We are unaware of any information concerning the mechanism by which the oxalate ion is excreted by the kidney, whether by glomerular filtration only or by a combination of glomerular filtration and renal-tubular excretion. In the latter case it is, at least theoretically, possible that either the hippurate ion or the benzoate ion, or both these, might compete with the oxalate ion for common transport mechanisms in the renal tubule epithelial cells, and that if the former ionic species were present in sufficiently high concentrations such competition would produce a decrease in the urinary oxalate excretion. The results of the experiments in which sodium benzoate was administered to normal subjects are not in accord with this explanation of the decrease in the urinary oxalate excretion which was observed when sodium benzoate was given to patients with primary hyperoxaluria. This tentative conclusion requires confirmation by the determination of the renal oxalate clearance, a procedure which will remain impracticable until the blood oxalate level can be satisfactorily determined (see above).

Primary hyperoxaluria appears to be a rare disease (Archer *et al.*, 1957a). It should, however, be considered as a possible diagnosis in patients with a history of renal calculi dating from early childhood. Confirmation of the diagnosis by measurement of the 24-hour urinary oxalate excretion (Archer *et al.*, 1957a, 1957b) is a relatively simple procedure which is within the scope of any routine chemical pathology laboratory. Early diagnosis is of importance in planning the lifelong combined medical and surgical supervision which these patients require, and the detection of additional cases would encourage further study of the possible underlying metabolic abnormality.

Summary

The natural history of primary hyperoxaluria is briefly reviewed and the previously reported cases which appear to be examples of the disease are summarized. A number of incompletely reported cases which present some features of the condition are mentioned.

Experimental studies which were performed on two cases of primary hyperoxaluria with the object of elucidating the nature of the defect from which these patients suffer, together with a limited number of comparable investigations which were carried out on two normal subjects, are described.

The persistently high urinary oxalate excretion which characterizes the condition is not due to excessive gastrointestinal oxalate absorption, nor does it appear, in the present state of our knowledge, to result from a low renal-oxalate threshold.

Depletion of the free glycine metabolic pool lowered the urinary oxalate excretion temporarily in the patients with primary hyperoxaluria. This is discussed in the light of contemporary knowledge concerning some aspects of glycine metabolism. It is suggested that the findings are compatible with the hypothesis that at least some of the urinary oxalate in patients with primary hyperoxaluria is derived from glycine, and that there may be a failure to degrade this amino-acid normally via glyoxylate to formate and carbon dioxide in these cases.

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ABNORMAL RESPONSES TO MUSCLE RELAXANTS IN CARCINOMATOUS NEUROPATHY

BY

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In recent years there has been increasing interest in the group of neurological disorders associated with carcinoma at different sites, but without the presence of metastases in the nervous system. Subacute cerebellar degeneration occurring with carcinoma outside the nervous system was reported by Greenfield (1934) and by Brain, Daniel, and Greenfield (1951), while Denny-Brown (1948) described sensory neuropathy in patients with bronchial carcinoma. Henson (1953), in a discussion on unusual manifestations of carcinoma of the bronchus, reported a group of cases with carcinoma of the lung in which a motor neuropathy and myopathy had developed. Several of these patients had a history of muscular fatigability suggestive of myasthenia. Henson, Russell, and Wilkinson (1954) published a clinicopathological study of 19 cases with various types of carcinomatous neuropathy and myopathy. Eight of these patients had proximal atrophic weakness of the limbs; some also had involvement of ocular and bulbar muscles. Four patients in this group exhibited myasthenic features, including improvement with neostigmine in some cases. Since patients with myasthenia gravis are abnormally sensitive to drugs which interfere with the function of the myoneural junction, it was to be expected that patients with carcinomatous neuropathy who had evidence of myasthenia might also be abnormally sensitive to the various muscle relaxants used in modern anaesthesia.

This paper reports five cases, three of which had carcinomatous neuropathy without myasthenic symptoms, while the other two had a carcinoma but the associated neurological disorder was so mild that its true nature was not appreciated on the patients' admission. In all five prolonged states of neuromuscular block developed after the use of muscle relaxants.

Case 1

A woman aged 65 developed a productive cough one year before her admission to hospital. Six months later she began to feel a general malaise, and one month before admission she noticed general weakness of all four limbs. A fortnight before admission she had a sudden onset of nausea with vomiting after every meal, and had remained in bed because of muscular weakness. The vomiting improved, but the weakness increased. There was no loss of weight. Thirty years previously she had had a subtotal thyroidectomy for thyrotoxicosis.

On admission she was moderately obese, and had a large nodular goitre. The cranial nerves were normal, and no abnormality was noted in the motor or sensory systems. All the tendon reflexes except the ankle-jerks were absent, and the plantar responses were flexor. There were no abnormal signs in the cardiovascular or respiratory systems and the blood pressure was 140/80.

Investigations.—X-ray examination of the chest showed the trachea deviated to the left by the enlarged thyroid and a triangular shadow at the right hilum, sagittal tomograms revealing a dense opacity anterior to the right hilum. The sputum was examined repeatedly for neoplastic cells, and one specimen contained a few groups of cells resembling spheroidal carcinoma cells.

On April 1, 1953, bronchoscopy, carried out under thiopentone and gallamine triethiodide ("flaxedil"), showed no abnormality in the right bronchial tree. Following the bronchoscopy she developed respiratory obstruction in the theatre, but after bronchial aspiration normal respiration was temporarily resumed. On the way back to the ward she again became cyanosed, and when examined in bed was pulseless and apnoeic. Treatment with nikethamide and neostigmine restored normal breathing, but two hours later respiration became slow and gasping, and her pulse, which was of poor volume, rose to 160 a minute. She remained in semi-coma, responding only to painful stimuli. Throughout the day she presented a varying neurological picture. At one stage there was generalized flaccidity, left more than right, while at another time, although the legs were flaccid, the arms were rigidly flexed and the plantar responses extensor.

On the day after bronchoscopy her breathing was regular, but she was still in coma. During the next two days her level of consciousness returned slowly to normal, but she continued to feel very weak and nauseated. An E.C.G. taken three days after the bronchoscopy suggested a recent anterior cardiac infarction, this investigation having been normal two weeks previously.

She was discharged home on June 12. The weakness of her legs became slowly worse, and her hands, especially the right, became weaker and more unsteady. She lost 28 lb. (12.7 kg.) in weight, developed a hoarse voice, and was readmitted on October 27. Her condition had greatly deteriorated. She was wasted and had an ataxic dysarthria. There were slight bilateral ptosis and a right lower facial weakness. There was wasting and weakness of all four limbs, most marked proximally in the lower limbs, and the trunk muscles were also weak. She had a cerebellar ataxia of the right upper limb. Sensation was normal, and the reflex abnormalities noted on the first admission were unchanged.

Electrodiagnostic tests on both tibialis anterior muscles showed evidence of a neuropathic lesion. C.S.F. examination and pyruvate tolerance tests were normal.

She died on March 7, 1954.

Summary of Necropsy.—Bronchopneumonia. Primary carcinoma (small polygonal and oat-celled) of bronchus of right upper lobe. Multiple colloidal adenomata enlarging residual, partly retrosternal, right lobe of thyroid gland. Carcinomatous mass at right hilum infiltrating oesophagus, but no further secondary growth found. Replacement of thymus by adipose tissue. Great wasting of all voluntary muscles. No visible abnormality in brain and spinal cord.

Microscopical Examination

Brain.—Throughout a large part of the vermis there was loss of the Purkinje cells, associated with gliosis which extended into the molecular layer, but there was no appreciable atrophy of the folia. Beneath the most affected parts the white matter contained scattered fat-granule cells and there was diffuse pallor of the myelin with appropriate stains. The lateral cerebellar lobes contained only a few such areas, and they were small. There was considerable gliosis about the dentate nuclei but without any obvious loss of neurones. Symmetrical foci of degeneration occupied by foam cells lay immediately dorsal to the nuclei emboliformis. The basal and hypothalamic nuclei were normal apart from a small knot of microglial cells in the ventral part of one of the optic thalami. The leptomeninges over the floor of the third ventricle contained a slight excess of mononuclear and polymorphonuclear leucocytes, and occasional perforating vessels in the optic chiasm were cuffed with round cells.

Spinal Cord.—The only abnormality was a small patch of degeneration, occupied by foam cells, in the right lateral border of the posterior columns in the second and fourth lumbar segments. This was not represented in either the tenth thoracic or first sacral segments. The posterior root ganglion of the right fourth lumbar segment contained a few residual nodes, and the root proximal to the ganglion showed a diffuse but uneven loss of nerve fibres.

Peripheral Nerves.—No abnormality was found in the right brachial plexus and right popliteal nerve.

Voluntary Muscles.—Samples of the right deltoid, levator scapulae, and levator palpebrae superioris appeared normal. Slight atrophy was found in the diaphragm, serratus magnus, and pectoralis major; moderate atrophy in right extensor sublimis digitorum and abductor pollicis brevis; considerable atrophy in the rectus abdominis muscle. The atrophy affected scattered fibres and was of an uneven non-specific character.

Myocardium.—Scattered muscle fibres throughout the left ventricle had undergone necrosis, with reactive cellular infiltration, mainly composed of mononuclear phagocytes. In some areas phagocytosis appeared to have been completed. Occasional small patches of fibrosis might be the residua of still older lesions. The right ventricle was similarly but less severely affected. (The heart weighed 319 g.)

Thymus.—The adipose tissue contained irregular islands and trabeculae of glandular tissue of normal appearance and devoid of germ centres.

Comment

A woman of 65 with a carcinomatous neuromyopathy of mixed type (motor and cerebellar). Clinically the muscular wasting and weakness preceded and was always a more prominent feature than the cerebellar disorder. After the use of gallamine during bronchoscopy she suffered a long period of respiratory difficulty with only partial response to neostigmine. Normal consciousness was not regained for two days. Necropsy confirmed the presence of a bronchial carcinoma. In the nervous system, cerebellar degeneration appeared to be the most important pathological feature. The myopathy is of an unspecific type. The remarkable changes in the myocardium are reminiscent of myasthenia gravis, but the complete absence of lymphorrhages in the voluntary muscles and of any germ centres in the thymus is against this diagnosis. Examination of the heart did not

disclose any evidence of myocardial infarction, in spite of the electrocardiographic changes seen shortly after bronchoscopy.

Case 2

For two years a man aged 54 had noticed a gradual loss of health. Eighteen months before admission he began to have weakness of both lower limbs, with unsteadiness of gait and difficulty in standing up after stooping. He also had occasional diplopia and some clumsiness of his hands. He lost 21 lb. (9.5 kg.) in weight. In 1937 he had been treated for pulmonary tuberculosis.

On examination he had early clubbing of the finger-nails and bilateral slight ptosis, right more than left. General wasting and slight weakness of the upper limbs, and also proximal wasting and weakness of the lower limbs, were found. There was a patchy loss to pin-prick in many parts of the body. Postural sense was normal in the upper limbs but impaired in both feet. The arm-jerks were absent except for the left triceps-jerk, the knee-jerks absent, and the ankle-jerks sluggish. The plantar responses were flexor. The trachea was deviated to the right and there were crepitations at the left apex anteriorly. Blood pressure was 110/70. While in hospital he complained of occasional diplopia, worse after exertion and in the mornings.

Chest x-ray examination showed calcified lesions in both upper lobes, more extensive on the right side, the appearances being those of a long-standing and healed tuberculous infection. In addition there was a lobulated mass above the left hilum, with some collapse of the apical segment of the left lower lobe. Tomograms gave further support for the diagnosis of carcinoma of the bronchus. The sputum contained anaplastic spheroidal carcinoma cells. The C.S.F. was normal.

Bronchoscopy was done on December 4, 1953, under cocaine analgesia, and this showed an ulcerating growth of the left lower lobe bronchus. On December 7 left pneumonectomy was carried out under thiopentone, gas, oxygen, and D-tubocurarine. After the operation he remained apnoeic for three hours despite injections of neostigmine. Spontaneous respiration then returned and his condition improved for a time, but later he developed increasing dyspnoea and was unable to cough up his sputum. He died on the fifth post-operative day after a period in a Drinker apparatus.

Summary of Necropsy.—Oedema of right lung. Recent left pneumonectomy for oat-cell carcinoma of the bronchus. Fibrocaceous and granulomatous tuberculosis at apex of right lung. Secondary carcinomatous deposit in medulla of right suprarenal, and three small similar deposits (up to 0.5 cm. in diameter) in cerebral hemispheres (right inferior frontal cortex, left corona radiata, and central white matter of right occipital lobe). No further visible abnormality in central nervous system and no other growth in body.

Microscopical Examination.—Secondary oat-cell carcinoma was verified in the right frontal cortex, but no further significant changes were found in the central nervous system. **Peripheral Nerves.**—A few residual nodules were present in the posterior root ganglia (right eighth cervical and first lumbar). The posterior root of the latter, proximal to the ganglion, had undergone some sclerosis with loss of nerve fibres, but there was no corresponding degeneration of the posterior column. Sections of the right brachial plexus and sciatic nerves appeared normal. **Voluntary Muscles.**—No definite abnormality was found in the right pectoralis major and right dome of the diaphragm. There was slight focal atrophy of the fibres in the right opponens pollicis, right psoas, and erector spinae muscles. This atrophy was not accompanied by cellular infiltration, and was of unspecific character.

Comment

A man of 54, with long-standing quiescent pulmonary tuberculosis, who developed a neuromyopathy in association with an oat-cell carcinoma of the left lung. D-Tubocurarine

B

was used during a pneumonectomy, and afterwards he remained apnoeic for three hours despite the use of neostigmine. Although spontaneous respiration returned, it was never normal, and he died five days after operation. The neurological disturbances cannot be attributed to the secondary carcinoma of the brain, since the foci observed were very small and remote from one another. The cerebellum was not affected. The changes in the posterior root ganglia were too slight to be significant. Those in the voluntary muscles examined appeared trivial in relation to the degree of clinical disturbance observed.

Case 3

This patient was a man aged 65. Six months before admission his legs gradually became weak, the right being more severely affected. He also had slight difficulty in swallowing. A month later, following an operation for rectal prolapse in which the drugs used during anaesthesia are not known, he developed weakness of the upper limbs, more marked proximally. Four months before admission he passed a large clot of blood per rectum. His fingers became stiff, but there were no pains or paraesthesiae. He lost about 14 lb. (6.4 kg.) in weight.

He was admitted to the London Hospital with a provisional diagnosis of carcinomatous neuropathy. On examination he was somewhat wasted. The pupillary reactions, especially in the left eye, were sluggish both to light and on convergence; the palate moved poorly in the midline, and the sternomastoids were slightly weak. All four limbs were hypotonic, and the muscles were very flabby on palpation. There was proximal atrophic weakness of the upper and lower limbs, with relatively good power in the limbs distally. The trunk muscles were also weak. No fasciculation was seen. Sensation was normal apart from slightly increased calf tenderness. All the tendon reflexes were absent, and the plantar responses were flexor. He had poor chest expansion, with bilateral scattered rhonchi. There was peripheral arteriosclerosis and his blood pressure was 140/80. No abnormality was found in the abdomen and rectal examination was normal.

X-ray examination of the chest showed the changes of emphysema, with bilateral patchy areas of loss of translucency suggesting inflammation, and partial collapse of the left lower lobe. Lumbar puncture, blood count, sedimentation rate, sputum, and barium-meal examination were all normal. Sigmoidoscopy was normal up to 13 cm., but faeces prevented any further passage of the sigmoidoscope. Muscle biopsy from the left gastrocnemius showed no histological abnormality. An injection of 1.5 mg. of neostigmine did not increase muscle power. Bronchoscopy showed partial collapse of the left lower lobe, but no evidence of bronchial carcinoma. Electrodiagnostic tests suggested the presence of a neuropathic lesion.

The muscle biopsy was done on December 21, 1954, under thiopentone, gas, oxygen, and trichlorethylene anaesthesia, without any ill-effects. On January 14, 1955, bronchoscopy was carried out under thiopentone and suxamethonium anaesthesia. After this he became much weaker in all muscle groups and was unable to stand. This increased weakness improved slowly during the next two weeks, by which time he had returned to the level of disability present on admission.

He was discharged from hospital and attended the out-patient department for three months, during which time there was further improvement in his limbs. He then returned to Australia, where he continued to make good progress until March, 1956, when he developed acute large-bowel obstruction and was admitted to the Royal Prince Alfred Hospital, Sydney, where a colostomy was performed. He died three days later from pulmonary complications "while bronchoscopy was being attempted." It is not known whether muscle relaxants were used at this time.

Post-mortem examination showed a ring carcinoma of the sigmoid colon, 20 cm. from the anal margin. Micro-

scopically this was a moderately well differentiated adenocarcinoma with involvement of the regional lymph nodes. In the lungs there were old tuberculous scars at both apices, and collapse of both lower lobes with hypostatic congestion. No histological examination was made of the nervous system or muscles, as the patient's previous history was not known when the necropsy was done. On his last admission to hospital he had merely stated that he had had an episode of muscular weakness which had improved. On examination at this time it was noted that he had "some muscular weakness" but that his tendon reflexes were present and equal.

Comment

A man of 65 with a clinical picture of carcinomatous neuropathy. During the search for the underlying carcinoma, his muscular weakness was greatly increased following the use of suxamethonium during bronchoscopy, and this increased weakness did not recover for two weeks. He subsequently had further improvement in his neurological condition, but died after an operation for carcinoma of the sigmoid colon, 21 months after the first neurological symptoms had been noted.

Case 4

One year before his admission to the London Hospital a man aged 68 had attended another hospital because of urinary symptoms, and a diagnosis of prostatic carcinoma was made. He was treated with stilboestrol. In the six months before his admission he had increasing frequency of micturition with occasional incontinence, and lost about 14 lb. (6.4 kg.). For one month he had walked with a stick and felt generally tired and weak.

On examination he had a hard and slightly enlarged prostate. The blood pressure was 140/90. No definite abnormalities were noted in the nervous system except that the reflexes in the lower limbs were very brisk and the plantar responses were equivocal. On January 31, 1955, an endoscopic resection of the prostate was done under thiopentone, gallamine, gas, oxygen, and trichlorethylene. After this operation he felt extremely weak, and when attempts were made to get him out of bed on the fourth post-operative day his legs were so weak that he could not stand.

On February 9 he was seen by Sir Russell Brain, who found a right Horner's syndrome, bilateral lower facial weakness, and general wasting and weakness of the upper and lower limbs. There was hypalgesia to pin-prick below the level of D5, and loss of vibration sense below the knees. The supinator jerks were diminished and the biceps- and triceps-jerks were normal. The knee-jerks were present but the ankle-jerks were much diminished. The plantar responses were both extensor. The tongue was smooth and red. Sir Russell Brain thought that the picture was due to a carcinomatous neuromyopathy, and commented that the appearance of the tongue resembled that of a deficiency syndrome.

Lumbar puncture yielded a spinal fluid of normal composition and under normal pressure. Electrodiagnostic tests were done before and after the injection of neostigmine. Before neostigmine the electromyograph from the left tibialis anterior showed no fibrillation but some spontaneous activity. On volition there was a reduced interference pattern with some coarse broken-up motor units, possibly showing fatigue. Twenty minutes after injection of 1.5 mg. of neostigmine there was a definite increase in interference pattern, all the motor units appearing more normal. After three-quarters of an hour the interference pattern was again reduced a little. In addition to the electrical changes there was a slight clinical improvement in power of the anterior tibial and triceps muscles, and there was no fasciculation after the injection of neostigmine.

On February 17 the serum cholinesterase was 36 μ l. CO₂/ml./min. (normal range, 53–102 μ l. CO₂/ml./min.—Thompson and Trounce, 1956).

The fragments of prostatic tissue removed by endoscopic resection were small and had been damaged during resection. No definite evidence of malignancy was found in the sections examined.

His condition gradually deteriorated, although he was given neostigmine by mouth, and he died 46 days after the endoscopic resection. Permission for necropsy could not be obtained.

Comment

A man of 68 was admitted for surgical treatment of carcinoma of the prostate. He developed general weakness for one month before admission, but there were no striking neurological abnormalities. After the use of gallamine during endoscopic resection he became profoundly weak, with signs of widespread impairment of function of the spinal cord, peripheral nerves, and muscles. The condition persisted and was ultimately fatal, although the muscular weakness showed a partial clinical and electromyographic response to neostigmine. Histological proof of the diagnosis of prostatic carcinoma was not obtained, but the clinical diagnosis was not in doubt.

Case 5

For about 10 years a woman aged 46 had had a non-productive cough. Four months before admission she developed an aching pain in the right scapular region. X-ray films of her chest showed enlargement of the right hilum, with a shadow in the right upper lobe. Three weeks before admission she began to notice weakness of all four limbs, and a week later took to her bed.

On admission there was slight diminution of air entry in the right upper lobe posteriorly. No abnormal signs were found in the nervous system. Blood pressure was 125/80. Four days later bronchoscopy was done under local anaesthesia. The orifice of the right middle lobe was slightly narrowed, and there was rigidity of the lower lobe bronchus below this level. Later on the same day an exploratory thoracotomy was done and mediastinal glands were removed for histological examination. This operation was carried out under thiopentone, gas, and oxygen anaesthesia. D-tubocurarine being used as a muscle relaxant.

After the operation she remained unconscious and apnoeic, and artificial ventilation was maintained. There was no response to an injection of 2.5 mg. of neostigmine. A second injection of neostigmine (2.5 mg.) was given four hours after the operation, and feeble respiratory movements were noted. After further doses of neostigmine respiration improved, and she was able to make some movements of the head and upper limbs. Throughout the night after operation spontaneous respiration was weak, with poor ventilation, but consciousness returned. During the post-operative period she was too ill to undergo full neurological examination, but she was noted to have extreme weakness of all muscles, including those of respiration. Treatment with neostigmine was continued, but she died of respiratory failure two days after operation. Intravenous edrophonium chloride ("tensilon") was given without benefit in the terminal stage of her illness.

Summary of Necropsy.—Bronchopneumonia. Carcinoma of bifurcation of apical bronchus to right upper lobe. Operation: recent thoracotomy. Primary oat-celled carcinoma (0.6 cm. diameter). Secondary deposits in four regional lymph nodes only. No visible abnormality in brain (examined after fixation) or in spinal cord. Thymus replaced by adipose tissue. An obese woman.

Microscopical Examination.—**Spinal Cord:** no visible abnormalities found in eighth cervical and third lumbar segments, apart from a linear haemorrhage in the right posterior horn of the former; probably an artifact. No sections were taken from other levels. **Voluntary Muscles:** the pectoralis major and erector spinae appeared normal. In the right quadriceps an occasional muscle fibre showed slight atrophy. The myocardium was not examined.

Comment

A woman of 46 years was admitted for investigation of a hilar mass seen on chest x-ray examination. Three weeks before admission she had complained of general weakness, but no obvious neurological abnormality was noted on admission. Following the use of D-tubocurarine during exploratory thoracotomy she developed generalized muscular paralysis, with apnoea. There was a partial response to neostigmine, but she died two days later. An oat-cell carcinoma of the bronchus was found at necropsy, but no significant abnormalities were present in the central nervous system or muscles.

Discussion

Although about 15 years ago myasthenia gravis was regarded by many clinicians as a distinct disease characterized by muscular weakness, abnormal fatigability, dramatic improvement after the use of neostigmine, and often the existence of hypertrophy or tumour formation of the thymus gland, it has become increasingly apparent (Paterson, 1956) that these features are often found in varying combinations in other disorders. It is more satisfactory to speak of the myasthenic syndrome, which has been reported in patients with thyroid disease (McEachern and Ross, 1942; Laurent, 1944; Sheldon and Walker, 1946; Millikan and Haines, 1953), polymyositis (Reese and Harman, 1954; Bonduelle, Bouygues, and Coulon, 1955), nutritional disorders (Denny-Brown, 1947), and carcinoma, particularly of the bronchus.

Apart from the detailed studies of carcinomatous neuropathy at the London Hospital (Henson, 1953; Henson *et al.*, 1954), there have been other reports of myasthenia in carcinomatous neuropathy. Anderson, Churchill-Davidson, and Richardson (1953) reported the case of a patient who was at first thought to have atypical myasthenia gravis, but who was later found to have a bronchial neoplasm. Bronchoscopy was done, using suxamethonium, and this was followed by a state of prolonged apnoea. This patient's muscular weakness was improved by neostigmine. Similar patients with myasthenia were reported by Mackenzie (1954), Shafar (1954), and Borrelli and Keen (1954).

Eaton and Lambert (1957) have reported briefly six cases with "a disorder resembling myasthenia gravis." Three had malignant tumours in the chest (two with bronchial carcinoma and one with a reticulum-cell lymphosarcoma), while two others had in their chest x-ray films abnormal shadows the nature of which was as yet uncertain. Electrodiagnostic tests showed fatigability similar to that found in myasthenia gravis. The action potential in response to a single electrical stimulus applied to a peripheral nerve was abnormally small, whereas in myasthenia gravis such potentials are usually of normal size in a case of similar severity. The patients responded poorly to neostigmine, but showed extreme sensitivity to curare used as a diagnostic test for myasthenia gravis.

In the cases recorded above no patient had a clinical history suggestive of myasthenia, and two (Cases 4 and 5) were not suspected of having any neurological disorder until the abnormal response to muscle relaxants was apparent.

Forms of Neuromuscular Block

It is not the purpose of this paper to discuss in detail the different types of neuromuscular block which are known to exist. The subject of neuromuscular transmission has been reviewed by Hunt and Kuffler (1950), Churchill-Davidson and Richardson (1953), and Paton (1953). The different forms of neuromuscular block include: (1) "Deficiency block" due to impaired liberation of acetylcholine by the motor-nerve endings. This occurs in experimental animals in severe hypocalcaemia, and permanently under the influence of botulinus toxin. (2) "Depolarization block," in which a state of prolonged depolarization

of the end-plate region makes it unresponsive to acetylcholine liberated at the nerve endings. This type of block may be produced by excessive amounts of acetylcholine (either injected or allowed to persist by the action of anticholinesterase compounds) and by suxamethonium and decamethonium. (3) "Competitive" or "non-depolarization block" produced by the curare group of drugs, which compete with acetylcholine for the receptors at the end-plate. (4) Mixed types of block which have been demonstrated in experimental animals with decamethonium, and were also reported by Churchill-Davidson and Richardson (1953) in a study of the effect of decamethonium on patients suffering from myasthenia gravis, where the drug appeared to cause depolarization block followed immediately by competitive inhibition.

A recent group of papers from the Johns Hopkins Hospital (Grob, Johns, and Harvey, 1956a, 1956b, 1956c, 1956d, 1956e; Johns, Grob, and Harvey, 1956) have given the results of detailed studies of neuromuscular transmission in normal subjects and in patients with myasthenia gravis. These authors conclude that in myasthenia gravis a neuromuscular block is present and that this may be reversible—that is, competitive—at some motor end-plates, and irreversible—that is, non-competitive—or partly reversible at others. The relative proportion in any muscle of these types of block was thought to explain the varying degrees of improvement with anticholinesterase compounds and the severity of the weakness which may be produced by excessive doses. Grob and his associates also put forward evidence that in myasthenia gravis the end-plate may respond abnormally to choline (derived from the breakdown of acetylcholine) with the production of a non-depolarization block.

Churchill-Davidson and Richardson (1957) have reported the case of a patient with myasthenia gravis who became neostigmine-resistant. After a period of artificial respiration without neostigmine she again became sensitive to this drug. She showed a similar return of sensitivity to neostigmine on another occasion, when, in addition to artificial respiration, she was given D-tubocurarine for eight days with the object of producing complete rest of the motor end-plate.

Modern Blocking Agents

The blocking agents used in modern anaesthesia fall into two main groups: those causing competitive inhibition (D-tubocurarine and gallamine) and those causing depolarization block (decamethonium and suxamethonium). With the former group neostigmine is normally effective in reversing the block, but with the depolarizing agents anticholinesterase compounds are ineffective and may prolong the block.

In reviewing the published cases of abnormal response to different blocking agents it is apparent that many of the reports are by anaesthetists who, while they are naturally interested in the pre-operative general condition of the patient, the type of operation, and the drugs used, have often failed to mention the underlying disease process; for example, several papers discuss operations for the relief of intestinal obstruction without stating whether this has been due to carcinoma or to some more benign cause.

Although suxamethonium was welcomed as a muscle relaxant of very short duration, as soon as it was widely used numerous instances were reported of prolonged apnoea following its use (Love, 1952; Harper, 1952; Hewer, 1952; Grant, 1952; Mackay, 1952; Ruddell, 1952; Reid and Neill, 1952; Wolfers, 1952; Bourne, 1953). Only in one case (Reid and Neill, 1952) was a carcinoma present, and in none was there any history of carcinomatous neuropathy.

Similar states of prolonged neuromuscular block have been observed with competitive blocking agents—gallamine (Condon, 1951; McGrath, 1956; Hunter, 1956) and with D-tubocurarine (Gray and Halton, 1948; Hunter, 1956;

McGrath, 1956; Kenny, 1956; Stewart, 1956; Montgomery, 1956; Scott and Clarke, 1956). In some of the patients who responded abnormally to D-tubocurarine, suxamethonium had also been used during the period of anaesthesia. Case 1 of Gray and Halton (1948) was a patient with bronchial carcinoma who had prolonged apnoea after bronchoscopy under thiopentone and curare. A carcinoma was also present in cases reported by McGrath (1956) and Kenny (1956).

Causes of Abnormal Response

There are many possible causes of abnormal response to muscle relaxants, and these have been reviewed by Churchill-Davidson (1955). They include:

- (1) Central action of the blocking agent (Ellis, Morgan, and de Beer, 1952).
- (2) The narcotic action of other drugs used during anaesthesia.
- (3) Carbon dioxide retention resulting from hypoventilation (Dripps, 1953; Scurr, 1954; Gray and Fenton, 1954; Davis, Ellis, Reese, and Grosskreutz, 1955).
- (4) Electrolyte disturbances, particularly alteration in potassium-ion distribution (Foldes, Hunt, and Ceravolo, 1952; Hunter, 1956; Scott and Clarke, 1956; Oldfield, 1956). Foster (1956) postulates that, with depletion of extracellular potassium, muscle relaxants may pass the blood-brain barrier and so exert a central effect—a possible explanation of the prolonged coma observed in Cases 1 and 5 in this paper, which persisted after the effects of the narcotic anaesthetic drugs should have ceased.
- (5) Cholinesterase deficiency (Evans, Gray, Lehmann, and Silk, 1952a, 1952b; Bourne, Collier, and Somers, 1952; Bourne, 1953; Hodges, 1953).
- (6) The combination of two types of blocking agent in the same operation (Beardsworth, 1956; Gordon, 1956; Gray, 1952; Hodges and Foldes, 1956; Verrill, 1956). Gray (1952) commented that "polypharmacy must be practised only with full realization of the interaction of the drugs that may be used."
- (7) In neuromuscular block after the use of depolarizing agents like suxamethonium, neostigmine may prolong the state of depolarization (Foldes, 1952; Binning, 1952). In contrast, in Grant's (1952) case a period of three days' respiratory arrest following the use of suxamethonium was brought to an end three hours after the injection of 1 mg. of neostigmine. This finding lends support to the view of Hodges and Foldes (1956) that a competitive type of block may develop with this relaxant.

Although many isolated instances, some of them fatal, of abnormal responses to muscle relaxants have appeared in various journals, in a survey of 1,000 deaths associated with anaesthesia, Edwards, Morton, Pask, and Wylie (1956) gave little prominence to the possible part played by these drugs. Keating (1956), in a monograph on anaesthetic accidents, devotes a chapter to the side-actions of the muscle relaxants. Although he states that "undiagnosed myasthenia gravis may be expected to arrive in the operating theatre of a large hospital about once a year," he does not consider the possibility of myasthenic responses in patients with carcinoma.

Myasthenic forms of carcinomatous neuropathy may give rise to anaesthetic difficulties in several ways. In the investigation of patients with unexplained neuropathies, bronchoscopy and other investigations may be done with the aid of muscle relaxants, and states of prolonged neuromuscular block may result as in Cases 1 and 3. In patients who are known to have carcinomatous neuropathy the use of blocking agents during surgical treatment may give rise to similar complications (Case 2). Lastly, in the investigation or treatment of patients with carcinoma in whom there is no overt neurological disorder the use of muscle relaxants may be followed by serious and possibly irreversible states of neuromuscular block (Cases 4 and 5). Such patients probably have subclinical forms of carcinomatous neuropathy which are disclosed by the abnormal reaction to the blocking agents.

Detailed pathological studies of patients with various forms of carcinomatous neuropathy and myopathy, including some patients with myasthenia, have been made by Henson, Russell, and Wilkinson (1954). Case 2 in the

present communication is of interest because the histological abnormalities in the nervous system and muscles are so trivial in comparison with the abnormalities which could be demonstrated clinically. Reports of temporary and occasionally of lasting remissions in patients with carcinomatous neuropathy, even when myasthenic features are lacking, suggest that the disorder of function is, initially at least, a biochemical disturbance which may be reversible in the early stages. The nature of this biochemical change, which may not be the same in all types of carcinomatous neuropathy, is at present quite unknown. Of the various possible factors that may precipitate an abnormal response to the muscle relaxants, few are likely to have been operative in the patients reported in this paper. Detailed electrolyte studies were not made.

The possibility of central action of the relaxant even in the absence of serious disturbance of potassium-ion distribution is supported by the periods of coma which occurred in Cases 1 and 5. Cholinesterase deficiency remains as an important possible contributing factor. The serum cholinesterase level in Case 4 was below the lower limits of normal. On the other hand, Henson *et al.* (1954) found no significant abnormality in the amount of this enzyme present in two patients with carcinomatous neuropathy, one of whom had myasthenic features.

It is of interest to note the varying response to neostigmine in the patients reported here. The drug was partially effective in reversing the abnormal block in Cases 1, 4, and 5, all of which had been given relaxants of the competitive type. Case 3, which reacted abnormally to suxamethonium, showed no improvement with neostigmine, although it was given several days after the use of the depolarizing agent. In Case 2 neostigmine had no effect on a state of prolonged neuromuscular block due to curare.

There remains a possibility that cholinesterase deficiency may be a factor in the myasthenia of carcinomatous neuropathy, although such a defect would not easily explain the abnormal sensitivity to drugs of the competitive type.

Wolfers (1952) suggests that the sensitivity of any individual to the relaxant drugs may vary from day to day, even in the absence of any peripheral neuropathy. His patient was given the same dose of suxamethonium on two occasions, with an interval of nine days. There was a period of three minutes' apnoea after the first dose and of 29 minutes' after the second. Wolfers could find no reason for this difference, and after the second and abnormal response the plasma cholinesterase was found to be normal.

It is not suggested that the use of muscle relaxants in patients with carcinomatous neuropathy will always be followed by abnormally prolonged neuromuscular block. Several patients with such a neuropathy are known to have been given these drugs without ill effect. Nevertheless the risks are great, even where there are no obvious myasthenic features.

Some Practical Points

The findings reported here suggest a number of practical points. In the first place all carcinoma patients who are likely to be exposed to the effects of the neuromuscular blocking agents should be examined with care to exclude, so far as is possible, the presence of any neurological disorder. It is easy to dismiss a story of "general weakness" as a result of the debilitating effects of a malignant growth without realizing that such a symptom may have significance as an indication of an early neuropathy. It is unjustifiable to advocate the prohibition of the use of muscle relaxants in all patients with carcinoma, but these drugs should be avoided when there is any suspicion of a neuromuscular disorder. The routine use of test doses to assess the patient's sensitivity to the relaxant may avoid unexpected complications in the form of prolonged states of apnoea and neuromuscular block.

Secondly, it is very important that anaesthetists and surgeons should be aware of the possible risk of using

muscle relaxants on patients in whom a carcinomatous neuropathy is suspected. The danger appears to be especially great in neuropathies due to bronchial carcinoma, and, where possible, bronchoscopy should be done under local anaesthesia alone. Although the majority of reported cases of carcinomatous neuropathy have been associated with bronchial carcinoma (17 of the 19 cases reported by Henson *et al.*, 1954), carcinoma at other sites may be responsible. Growths of the breast and ovary are already recognized as important in the production of neuropathy; in Case 3 a carcinoma of the sigmoid colon was present, while in Case 4 the neuropathy was due to a carcinoma of the prostate, although histological proof of this could not be obtained. These findings emphasize the need for a widespread search for a primary growth in suspected cases of carcinomatous neuropathy.

When prolonged states of neuromuscular block follow the use of one of the muscle relaxants, carcinomatous neuropathy should be considered as a possible explanation of the abnormal response to the drug.

Finally, patients with the different types of carcinomatous neuropathy must be investigated more intensively in the future, using combined clinical, biochemical, histochemical, and electromyographic methods of study, which may help to solve the problems of the metabolic abnormalities which are present. Since the time relations between the onset of the neuropathy and of the discovery of the carcinoma are so variable (Henson *et al.*, 1954) these investigations should be repeated at intervals, and where applicable particular attention should be given to any changes that may follow the removal of the carcinoma. Similar investigations may be helpful in other patients with unexplained neuromuscular disorders not associated with carcinoma.

Summary

Three patients with carcinomatous neuropathy but without overt myasthenia showed abnormal responses to muscle relaxants. Two other patients with carcinoma but without obvious neurological disorder showed similar abnormal sensitivity to these drugs.

The risks of using neuromuscular blocking agents in patients with carcinomatous neuropathy is discussed.

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A STUDY IN THE TRANSMISSION OF MATERNAL ANTIBODIES

BY

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The agent in the milk of mice which Bittner (1937) discovered to be concerned with the development of breast cancer in these animals has been the subject of intensive research, and much is now known about its chemical, physical, and biological properties. In all these it behaves like a virus, and it now seems probable that, given the appropriate murine, genetic, and hormonal background, the presence or absence of the mammary agent is responsible for the appearance, or the failure to appear, of mammary cancer in this species. The possibility that such a mechanism might operate in the development of human breast cancer has been widely canvassed.

Three methods of investigation have been undertaken to probe this important matter. In the first, human milk has been studied under the electron microscope (Passey and Dmochowski, 1951; Gross *et al.*, 1952) and particles have been observed microscopically resembling the particles in mouse's milk which have been identified with the mammary cancer agent. This finding, however, can do no more than suggest the possibility of a relation between the observation of such particles and the subsequent development of breast cancer. Indeed, even if a relation could be established, studies of this sort, whilst of the greatest theoretical interest, would not answer the