ALZHEIMER'S DISEASE CONFIRMED BY CEREBRAL BIOPSY: A THERAPEUTIC TRIAL WITH CORTISONE AND A.C.T.H.

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THIS paper describes treatment with cortisone and A.C.T.H. of two patients in whom Alzheimer's Disease (A.D.) had been confirmed histologically by cerebral biopsy.

A.D. is a progressive dementia which usually occurs between the ages of 40 and 60 years, and there is no known specific treatment. Intellectual deterioration, which progresses insidiously over a period of 2–10 years, leads to gross dementia, and the inevitable problems of care and supervision often necessitate removal to an institution. Histologically the disease is characterized by atrophy of cortical nerve cells and the presence within the cortex of argentophile plaques which are demonstrable by the silver impregnation techniques of Bielschowsky or von Braunmühl (see Fig. 1); these plaques have a mixed granular and fibrillary structure. The same silver methods also show irregular thickening and disorientation of the nerve cell fibrils, which form "tangles" and "loops" (see Fig. 2). Identical plaques and neurofibrillary changes are also seen in senile dementia, the term "senile plaque" being used in both diseases.

In recent years A.D. has been reviewed by McMenemey (1940 and 1941), Newton (1948), Sjögren *et al.* (1952) and Neumann and Cohn (1953). Further review is outside the scope of this communication, and for detailed clinical and pathological features reference should be made to these papers. We have accepted the postulate of McMenemey (1940) that "All cases, at any age, showing an abundance of senile plaques, neurofibrillary changes and cell atrophy, which cannot be regarded as senile dementia, belong to the Alzheimer category." Stengel (1943) attempted to differentiate the disease on clinical grounds but our experience, in common with that of other authors (Newton, 1948; Sjögren *et al.*, 1952; Green *et al.*, 1952) is that it may be difficult to separate A.D. clinically from other diffuse diseases of the cortex.

Because of the inadequacy of all forms of therapy, it was decided to assess the effects of cortisone and A.C.T.H. in A.D. The use of these drugs in the treatment of incurable diseases of the nervous system has since been described by Glaser and Merritt (1952) with negative results. Their cases included Disseminated Sclerosis, Amyotrophic Lateral Sclerosis, Progressive Muscular Atrophy, etc., but not A.D. Two patients who showed mental deterioration and other features which approximated clinically to those associated with A.D. were selected for therapeutic trial. Before starting treatment, it was essential that the diagnoses were established beyond reasonable doubt, and it was possible

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to do this only with the help of cerebral biopsy. This procedure was therefore undertaken after carefully weighing the possibilities of a new form of treatment against the hopelessness of doing nothing. Pick's Disease had already been confirmed by cerebral biopsy (Polatin *et al.*, 1948) and since we applied it to A.D., Green *et al.* (1952) and Goodman (1953) have recorded cases of A.D.

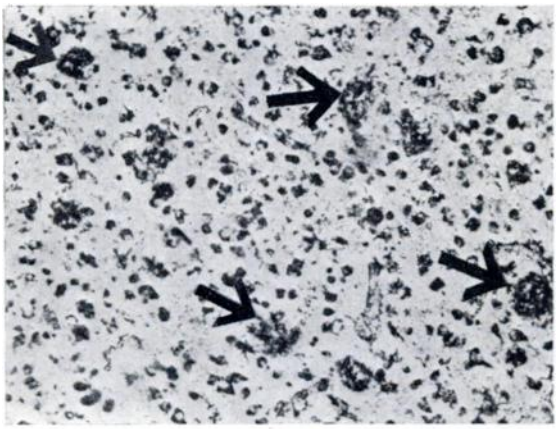

FIG. 1.—Cerebral biopsy showing argentophile plaques in the cortex (von Braunmühl's method).

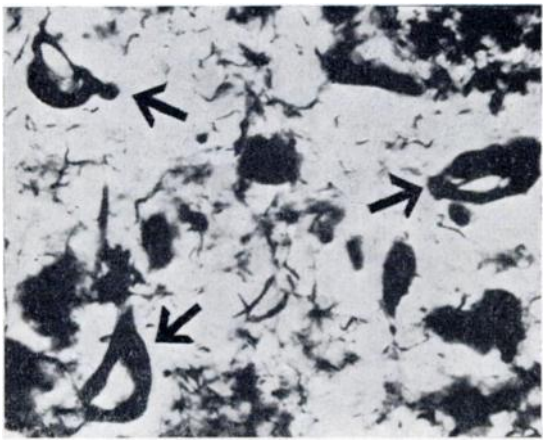

FIG. 2.—Cerebral biopsy showing neurofibrillary changes (von Braunmühl's method).

similarly confirmed. It was realized that a negative biopsy would not necessarily exclude A.D. as the lesions are usually said to be irregularly distributed throughout the brain; slight changes would also fail to establish a firm diagnosis. These are mainly theoretical objections, for in their paper on cerebral biopsy on presenile dementia Green *et al.* (1952) state, "Considering the severity and omnipresence of Alzheimer cells and senile plaques in A.D., it is difficult to imagine that they would be entirely absent in even a small piece of tissue such as a biopsy." Both our patients showed abundant Alzheimer changes which, together with the clinical findings, confirmed that the disease was present.

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Case Reports

Case 1. H.C., male, aged 52, was referred to the O.P.D. of the Midland Hospital for Nervous Diseases on 27.12.51 with a history of rapid deterioration both of memory and general efficiency over the past 18 months. Prior to this he had been an energetic person, holding a responsible job for over 20 years, and played an active part in the works' cricket team. His wife now had to do everything for him, including dressing. The first mental symptoms were of a depressive nature and he had elsewhere received a course of E.C.T. without benefit.

On 29.3.52 he was admitted to the Queen Elizabeth Hospital. He rarely talked spontaneously and his reactions to questions or requests were delayed and often inappropriate. Memory was grossly impaired. He was unable to give more than his surname, and said he was 13 years old. He was almost completely disorientated with respect to time, to place and to person, and in addition to a gross apraxia exhibited perseveration in the form of hand and of brow-rubbing. Apart from a B.P. of 200/110 physical examination was negative.

The EEG report stated: "The EEG is grossly and continuously abnormal. Alpha rhythm is almost absent, occurring only sporadically for very short periods in the posterior leads. There is much mixed delta and theta activity from 1·5–3·5 c/s and 4–6 c/s in all leads. This is most marked anteriorly and posteriorly, and is greater on the right side than on the left. The delta waves show phase-reversal at the temporal electrodes on both sides, and frequently occur in short bursts of three or four successive waves synchronously on the two sides in the anterior and posterior leads, followed by longer runs of theta, or mixed theta and delta activity of lower amplitude. The record also shows a small amount of very low voltage fast activity at 20–22 c/s which appears mainly in the left-sided leads."

Ventriculography was performed by Mr. E. A. Turner and showed appearances consistent with gross cortical atrophy. Through the right parietal burr hole a piece of brain was removed for histology (described below).

Cortisone (intramuscular) was then given as follows:

200	mgm./day	for	3	days
100	,,	,,	21	,,
25	,,	,,	3	,,

After an interval of a week A.C.T.H. was given as follows:

100	mgm./day	for	2	days
75	,,	,,	2	,,
100	,,	,,	12	,,

and reducing by 20 mgm. per day subsequently.

A second biopsy was taken after administration of Cortisone.

There was no clinical improvement either after Cortisone or A.C.T.H. and the patient was later transferred to an Institution where deterioration continued.

Case 2. F.S., female, aged 54, was referred to the O.P.D. of the General Hospital, Birmingham on 4.9.52 with a history of progressive mental deterioration over the past four years. Prior to this she had been a conscientious and efficient housewife who had managed her home and brought up her children successfully. There was progressive confusion and inability to accept responsibility. In the year prior to admission deterioration had been more rapid and she could no longer dress herself or maintain a conversation and her memory for recent events was greatly restricted. She showed none of the restlessness regarded by some as being typical of A.D., and though she had lost the ability to read, she would sit quietly facing an open book which was, as often as not, wrong side up. Physical examination was negative apart from a B.P. of 160/120.

The results of electroencephalography and ventriculography were similar to those on Case 1.

Biopsy was performed as in Case 1. For histology report see below.

Cortisone (intramuscular) was given in the following dosage:

300	mgm./day	for	1	day
200	,,	,,	1	,,
100	,,	,,	1	,,
200	,,	,,	2	days
300	,,	,,	3	,,
100	,,	,,	30	,,

Again there was no clinical improvement and the patient was transferred to an institution where her deterioration continued.

Psychometrics of a formal nature were not possible owing to the gross deterioration of both patients. On the other hand, the few remaining skills offered an excellent base-line to assess improvement.

Histology

The biopsies from both patients showed essentially the same histo-pathology and are therefore described together. They were fixed in 4 per cent. formaldehyde-saline immediately after removal and where possible, fragments were cut off

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and fixed separately in formol-ammonium bromide. Frozen and paraffin sections were cut, stained by a variety of methods and compared with control sections of normal brain.

The cortex showed focal loss of neurones, marginal gliosis and an increase in intra-neuronal lipo-fuscin pigment ("pigment atrophy"). With silver impregnation abundant senile plaques and neurofibrillary alterations were seen (see Figs. 1 and 2). The plaques had the classical structure described by Critchley (1929), and although present throughout the cortex, were more numerous in the outer layers. The white matter showed axonal degeneration, hyperplasia of astrocytes and mucoid degeneration of oligodendroglia. No definite relation of plaques to blood vessels could be seen.

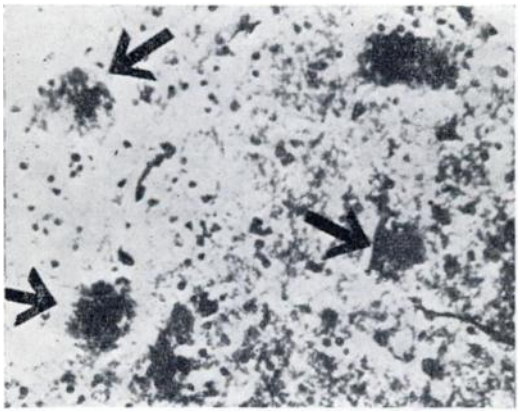

FIG. 3.—Cerebral biopsy showing a positive reaction at the site of the plaques (per-iodic acid-silver method).

Coarsely granular clumps of material staining positively by the per-iodic acid–Schiff technique (P.A.S.) were seen at the site of the argentophile plaques. This granular P.A.S. positive material was amylase fast and was superimposed on a diffuse, P.A.S. positive "background", which corresponded approximately with the size of the plaques seen with silver impregnation. The "background" was more strongly positive than the faint P.A.S. reaction given by the cortical ground substance. A positive reaction at the site of the plaques was also given by the per-iodic acid-silver method for neurones (Dixon, 1953b): this method, like P.A.S., also stained the intraneuronal lipo-fuscin pigment. Substances staining positively with the Alcian-blue stain for mucin, sudan IV (frozen sections) and sudan-black (frozen and paraffin sections) for lipids and the methyl violet reaction for amyloid were less consistently demonstrable. Metachromasia with toluidine blue was also seen at the site of the plaques. Granules of P.A.S. positive material were noted in glial cells, both in the cortex and white matter. The changes appeared to be more marked in the second biopsy of Case 1.

DISCUSSION

Cortisone and A.C.T.H. had no beneficial effect on the clinical course of the disease in the two patients treated. Our impression was that deterioration was perhaps accelerated by these drugs and the biopsy taken after treatment of patient 1 showed changes which were more marked than those seen before treatment. In a progressive disease one cannot draw conclusions regarding

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worsening, especially as the histological changes of A.D. may vary quantitatively throughout the brain. Thus an apparent increase could have resulted from chance sampling. In view of recent observations describing enhancement of the production of experimental amyloidosis by cortisone (Teilum, 1952; Peräsalo and Latvalahti, 1954) and as amyloid material has been shown to be present in Alzheimer plaques (Divry, 1927), further attempts to treat A.D. with cortisone would seem to us to be contraindicated.

It is of interest to note the gross EEG changes in both patients. We have noted similar changes in other patients who presented clinical features comparable with those described, only with much less mental deterioration; as biopsies were not performed on these patients, however, the diagnosis of A.D. was not definitely established. It is not possible to generalize on the EEG findings, but there is at least an impression that they may be of early significance. This observation is in accord with that of Delay *et al.* (1944) who reported an absence of alpha waves over areas of cortical atrophy in cases of dementia.

Our histological findings have demonstrated histochemical changes at the site of the plaques. Hiroisi and Lee (1936) found "mucin", and Divry (1927) found "amyloid", and we have noted similar changes in our two cases. The positive P.A.S. and per-iodic acid-silver reactions described seem to indicate the presence of carbohydrate containing material, which appeared to be in excess of that shown by mucin and amyloid stains. Certain non-carbohydrate containing lipid substances, e.g. phospholipids are also said to give a positive P.A.S. reaction and may be present in the plaques. The presence of lipid substances is suggested by our finding that the P.A.S. and per-iodic acid-silver reactions were more strongly positive on frozen sections than on paraffin sections which had been treated with fat solvents. Sudan-black—which stains phosphatide and cerebroside—also gave a stronger reaction on frozen sections. A distinction between the lipid groups was, however, not possible on our material as the limited amount of tissue available from these biopsies restricted further investigation of the question. The staining properties of part of the P.A.S. positive material resembled that of the granules of lipo-fuscin pigment found in cortical neurones (Dixon and Herbertson, 1950, 1951). Dixon (1953a) found similar granular material in phagocytic cells infiltrating necrotic cerebral cortex and suggested that these granules originated in part from lipo-fuscin that had persisted and been phagocytosed after disintegration of neurones.

TABLE I

Showing the Histochemical Reactions at the Site of the Plaques

	Frozen Sections	Paraffin Sections	Significance
1. Reaction with P.A.S.	++	+	Could be due to glycogen, mucopolysaccharide, mucoprotein, glyco *or* phospholipid.
2. Reaction with P.A.-silver	++	+	
3. Reaction with P.A.S. after incubation with salivary amylase	++	+	Excludes glycogen.
4. Staining with Alcian-blue		+	Probably mucopolysaccharide present.
5. Metachromasia with toluidine blue		+–	
6. Metachromasia with methyl violet		+	"Amyloid".
7. Staining with sudan IV		+–	Neutral fat present in some plaques.
8. Staining with sudan-black	+(+)	+	Probably glyco or phospholipid present.
9. Prussian blue reaction		–	No ferric iron.

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An increase in neuronal lipo-fuscin has often been noted in A.D. and it may be that part of the P.A.S. positive material in the plaques originates in the way suggested by Dixon after atrophy of neurones. It also seems possible that the argentophilia shown by the plaques is partly due to the affinity of focal, intracortical deposits of chemical substances for metallic silver. Table I shows that the following substances are probably present at the site of the plaques: neutral fat, "amyloid" material, muco-polysaccharide ("mucin") and glyco- and/or phospho-lipid. The per-iodic acid-silver method (Dixon, 1953b) on frozen sections demonstrates the Alzheimer plaques so clearly that it provides a useful supplementary technique for the rapid diagnosis of A.D. Further studies with modern histochemical techniques are needed and may help to contribute to our knowledge of this disease.

Summary

Two patients with Alzheimer's Disease, confirmed by cerebral biopsy, did not benefit from treatment with cortisone and A.C.T.H. The histochemical changes are briefly discussed. The per-iodic acid-silver method on frozen sections (Dixon, 1953b) demonstrates Alzheimer plaques clearly.

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Addendum

Since this paper was prepared Corsellis, J. A. N. and Brierley, J. B. have described the histochemical findings in two cases of atypical Alzheimer's Disease (*Brain*, 1954, **77,** 571). In both of these cases an abnormal substance, probably a mucopolysaccharide, was found in the plaque cores, blood-vessels and as free-lying fragments.

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