

crop of petechiae, which gradually faded. The thrombocytopenia was quite transient; a platelet count below 100,000 was present for less than 48 hours, but about five days were required for it to rise again to over 200,000. The thrombocytopenia was further documented by abnormal clot-retraction of both plasma and whole blood and borderline low prothrombin consumption times during this period. The bone-marrow examination at the same time disclosed numerically adequate and morphologically normal megakaryocytes; therefore the fault did not seem to be one of platelet production. It is our feeling that the cause of the thrombocytopenia in this setting is overconsumption of platelets, probably as a result of capillary damage, with resultant capillary haemorrhages (petechiae). Microthrombi, formed in areas of capillary damage, cause deposition of platelets as well as usage of the other coagulation factors which, if widespread enough, might result in transient depletion of all the factors concerned in blood coagulation, including platelets.

No necropsy data are available on human cases of louping-ill. Pathological material on Omsk haemorrhagic fever has suggested to Russian workers that the basic lesion involves the capillaries (Gajdusek, 1953). In a few reported human necropsies of Kyasanur Forest disease there was extensive oozing of blood into the lungs and massive gastro-intestinal haemorrhage (Work *et al.*, 1959). Both leucopenia and thrombocytopenia are seen in Omsk haemorrhagic fever and Kyasanur Forest disease. Webb and Rao (1961) noted phagocytosis of erythrocytes, leucocytes, and platelets by peripheral blood monocytes in their patients with Kyasanur Forest disease. This may be an additional explanation for the thrombocytopenia and leucopenia observed in our case.

Previous reports of louping-ill in man have stressed the variability of the clinical picture and have pointed out that either the prodromal influenza-like phase or the later encephalitic phase may be absent entirely (Rivers and Horsfall, 1959). The reports have stressed that louping-ill should be suspected whenever a person exposed to the L.I. virus acquires a febrile meningoencephalitic illness. This case illustrates that louping-ill in man need not be manifested as a central nervous system disorder.

Immunologically, a very close relationship exists among all members of the Russian tick-borne virus complex; that haemorrhagic manifestations may occur in louping-ill suggests also a clinical relationship between L.I. virus and the known haemorrhagic strains of this virus complex.

It follows from the foregoing that the diagnosis of louping-ill in man cannot be made on clinical grounds alone. We should enlarge upon this point to emphasize that in the individual patient the clinical symptomatology with most arbovirus infections is so variable that an accurate diagnosis based solely on clinical data is not possible.

### Summary

The case of a laboratory technician accidentally infected with the virus of louping-ill is presented. His illness could not be distinguished clinically from Kyasanur Forest disease as described by Work *et al.* (1959) but differed from previously reported human cases of louping-ill in two ways: (1) there were no central nervous system symptoms and (2) there were thrombocytopenia and mild haemorrhagic manifestations. The implications of this clinical relationship of louping-ill to Omsk haemorrhagic fever and Kyasanur Forest disease are discussed.

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## Autoimmunity and Thyrotoxicosis

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It is well known that various degrees of autoimmune thyroiditis, characterized by focal chronic inflammation, usually with the presence in the blood of thyroid autoantibodies, are to be found in most patients with thyrotoxicosis. In the past we, and probably many others, have assumed that the hyperplastic

thyrotoxic thyroid gland, which is very rich in the "microsomal" epithelial autoantigen, provides an abnormally strong antigenic stimulus, and that this is responsible for the commonly associated autoimmunity. However, the following three pieces of evidence have led us to doubt the validity of this assumption.

### I. Familial Associations of Thyroid Disorders and Thyroid Autoimmunity

It has been shown that in some families a high incidence of thyroid autoantibodies is associated with a high incidence

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of various thyroid disorders, including autoimmune thyroiditis, thyrotoxicosis, and non-toxic goitre (Roitt and Doniach, 1960 ; Hall *et al.*, 1960, 1962). This association is supported by the results of an immunological study of thyrotoxic patients, in which it was observed that various thyroid disorders, including thyrotoxicosis, occurred particularly among the relatives of those thyrotoxic patients whose serum contained antibody to the thyroid epithelial microsomal antigen (Buchanan *et al.*, 1962). These observations are explicable on the basis that a genetic factor determining the development of thyroid autoimmunity may be responsible for the development of a number of thyroid diseases, including thyrotoxicosis, as Hall *et al.* (1962) have already suggested. A second, less likely, explanation is that there are two genetic factors which are in some way linked, one of which determines the development of autoimmunity, the other the development of various thyroid disorders.

### II. Thyrotoxicosis and Gastric Autoimmunity

Autoantibody to a microsomal antigen of gastric parietal cells is present in the serum of most patients with pernicious anaemia (Markson and Moore, 1962 ; Irvine *et al.*, 1962 ; Taylor *et al.*, 1962), and is occasionally encountered apart from pernicious anaemia, when it is usually associated with chronic gastritis (Adams *et al.*, 1964 ; te Velde *et al.*, 1964). This antibody has been demonstrated in the serum of 33% of patients with thyrotoxicosis (Doniach *et al.*, 1963). To confirm this important observation and to determine whether thyroid and gastric autoimmunity tend to occur especially in the same thyrotoxic individuals, serum was obtained from 195 thyrotoxic patients, most of whom had received treatment, attending consecutively at an out-patient thyroid clinic at the Western Infirmary, Glasgow.

Tests for antibodies to the microsomal antigens of thyroid epithelium and gastric parietal cells were performed upon a 1 in 4 dilution of each patient's serum, using Coon's indirect immunofluorescent method, by the technique already described for gastric antibody (Adams *et al.*, 1964). Unfixed sections of thyrotoxic thyroid tissue were used in the tests for thyroid antibody. Antibodies to gastric parietal cells and to thyroid epithelial cytoplasm were detected in 32% and 65% of sera respectively. A comparison of the occurrence of the two antibodies in individual patients is shown in Table I, statistical analysis of which indicates that there is a higher incidence of gastric antibody in patients with thyroid antibody than in those without thyroid antibody ( $\chi^2=6.56$  ;  $P=0.01$ ). It is thus

TABLE I.—*Thyroid and Gastric Microsomal Antibodies in the Serum of 195 Patients with Thyrotoxicosis*

|                               | Thyroid Antibody |    |
|-------------------------------|------------------|----|
|                               | +                | -  |
| Gastric antibody { + :: :: :: | 47               | 16 |
| { - :: :: ::                  | 73               | 59 |

apparent that some patients with thyrotoxicosis have a particular tendency to develop both gastric and thyroid autoimmunity. We have considered the following four possible explanations.

1. *That the thyroid epithelial and gastric parietal cells contain cross-reacting autoantigens*, autoantibody to one cell type being capable of reacting with the other. This possibility is excluded by the occurrence of either antibody alone in the serum of some patients. Furthermore, it has been demonstrated that either antibody can be selectively absorbed by the corresponding organ extract (Irvine, 1963a), and this has been our own experience.

2. *That in some cases of thyrotoxicosis, both the thyroid and gastric mucosa provide increased antigenic stimuli*. We have already given reason to doubt that this possibility, which has been termed the "antigen-leak" theory, is a major causal factor in the development of thyroid autoimmunity, and evidence against its importance has been provided elsewhere (Anderson *et al.*, 1961 ; Irvine, 1963a,

1963b). Moreover, its acceptance as a major cause of autoimmunity would presumably necessitate the inclusion of the adrenal cortex as the third member of a "leaky trio," since adrenal cortical antibodies in idiopathic Addison's disease are often associated with thyroid autoimmunity (Anderson *et al.*, 1957 ; Blizzard *et al.*, 1962 ; Blizzard and Kyle, 1963) and with gastric autoimmunity (Irvine, 1963c).

3. *That thyrotoxicosis predisposes to autoimmunity*. This possibility receives indirect support from the demonstration that administration of thyroxine to guinea-pigs results in increased production of antibodies and of tuberculin sensitivity in response to antigenic stimulation (Long, 1957). However, assuming that the gastric lesion of pernicious anaemia represents the end-stage of chronic gastritis (Davidson and Markson, 1955 ; Magnus, 1958), then the association of pernicious anaemia furnishes evidence against the possibility that chronic gastritis is a consequence of thyrotoxicosis, for in many cases the onset of pernicious anaemia precedes the onset of thyrotoxicosis (Wilkinson, 1949 ; McNicol, 1961 ; Bock and Witts, 1963), and yet pernicious anaemia develops only after a long period of severe gastric secretory insufficiency. Accordingly, in many instances the onset of chronic gastritis must precede thyrotoxicosis by some years.

4. *That autoimmunity predisposes to thyrotoxicosis*. We know of no serious objection to this, and in view of the evidence against the other three we consider it to be the most likely possibility.

### III. Associations Between "Autoimmune" Diseases and Thyrotoxicosis

Mention has been made above of associations of autoantibodies and thyrotoxicosis. Further indications that thyrotoxicosis may be an autoimmune disease is provided by the following evidence that it tends to occur in association with various diseases which are accompanied by organ-specific autoantibodies. These diseases include autoimmune thyroiditis (Hashimoto's disease, primary hypothyroidism, and focal chronic thyroiditis), chronic gastritis affecting the gastric fundal mucosa and including the atrophic gastritis of pernicious anaemia, adrenocortical atrophy (idiopathic Addison's disease), and myasthenia gravis.

Table II lists pairs of these diseases, which have been reported to be associated with increased frequency. In Table III are listed reported associations of thyrotoxicosis. The establishment of the true incidence of associations between diseases is often difficult, and some of those listed may be open to criticism.

TABLE II.—*Associations Between Autoimmune Diseases and Diseases Associated with Autoimmune Thyroiditis*

Chronic gastritis (including pernicious anaemia) (Tudhope and Wilson, 1960, 1962 ; Williams and Doniach, 1962).  
Idiopathic Addison's disease (Schmidt, 1926 ; Wells, 1930 ; Sloper, 1953 ; etc.)  
Myasthenia gravis (Simpson, 1964).

*Diseases Associated with Chronic Gastritis*

Idiopathic Addison's disease (Smith *et al.* 1961 ; Irvine, 1963c)  
Myasthenia gravis (Simpson, 1964)

TABLE III.—*Associations of Thyrotoxicosis*

Autoimmune thyroiditis. Very well known  
Pernicious anaemia (Wilkinson, 1949 ; Tudhope and Wilson, 1960 ; McNicol, 1961)  
Idiopathic Addison's disease (Blizzard and Kyle, 1963 ; Irvine, 1963c)  
Myasthenia gravis (Osserman and Silver, 1961 ; Simpson, 1964)

In particular, the association between idiopathic Addison's disease and thyrotoxicosis is thought by some to be rare (Rupp and Paschkis, 1957 ; Stewart *et al.*, 1962). However, two recent reports, supported by immunological investigations, suggest the contrary. Thus Blizzard and Kyle (1963) investigated 71 cases in which the diagnosis was "clearly established." Of 68 patients in whom there was no evidence to suggest a tuberculous cause, three were also stated to have thyrotoxicosis, and in two of these the diagnosis of Addison's disease is supported by the detection of antibody to cells of the adrenal cortex. Irvine (1963c) investigated 15 cases of Addison's disease thought to be non-tuberculous ; two of these were regarded as having had thyrotoxicosis.

### Discussion

From the above evidence it may be concluded that certain "autoimmune diseases" tend to occur together in various combinations and that thyrotoxicosis also participates in combinations with these diseases. In advancing these conclusions as evidence suggesting that thyrotoxicosis is an autoimmune disease, we are well aware that, with the possible exception of certain blood dyscrasias, no pathological process has been shown to be the result of autoimmunity: the evidence is perhaps strongest, but still not conclusive, in relation to chronic thyroiditis.

Our evidence that thyrotoxicosis is an autoimmune disease is based entirely on its belonging to a group of diseases which tend to accompany one another and in which pathological changes in a particular tissue are commonly associated with the development of autoantibodies to that tissue. We are certainly not suggesting that any of the known thyroid autoantibodies is the cause of thyrotoxicosis. However, it is of considerable interest that in 1957 Adams and Purves reported that the abnormal thyroid stimulator (L.A.T.S.) demonstrable in the blood in some cases of thyrotoxicosis is present in the  $\gamma$ -globulin fraction of serum, while Kriss *et al.* (1964) have reported that L.A.T.S. has the characters of a 7S- $\gamma$ -globulin, and have suggested that it may be an autoantibody to the thyroid. If this claim is substantiated it seems probable that thyrotoxicosis will prove to be the first organ-specific autoimmune disease attributable to a circulating antibody, for the only known biological effect of L.A.T.S. is its stimulating effect upon the thyroid of various experimental animals.

### Summary

The reported high incidences of thyroid and gastric antibodies in the serum of thyrotoxic patients was confirmed, and it was shown that the two types of autoimmunity tend to occur especially in the same thyrotoxic individuals. Evidence that a genetically determined factor predisposes to various organ-specific autoimmunities is reviewed, and it is concluded, from the known occurrence of various autoimmunities in patients with thyrotoxicosis, that autoimmunization plays an important aetiological part in thyrotoxicosis itself.

ADDENDUM.—Since this paper was submitted for publication the possible autoimmune nature of thyrotoxicosis has been discussed by D. Doniach and I. M. Roitt in *Seminars in Haematology*, 1964, 1, 313.

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## Low Incidence of Latent Trichinosis Near Blackpool Compared with Incidence Elsewhere in England and Wales

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Outbreaks of trichinosis are rare in England and Wales compared with Europe and the U.S.A. For each outbreak, however, there must be many latent cases associated with those that are diagnosed, and there must also be other sporadic infections occurring independently of these outbreaks. Outbreaks in which the parasite was demonstrated have occurred in Workington (1874), Thaxted, Essex (1879), Swansea (1930), Haverfordwest (1939), Wolverhampton (1941), Harpenden (1941), Penrith (1941), Birmingham (1941), Lewisham (1941), Barry, Glamorganshire (1952), and Liverpool (1953).

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The outbreak in Wolverhampton provoked an inquiry by May Young (1947) on the incidence of latent trichinosis in England and Wales, and she carried out an investigation on cadavers in Birmingham, Wolverhampton, Bristol, Llandough, Cardiff, and Leeds. The Liverpool outbreak in 1953 reopened the question of the incidence of latent infections.

Outbreaks of infection are focal and isolated; even in 1941, the second year of the war, when meat production and distribution had altered, there was no apparent connexion between the separate outbreaks. It seemed to us that the latent infections might also be focal, and that the "average incidence of 10%" in the population in the United Kingdom was spurious. For most cities, and certainly for Liverpool, the pork is produced elsewhere, and in most rural areas in this country it is produced