- DEMICK, P.E. & CAVANAGH, D. (1958) Unilateral tubal twin pregnancy. *Amer. J. Obstet. Gynec.* **76**, 533.
- EVANS, G.E. & GOYANES, E. (1952) Bilateral ectopic gestation. *Amer. J. Obstet. Gynec.* **64**, 444.
- FARA, F.J. & VARGA, A. (1957) Interstitial twin pregnancy with cornual rupture. *Obstet. and Gynec.* **10**, 579.
- FILL, L. & ROSS, C.V. (1957) Unilateral tubal twin pregnancy. *Obstet. and Gynec.* **9**, 358.
- GOODMAN, D., ELIA, A.D. & FRIEDEL, G.H. (1960) Simultaneously aborted intrauterine and tubal pregnancies. *Obstet. and Gynec.* **16**, 53.
- GREEN, G.H. & WEST, S.R. (1963) Ovarian twin pregnancy. *Obstet. and Gynec.* **21**, 126.
- KAZMAN, H.A. & BARNETT, L.A. (1953) Simultaneous ruptured ectopic and intrauterine pregnancy. *Surgery*, **33**, 391.
- LAWSON, J.G. & CHOULER, J.G. (1955) A case of primary ovarian pregnancy with coexisting intrauterine gestation. *J. Obstet. Gynaec. Brit. Emp.* **62**, 951.
- LOH, W.P. & LOH, H.Y. (1962) Unilateral tubal twin pregnancy with intraperitoneal rupture. *Obstet. and Gynec.* **19**, 267.
- MODAVI, O. (1962) Primary twin ovarian pregnancy with ovarian endometriosis. *J. Obstet. Gynaec. Brit. Cwlth.* **69**, 655.
- NANDI, G. (1953) Combined full-time intrauterine and extrauterine pregnancy with survival of mother and both children. *J. Obstet. Gynaec. Brit. Emp.* **60**, 114.
- RANNELS, H.W. (1953) Simultaneous intrauterine and extrauterine (ovarian) pregnancy. *Obstet. and Gynec.* **2**, 281.
- UNGER, H.M. (1955) Intratubal twin pregnancy with rupture. *Amer. J. Obstet. Gynec.* **69**, 1362.
- WILLIAMS, P.C. (1957) Bilateral tubal pregnancy. *Amer. J. Obstet. Gynec.* **74**, 1132.
- ZAROU, G.S. & SY, A. (1952) Combined intrauterine and extrauterine pregnancy progressing to term. *Amer. J. Obstet. Gynec.* **64**, 1338.

Simultaneous myasthenia gravis and pernicious anaemia:

A case report with organ antibody studies

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MYASTHENIA GRAVIS and pernicious anaemia are both conditions in which organ-specific auto-antibodies are being reported with increasing frequency. Their coexistence in a single patient provides some support for the belief that they have a common pathogenesis, namely a breakdown in the immunological self-recognition mechanisms leading to autoimmune disease.

This combination occurred in eleven of 857 cases of myasthenia gravis seen at the Mayo Clinic prior to 1960 and reviewed by Howard, Silverstein & Mulder (1965) but no antibody studies were performed in that series. Nine cases of macrocytic anaemia were noted in Simpson's series of 491 myasthenic patients (Simpson, 1960, 1964). Simpson (1966) states that some, if not all, of these patients were later shown certainly to have pernicious anaemia. Only one, however, was available for immunological studies and in that patient the further complication of Hashimoto's disease was found at necropsy; gastric and thyroid antibodies were demonstrated. The only other report of the coexistence of pernicious anaemia and myasthenia gravis alone which we have been able to trace is that of Rowland *et al.* (1956). This was, of course, prior to the era of

organ-specific antibody studies in these diseases.

The present report is of a further instance of this association, and in this case the two diseases presented simultaneously. Immunofluorescence studies showed the presence in the patient's serum of organ specific antibodies to the 'target tissues' of both of these diseases, namely skeletal muscle and gastric mucosa. We have also reviewed the case histories of all the myasthenic patients seen at this hospital since 1953 and some of those seen at the attached Bristol Eye Hospital. There were no further instances of pernicious anaemia in a total of thirty-seven cases, but several patients did have other diseases, possibly autoimmune, which we mention below.

Case report

A 62-year-old French polisher developed double vision and drooping of the left eyelid within the course of a week in March 1965. He was seen by one of us on 10 June, when he also admitted to dropping of the jaw on talking, difficulty in chewing and exhaustion after the slightest exertion. Symptoms were absent on waking, were improved by rest and were made noticeably worse by sunlight. He had lost 20 lb in weight in the

previous 9 months. He had suffered from psoriasis for many years, had had rheumatic fever in 1930 and a hypersensitivity reaction to penicillin in 1950. There was no family history of anaemia or muscle weakness.

An asymmetrical ptosis, impairment of lateral and upward ocular deviation, palatal dysphonia and jaw muscle weakness were noted, with marked fatigueability of the affected muscles. The only other findings were pallor and smoothness of the tongue. The diagnosis of myasthenia gravis was suggested by these findings and by his myasthenic facies. It was confirmed by a dramatic response to intravenous edrophonium chloride and great improvement in his symptoms on oral prostigmine treatment. Radiographs of chest and thoracic inlet were normal and tomograms did not reveal any thymic mass. A barium meal showed a small reducible hiatus hernia.

Haematological investigations

Haemoglobin 9.3 g/100 ml, PCV 28%, MCHC 33%, ESR 31 mm/1 hr. The peripheral blood film showed well-marked macrocytosis, anisocytosis and ovalocytosis, with a 'shift to the right' of the neutrophils. Smears of the sternal marrow showed hyperplastic erythropoiesis with well-marked megaloblastic change and numerous giant metamyelocytes in the granulocytic series. The diagnosis of Addisonian pernicious anaemia was established by an augmented histamine test meal which revealed absolute achlorhydria, and a Schilling test which showed 0.6% urinary excretion of Co⁵⁸-labelled vitamin B₁₂ in 24 hr. When repeated with oral intrinsic factor the excretion rose to 13.5%.

Total serum proteins were 6.5 g and the electrophoretic strip showed no abnormality (γ -globulins were 1.3 g/100 ml). Protein-bound iodine was 4.4 μ g/100 ml, a low normal result in our laboratory.

Immunological studies

By the indirect immunofluorescence technique using a highly purified anti-7S- γ -globulin-fluorescein conjugate (Beutner *et al.*, 1962), the patient's serum was shown to contain antibodies reacting against the following tissues:

(a) Human skeletal muscle: at a dilution greater than 1 : 60.

(b) Human cardiac muscle: at a dilution greater than 1 : 60.

(c) Calf thymic epithelial cells: at a dilution greater than 1 : 60.

(d) Human gastric parietal cells (by the technique of Taylor *et al.*, 1962): at a dilution of 1 : 10.

Similar tests for antibodies to thyroid acinar-cell cytoplasm and anti-nuclear factor were negative.

The tests for antibodies to intrinsic factor (Ardeman & Chanarin, 1963) and thyroglobulin (using coated tanned red cells, Burroughs Wellcome Ltd) were also negative as were the LE-cell test (on two occasions), the latex fixation test (Stayne laboratories, Ltd) and the Wasserman reactions (Cardiolipin WR, Reiter protein CFT and PPR).

Progress

A maximum reticulocytosis of 13% occurred on the 6th day after commencing treatment with intramuscular vitamin B₁₂, 1000 μ g twice weekly, and reasonable control of his myasthenic symptoms were achieved by oral pyridostigmine 120 mg q.d.s., autonomic side effects being minimized by propantheline 15 mg q.d.s. An exacerbation with respiratory distress necessitated his re-admission in September 1965, and prostigmine was substituted for pyridostigmine. In view of the progression and spread of his symptoms a therapeutic trial of steroids was made with negative results and an underlying carcinoma was looked for and excluded. His anaemia has completely responded to therapy.

In April 1966 his condition worsened; he was readmitted and developed a myasthenic crisis and a popliteal artery occlusion. Following tracheostomy, intermittent positive pressure respiration, the cessation of all anticholinergic therapy for 10 days and anticoagulants, there was a marked improvement. Thereafter he remained well controlled on prostigmine 15 mg 4-hourly and vitamin B₁₂ 1000 μ g fortnightly.

Discussion

The suggestion that myasthenia gravis might be an autoimmune disease first arose from the similarities noted between the histological appearances of the thymus in this disease and the thyroid gland in Hashimoto's disease (Castleman, 1955), and by reason of certain clinical features reminiscent of other autoimmune diseases, namely the female preponderance, maximal onset in young adults, fluctuant course and occasional association with these other diseases (Simpson, 1960). Considerable support has been given to this idea by the demonstration by immunofluorescence in 30–50% of cases of myasthenia gravis, of circulating complement-fixing antibodies to skeletal muscle (Strauss *et al.*, 1960; Feldkamp, Van der Geld & Oosterhuis, 1963) and cardiac muscle (Beutner *et al.*, 1962). Some of the antibodies were shown to react with the patients' own muscle tissue, thus constituting true autoantibodies (Beutner *et al.*, 1962). Antibodies cross-reacting with both skeletal

muscle and thymic epithelial cells were then described (Van der Geld & Oosterhuis, 1963), and the recent demonstrations by light microscopy (Henry, 1966) and electron microscopy (Van de Velde *et al.*, 1966) of striated muscle cells within the thymus which also react with skeletal-muscle antibodies (Feltkamp-Vroom, 1966) add credence to the postulate that in myasthenia gravis immunologically competent cells might acquire anti-muscle specificity in the thymus whence they emigrate to cause the disease peripherally.

Other evidence suggesting that immune mechanisms might operate in this disease were the *in-vitro* cytolytic effects of myasthenic sera on frog muscle cells (Nastuk, Strauss & Osserman, 1959), lowered serum complement levels in active phases of myasthenia (Nastuk, Plescia & Osserman, 1960) and the production of γ -globulin by cells of the abnormal germinal-centres in myasthenic thymuses (White & Marshall, 1962). Anti-thyroid antibodies (Feldkamp *et al.*, 1963; Simpson, 1964) and the anti-nuclear and rheumatoid factors (White & Marshall, 1962; Simpson, 1964) have also been found to be increased in series of cases of myasthenia gravis. It is, of course, by no means proven that the humoral antibodies are causative, rather than secondary, phenomena in myasthenia gravis, as was recently emphasized by Wolf *et al.* (1965).

The association of myasthenia gravis with several other diseases thought to be of autoimmune aetiology is fairly well documented (Downes, Greenwood & Wray, 1966). Since 1954 reports have appeared of the coexistence of myasthenia gravis and systemic lupus erythematosus (Downes *et al.*, 1966, who list the published reports). The association with the 'prototype' single-organ autoimmune disease, Hashimoto's thyroiditis, has only been reported recently (Simpson, 1964; Daly & Jackson, 1964) but the associations with spontaneous myxoedema and

particularly thyrotoxicosis have been recognized for many years (Sahay, Blendis & Greene, 1965, who review the literature). Fairly numerous instances of the coexistence of myasthenia and rheumatoid arthritis have also appeared (Simpson, 1960; White & Marshall, 1962) and some of diabetes with myasthenia (Simpson, 1964).

Our search of the case histories of the twenty-six myasthenic patients seen at this hospital since 1953 and the eleven cases of ocular myasthenia which we were able to trace at the Eye Hospital, revealed several instances of the association of myasthenia gravis with some of the above-mentioned diseases reported in the literature (Table 1). In two other cases myasthenia was associated respectively with multiple sclerosis, and iron deficiency anaemia with achlorhydria, both of which conditions have been considered as possible candidates for the appellation 'auto-immune disease' (see Kuwert *et al.*, 1965; and Dagg *et al.*, 1964, respectively).

In the case of pernicious anaemia there is also now a considerable amount of evidence suggesting an autoimmune aetiology. The atrophic gastritis invariably found shows histological features strikingly analogous to those of the thyroid in Hashimoto's disease (Markson & Moore, 1962). Approximately 80% of pernicious anaemia patients have antibodies against gastric parietal cells (Irvine *et al.*, 1962; Markson & Moore, 1962; Taylor *et al.*, 1962) and about 55% have antibodies to intrinsic factor (Ardeman & Chanarin, 1963). An appreciable proportion also have anti-thyroid antibodies (Irvine *et al.*, 1962). Like myasthenia gravis, pernicious anaemia also shows a clear clinical association with diseases of the thyroid (Tudhope & Wilson, 1962) and a high incidence of thyroiditis has been found at necropsy in pernicious anaemia (Williams & Doniach, 1962).

The combination of myasthenia gravis with pernicious anaemia was first mentioned by Row-

TABLE 1
Associated diseases found in thirty-seven cases of myasthenia diagnosed at the Bristol Royal Infirmary since 1953

Sex	Associated disease	Age of onset (years)	Age of onset of myasthenia (years)
M	Pernicious anaemia (present report)	62	62
F	Hypothyroidism	32	31
F	Hypothyroidism	55	53
F	Thyrotoxicosis	28	30
M	Thyrotoxicosis	51	53
F	Diabetes mellitus	14	15
M	Portal cirrhosis	58	54
F	Retrobulbar neuritis, disseminated sclerosis	17	43
F	Iron-deficiency anaemia and gastric achlorhydria	27	23

land *et al.* (1956), and Howard *et al.* (1965) found that eleven such cases had been seen at the Mayo Clinic up till 1960, but no antibody studies had been performed on those patients. Simpson (1960, 1964) states that nine of his series of 491 cases of myasthenia also had pernicious anaemia. The serum of one of these, a female aged 75 years, was tested for anti-nuclear factor and found negative. Antibody studies were not possible on the other patients except for a female aged 72 years, who at necropsy was found also to have had Hashimoto's disease. Her serum contained gastric complement-fixing and anti-thyroglobulin antibodies. Two other case reports of the triple disease combination of myasthenia, pernicious anaemia and myxoedema (or Hashimoto's disease respectively), which were diagnosed during life, have appeared recently: in one, Reaves (1965) demonstrated complement-fixing gastric and thyroid antibodies and gastric and skeletal-muscle antibodies by immunofluorescence; and Singer & Sahay (1966) report the finding in their case of skeletal muscle, thyroglobulin and thyroid cell antibodies, and gastric parietal cell and intrinsic factor antibodies.

The present case constituted the sole instance of the coexistence of pernicious anaemia and myasthenia gravis in the thirty-seven Bristol cases. He showed no clinical or immunological evidence of thyroid disease, but it is of interest that he had a low-normal protein-bound iodine level. While the onset of myasthenia in the over-60 age-group is uncommon, at this age the condition is slightly more common in men than in women (Simpson, 1960). The clinical criteria on which the diagnosis of myasthenia rests, namely weakness in voluntary muscle following repetitive activation, a tendency to recover with rest and therapeutic response to anticholinesterase drugs, were all present; and the diagnosis of pernicious anaemia, although the anaemia was still relatively mild, was fully established by the laboratory tests and the therapeutic response to vitamin B₁₂. Antibodies were present to both gastric parietal cells and muscle, both skeletal and cardiac. In addition antibodies to thymic epithelial cells were demonstrated. The simultaneous onset of these two suspectedly autoimmune diseases, and the presence of the organ specific antibodies, seem to provide some further evidence of their both being related to an underlying disturbance of immunological mechanisms.

Summary

A case is described in which myasthenia gravis and pernicious anaemia presented simultaneously in a 62-year-old man. Both diagnoses were fully established by the appropriate tests. Circulating antibodies to skeletal and cardiac muscle, calf

thymus epithelial cells, and gastric parietal cells, were demonstrated by immunofluorescence.

The evidence suggesting a possible role of autoimmune processes in these two diseases is discussed.

No further instances of this association were found in a review of thirty-seven cases of myasthenia, but several other associated diseases of possibly autoimmune nature were noted in these other patients.

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References

- ARDEMAN, S. & CHANARIN, I. (1963) A method for the assay of human gastric intrinsic factor and the detection and titration of antibodies against intrinsic factor. *Lancet*, **ii**, 1350.
- BEUTNER, E.H., WITEBSKY, E., RICKEN, D. & ADLER, R.H. (1962) Studies on autoantibodies in myasthenia gravis. *J. Amer. med. Ass.* **182**, 46.
- CASTLEMAN, B. (1955) *Atlas of Tumour Pathology*, Section 5, Fasc. 19. Armed Forces Institute of Pathology, Washington, D.C.
- DAGG, J.H., GOLDBERG, A., ANDERSON, J.R., BECK, J.S. & GRAY, K.G. (1964) Autoimmunity in iron-deficiency anaemia. *Brit. med. J.* **i**, 1349.
- DALY, J.J. & JACKSON, E. (1964) Case of Hashimoto's disease with myasthenia gravis. *Brit. med. J.* **i**, 748.
- DOWNES, J.M., GREENWOOD, B.M. & WRAY, S.H. (1966) Autoimmune aspects of myasthenia gravis. *Quart. J. Med.* **137**, 85.
- FELDKAMP, T.E.W., VAN DER GELD, H. & OOSTERHUIS, H.J.G.H. (1963) Studies on sera from cases of myasthenia gravis, using the fluorescent antibody technique. *Vox Sang. (Basel)*, **8**, 317.
- FELTKAMP-VROOM, T. (1966) Myoid cells in human thymus. *Lancet*, **i**, 1320.
- HENRY, K. (1966) Mucin secretion and striated muscle in the human thymus. *Lancet*, **i**, 183.
- HOWARD, F.M., SILVERSTEIN, M.N. & MULDER, D.W. (1965) The co-existence of myasthenia gravis and pernicious anaemia. *Amer. J. med. Sci.* **250**, 518.
- IRVINE, W.J., DAVIES, S.H., DELAMORE, I.W. & WILLIAMS, A.W. (1962) Immunological relationship between pernicious anaemia and thyroid disease. *Brit. med. J.* **ii**, 454.
- KUWERT, E., PETTE, E., FIRNHABER, W. & MAI, K. (1965) Demonstration of complement in spinal fluid in multiple sclerosis. *Ann. N.Y. Acad. Sci.* **122**, 429.
- MARKSON, J.L. & MOORE, J.M. (1962) Thyroid autoantibodies in pernicious anaemia. *Brit. med. J.* **ii**, 1352.
- NASTUK, W.L., PLESCIA, O.J. & OSSERMAN, K.E. (1960) Changes in serum complement activity in patients with myasthenia gravis. *Proc. soc. exp. Biol. (N.Y.)*, **105**, 177.
- NASTUK, W.L., STRAUSS, A.J.L. & OSSERMAN, K.E. (1959) Search for a neuromuscular blocking agent in the blood of patients with myasthenia gravis. *Amer. J. Med.* **26**, 394.
- REAVES, L.E., III. (1965) Altered immunologic mechanisms in diseases of unknown cause. *Geriatrics*, **20**, 707.

- ROWLAND, L.P., HOEFER, P.F.A., ARANOW, H., JR. & MERRITT, H.H. (1956) Fatalities in myasthenia gravis. *Neurology (Minneapolis)*, **6**, 307.
- SAHAY, B.M., BLENDIS, L.M. & GREENE, R. (1965) Relation between myasthenia gravis and thyroid disease. *Brit. med. J.* **i**, 762.
- SIMPSON, J.A. (1960) Myasthenia gravis: a new hypothesis. *Scott. med. J.* **5**, 419.
- SIMPSON, J.A. (1964) Immunological disturbances in myasthenia gravis with a report of Hashimoto's disease developing after thymectomy. *J. Neurol. Neurosurg. Psychiat.* **27**, 485.
- SIMPSON, J.A. (1966) Myasthenia gravis as an autoimmune disease: clinical aspects. *Ann. N.Y. Acad. Sci.* **135**, 506.
- SINGER, W. & SAHAY, B.M. (1966) Myasthenia gravis, Hashimoto's disease and pernicious anaemia. *Brit. med. J.* **i**, 904.
- STRAUSS, A.J.L., SEEGAL, B.C., HSU, K.C., BURKHOLDER, P.M., NASTUK, W.L. & OSSERMAN, K.E. (1960) Immunofluorescence demonstration of muscle binding complement fixing globulin fraction in myasthenia gravis. *Proc. Soc. exp. Biol. (N.Y.)*, **105**, 184.
- TAYLOR, K.B., ROITT, I.M., DONIACH, D., COUCHMAN, K.G. & SHAPLAND, C. (1962) Autoimmune phenomena in pernicious anaemia: gastric antibodies. *Brit. med. J.* **ii**, 1347.
- TUDHOPE, G.R. & WILSON, G.M. (1962) Deficiency of vitamin B₁₂ in hypothyroidism. *Lancet*, **i**, 703.
- VAN DE VELDE, R.L., FRIEDMAN, N.B., MILCH, M. & SMITH, J. (1966) Muscular elements of the thymus. *Fed. Proc.* **25**, Part 1, 661.
- VAN DER GELD, H. & OOSTERHUIS, H.J.G.H. (1963) Muscle and thymus antibodies in myasthenia gravis. *Vox Sang. (Basel)*, **8**, 196.
- WHITE, R. G. & MARSHALL, A.H.E. (1962) The autoimmune response in myasthenia gravis. *Lancet*, **ii**, 120.
- WILLIAMS, E.D. & DONIACH, I. (1962) The post-mortem incidence of focal thyroiditis. *J. Path. Bact.* **83**, 255.
- WOLF, S.M., ROWLAND, L.P., SCHOTLAND, D.L., MCKINNEY, A.S., HOEFER, P.F.A. & ARANOW, H., JR. (1966) Myasthenia as an autoimmune disease: clinical aspects. *Ann. N.Y. Acad. Sci.* **135**, 517.

Hepatoblastoma presenting as an acute abdomen

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PRIMARY liver tumours in infants and children are extremely uncommon (Edmondson, 1956). Packard & Palmer (1955) reported an incidence of only nine cases among 126,000 admissions to a Children's Hospital. Stowens (1959) found only four hepatomas in a series of 2172 tumours in infancy and childhood. Hepatomas are generally evident before the end of the second year of life. Although the sex incidence varies in different series, malignant liver tumours appear to be commoner in male children (Borman, Harbott & Morris, 1961).

Case report

The patient, a 6-year-old Sinhalese girl, was admitted to the General Hospital, Kandy (Ceylon) at 23.00 hours on 28 January 1966 with abdominal pain confined to the right iliac fossa of sudden onset that morning. She had vomited twice at the onset. There was no previous history of any significance.

On examination the patient's general condition was good; pulse, 104/min; respiration, 24/min; temperature, 98.4°F. She was tender in both right

iliac fossae and the left hypochondrium, but her abdomen was soft. No other abnormality was detected. Urine: no abnormality, WBC 10,000/mm³ (neutrophils 80%, lymphocytes 16%, eosinophils 4%).

Next morning her pulse was 98/min, respiration 24/min and she appeared pale. There was tenderness and guarding in the right iliac fossa. A diagnosis of acute appendicitis was made.

Operation (by M.K.). A right grid-iron incision was made. The peritoneum was blue, and dark brownish blood gushed out on opening the peritoneal cavity. The incision was closed and a long right paramedian incision was made. There was about a pint of free dark blood in the peritoneal cavity. The bleeding was found to occur from a rupture of a tumour of the liver. The tumour was oval in shape (3 × 2 × 1½ in.) and was situated on the inferior surface of the liver about 1 in. to the right of the gall bladder. Greyish friable tumour material and blood was found to exude from a rupture about 1 in. long on its inferior surface. The tumour appeared to be encapsulated. Two slender vascular strands were found to con-