw in eating and talking without movement of the occipito-atlantal or upper cervical joints. This is not so with a short collar fitting closely under the chin, when such movement is actually exaggerated. It has been stated that "the socially unacceptable nature of most cervical

collars limits their use to some extent" (*Lancet*, 1958). It has also been suggested that conservative treatment should not include the prolonged use of collars, because prolonged complete immobilization allows neck muscles to atrophy or become lax (Allen, 1952).

Both these views are misguided. A patient who has signs of progressive degeneration of the spinal cord with the prospect of quadriplegia should not be deterred, by self-consciousness about his appearance, from timely immobilization in a light Minerva type of collar if this has a good chance of halting or reversing the disease. While such a collar gives more complete immobilization than a short "under the chin" model, it does not allow the muscles to atrophy any more than does a walking-plaster on a limb. The patient remains ambulant, and can in many cases return to work in his collar.

Such a collar has, we believe, allowed striking improvement in a number of our severely disabled cases, and should be used more often. It should be used reasonably early. Good results cannot be expected where symptoms have been present for over a year. It is impracticable where the patient is bedfast. In one or two cases where an otherwise disabled patient has been able to sit up, the Zimmer type of traction has been a useful temporary expedient. Otherwise we have not found traction helpful.

While cases of prolapsed nucleus pulposus require prompt operation and should be recognized, satisfactory recovery from severe neurological disability in myelopathy from cervical spondylosis can occur with a conservative regime. The principle of rest is easier to understand and apply than operative measures. It also has obvious advantages where the diagnosis may remain in doubt.

Summary

The differential diagnosis, treatment, and prognosis of 60 cases with cervical disk lesions followed up for periods of two to ten years are reviewed.

The importance of differentiating the various types of disk lesion and concomitant spinal cord and other disorders is stressed, as is the necessity of a long follow-up.

Improved results in cases of cervical spondylosis with myelopathy have been associated with a conservative regime, and in particular the use of a light Minerva collar.

We thank Mr. G. L. Alexander and Mr. A. Hulme, who have kindly allowed cases under their care to be included in this survey; and Dr. H. L. Hoffman, who has been associated with the treatment of some of these cases.

REFERENCES

- Allen, K. L. (1952). *J. Neurol. Neurosurg. Psychiat.*, **15**, 20.
 Bradshaw, P. (1957). *Quart. J. Med.*, **26**, 177.
 Brain, W. R. (1948). *Proc. roy. Soc. Med.*, **41**, 509.
 — Northfield, D., and Wilkinson, M. (1952). *Brain*, **75**, 187.
 — and Wilkinson, M. (1957). *Ibid.*, **80**, 456.
 — (1958). *Ibid.*, **81**, 275.
 Clarke, E. (1958). *Brit. med. J.*, **1**, 1282.
 — and Robinson, P. K. (1956). *Brain*, **79**, 483.
 Cloward, R. B. (1958). *J. Neurosurg.*, **15**, 602.
 Frykholm, R. (1951). *Acta Chir. Scand.*, Suppl. 160.
 Jefferson, M. (1951). *Lancet*, **1**, 129.
Lancet, 1958, **1**, 216.
 Mayfield, F. H. (1955). *Clin. Neurosurg.*, **2**, 83.
 Miller, H. (1956). *Proc. roy. Soc. Med.*, **49**, 200.
 Northfield, D. W. C. (1955). *Brit. med. J.*, **2**, 1474.
 O'Connell, J. E. A. (1955). *Brit. J. Surg.*, **43**, 225.
 — (1956). *Proc. roy. Soc. Med.*, **49**, 202.
 Odom, G. L., Finney, W., and Woodhall, B. (1958). *J. Amer. med. Ass.*, **166**, 23.
 Pallis, C., Jones, A. M., and Spillane, J. D. (1954). *Brain*, **77**, 274.
 Russell, W. R. (1956). *Proc. roy. Soc. Med.*, **49**, 198.
 Scoville, W. B. (1954). *Conn. med. J.*, **18**, 894.
 — (1958). *J. Neurosurg.*, **15**, 615.

GENETIC CONTROL OF ISONIAZID METABOLISM IN MAN

BY

DAVID A. PRICE EVANS,* M.D., M.Sc., M.R.C.P.

KEITH A. MANLEY, M.B., M.R.C.P.

AND

VICTOR A. McKUSICK, M.D.

*Division of Medical Genetics of the Department of Medicine,
Johns Hopkins University School of Medicine, Baltimore,
Md., U.S.A.*

Isoniazid (l-isonicotinyl hydrazide) was first synthesized by Meyer and Mally in 1912, but its chemotherapeutic value was not discovered until forty years later. Grunberg and Schnitzer (1952) and Grunberg *et al.* (1952) showed that the compound was bacteriostatic against *Mycobacterium tuberculosis* strain H37Rv *in vitro*, and that it protected mice from developing tuberculosis when they were injected with tubercle bacilli intravenously. Robitzek *et al.* (1952) and Selikoff and Robitzek (1952) showed that the compound was effective in the treatment of human tuberculosis.

A considerable amount of work has been done on the metabolism of isoniazid both in animals and in man. These studies have shown that there is rapid and complete absorption of the drug, giving an initial high blood-level. When this falls the greater part of the compound appears in the urine within 24 hours of oral administration (Elmendorf *et al.*, 1952; Barclay *et al.*, 1953).

A large variation in the metabolism of isoniazid was found to exist among human beings by Bönicke and Reif (1953), Hughes (1953), Hughes *et al.* (1954, 1955). Distribution histograms of the percentage of the administered isoniazid which is excreted in the free form in the urine were given by Biehl (1956, 1957). These were bimodal, suggesting that individuals belong to one of two classes—either rapid or slow inactivators.

Mitchell *et al.* (1958) thought that this polymorphism for isoniazid metabolism in man might be genetically determined, and support for this view was afforded by the finding that groups of Japanese subjects contain a much larger proportion of rapid inactivators than groups of Caucasian subjects (Harris *et al.*, 1958).

To test the genetic hypothesis a study of 20 families was carried out by means of a microbiological method by Knight *et al.* (1959) and reported while the present study was in progress. They showed that it was probable that "slow inactivators" of isoniazid (who have high blood-levels of the free compound and excrete a high proportion of the free drug in the urine) were recessive to the "rapid inactivators," and, moreover, that the genes concerned were autosomal (see Table I).

The primary purpose of this paper is to report the results in a larger series of families (53) than that of

*Now in the Department of Medicine, University of Liverpool.