who takes on responsibility for the long-term care of an addict is, in the author's opinion, performing a public service in keeping his patient out of trouble. Mention has already been made of the desirability of obtaining a second opinion on the case and of informing the Home Office.

The story given by the addict who comes to a casualty department asking for drugs cannot be accepted unreservedly and whenever possible must be checked—for example, by a telephone call to the addict's own doctor or to local dispensing chemists. It is suggested that drugs should only be given to addicts showing signs of withdrawal. Others who claim that their supply has run out but are not suffering as a result can be told to report back later if necessary. The addict who is trying to obtain extra drugs, perhaps for re-sale, is unlikely to come back with signs of withdrawal. It may be justifiable and indeed a necessary act of kindness occasionally (for instance at night) to give a suffering addict a dose of heroin, which he should inject himself before leaving the hospital. If he seems in need of a larger supply, say in the event of his own doctor being ill, it is suggested that he be given a prescription to take to a chemist rather than to the hospital dispensary. The official system of checking Dangerous Drug prescriptions can thus more easily detect addicts who are illegally obtaining supplies from two doctors simultaneously. If an addict is supplied with drugs by the hospital his own doctor should later be informed.

Addicts admitted to hospital for reasons other than attempted cure of their craving should be allowed their normal amounts of drugs while in the ward. Otherwise they will discharge themselves even though urgently needing treatment for serious or painful conditions.

Summary

In one year, 30 heroin (diacetylmorphine) addicts, most of whom also took cocaine, were seen in a casualty department in London. Most were obtaining regular supplies of drugs legally on prescription.

Addicts often came to the hospital seeking supplies of drugs. They also came for treatment of infections due to unsterile injections ; one died from bacterial endocarditis. Six addicts presented with barbiturate poisoning.

The physical features of heroin addicts are described. They are easily identified by the scars of multiple injections.

Some addicts were transferred elsewhere for in-patient withdrawal treatment, but the relapse rate was high.

The problem of heroin addiction in Britain is discussed. There has been a recent increase in the relatively small number here that could not be explained by an influx of Canadian addicts, many of whom soon returned home.

The legal position of the doctor treating the addict is outlined, and compared with the situation in the U.S.A.

Some suggestions on the management of addicts are made.

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Pernicious Anaemia, Myxoedema, and Hypogammaglobulinaemia — A Family Study

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Early in the history of pernicious anaemia it was recognized that the condition occurred occasionally in members of the same family (Sinkler and Eschner, 1896). The suggestion was made that there may be genetically determined factors in the aetiology of the disease. Many additional families (Gulland, 1907 ; Bartlett, 1913 ; Hurst, 1927) were reported and some large-scale surveys have revealed an increased incidence of pernicious anaemia in relatives of affected patients. Different workers have reported incidence varying from 5% (Levine and Ladd, 1921), 8% (Stamos, 1940) to 18% (Castle and Minot, 1936).

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There appears to be a particularly high family incidence in those rare cases where the condition occurs in children and young adults (Reisner, Wolff, McKay, and Doyle, 1951 ; Mollin, Baker, and Doniach, 1955 ; Leikin, 1960 ; Lambert, Prankerd, and Smellie, 1961).

The present study is of a family (see Fig. 1) in whom the mother and daughter have pernicious anaemia. The mother also has myxoedema and the daughter has hypogammaglobulinaemia. In addition, the mother's sister has no absorption of vitamin B_{12}, demonstrated by a Schilling (1953) test, and hypergammaglobulinaemia.

Case 1

The patient was a housewife aged 56. In 1936, when aged 31, she attended the London Hospital complaining of having had faints,

weakness, and a sore tongue for two years. She had also had tingling of the feet. She was pale and her tongue was smooth. A note was made at the time that her mother was attending the hospital for injections for pernicious anaemia. Investigations were as follows: the haemoglobin was 11 g./100 ml. (75%) with a red-cell count of 2,850,000/c.mm., giving a colour index of 1.28 and a mean corpuscular diameter of 8.8 μ. The white-cell and differential counts were normal. A histamine (0.5 mg.) test meal showed the " slightest
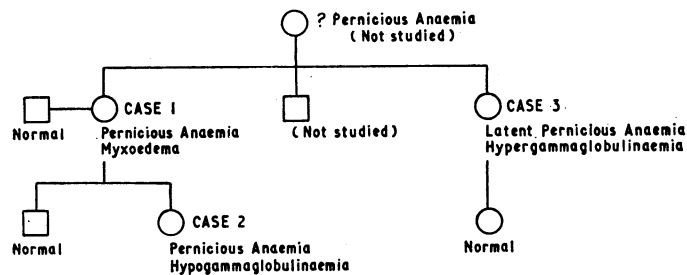

FIG. 1.—The family tree.

trace of free acid." She was given injections of liver extract with satisfactory haematological response (maximum reticulocyte count 4.6% on fourth day). There was no further complaint of tingling of the feet. She remained well for many years, the haemoglobin being above 13.2 g./100 ml. (90%) except during two pregnancies in 1939 and 1941.

In 1959, at a routine visit, she complained of hoarseness. Her appearance was suggestive of myxoedema, with cold dry skin and sparse dry hair. A radioactive iodine test showed that only 2% of an orally administered dose was taken up by the thyroid at 24 hours, confirming the clinical diagnosis of hypothyroidism. She improved after treatment with thyroid extract. In March 1962 she was admitted to hospital with jaundice and severe abdominal pain. The symptoms subsided within a week, but a sterile pleural effusion developed. During this admission the haemoglobin was 13.2 g./100 ml. (90%) with a white-cell count of 23,000, predominantly polymorphonuclear cells. Serum protein electrophoresis revealed a normal pattern. A cholecystogram showed poor concentration by the gall-bladder and no opaque calculi were seen. It was thought that she had had obstructive jaundice due to a gall-stone and the pleural effusion to be a reaction to a small cholangiolitic abscess. She was treated with penicillin injections, being discharged after four weeks feeling very well. Shortly after discharge a Schilling test showed no radioactivity in a 24-hour specimen of urine after oral administration of 0.5 microcurie of ^{58}Co vitamin B₁₂ (0.5 μg.). The test was repeated in December 1962 and 100 μg. of intrinsic factor given at the same time: 21.2% of the administered dose appeared in the urine.

Case 2

The patient, a secretary aged 23, was the daughter of the previous patient. When first seen in March 1962 she complained of excessive tiredness since an attack of " flu " three months previously. She had also noticed increasing breathlessness on exertion. She had lost a few pounds in weight but was otherwise well. She had no history of gastro-intestinal disorder or menstrual abnormality.

At the age of 12 years she developed urticaria, from which she had suffered intermittently until the age of 20. She had had several attacks of angioneurotic oedema, and on five occasions had choking and difficulty in breathing, requiring injections of adrenaline for relief. There had been no attacks for three years, but the urticaria has recurred since she came under observation. Aspirin and aspirin-containing drugs are known to bring on these attacks. At the age of 18 she had a febrile illness associated with drowsiness and signs of meningeal irritation. She was admitted to the local fever hospital and a diagnosis of acute benign encephalomyelitis was made. Examination of the blood at that time showed a haemoglobin of 7.3 g./100 ml. (50%). The red cells showed poikilocytosis and polychromasia. She was treated with iron by mouth, but two months later the haemoglobin was only 8.7 g./100 ml. (60%). A course of intramuscular iron was given, after

which no further blood examination was made. She had not taken iron by mouth again nor had further injections.

On examination after admission to hospital in May 1962 she was pale, had a smooth tongue, and her spleen was palpable. There were no abnormal neurological signs. On investigation the haemoglobin was 6.6 g./100 ml. (46%), and the mean corpuscular haemoglobin concentration was 35%. The red cells showed marked anisocytosis and poikilocytosis and there were fairly frequent macrocytes and some polychromatic cells. A very occasional nucleated red cell and one late megaloblast were seen. Of the red cells 3.2% were reticulocytes. The white-cell count was 6,800/c.mm. (47% neutrophils, 43% lymphocytes, 4% eosinophils, 2% monocytes, 2% metamyelocytes, 2% neutrophil myelocytes). Platelets appeared plentiful. Examination of a sternal-marrow specimen showed erythropoiesis to be almost entirely megaloblastic, all stages of megaloblasts being seen, many of the late ones containing Howell-Jolly bodies. Leucopoiesis showed numerous macromyelocytes and giant metamyelocytes. An increased number of mitotic figures were seen. The megakaryocytes were reduced in number and appeared to be poor in platelet production. No plasma cells were seen. Plasma proteins were 5.6 g./100 ml. (albumin 3.9 g., globulin 1.7 g.). Serum electrophoresis showed a virtual absence of gamma-globulin (Fig. 2). Serum bilirubin was 0.7 mg./100 ml. and the urine contained an excess of urobilinogen. The other liver-function tests were normal. The direct antiglobulin test was weakly positive
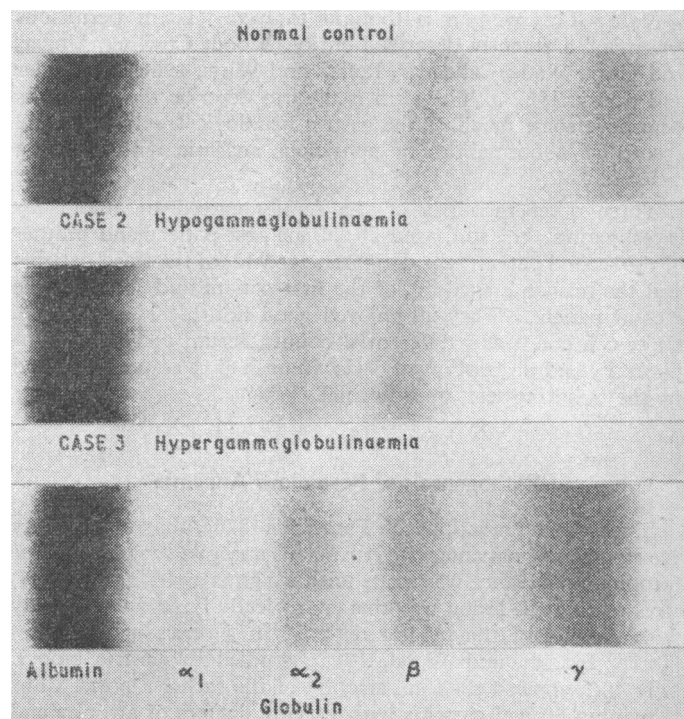

FIG. 2.—Serum electrophoretic strips from Cases 2 and 3, with a normal control.

at 1 in 60 and positive at 1 in 8. Gastric analysis showed histamine-fast achlorhydria to maximal histamine stimulation (0.04 mg./kg. body weight). Barium meal and follow-through examination were normal and there was no flocculation of barium in the small bowel. Faecal fat in samples collected over five days showed an excretion of 3.5 g./day. A Schilling test showed excretion of only 2.5% of an orally administered dose of ^{58}Co vitamin B₁₂ in a 24-hour collection of urine.

Treatment with vitamin B₁₂ produced an excellent response (reticulocytes 46%). As the haemoglobin rose it became apparent that iron deficiency was also present. With oral iron the haemoglobin rose to 14.9 g. (102%). The antiglobulin test was negative after the first injection of vitamin B₁₂. The Schilling test was repeated in December 1962 with 100 mg. of intrinsic factor, and 13.5% of the administered dose appeared in the urine.

Estimation of the gamma-globulin by the gel-diffusion precipitation reaction showed a value of 60 mg./100 ml. In addition the gamma-macroglobulin components were: B₂ 6% and B₂ less than

12% of standard "normal" serum. This low B_{2A} level confirmed the previous finding of virtual absence of isoagglutinins, though her red cells grouped as O rhesus positive.

Note: This girl has pernicious anaemia and hypogammaglobulinaemia. Megaloblastic anaemia has been reported in some cases of hypogammaglobulinaemia as being due to steatorrhoea (Sanford, Favour, and Tribeman, 1954 ; Rohn, Behnke, and Bond, 1955 ; Rosecan, Trobaugh, and Danforth, 1955 ; Gitlin, Gross, and Janeway, 1959 ; Cohen, Paley, and Janowitz, 1961). This patient had normal stools, with no excess of faecal fat measured over five days, and the impaired absorption of vitamin B_{12} was corrected by the administration of intrinsic factor.

Case 3

A housewife aged 52, sister of the patient in Case 1, agreed to attend for investigation. She had been in good health all her life. The haemoglobulin was 13.5 g./100 ml. (93%) and the white-cell count was 11,000/c.mm., with a normal differential count. Serum protein electrophoresis showed an increase in the gamma-globulin (Fig. 2). A Schilling test showed excretion of 0% of an orally administered dose of ^{58}Co vitamin B_{12} in a 24-hour specimen of urine. This increased to 13.6% when the test was repeated with 100 mg. of intrinsic factor.

Note: This woman is thought to have "latent pernicious anaemia," a recently described entity (Wood, Cowling, Ungar, and Gray, 1960 ; Callender, Retief, and Witts, 1960 ; Callender and Spray, 1962). The term is used to describe those patients who have some or all of the gastric histological, secretory, and absorptive abnormalities of pernicious anaemia without being anaemic.

Three other members of the family agreed to attend for investigation: the son, aged 20, of the first patient and brother of the second patient; the daughter, aged 12, of the third patient; and the husband, aged 58, of the first patient and father of the second patient. They all enjoyed good health. Haemoglobin, white-cell count and differential counts, serum protein electrophoresis, and absorption of ^{58}Co vitamin B_{12}, as demonstrated by the Schilling test, were normal.

Pathogenesis of Pernicious Anaemia

Since the observations of Fenwick (1870), that at necropsy the stomach of patients with pernicious anaemia showed extreme atrophy, no advance was made until Magnus and Ungley (1938) stressed that the lesion was characteristically limited to the body with sparing of the pyloric region. In a series of 100 cases (Joske, Finckh, and Wood, 1955), studied by gastric biopsy, only 40% showed the total atrophy of the earlier reports. The remaining 60 had gastritis with varying degrees of atrophy and cellular infiltration. These findings have been confirmed by other workers (Magnus, 1958). Studies in patients without pernicious anaemia (Davidson and Markson, 1955 ; Joske *et al.*, 1955) have shown the same range of findings, although the changes were less frequently severe. Fully developed gastric atrophy has been reported as preceding the development of pernicious anaemia by some years (Robertson, Wood, and Joske, 1955). For years following Castle's work, the cause of pernicious anaemia had been thought to be impaired secretion of intrinsic factor due to gastric atrophy, although this view had been questioned by some authorities (Askey, 1944 ; Murphy, 1948). Several cases have now been reported of proved pernicious anaemia in children and young adults where gastric biopsy revealed normal gastric mucosa (Mollin *et al.*, 1955 ; Leikin, 1960 ; Lambert *et al.*, 1961). It becomes apparent either that gastric atrophy is not essential to the development of pernicious anaemia or that pernicious anaemia in children and that in adults are different diseases. However, its occurrence in both age-groups within the same family makes the latter suggestion unlikely.

Histamine-fast achlorhydria is the almost invariable finding when the gastric secretion of hydrochloric acid is examined in pernicious anaemia. This correlates well with the atrophic gastritis or gastric atrophy usually found, but, again, normal acid secretion is sometimes demonstrated, especially in children. Studies of the gastric mucosa and acid secretion in relatives of patients with pernicious anaemia (Callender and Denborough, 1957 ; McIntyre, Hahn, Conley, and Glass, 1959) have revealed that gastric atrophy and atrophic gastritis and achlorhydria are commoner than in normal controls. Studies of vitamin B_{12} absorption have helped to make the position clearer.

McIntyre *et al.* (1959) carried out a comprehensive survey of relatives of sufferers from pernicious anaemia and of controls, using a slightly modified Schilling test to measure radioactive vitamin-B_{12} absorption. Eight out of 97 controls excreted less than 15% of the administered dose, whereas 40 out of 106 relatives excreted less than 15%—a result thought to be highly significant. There was also an increase in borderline cases with increase in age in the family group. A few cases in the control groups showed very low absorption without haematological abnormality, but a family study of one of these revealed that the father had died of pernicious anaemia and a grandmother of subacute combined degeneration of the cord. From their studies they believed that the genetic basis for the transmission of pernicious anaemia constituted a susceptibility to develop the disease. It was suggested that those so predisposed may be discovered by a study of physiological and/or morphological factors before the full development of the condition. They likened the situation to that of gout and the discovery of hyper-uricaemia in unaffected relatives.

A further possible mechanism in the pathogenesis of pernicious anaemia was suggested by the work of Taylor and Morton (1958) and of Schwartz (1958), who demonstrated intrinsic-factor antagonists in the serum of patients with the disease. These workers thought that they were dealing with a true antibody, localized to the globulin and disappearing with the use of hydrocortisone. Taylor (1959), in particular, thought pernicious anaemia likely to be an autoimmune disease. Irvine, Davies, Delamore, and Wynn-Williams (1962), and Taylor, Roitt, Doniach, Couchman, and Shapland (1962) have shown that the serum of a high proportion of patients with pernicious anaemia has antibody to an antigen prepared from cells of the parietal region of human stomach. These findings are not incompatible with a genetic basis in the aetiology of pernicious anaemia, since genetic mechanisms have been invoked in autoimmune disease, notably by Burnet (1959). Irvine *et al.* (1962) also showed that 37% of patients with pernicious anaemia have complement-fixing antibodies to thyroid compared with 4% of hospital controls. In addition, 22% of cases of spontaneous hypothyroidism, 29% of cases of Hashimoto's disease, and 4% of hospital controls showed complement-fixing antibodies to stomach. Markson and Moore (1962) also demonstrated an increased incidence of thyroid antibodies in pernicious anaemia.

Pernicious Anaemia and Thyroid Disease

The combination of pernicious anaemia and thyroid disease has been described previously by many authors (Kerppola, 1923 ; Wilkinson, 1933 ; Murphy and Howard, 1936). The concept of a specific hyperchromic anaemia due to thyroid deficiency was put forward by Bomford (1938), who described four such cases and one of true pernicious anaemia among 10 anaemic myxoedemic patients.

Tudhope and Wilson (1960, 1962) studied a number of cases of hypothyroidism with anaemia, using serum-vitamin-B_{12} levels, vitamin-B_{12} absorption tests, gastric biopsy, and gastric acidity after maximal histamine stimulation. Their first report (1960) refers to 166 cases of hypothyroidism, 116 of which were investigated haematologically. Twenty-seven were found to be

anaemic and 13 (7.8%) in fact had pernicious anaemia. They noticed that pernicious anaemia occurred more commonly (10.3%) in cases of spontaneous hypothyroidism than when thyroid underactivity followed irradiation or surgery (4.3%), and their second study (Tudhope and Wilson, 1962) was carried out on spontaneous primary hypothyroidism (including some cases from the previous series). Nine cases had pernicious anaemia with all the expected findings, but some of the results in the remainder are of interest. Of the 52 cases tested, 24 had histamine-fast achlorhydria. Fifteen of these had serum-vitamin-B_{12} levels that were lower than most normals, although not as low as the overt pernicious anaemia cases, the range being 79–416 $\mu\mu$g., with a mean of 158 $\mu\mu$g. This compares with a mean of over 200 $\mu\mu$g. in all hypothyroid cases without achlorhydria. Eleven of these cases were investigated further and seven were also found to have impaired vitamin-B_{12} absorption, although all had normal bone-marrow and peripheral blood, being further instances of latent pernicious anaemia. Five of these have been followed for four years, and although in some instances the serum vitamin-B_{12} and vitamin-B_{12} absorption have fallen further in spite of adequate thyroid replacement therapy, no case of overt pernicious anaemia has yet occurred among them. Thus, in addition to overt pernicious anaemia, a latent form of the illness is apparently not uncommonly associated with hyperthyroidism and occurs especially in patients with histamine-fast achlorhydria.

Roitt and Doniach (1958) have demonstrated that most cases of primary adult myxoedema have an autoimmune basis, and this mechanism has also been suggested in the aetiology of pernicious anaemia (Taylor, 1959 ; Schwartz, 1960). Owen and Smart (1958) detected thyroid auto-antibodies in a case of pernicious anaemia without thyroid disease. Further evidence of an immunological relationship has been provided by the work of Irvine *et al.* (1962) and of Markson and Moore (1962) mentioned in the preceding section, and Williams and Doniach (1962) showed an increase in the post-mortem incidence and severity of thyroiditis in pernicious anaemia.

Pernicious Anaemia and Hypogammaglobulinaemia

The level of gamma-globulin in normal serum is from 600 to 1,500 mg./100 ml. (Petermann, 1960). The M.R.C. working party accepted a level of less than 200 mg. for the diagnosis of hypogammaglobulinaemia (Kekwick, Vallet, Cutbush, Mollison, Thomas, Gell, and Soothill, 1961). Primary and secondary varieties of the condition are recognized. Primary hypogammaglobulinaemia is further subdivided into congenital and acquired forms. Primary congenital hypogammaglobulinaemia appears to be inherited as a sex-linked recessive characteristic (Gitlin, 1955). The disorder has so far appeared only in male patients, and the evidence suggests that it is transmitted through females (Porter, 1955 ; Jamieson and Kerr, 1962). In this form the lymph nodes are almost entirely lacking in normal follicles and plasma cells. It seems likely that the disorder is due to a genetic variation involving the lack of formation or suppression of plasma cells. The primary acquired form affects adults of either sex. Important features are an increased susceptibility to bacterial infection, absence of antibodies from the blood and tissues, and failure of antibody formation in response to antigenic stimulation. Characteristic findings in the primary condition are the absence of plasma cells from the bone-marrow and the frequent absence of isohaemagglutinins, indicating an additional deficiency of beta-2 macroglobulin (Soothill, 1962). Transient neutropenia and lymphopenia have been described (Domz and Dickson, 1957).

Secondary hypogammaglobulinaemia has been recorded in association with a number of conditions. It is most often found with diseases of the reticulo-endothelial system such as multiple myeloma, Hodgkin's disease, lymphoma, chronic lymphatic leukaemia, and thymic tumours. A difference from the primary

form is that plasma cells may be found in the bone-marrow. The occurrence of pernicious anaemia and hypogammaglobulinaemia in the same patient was first described by Klayman and Brandborg (1955). They diagnosed pernicious anaemia in a man aged 41 who was known to have had hypogammaglobulinaemia for eight years. Lewis and Brown (1957) reported the case of a man with the features of hypogammaglobulinaemia from the age of 18 years who was found to have pernicious anaemia and diabetes mellitus when aged 30. Gibbs and Pryor (1961) and Paull (1961) have added further cases of pernicious anaemia with hypogammaglobulinaemia. Crowder, Thompson, and Kupfer (1959) reported the case of a further patient with this combination who was also subject to multiple allergies. Case 2 in the present series therefore provides a second example of this syndrome. Asthma and urticaria in patients with hypogammaglobulinaemia have been described by Zbar, Cippes, and Alterman (1956), Freedman, Brown, and Myers (1958), and Painter and Korst (1959). This is less of an anomaly than may at first appear, since the tissue antibodies involved in such allergic processes are not exclusively gamma-globulin, but are also found in the alpha-2 and beta components (Cann and Loveless, 1954 ; Sehon, Fyles, and Rose, 1955 ; Cooke, Menzel, Myers, Skaggs, Zeman, 1956 ; Painter and Korst, 1959). The failure in these patients to develop sufficient gamma-globulin antibodies in response to microbial invasion renders them prone to frequent infections and thereby to infective allergy.

Discussion

Burnet (1959), in proposing his clonal selection theory of acquired immunity, has suggested that the autoimmune diseases are genetically determined. The heredity and the autoimmune basis of pernicious anaemia have already been discussed. The occurrence of Hashimoto's disease in several members of the same family (Dunning, 1959 ; Smart and Owen, 1960 ; Irvine, Macgregor, Stuart, and Hall, 1961 ; de Groot, Hall, McDermott, and Davis, 1962) has been reported, and, in addition, thyroid antibodies have been found in the serum of members of families suffering from Hashimoto's disease (Hall, Owen, and Smart, 1960). The immunological relationship between pernicious anaemia and thyroid disease (Owen and Smart, 1958 ; Irvine *et al.*, 1962) has been alluded to. Further evidence of interrelationship between different autoimmune diseases is provided by the occurrence of Hashimoto's disease and systemic lupus erythematosus in the same patients (White, Bass, and Williams, 1960). In addition, systemic lupus erythematosus has occurred in different members of the same family (Davis and Gutridge, 1951 ; Pirofsky and Shearn, 1953 ; Leonhardt, 1957 ; Marlow, Peabody, and Nickel, 1960). Leonhardt also found hypergammaglobulinaemia in five siblings of three sisters with systemic lupus erythematosus. Serological studies have shown a high incidence of L.E. factor within families (Garcia-Morteo, Franklin, McEwen, Phythyon, and Tanner, 1961). Citron (1957) and Zelman and Lewin (1958) observed a raised gamma-globulin level in sera from relatives of patients with hypogammaglobulinaemia of the adult type. Hijmans, Doniach, Roitt, and Holborow (1961) noted the serological overlap between different autoimmune diseases, notably lupus erythematosus, rheumatoid arthritis, and thyroid autoimmune disease. In a most interesting family described by Wolf (1962) several members suffered from different collagen diseases, lymphomas, and also thrombocytopenic purpura. One, a woman of 30, also had hypogammaglobulinaemia. Hypogammaglobulinaemia has been reported with rheumatoid arthritis (Good, Rötstein, and Mazzitello, 1957), and rheumatoid arthritis in the relatives of patients with hypogammaglobulinaemia (Rötstein and Good, 1962).

Many cases of primary acquired and secondary hypogammaglobulinaemia may be manifestations of a genetically determined state of altered tissue sensitivity. This may declare itself in one

or more of a number of ways, the particular manifestation being determined by exposure to external stimuli such as infection. The same manifestation may occur more frequently in different members of the same family because in normal circumstances they will be exposed to similar stimuli, especially infection. Alternatively, particular organs or systems may be at increased risk because of more specific inherited abnormalities.

ADDENDUM.—Since this paper was prepared, Case 1 has developed an acquired haemolytic anaemia with thrombocytopenia. The Coombs test was positive, and tests with anti-human globulin in serial dilutions indicated that the cells were coated with an antibody of the warm type. She has been treated with prednisone and has improved, the haemoglobin increasing from 6.7 g. per 100 ml. (46%) to 12.7 g. per 100 ml. (87%).

Summary

A family is described in which two members had pernicious anaemia and one had latent pernicious anaemia. This was associated with myxoedema, hypogammaglobulinaemia, and hypergammaglobulinaemia respectively. These observations are discussed in the light of present concepts of autoimmune diseases.

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