Duret, R., and Jacobs, E. (1959). *Acta gastro-ent. belg.*, **22**, 282.
Fentress, V., and Sandweiss, D. J. (1957). *J. Amer. med. Ass.*, **165**, 21
Galambos, J. T., and Kirsner, J. B. (1955). *Arch. intern. Med.*, **96**, 752.
Kay, A. W. (1953). *Brit. med. J.*, **2**, 77.
Kirsner, J. B., and Ford, H. (1955). *J. Lab. clin. Med.*, **46**, 307.
Marks, I. N., and Shay, H. (1960). *Amer. J. dig. Dis.*, **5**, 1.
Mortimer D. C. (1959). *Canad. med. Ass. J.*, **80**, 607.
Pinto Correia, J. (1961). *Bol. clin. Hosp. Lisboa*, **25**, 141.
Poliner, I. J., Hayes, M. A., and Spiro, H. M. (1957). *New Engl. J. Med.*, **256**, 1051.
de Rubertis, C., Marfisi, A., and Pierangeli, A. (1960). *Ann. ital. Chir.*, **37**, 223.
Segal, H. L., and Miller, L. L. (1955). *Gastroenterology*, **29**, 633.
—— —— and Morton, J. J. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 218.
—— —— and Plumb, E. J (1957). *Monogr. on Ther.*, **2**, 147.
—— Rumbold, J. C., Friedman, B. L., and Finigan, M. M. (1959). *New Engl. J. Med.*, **261**, 544.
—— Shepardson, C. R., and Plain, G. L. (1959b). Ibid., **261**, 542.
Shay, H., Ostreve, R., and Siplet, H. (1954). *J. Amer. med. Ass.*, **156**, 224.

THIRTY-EIGHT CASES OF THE GUILLAIN-BARRÉ SYNDROME: AN IMMUNOLOGICAL STUDY

BY

S. C. MELNICK,* M.B., B.Sc., M.R.C.P.

Department of Medicine, Queen Elizabeth Hospital, and the Regional Virus Laboratory, Little Bromwich Hospital, Birmingham

The Guillain–Barré syndrome (Guillain, Barré, and Strohl, 1916) has numerous alternative names—for example, acute peripheral neuritis, acute infective or post-infective polyneuritis, acute polyradiculitis, acute encephalo-myeloradiculitis, etc. This confusion of nomenclature reflects our ignorance of the aetiology of this condition or group of conditions, and justifies the continued use of the eponymous title.

When Waksman and Adams (1955, 1956,), by the inoculation into rabbits, guinea-pigs, and mice of homologous or heterologous peripheral nerve tissue with suitable adjuvant, produced "experimental allergic neuritis" an experimental model became available which to some extent resembles the Guillain–Barré syndrome. These authors suggested, therefore, that the possibility of this syndrome being an "autoimmune disease" should be investigated.

Patients and Methods

Guillain–Barré Syndrome.—Thirty-eight cases have been studied (22 males and 16 females). With one exception (a patient who died before the commencement of this investigation but whose clinical history and post-mortem findings were typical) all of them were interrogated and examined personally; many had electromyographic and nerve-conduction studies, and a few had motor-point muscle biopsies (Coers and Woolf, 1959). The diagnostic criteria comprised an afebrile, acute, or subacute neurological illness which resulted in flaccid weakness, sensory impairment, and absence of deep reflexes. The findings were usually symmetrical in all four limbs, and cranial-nerve palsies were also present in some cases. A less constant feature was an antecedent infective illness, usually of "influenzal" type. Some patients had a period of apparent well-being between the initial illness and the onset of the neurological syndrome. Each diagnosis was confirmed by one or more of a panel of consultant neurologists. In 30 cases there was the characteristic finding of a raised protein level in the cerebrospinal fluid (more than 50 mg./100 ml.) with a normal cell count (albumino-cytological dissociation). Reasons are given later for making the diagnosis of Guillain–Barré syndrome in eight other cases who differed from the main group only in having cerebrospinal fluids that were entirely normal to routine laboratory testing.

Other Types of Neuropathy (56 cases).—Details of these, together with those of the Guillain–Barré syndrome, are given in Tables I and II. The "chronic" neuropathies were characterized by a more insidious onset of symptoms and by either getting no better or even worse after an arbitrary period of six months. With the exception of the diabetic neuropathies all these cases were also personally examined. The pathogenesis of diabetic neuropathy is by no means fully established, and for the purpose of this survey one symptom—usually pain or sensory disturbance in the legs—and one sign—for example, loss of ankle-jerks, or some sensory loss, together with the diabetes—were regarded as minimal diagnostic criteria.

TABLE I.—*Incidence of Antibodies to Nervous Tissue in Different Types of Peripheral Neuropathy*

Type of Neuropathy	C.F. Titres		
	Negative	1 : 8	>1 : 8
Gullain-Barré syndrome	19	7	12
Fully recovered cases of G.-B. syndrome	8	0	0
Chronic	4	2	4
Recurrent	4	0	0
In "collagen disease"	1	2	1
Carcinomatous	3	0	1
Diabetic	17	1	1
Miscellaneous (see Table II)	4	2	1
Total	41	7	8

TABLE II.—*Antibodies to Nervous Tissue in Various Neuropathies*

Diagnosis	No. of Cases Studied	C.F.T.
Alcoholic polyneuritis	1	Negative
Steatorrhoea polyneuritis	1	,,
Peroneal muscular atrophy	1	,,
Leprosy	1	,,
Haemochromatosis	1	1 : 16
Hypertrophic polyneuritis	1	1 : 8
Sensory neuropathy	1	1 : 32

Other Conditions.—A total of 1,218 other subjects were examined serologically, but as it was not possible to examine all these patients personally, they were classified as follows, mainly according to the clinical notes provided with the specimens: (*a*) 183 normal subjects: healthy medical and laboratory staff and blood donors; (*b*) 608 patients whose sera were referred for routine virological (or bacteriological) testing; (*c*) 59 general medical cases—for example, ischaemic heart diseases, cardiac arhythmias—in whose aetiology "allergic" mechanisms were not suspected; (*d*) 198 cases of neurological disease, specifically excluding the demyelinating diseases of the central nervous system (cases of suspected or proved poliomyelitis and viral meningitis were included in this group); (*e*) 86 cases of demyelinating disease, consisting of disseminated sclerosis (17 cases), retrobulbar neuritis (11 cases), and acute encephalitis (58 cases): apart from some cases of "acute encephalitis" alternative diagnosis had been as

*Jeff Hall Research Fellow, National Fund for Poliomyelitis Research.

far as possible excluded; (*f*) 84 cases of hypersensitivity diseases; these showed no signs of peripheral nerve lesions. Results of the six groups are summarized in Table V: Apart from groups *d* and *e* none of the patients studied were known to be suffering from any neurological disease.

Sera

From as many cases as possible at least two sera ("acute" and convalescent) were examined, and from some cases up to five specimens were obtained at intervals of approximately 10–14 days. After being heated to 56° C. for 30 minutes, they were stored in divided portions at −20° C.

Cerebrospinal Fluids

These were obtained by routine lumbar puncture from 64 assorted neurological cases which included 25 of the Guillain–Barré syndrome. They were used for complement-fixation tests "neat," and in addition samples from nine cases of the Guillain–Barré syndrome and three of chronic peripheral neuropathy were concentrated by negative-pressure ultrafiltration through Visking dialysis tubing to give C.S.F. protein levels of 0.5–1 g./100 ml.

Antigens.—These consisted of homogenates prepared from the following human organs: liver, lung, kidney, normal thyroid, "toxic" thyroid, muscle, heart, spleen, adrenal, foetal skin; Wassermann antigen was also used. With the exception of pieces of thyroid gland, removed surgically from patients with primary thyrotoxicosis, the organs were obtained from routine necropsies as soon as possible after death and were not involved directly in any obvious disease process. In view of the special interest in antibodies to nervous tissue, both the peripheral and central nervous system were used as sources of antigen and consisted of peripheral nerve, posterior root ganglia, spinal cord, brain stem, cerebellum, cerebral cortex, and white matter. The antigen preparations used routinely were prepared as 25–30% (w/v) suspensions in veronal buffered saline (V.B.S.) or 0.25 M sucrose solutions which were kept cool by an ice-jacket during homogenization in an M.S.E. homogenizer used at maximum speed for three minutes. The antigen preparations were clarified by removing most of the coarse particulate matter by initial centrifugation at 3,000 r.p.m. for 15 minutes and further clarified by centrifugation at 10,000 r.p.m. for 30 minutes in a refrigerated angle centrifuge. No loss of antigen activity was found after the second centrifugation. The antigen was stored at about −70° C. in a dry ice cabinet; it was found to lose some activity within a few days when stored at −20° C.

Complement-Fixation Test (C.F.T.).—A standard volume (0.03 ml.) of each reagent was used. To determine the optimum antigen concentration "chess-board" titrations were set up. Three M.H.D. complement was used throughout. V.B.S. was used throughout as diluent. After overnight fixation at +4° C. a suspension of 2% sheep red cells (standardized photo-electrically and sensitized maximally) was added and the trays were incubated at 37° C. for 30 minutes in a water-bath. Fifty per cent. haemolysis was taken as the titration end-point.

Other Techniques

Sera from 12 cases of the Guillain–Barré syndrome were tested for precipitating antibodies by the capillary tube and gel-diffusion techniques and were found to be negative.

The tanned-cell haemagglutination technique (Boyden, 1951) had given negative results with this antigen-antibody system.

Results

With the complement-fixation test a serum titration end-point of 1:8 is regarded as weakly positive. Titres of 1:16 or over are regarded as more definitely positive. Where the titration end-point lay between two dilutions the result is recorded as the lower dilution. For conciseness titres are recorded as negative, 1:8, >1:8, except in Table III, where detailed figures are given in the case of the Guillain–Barré syndrome of antibody titres to all the tissues studied.

Antibodies to Nervous Tissue

The results of preliminary experiments indicated that all the peripheral and central nervous tissue extracts gave comparable results with positive sera in the C.F.T. It was of particular interest to note that cerebral white matter was no more active than cerebral cortex. Spinal cord was therefore used routinely and gave consistent results.

On Table IV the cases studied are divided into three broad groups: (*a*) normal subjects, (*b*) all types of clinical diseases, and (*c*) Guillain–Barré syndrome (other forms of neuropathy are excluded at this stage). Of the

TABLE IV.—*General Incidence of Antibodies to Nervous Tissue*

C.F.T.	Normal Subjects	Guillain–Barré Syndrome	All Other Diseases
Negative ..	178 (97·2%)	19 (50·0%)	969 (93·7%)
1:8 ..	4 (2·2%)	7 (18·4%)	32 (3·1%)
>1:8 ..	1 (0·6%)	12 (31·6%)	34 (3·2%)
		X^2=100·6; n=2; P<0·001	

TABLE III.—*Antibodies to Various Tissues in the Guillain–Barré Syndrome*

C.F.T.	Number of Sera											
	Spinal Cord	Kidney	Heart	Spleen	Muscle	Liver	Adrenal	WR	Normal Thyroid	Thyrotoxic Thyroid	Lung	Foetal Skin
Negative ..	19	26	30	30	6	32	17	36	18	18	19	7
1:8 ..	7	10	7	6	1	5	1	0	1	0	0	0
1:16 ..	4	0	0	1	0	0	0	0	0	0	0	0
1:32 ..	3	0	0	0	0	0	0	0	0	0	0	0
1:64 ..	0	0	0	0	0	0	1	0	0	0	0	0
1:128 ..	5	0	0	0	0	0	0	2	0	0	0	0
Total ..	38	36	37	37	7	37	19	38	19	18	19	7
	Percentages											
1:8 ..	18·5	27·0	19·0	16·3	14·3	13·5	5·5	0	5·0	0	0	0
>1:8 ..	31·5	0	0	2·7	0	0	5·5	5·0	0	0	0	0
Total ..	50·0	27·0	19·0	19·0	14·3	13·5	11·0	5·0	5·0	0	0	0

TABLE V.—*Incidence of Complement-fixing Antibody to Nervous Tissue*

C.F.T.	Normal Subjects	Guillain-Barré Syndome	Hypersensitivity Diseases	Demyelin. Disease	Neurological (Exc. Demyelin.)	General Medical Diseases	Miscellaneous (Virological)
Negative ..	178 (97·2%)	19 (50·0%)	58 (69%)	77 (89·0%)	192 (97·0%)	57 (96·6%)	585 (96·2%)
1 : 8	4 (2·2%)	7 (18·4%)	11 (13·1%)	4 (5·0%)	2 (1·0%)	1 (1·7%)	14 (2·3%)
>1 : 8	1 (0·6%)	12 (31·6%)	15 (17·9%)	5 (6·0%)	4 (2·0%)	1 (1·7%)	9 (1·5%)
Total no. of cases	183	38	84	86	198	59	608

38 cases of the Guillain-Barré syndrome, 19 (50%) had antibodies to nervous tissue (see also Table I). There were very few positive sera in the normal group (2.7% ; the impression that the incidence of positive sera in the Guillain-Barré syndrome is greater than in all other diseases together (6.4%) is statistically confirmed $\chi^2 = 100.6$, $n = 2$; $0.001 > P > 0.0001$). The detailed classification into groups of diseases (Table V), however, reveals more information, and where there were sufficient numbers of positive results the significance of difference between these groups was assessed (Table VI). General medical disorders with only 2/59 positive sera could not be included in this analysis.

The following conclusions could be drawn. (1) That demyelinating central nervous diseases, despite the low proportion of positive results, do show a significantly higher incidence of positive sera—that is, sera containing antibody to nervous tissue—than the groups of miscellaneous virological or neurological (excluding demyelinating) disease. (2) In patients with the Guillain-Barré syndrome and those with hypensensitivity diseases there is a statistically significant higher incidence of positive sera than in those with demyelinating disease. (3) There is no statistical difference, however, between the incidence of complement-fixing antibodies to nervous tissue in the Guillain-Barré syndrome and the hypersensitivity diseases. The conditions classified as hypersensitivity diseases are listed in Table VII and the highest incidence of antibodies to nervous tissue occurs in systemic lupus erythematosus (S.L.E.) (9/12 cases) and hepatic cirrhosis (7/16 cases).

TABLE VI.—*Incidence of Antibodies to Nervous Tissue—The Significance of Differences*

Disease Groups Compared	Proportions with Positive C.F.T.	χ^2	n	P	Conclusions
Mixed virological .. Non-demyelinating ..	23/608 (3·7%) 6/198 (3·0%)	0·008	1	>0·95	Not significant
Mixed virological .. Demyelinating	23/608 (3·7%) 9/86 (10·5%)	15·9	1	<0·01	Significant
Demyelinating Non-demyelinating ..	9/86 (10·5%) 6/198 (3·0%)	6·7	1	<0·01	Significant
G.-B. syndrome Demyelinating	19/38 (50·0%) 9/86 (10·5%)	23·3	1	<0·01	Significant
Hypersensitivity Demyelinating	26/84 (31·0%) 9/86 (10·5%)	10·9	1	<0·01	Significant
G.-B. syndrome Hypersensitivity	19/38 (50·0%) 26/84 (31·0%)	3·1	2*	>0·2<0·3	Not significant

* 2 degrees of freedom (titres of 1 : 8 and >1 : 8).

TABLE VII.—*Antibodies to Nervous Tissue in Hypersensitivity Diseases*

? "Autoimmune Diseases"					"Exogenous" Allergic Diseases				
Diagnosis	No. of Patients	Serum Titres Neg.	1 : 8	>1 : 8	Diagnosis	No. of Patients	Serum Titres Neg.	1 : 8	>1 : 8
S.L.E.* ..	12	3	3	6	Rheumatic fever	5	5	0	0
Dermatomyositis	1	1	0	0	Acute nephritis	2	2	0	0
Rheumatoid arthritis ..	4	3	0	1	Asthma ..	19	17	1	1‡
Aseptic monoarthritis ..	1	1	0	0	Hay-fever ..	1	0	1	0
Haemolytic anaemia:					Drug hypersensitivity ..	1	0	0	1
With cold agglutinins†	2	1	1	0	Stevens-Johnson syndrome ..	2	1	0	1
No cold agglutinins†	1	1	0	0	Farmers' lung	8	6	2	0
Hepatic cirrhosis	16	9	2	5	Periarteritis nodosa ..	2	1	1	0
Hepatic cirrhosis and myxoedema	1	1	0	0	Giant-cell arteritis	1	1	0	0
Hepatic cirrhosis with ulcerative colitis ..	1	1	0	0					
Ulcerative colitis	2	2	0	0					
Hashimoto's disease ..	2	2	0	0					
Total ..	43	25	6	12	Total ..	41	33	5	3

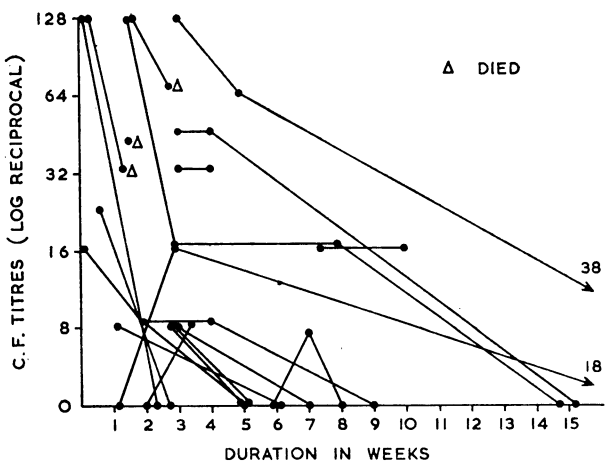
* All had positive L.E. cell tests. † Negative Coombs test. ‡ Also had serological evidence of recent influenza A infection.

Level of Antibody Titre Related to Duration of the Guillain-Barré Syndrome.—Serial studies have been performed wherever possible and changes in titre of antibody are recorded in Table VIII and the Chart. Complement-fixation titres as high as 1 : 128 were found in two patients after only one day of symptoms and

TABLE VIII.—*Guillain-Barré Syndrome: Titres of Antibody to Nervous Tissue Related to Duration of Illness*

Patient	1st Serum Duration (Days)	1st Serum Titre	2nd Serum Duration (Days)	2nd Serum Titre	3rd Serum Duration (Days)	3rd Serum Titre
G.M.	1	1 : 128	9*	1 : 32*	—	—
A.T.	1	1 : 128	17	Neg.	—	—
K.C.	1	1 : 16	14	1 : 8	35	Neg.
G.W.	5	1 : 16	19	Neg.	—	—
D.J.	7	1 : 128	21	1 : 16	56	1 : 16
D.S.†	8	1 : 128	18	1 : 64	—	—
W.E.†	8	1 : 32	—	—	—	—
L.T.	9	Neg.	19	1 : 16	123	Neg.
S.J.	10	1 : 8	44	Neg.	—	—
S.P.	14	Neg.	25	1 : 8	—	—
E.A.	14	1 : 8	28	1 : 8	63	Neg.
F.T.	21	1 : 8	35	Neg.	—	—
E.C.	21	1 : 32	28	1 : 32	105	Neg.
R.E.	21	1 : 8	35	Neg.	—	—
C.D.	21	1 : 8	35	"	—	—
T.G.	21	1 : 128	31	1 : 64	226	Neg.
D.H.	21	1 : 32	28	1 : 32	—	—
S.R.	38	Neg.	49	1 : 8	56	Neg.
E.M.	53	1 : 16	73	1 : 16	—	—

* Post-mortem serum. † Subsequently died.



Titres of antibody to nervous tissue related to duration of Guillain-Barré syndrome.

signs. These (and four other high titres found in the first week) dropped sharply, and subsequent sera obtained between the 9th and 56th days were either negative or else showed a fourfold fall in antibody titre in five out of six cases (the sixth patient died before a second serum could be obtained). But there were two patients whose first serum was negative, the second contained antibody, and the third serum was again negative. These titres were not as high as some of those occurring early in the course of the disease.

Antibodies to Nervous Tissue in Other Forms of Peripheral Neuropathy.—From the given results in Table II it was clear that there was an appreciable incidence of nervous-tissue antibodies in such cases (15/48, if the eight cases of fully recovered Guillain–Barré syndrome whose sera were not examined during their illness are excluded). This proportion is not significantly different from that found in the Guillain–Barré syndrome ($\chi^2=3.2$; $n=2$; $0.2>P>0.1$). Further analysis of these results (Tables I and II) however, reveal that positive sera were particularly found among the chronic neuropathies (6/10 cases) and collagen neuropathies (3/4 cases). There were, however, three positive cases in the miscellaneous group—haemochromatosis, sensory neuropathy, and hypertrophic polyneuritis.

Antibodies to Other Tissue Antigens

Sera from patients with the Guillain–Barré syndrome and all other subjects studied were compared for antibody content to various non-nervous tissues. Apart from patients with the Guillain–Barré syndrome and the hypersensitivity diseases few positive reactions were obtained. The antibody titres to different tissues found in these two groups are compared in Table IX. It is

TABLE IX.—*A Comparison of Antibodies to Various Tissues in the Guillain-Barré Syndrome and Hypersensitivity Diseases*

Tissues	Guillain–Barré Syndrome				Hypersensitivity Diseases			
	Numbers			Total Positive	Numbers			Total Positive
	Neg.	1 : 8	>1:8		Neg.	1 : 8	>1:8	
Spinal cord ..	19	7	12	50%	58	11	15	31%
Kidney ..	26	10	0	27·0%	44	7	12	30%
Spleen ..	30	6	1	19·0%	53	4	10	21%
Adrenal ..	17	1	1	11·0%	42	0	10	19%
Heart	30	7	0	19·0%	71	7	6	15%
Normal thyroid	18	1	0	5·0%	47	6	2	15%
"Toxic" ,, ..	18	0	0		33	2	3	13%
Lung ..	19	0	0		52	2	1	6%
Liver ..	32	5	0	13·5%	79	2	3	6%
W.R.	36	0	2	5·0%	81	1	2	3%
Foetal skin ..	7	0	0		39	1	0	3%
Muscle ..	6	1	0	14·3%	52	1	0	2%

clear that, while both groups have an approximately equal incidence of such antibodies, with few exceptions titres tend to be low in the Guillain–Barré syndrome and high in the hypersensitivity diseases.

A further point of interest was the occurrence of biologically false-positive Wassermann reactions in two cases of the Guillain–Barré syndrome during the acute phase.

Relationship of Serological Findings to Protein Level of C.S.F. in Guillain–Barré Syndrome.—Thirty cases had elevated protein concentrations in the lumbar cerebrospinal fluid and normal levels were found in eight cases. There was no correlation between the clinical severity and the protein level, nor were there any obvious differences in the incidence or levels of C.F. antibodies to nervous tissue in the two groups ; numbers are as yet too small for statistical assessment.

C.F. Antibodies to Nervous Tissue in the C.S.F.

These were found only in 4/15 cases of the Guillain–Barré syndrome, 1/4 cases of chronic peripheral neuropathy, and 1/35 cases of assorted neurological diseases. Concentration of the C.S.F. did not increase the incidence of positive results.

There was no significant incidence of antibodies to other tissues in these specimens.

Discussion

Nearly all searches for circulating complement-fixing antibodies to nervous tissue have been made in sera from cases of disseminated sclerosis ; positive results in some cases have been claimed by Sachs and Steiner (1934), Roemer *et al.* (1953), Frick (1954), Delank (1957), and Raskin (1955), though these results were obtained only by using alcoholic extracts of formalin-fixed brains from cases of disseminated sclerosis as antigens. Detailed investigation of comprehensive control groups of normal subjects or other diseases were not reported by these authors, nor were any attempts made to assess the organ-specificity of the reaction.

Ahrengot (1957), using alcoholic extracts, and Mackay and Larkin (1958), using saline extracts of normal brain, have performed C.F.T.s against sera from cases of disseminated sclerosis ; their findings were essentially negative.

While the rationale for the present renewed search for nervous-tissue antibodies was based on the results obtained in experimental allergic neuritis, it was further stimulated by the recent renewed interest in circulating tissue antibodies in a variety of clinical and experimental conditions, particularly in Hashimoto's disease and experimental autoimmune thyroiditis. In this context Witebsky *et al.* (1957) suggested four criteria that must be satisfied before a clinical condition can be regarded as an autoimmune disease : (1) " direct demonstration of free, circulating antibodies that are active at body temperature, or of cell-bound antibodies by indirect means " ; (2) " recognition of the specific antigen against which the antibody is directed " ; (3) " production of antibodies against the same antigen in experimental animals " ; and (4) " appearance of pathological changes in corresponding tissues of an actively sensitized animal that are basically similar to those in human diseases."

Circulating antibodies may not themselves be directly responsible for the nervous lesions ; it may be that they reflect an immunological disturbance in which delayed cellular hypersensitivity also plays a part, though there is no evidence for this in the Guillain–Barré syndrome. The results obtained by Waksman and Adams (1955, 1956), and confirmed by Heitmann and Mannweiler (1957), however, have provided evidence towards satisfying Witebsky's third and fourth criteria.

The present investigation has shown that complement-fixing antibodies to normal human nervous tissues do occur and are most often found in the Guillain–Barré syndrome and in hypersensitivity diseases. Further analysis of the latter group (Table VII) reveals that sera from cases of S.L.E. and multilobular cirrhosis of the liver have a particularly high incidence. This is of special interest, as there is evidence that autoimmune mechanisms are concerned in both S.L.E. (Dameshek, 1958) and cirrhosis of the liver (Dausset and Marchal, 1958 ; Hunter *et al.*, 1960).

Other Forms of Peripheral Neuropathy

This is the only other group to give a significant incidence of positive sera. Though a comparatively small number of these have been studied so far (Tables I and II), the occurrence of antibodies to nervous tissue in particular varieties of neuropathy merits comment.

Chronic Neuropathies (Positive sera from 6/10 cases).—Doubts have been expressed whether the Guillain–Barré syndrome is a nosological entity, and recently (*Lancet,* 1960) it has been suggested that some cases of peripheral neuropathy of more insidious onset and progression may be aetiologically related. In substantiation of this view it was claimed that, as in the Guillain–Barré syndrome, some chronic neuropathies are also post-infectious. The results in the present study reveal an incidence of positive sera comparable with that found in the Guillain–Barré syndrome cases, and this might be regarded as further supporting evidence for this view.

"Collagen Neuropathies" (Positive sera from 3/4 patients).—The importance of autoimmune mechanisms in their group in general and S.L.E. in particular has already been mentioned and is presumably equally relevant when peripheral neuropathy is a feature.

Carcinomatous Neuropathy.—Russell Brain and Henson (1958) suggested an immunopathological mechanism as one of several possible causes of carcinomatous neuropathy. In only one of the four patients studied here could complement-fixing antibodies be found.

In the case of *diabetic neuropathy,* where immune mechanisms are highly improbable, the low incidence (2/19) of antibody to nervous tissue is entirely consistent with this view.

Recurrent Neuropathy.—No antibodies to nervous tissue have been found in sera from the four cases that have been studied even though on clinical grounds each recurrence was very much like a single attack of the Guillain–Barré syndrome.

Findings in Other Diseases.—Of the other groups, neither the encephalitides nor demyelinating diseases had an incidence of positive results comparable with that found in the Guillain–Barré syndrome. While this is in agreement with earlier reports already referred to, it contrasts with the preliminary report of Roberts (1962), who obtained positive results in 41% of 59 cases of disseminated sclerosis.

Nevertheless, the fact that similar antibodies are present in diseases where there is no obvious neurological involvement must be explained. There are at least two possible reasons for this. (1) There may be two types of complement-fixing antibody reacting with different antigenic components of the crude extracts being used at present—namely, one reacting with sera from some cases of peripheral neuropathy and the other with sera from other positive subjects. (2) That the so-called "antibody" is entirely non-specific.

Indirect evidence in favour of the first possibility comes from the results of Roitt and Doniach (1958), who have shown that sera from many cases of Hashimoto's disease contain complement-fixing antibody that reacts only with the microsomal fraction of thyroid gland (particularly if the gland is obtained from cases of thyrotoxicosis), whereas sera from other conditions which react with thyroid tissue do not react specifically with the microsomal fraction. Experiments with sera from the Guillain–Barré syndrome suggested that the nervous-tissue antigen is also in the microsomal fraction, or is adsorbed on to the surface of these particles.

The second possibility—that the antibody is "non-specific"—arises from the investigations of Gajdusek (1958), who reported the presence of complement-fixing antibodies to a wide variety of tissues. These antibodies react equally well with both human and rat tissues, a fact that has been confirmed by Asherson (1959), who also showed that the antigen is not confined to any particular cell component. Gajdusek called this the "autoimmune" complement-fixation (A.I.C.F.) reaction and showed that liver and kidney preparations were the best antigens and that sera from cases of S.L.E., infective hepatitis, cirrhosis of the liver, and the paraproteinaemias had a high incidence of such antibodies, often to high titres. Many aspects of this work have been confirmed by Hackett *et al.* (1960) and by Deicher *et al.* (1960).

The methods of antigen preparation and the technique used for the C.F.T. in the present work are similar to those used by Gajdusek and the other authors. With the exception of the work of Mackay and Larkin (1958), already referred to, the A.I.C.F. reaction has not been studied in neurological diseases, and nervous-tissue preparations have not been used. As with other tissue antibodies, the highest incidence of antibodies to nervous tissue in non-neurological diseases has been found in such diseases as S.L.E. and cirrhosis of the liver, and it would seem reasonable to suppose that their occurrence is simply another manifestation of this non-specific A.I.C.F. reaction. It is therefore also possible that the nervous-tissues antibody in the Guillain–Barrié syndrome and other neuropathies is also a non-specific phenomenon. This seems a little less likely when one compares the incidence of occurrence of antibodies to other tissues in the hypersensitivity diseases (where it is high) with the Guillain–Barré syndrome (where it is low) (Table IX). The occurrence of antibodies to other tissues in the Guillain–Barré syndrome has also to be considered in the light of the description of Sabin and Aring (1941) of histological changes in the kidneys, liver, heart, and adrenal glands of such patients.

The delayed rise and fall in antibody titre found in three cases of Guillain–Barré syndrome (Table VIII and Chart) may be the result of nervous tissue damage due to other causes, and this is even more likely to be the explanation of rising titres of antineural antibodies found in other forms of peripheral neuropathy—for example, haemochromatosis (Melnick and Whitfield, 1962). On the other hand, the high antibody titres found within the first week in six cases of Guillain–Barré syndrome suggests that these antibodies may precede clinically detectable nervous damage.

The importance of albumino-cytological dissociation as a criterion for the diagnosis of the Guillain–Barré syndrome has been much disputed. Thus Haymaker and Kernohan (1949) in their extensive review concluded that neither the protein level in the C.S.F. nor the white-cell count was of critical importance. On the other hand, Osler and Sidell (1960) suggested that a raised protein level in the C.S.F. should be retained as an important diagnostic criterion. In the cases reported here there was no obvious clinical distinction between cases with raised C.S.F. protein and those where it was normal, nor have any serological differences been

demonstrated. These results therefore favour the opinion held by Haymaker and Kernohan.

The theory that the Guillain-Barré syndrome has an allergic basis is not new. It was first suggested by Lugaro (1904) and later by Grünewald (1922-3), although their concepts of allergy differed considerably from those held at present.

From their observations of the Guillain-Barré syndrome occurring after typhoid immunization Bannwarth (1948) and Pette (1949) concluded that the disease could occur as a result of an exogenously induced hypersensitivity state. This concept has been renewed and extended by Miller and Stanton (1954). Stanton *et al.* (1953) also noted the tendency for the syndrome to occur after specific infections, and suggested that these cases developed an allergy to their peripheral nervous systems by a mechanism analogous to that of the post-infective encephalitides.

In conclusion a comparison of the clinical and experimental findings in my cases of the Guillain-Barré syndrome with those found in experimental allergic neuritis by Waksman and Adams is summarized in Table X. This suggests that they have many features in common, and it is possible that the differences referred to in the table may be due to differences in species reactivity.

TABLE X.—*Guillain-Barré Syndrome Compared with Experimental Allergic Neuritis*

Guillain-Barré Syndrome	Experimental Allergic Neuritis (Waksman and Adams, 1955, 1956)
Similarities	
1. Often an antecedent infection	Inoculation of peripheral nerve
2. Average latent period 14 days (1 day–6 weeks)	Average latent period 14 days
3. Flaccid paralysis	Flaccid paralysis
4. No correlation between C.S.F. protein level and clinical state	No correlation between C.S.F. protein level and neurological state
5. C.F. antibodies to nervous tissues in *some* cases. Spinal cord a good antigen preparation	C.F. antibodies to nervous tissues in *some* cases. Spinal cord a good antigen preparation
6. No correlation between C.F. antibody titres and clinical state	No correlation between C.F. antibody titres and neurological state
7. Tendency to spontaneous remission	Tendency to spontaneous remission
8. Lesions mainly in nerve roots	Lesions mainly in nerve roots
9. Lymphocytic infiltration in liver, kidneys, heart, and adrenal glands (Sabin and Aring, 1941)	Lymphocytic infiltration of liver, heart, lungs, and adrenals
Differences	
1. No increase in C.S.F. cell count	Sometimes moderate C.S.F. pleocytosis. When present shows positive correlation with meningeal inflammation
2. Earliest findings are oedema of nerve roots and swelling of myelin sheaths. Lymphocytic infiltration comes later and is scanty (Haymaker and Kernohan, 1949)	Early marked perivenous and perineural histiocytic and (less marked) lymphocytic infiltration

Summary

Fifty per cent. of 38 subjects with the Guillain-Barré syndrome had circulating complement-fixing antibodies to nervous tissue. Over 1,200 other subjects were also studied; only certain other types of peripheral neuropathy and the hypersensitivity diseases showed a comparable incidence (31%). The incidence and titres of antibodies to a variety of other tissues were also studied and found to be lower in the Guillain-Barré syndrome than in the hypersensitivity diseases. Some subjects with the Guillain-Barré syndrome showed antibodies of high titre to nervous tissue within 24 hours of onset. This syndrome, when compared with "experimental allergic neuritis" in animals, shows many features in common.

I am especially grateful for the advice of Dr. T. H. Flewett and the technical assistance of Mrs. B. A. M. Harvey. Thanks are also due to Professor W. Melville Arnott for the opportunity of making this study, to Professor P. G. Gell and Dr. J. A. H. Waterhouse (medical statistics) for advice, and to consultants of the United Birmingham Hospitals and Birmingham Regional Hospital Board for access to their patients.

REFERENCES

Ahrengot, V. (1957). *Acta psychiat. (Kbh.)*, **32**, 192.
Asherson, G. L. (1959). *Brit. J. exp. Path.*, **40**, 209.
Bannwarth, A. (1948). *Arch. Psychiat. Nervenkr.*, **180**, 531.
Boyden, S. V. (1951). *J. exp. Med.*, **93**, 107.
Brain, Sir W. Russell, and Henson, R. A. (1958). *Lancet*, **2**, 971.
Coers, C., and Woolf, A. L. (1959). *The Innervation of Muscle: A Biopsy Study*. Blackwell, Oxford.
Dameshek, W. (1958). *Ann. intern. Med.*, **48**, 707.
Dausset, J., and Marchal, G. (1958). *Immunopathology: 1st International Symposium*, edited by P. Grabar and P. Miescher, p. 113. Basel.
Deicher, H. G. R., Holman, H. R., and Kunkel, H. G. (1960). *Arthr. and Rheum.*, **3**, 1.
Delank, H. W. (1957). *Arch. Psychiat. Nervenkr.*, **195**, 383.
Frick, E. (1954). *Klin. Wschr.*, **32**, 450.
Gajdusek, D. C. (1958). *Arch. intern. Med.*, **101**, 9.
Grünewald, E. A. (1922-3). *J. Psychol. Neurol. (Lpz.)*, **29**, 55, 403.
Guillain, G., Barré, J. A., and Strohl, A. (1916). *Bull. Soc. méd. Hôp. Paris*, **40**, 1462.
Hackett, E., Beech, M., and Forbes, I. J. (1960). *Brit. med. J.*, **2**, 17.
Haymaker, W., and Kernohan, J. W. (1949). *Medicine (Baltimore)*, **28**, 59.
Heitmann, R., and Mannweiler, K. (1957). *Dtsch. Z. Nervenheilk.*, **177**, 28.
Hunter, F. M., Sparks, R. D., and Salzman, R. T. (1960). *Gastroenterology*, **39**, 394.
Lancet, 1960, **2**, 84.
Lugaro, E. (1904). *Handbuch der pathologischen Anatomie des Nervensystems*, p. 1113. Flatau, Jacobsohn, and Minor, Berlin
Mackay, I. R., and Larkin, L. (1958). *Aust. Ann. Med.*, **7**, 251.
Melnick, S. C., and Whitfield, A. G. (1962). *Postgrad. med. J.*, **38**, 580.
Miller, H. G., and Stanton, J. B. (1954). *Quart. J. Med.*, **23**, 1.
Osler, L. D., and Sidell, A. D. (1960). *New Engl. J. Med.*, **262**, 964.
Pette, H. (1949). *Verh. dtsch. Ges. inn. Med.*, **55**, 92.
Raskin, N. (1955). *Arch. Neurol. Psychiat. (Chic.)*, **73**, 645.
Roberts, S. D. (1962). *Lancet*, **1**, 164.
Roemer, G. B., Schrader, A., and Schild, W. (1953). *Klin. Wschr.*, **31**, 946.
Roitt, I. M., and Doniach, D. (1958). *Lancet*, **2**, 1027.
Sabin, A. B., and Aring, C. D. (1941). *Amer. J. Path.*, **17**, 469.
Sachs, H., and Steiner, G. (1934). *Klin. Wschr.*, **13**, 1714.
Stanton, J. B., Miller, H. G., and Gibbons, J. L. (1953). *Rev. neurol.*, **89**, 46.
Waksman, B. H., and Adams, R. D. (1955). *J. exp. Med.*, **102**, 213.
—— —— (1956). *J. Neuropath. exp. Neurol.*, **15**, 293.
Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, J. W. (1957). *J. Amer. med. Ass.*, **164**, 1439.

A group of French technologists are setting up an International Leisure Office in Paris, and they have adopted a sevenfold classification of leisure activities: (1) semi-leisure: hobbies which bring in pocket-money; (2) relaxation—for example, reclining on a *chaise longue*; (3) distractions, such as hunting, shooting, fishing; (4) artistic pursuits: plays, concerts, and so on; (5) intellectual pastimes: chess, reading, conversation; (6) self-education or personal research; (7) social work, such as visiting the sick. M. Georges Ville, head of the French Society of Civil Engineers, remarks: "Time must be filled if it is to be lived, whether one calls it work or leisure. The essence of leisure time is its freedom. But this freedom should not necessarily be devoted to boredom and *dolce far niente*, emptied of all thought, nor to dissipation in disorder and the degradation of the personality. Like the whole of life, it should be devoted to activity free as to its choice and its rhythm, in which the pulsation of the human personality and its forward drive is maintained." This passage, says Christopher Johnson, demonstrates the utter untranslatability not only of French words, but of the ideas themselves, into English. It may sound impossibly high-minded, but a lot of good is likely to come of such thinking when these French technologists get down to brass tacks. (Christopher Johnson, *New Society*, November 22, 1962.)