of oestrone per 24 hours was found. Twelve days after hypophysectomy amounts of oestrogen ranging from 2.7 to 7.4 μg. (total oestrogen per 24 hours) were found in five of six specimens. In nine subsequent assays no oestrogen could be detected in the urine.

The last patient, (No. 11, Fig. 4) cannot be grouped with the preceding ten since no pre-operative assays were carried out. However, specimens of urine were obtained intermittently between 8 and 11 months after hypophysectomy. This patient,

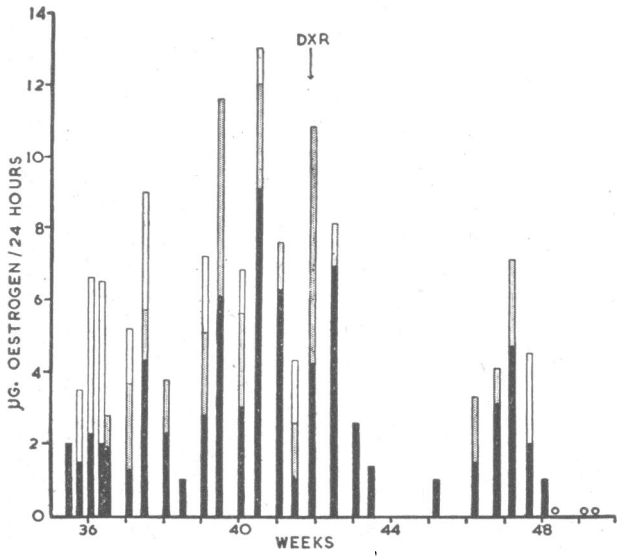

FIG. 4.—Excretion of oestrogen after hypophysectomy. Patient 11, aged 48; menopausal. DXR=deep *x*-ray treatment.

aged 48, with intact ovaries and adrenal glands, excreted between 1 and 12 μg. of total oestrogen per 24 hours over most of this period. After *x*-ray treatment there appeared to be a steady decline in the amount of oestrogen excreted, and in the last three specimens of urine available before death no oestrogen could be detected.

Discussion

The results show that oestrogen excretion continued after hypophysectomy in 7 of 11 patients in this series. If the secretion of oestrogen is controlled solely by the pituitary gland the simplest explanation of these results is that in only four cases (Nos. 4, 5, 6, and 7) was hypophysectomy effective in lowering the amount of circulating trophic hormones below that required for the continued secretion of oestrogen by the target organs. In the remaining cases enough pituitary tissue may have been left at operation to enable the target organs to function at an unchanged rate (Patients 1, 2, and 3), or rapidly regenerating tissue may have been responsible for an excessive production of trophic hormones to account for the increased excretion of oestrogen seen in Patients 8 and 9, and occurring temporarily in Patient 10.

An additional factor which may account for some part of the continued secretion of oestrogen is the presence of accessory pituitary tissue, which is often found in man (see Melchionna and Moore, 1938; Boyd, 1956). From a comparison of the histological appearance of this tissue in the presence and absence of the pituitary, Müller (1956) concluded that pharyngeal pituitary tissue in man after hypophysectomy is capable of secretory activity.

It is unlikely that the continued secretion of oestrogen was due to incomplete atrophy of the adrenal glands at the time the oestrogen estimations were carried out. Judged by 17-oxysteroid production, adrenal atrophy is complete within nine days (Luft *et al.*, 1955), but it is possible that different mechanisms for the synthesis of the various adrenal hormones may be differentially affected by removal of the pituitary gland. Most of the estimations were carried out at least three weeks after the removal of the pituitary, and Patient 11 was excreting oestrogen almost a year after operation.

Whatever the source of the oestrogen found in the urine of these patients, and whatever the factors controlling oestrogen secretion, it is clear that some caution must be exercised before the failure of a patient to respond clinically to hypophysectomy is ascribed to hormone independence of the tumour. Hormone independence cannot be assumed without appropriate measurement of hormone secretion.

Summary

In 4 of 10 patients little or no oestrogen was found in the urine after hypophysectomy. Three patients showed unchanged levels of oestrogen excretion and three showed increased levels. Yet another patient studied almost a year after operation was excreting appreciable amounts of oestrogen.

Since 7 of the 11 patients continued to excrete oestrogen after hypophysectomy, it cannot be safely assumed that a breast cancer is hormone-independent if, following operation, there is no favourable clinical response.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS AND RELATED SYNDROMES

BY

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In addition to their clinical interest the well-defined neurological syndromes which occur in the course of the acute specific fevers form a useful starting-point for a consideration of the aetiology and pathogenesis of similar syndromes encountered in other clinical contexts. There is, for example, a well-recognized resemblance between post-exanthematous encephalitis and the similar illnesses which sometimes complicate Jennerian vaccination (Miller, 1953a) and other prophylactic inoculations (Miller and Stanton, 1954a). It is tempting also to speculate on possible relationships between these syndromes and other acute demyelinating diseases in which no such clear-cut aetiological agent is evident, and to compare such naturally occurring forms with the examples of demyelinating encephalitis which have been produced in experimental animals. It is our purpose in the present paper to compare and contrast these various

syndromes to see if we may reach any valid conclusions regarding the underlying pathogenetic mechanisms involved.

Complications of the Acute Specific Fevers

At the outset of this study we became aware of the paucity of reliable information about the natural history of neurological complications of the acute specific fevers, which constitute the paradigm of this group of diseases, and our first step was to review the available world literature on this subject. The results of this study, comprehensive in the case of measles, chicken-pox, and rubella, and less exhaustive but fairly complete in mumps, scarlet fever, and pertussis, are now complete (Miller, Stanton, and Gibbons, 1956). From this work we have been able to obtain a fairly clear picture of the forms which these complications may take. We have few valid figures regarding their incidence, but a good deal of reasonably reliable comparative information about their clinical features, natural history, prognosis, and sequelae. From a consideration of the relatively few fatal cases which have been adequately studied and reported we have also gained useful information concerning the march of histopathological changes involved.

If for a moment we consider only the neurological complications of measles, varicella, and rubella, on which our information is more complete, we can say that in all three fevers about 90% of neurological complications take the form of encephalitis or encephalomyelitis, the small minority comprising examples of uncomplicated myelitis or polyradiculitis. The average latent period between the appearance of the rash and the onset of encephalitis is from four days rubella) to six days (varicella). In each disease polyradiculitis has an average latent period twice as long as that of encephalitis, myelitis occupying an intermediate position. Occasionally, and especially in rubella, encephalitis precedes the rash, but this has not been recorded in the case of myelitis or polyradiculitis. There is no correlation, positive or negative, between the severity of the exanthem and the appearance of encephalitis. Both sexes may be affected, but the sex ratio varies somewhat between the three diseases, while all these neurological complications are much commoner in the older subjects of the exanthemata—for example, over 10 years of age. Only in the case of measles are the data adequate for a reliable assessment of incidence, and in this disease encephalitis probably complicates 1 in every 1,000 cases : the incidence in rubella is almost certainly less. The mortality in measles and rubella encephalitis is about 20%, that of varicella encephalitis 10%.

Most often these encephalitic illnesses begin abruptly with convulsions followed by coma. Rather less frequently there is a gradual lapse into stupor. A rise of temperature usually accompanies the onset, and the neurological picture is polymorphic, some of the signs being transient and others more persistent. Hemiplegia, tetraplegia, ataxia, involuntary movements, retention of urine, cranial nerve palsies, and meningism are all common findings, and it is not possible to distinguish on neurological grounds between the encephalitis of measles and that of rubella or varicella. However, in the latter form coma, convulsions, hemiplegia, and extensor plantar responses are all comparatively less common, while ataxia and nystagmus are seen more than twice as often as in measles or rubella. The spinal fluid may be normal throughout, but often shows a lymphocytic pleocytosis, occasionally with a slight rise of protein content. When death occurs in para-exanthematous encephalitis, it usually takes place within three days, and practically always within a week of the onset. In surviving cases, a remarkable degree of recovery is usual, and 80% of surviving patients show no disability by the end of six weeks. Sequelae are more common in younger patients, and except for residual hemiplegia or paraplegia are more often psychiatric than neurological. The lowest incidence of sequelae appears to be after rubella encephalitis, though this may be in part due to the fact that this form of encephalitis, like the initiating exanthem, has the highest age incidence of the three.

Myelitis, both transverse and ascending in type, has been reported in measles, varicella, and rubella, also polyradiculitis, clinically indistinguishable from "acute infective polyneuritis" and in many cases showing the cyto-albuminological dissociation in the spinal fluid characteristic of the Landry–Guillain–Barré syndrome. Good recovery is usual in both the polyradicular and the myelitic forms, though the latter may have a mortality of up to 20% and occasionally results in a severe residual paraplegia.

Pathological Findings in Fatal Cases

The reports of pathological findings in fatal cases of encephalitis complicating measles, varicella, and rubella describe acute lesions disseminated throughout the nervous system, beginning with congestion and oedema and ending, if the patient survives long enough, with the fully developed picture of perivenous infiltration and demyelination (perivenous encephalomyelitis). These changes cannot be rigidly correlated with the severity or duration of clinical symptoms, but they do reveal a fairly well defined progression, which can be reconstructed by a consideration of material drawn from patients dying at varying intervals after the onset of encephalitic symptoms. The initial change in the brain appears to be congestion, followed within a few hours by patchy swelling in the walls of the smaller venules and their mural infiltration with mononuclear cells. Patchy perivenous oedema, which may progress to haemorrhage, follows rapidly.

In fulminating illnesses these changes give rise to rapidly fatal cerebral purpura, but in progressive cases perivenous infiltration with lymphocytes and microglial elements is seen, followed by demyelination. Such changes may be encountered within 48 hours of the clinical onset, and a few days later fat phagocytosis ensues, leaving demyelinated areas which may appear confluent. These changes affect mainly the white matter of the nervous system (leuco-encephalitis), while nerve-cell changes are much less constant and may indeed be absent throughout. Valuable information is provided by the reports of Malamud (1939) and Van Bogaert (1949) on cerebral histopathology in three patients dying from unrelated causes some years after measles encephalitis. Van Bogaert interpreted the findings in his case as revealing no residual pathological evidence of the preceding encephalitis, which must have arisen on the basis of entirely reversible changes, while Malamud found only well-defined areas of demyelination, non-progressive and with no sign of the extending fibrous gliosis characteristic of disseminated sclerosis.

Pathological evidence is not available in polyradiculitis complicating these fevers, but in myelitic cases both diffuse perivascular demyelinating lesions and focal vascular occlusions have been described, the latter possibly based on the arteritic lesions which are so common a histopathological feature of this group of disorders.

We have also found some evidence (Miller *et al.*, 1956) that a clinically and pathologically identical triad of encephalitis, myelitis, and polyradiculitis is occasionally encountered as a complication both of mumps and of scarlet fever. In both these diseases, however, such syndromes are much less frequent than a benign lymphocytic meningitis. In the case of scarlet fever, the situation is further confused by a group of neurological complications arising on the basis of secondary factors such as venous thrombophlebitis and renal hypertension. There can be no doubt, on the other hand, that the neurological complications of pertussis fall into an entirely separate class, radically different both clinically and pathologically from the perivenous demyelinating encephalomyelitis characteristic of measles, varicella, and rubella.

Syndromes Following Non-specific Infections

In comparing these para-exanthematous syndromes with other forms of encephalitis, myelitis, and polyradiculitis, we will leave aside both the virus encephalitides, and also such entities as syphilitic myelitis, and will consider primarily

those forms which fall within the group of acute disseminated encephalomyelitis, the diagnostic criteria of which were formulated in a classical paper by McAlpine (1931). These include forms of encephalitis, encephalomyelitis, myelitis, and neuromyelitis optica (Devic's disease) arising after comparatively trivial non-specific infections, body-chilling, mild or surgical trauma, or on occasion without any apparent external provoking factor. Such diseases are not very uncommon, and manifest themselves by an acute onset with coma or stupor in encephalitic forms, and rapidly increasing signs of spinal-cord damage in the myelitic forms, which may be transverse or ascending in type. After progressing for a period which varies from a few days to a few weeks, the condition becomes stationary and subsequent recovery is often surprisingly complete, although sequelae such as hemiplegia, paraplegia, or symptomless extensor plantar responses may be demonstrable. The mortality in encephalomyelitic types is between 20 and 30%.

It is interesting that in these spontaneous forms recurrence has often been observed (Miller and Evans, 1953; Miller and Gibbons, 1954), whereas it has never been reported in those cases arising in relation to the specific fevers. It is possible, however, that relapse may occasionally occur in the latter, and Sir Russell Brain (1956, personal communication) has seen this in a case of mumps polyradiculitis. Neuromyelitis optica, as well as occurring spontaneously and after banal infections, has also been observed as a complication of measles (Brain, 1951; Janbon *et al.*, 1951).

Histopathologically these cases are characterized by areas of patchy demyelination, but inflammatory cells and neuronal degeneration are both inconspicuous. Some perivascular cuffs of lymphocytes are present, and occasional petechial haemorrhages are found. These changes are clearly very similar qualitatively to those of para-exanthematous encephalomyelitis; indeed, pathologically as well as clinically it is impossible to identify any single feature which permits of clear differentiation between the two groups. In the absence of adequate pathological evidence we can do no more than draw attention at this point to the parallel similarity in clinical features of the Landry–Guillain–Barré syndrome whether it occurs "spontaneously" or as a complication of the acute specific fevers.

Mention has already been made of post-vaccinal encephalitis, and a further group of neurological cases bearing a striking resemblance to those complicating the exanthemata is encountered following the administration of serum and other prophylactic inoculations. We have described these in detail elsewhere (Miller and Stanton, 1954a), and here would merely emphasize that such complications may involve the neuraxis at any or every level, giving rise to encephalitis, myelitis, or polyradiculitis, in pure or mixed forms, and in proportions which vary to some extent with the nature of the antigen employed. Such pathological reports as have been made in these cases reveal changes analogous to those seen in non-specific acute disseminated encephalomyelitis, post-vaccinal encephalitis, and the para-exanthematous syndromes already described.

A Common Pattern

In all the conditions discussed above it is possible to discern a broad common pattern. The pathogenetic mechanisms involved, whatever they are, can damage the neuraxis at any level, whether nerve root, cord, or brain. The resulting clinical picture may be discrete or mixed, but the histopathological basis in all cases is remarkably similar, and essentially based on a lesion the end-result of which is perivenous demyelination. The origin of such a non-specific syndrome in invasion of the nervous system by a neurotropic virus is unsupported by any positive evidence, flies in the face of the aetiological facts, and has been generally discarded. The dissimilarity between the histopathological changes of perivenous encephalomyelitis and those of any authenticated virus infection of the nervous system militates equally against acceptance of the alternative hypothesis, which regarded these diseases as manifestations of the activity of an unidentified latent and ubiquitous virus already present in the patient's tissues, potentiated by the recently preceding infection or other insult to the nervous system.

In this connexion it seems likely that some importance may attach to the evidence now available of experimental demyelination produced in animals by repeated injections of heterologous or homologous brain emulsions, with or without adjuvants. This evidence has been reviewed by Wolf (1952). By these means a perivenous demyelinating lesion can be produced, disseminated throughout brain and cord, which is closely analogous histopathologically to the human diseases under consideration. More recently Waksman and Adams (1955) have produced in rabbits a comparable experimental allergic polyneuritis with cyto-albuminological dissociation in the spinal fluid and characteristic lesions in spinal nerve roots, ganglia, and nerves. The similarity of these experiments to the occasional disastrous "neuroparalytic accidents" occurring during human inoculation with extracts of animal nervous tissue in the course of antirabic treatment is striking.

The resemblance of the histopathological changes described in these experimental animals to those of acute disseminated and para-exanthematous encephalitis in man suggests the possibility that these latter conditions may also be allergic in origin. Russell (1955), in comparing the rare acute haemorrhagic leuco-encephalitis in man with acute disseminated encephalomyelitis, has suggested that these are variants of a single pathological process, differing mainly in the acuteness and intensity with which the nervous system is attacked by a common pathological process. In support of the view that this process is allergic, she has demonstrated the development of foci of plasma cells in the human spleen both in acute disseminated encephalomyelitis and in haemorrhagic leuco-encephalitis. Marshall and White (1950) had already shown that plasma blasts, and later mature plasma cells, appear in the spleen in a few days when antigens are administered to rabbits. In this connexion also the recent finding by Lander (1955) of typical acute haemorrhagic leuco-encephalitis in the brain of a man dying on the fifth day of haemorrhagic varicella, and the earlier report by Shallard and Latham (1945) of the same condition complicating measles, are of particular interest.

Appearances similar to those of acute haemorrhagic leuco-encephalitis are occasionally encountered in fatal cases of drug encephalopathy, and Russell (1937), dealing with "encephalitis" due to arsphenamine, and Cavanagh (1953), describing similar cases following the administration of streptomycin and P.A.S., raise the possibility of hypersensitivity as the probable underlying mechanism.

Conclusions

A whole range of apparently related and strikingly similar syndromes of damage to the neuraxis can arise in widely differing clinical circumstances in man. Such syndromes may appear after chilling or trivial injury, following non-specific infections or the specific exanthemata, and after Jennerian vaccination, serum administration, or prophylactic inoculation of many kinds. There is evidence also that they may follow the administration of such drugs as arsphenamine, streptomycin, and P.A.S., and it would seem unlikely that these particular drugs will prove to be unique in this connexion. The neurological disorders under discussion may also arise apparently spontaneously. In all these varying circumstances the histopathological findings are those of an acute disseminated perivenous demyelinating encephalomyelitis or of acute haemorrhagic leuco-encephalitis, a variant of the same condition in hyperacute form.

These diseases seem to be essentially mesodermal, based primarily on an inflammatory-exudative reaction arising in the vascular and supporting tissues of the neuraxis, secondarily involving neuronal elements (axons), and producing neurological symptoms, either by pressure (radiculitis) or by toxic effusion (perivenous reaction). It seems probable that

some common pathogenetic factor intervenes between the operation of the initial aetiological agent and this non-specific disseminated tissue-reaction in the nervous system which is responsible for the clinical end-result. That the common intervening factor is anaphylactic sensitization is suggested not only by the striking similarity of the syndromes to the allergic encephalomyelitis and polyradiculitis which have been experimentally produced in the laboratory animal, but also by the graphic illustration of the "neuroparalytic accidents" of rabies therapy.

The not very infrequent recurrence of acute disseminated encephalomyelitis when it follows non-specific infections—for example, of the upper respiratory tract—and its extreme rarity in post-exanthematous cases is in such circumstances to be interpreted as a reflection of the brief immunity bestowed by banal infections, with the opportunities afforded for repeated antigenic insults to the nervous system, in contrast with the lasting immunity usually conferred by a specific fever. Evidence of some clinical variation within the group—for example, the predilection of varicella encephalitis for the cerebellar system, or that of allergic reactions to horse serum for the spinal roots—can also on this hypothesis be attributed, in part at any rate, to qualitative differences in the antigen involved. There is convincing evidence of an analogous variation in the localization of somatic pathological changes in serum reactions when changes are made in the serum fractions injected (Hawn and Janeway, 1947), while more direct evidence has recently been furnished by the demonstration of Waksman and Adams (1955) that, while an allergic encephalomyelitis can be regularly provoked in the rabbit by single or repeated injection of an extract prepared from brain, spinal cord, or optic nerve, this syndrome is replaced by polyradiculitis if peripheral nerve is the source of the extract employed. It is probable that there are other factors, both endogenous and exogenous, which operate in the localization of these pathological changes.

That some individuals are especially prone to such reactions appears to be beyond doubt: there are a number of cases on record where a patient survived one post-exanthematous illness to fall victim to a further neurological disorder in relation either to another fever or to a non-specific infection. The occurrence of familial cases both after specific and after banal infections similarly argues a familial as well as personal predisposition, and in one family personally reported (Miller and Gibbons, 1954) recurrent episodes of encephalitic illness in three patients followed a very similar clinical pattern, though they varied in severity. Like other observers we have been impressed also by the frequently encephalitic incidence of such syndromes in dull and backward, socially inadequate, or frankly psychopathic subjects. It is our impression that this does not apply in myelitic illnesses, in which there is fairly often, however, an unequivocal history of recent exposure to cold or wet, or of violent exertion.

As we have shown elsewhere (Stanton *et al.*, 1953), the conception of a disseminated neuraxitis of varying aetiology which may involve the nervous system at any level also makes it easier to understand some well-recognized clinical phenomena which remain inexplicable if we continue to think of encephalitis, myelitis, and polyradiculoneuritis as separate disease-entities; we have in mind such events as a phase of meningism and mental disorientation in myelitis or the Landry–Guillain–Barré syndrome, the discovery of a localized flaccid palsy of root distribution after recovery from measles encephalitis, or the finding of a transient sensory level on the trunk in a patient with encephalitis following vaccination.

The hypothesis that acute disseminated encephalomyelitis is an allergic disorder has led to various attempts at treatment. In view of the natural history of the syndrome, and especially its frequent tendency to dramatic spontaneous improvement, the assessment of such trials is difficult and cannot at present be considered to have furnished any valid evidence on the question of aetiology. That the development of allergic encephalomyelitis in the experimental animal can be prevented by the prior administration of corticotrophin has, however, been conclusively demonstrated by Moyer *et al.* (1950). The use of corticotrophin and cortisone in human acute disseminated encephalomyelitis has been described by Ligterink (1951), Garrison (1952), Miller (1953b), and Miller and Gibbons (1953, 1954). This experience has recently been summarized by Selling and Meilman (1955). We find ourselves in substantial agreement with their assessment that two-thirds of such cases treated may be regarded as benefited, in that early unequivocal improvement has been observed in patients previously deteriorating. Very severe cases and illnesses of some duration may show little or no response. Occasionally, however, rapid restoration of consciousness or unequivocal improvement in spinal-cord function may occur within a few hours of instituting treatment, relapsing as quickly when the hormone is withdrawn, and promptly responding to further therapy. This has been observed too often to be coincidental.

Opportunities for the treatment of neurological complications of serum sickness are rare, but response was observed in one case personally treated with cortisone (Miller and Stanton, 1954b), while in a subsequent instance of acute polyradiculitis complicating severe serum sickness dramatic relief of paresis with restoration of deep reflexes was obtained within a matter of hours. The results of treatment of polyradiculitis with cortisone have recently been reviewed (Jackson, Miller, and Schapira, 1957). About three-quarters of such cases seem to show a response. In about half of these it would appear that the natural course of the disease is appreciably shortened. Many such patients make a complete recovery within a month, which is certainly very uncommon in untreated cases. In a considerable number of instances, however, striking partial initial improvement during the first few days of treatment is rapidly arrested, and, despite the continued administration of the drug, recovery thereafter takes its accustomed slow course. Jackson *et al.* (1957) suggest that symptoms of neurological deficit directly resulting from oedema are dissipated under the influence of the drug, which does not, however, affect signs due to axonal damage, reparable only by the slower natural processes of regeneration.

In general it may be said that the results of corticotrophin and cortisone therapy in these acute neurological illnesses do nothing to discredit the allergic hypothesis of their origin and even yield some admittedly equivocal evidence in its favour. Recorded evidence is compatible with the hypothesis that the hormone may diminish the initial mesodermal inflammatory reaction, but is without influence on symptoms due to established axonal damage.

Summary

The natural history of the neurological complications of various specific fevers is briefly indicated. These syndromes are compared with other forms of acute demyelinating encephalomyelitis arising after non-specific infections, vaccination and prophylactic inoculation, the administration of drugs, trivial injury, or occurring spontaneously. The clinical and histopathological resemblance between these diseases and the experimental allergic encephalomyelitis and polyradiculitis produced in animals by the injection of brain emulsions suggests that all these syndromes in man may represent manifestations of an anaphylactic neuraxitis. The implications of this conclusion in the field of therapy are discussed.

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LYMPHADENOID GOITRE (HASHIMOTO'S DISEASE)

DIAGNOSTIC AND BIOCHEMICAL ASPECTS

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In most cases the diagnosis of lymphadenoid goitre is first made by the pathologist after thyroidectomy (Statland *et al.*, 1951 ; Lindsay *et al.*, 1952). Clinically, this type of goitre may be confused with " simple " non-toxic goitre ; but thyroid carcinoma is often suspected because of the firm texture of the gland, leading the surgeon to undertake total thyroidectomy, with the attendant risk of post-operative tetany and vocal-cord paralysis. Since lymphadenoid goitres are non-malignant and many respond to thyroxine administration, it is important to establish the diagnosis pre-operatively.

The clinical picture has already been fully described (Joll, 1939 ; Schilling, 1945 ; Statland *et al.*, 1951 ; Lindsay *et al.*, 1952 ; Blake and Sturgeon, 1953). In diagnosis much help can be obtained with radioactive iodine (^{131}I) tracer tests combined with basal metabolic rate (B.M.R.) and serum cholesterol estimation ; the changes in serum protein pattern which occur are also of diagnostic value.

We report here various tests with ^{131}I on 28 patients with Hashimoto's disease, and biochemical studies in which the serum protein abnormalities before and after treatment with thyroid hormones were observed and correlated with the state of thyroid activity in 11 of the patients (Table I). Serum protein studies were also made in 25 cases previously subjected to thyroidectomy for Hashimoto's struma, and in two control series consisting of 25 patients with other types of goitre and 8 myxoedematous patients without goitre.

Clinical Features

The group tested with ^{131}I consisted of 26 women and two men aged 28–68 (mean 52 years) who had noticed the goitre a few weeks to 15 years previously. There was a history of thyrotoxicosis in one case, but most patients presented with a feeling of pressure in the neck and symptoms suggesting hypothyroidism (17 of the 28). Thyroid pain was present in four cases. All the goitres were firm, of uniform consistency, and involved the entire gland, the enlargement being mostly symmetrical and thyroid-shaped with well-delineated upper poles and pyramidal lobe ; but in five cases the swelling was predominantly unilateral, and in three others the gland had a nodular surface. Histological proof of lymphadenoid goitre is available in 12 cases, the diagnosis in the remainder being based on clinical findings and investigations and the subsequent shrinkage of the goitre on administration of thyroid hormones.

Five cases are described, two to illustrate atypical clinical features suggestive of subacute thyroiditis, and the other three for the detailed investigations.

Illustrative Cases

Case 1

E. M., housewife aged 43. May, 1953, rapid swelling of thyroid, with increasing tenderness and throbbing, four weeks after onset of stomatitis and gingivitis associated with removal of septic teeth, symptoms reaching a maximum within next two months, with general lassitude and pain radiating to ears and back of head, accompanied by feeling of pressure in neck. September, 1953, thyroid estimated three to four times normal size, right lobe large, firm, and tender, left lobe softer and smaller. Gingivitis still present, with enlarged, tender lymph nodes in neck. Skin cool, no tremor. T. 98° F. (36.7° C.), P.R. 70, B.P. 140/65 mm. Hg. W.B.C. 5,300 per c.mm. E.S.R. 49 mm. (Wintrobe). ^{131}I uptake 72% in 24 hours, with thyroid-shaped distribution showing uptake over area of maximum swelling and pain. Swelling gradually subsided without thyroid medication, reaching almost normal size in December, 1953, though gland still firm and tender. Repeat ^{131}I uptake 69% ; E.S.R. 48 mm. ; B.M.R. −26%. Partial thyroidectomy performed in view of persistent pain and pressure symptoms ; weight of gland 20 g. Histology, lymphadenoid goitre.

Case 2

Y. C., housewife aged 56. On admission: three weeks' painful, firm thyroid swelling, more marked on right, with feeling of pressure. B.M.R. −10%. Serum cholesterol 233 mg. per 100 ml. E.S.R. 77 mm. (Westergren). Plasma proteins: total 8.25 g. per 100 ml. (albumin 4.45 g., globulin 3.8 g., gamma globulin 2.3 g.). Thymol turbidity 15 units ; alkaline phosphatase 4.2 units ; bilirubin 0.12 mg. per 100 ml. ^{131}I uptake 65%, urine excretion 13%, in 24 hours. Topography showed bilateral uptake with maximum over tender right lobe. Within two weeks pain subsided and swelling diminished. ^{131}I uptake three months later, 52% in 24 hours. Owing to persistent discomfort and patient's fear of cancer, subtotal thyroidectomy performed five months after onset of goitre ; weight of gland 42 g. Histology, lymphadenoid goitre.

Comment.—Clinically, Cases 1 and 2 suggested either haemorrhage into a thyroid cyst or subacute thyroiditis. The tender, firm goitre and the raised E.S.R. were thought to indicate thyroiditis (Blake and Sturgeon, 1953). Iodine uptake is usually completely suppressed in the acute stage of de Quervain's thyroiditis (McConahey and Keating, 1951 ; Crile, 1952 ; Fraser and Harrison, 1952), but a raised uptake has been reported in the recovery stage (Freedberg *et al.*, 1952 ; Trunnell, 1955) and is thought to be a rebound phenomenon. Our patients were tested some time after the onset of illness, and this delay was thought to explain their high iodine uptake. The distribution of ^{131}I was unlike that in thyroid cyst or carcinoma. The other atypical feature was the fairly rapid onset and the subsequent recession of the goitre without treatment.

Case 3

J. C., housewife aged 38. Goitre since 1947, with attacks of neck pain since 1948 and increasing lassitude since 1950. When seen in 1953 there was a large, firm, horseshoe-shaped goitre. B.M.R. −18%. ^{131}I uptake 66% in 24 hours, with symmetrical distribution. Treated with thyroid, 2–3 gr. (0.13–0.2 g.) daily, with return of normal energy and reduction in size of goitre to less than half. Twice stopped taking