THE HALF-LIFE OF IMMUNE GLOBULIN G IN CHRONIC BENIGN CRYPTOGENIC HYPERGAMMAGLOBULINAEMIC PURPURA WITH PIGMENTATION

And a Report of a Case

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THE purpose of reporting this case is to add evidence that the syndrome is truly an entity, to record the high level of immune globulin G, and to report that the half-life of the immune globulin G in this case is normal or diminished. The elevation of the serum immune globulin G is due to excessive production, and not to slow or diminished removal from the plasma.

Waldenström reported the syndrome in 1943, and then reported this and a different dysproteinaemic disease, macroglobulinaemia, in a single paper in 1948. Physicians are still sometimes confused because the hyperglobulinaemia and the macroglobulinaemia both have borne his name. It has also been confusing that purpura occurs in the course of several hyperglobulinaemic diseases. Chronic benign cryptogenic hypergammaglobulinaemia with purpura and skin pigmentation differs from macroglobulinaemia inter alia in the patient remaining generally well, the course being benign, the bone marrow being normal, the lymph glands not being enlarged, and the dysproteinaemia being an excess of immune globulin G and not an excess of a macroglobulin. It is more rare than macroglobulinaemia.

Not every case of purpura and hyperglobulinaemia is Waldenström's hyperglobulinaemic purpura, which is very uncommon. It is characterised by frequent crops of small purpuric spots, repeated over many years, predominantly on the lower legs, the spots being obscured in time by permanent heavy brown pigmentation of the affected skin. The serum protein electrophoresis shows a high peak in the gammaglobulin area. The main rise is in the immune globulin G fraction which reaches 3 grammes and over. There may be occasional swelling of a parotid gland. The lacrimal glands may be affected, with some diminution of tear production. Corneal damage may occur and probably is in some degree due to dryness of the eyes. Dryness of the mouth is not severe, nor is the dryness of the eyes. As time goes by, the pigmentation of the lower legs deepens. Eventually the pigmentation is much more striking than the original purpura, and then, though the purpura still occurs, it can hardly be seen. Small keratoses may appear in the pigmented skin. The disease lasts so long as life itself. The only serious disability is impairment of sight if the corneal damage is severe. There is no bleeding tendency. The cause is unknown. The dark skin and the protein changes are reminiscent of kala-azar, but no infection or infestation has been identified.

CASE REPORT

The present patient is a married woman born in 1925. The skin changes and the general condition can be seen in Figures 1 and 2. One of us has observed the

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patient for 17 years, since the purpura first appeared in 1955. She remains well from a general point of view, and indeed never was generally ill. The main disability is some opacification of the cornea, due at least in part to dendritic ulceration. Fresh purpuric spots on non-pigmented skin may occasionally be seen on the forearms if she has been carrying a basket, or very infrequently on the lower abdomen. Multiple keratoses have arisen on the pigmented skin of the lower legs. There is no itching and there are no ecchymoses. The abnormality does not resemble lichen amyloidosus. There has been no oedema. There was one short spell of unilateral parotid gland swelling. In earlier years the spleen tip could just be palpated, but lately that is not so. There has regularly been a moderate anaemia with nondescript peripheral blood findings. There was no granulocytopenia and no lymphocytosis. Platelet count normal. The total white cell count has ranged from 3,600 to 5,400. The white cells contained no inclusions. The serum iron has been low and on one occasion the serum folic acid was low. For a long time she was troubled with pain about the left temporal area, for which no cause could be found. Perhaps it was due to the keratopathy or lacrimal adenopathy. There have been no signs of arthritis, arteritis, renal disease or tubular acidosis. In 1963 there was rather severe herpes febrilis on the face in the course of an attack of bronchopneumonia. Earlier in the same year she had
had herpes zoster. Except with such occasional infections there has been no fever. She has had no frequent or severe or unusual infections. There has been no enlargement of lymph glands, no cosinophilia, and no evidence of liver disease. The bromsulphthalein test was normal. There is neither hyperthyroidism nor hypothyroidism. No evidence of small intestine or colon disease or chronic bronchopulmonary disorder has appeared. Menstruation has been regular. Cold produces no ill effects. There is no peripheral circulatory or ischaemic abnormality. There is no enlargement of the thymus to be seen in the chest x-ray. The bone marrow is normal. Blood group is A, Rh positive. The colour vision is normal and chromosome analysis 46/XX.

The serum protein electrophoreses showing the high gammaglobulin peak can
be seen in Fig. 3. The serum untracentrifugation pattern showing an excess of 7 S component can be seen in Figure 4. The serum immune globulin estimations showing the high level of immune globulin G and a modest rise in immune globulin M can be seen in Table I. Serum albumin is normal, serum fibrinogen 380 mgm. per cent and serum cholesterol 139 mgm. per cent. The plasma specific gravity is 1.035 and E.S.R. 120. The urine contains no abnormal protein and no light chains. There has been no amino-aciduria. Histological examination of keratotic lesions on the leg showed no evidence of amyloid.

The following serological tests are positive – antinuclear factor, smooth muscle antibodies, and rheumatoid arthritis latex test. Wassermann and Reiter protein complement fixation tests anticomplementary. Antistreptolysin titre is 1/625. The following tests are negative – mitochondrial antibodies, parietal cell antibodies, intrinsic factor antibodies, complement fixation test against thyroid microsomes, tanned red cell agglutination, Rose-Waaler, venereal diseases reference laboratory, fluorescent treponemal antibody, Paul-Bunnell, brucella, Widal, and leptospiral agglutination. Direct Coomb’s test is negative. There are no irregular red cell antibodies and the anti-B titre is 1/4.

Australian antigen negative in immune diffusion test. Serological tests for the following viruses all showed results, as the reciprocal of antibody titre, of less than 10 – adenoviruses, psittacosis/lymphogranuloma, Q fever, mycoplasma pneumonieae, mumps V, measles, lymphocytic choriomeningitis, herpes simplex and louping ill.

Her father and mother were not related. She is one of 10 brothers and sisters. The rest are healthy. She has one son who was considered to have coeliac disease in early childhood and was treated with a gluten-free diet. He is now tall and is athletic. The son has no abnormality of his serum proteins, nor have the three brothers and four sisters who have been examined.

**MEASUREMENT OF IgG TURNOVER**

The method of investigation followed the techniques described in detail by Veall and Vetter (1958) for plasma protein turnover studies. The IgG fraction was separated from the patient’s serum and labelled with Iodine-125 by Dr. A. S. McFarlane, to whom we are deeply indebted. Lugol’s iodine solution was given daily to the patient and a control, starting two days before administration of the radioactive dose and continuing throughout the study, to block the uptake of radiiodine by the thyroid. One hundred microcuries $^{125}$I–IgG were administered intravenously to the patient and the control, and samples of plasma and 24 hour
urine specimens were collected daily for 14 days. The radioactivity in the plasma was expressed as a percentage of the 10 minute plasma sample, and the quantity of radioactivity in the 24 hour urine collections expressed as a percentage of the dose given, from which the percentages remaining in the total body of each subject on successive days were calculated. These values are displayed on semilogarithmic paper against time in Figure 5, and Table II summarises the results obtained from both the patient and the control subjects.

The equilibrium time, $T_e$, at which the amount of labelled IgG passing from the plasma to the extravascular fluid equals the amount passing in the opposite direction, is less for the patient than the control, being 3.2 and 4.5 days respectively. The plasma IgG pool was calculated by multiplying the plasma volume, determined from the radioactivity detected in the 10 minute plasma sample, and the plasma IgG concentration. For each 24 hour period the plasma IgG degradation rate constant was obtained by dividing the percentage of the dose of radio-iodine excreted in the urine by the average amount remaining in the plasma during the same period. The average plasma IgG degradation rate constant ($k_1$) was 12.8 per cent per day for the patient and 8.3 per cent for the control. These values are the slopes of the tangents to the plasma curves at the respective equilibrium times shown in Figure 5.

Utilizing the relationship that the half-life ($T_{1/2}$ days) equals 0.693 divided by the plasma degradation rate constant $k_1$, the metabolic degradation of the plasma IgG pool in the patient and the control was found to be characterised by a half period 5.4 and 8.3 days respectively. The difference between the percentage of the radioactive dose remaining in the total body and that in the plasma provides the percentage remaining in the extravascular IgG pool, and from this the total IgG pool in the patient and the control were determined. The half-life of the total IgG pool estimated from the total body curve was 10.1 and 14.9 days for the patient and the control respectively.

### Table II. Summary of results obtained in patient and control, using the patient's labelled IgG to examine turnover.

|                  | Patient | Control | Units |
|------------------|---------|---------|-------|
| Weight           | 68.2    | 89.1    | kg    |
| Plasma IgG conc. | 3.5     | 0.95    | g/100 ml |
| Plasma Volume    | 45.7    | 39.5    | ml/kg |
| Plasma IgG pool  | 1.60    | 0.38    | g/kg  |
| Plasma IgG Degradation Rate Constant ($k_1$) | 12.8 | 8.3 | % per day |
| Plasma IgG Metabolic Degradation Rate | 0.205 | 0.032 | g/d/kg |
| Equilibrium Time ($T_e$) | 3.2 | 4.5 | days |
| Plasma IgG Half-life ($T_{1/2}$) | 5.4 | 8.3 | days |
| Intravascular: Extravascular distribution | 1: 0.86 | 1: 0.80 | |
| Total IgG Pool   | 2.98    | 0.69    | g/kg  |
| Total IgG, Half-life | 10.1 | 14.9 | days |

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FIG. 5. Rates of disappearance of the patient's IgG from the plasma and from the total body in the patient are more rapid than in a control.
These results indicate that the high plasma concentration and total IgG pool in the patient are due to an increased production of immune globulin G. The breakdown of this labelled protein is more rapid in the patient, in whom its half-life is shorter, 5.4 days, compared with 8.3 days in the plasma pool of the control subject.


discussion

These cases are very rare, but the reports of Waldenström (1948, and 1952—cases 5 and 6), Taylor and Battle (1954), Sheon et al (1966), Kay and Robertson (1955), Seiden and Wurzel (1956), Hambrick (1958), Strauss (1959) and Weiss et al (1963) lead us to think that this is a disease sui generis. It has to be distinguished from other pigmented purpuric eruptions (Hambrick 1958, Randall et al 1951), and from other examples of dysproteinæmia with purpura such as occur in macroglobulinaemia, cryoglobulinaemia, myeloma and Hodgkin's disease (Krauss and Sokal 1966). Nor does the case of Savin (1965) belong to this syndrome. Though there was purpura for 14 years, it was intermittent. The globulin was a beta globulin. There was a marrow plasmacytosis. There was extreme lipidaemia, and the patient died of coronary artery occlusion. We think that the lack of disability, the benign course for many years, the type of chronic purpura and pigmentation described and illustrated here, a serum immune globulin G over 3 grammes, and the absence of known causes of hyperglobulinaemia (such as plasmacytoma, leishmaniasis and lymphogranuloma venereum) are sufficient to make a provisional diagnosis. Solitary plasmacytoma should be excluded by x-ray examination of the skeleton.

Though the course may be generally benign for many years, tumorous or neoplastic complications may in some cases occur in the end. The case of Taylor and Battle (1954) in the seventeenth year of observation developed a plasmacytoma of tongue (Sheon et al 1966). It was treated with radiation and the patient was alive and well four years later. The case of Rogers and Welch (1957) was probably one of hyperglobulinaemic purpura of this kind, and myeloma supervened in the eleventh year. Although there was no purpura or pigmentation, the case of 'benign' chronic hyperglobulinaemia of Kyle and Bayrd (1966) developed myeloma in the eighteenth year of observation. Nevertheless such an outcome would not invalidate the original diagnosis. Such a tumorous complication may be analogous to carcinoma occurring after many years in ulcerative colitis, or in a Plummer-Vinson stricture. It may be a result of a longstanding disturbance (in this case at least immunological) and not a part of it from the beginning.

In Hambrick's case (1958) the spleen was examined histologically. The pulp contained a "considerable number" of plasma cells. The lymph glands showed a "moderate number" of plasma cells. In case 5 of Waldenström (1952) the spleen was examined histologically and nothing remarkable found. Bone marrow biopsy in these cases has shown no evidence of myeloma, unless or until myeloma supervened. We have found no report of amyloidosis being observed.

The half-life of the total IgG pool in normal people using their labelled IgG has been reported to be from 17 to 32 days (Solomon et al 1963). The half-life of the patient's IgG in herself is much less than that. There is no evidence of any
loss of IgG or of its breakdown products in the patient’s urine and, although we
cannot exclude loss from the alimentary tract mucous membrane, there seems no
reason to suppose it. The shortened half-life must then be due to a rate of katab-
olism quicker than normal. The half-life of the patient’s IgG in the control is
similar to, if a little less than, the reported normal. It must be remembered that
we do not know what the life of IgG from a normal person would be in the
patient. Rapid katabolism cannot however explain the high serum level of IgG,
which must be due to over-production. The over-production of IgG cannot be
accounted for by any tumour, nor by hypertrophy of any tissue. We have not
found an increase in the plasma cell population. We cannot explain the shortened
half-life of the patient’s IgG in the patient compared to the control, unless
perhaps an antibody to her own IgG is present, or unless the IgG is in part an
antibody rapidly reacting with an antigen and being removed quickly from the
IgG pool. Capra et al (1971) have reported the presence of antigammaglobulins
of IgG type in hyperglobulinaemic purpura, and they consider that in the majority
of such patients the increase in IgG is mainly due to an increase in antigamma-
globulin of IgG type.

SUMMARY

A case of chronic hypergammaglobulinaemic purpura with pigmentation has
been observed for 17 years. Corneal damage is the main disability. The course
has been otherwise benign, and consistent with the disorder being an entity distinct
from other dysproteinaemias. The pattern is that of the type case of Walden-
ström’s original description.

Immune globulin G is much increased in amount in the patient’s serum. There
is a modest increase in immune globulin M. The half-life of the immune globulin G
is less than normal, and not prolonged, as had been thought possible.

Criteria for diagnosis are suggested. Precision is necessary in distinguishing the
various dysproteinaemic syndromes associated with purpura.

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