Mechanisms in secondary hypogammaglobulinaemia

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Hypogammaglobulinaemia refers to the low levels of circulating antibodies associated with a decreased gammaglobulin zone on electrophoresis. Since IgG is the predominant immunoglobulin a deficiency of it will most readily affect the gammaglobulin zone. Deficiencies of IgA and IgM will not necessarily result in a visual decrease in the latter. For practical purposes the clinically important states are the low immunoglobulin levels associated with disease. For IgG, severe hypogammaglobulinaemia is defined as a serum level in an adult of less than 2.0 g/l (MRC Working Party, 1969). At this level 70% of patients suffer severe infection (Hobbs, 1968). During the first six months of life infants commonly have levels below 2.0 g/l, so that in this period 1.0 g/l is better taken as the critical level.

If the onset occurs before the age of 3 years (during which time children are building up their memory bank of IgG responses) the residual IgG is poorer in quality than in an adult and infection is much more of a problem. In adults the quality can be so good that down to 1.0 g/l there is no obvious infection, but the usually preceding loss of IgA and IgM can predispose to gut disturbances and malabsorption and loss of weight are common.

In some cases primary humoral responses may be affected and infection with organisms not previously encountered may occur long before levels of immunoglobulins are seen. Hypogammaglobulinaemia may be a result of a longer term inhibition of the humoral immune system, which may be preceded in the early stages by failure to mount a primary response. A normal gammaglobulin level does not necessarily exclude specific humoral response deficiencies (Hobbs, 1966; Hobbs, 1969). The immunoglobulin deficiency can arise from a variety of immunological abnormalities, which may be genetically determined or may be secondary to some other condition.

Secondary hypogammaglobulinaemia is 10-100 times more common than the primary forms. In this paper we shall consider clinical conditions which give rise to secondary hypogammaglobulinaemia, with particular reference to the mechanisms producing it. These may be considered under five broad headings (Table 1; Hobbs, 1971).

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<tr>
<th>Table 1</th>
<th>Secondary hypogammaglobulinaemia</th>
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<td>Transient</td>
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The first category is that of transient hypogammaglobulinaemia of infancy. It is often referred to as a primary immunodeficiency, but this is strictly incorrect. It is not sex-linked, occurring equally in boys and girls at a rate of about 4% of live births (Hobbs, 1968), and normal levels of circulating antibodies are achieved in most instances after a slow start, indicating that there is no genetic lesion. Genetic (primary) hypogammaglobulinaemia has an incidence of 1 per 100 000 males and 1 per million females, so that the suggestion by Soothill (1968) that transient hypogammaglobulinaemia could be due to a heterozygous state could at most account for 1 per 316 males or 1 per 1000 females—that is, 5% of the observed cases.

**Transient hypogammaglobulinaemia of infancy**

Infants are born with IgG derived from the maternal circulation by placental transfer. The IgG level, at first usually within normal adult limits, falls as it is diluted and catabolised. The lowest levels are reached between four and six months, after which they rise as the infant’s own IgG synthesis takes over. Some babies present at this four- to six-month stage with frequent or severe infections and have very low IgG levels. A subsequent rise in immunoglobulin levels enables a retrospective diagnosis of transient hypogammaglobulinaemia to be made. Up to 4% of babies fail to replace maternal IgG in time and 1% suffer severe hypogammaglobulinaemia.

In most cases the mechanism of this ‘delayed
maturity' is unknown. Perhaps the affected infants are at the lower limit of the normal distribution. Alternatively, some special mechanism may operate such as excessive T-cell suppressor activity similar to that which limits antibody responses in some strains of young mice (Mosier and Johnson, 1975). However, in infants from birth to six months the mean number of T cells in the peripheral blood rises only from 80/mm³ to 250/mm³ with the highest at 700/mm³ (Hobbs et al., 1978). These are low numbers to include excessive T-cell suppressor activity, but it must be admitted that T-suppressor activity in affected infants has not been investigated directly. In the same study (Hobbs et al., 1978) numbers of lymphocytes bearing surface immunoglobulin were found to be some three times higher than in adults. The abnormally low numbers of blood B lymphocytes reported in infants with transient hypogammaglobulinaemia (Moscatelli et al., 1973) thus seems worthy of further attention.

In some cases the reason for the observed hypogammaglobulinaemia seems more apparent. For instance, if the fetus has genetic determinants (for example, Gm) different from the mother then 7S alloantibodies directed against the fetal gammaglobulin may pass the placenta and play an aetiological role in transient hypogammaglobulinaemia (Fudenberg and Fudenberg, 1964). There have also been several reports of placental transfer of an IgG paraprotein (Radl et al., 1968; Littlewood et al., 1970) resulting in low levels of 'good quality' antibodies and prolonged immunosuppression (Littlewood and Payne, 1977). This is probably due to the transfer of a humoral immunosuppressive agent, not simply to the paraprotein level, since the prolonged suppression affects IgA and IgM as well as the IgG. Infants given gammaglobulin therapy show no suppression of IgA and IgM.

Premature babies are also at risk. Maternal IgG is largely transferred in the last trimester of pregnancy. Babies born before 22 weeks have severe agammaglobulinaemia and those born before 34 weeks' gestation may be expected to develop agammaglobulinaemia within the first two months of life (see Fig. 1). The use of a single injection of prophylactic gammaglobulin for such babies (Hobbs and Davis, 1967) does not delay subsequent matura-
tion and reduces morbidity and mortality. The reward of normal healthy children seems a much better yield than that from most current gammaglobulin therapy.

Marrow disorders

Hypogammaglobulinaemia may be found in disorders that severely affect all the red marrow of the bones such as marrow hypoplasia, extensive bony metastases, myelosclerosis, and paroxysmal nocturnal haemoglobinuria.

In mammals some 60% of antibodies are synthesised in the marrow (Askonas and White, 1956) and 66% of the plasma cells are producing IgG. Predictably, therefore, in conditions where the marrow is suppressed or extensively replaced there is a fall particularly in IgG levels with less effect on IgA and IgM except in patients dying of cancer (Hobbs, 1968).

Short survival of mainly IgG

Hypogammaglobulinaemia involving predominantly IgG may be associated with an increased fractional catabolic rate (FCR). This may be specific for IgG or be due to a general increase in protein metabolism. Increased FCR is also seen in protein-losing states such as the nephrotic syndrome and protein-losing enteropathy.

The normal adult serum concentration of IgG is in the range 5.0-16.0 g/l (the intravascular pool represents some 45% of the total IgG) with a half life of 23 days. The FCR is about 0.067, or 7%, with some variation due to IgG subclasses. Hypercatabolism will affect IgG concentration, owing to its long half life, much more profoundly than IgA or IgM with shorter half lives. The most representative example of hypogammaglobulinaemia due to hypercatabolism is that of myotonic dystrophy. In this disease concentrations of most serum proteins are normal. The IgG pool is distinctly reduced and this is attributed to a defect in IgG metabolism (Wochner et al., 1966). The half life of radioiodinated IgG in these patients is only 11-4 days. The IgG isolated from them behaves normally in healthy controls. The short survival of IgG in myotonic dystrophy most probably results from loss of the intravascular IgG protective mechanism which normally operates (Brambell et al., 1964).

A short IgG half life has also been found in a patient with Sjögren's disease. The patient had a mixed IgG:IgM cryoglobulin and a shortened survival of IgG (Waldmann et al., 1971). The association of the IgG with a monoclonal IgM may have prevented reaction with the IgG protective mechanism.

Increased protein catabolism also plays a role in the hypogammaglobulinaemia seen in protein-calorie malnutrition and this, and the protein-losing states, are much more frequent and important causes of hypogammaglobulinaemia.

In the nephrotic syndrome the sieving properties of the glomerular membrane are preserved to some extent in most patients and the smaller immunoglobulin molecules are more readily lost than the
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Fig. 1  Mechanism of hypogammaglobulinaemia in the premature infant. Preterm infants have low levels of maternal IgG which may fall to dangerously low levels before the infant's own IgG takeover.

larger ones. Thus there is a reduced serum concentration, particularly of IgG, associated with a shortened survival time. The urinary loss of IgG, however, fails to account for the low serum levels observed (Hobbs, 1968; Shakib et al., 1977). In the nephrotic syndrome IgG catabolism may be increased up to ninefold (Andersen, 1963). Renal tubular metabolism of albumin contributes to the loss of serum albumin, lower levels of which are found in nephrosis than could be expected from urinary loss alone (Waldmann et al., 1972).

In idiopathic minimal-change nephrotic syndrome of children IgG concentrations are lower in non-proteinuric patients in long-term remission, and it has been postulated that these patients have a T cell defect such that antigenic stimulation fails to elicit a normal IgM to IgG 'switch' (Giangiacomo et al., 1975). It has also been suggested that the primary disease resulting in the nephrotic syndrome is of the immune system. Cultures of lymphocytes from these patients have been found to release a lymphokine-type factor that enhances vascular permeability (Lagruë et al., 1975).

Recently it has been speculated that one of two mechanisms might be operational in producing the low concentrations of IgG seen in nephrotic patients in remission (Shakib et al., 1977). The continued urinary loss of IgG might cause excessive stimulation of IgG-producing clones until the feed-back mechanism fails from exhaustion. Alternatively the feed-back mechanism is stimulated by peptides resulting from IgG catabolism, and since these are lacking when intact IgG is lost the feed-back mechanism fails to operate.

In protein-losing enteropathy the protein loss is more often non-selective. The resulting hypogamma-
globulinaemia is of all immunoglobulin classes. Protein loss is more difficult to assess than in the nephrotic syndrome but additional factors other than direct loss do not seem to be involved, since the increased FCR above normal is about the same for all proteins studied. Nevertheless, because IgA and IgM already have short half lives (5-6 days) they are reduced only to the lower half of the normal range, whereas IgG becomes subnormal. This pattern of acquired immunoglobulin deficiency (Fig. 2, Pattern A) is characteristic of 'catabolic hypogammaglobulinaemia' (Hobbs, 1971), and its recognition in association with a low serum albumin has been the first pointer to a confirmed diagnosis of protein-losing enteropathy in 36 out of 38 patients we have studied.

**Toxic factors**

Immunoglobulin deficiency in this group is thought to result from toxic factors and includes the hypogammaglobulinaemia associated with prolonged uraemia, gluten-sensitive enteropathy, cytotoxic and radiation therapy, and after severe infection.

Increased susceptibility to infection is associated with renal failure. It has also long been known that allograft survival is prolonged in uraemic patients (Hume et al., 1955). Apart from impaired cell-mediated immunity there is suppression of primary immune responses. The capacity to produce IgG, IgA, and IgM is significantly depressed (Wilson et al., 1965). Failure to mount a normal immune response may be shown in the presence of normal immunoglobulin levels. However, patients kept alive with dialysis and chemotherapy show a readily observed fall in immunoglobulin concentrations. The immunoglobulins with the shorter half lives (IgA and IgM) fall before IgG, again indicating decreased synthesis. Byron et al. (1976a) found that uraemic patients responded poorly to *Salmonella paratyphi A* and B antigens. The induced antibody titre usually fell with decreasing glomerular filtration rate. Also the reduced humoral immune potential did not appear to result from protein depletion but rather from a defect in one or more of the steps that normally lead to the synthesis of antibody molecules. Byron et al. (1976b) later investigated the effects of haemodialysis. Regular haemodialysis for three months improved cellular but not humoral responses, although the patients had been expected to produce a secondary response as a result of the primary dose of antigen before dialysis. This suggests that prolonged uraemia has an effect on the generation of new immunological memory in the humoral compartment.

Depression of IgM has been observed in patients with coeliac disease (Hobbs and Hepner, 1968). The toxic effect is thought not to be due to gluten itself or to agglutinating antibodies found in such patients.

The hypogammaglobulinaemia which infrequently results from the long-continued use of cytotoxic drugs or from irradiation is probably due to the general toxicity of these agents rather than to a selective mechanism.

The general cytotoxic effects of drugs does not seem to be directed against specific cell types. They

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**Fig. 2** Serum immunoglobulin patterns drawn to log. scales. Solid lines represent 100% of mean adult normal, broken lines 2 SD limits.
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act by interfering with basic metabolic processes necessary for cell division, particularly differentiation and protein synthesis, so that lymphoid cells are vulnerable during the cellular proliferation stage of the immune response. Radiation can destroy lymphocytes directly and also deplete stem cells.

Corticosteroids depress humoral immunity in steroid-sensitive animals (Chatterjee, 1973), primarily by inhibition or lysis of lymphocytes (Claman, 1972). Hypogammaglobulinaemia as a result of the therapeutic doses used in man has not been demonstrated. High doses of corticosteroids can affect protein catabolism and therefore lower the circulating concentration of proteins with long half lives such as IgG. It should also be borne in mind that the effects of drugs are very dose-dependent (for review see Berenbaum, 1975).

Toxic mechanisms are also thought to be responsible for the hypogammaglobulinaemia associated with severe infection in adults, rubella infection in utero, and in some cases of malnutrition.

The toxæmia of infection remains ill-defined. The hypogammaglobulinaemia acquired in utero coincident with rubella (Soothill et al., 1966) may be due to interference with cell proliferation at the same time as a strong antigenic stimulus is introduced (South et al., 1975). As a result of the antigenic stimulus, cells may be forced into preferentially manufacturing IgM with total commitment of the immature immune system to rubella virus antigens. In many affected infants IgM concentrations are indeed raised, with low levels of IgA and IgG, although in some the IgM is also low (Soothill et al., 1966). The hypogammaglobulinaemia is usually transient although IgA deficiency may be permanent.

Hypogammaglobulinaemia may be associated with malnutrition, which can affect both T-cell and B-cell responses. Moderate chronic protein deprivation, however, results in B-cell defects without corresponding T-cell defects. Experimentally the same effect has been seen in rats fed a diet restricted in specific amino-acids (Good and Jose, 1975). In infants with B-cell defects resulting from such malnutrition restoring normal diet does not necessarily result in a return of immunoglobulin levels to normal. As late as 6-12 months after an ideal diet certain infants deprived of essential nutrients during the first few weeks or months of life show residual deficiencies.

Antibody deficiency secondary to lymphoid neoplasia

Lymphoid neoplasia is the commonest condition associated with immunoglobulin deficiency. IgM is usually affected more than IgA, which in turn is affected more than IgG (Fig. 2, Pattern B). This cannot be explained by relative half lives, since the suppression of IgM may precede that of IgA by many months (Hobbs, 1968). The longer-lasting diseases show the most severe suppression (Table 2).

Table 2 Progressive immunosuppression in patient with Waldenstrom's macroglobulinaemia

<table>
<thead>
<tr>
<th>Date</th>
<th>Total protein (g/l)</th>
<th>Paraprotein (g/l)</th>
<th>Albumin (g/l)</th>
<th>IgG (g/l)</th>
<th>IgA (g/l)</th>
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</thead>
<tbody>
<tr>
<td>20.6.74</td>
<td>81</td>
<td>12</td>
<td>31</td>
<td>9.9</td>
<td>1.5</td>
</tr>
<tr>
<td>26.7.75</td>
<td>82</td>
<td>18</td>
<td>29</td>
<td>9.1</td>
<td>1.6</td>
</tr>
<tr>
<td>28.9.76</td>
<td>77</td>
<td>18</td>
<td>25</td>
<td>6.3</td>
<td>1.3</td>
</tr>
<tr>
<td>31.5.77</td>
<td>76</td>
<td>17</td>
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<tr>
<td>6.6.78</td>
<td>81</td>
<td>28</td>
<td>25</td>
<td>5.1</td>
<td>0.5</td>
</tr>
<tr>
<td>30.1.79</td>
<td>82</td>
<td>21</td>
<td>29</td>
<td>4.0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Normal ranges: albumin 27-42 g/l, IgG 5.0-14.0 g/l, IgA 0.5-4.0 g/l.

In patients with chronic lymphocytic leukaemia the lowest immunoglobulin concentrations were associated with conditions of longest duration (Fairley and Scott, 1961). Among the malignant immunocytomata severe reductions in all immunoglobulins, other than the paraprotein, are seen, particularly with IgG paraproteinaemia (Hobbs, 1967). Susceptibility to infection in myelomatosis correlates well with deficiency of normal immunoglobulins (Drivsholm, 1964; Hobbs, 1971).

After successful treatment only 17% of patients with myelomatosis show recovery of normal immunoglobulin (Hobbs, 1969). We have the impression that initially the normal clones are just suppressed and can recover, as happens when rapidly growing Bence-Jones type myeloma responds to treatment or when early, apparently solitary, tumours are resected (Hobbs, 1966). As time goes by, however, it appears that normal clones are deleted never to return. This is especially true for spindle-cell thymoma, which can be present nine years before the hypogammaglobulinaemia is severe enough to affect the patient. Our own cases and inquiries around the world show no immunoglobulin recovery in 16 patients traced in whom the tumour was resected.

The immunosuppression observed in patients with lymphoid neoplasia can generally be attributed to decreased production of immunoglobulin (Anderson, 1963; Barth et al., 1964; Waldmann and Strober, 1969) resulting in failure to mount a primary antibody response to antigenic challenge. In 6 out of 11 patients with myelomatosis and very high concentrations of IgG paraprotein increased catabolism of non-paraprotein IgG resulted in lowered concentrations of normal IgG (Solomon et al., 1963).

The mechanism of the immunoglobulin suppression in lymphoid neoplasia is by no means clear. The possibility that it is simply displacement of normal
plasma cells by the tumour cells or misappropriation of available amino-acids has been largely discounted (Hobbs, 1971). Theories ascribing decreased polyclonal immunoglobulin synthesis to simple inhibition by the raised monoclonal immunoglobulin level are also inadequate because immunosuppression is also seen in the rare 'non-secreting' plasma cell malignancies (Hobbs, 1967). Secondly, there seems to be no direct correlation between immunosuppression and tumour mass when this can be reasonably assessed—for example, solitary immunocytoplasma (Hobbs, 1966)—or with paraprotein production (Hobbs, 1967). Thirdly, most cases of benign paraproteinaemia do not show immunosuppression (Hobbs, 1967) even when followed up over a long period of time (Table 3).

<table>
<thead>
<tr>
<th>Year</th>
<th>Total protein (g/l)</th>
<th>Paraprotein (g/l)</th>
<th>IgA (g/l)</th>
<th>IgM (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>70</td>
<td>12</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>1978</td>
<td>72</td>
<td>14</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>1970</td>
<td>76</td>
<td>9</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>1976</td>
<td>71</td>
<td>8</td>
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<td>1.8</td>
</tr>
<tr>
<td>1972</td>
<td>70</td>
<td>12</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>1978</td>
<td>74</td>
<td>10</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>1971</td>
<td>75</td>
<td>3</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>1976</td>
<td>72</td>
<td>7</td>
<td>1.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

It has been claimed that the normal B cell population is taken over by messenger-RNA transferred from the tumour clone, since in hosts with plasma cell tumours peripheral blood lymphocytes may have surface immunoglobulin markers with the idiotype characteristics of the myeloma protein (Yakulis et al., 1972). But other work, reviewed by Warner and Kreuger (1978), indicates that lymphocytes carrying normal B-cell markers persist in most hosts alongside those bearing idiotype markers, and that the presence of the latter, which disappear during remissions, may be better ascribed to dissemination of the tumour. However, normal cells encased in Millipore chambers and implanted in tumour-bearing mice no longer mount a primary antibody response to sheep red blood cells and are claimed to have acquired surface immunoglobulin with the idiotype specificity of the myeloma protein (Yakulis et al., 1972). There appears to be a soluble factor involved which induces in normal cells the immune alterations observed, as postulated and possibly first demonstrated by Hobbs (1966, 1970).

Considerable attention has been paid to investigating the identity of the soluble factor involved. There is evidence that myeloma cells, for instance, may release RNA molecules that alter the surface immunoglobulin on B lymphocytes, thus interfering with host recognition of antigen and subsequent antibody formation (Heller et al., 1973; Giacomoni et al., 1974). RNA extracted from antibody-producing lymphocytes has been shown, by several investigators, to be capable of transferring information determining antibody specificity to uncommitted cells. Also RNA-rich extract from the plasma of patients with myeloma changes the surface immunoglobulin on normal lymphocytes (Chen et al., 1975). Results from the third MRC myeloma trial (to be published) have shown selective deletion of gut mucosal plasma cells bearing the same light chain type as that of the myeloma protein. This may not be due to normal regulatory factors, for these seem to produce polyclonal (kappa and lambda) inhibition. Furthermore, it does not suggest 'm-RNA' takeover, which would increase plasma cells with the same light chain type. Alternatively, it has been proposed that myeloma tumour cells release specific mitotic inhibitors (chalones) which block the critical expansion of normal B lymphocyte clones in response to antigenic challenge (Salmon, 1974; Tanaka, Patchaiyapong and Zolla, 1974).

Both of the above mechanisms assume that the inhibitory effects seen are due directly to a product of the myeloma cells. Other evidence suggests that one mechanism for the humoral deficiency seen in patients with myeloma is inhibition of B cell function by host suppressor cells (Broder et al., 1975). Circulating mononuclear cells from myeloma patients suppressed immunoglobulin synthesis by cocultured normal lymphocytes, and removal of phagocytic mononuclear cells from lymphocyte populations of one patient led to an almost tenfold increase in polyclonal immunoglobulin synthesis. Suppressor cell activity in patients with common variable immunodeficiency has also been described (Waldmann et al., 1974).

Katzman (1978) and Paglieroni and MacKenzie (1977) have suggested that there are multiple levels of immune dysfunction in lymphoid neoplasias and that a single theory of pathogenesis is inadequate. Katzman, in fact, indicates that soluble factors may be products of both tumour and host cells. Tumour cells produce a high molecular weight suppressor which when injected into normal mice causes release of a low molecular weight (10 000-20 000) suppressor by the host. The high molecular weight suppressor may be the same as the RNA factor discussed above, and the low molecular weight product may be the factor which has previously been identified in host regulatory macrophages (Krakauer et al., 1977).
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In summary, the immune defect resulting in hypogammaglobulinaemia in myeloma patients appears to be the inability of peripheral B lymphocytes to proceed to mature plasma cells and secrete immunoglobulin. Normal numbers of antigen-binding cells are present and they show a normal proliferative response to PHA (MacKenzie and Paglieroni, 1977). The ability of tumour factors to induce host suppressor factors may result in the suppressive effects on the host regulatory mechanisms. Some of these same suppressor effects have been observed in the sera of normal mice during the primary antibody response. It remains to be seen whether the immunosuppression of lymphoid neoplasia represents an amplified normal regulatory mechanism. Alternatively, the malignancy and the resulting immunosuppression could be dual manifestations of some alteration in the normal immune regulatory mechanisms, since some lymphoid neoplasia undoubtedly follows on preceding immunodeficiency (Fudenberg, 1966).

References


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