THE
HÆMOLYTIC ANÆMIAS

Congenital and Acquired

PART II—THE AUTO-IMMUNE HÆMOLYTIC ANÆMIAS

By

J. V. DACIE

M.D. (Lond.), Hon. M.D. (Uppsala), F.R.C.P. (Lond.)

Professor of Hæmatology, University of London

(Postgraduate Medical School of London)

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Part II: The Auto-Immune Hæmolytic Anæmias

PREFACE TO THE SECOND EDITION (PART II)

THE second edition of this book has taken far longer to complete than I had hoped. The present volume is in fact only an instalment, for it deals solely with the clinical, hæmatological and serological aspects of the auto-immune hæmolytic anæmias and with their ætiology, pathogenesis and treatment. A break at this point seemed both practical and sensible, for to complete the book would have meant a further delay in publication of at least one year. The secondary or symptomatic hæmolytic anæmias, the drug-induced hæmolytic anæmias, paroxysmal nocturnal hæmoglobinuria and hæmolytic disease of the newborn will thus be dealt with in a third and final volume.

Once again, I should like to record my indebtedness to the many friends who have referred patients to me, and to past and present members of the medical and laboratory staff of the Postgraduate Medical School of London and Hammersmith Hospital who have collaborated in the investigation of patients.

I am indebted to the Editor of the *British Medical Bulletin* and the Medical Department of the British Council for permission to reproduce Figs. 168 and 169, to Blackwell Scientific Publications for permission to reproduce from the *British Journal of Haematology* Figs. 145, 151, 158, 159, 165, 166 and 167, and to the Editor of *Lectures on the Scientific Basis of Medicine*, Vol. 7, and the Athlone Press for permission to reproduce Fig. 145. I am particularly indebted to Mr. W. L. Marsh, F.I.M.L.T., for permission to reproduce Fig. 158.

The illustrations new to this edition have been drawn for me by Mr. D. Banks and Dr. S. M. Lewis and the new photomicrographs have been taken by Mr. W. H. Brackenbury. I am very grateful for their skill and patience. Miss R. Frearson's accurate typing of the manuscript has been of incalculable help to me and I am also greatly indebted to Dr. S. M. Lewis for his help in proof-reading. Once again, I have received every possible help and encouragement from Messrs. J and J. A. Rivers of J. & A. Churchill Ltd.

J. V. DACIE

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CHAPTER 7

THE AUTO-IMMUNE HÆMOLYTIC ANÆMIAS

I. "IDIOPATHIC" TYPE: GENERAL, CLINICAL AND HÆMATOLOGICAL FEATURES

THE term acquired hæmolytic anæmia or acquired hæmolytic disease is descriptive of a situation where the life-span of the erythrocytes is reduced for reasons other than congenital defects of the cells themselves. An excessive rate of hæmolysis *in vivo* is in fact a common phenomenon in disease and it appears that it can be produced by a variety of different mechanisms.

Broadly speaking, three main types of acquired hæmolytic anæmia can be distinguished: (1) the hæmolysis[1] dominates the clinical picture and is apparently unaccompanied by any other co-existing disease—such cases are often referred to as "primary" or "idiopathic" acquired hæmolytic anæmias; (2) the hæmolysis, which may or may not dominate the clinical picture, is clearly associated with some well-defined underlying disease—such cases are referred to as secondary or symptomatic, and (3) the hæmolysis follows the taking of some drug or exposure to a toxic chemical.

Probably the most important type of acquired hæmolytic anæmia is that associated with the formation of auto-antibodies active against the patients' own erythrocytes. These are the so-called "auto-immune" hæmolytic anæmias. It must not, however, be thought that all cases of acquired hæmolytic anæmia can be explained in this way. "Non-auto-antibody" types certainly exist.

The relative incidence of the auto-antibody and "non-auto-antibody" types is uncertain. Certainly, the auto-antibody type has been most studied and written about and this undoubtedly give an erroneous impression of its relative frequency. Nevertheless, it seems likely that the majority of cases of acquired hæmolytic anæmia of unknown origin ("idiopathic" cases) are auto-antibody induced, while the reverse is probably true of cases of secondary hæmolytic anæmia. The mechanisms, other than the

[1] Hæmolysis in this context is used as a synonym for an increased rate of erythrocyte destruction. It does *not* imply that this is due to any particular mechanism such as amboceptor-complement lysis.

action of auto-antibodies, causing acquired hæmolytic anæmia of either "idiopathic" or secondary types are probably diverse; they are at the moment almost completely unknown. Further details are given in Chapters 14 and 15.

In the majority of instances the ætiology of auto-immune hæmolytic anæmia is unknown and the disease has to be referred to by the unsatisfactory terms "primary" or "idiopathic"; in other patients the hæmolysis is the sequel to an infection such as virus pneumonia, or is associated with an additional pathological process such as chronic lymphocytic leukæmia, reticulosarcoma or disseminated lupus erythematosus. These secondary cases are probably less rare than was at one time thought.

Statistical studies on several large series of patients have recently been published. Lal and Speiser (1957) listed 48 out of 97 cases of acquired hæmolytic anæmia of the warm-antibody type as being secondary cases. Other published figures include data for the cold-antibody type in addition. van Loghem, van der Hart and Dorfmeier (1958) recorded that 67 out of 122 cases were secondary in type, Revol and co-workers (1958) seven out of 27 cases and Dausset and Colombani (1959) 35 out of 128 cases.

The present author's own data up to the time of writing are given in Tables 13 and 14. A total of 175 patients have been investigated in the Department of Hæmatology of the Postgraduate Medical School of London between 1947 and 1961. Of these 108

Table 13

Analysis of 175 Cases of Auto-Immune Hæmolytic Anæmia Studied between 1947 and 1961

Type of antibody	Type of disease	No. of cases	Sex	
			Males	Females
Warm	"Idiopathic"	89	40	49
	Secondary	40	14	26
Cold	"Idiopathic"	19	5	14
	Secondary	19	6	13
	Paroxysmal cold hæmoglobinuria	8	5	3
Total		175	70	105

Table 14

Analysis of 59 Cases of Secondary Auto-Immune Hæmolytic Anæmia Studied between 1947 and 1961

Underlying or associated disease	Type of antibody	
	Warm	Cold
Neoplastic		
Chronic lymphocytic leukæmia Reticulosarcoma Lymphoma	15	5
Lymphadenoma	1	1
Other leukæmias	2	0
Carcinoma	1	0
Infections		
Probable or possible virus pneumonia	0	11
*Infectious mononucleosis	1	0
*Cirrhosis and hepatitis	2	0
*Other infections—Measles Tb SBE† Bronchopneumonia Bronchiectasis	9	0
Disseminated lupus erythematosus	6	0
Rheumatoid arthritis	1	2
Ulcerative colitis	2	0

* The ætiological relationship between the associated disease and the hæmolytic anæmia is far from clear in these cases.

† Subacute bacterial endocarditis.

were judged to be "idiopathic" and 59 secondary.[1] The disorders to which the hæmolytic anæmia was thought to be secondary are given in Table 14; malignant disease of the lympho-reticular system, particularly chronic lymphocytic leukæmia and reticulosarcoma, virus pneumonia and disseminated lupus erythematosus are conspicuous as underlying associations.

The *auto-immune types of hæmolytic anæmia* may be classified as follows:

(*a*) "Idiopathic" auto-immune hæmolytic anæmia: Chapters 7 and 8.

[1] Excluding eight cases of paroxysmal cold hæmoglobinuria.

(*b*) Secondary auto-immune hæmolytic anæmia: Chapters 9 (hæmolytic anæmia following virus pneumonia and other virus infections) and 13 (hæmolytic anæmia associated with chronic lymphocytic leukæmia, reticulosarcoma, etc.).

(*c*) Paroxysmal cold hæmoglobinuria: Chapter 10.

In the present chapter the clinical and hæmatological features of the "idiopathic" type of auto-immune hæmolytic anæmia are reviewed. Serological findings are described in Chapter 8 and ætiology and pathogenesis, and treatment, dealt with in Chapters 11 and 12, respectively.

"IDIOPATHIC" AUTO-IMMUNE HÆMOLYTIC ANÆMIA

History. Hayem (1898) is generally credited with giving the first recognizable description of acquired hæmolytic anæmia under the title "Ictère infectieux chronique splénomégalique" and of differentiating anæmia with jaundice from disease of the liver. It was in France, too, that the first observations were made that suggested that hæmolytic anæmia might be caused by the development of auto-antibodies. From 1908 onwards Widal, Abrami and Brulé (1908a and b; 1909) in a series of papers gave the first accurate descriptions of "l'ictère hémolytique acquis." Significantly, they stressed that autohæmagglutination was characteristic of the cases they studied, and Le Gendre and Brulé (1909), in emphasizing the differences between the congenital and acquired forms of hæmolytic jaundice, stated that in the acquired form "auto-agglutination des hématies restait constamment, intense et rapide, prenait une veritable valeur diagnostique."

Other important observations were made in France at about the same time. Chauffard and Troisier (1908) and Chauffard and Vincent (1909) described as suffering from "ictère hémolysinique" and "hémoglobinurie hémolysinique" patients in whom intense hæmolysis was taking place *in vivo* and whose sera appeared to contain abnormal hæmolysins.

These pioneer studies were to some extent forgotten in the succeeding decades, and 30 years or so passed without much progress being made. Several publications, however, certainly deserve mention. In 1925, Lederer described three patients who had suffered from acute hæmolytic episodes of sudden onset and of short duration. In each case recovery seemed to take place following blood transfusion. Brill (1926), too, reported what appeared to be a similar type of case and subsequently Lederer (1930) described three further patients. While the identity of these cases with auto-immune hæmolytic anæmia is in doubt, some, at least, probably were examples of the syndrome. In none, however, were serological studies carried out.

There was confusion, too, at this time between acquired hæmolytic anæmia and latent congenital hæmolytic anæmia first appearing in adult life and in England at least (in the early and mid 1930's) the current teaching was that most cases of acute "acquired" hæmolytic anæmia were in fact congenital, *i.e.*, really examples of hereditary spherocytosis (see Vaughan, 1936). The presence of spherocytosis in both types of case and the lack of a reliable and distinguishing serological test go a long way to explain this confusion. The merit of Dyke and Young's (1938) paper, in which they described six cases of chronic macrocytic hæmolytic anæmia, is that they clearly distinguished them from hereditary spherocytosis, on the basis of the macrocytic blood picture and the often poor and uncertain response to splenectomy. Again, however, serological findings were not mentioned.

In 1938 Dameshek and Schwartz (1938a) again reported the presence of abnormal hæmolysins in patients suffering from acute (acquired) hæmolytic anæmia. They also showed clearly, both in man and in animals, that spherocytosis and increased osmotic fragility might develop during the course of acquired hæmolytic anæmia (Dameshek and Schwartz, 1938b).

In 1954, Coombs, Mourant and Race showed that erythrocytes sensitized by "incomplete" forms of Rh iso-antibodies were agglutinated by anti-human-globulin sera prepared by immunizing rabbits against human serum proteins. This discovery provided a new tool in immunological research. It was soon applied to the investigation of cases of hæmolytic anæmia. In 1946, Boorman, Dodd and Loutit, and Loutit and Mollison, reported that the "direct" antiglobulin reaction (Coombs's test) was positive in a number of patients suffering from "idiopathic" acquired hæmolytic anæmia, whilst the test was negative in patients suffering from congenital and other types of hæmolytic anæmia. In 1947, Morton and Pickles reported that the enzyme trypsin increased the susceptibility of human erythrocytes to certain types of antibodies. The enzyme-treated cell technique has also proved to be extremely useful. Both methods have helped enormously in the understanding of the pathogenesis of acquired hæmolytic anæmia by demonstrating the presence of incomplete antibodies in cases where other techniques had failed to do so.

During the last 10 years or so the antibodies of acquired hæmolytic anæmia have been extensively studied and the concept of auto-immunization as a cause of antibody formation has been widely accepted. Two main types of antibody have been recognized, a warm type active at body temperature and a cold type usually inactive at body temperature although active at temperatures a few degrees lower. Further information concerning the development of knowledge of the auto-immune hæmolytic anæmias

is to be found in Dameshek and Schwartz's (1940) review and in the more recent monographs of Hennemann (1957) and Schubothe (1959).

It is worth recording that acquired hæmolytic anæmia of apparent auto-immune origin has been reported, although rarely, outside the human species, *e.g.*, by Miller, Swisher and Young (1954) in a dog and by Bielschowsky, Helyer and Howie (1959) in an inbred strain of mice.

Synonyms and Eponyms. L'ictère hémolytique acquis (Widal, Abrami and Brulé, 1909); erworbener hämolytischer splenomegalischer Ikterus, Typus Hayem-Widal (Micheli, 1911); acquired acholuric jaundice (Eason, 1918); acute hemolytic anemia (Lederer, 1925; Dameshek and Schwartz, 1940); immuno-hemolytic anemia (Evans *et al.*, 1951); autoimmune hemolytic disease (Young, Miller and Christian, 1951); antiglobulin-positive hemolytic anemia (Osgood, 1961).

Some Continental workers (*e.g.*, Marcolongo, 1953) have referred to different forms of "idiopathic" acquired hæmolytic anæmia by the eponyms "Hayem-Widal", "Dyke-Young", "Loutit" and "Lederer-Brill", whilst the term "Lederer's Anæmia" has been widely used in British and American literature. As will be discussed later, wide differences exist between patients in respect of their clinical histories and in the results of laboratory tests. Nevertheless, it seems unwise to attempt to separate on the basis mainly of clinical differences a disease of such variable intensity as auto-immune hæmolytic anæmia into subgroups labelled with eponyms, *e.g.*, into the "Lederer type" (acute transient) or "Dyke-Young type" (chronic macrocytic), unless the distinction is backed by real differences in ætiology or pathogenesis which in the present instance is not the case.

The eponyms "Hayem-Widal" (Micheli, 1911, etc.), recalling pioneer clinical and serological observations or "Loutit" (Maier, 1948), recalling the first demonstration of positive antiglobulin tests in acquired hæmolytic anæmia, are more worthy of perpetuation, and an amalgam of the three names to "Hayem-Widal-Loutit anæmia" would not be inappropriate; but it suffers from being uninformative compared with "auto-immune hæmolytic anæmia" and can hardly be recommended.

In the discussion which follows one clinical syndrome will be separated off from the general syndrome of auto-immune hæmolytic anæmia. This is the "cold-hæmagglutinin syndrome" which is associated with the presence in the blood of cold auto-antibodies in high concentrations. A clear distinction too will be made between "warm" and "cold" auto-antibodies when the serological findings in auto-immune hæmolytic anæmia are discussed in Chapter 8.

General Features of Auto-Immune Hæmolytic Anæmia

Literature. Recent reviews and monographs dealing with both the clinical and laboratory aspects include those of Dameshek and Schwartz (1940), Dreyfus, Dausset and Vidal (1951), Young, Miller and Christian (1951), Baumgartner (1952, 1956b), Marcolongo (1953), Heilmeyer (1953), Young and Miller (1953a), Dacie (1954, p. 164), Lejeune (1954), Dausset (1956), Letman (1957), Hennemann (1957), Schubothe (1957, 1958, 1959), Oettgen and Kindler (1959) and Braaker (1960). Dameshek and Schwartz's (1940) review and the monographs of Hennemann (1957) and Schubothe (1958, 1959) are particularly valuable because of their extensive bibliographies.

Race and Inheritance. As far as is known, auto-immune hæmolytic anæmia is not confined to any particular race or races. However, most of the published case reports have dealt so far with patients of European origin. It has generally been thought that there is no evidence for a genetic basis for the disease. Kissmeyer-Nielson, Bent-Hansen and Kieler (1952), however, published an account of a family in which both a mother and her daughter developed a hæmolytic anæmia of an auto-immune type. This observation is clearly exceptional, but it is difficult to dismiss it as mere coincidence. On the other hand, one of the author's patients had an unaffected sister who was probably an identical twin (Case 9 of Dacie, 1954). It should be added perhaps that Wasastjerna (1959) has recorded a single instance of combined hæmolytic anæmia and Hashimoto's disease where anti-erythrocyte and anti-thyroid antibodies were formed by the same patient.

In animals, however, Bielschowsky, Helyer and Howie (1959) have demonstrated that genetic factors can influence the occurrence of apparent auto-immune hæmolytic anæmia in mice. In a highly inbred strain it was found that eventually almost 100% of the mice became affected from 3 months of age onwards. Although the relevance of these observations to man is disputable, they should encourage further search for genetic factors acting in the human disease.

The occurrence of auto-immune hæmolytic disease combined with or superimposed upon an underlying congenital hæmolytic anæmia has occasionally been reported, *e.g.*, by Kaplan and Zuelzer (1950). Michel, Bornemann and Thomas's (1955–56) case is a little less satisfactory, for although their patient was thought to have been anæmic since childhood, the family history was negative. Whether such cases should be looked upon purely as coincidental or whether the presence of a congenital hæmolytic anæmia predisposes to the development of auto-immune hæmolytic anæmia subsequently is still uncertain.

Blood Groups. Hunt and Lucia (1953) claimed to have demonstrated a statistically significant increase of blood-group O in cases of acquired hæmolytic anæmia: 78% of 27 patients were group O compared with 48% of 31 patients with congenital hæmolytic anæmias and 45% of their controls. These observations were supported by further figures from Australia, Clemens and Walsh (1954–55) reporting that 62% of 66 patients with acquired hæmolytic anæmia (giving positive direct antiglobulin tests) were group O. However, this apparent association between group O and auto-immune hæmolytic anæmia has not been confirmed by subsequent reports based on larger series. Lal and Speiser (1957) found that 39% of 97 cases of the "idiopathic" warm-antibody type were group O, a figure not significantly different from that of the general population. Dunsford and Owen (1960) came to the same conclusion: out of 127 patients with acquired hæmolytic anæmia (giving positive antiglobulin tests) 47·2% were group O compared with 45·4% of their controls. The author's own data also do not support any strong association with group O. The blood groups of 120 patients (warm and cold antibodies) are known: 40% are group O, 44% group A, 13·5% group B and 2·5% group AB.

Sex. Both sexes are affected. Sacks, Workman and Jahn (1952), reviewing 147 cases of "idiopathic" and secondary acquired hæmolytic anæmia from the literature as well as 19 cases of their own, found that two-thirds of the patients were females.

Dausset and Malinvaud (1954) and Dausset and Colombani (1959) have also reported an excess of females, but only in the "idiopathic" type of the disease. Dausset's latest figures are: 61% of 93 patients with the "idiopathic" disease were females (said to be significant at the 95% probability level) and 60% of 35 patients with secondary hæmolytic anæmia were males. Lal and Speiser's (1957) date show an apparent but not statistically significant, excess of females in both the "idiopathic" and secondary groups, *i.e.*, 55% of 49 patients and 62·5% of 48 patients with the "idiopathic" and secondary types of disease, respectively, were females. The present author's own data are illustrated in Table 13: 58% of 108 patients with the "idiopathic" disease were female and 66% of 59 patients with the secondary type of disease were female. Taking all these series together, it seems probable that auto-immune hæmolytic anæmia is really slightly more frequent in females than males. There is no obvious association with pregnancy or parity.

Age. Subjects of all ages are affected, from infants in the first

few months of life until old age. The age incidence of the patients with auto-immune hæmolytic anæmia of the warm-antibody type the author has personally investigated is illustrated in Fig. 119. The youngest patient was aged 5 months and the oldest aged 78 years when their illness was first diagnosed. The age incidence in auto-immune hæmolytic anæmia of the cold-antibody type is, if

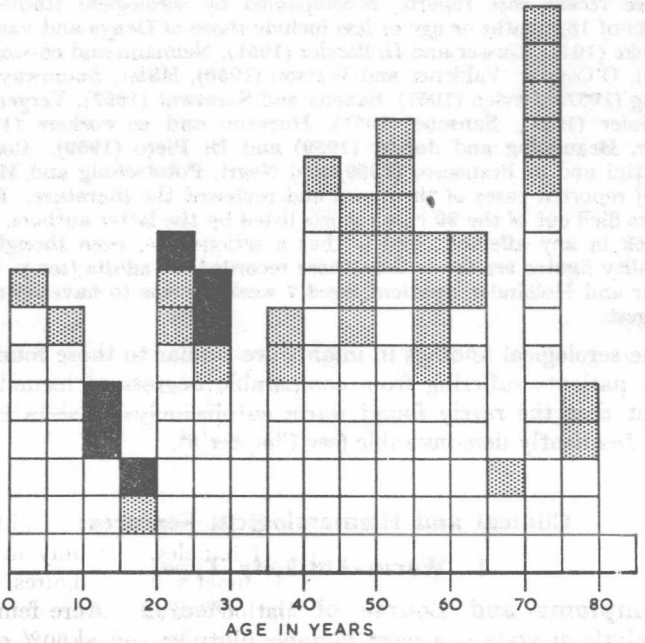

FIG. 119. Age distribution of 125 patients suffering from auto-immune hæmolytic anæmia of the warm-antibody type. *Open squares* = "idiopathic" cases; *dotted squares* = secondary cases (excluding DLE); *filled-in squares* = cases associated with disseminated lupus erythematosus (DLE).

paroxysmal cold hæmoglobinuria is excluded, different; this type, which must be very rare in infants and young subjects, if it occurs at all, affects elderly people particularly (see Fig. 132, p. 369).

The occurrence of the warm-antibody type in infants and young children is remarkable—particularly when current theories of ætiology are considered (see p. 597), and many records are now available in the world literature. The disease is often of explosive onset and hyperacute, and correspondingly serious, but sometimes

it is of short duration and there may be complete recovery within a few weeks.

The hyperacute cases of short duration correspond with those often referred to in the past as "Lederer's anæmia" (*e.g.*, Lederer, 1925, Case 2; 1930, Case 3; Patterson and Stewart Smith, 1936; Giordano and Blum, 1937, Case 1; Baxter and Everhart, 1938; Betke *et al.*, 1953). Of these cases, however, only two (Lederer's patients, cited above) were small infants.

More recent case reports, accompanied by serological studies, in infants of 13 months or age or less include those of Denys and van den Broucke (1947), Gasser and Holländer (1951), Neimann and co-workers (1956), O'Connor, Vakiener and Watson (1956), Miller, Shumway and Young (1957), Larsen (1957), Saxena and Saraswat (1957), Verger and Moulinier (1957), Sansone (1957), Horveno and co-workers (1958), Roger, Beaudoing and Jobert (1959) and Di Piero (1959). Colleta, Schettini and di Francesco (1959) and Negri, Pototschnig and Maiolo (1960) reported cases of their own and reviewed the literature. Eight infants died out of the 29 case reports listed by the latter authors. The outlook in any affected child is thus a serious one, even though the mortality figures are lower than those recorded for adults (see p. 692). Gasser and Holländer's patient, aged 7 weeks, seems to have been the youngest.

The serological findings in infants are similar to those found in adult patients suffering from comparable degrees of hæmolysis, except that the rarely found warm autohæmolysins seem to be more frequently demonstrable (see Chapter 8).

Clinical and Hæmatological Features:

1. Warm-Antibody Type

Symptoms and Course of the Disease. Auto-immune hæmolytic anæmia is a most variable disorder and almost every grade of severity may be met with. In some patients the illness may be a chronic one extending over years and the only symptoms complained of may be those common to chronic mild anæmia of any cause, *e.g.*, undue tiredness and mild dyspnœa on exertion. In more severely affected patients the severity of the anæmia often leads to serious dyspnœa and incapacity. Sometimes, chronic jaundice may be the patient's chief complaint, but this is a very variable symptom. In the most severely affected patients—often infants or young children although not exclusively so—the onset may be very sudden instead of being insidious, the chief features of the disease being rapidly increasing anæmia and increasing jaundice often accompanied by pyrexia and shock-like prostration and in the worst cases by a state of partial coma. Hæmoglobinuria is

a frequent accompaniment in such cases and the name "acute hæmolytic anæmia" is then more than justified. Massive hæmoglobinuria does not as a rule last more than a few days. If it persists despite all attempts at treatment, the outlook is grave, but Miller, Shumway and Young (1957) nevertheless reported the gradual recovery of a 14-year-old negress after 14 days' hæmoglobinuria.

Occasionally, a patient may suffer from repeated attacks of hæmolysis separated by spontaneous remissions. Young and Miller (1953b) described for instance a patient who had suffered from six episodes of acute hæmolysis within 4 years of the initial attack for which splenectomy had been performed. According to Crosby (1955) and Crosby and Rappaport (1957) hæmolytic crises are more frequent in the winter months. In children, as has already been emphasized (p. 349), the disease not infrequently appears as an acute (sometimes fulminating) disorder, fortunately often of relatively short duration (a matter of weeks or even days), but chronic and relapsing cases have been reported (Verger and Moulinier, 1957; Larson, 1957).

Dreyfus, Dausset and Vidal (1951) referred to the occurrence of superficial thrombophlebitis and the frequent presence of gallstones (usually causing no symptoms) in long-standing cases. Young, Miller and Christian (1951) also mentioned thrombophlebitis as occurring repeatedly in association with hæmolytic episodes (see also p. 384).

Amongst rarely recorded symptoms may be mentioned precordial pain (with ECG evidence pointing to infarction) and headache (associated with an abnormal EEG, see also Sansone (1957)), both attributed by Christen and Jaccottet (1958) to microthrombi formed by agglutinated erythrocytes. Dreyfus, Dausset and Vidal (1951) recorded the presence in one of their patients of a complex neurological syndrome which cleared up almost completely when the hæmolytic process was alleviated following splenectomy.

In "idiopathic" cases of auto-immune hæmolytic anæmia the disease starts without apparent cause, but sometimes a history of recent infection of some sort may be elicited; certainly clinical relapse may seem to be precipitated in this way. Christian and Jaccottet (1958) reported the remarkable observation that a bee sting precipitated a relapse in one of their patients.

It is uncertain whether drug-taking is ever a precipitating factor. Where this has seemed possible (*e.g.*, in de Gruchy's (1954) Case 6) the patient's underlying disease may have been the more (or perhaps the only) important factor.