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POISONING BY METHYL MERCURY COMPOUNDS[1]

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With Plates 10 to 15

ORGANIC compounds of mercury were first used in chemical research in 1863, in therapeutics in 1887, and in the manufacture of seed dressings in 1914. Those with hydrocarbon groups of low molecular weight have been found the most toxic, and the only cases of poisoning recorded in man have been due to methyl derivatives.

Frankland and Duppa (1863) used di-methyl mercury in the course of some research work undertaken at St. Bartholomew's Hospital to determine the valency of metals and metallic compounds, and two laboratory technicians engaged in this work developed symptoms of poisoning and died (Edwards, 1865, 1866). One of them was a German aged 30 years, who had been exposed to di-methyl mercury for three months. He complained of numbness of the hands, deafness, poor vision, and sore gums. He was found to be slow and dull in manner, unsteady in gait, and unable to stand without support. There was no motor palsy, and the fundi were normal. Within a week he became rapidly worse, restless, unable to answer questions, incontinent of urine, and comatose. He died two weeks after the onset of his symptoms.

A second technician, aged 23 years, had worked in the laboratory for twelve months and had handled di-methyl mercury three months previously for a period of two weeks only. A month after this exposure he complained of sore gums, salivation, numbness of the feet, hands, and tongue, deafness, and dimness of vision. He answered questions only very slowly and with indistinct speech. There was ataxia, but no weakness of the upper limbs. Three weeks later he had difficulty in swallowing, was unable to speak, had incontinence of urine and faeces, and was often restless and violent. He remained in a confused state, and died of pneumonia twelve months after the onset of his symptoms. A third technician was affected with symptoms similar in character to those already described, but less severe in degree, and he eventually recovered. The story of these deaths has been handed down verbally from one generation of chemists to another.

In 1887 Hepp used hypodermic injections of di-ethyl mercury in the

treatment of syphilis.   He gave doses ranging from 0·1 to 1·0 c.c. of a 1 per
cent. solution of this substance.   No patient received more than two injec-
tions, for in the meantime animal experiments had been carried out which
suggested that the substance was highly toxic.   The picture of di-ethyl
mercury poisoning in animals was found to differ from that of poisoning by
inorganic mercury compounds.   There was only moderate inflammation of
the intestinal tract, but the nervous system was constantly involved.   An
ascending paralysis was combined in some animals with ataxia.   Inco-
ordination of movement was noticed especially in rabbits, and motor
paralysis in dogs and cats.   Tremor, blindness, loss of sense of smell, transient
deafness, and attacks of wrath on the slightest provocation were also
noticed in many of the dogs.

Mercury compounds used as seed dressings.   Seed-borne diseases of cereals
were first treated by organic compounds of mercury by Riehm in 1914.
To-day their use in the prevention of such diseases as bunt of wheat (*Tilletia
tritici*) (Plate 10, Fig. 6), covered smut of barley (*Ustilago hordei*), leaf stripe
of oats (*Helminthosporium avenae*), and leaf stripe of barley (*Helminthosporium
gramineum*) is a well-established principle of plant hygiene (Martin, 1936).
The first of these seed disinfectants to be successful was Uspulun, placed on
the market in 1915 by Messrs. Bayer.   It was probably of the structure
$Cl(OH)C_6H_3.Hg.OSO_3Na$.   Germesan introduced about 1920 by the Saccharin
Fabrik A.-G. contained cresyl mercury cyanide (HO) (CH_3) $C_6H_3.Hg.CN$.
Ceresan introduced by the I.G. Farbenindustrie A.-G. was reported to
contain as the active ingredient phenyl mercury acetate, $C_6H_5.Hg.O.CO.CH_3$
(Plate 11, Fig. 7).   Agrosan–G, introduced by Imperial Chemical Industries,
Ltd., contained mercury in the form of tolyl mercury acetate, $CH_3.C_6H_4.$
$Hg.O.CO.CH_3$.   Of the recently introduced products one contains ethyl
mercury chloride, $C_2H_5Hg.Cl$, and another ethyl mercury phosphate,
$C_2H_5.Hg.H_2PO_4$.

The relationship between the molecular structure and the fungicidal
activity of organic compounds of mercury has also been investigated.   Riehm
(1923) determined the minimum concentration of different compounds neces-
sary to inhibit germination of bunt spores under standard conditions.
Gassner and Esdorn (1923) used a similar method and were able to
demonstrate the importance of molecular structure in determining the
fungicidal properties of these compounds.   Thus, inhibition of germination
under standard conditions was produced by different compounds in the
following proportion : mercuric chloride 0·025, chlor-phenol mercury 0·07,
and methyl mercury iodide 0·001.   Methyl mercury iodide, $CH_3.Hg.I$, was
thus the most active of the compounds tested, but was discarded by these
authors on the score of its highly poisonous character.   Weston and Booer
(1935), employing tolyl, ethyl, phenyl, and methyl mercury compounds
against a large number of seed-borne diseases of cereals, confirmed the view
that the fungicidal properties decrease with increase of the molecular weight
of the hydrocarbon group.

The manufacture of phenyl and tolyl mercury compounds in large quantities by Imperial Chemical Industries, Ltd. in this country and I.G. Farbenindustrie A.-G. in Germany has been carried on by automatic methods in completely enclosed apparatus. The products are used mainly in the form of dusts, though sometimes they are employed in solution. So far as is known, no mishap worse than an occasional burn on the skin has occurred in handling them. If an organic mercury compound comes in contact with the skin, warmth and redness occur after about six hours, and blistering after eighteen to twenty-four hours. The blister contains serous fluid, and the lesion remaining after it bursts may take three weeks to heal.

The purpose of this communication is to record four cases of poisoning by inhalation of methyl mercury compounds in a factory where fungicidal dusts were manufactured without the use of completely enclosed apparatus. The cases are unique because they occurred in the only factory where this substance has ever been made, and for obvious reasons it should not be made again in similar circumstances. With the exception of tremor, the symptoms of poisoning by metallic mercury, namely, salivation, stomatitis, and erethism, were absent, and the nervous system alone was involved. There was severe generalized ataxia, dysarthria, and gross constriction of the visual fields, memory and intelligence being unaffected. The illness of these men was in some ways comparable to that of the two technicians who died at St. Bartholomew's Hospital. The selective effect on certain parts of the nervous system of the chemical substances responsible was confirmed by experiments on rats and a monkey. In these animals methyl mercury compounds caused an intense and widespread degeneration of certain sensory paths of the nervous system, the peripheral nerves and posterior spinal roots being affected first, and the spinal cord and certain neurones in the middle lobe of the cerebellum later.

Technique of manufacture of seed dressings. In the factory where our patients worked the manufacture of methyl mercury nitrate seed dressing was carried out in two stages. The first step was the preparation of methyl iodide from methyl alcohol, phosphorus, and iodine. This was then allowed to react with mercury under the influence of the light from electric lamps, and methyl mercury iodide was formed. Flasks containing this substance as a solid were tapped on rubber sheets until the contents were loose and broken up. This work was done in a room about sixteen feet square, with four skylights, two windows, and a large double door, all of which were kept open.

In the second stage the dry methyl mercury iodide was mixed intimately with mercuric nitrate solution in a power-driven pestle-and-mortar mill. By double decomposition methyl mercury nitrate and mercuric iodide were formed. The latter, being insoluble, was separated by filtration, and an almost saturated solution of methyl mercury nitrate was obtained. The solution of this substance was diluted and mixed with an inert powder in a mechanical mixer. The mixture was damp and there was therefore no escape of dust. The damp dust was transferred to a drying chamber, and

when dry it was ground in a mill and was then ready for packing. This work was done by men wearing dust masks, goggles, and elbow gloves, working in a room about 40 feet square in which good ventilation was ensured through windows, skylights, and gaps in the walls.

Prevention of poisoning. Of twelve men who were exposed to methyl mercury compounds under the conditions described, but did not develop any symptoms, eight excreted mercury in the urine and four did not. The spectrophotometric test used was sensitive to 0·001 mg. of mercury per litre, so that the quantities of mercury excreted in the urine were probably very small. The fact that eight men, exposed in a similar way to the four patients, excreted mercury in the urine, yet showed no symptoms or signs of disease, suggests that most of the workers absorbed mercury compounds, but that only four of the sixteen were susceptible to them.

In the manufacture of organic mercury compounds adequate precautions must be taken to ensure that dusts and vapours do not come in contact with the skin and are not inhaled. The use of gloves and respirators is inadequate as a means of protection; the whole process of manufacture, including the final packing of the dust, should be carried out mechanically in enclosed apparatus. Compared to the factory worker the farmer runs little risk. He should, however, be protected both by warnings that mercurial dressings are poisonous, and by schemes whereby he can obtain from the seed merchant seed already dressed. The seed merchant should dress the seed in completely closed apparatus (Plate 12, Fig. 10).

Case Reports

Case 1. E. L., a man of 33 years (L. H. Reg. No. 30240/1937).

Clinical history. The patient was a labourer in a chemical factory, and he was first employed in making seed dressings five months before admission. The work involved the handling of mercury, methyl iodide, and methyl mercury iodide. A month later he developed thirst, polyuria, and intermittent glycosuria, which lasted three weeks. Investigation showed a normal response to a glucose tolerance test. After about three months of the work he complained that his whole body was going numb and tingling. He began to notice weakness of his arms and legs, and unsteadiness in his gait. His condition became worse, and after four months' employment he was put on night work at his own request, so that he no longer handled organic mercury compounds. He became clumsy, dropped trays, began to stagger about, and collapsed on the floor on several occasions. His speech became difficult and slurred, and it was noticed that he sometimes could not see objects held in front of his face.

Previous history. Served in the army in England and in India from 1922 to 1929. Attending a clinic with gonorrhoea.

Family history. Father died in diabetic coma. Mother and nine siblings alive and well.

Condition on admission. Thin, worried man of hysterical temperament. Afebrile. Slight exophthalmos. No abnormality in respiratory, cardiovascular, or gastro-intestinal systems. Nervous system : lies in bed, apathetic and dazed; speech indistinct and explosive in character; he hears a watch

normally, but he cannot quickly comprehend the meaning of spoken speech ; cranial nerves, no abnormality detected ; fundi normal ; fields of vision not tested. Gross inco-ordination of upper and lower limbs. Tendon reflexes equal and exaggerated ; plantar responses flexor. Clumsy movements and ataxic gait. Sensation to pin-prick and light touch unimpaired.

Special examinations. Blood count : red cells 4,500,000 per c.mm., haemoglobin 87 per cent. (Haldane), colour index 0·96, white cells 8,400 per c.mm., differential count normal. Blood Wassermann reaction negative.
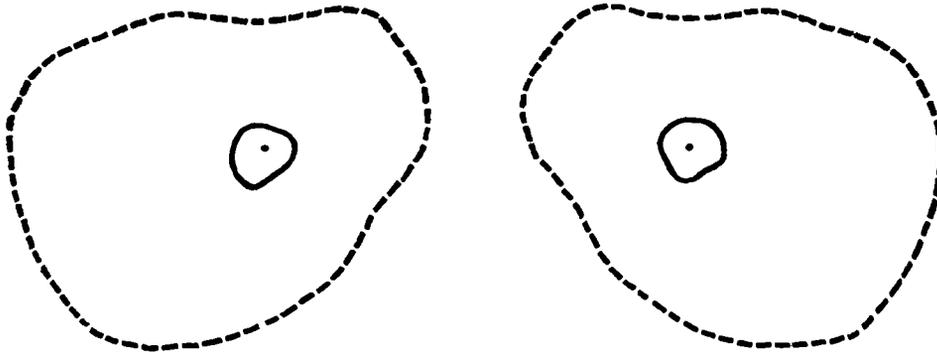
OBJECT, 4° WHITE

FIG. 1. The visual fields of Case 1.

Lumbar puncture : fluid clear and colourless ; no excess of white cells ; protein 50 mg. per 100 c.c. ; Wassermann reaction negative. Urine : no albumin, no sugar, spectrophotometric test for mercury negative.

The condition was thought to be hysterical until the other cases occurred and were found to be comparable. He discharged himself after five weeks in hospital.

Condition five months after onset of symptoms. The patient stated that his condition was improving. His chief symptoms were a need to listen carefully to speech in order to understand its meaning, difficulty in performing co-ordinated movements with hands, unsteady gait, and difficulty in speaking. He could feed and dress himself, but only slowly and clumsily.

Physical examination (Dr. Swithin Meadows) : Normally orientated in space and time ; no gross memory defect ; attentive and co-operative. Can understand slowly but not quickly spoken speech, whether this is loud or soft. Fundi normal. Visual acuity ; right eye 6/6, left eye 6/12. Visual fields : gross peripheral constriction (Fig. 1). Loss of sense of position in nose and lips. Other cranial nerves normal. Upper limbs : no definite weakness, wasting, or alteration in tone. Considerable ataxia, especially with eyes closed. Lower limbs : power good, but impaired if he does not watch his feet. Tone normal. Moderate ataxia, worse with eyes closed. Reflexes all brisk and equal. Plantar responses flexor. Sensation : postural sense grossly impaired in all fingers and toes ; stereognosis, vibration sense and two-point discrimination impaired in fingers ; appreciation of pin-prick and light touch normal. Gait slow with short mincing steps ; it resembles a hysterical gait, but it is definitely ataxic.

Progress. Three years after the onset of symptoms there was little change in the physical signs. Visual fields constricted. Fundi normal. He was able to do light unskilled work.

Case 2. A. H., a boy of 16 years (L. H. Reg. No. 30569/1937).

Clinical history. Four months before admission the patient left a technical school with distinctions to his credit. He had been described as 'a boy of more than average ability'. From this time onwards he was employed as a technical assistant in a laboratory attached to a plant for the manufacture of mercury compounds, including seed dressings. His work involved the handling of methyl iodide and of certain volatile organic mercury compounds, including methyl mercury iodide, nitrate, and phosphate, as well as of ordinary laboratory reagents. No special ventilation was provided, but he wore a mask and gloves while at work, and five weeks before admission towards the end of the third month of his work in the laboratory he first noticed 'funny numbness' starting in the tips of his fingers and toes, and spreading to his hands and feet. This feeling increased, and he began to have difficulty in performing such complicated movements as buttoning and unbuttoning his clothes. Three weeks before admission a change was noticed in his usually amiable and courteous disposition. He appeared irritable and began to use abusive language in his home. Two weeks before admission his speech became slow and difficult, and he noticed difficulty in understanding what was said to him, though his perception of sound remained unaltered. At the same time he noticed that although he could see clearly he would fail to observe certain objects in his field of vision, especially moving ones, and was therefore nearly run over by approaching motor-cars. He could see lettering clearly, but his speed of reading was much reduced. Two days later he began to be unsteady on his legs, and was seen to stagger as he walked. He was also becoming increasingly irritable and morose. Four days before admission be became obviously clumsy and had difficulty in handling a knife and fork, and in inserting food into his mouth, though his appetite remained normal. Two days before admission his determination in spite of increasing disabilities to remain at work was frustrated by his mother, who hid his trousers.

Previous history. Chicken-pox, measles, scarlet fever, and tonsillitis as a child; no other illnesses.

Family history. Father and mother and one sibling alive and well. A maternal aunt had died of amyotrophic lateral sclerosis.

Condition on admission. A boy of spare build but healthy appearance. Weight 9 st. 2 lb. Afebrile. No abnormality discovered in the respiratory, cardiovascular, or gastro-intestinal systems. Nervous system (Dr. Swithin Meadows): He sleeps a great part of the day, lying curled up on his right side. When roused he appears to take less than a normal amount of interest in his surroundings, but when allowance has been made for his difficulties in speech and hearing it appears that his memory and intellectual faculties are unimpaired. Orientation normal. No hallucinations or delusions. Speech dysarthric, slow, and slurred. Hearing: able to hear quite well even a low voice if spoken to slowly. He cannot understand quick speech however loud. Aural report by Mr. Charles Keogh : 'Air conduction, allowing for delay in reception, is within normal limits. Bone conduction is diminished. This phenomenon is due to slow cerebration.' Vision: can read small print. Gross peripheral constriction of visual fields (Fig. 2). Cranial nerves: fundi, pupils, and ocular movements normal; slight lower right facial weakness; loss of sense of position in tongue, nose, and lips; cranial nerves otherwise normal. Upper limbs: no definite weakness, wasting, or alteration in tone; marked inco-ordination, especially for fine movements; takes two minutes to fasten four buttons; outstretched hands wander if eyes closed, and left hand

tends to drop; finger–nose test very clumsily performed; rapidly alternating movements poorly performed. Trunk: able to sit up without using arms. Lower limbs: power fairly good; moderate pyramidal spasticity; marked inco-ordination; reflexes all present and equal; knee- and ankle-jerks exaggerated; plantar responses, right flexor, left extensor. Sensation: gross postural loss in fingers, toes, and face; two-point discrimination grossly impaired at finger-tips; astereognosis so severe in hands that he cannot tell
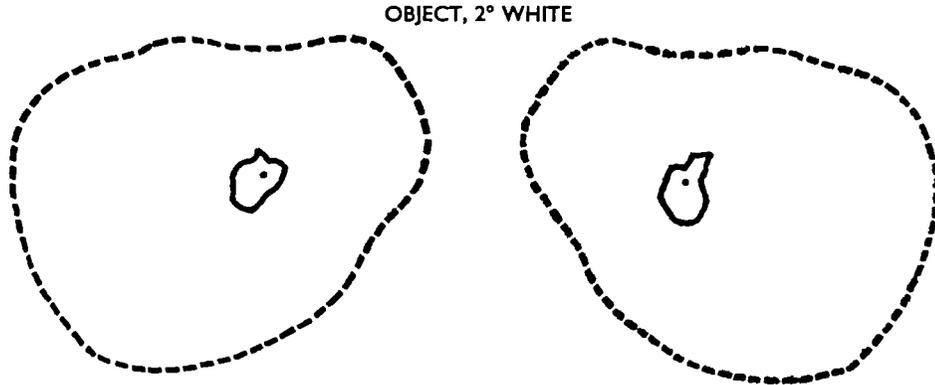
OBJECT, 2° WHITE

FIG. 2. The visual fields of Case 2.

with his eyes shut the difference between a coin and a bunch of keys; vibration and other forms of sensation normal. Gait very ataxic, walks on wide base, Romberg's sign positive.

Special examinations. Blood count: red cells 5,300,000 per c.mm., haemoglobin 95 per cent. (Haldane), colour index 0·89, white cells 5,000 per c.mm., differential count normal, reticulocytes less than 2 per cent., no abnormality seen in stained film. Blood Wassermann reaction negative. Lumbar puncture: pressure 90 mm. of C.S.F.; Queckenstedt's test normal; fluid clear and colourless; no excess of white cells; protein, 40 mg. per 100 c.c.; Wassermann reaction negative; colloidal gold curve 0 0 1 2 2 2 2 1 0 0. Blood-urea 28 mg. per 100 c.c. Urine: no albumin or sugar, occasional leucocytes in deposit; mercury detected by spectrophotometric test.

Progress. After admission the patient's condition became slowly and steadily worse. He slept for increasing periods, and his speech, hearing, and general condition all deteriorated. Eight weeks after the onset of his symptoms his condition was at its worst. He lay curled up on his side, completely helpless and apathetic. His ataxia was so severe that he could not perform even the simplest movements for himself. Saliva dribbled from his mouth, and he choked and spluttered when fed. He scarcely attempted to speak, and when he did so produced explosive vowel sounds whose meaning could rarely be recognized. He could understand only the simplest statements spoken very slowly. He was severely constipated, but was never incontinent at any time. He became emaciated. Nine weeks after the onset of symptoms signs of slight improvement were noticed, and he began to take more interest in his surroundings. At the same time it became easier to feed him, and he was first made to walk up and down the ward with support on each side. He responded so much better to written than to spoken questions and requests that this method was used for communication. Thirteen weeks after the onset of symptoms he began to have massage and re-educative movements (Sir Robert Stanton Woods). By this time he could just hold a tumbler and

put it to his mouth almost unaided, though ataxia was still very obvious. His condition was thus very slowly improving. Seventeen weeks after the onset of symptoms he could still produce no articulate sounds, but he began to attempt to do so. He learned to communicate by spelling out words and sentences on a printed alphabet which he carried with him. His walking was improving, but his gait was still ataxic and 'slapping'. Two weeks later he began to perform simple movements for himself, and for the first time walked a few paces unaided. After sixteen weeks he first began to produce vowel sounds, and was treated in a speech clinic (Miss Muriel Murphy). After much patient practice in front of a mirror, the explosive consonants were gradually mastered. The lips, the tongue, and later the soft palate responded to voluntary effort, and occasionally the alveolar consonants were successfully pronounced. From then onwards his speech slowly but steadily improved. Six months after admission he could walk unaided on the level. A month later he began to use a typewriter, chiefly with his left hand, and at first slowly and laboriously. For another month he made no attempt to speak spontaneously. His general condition throughout this time continued to improve; he became better nourished, more responsive, interested in his appearance, and gradually able to do more for himself. Eight months after the onset of symptoms he walked fifty times round the hospital garden unaided, a distance of about four miles. As communication became easier it was apparent that his memory and intelligence had been little, if at all, affected, and that he had a ready sense of humour and considerable personal charm. He was keenly interested in everything around him, able to remember all that had happened, and to discuss accurately and intelligibly technical problems connected with his occupation before he was ill. From his own accounts it was apparent that even at his worst his memory and intellectual functions were little clouded, though he was quite unable to express himself. From then onwards improvement was maintained. After nine months it was possible to understand about half what he said, and he gradually gave up the use of his alphabet. Two years after the onset of symptoms he was able to walk up and down stairs quite unaided and could dress and feed himself, but in all these movements his ataxia was still very evident. A fine uniform tremor had developed in the upper limbs, head, and neck. His speech remained hesitating and explosive, but was quite readily understood. Hearing was practically normal. He could hold a pencil and a pen, write a letter in scrawling and unsteady letters, and his writing was still improving (Plate 11, Fig. 8). To those who had watched him throughout his illness it seemed likely that his actual neurological condition had improved little, if at all. His visual fields were practically unaltered since they were first charted. His ataxia was still gross, and his left plantar response was still extensor. Astereognosis was well marked, and his attempts to recognize with his eyes shut objects placed in his hand were still exceedingly poor. The optic disks remained normal. The striking improvement in the condition must be attributed to re-education, and the degree to which this was successful is a tribute to the determination of the patient and to the skill and patience of members of the nursing staff, the massage staff, and the speech clinic, who were all concerned in treating him.

Case 3.   E. C.-L., a man of 33 years (L. H. Reg. No. 30668/1937).

Clinical history.   Five months before admission the patient started work in a chemical factory in a department for the manufacture of seed dressings. His job was to pour a solution of 2 pounds of methyl mercury nitrate from

a jug into 28 pounds of an inert powder in a mixer. He then dried the wet mixture in trays in an oven, and finally ground the resulting product to a powder, which was packed in boxes. He repeated this process about seven times each day. The work was dusty and he therefore wore gloves and a canister respirator. After two months' work he got two burns on the right forearm. They started as blisters, the larger about an inch in diameter, and took nine days to heal. Subsequently he ceased to handle organic mercury

OBJECT, ¼° WHITE
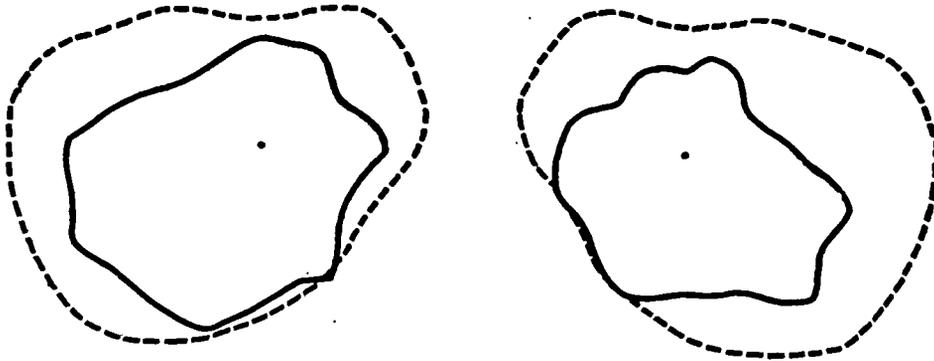
FIG. 3. The visual fields of Case 3.

compounds and worked a chlorinator in the manufacture of inorganic salts of mercury.

Three weeks before admission he noticed that he could not read as fast as usual, and a week later his fingers and then the whole of each hand tingled and became numb. One week before admission he began to have difficulty in understanding what was said to him unless it was spoken slowly and deliberately. He had trouble in fastening his collar-stud, and had to get his wife to do up the buttons of his shirt. He noticed difficulty in finding with his hand a sixpence in his pocket. His speech and hearing were normal.

Previous history. Tonsillitis as a child. Vision defective since schooldays. No other illnesses.

Family history. Mother died of cancer. Father and two siblings alive and well.

Condition on admission. Well-nourished, healthy-looking man. Weight 10 st. 11 lb. Afebrile. No abnormality discovered in the respiratory, cardiovascular, or gastro-intestinal systems. Nervous system (Dr. Swithin Meadows): No mental abnormality; speech rather slow; hearing normal; visual fields, slight concentric constriction (Fig. 3). Visual acuity: right eye 6/18, left eye 6/12. Fundi: disks normal, pigmented area below the right macula. Other cranial nerves normal. Upper limbs: no weakness, wasting, or alteration in tone; slight tremor and unsteadiness in finger–nose test, worse on right side; rather slow in fastening buttons; two-point discrimination impaired in finger-tips at 0·5 cm. and 1 cm.; no astereognosis. Lower limbs: no weakness or wasting; tendon reflexes normal; plantar responses flexor; two-point discrimination normal in soles; appreciation of pin-prick, cotton-wool touch, vibration, and posture all normal.

Special examinations. Blood count: red cells 4,300,000 per c.mm., haemoglobin 83 per cent. (Haldane), colour index 0·96, white cells 10,160 per c.mm., differential count normal. Blood Wassermann reaction

negative. Urine: no albumin, no sugar, spectrophotometric test for mercury positive.   .

Progress. Two years and six months after the onset of symptoms there was no change in the physical signs. The visual fields remained constricted and the fundi normal. He was working as an unskilled labourer.

Case 4.   S. R., a man of 23 years (L. H. Reg. No. 30735/1937).

Clinical history. For two years before admission the patient had been employed in a chemical factory, at first in connexion with the manufacture of inorganic mercury compounds. Six months before admission the gums were tender and the teeth loose, but there was no salivation. Thirty-one teeth were removed in four operations. Five months before admission he was employed for four months in the manufacture of seed dressings. This work involved exposure to dusts of methyl mercury phosphate and nitrate. He wore rubber gloves, but dust got inside them and he had numerous burns on his fingers. For four weeks before admission there had been no exposure to mercury compounds. Three weeks before admission he noticed a peculiarity in vision ; distant objects were blurred, and he experienced difficulty in seeing ' around corners '. There was no diplopia. At the same time there was a feeling of ' pins and needles ' and numbness in the tip of the tongue and in the finger-tips, the latter sensation spreading after a few days up his arms. Slight unsteadiness of gait was noticed. One week before admission the speech became ' thicker ' and slower, the movements more jerky, and the hands clumsy, causing difficulty in dressing. The vision became worse : ' I can see all right in front, but it 's at the sides I can't see.'

Previous history. Squint and stutter since childhood. Right peritonsillar abscess one year previously.

Family history. Father, aged 58 years, suffers from heart disease. Mother died of strangulated hernia. Five siblings alive and well.

Condition on admission. Tall fair lad ; edentulous. No abnormality in gastro-intestinal, respiratory, or cardiovascular systems. Nervous system (Dr. Swithin Meadows): Quiet ; memory fairly good ; no marked mental changes ; speech normal except for stutter since childhood. Cranial nerves : pupils and fundi normal; moderate bilateral ptosis; irregular fine nystagmus on deviation to right, left, and upwards ; concomitant convergent squint. Visual fields : concentric constriction which became rapidly worse as shown by perimetry tests taken four weeks (Fig. 4) and six weeks (Fig. 5) after the onset of symptoms. Visual acuity: right eye 6/6, left eye 6/12. No defect of hearing to rough tests ; can understand loud, quickly spoken speech. Other cranial nerves normal. Upper limbs : no wasting, weakness, or alteration in tone ; well-marked inco-ordination worse with eyes closed ; difficulty with fine and rapidly alternating movements ; outstretched hands tend to drop if eyes closed. Lower limbs : no wasting, weakness, or alteration in tone ; well-marked inco-ordination ; reflexes all present and equal; both plantar responses extensor. Postural sensibility grossly impaired in fingers, slightly impaired in toes, and absent in lips. Two-point discrimination impaired at finger-tips. Astereognosis in hands. Perception of vibration and other forms of sensation normal. Gait : well-marked ataxia, worse with eyes closed ; can just walk alone with eyes open ; Romberg's sign positive.

Special examinations. Blood count: red cells 5,200,000 per c.mm., haemoglobin 104 per cent. (Haldane), colour index 0·99, white cells 6,700 per c.mm., differential count normal, reticulocytes less than 2 per cent., no abnormality seen in stained film. Blood Wassermann reaction negative. Lumbar

puncture : no excess of white cells ; protein 55 mg. per 100 c.c. ; Wassermann reaction negative ; colloidal gold curve 0 0 1 1 2 2 2 1 1 0. Blood-urea varied from 34 to 64 mg. per 100 c.c. Urine: acid, cloud of albumin, slight reduction of Fehling's solution on cooling ; deposit, many epithelial cells, no casts ; spectrophotometric test for mercury positive.
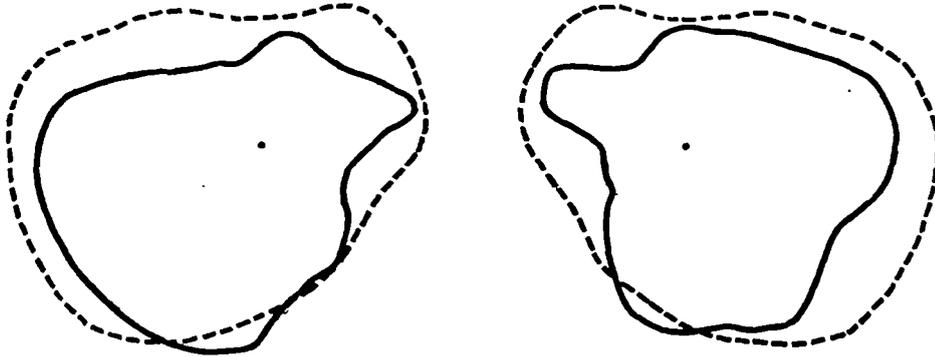
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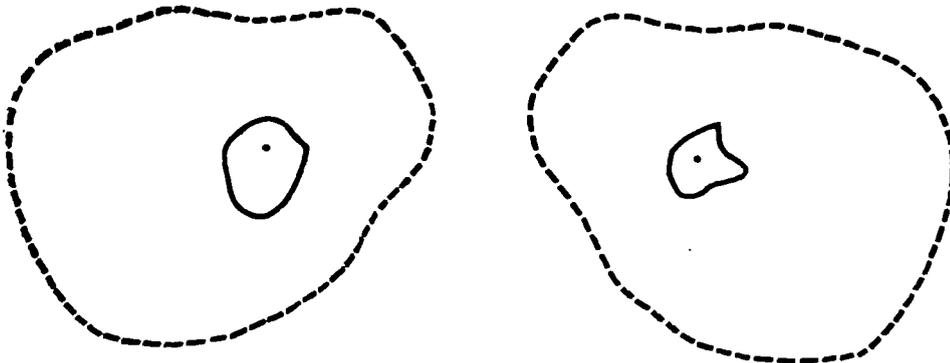

FIG. 4.   The visual fields of Case 4 on April 20, 1937.

OBJECT, 4° WHITE

FIG. 5.   The visual fields of Case 4 on May 3, 1937.

Progress. After admission the patient's condition became slowly and progressively worse. He became drowsy, unable to walk, unable to feed himself, and his speech became increasingly slow and hesitant. Five weeks after the onset of symptoms he was at his worst. He looked ashen and very ill, was drowsy and quite helpless, and unless disturbed remained completely apathetic. Food placed in his mouth would remain unswallowed, and his expression was that of a slobbering idiot. Speech was limited to two or three words and was almost unintelligible. From that time onwards there was a slight but very slow improvement. His general condition improved, he was less drowsy than before, and began to take a little interest in his surroundings. He began to make attempts to walk, supported by two assistants (Plate 12, Fig. 9). Eight weeks after the onset of symptoms he developed a left femoral thrombosis, which pursued an uneventful course. Six weeks later slight improvement in speech occurred ; he began to make some attempts to articulate, and was able to sit up in a chair. After this little change occurred. The patient was discharged after twelve months.

His general condition was good for one who had been in bed so long. He was, however, still grossly ataxic, quite helpless, and unable to stand unaided or walk without support from two assistants. He was quite unable to feed himself or to perform the simplest act unaided. His speech was limited to a few scarcely recognizable explosive sounds. His visual fields remained severely constricted, and his plantar reflexes extensor. Three years after the onset of symptoms he was still totally disabled.

ANIMAL EXPERIMENTS

(R.R.B. and D.S.R.)

Four experiments were undertaken to determine firstly whether symptoms similar to those observed in the four patients could be reproduced in animals by exposure to any of the suspected poisons; and secondly to provide material for pathological study.

Experiment I. Fourteen healthy, adult, albino or pied Norwegian rats (nos. 1 to 14) were used. Doses of 1·0 mg. of methyl mercury iodide, methyl mercury nitrate, or mercuric iodide were administered daily to each of a group of rats, and a further group was kept under similiar conditions as a control. The mercury compounds were given by stomach tube, 1 mg. of methyl mercury iodide being dissolved in 1 c.c. of olive oil, 1 mg. of methyl mercury nitrate in 1 c.c. of water, and 1 mg. of mercuric iodide in 1 c.c. of a weak aqueous solution of potassium iodide. On the nineteenth day the dose of each substance was increased to 2 mg. per diem. The rats were fed on a prepared rat food and given drinking water, both in unlimited quantities. Four rats (nos. 2, 3, 5, and 8) died shortly after the passage of the stomach tube during the first few days of the experiment. Their deaths were due to inexpert manipulation, and their tissues were used for histological comparison with those of other members of the series.

Three rats (nos. 1, 13, and 14) were given an average dose of 36 mg. of methyl mercury iodide dissolved in olive oil over an average period of twenty-nine days, and two (nos. 4 and 6) were given an average dose of 34 mg. of methyl mercury nitrate dissolved in water over a period of twenty-nine days. No abnormality was noticed for two weeks in the rats given methyl mercury nitrate and for three weeks in the rats given methyl mercury iodide. Thereafter the symptoms observed were similar in both groups; all the animals showed a rapid loss of weight. (Methyl mercury nitrate rats: average weight before experiment 280 gm., at conclusion of experiment 175 gm. Methyl mercury iodide rats: before experiment 366 gm., after 270 gm.)

In the fourth week all five rats became obviously ill; in each case the first abnormality noted was a clumsiness in the use of the hind legs, which appeared to be due partly to weakness and partly to ataxia. At the same time the animals' feet became redder and colder than those of the controls. As the condition progressed the hind legs were severely affected, so that the animals' hind quarters swayed from side to side when they moved. They

sat huddled up, with little interest in food or drink unless disturbed. When disturbed those worst affected moved with their front legs and dragged their hind ones. In some animals it was thought that the front legs were also slightly affected. All the rats became moribund within a week of showing symptoms, except rat no. 14 (methyl mercury iodide) which survived for eleven days.

The rats treated with mercuric iodide and the rats kept as normal controls all maintained their weight and showed no abnormality.

For the remaining experiments a wooden box fitted with a glass window was provided and was made as nearly as possible air-tight. An inlet and an outlet pipe were inserted. The outlet was connected to an electrically driven pump. The inlet was connected to a small glass chamber, in which there was placed about 10 gm. of crystalline methyl mercury iodide, so that air, laden with the vapour of methyl mercury iodide, could be drawn through the box. The exhaust from the pump was bubbled through two bottles of strong caustic soda, after which the smell of a methyl mercury compound could not be recognized.

Experiment II. In this experiment a cage of four rats (nos. 15 to 18) was placed in the box for periods of about eight hours a day, an average exposure of 156 hours being given in twenty-two days. The rats in this experiment were not weighed. From the beginning it was noticed that the rats usually kept to the end of the cage away from the inlet tube. They either slept or spent much of their time rubbing their noses and faces. Their eyes were reddened, and some had a crusted serous discharge about their nostrils. At times they appeared dazed; after the tenth day some of them had attacks of hiccup. On the fifteenth day of exposure they appeared irritable; when disturbed they would bite each other's tails and ears, and for the first time two of them bit the hand that fed them. On the nineteenth day one rat (no. 15) had become severely ataxic, so that it fell over when it shook itself. Within a few days the other three (nos. 16, 17, and 18) were similarly affected, and died or rapidly became moribund.

Experiment III. In this experiment ten rats (nos. 19 to 28) of average weight 270 gm. were exposed under similar conditions for shorter periods. Two rats (nos. 19 and 20) were removed on the eighth day, after thirty-seven hours' exposure, and remained apparently unaffected except for some loss of weight which was afterwards rapidly regained. On the fourteenth day, after sixty-four hours' exposure, rat no. 28 appeared slightly clumsy in the hind legs and was therefore not exposed again. The seven remaining rats were exposed for the last time on the sixteenth day (total exposure seventy-one hours). By the twenty-first day the average weight had fallen to 226 gm., and two of the rats (nos. 25 and 28) were unmistakably clumsy with their hind legs. One other rat (no. 22) became clumsy on the twenty-fifth day, nine days after the last exposure.

Of the original ten rats, therefore, three (Group A) were definitely affected, became grossly ataxic, particularly in the hind legs, and were at times

incontinent; of these three, one (no. 25) developed symptoms five days after the last exposure, showed symptoms for eleven days, and died on the thirty-second day; one (no. 28) developed symptoms on the fourteenth day, with no latent period after exposure, and was killed when found moribund on the thirty-sixth day; and one (no. 22) developed symptoms nine days after the last exposure, and was killed at the end of twelve weeks. By this time the general condition of this animal had improved and it was increasing in weight. Its gait, however, was jerky, and the hind legs were often dragged in walking. At times, notably about three weeks before death, it was unable to climb up on to its cage. Examination of the blood by Dr. A. M. Barrett a few days before death showed a normal picture according to the findings of Wintrobe, Shumacker, and Schmidt (1936). Four more rats (Group B) were thought to be slightly clumsy with their hind legs, but the condition did not progress after exposure ceased; these were killed six months later. The remaining three rats (Group C), apart from temporary loss of weight, appeared quite unaffected.

Experiment IV. A fully grown female monkey (*Macacus rhesus*), weighing 4 lb. 12 oz. at the end of the experiment, was exposed to methyl mercury iodide vapour in the same box used in the experiments on rats, and under similar conditions. On the first day the animal was placed in the box for one and a half hours without exposure to methyl mercury iodide vapour. She remained active and appeared in no way distressed. Thereafter she was exposed to the vapour for daily periods increasing from one to seven and a half hours until a total of seventy-one hours' exposure had been given in twenty-one days. During this time she became obviously thinner; towards the end of it she began to appear subdued and somewhat bedraggled. After sixty hours' exposure she sat in a more flexed position with fore as well as hind feet on the floor of the cage. At times she coughed, sneezed, and brought up small quantities of mucus, and her conjunctivae were reddened.

On the twenty-fourth day, three days after the last exposure, she was very quiet and sat holding the bars of the cage. When she was disturbed she appeared irritable, weak in the hind legs, and clumsy in her movements. Though usually extremely agile, she almost fell over when crossing her cage and had to clutch at its bars to save herself; she also knocked over her milk bowl.

On the twenty-fifth day her condition was worse, and the fore limbs were affected. She snatched her food clumsily, dropped it, and had difficulty in picking it out from the hay; she then sometimes attempted to pick it up with her mouth. Her eating had become untidy, and she ceased to stuff food into her cheeks, as was her usual custom.

On the twenty-sixth day, five days after the last exposure, she was miserable, weak, and severely ataxic. She was found prostrate on the bottom of her cage. On attempting to get up she fell over backwards. Efforts to feed her with milk from a pipette were unsuccessful, and she was therefore killed with chloroform.

Pathological Examination

Experiments I and II. The four rats (nos. 2, 3, 5, and 8) that were lost during the first few days of Experiment I from faulty manipulation of the stomach tube showed no histological abnormality of the nervous system. They will not be discussed further. The pathological changes observed in the remaining animals in Experiment I were indistinguishable from those found in Experiment II. They will therefore be described together.

Macroscopic examination. A variable degree of emaciation was present in seven of the nine rats. In five of these pinhead and linear haemorrhagic erosions were found in the squamous and glandular portions of the stomach. Severe cloudy swelling of the kidneys was observed in three. Chronic abscesses of the lung, of the kind prevalent in laboratory rats, were found in five animals. The other tissues appeared healthy.

When the examination of the internal organs was complete the brain and upper part of the spinal cord were exposed by removing the bone, and the muscle was cleared from the remainder of the vertebrae. The central nervous system was then fixed *in situ* in 4 per cent. saline formaldehyde. By this means the danger of trauma and consequent production of artifacts in the myelin sheaths of the nerve roots and spinal cord was minimized. The dissection was completed when the tissues had become hardened.

Microscopic examination. Coronal sections of the brain, transverse sections of the spinal ˙cord, and longitudinal sections of the optic and trigeminal nerves, a selection of the spinal nerve roots and peripheral nerves were examined both by the frozen-section technique and by different stains after embedding in paraffin. While the Marchi preparations of the spinal cord were embedded in celloidin in the usual way, corresponding preparations of nerve roots and peripheral nerves were teased in pure glycerine under a binocular dissecting microscope as recommended by Duncan (1930). This method was preferred on account of the minute size of some of the structures, for example the spinal nerve roots, and proved both satisfactory and simple.

The nervous system. In all animals there was a severe degeneration of Wallerian type in the peripheral nerves, the posterior spinal roots, and the trigeminal nerves. The peripheral nerves examined were the sciatic, femoral, and portions of the brachial plexus dissected from beneath the scapulae. In the earliest stage there was little Sudanophil material in the sheaths, but, as shown by Spielmeyer's method in frozen sections, there was great fragmentation of the myelin into ovoid masses and globules of varying size (Plate 12, Fig. 11). Teased Marchi preparations showed a corresponding early degeneration of the myelin sheaths. In a rat (no. 15, Expt. II) which had exhibited symptoms for two days before death there were abundant Sudanophil droplets in the sheaths. A comparison of the changes in the different specimens examined showed that the nerves of the hind limbs, the corresponding posterior spinal roots, and the trigeminal nerves were affected with somewhat greater severity than the nerves of the brachial plexus. At no stage

did the anterior spinal roots show any change beyond the rare finding of one or two degenerating fibres in a single preparation. The cell bodies of neurones in the posterior root and Gasserian ganglia occasionally showed slight eccentricity of the nucleus accompanied by chromatolysis. Pyknosis was rare. No definite changes were present in the brain and spinal cord, with the exception of rat no. 14 (Expt. I) where a positive Marchi reaction was obtained in the posterior columns of the cord. This rat developed symptoms eleven days before death, thus surviving for a longer period than the others of this group (see Expt. III). The cerebellum of this rat also showed an early stage of a degeneration which will be described under Expt. III.

In one rat only (no. 16, Expt. II) the optic nerve showed a diffuse degeneration of the myelin sheaths, and small collections of fat-granule cells amongst the fibres. There was no inflammatory exudate apart from these phagocytes. The optic nerves were normal in six other rats of this series; they were not examined in two.

Other organs. In all the animals in Expt. II the conjunctiva showed acute purulent inflammation and, in a lesser degree, there was an acute interstitial keratitis. In the kidneys great oedema was associated with severe dropsical and hyaline-droplet degeneration of the epithelium of the convoluted tubules. In places there was tubular necrosis, and the lumina were often blocked with cellular debris. There was a little fatty degeneration in a few groups of convoluted tubules. The presence of a good many karyokineses in the lining cells afforded evidence of epithelial regeneration. The spleen showed a conspicuous storage of iron pigment in the macrophages of the pulp, and a variable degree of acute inflammation.

Experiment III. In this experiment, in which the rats received a smaller dose by inhalation and survived for longer periods, the following additional features were observed:

(I) *Group A (exhibiting symptoms). Nervous system.* A positive Marchi reaction was obtained (Plate 13, Fig. 12) in the posterior column in all three rats, being conspicuous in rats nos. 25 and 28, which died eleven and twenty-two days respectively after the onset of symptoms, and slight in rat no. 22 which was killed after twelve weeks. It will be recalled that rat no. 14 of Expt. II showed a similar degeneration of the spinal cord. As shown in Plate 13, Fig. 12, the degeneration involved the dorsal two-thirds only of the posterior columns, the anterior third being occupied in the rat by the crossed pyramidal tracts. A more advanced stage of degeneration, demonstrable by the Weigert-Pal method, was present in rat no. 22 (Plate 13, Fig. 13), but in none of the rats that died at earlier stages. Plate 13, Fig. 13, also shows the severe wasting of the posterior roots.

In the brain-stem a degeneration of the descending or spinal root of the trigeminal nerve was present (Plate 14, Fig. 16). No evidence of degeneration was found in the ascending or mesencephalic root of the trigeminal nerve. In these rats and in rat no. 14 of Expt. I there was also a patchy degeneration in the granular layer of the middle lobe of the cerebellum. At

the earliest stage recognized (eleven days after the onset of symptoms) there was severe pyknosis and karyorrhexis of the cells in the affected areas. At twenty-three days (rat no. 28) there were, in addition, many small concentrically laminated haematoxyphil bodies amongst the degenerating cells (Plate 13, Fig. 14). These appeared to arise as minute spheres in the cytoplasm of degenerating cells, the larger forms being extracellular. In the early stages they gave negative reactions for iron, calcium, and amyloid material, and appeared to be of an albuminous nature. In a rat (no. 22) killed twelve weeks after the onset of symptoms the bodies were much larger and then gave a positive reaction with von Kossa's method for calcium (Plate 13, Fig. 15). They gave no reaction for iron. Their presence was not associated with any demonstrable change either in the neighbouring Purkinje cells or in the myelinated fibres of the adjacent white matter. An idea of the size and distribution of the foci is seen in Plate 14, Fig. 16.

No changes were found in the cerebral hemispheres or optic nerves in these rats.

Other organs. A later stage of nephritis was demonstrated in rats nos. 14 and 28 by the presence of rays of early fibrosis in the cortex in which were present numerous fibroblasts, plasma cells, and a few neutrophil leucocytes. The glomeruli and blood-vessels were unaltered. In rat no. 25 albuminous and slight fatty degeneration of the tubules only was present. In rat no. 22 the kidneys were normal.

(II) *Group B.* The four rats of this group, thought to be slightly affected at the end of the experiment, were killed after twelve weeks had elapsed. Two of them showed a very slight degeneration of the posterior columns in frozen sections stained with Sudan III and in paraffin sections stained with Loyez' haematoxylin. Other parts of the central nervous system appeared normal. The two remaining rats were unaffected.

Experiment IV (Monkey). Macroscopic examination. Apart from slight congestion and cloudy swelling of the kidneys, the organs appeared healthy to the naked eye. The brain and spinal cord were removed and fixed in 4 per cent. saline formaldehyde. Segments of the right vagus, left sciatic, right anterior tibial, right ulnar, right median, and right radial nerves were pinned, without stretching, on a cork float during fixation.

Microscopic examination. Marchi preparations of the peripheral nerves were made, as in the rats, by teasing in glycerine. All showed early focal degeneration of the myelin sheaths (Plate 14, Fig. 17). Black droplets the size of, or slightly larger than, red blood corpuscles appeared most frequently in the sheaths near the nodes of Ranvier. Ovoid or sausage-shaped masses were rarer. The order of severity of the degeneration was approximately (1) median, ulnar, and radial, (2) vagus and sciatic, (3) anterior tibial. Frozen sections stained with Sudan III showed no fatty droplets in the sciatic nerve and posterior spinal roots. In the posterior root ganglia and the Gasserian ganglion severe degeneration of the ganglion cells was accompanied

by considerable leucocytic infiltration both of the interstitial tissue and of cells in which karyorrhexis was taking place (Plate 14, Fig. 18). The capsular cells in these also showed proliferation and occasionally contained a little fat. The myelin sheaths in the trigeminal nerve were often broken up into droplets and sausage-shaped masses of variable size. In Spielmeyer preparations of a lumbar posterior root ganglion there was considerable fragmentation of the myelin sheaths within the ganglion, but little in the central and distal segments of the posterior root, and none in the attached anterior root.

No histological changes were present in the spinal cord. Sections through different parts of the cortex, basal ganglia, and brain-stem showed occasional foci in which the sheaths of perforating vessels were infiltrated with a few leucocytes, small lymphocytes, and monocytes (Plate 15, Fig. 19). There was no meningitis. In addition the grey matter of the cerebrum and brain-stem was very sparsely infiltrated with neutrophil leucocytes which tended to lie against the cell bodies of the neurones. Preparations to demonstrate microglia and oligodendroglia showed remarkable microglial activity both in the cerebral cortex and in the basal ganglia. The cells were for the most part greatly swollen and of bizarre form (Plate 15, Fig. 20). Many of them formed greatly elongated rod cells such as characterize general paralysis of the insane; such cells often lay in close apposition to the apical dendrite of the pyramidal cells. In other places they were wrapped about the bodies of degenerating neurones. The oligodendroglial cells with their processes appeared normal. Bielschowsky preparations showed many normal nerve-cells, interspersed amongst which were a considerable number which showed all stages of disintegration. Both the frontal and occipital cortex were affected with apparently equal severity. The cerebellar cortex was unaffected, but the nuclei in the roof of the fourth ventricle were very sparsely infiltrated with leucocytes.

Sections through the optic nerve and eyeball showed no histological changes in the nerve or retina. There was, however, severe degeneration of the myelin sheaths of the ciliary nerves in the sclerotic coat. There was leucocytic infiltration of the conjunctiva, the cornea being unaffected.

Other organs. Lungs: the walls of the bronchi and adjacent tissues were infiltrated with neutrophil leucocytes, but there was no definite consolidation. Both liver and myocardium showed focal fatty degeneration. In the kidneys the tubules had undergone albuminous, with a little fatty and hyaline-droplet, degeneration. There was much desquamation of cells, mixed with cellular and eosinophil debris, into the lumina. The glomeruli were normal save for albuminous degeneration of the epithelium of Bowman's capsule. A few leucocytes were sparsely scattered throughout the interstitial tissue of the cortex. There was acute inflammation of the pulp of the spleen. The mucosa of the stomach showed a focus of subacute inflammatory reaction without ulceration.

Discussion

The above experiments show that a sensory nervous disturbance of wide distribution was constantly induced by the exposure of animals to methyl mercury iodide and methyl mercury nitrate. The effects were the same whether the substance was given by ingestion or by inhalation ; symptoms were not observed until the animals had been exposed for a period of from two to three weeks. In rats nos. 22 and 25 (Expt. III) a short latent period was observed between the termination of exposure and the development of neurological symptoms ; a similar latent period occurred in the monkey before the onset of severe neurological symptoms. The symptoms, as in the human cases, appeared principally to consist of severe ataxia with loss of sense of position and of muscular co-ordination. The affection was far more severe and generalized in the monkey than in the rats, which is remarkable in view of the fact that the monkey received a much smaller dose in proportion to its size than the rats in Expt. III, only a few of which were affected. This suggests that the primates may be more susceptible than rats to the organic compounds of mercury.

The histological lesions produced were uniform throughout the rat experiments, consisting, in the early stages, of a severe Wallerian degeneration in the peripheral nerves, posterior spinal roots, and trigeminal nerve, followed later by degenerations in the posterior columns and the descending root of the trigeminal nerve. It is of interest that the mesencephalic root of the trigeminal was unaffected since this has been considered to carry the proprioceptive fibres to the muscles of mastication. An appreciable lag was observed before degeneration could be demonstrated in the spinal cord, the earliest examples being in two rats in which death had taken place eleven days after the onset of symptoms. This difference in reaction of the extramedullary and intramedullary segments of the nerves has been recognized by Richter (1935) who records that eighteen days after cross-section of a spinal root, he found lipoid stages of degeneration in the extramedullary segment, whereas only a Marchi-stage of the degeneration had been reached in the intramedullary course of the affected fibres.

The focal degeneration of the cells of the granular layer of the middle lobe of the cerebellum observed in the later stages of intoxication in the rats was the only parenchymatous change found in the brain in these animals. It was not correlated with any alteration in the spino-cerebellar tracts or in the neighbouring Purkinje cells. Since it is not a form of neurone degeneration recognized in human pathology, its significance is difficult to estimate.

In the monkey, on the other hand, the cerebellar cortex was unaffected, but the grey matter of other parts of the brain, notably the cerebrum, showed a diffuse encephalitis associated with the disintegration of many neurones and a degree of microglial activity comparable with that seen in severe general paresis in human subjects. It is remarkable that the oligodendroglial cells

in such areas were devoid of 'acute swelling', a change that is known to
accompany severe intoxication (Penfield and Cone, 1926).

The degeneration of the optic nerve found in one rat is of doubtful signifi-
cance in relation to the mercurial poisoning, in view of the normal appearance
of this nerve in the other rats and in the monkey. It is not known whether
peripheral vision was affected in these animals.

Of the other tissues examined the conjunctiva and cornea demonstrated
the irritating effects of volatile methyl mercury iodide, since the inflammation
was confined to those animals that had received the poison by inhalation. It
has long been recognized that inorganic mercury compounds cause a profound
degeneration of the kidneys, and the organic compounds clearly share in this
property. Acute stages of degeneration and, in a few rats, the early stages
of fibrosis were observed in these experiments. Acute inflammation of the
spleen and, in the rats, much siderosis were also constantly present. The
significance of this is obscure. In one rat, exhibiting a chronic stage of the
intoxication, an examination of the blood shortly before it was killed
revealed no abnormality.

The clinical course taken by these experimental animals offers so close a
parallel to that shown by the human subjects that the pathological basis of
the condition is probably common to both. The human symptomatology
suggests that a widespread peripheral neuritis was followed by a degeneration
of the posterior columns. The tabetic picture is complicated by a corre-
sponding sensory disturbance of the trigeminal nerve and a marked constric-
tion of the visual fields. While the trigeminal changes were demonstrated
experimentally to be due to an intense Wallerian degeneration of the fifth
nerves, the visual disturbance remains unexplained. The retina and optic
tracts appeared normal in the monkey and in all but one rat. In the monkey,
however, the cerebral cortex showed an encephalitis resembling that of
general paralysis of the insane. The absence of similar changes in the rats
indicates a difference in the susceptibility of the cortical neurones in different
species. Hence it may well be that in man the optic tracts are involved in
a manner that awaits demonstration. The presence of degeneration in the
granular layer of the middle lobe of the cerebellum in some rats suggests
that the ataxia observed in the human subjects may have been in part of
cerebellar though predominantly of posterior column origin.

Summary

1. Seed disinfectants containing organic mercury compounds are used to
prevent smut diseases of cereals. Some of these compounds are toxic
to man and animals, and it has been found that those with hydrocarbon
groups of low molecular weight are the more actively fungicidal and toxic.

2. Four cases of poisoning resulting from the inhalation of methyl mercury
compounds are recorded. With the exception of tremor, the symptoms
of poisoning by inorganic mercury were absent, and the nervous system

alone was affected. Severe generalized ataxia, dysarthria, and gross constriction of the visual fields were present in all the cases, and one or both plantar responses were extensor in type in two. Memory and intelligence were unaffected.

3. Experiments on a number of rats and a monkey showed that methyl mercury iodide and nitrate damage selectively certain parts of the nervous system. In the rats, on which multiple observations were possible, the peripheral nerves and posterior spinal roots were affected first, and the posterior columns and the granular layer of the middle lobe of the cerebellum later.

4. The correlation of the clinical picture observed in human cases with the pathological findings in experimental animals is discussed.

5. Measures necessary to prevent poisoning by organic mercury compounds in the manufacture and use of seed dressings are outlined.

It is a pleasure to acknowledge the kindness of the employers of our patients. They supplied us with detailed information and gave us free access to their works. We are grateful to Drs. George Riddoch, Russell Brain, Swithin Meadows, and Henry Wilson for their help and advice in handling the cases, and to Dr. Richard Asher for assistance with the animal experiments. For their help with chemical problems we are indebted to Messrs. J. R. Booer, G. Six, and R. T. Bowler. We gratefully acknowledge the kindness of Professor Harris in giving us accommodation for animal experiments in the Department of Physiology of the London Hospital Medical College.

For permission to use Figs. 6 and 7 we are indebted to Bayer Products, Ltd., and for Fig. 10 to E. R. and F. Turner, Ltd., Ipswich. We wish, however, to make it clear that neither of these firms was in any way concerned with the production or handling of the substances responsible for the poisoning described in this paper.

Dr. Dorothy S. Russell carried out the histological investigations whilst working for the Medical Research Council.

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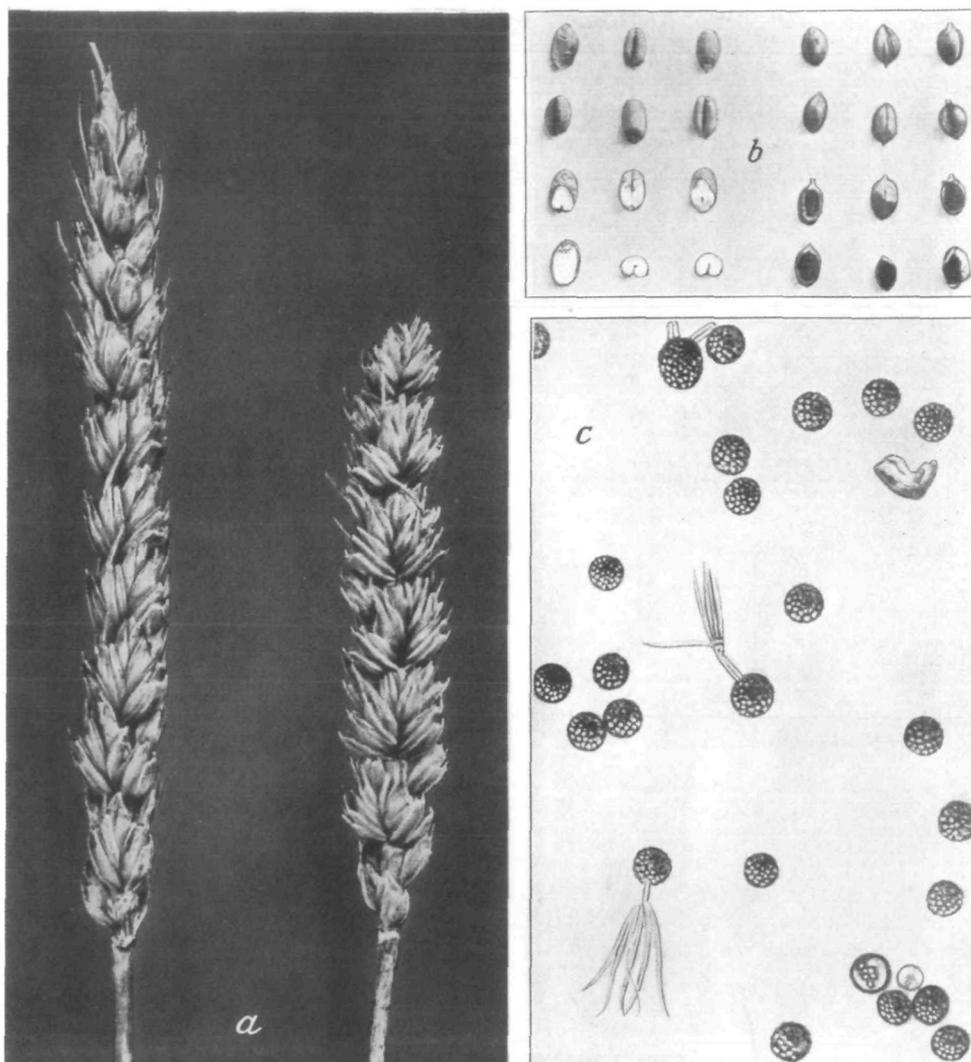Wintrobe, M. M., Shumacker, H. B., and Schmidt, W. J., *Amer. Journ. Physiol.*, Balt., 1935–36, cxiv. 502.

FIG. 6. Bunt of wheat (*Tilletia tritici*)

a. Healthy wheat ear on the left, bunted ear on the right. The chaffy scales are pushed apart, but otherwise the external appearance is little altered.

b. Clean grain on the left, bunted grain on the right. Each bunt ball is a black mass of 4 to 9 million spores.

c. Photomicrograph of germinating spores, each about 0·02 mm. in diameter.

FIG. 7. Effect of phenyl mercury acetate on oats affected by leaf stripe (*Helminthosporium avenae*). The treated seedlings are on the left, the untreated on the right.

FIG. 8. Handwriting in Case 2. *a.* Before illness began. *b.* Nine months after onset of first symptoms. *c.* Twelve months after. *d.* Eighteen months after. *e.* Two years after
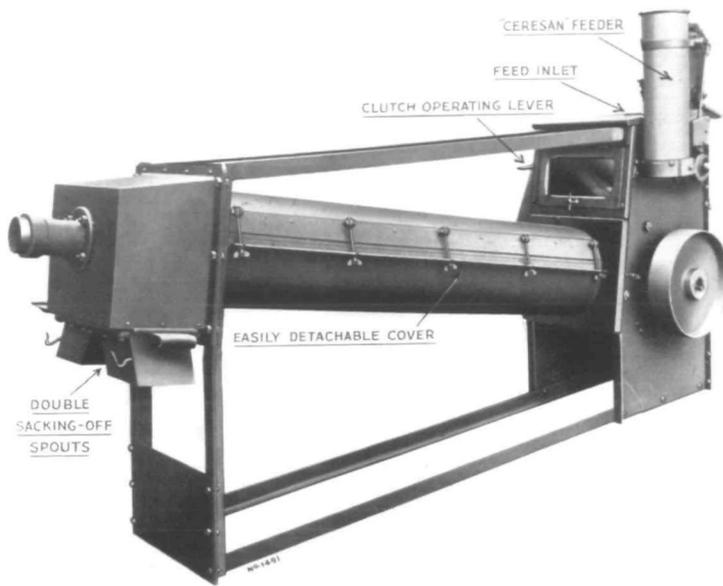
Fig. 10. The Turner Ceresan Seed Dresser

Fig. 9. Case 4
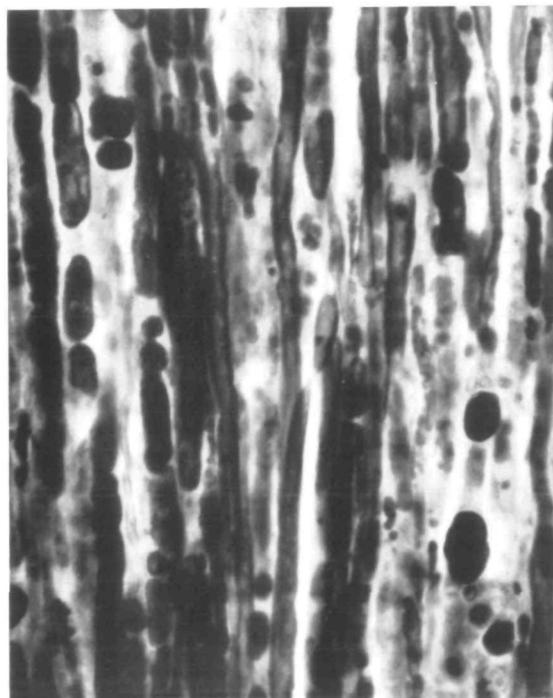
Fig. 11. Rat no. 17. Longitudinal section of posterior lumbar root showing fragmentation of myelin sheaths. Spielmeyer. × 470
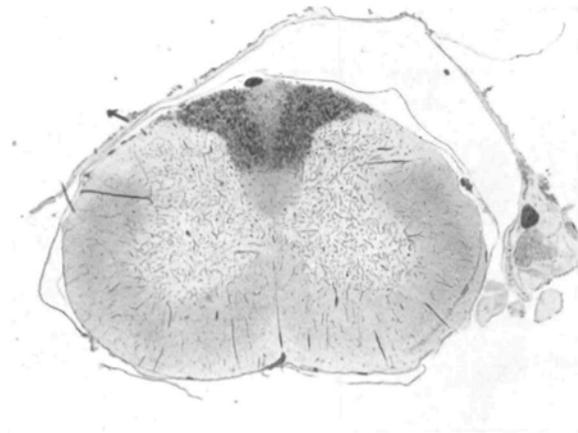
FIG. 12. Rat no. 25. Cervical cord showing early degeneration of posterior columns. Marchi. × 19

FIG. 14. Rat no. 28. Granular layer of cerebellum showing pyknosis of nuclei amongst which are numerous, more lightly stained, spherical bodies. Haematoxylin and eosin. × 500

FIG. 13. Rat no. 22. Cervical cord showing later stage of degeneration of posterior columns. Note wasting of posterior root. Weigert-Pal. × 12·5
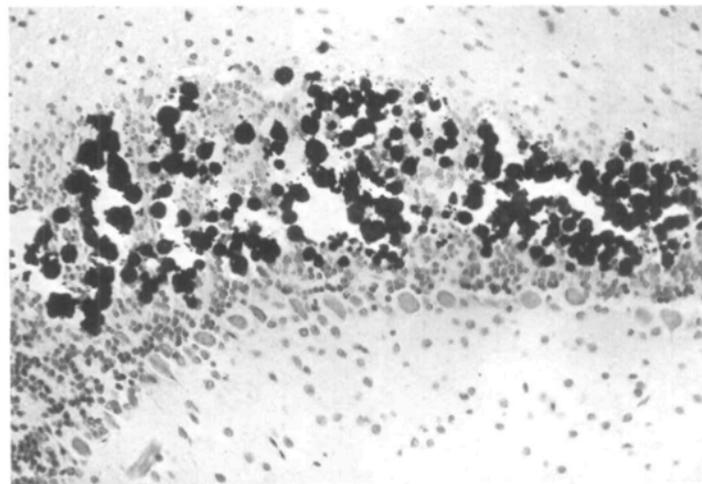
FIG. 15. Rat no. 22. Cerebellar cortex showing later stage of degeneration of granular layer now containing numerous calco-spherites (black). Von Kossa. × 160
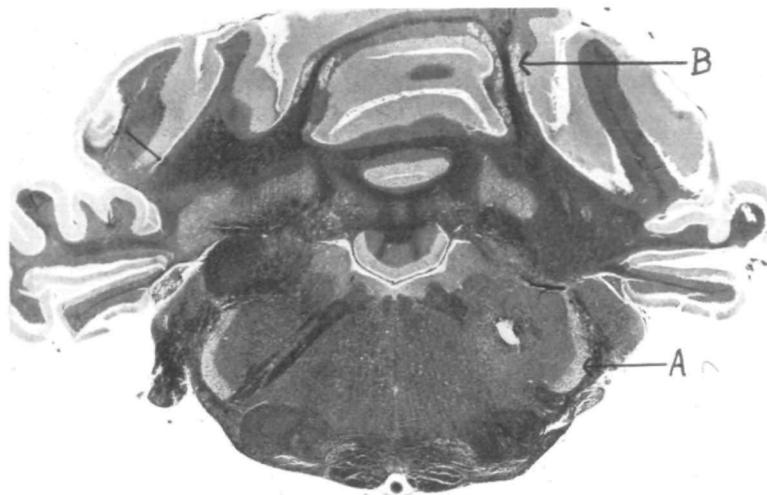
FIG. 16. Rat no. 22. Cerebellum and medulla oblongata showing
(A) pallor of descending root of trigeminal nerve, (B) pale areas in
granular layer of middle lobe of cerebellum, corresponding to foci
shown in Fig. 15. Loyez' haematoxylin. × 8·6

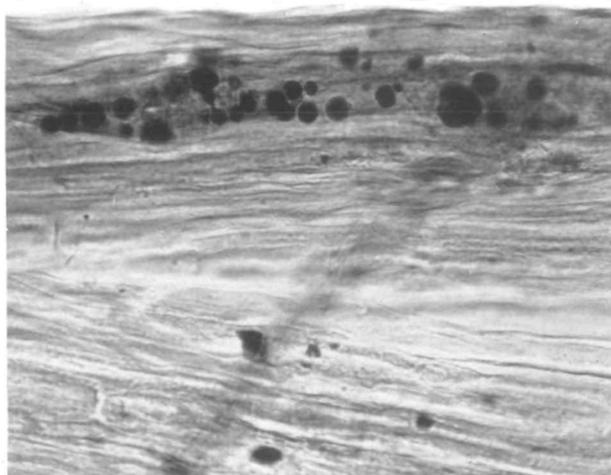

FIG. 17. Monkey. Ulnar nerve showing early degener-
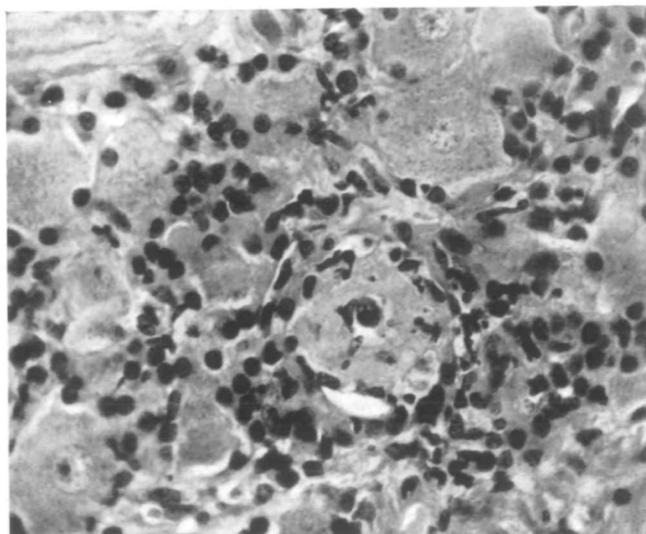ation of myelin sheaths. Marchi. × 370

FIG. 18. Monkey. Posterior root ganglion showing de-
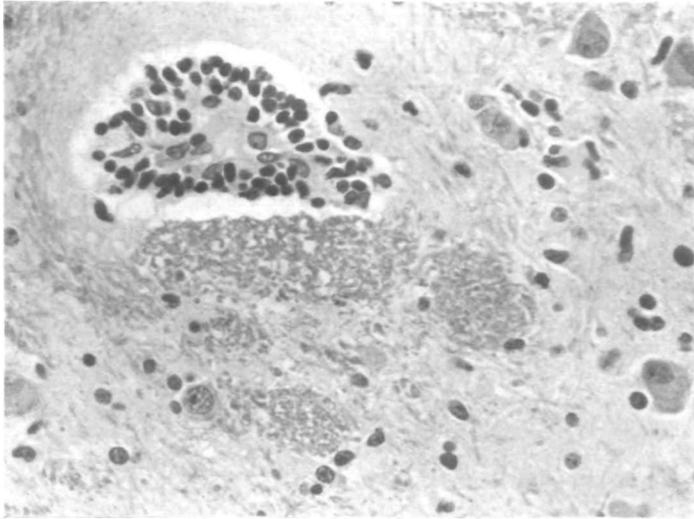generation of neurone in centre of field. Haematoxylin
and eosin. × 370

FIG. 19. Monkey. Optic thalamus showing perivascular cuffing. A few neutrophil leucocytes are present in the adjacent nervous tissue. Haematoxylin and eosin. × 370
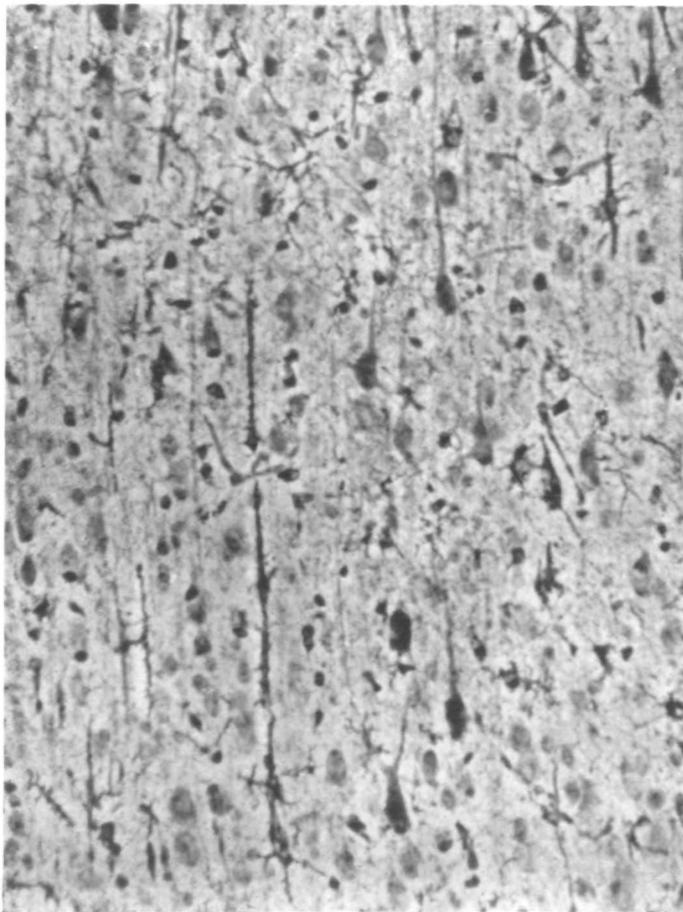

FIG. 20. Monkey. Frontal cortex showing increase of microglia with formation of conspicuous rod cells (left of centre). Penfield's modification. × 220