Table 3
Ætiological classification of immunity deficiency states

Genetic
Sex-linked → ADS
? Autosomal recessive (? other) → ADS, CIDS, combined IDS
Reticular dysgenesis
Aldrich's disease
With ataxia telangiectasia
DiGeorge's disease (with hypoparathyroidism)
Late-onset ADS with familial immunological abnormalities
Physiological
Neonatal IgM and IgA ADS
IgG trough
Transient ADS
Loss
Urine, gut, &c. → ADS
Experimental thoracic duct cannulation → CIDS
Environmental
Drugs, poisons, X-rays → ADS or combined IDS
Congenital rubella → ADS (? combined IDS)
? *Autoimmune* (? genetic)
Associated with neoplasia → ADS, CIDS and combined IDS

ADS = antibody deficiency syndrome
CIDS = cellular immunity deficiency syndrome

1962, Wollheim *et al.* 1964), illustrate this. None the less, there is good reason to believe that there is a sex-linked abnormality of antibody deficiency syndrome associated with deficiencies of one or more immunoglobulins, though even here there may be qualitative as well as quantitative deficiency of immunoglobulins (Soothill & Rowe 1968). The association of demonstrable immunity deficiency with odd symptom complexes which are familial, but for which there is no satisfactory unifying hypothesis, provides evidence of recognizable disease entities of genetic cause, such as Aldrich's disease, and immunity deficiency and ataxia telangiectasia. The details of the immunity deficiency syndromes in these diseases (they are probably of the combined type) need further study.

We can therefore make a start in the four-tier system of classification of immunity deficiency states, but the detection of correlations between these systems is only in its infancy.

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Secondary Antibody Deficiency

The antibody deficiency associated with certain conditions is believed to result somehow from those conditions and has, therefore, been called secondary. After defining criteria, I will consider the incidence and five ætiological categories of secondary antibody deficiency.

In 107 normal adults the serum immunoglobulin levels showed a log-normal distribution. The 2 SD ranges in mg/100 ml were γG 500–1,600, γA 125–425, γM 47–170: levels below these limits are called subnormal. *Severe hypogammaglobulinæmia* here follows the MRC criterion and is defined as a serum γG level of less than 200 mg/100 ml. At this very low level 70% of patients are known to suffer excessive infection due to antibody deficiency (Hobbs 1966). Hypogammaglobulinæmia can, of course, be detected by simple serum electrophoresis, but it is possible for an apparently normal γ-globulin to be associated with antibody deficiency, a condition for which the term dysgammaglobulinæmia is used. Strictly speaking,

Table 1
Frequency of immunoglobulin deficiency among patients at the Hammersmith Hospital

Subnormal serum γG levels of secondary type were found in 445 (2%) patients, though only 106 were proven as below 200 mg/100 ml. Secondary deficiency is commoner than primary

Severe hypogammaglobulinæmia (γG <200 mg/100 ml)	*No. of cases*
Total examined	20,000
Primary	10
Secondary	106 (0·5%) + 24●
Dysgammaglobulinæmia (γM/γA deficiency only)	
Total examined	11,000
Primary	59
Secondary	112 (1%)

● In this consecutive series 24 patients with γG-myelomatosis had severe reduction of normal serum immunoglobulins, but normal γG could not be measured

this term can only be used when such antibody deficiency has been established after challenging the patient with a series of antigens. In practice (Hobbs *et al.* 1967), most cases of dysgammaglobulinæmia are associated with a severe deficiency of γM and/or γA globulin and, for convenience, *dysgammaglobulinæmia* will be used here to cover such patients who had γG levels within the normal range.

Table 1 shows the incidence of immunoglobulin deficiency found at Hammersmith Hospital. During the past four years, 20,000 new hospital patients were screened by serum electrophoresis and all sera showing a low γ-globulin were checked by immunological measurements. Severe hypogammaglobulinæmia was secondary ten times more often than primary and was present in 0·5%. Subnormal serum γG of secondary type was found in 445 patients, 2%. For various reasons serum immunoglobulins have been measured in 11,000 patients: dysgammaglobulinæmia was found to be commoner than severe hypogammaglobulinæmia and the secondary forms occurred in 1% of patients. Secondary immunoglobulin deficiency and probably antibody deficiency was thus found in 3%, and likely to present as severe infection in over 1% of hospital patients. That it is indeed common is confirmed by the numbers of cases detected by other workers: 100 by Bernier (1964), 118 by Claman *et al.* (1966) and 70 by Andersen & Ward (1966).

Table 2

Ætiological categories of secondary immunoglobulin deficiency among patients at the Hammersmith Hospital

	Patients with	
	γG<200 mg/100 ml (Total 106) %	*γM/γA deficiency only (Total 112)* %
Physiological	34	–
Catabolic	17	0
Marrow disorders	7	0
Toxic	7	37
Primary reticuloendothelial neoplasia	35	63

The ætiology of secondary antibody deficiency can be considered under the five headings shown in Table 2. Table 3 shows the numbers studied with details of the subnormal levels found.

Physiological hypogammaglobulinæmia mainly occurs in babies born prematurely. It can also occur in those born at full term who for some unknown reason are slow to mature, though this usually affects only γG levels, γA and γM being normal for age. These are common and important

Table 3

Incidence of secondary immunoglobulin deficiency

Totals of severe γG deficiency (easily detectable by serum electrophoresis; shown on the right) and γM/γA deficiency only (only detected by immunoglobulin assay) within the consecutive series of new Hammersmith patients are abstracted in Tables 1 and 2

	Total number studied	*No. with subnormal serum level* γG	γA	γM	*Patients with γG<200 mg/100 ml* No.
Physiological hypogammaglobulinæmia					
Prematurity	170	113	–	–	24
Delayed maturity	*c.* 1,000	37	3	3	13
Catabolic hypogammaglobulinæmia					
Nephrotic syndrome	69	61	11	2	14
Protein-losing enteropathy	18	10	5	3	2
Severe malnutrition	17	8	0	0	0
Dystrophia myotonica	7	4	0	2	2
Thoracic duct fistula	1	1	0	0	0
Hypogammaglobulinæmia with marrow disorders					
Marrow hypoplasia	35	18	3	2	4
Extensive bony metastases	*c.*200	22	5	18	2
Myelosclerosis	8	5	3	2	1
Paroxysmal nocturnal hæmoglobinuria	21	4	2	1	0
Immunoglobulin deficiency probably due to toxic factors					
Prolonged uræmia	39	29	18	23	3
High levels of corticosteroids	*c.*100	3	0	1	0
Cytotoxic therapy	54	3	3	4	1
Diazoxide therapy	2	2	0	0	0
Gluten-sensitive enteropathy	79	4	2	32	0
Thyrotoxicosis	30	3	0	2	0
Diabetes mellitus without proteinuria	*c.*50	6	0	1	0
Following severe infection	*c.*100	3	0	0	0
Congenital heart disease (? rubella *in utero*)	*c.*100	7	1	3	3
Immunoglobulin deficiency with primary reticulo-endothelial neoplasia					
Reticulosarcoma	20	2	3	6	0
Mycosis fungoides	8	1	1	1	0
Hodgkin's disease	68	6	11	28	0
Lymphosarcoma	44	15	24	28	1
Giant follicular lymphoma	13	5	8	8	3
Chronic lymphatic leukæmia	58	35	44	44	6
Thymoma	3	3	3	3	3
Myelomatosis● paraprotein type:					
γG	150	'120'■	140	141	68%
γA	70	56	–	59	28%
γμ (Bence-Jones protein only)	60	46	47	57	18%
γD	9	7	6	9	11%
γM	7	7	7	–	14%
No paraprotein detected	6	6	6	6	17%
Macroglobulinæmia: γM	42	22	32	–	5%

●Consecutive cases from MRC myeloma trial together with those found among the 20,000 patients from the Hammersmith Hospital

■ *See* footnote to Table 1

causes of severe hypogammaglobulinæmia which can be one factor in some cot deaths. Maternal γG is transferred across the placenta during the last trimester of pregnancy. Babies born prematurely get off to a bad start. At twenty weeks gestation they will be at severe risk and up to thirty weeks, although the initial γG level will appear adequate at about 400 mg/100 ml, it is likely to be followed by a severe fall to less than 100 mg/100 ml. Prophylactic γ-globulin treatment in such cases can reduce the high incidence of infection (Hobbs & Davis 1967). The take-over of the normal baby is usually accomplished without a dangerous fall in the γG globulin level, which usually gains adult levels by the age of 3 years. γM globulin matures even faster in nine months and there is some present at birth. γA globulin matures slowly, appearing at about four weeks and not gaining adult levels until puberty. Some infants are slow starters and allow the maternal γG to fall very low. This is much commoner than, and needs to be distinguished from, hereditary inability to make immunoglobulins. As Soothill (1962) pointed out, the genetic defect most commonly causes severe deficiency of all three immunoglobulins whereas those with delayed maturity usually have a normal γM and γA for their age. Where the latter is found the infants can still be tided over with γ-globulin treatment but before each dose the γG level should be checked to see if they have started making their own γG. Some of ours have taken up to the age of 5 years before gaining full adult levels, though most have needed only watching or short courses of treatment.

Catabolic hypogammaglobulinæmia is found in diseases with increased turnover of proteins. It is this increased turnover which lowers the γG level, with much less effect on γA or γM. The actual γG-globulin lost in the urine in the nephrotic syndrome is usually less than 1 g daily and cannot account for the failure to maintain a normal γG level, usually requiring the synthesis of only 3 g a day. Andersen (1963) has shown in these diseases that γG catabolism is in fact increased up to 9 g a day: it seems the γG level suffers in the mad drive to increase protein turnover in general. This probably accounts for the low γG seen in severe malnutrition and thoracic duct fistula and it has recently been shown that γG catabolism is increased in dystrophia myotonica (Wochner *et al.* 1966). Probably because the turnover of γG decreases with a falling serum level, severe hypogammaglobulinæmia is not so frequent.

Marrow disorders: In this group Dr M Lewis and I have found a surprisingly high frequency of subnormal γG levels, with little effect on γA or γM levels except in patients dying of cancer. When Askonas & White (1956) accounted for antibodies produced in the guinea-pig, they showed that up to 60% were synthesized within the bone marrow. This could explain much of the fall in γG level seen when the bone marrow is extensively replaced or suppressed and would also explain why γA and γM are not usually so affected. Recently Kaplan *et al.* (1966) found γM antibodies against γG-globulin in the sera of patients with paroxysmal nocturnal hæmoglobinuria and this may be a factor in this subgroup.

Toxic factors: Immunoglobulin deficiency in the fourth group is thought to be the result of toxic factors. Renal failure has long been known to be associated with increased susceptibility to infection. Formerly such patients died, usually with apparently normal γ-globulin. Today dialysis and chemotherapy have kept many alive so that falls in the immunoglobulin levels are readily observed. Those with the shorter half-lives, γA 6 days and γM 5 days, fall first and γG follows in a month or two if the renal failure persists. With recovery from uræmia all the immunoglobulins usually return to normal levels and I think this clearly implicates a toxic effect of the uræmia. In therapeutic dosage corticosteroids and cytotoxic drugs, even azathioprine, do not commonly result in hypogammaglobulinæmia. It is well known that such treatment (especially combined) predisposes to infection but the mechanism remains obscure. Diazoxide, a new drug used for the treatment of hypoglycæmia in childhood, has been shown to depress the γG level though neither in our two patients nor in the published cases (Baker & Miller 1967) are levels reduced to a severe degree. In a large series of patients with cœliac disease, a depression of γM globulin has been shown (Hobbs & Hepner 1968). This is particularly so before treatment with a gluten-free diet, whereupon γM recovers and can be depressed again by reintroducing gluten into the diet. This seems to be largely a toxic effect of gluten in these sensitive subjects. For want of a better explanation the few patients with thyrotoxicosis and diabetes mellitus without proteinuria who have had subnormal immunoglobulin levels are classified here although increased catabolism has not been excluded. True transient hypogammaglobulinæmia sometimes occurs in adults: after a previously normal γG level a very low one can be seen with severe infection and can subsequently recover. This seems to be the exception; most patients in fact show the expected increase in immunoglobulins but 3 who were very ill indeed did show a fall, with eventual recovery. These are men-

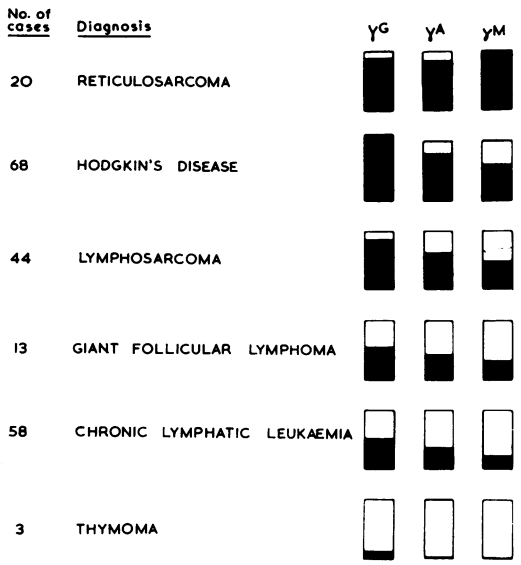

Fig 1 *Immunoglobulin deficiency in 206 patients with malignant reticuloses. The white boxes indicate 100% mean adult serum levels; the black areas the mean levels found in patients with malignant reticuloses. In general, deficiency becomes more severe with longer duration of disease, and affects γM more than γA, more than γG*

tioned to stress that the ill-defined toxæmia of infection can be a very real thing with suppression of normal defence mechanisms. Soothill *et al.* (1966) have described hypogammaglobulinæmia as acquired *in utero* coincident with rubella and this best accounts for our findings in association with congenital heart disease.

Primary reticuloendothelial neoplasia: This group is the largest. In Table 3 and Fig 1 malignant reticuloses have been placed in order of increasing incidence and severity of hypogammaglobulinæmia. It is apparent that the longer-lasting diseases such as giant follicular lymphoma and chronic lymphatic leukæmia achieve the lowest levels. Fairley & Scott (1961) clearly showed lower γ-globulin levels in patients who had had their chronic lymphatic leukæmia longer. Thymoma may also be very slow to develop; one case took nine years (Wollheim *et al.* 1964). On the other hand, the rapidly fatal reticulosarcoma hardly has time to affect the immunoglobulins. This can be seen in Fig 1 which also shows that, in the other conditions illustrated, γM is affected more than γA, which is in turn affected more than γG; moreover, this is not a reflection of half-life, for γM deficiency can be found months before γA deficiency, which can appear a year or more before γG falls. In patients followed over the four years, I have often observed this sequence develop and in only one patient has γA deficiency been found before γM deficiency. Of the 206 patients shown in Fig 1 18% have had severe infections with pyogenic bacteria and the incidence correlates well with the γG level. Infections occurred in 11 of 13 patients with γG <200, 23 of 54 with 200–500 and in 3 of 149 with >500 mg/100 ml. A further 10% have had proven candidiasis or pneumocystis carinii which could not be correlated with γG deficiency, and seemed related to γM deficiency, but the status of cellular immunity was not fully investigated, and this is known to be defective in such patients (Lawler *et al.* 1967).

Continuing with this group we come to malignant paraproteinæmia and in Table 3 is included the experience afforded by the MRC myeloma trial in addition to that at Hammersmith. The 'severe' groups on the right are therefore expressed as percentages, and only the Hammersmith data were added into the totals in Table 1 and 2. In myelomatosis severe reductions are most commonly seen with γG paraproteins. Infection has been a problem in 60% of patients with γG myelomatosis, but in only 33% with γA and 20% with γμ. These results agree with those of Drivsholm (1964) and correlate closely with severe deficiency of normal immunoglobulins. Some 30% of patients with macroglobulinæmia also suffer excessive infection which cannot be correlated with γG deficiency. Rather it seems that excess γM-globulin can nonspecifically coat the neutrophils and impair phagocytosis (Penny & Galton 1966). While it is true that the immune paresis associated with reticuloendothelial malignancy can be mediated through defects of the cellular immune responses and also secondary effects on phagocytosis, most of the clinical infections can be correlated to immunoglobulin deficiency. How does this arise?

In about half the patients with γG-myelomatosis it has been shown that the high serum level of γG-paraprotein is associated with increased catabolism of normal γG-globulin and this can result in a lower level of normal γG-globulin (Solomon *et al.* 1963). However, in the other half of γG-myelomatosis and with other types (i.e. in 80% of malignant paraproteinæmia) and in chronic lymphatic leukemia it has been established that decreased γG synthesis is responsible (Andersen 1963). Similarly γM and γA deficiency are mainly due to decreased synthesis (Barth *et al.* 1964).

How does this suppression of normal immunoglobulin synthesis occur? Simple displacement of the normal plasma cells by neoplastic cells seems unlikely, because in the marrow this would also

result in leucoerythroblastic anæmia, which in fact is found in less than 5% of these patients. Marrow occupation would also depress γG first, as shown in Group C, whereas this is usually the last to fall. Furthermore, γA is largely derived from the gut which is rarely directly involved by tumour. It has also been suggested that the neoplastic cells misappropriate available amino acids at the expense of normal plasma cells. Immunoglobulin deficiency is, however, unusual with most other types of neoplasia and even among the reticuloendothelial malignancies it cannot be correlated with the extent of the tumour. These theories also fall down with localized tumours which can be associated with immunoglobulin deficiency. In two patients removal of an apparently solitary myeloma was found to restore immunoglobulin levels to normal (Hobbs 1966). In 2 other patients with severe hypogammaglobulinæmia (γG 160, 140 mg/100 ml) and gross splenomegaly, splenectomy was followed by recovery of γG levels (500, 800 mg/100 ml). In these 2 cases, which are very much the exception, histology revealed giant follicular lymphomatosis of the spleen, quite distinct from the hyperplasia typical of adult hypogammaglobulinæmia. Neither patient has yet shown metastases at two and three years respectively. The findings in the above 4 patients suggest that reticuloendothelial tumours can release some humoral substance which can inhibit the synthesis of normal immunoglobulins.

Throughout the above discussion it has been assumed the reticuloendothelial malignancy came first, and indeed the picture of worsening hypogammaglobulinæmia with longer duration of disease suggests this is the usual pattern. However, it is also possible that hypogammaglobulinæmia itself results in overstimulation of the cellular mechanisms of immunity to a degree increasing the risk of neoplastic mutation. Recently Fudenberg (1966) has reviewed the evidence which supports the belief that antibody deficiency can sometimes be primary to reticuloendothelial neoplasia.

In summary, secondary immunoglobulin deficiency is much commoner than the primary types and an important mechanism for symptoms in 1% of hospital patients. It can be classified into five ætiological categories the first three of which largely affect only γG levels, the latter two characteristically reducing γM initially, then γA and finally γG. Diagnosis and treatment with γ-globulin is especially rewarding in the physiological group and can be helpful with marrow disorders and with the more slowly progressive reticuloendothelial malignancy.

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Combined Cellular and Humoral Deficiency States

A classification of diseases due to deficiencies of immune mechanisms is given by Soothill (1968). I review here some of the clinical observations on which this attempt at classification is based. It refers mostly to congenital deficiencies with manifestation in early life, quite often genetically transmitted and seen predominantly by the pædiatrician. The leading clinical sign of all these diseases is increased susceptibility to and abnormal reaction against infections.

The first clear-cut disease entity in this group was described in 1952 by Bruton and by Janeway