THE CLINICAL DIFFERENTIATION OF PICK'S DISEASE

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INTRODUCTION

THE aim of this paper is to show how, in our view, the diagnosis of Pick's pre-senile dementia can be made in some cases during life on clinical grounds alone.

We present a description and discussion of three cases examined by us in detail. In all three cases, the diagnosis of Pick's disease was made before death and confirmed at autopsy. During the period these patients were in hospital, we did not make this diagnosis in any other case under our care, and encountered no unexpected cases of Pick's disease among our autopsies.

On the basis of this material we conclude that the pathological changes in some cases of Pick's disease give rise to a fairly distinct clinical picture, which we endeavour to describe.

Established Concept of the Disease

Pick's disease, which was first described over sixty years ago, has never been a well-defined clinical entity. This lack of definition is apparent from the beginning of its historical course, for Pick himself was not concerned with demarcating a particular syndrome: his avowed intention in describing various temporal lobe atrophies was to clarify contemporary concepts of aphasia. The pathological basis of Pick's own cases was varied. He himself considered that those occurring in the older age-groups were part and parcel of the syndrome of senile dementia, but one of his younger patients showed a cerebro-vascular condition secondary to Bright's disease, while another had clinical signs of G.P.I., in addition to cysticercosis of the temporal lobe. A further complication arises from the fact that Pick described lobar atrophies other than temporal, analysing these in terms of a particular resultant organic defect; for instance, occipital lobe atrophy in relation to apperceptive blindness.

Pick's accumulated research on lobar atrophies has been subjected to much sifting out and working over by succeeding writers, as a result of which it has been deduced:

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(1) that circumscribed cerebral atrophy can occur independently of a "senile" cerebral atrophy and that pathological changes in the form of silver-staining plaques and neurofibrillary changes need not be present.

(2) that such circumscribed cerebral atrophy, involving both grey and white matter, with disappearance and distortion of ganglion-cells (some, on occasion, showing peculiar silver-staining inclusions), is a distinct pathological entity, and belongs more properly to the pre-senile group of degenerative disorders. It is accepted that a minor degree of atherosclerosis may sometimes co-exist without being a factor in the causation of the disease.

(3) that the sites of greatest predilection are the frontal and temporal lobes.

It is to this type of circumscribed lobar atrophy that the descriptive term Pick's disease has been applied. It may be concluded from such vague general assumptions that the pathological picture is far from uniform, in relation to both localization and histological findings. A perusal of the hundred or more published cases indicates that the clinical picture also lacks uniformity. There is, however, a tendency to group a certain number of symptoms as characteristic of the commonest variant, the fronto-temporal, and this constitutes the usual textbook description of Pick's disease.

Case Material

In the first case the diagnosis of Pick's disease was made tentatively and was suggested mainly by a consideration of the unique clinical picture, for which it seemed necessary to postulate an atrophying lesion affecting mainly the frontal and temporal lobes. The later two cases showed a striking similarity to the first, and we have felt justified in concluding that all three belong to the same distinct clinical and pathological grouping. (It may be, of course, that we have merely been fortunate in seeing in rapid succession three examples of one particular variant of Pick's disease, and that our conclusions would not be valid for the whole group.)

The clinical features to which we would particularly draw attention, as being distinctive in these cases, may be briefly indicated before the cases themselves are described.

1. Especially prominent was the relative retention, until a late stage in the disease, of our patients' concepts of space and time, concepts regarded as dependent on intact functioning of the parietal lobe. This finding alone appeared to indicate that the lesion originated in the anterior portion of the brain.
2. When suitably examined and observed over a sufficient period, it was found that the faculty of memory was less disturbed in these patients than might appear from their response to formal tests. This finding has been emphasized in previous commentaries, first and notably by Kahn and Thompson (1934), and later by other writers including Nichols and Weigner (1938).
3. The particular type of amnestic aphasia shown by all three patients also appeared to have diagnostic value.
4. More subtle mental changes, less readily attributable to a lesion in this or that cerebral area, yet showing a similar pattern in all three cases and

therefore adding their quota to the demarcation of a particular syndrome, were those relating to personality, affective response, and reaction to testing. The reaction to testing was particularly striking: all three patients showed a marked disinclination to co-operate in formal tests, so much so that assessment of their mental functions had to be made in large measure indirectly by listening to their spontaneous conversation and observing their behaviour.

5. Finally, we were impressed by the occurrence in all our three patients of a physical sign in the form of generalized hyperalgesia. This sign, although mentioned on rare occasions as an incidental finding in clinical descriptions of patients with Pick's disease, has never to our knowledge been regarded as either worthy of comment or of diagnostic importance.

Case 1

Summary: A housewife at the age of 57 began to show personality changes in the form of decreased maternal affection, indolence in the carrying out of domestic tasks (with exaggerated attention to her own welfare) and an obstinate repetition of habitual actions, regardless of their expediency. Over the ensuing four years, aphasic defects became obvious. Her practical performance deteriorated, but she could still find her way about the city, knew the days of the week, and her actions indicated that her memory was not grossly deficient. She complained of generalized pain and winced when any part of her body was touched.

On admission to hospital, some six years after symptoms first appeared, she was still capable of rudimentary conversation and was orientated for space and time. Two years after admission, she sank into a state of hebetude—all initiative lost and speech reduced to a few stereotyped phrases—and this state continued until her death nine months later.

Total duration of illness eight and a half years.

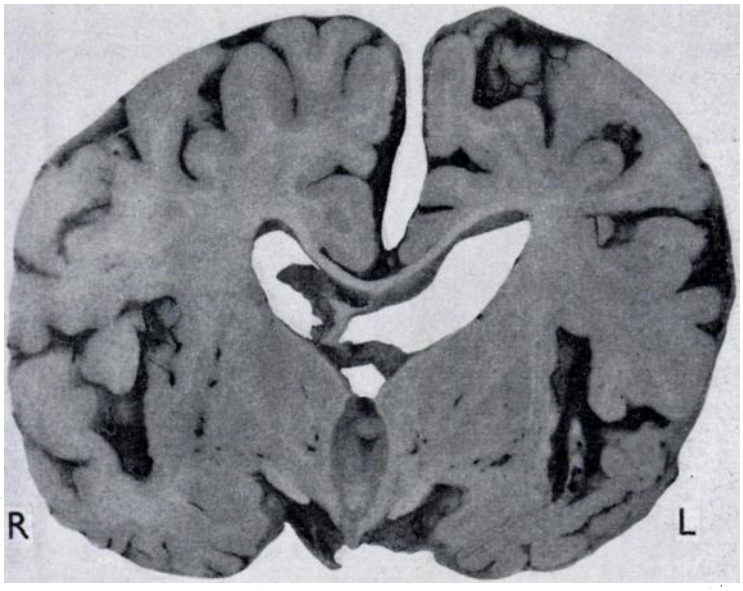

FIG. 1. (*Case 1*)
Coronal section cerebrum showing severe atrophy of both temporal lobes and compensatory hydrocephalus.

Mrs. Elizabeth R., aged 63, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders, on 22 March, 1949.

Family and Personal History: Her mother displayed mild mental symptoms for some months before her death in her late seventies. One sister suffered from a right hemiplegia and epilepsy, the alleged sequelae of an injury in infancy, and died aged 40. The patient married, at the age of 24, a tradesman who rose to a managerial position, and had a son and two daughters, a third daughter having died of meningitis in infancy. She had always enjoyed good health and was described as affectionate, hospitable, on occasion obstinate, prone to minor extravagances, meticulous in her domestic arrangements, an excellent cook and dressmaker.

Phase 1—1943-1947: The first abnormal sign was the patent's unaccountable and frequently expressed hostility to her elder daughter whom she compared unfavourably to her younger daughter, then absent on war service. She became indolent and slovenly in domestic matters, dusting around objects instead of lifting them, sweeping the refuse from the floor under the mat. She often remarked "I can't be bothered doing that today". She made no effort to accommodate to wartime rationing, and if she could not obtain meat for the midday meal, she told her family "You will have to go to the canteen today". She always prepared the evening meal, but served up the same dish again and again. She lost her former interest in dressmaking, but in 1945, was still able to make a dress for her daughter, albeit the latter had to "stand over her" encouraging her to complete it. She showed increasing querulousness, ceased expressing gratitude and rarely laughed spontaneously, although she smiled in an automatic way when greeting friends. She was never seen to weep. Her son, serving in India, noted that her letters became steadily more egotistical and complaining in content, and more mechanical in style, with repetition of stereotyped phrases. In time, she ceased referring to news contained in his letters to her—"it was as if she never received them". On his return from abroad in 1946, after four years' absence, he noted a marked deterioration in his mother's efficiency. The shirts she laundered for him were too crumpled to wear. She served up the same hastily prepared dish of sausages and potatoes at every meal. When criticism was made, "She wasn't a bit hurt, just took it for granted. Sometimes she contradicted us, but she did it without emotion". In many of her actions she displayed what seemed to the observer wilful obstinacy. One such concerned her habit of scattering crumbs for the birds in the garden. As she now did this with extreme prodigality, she was warned that the food attracted rodents. She paid no heed to this advice. When her husband tactfully fitted up a tray for the food, she ignored it, but if accosted she would walk towards the bird tray, wait till her observer had gone, and then scatter the bread on the ground.

Phase 2—1947-1949—(year of hospital admission). Her husband died in 1947 and although she had continued to evince more regard for him than for her family she displayed no emotion at his death. She spent the day of the funeral in a vigorous search for his pipe and tobacco pouch in order to give these to her brother.

From this time onwards her behaviour showed increasing stereotypy. She rose every day at 6.30 a.m., and after giving her family morning tea in bed, she sat about in a dirty dressing-gown reading newspapers—retailing to her family the more horrific events—playing patience or doing cross-word puzzles (she solved these by looking up the answers). She took no part in the preparation of the family evening meal, but cooked her own meal which invariably consisted of fried sausages. She poured the liquid fat into the sink where it congealed, or if forcibly prevented, threw it on the fire undeterred by the resultant blaze. Promptly at 9 p.m., she filled her two hot water bottles and went to bed.

On the same two days of each week, she went out to buy her food, always visiting the same shops and making the same purchase. Every Thursday, she drew her Widow's Pension at the Post Office, where it was noted that she could not always give her husband's Christian name to the clerk. She never lost her way. She could tell the time on the clock and always knew the day, month and year, although, as an aid to memory, she kept a block calendar, tearing off the relevant page each day. Throughout this period she had difficulty in finding the names of persons and objects and employed periphrases to describe what she was trying to name. She showed at one and the same time a decreased ability to understand the conversation of others and an absence of striving to do so.

Physical symptoms appearing during this period were

(a) *Generalized Pain*: She frequently remarked in the morning "I'm sore all over—I

never slept all night with it". When her daughter took her arm or the cat rubbed against her ankles, she cried out as if experiencing unbearable pain. Once when her doctor attempted to estimate her blood pressure, she gave an agonized cry and attempted to strike him. (b) *Somnolence*: She tended to fall asleep at all times of the day and always went to bed at 9 p.m.

Physical Examination (*following admission*): The patient, a seemingly stolid healthy middle-aged woman, was 5 ft. 4 in. in height and weighed over thirteen stones. B.P. 160/100. Apart from a generalized hyperalgesia which caused her to resent all physical examination, no abnormality was elicited on physical examination or laboratory testing. Blood W.R. negative. C.S.F. findings were likewise negative, and straight X-rays of skull revealed no abnormality. Because of her deficient understanding it was impossible to measure accurately the curious dysaesthesia which she exhibited. Pinprick applied to all areas of the body revealed a seemingly lowered threshold to pain. Venepuncture was only achieved after physical restraint, and lumbar puncture—a procedure in which the patient had no visual threat of the approaching needle—required a general anaesthetic. Conventional pressure such as that utilized in abdominal palpation or the application of a manometer cuff or even the more friendly linkage of her arm with that of a nurse caused immediate wincing and withdrawal, while more severe pressure, e.g., inflation of the manometer cuff, called forth expressions of excruciating pain and motions of self-defence.

Mental Examination: Her behaviour showed alternating restlessness when for instance she rummaged in the ward clothes cupboards and scrutinized the name tapes on the various articles, and placid contentment, when she sat quietly playing patience and ostensibly reading magazines. On occasion she played a few simple tunes on the piano. She was able to feed herself and was not incontinent.

Formal testing of her mental faculties was difficult because of her pronounced disinclination to attend. She showed no anxious striving to succeed and frequently pushed test material away, saying, "It's all right, all right", or "I can't be bothered". Her understanding of spoken speech was markedly defective. Even simple questions were not always comprehended, in which case her response was "what do you mean?" or "I don't know". She never confabulated. Her conversation showed stereotypy of content and form. Her vocabulary was restricted, her grammatical constructions simple. On occasion, however, she used elaborate words accurately, e.g., "ridiculous", "evidently". Her frequently reiterated rendering of a conversation between herself and her husband immediately before the latter's death illustrates her asphasic defects. "In November, he just said to me it was his birthday, you see, 64. He just said to me he would not come to me for his dinner, it was Friday, but he said to go into the town just after five, and we would go and have our tea and go to the pictures after that. Coming home, he said, if you and I are spared until I am 65 I will go away into the country and we will let that crew (their family) go wherever they like. I was just hoping that it would be all right, but he died in the November—December. I was very vexed I had lost him." As the above passage illustrates she could convey information relating to numbers with considerable accuracy. Furthermore, she often introduced numerical references which were superfluous or irrelevant to their context, i.e., while elaborating her frequent complaint of her children's alleged impertinence to her, she exclaimed, "you would not think it my house at all," adding the seeming *non sequitur*, "I think it was £2,000 we paid for it" (the house). Her articulation was clear and she never uttered neologisms or distorted particles of words. She described the functions of objects presented to her if unable to name them. She had difficulty with genders and pronouns, at times using the word "son" to refer to her son, husband, brother or father. In relating the deaths of her parents, she said "My son [father] died first, then it was a good long time before my mother died. It just so happened that after he died, I went to him . . . to her, and made him [her] come to my house to stay, but it was just a while before he died . . . before she died, but she was even older than him. I am sure she was bound to be about eighty at that time. My son [father] he was sixty-nine when he died."

She was able to sign her name, but refused to write to dictation. Her reading of printed name cards was erratic, e.g., she read "telephone" and "Bluebell Matches" but refused to read "apples". She refused to approximate name cards to their appropriate objects. Her handling of illustrated papers suggested that she understood some part of their content, but she never commented on them. She could count concrete objects laid before her, but would not essay simple mental arithmetic.

She could tell the time on a clock face and assess the time of day. At first she could give the day and date of the month correctly, but soon lost this ability. Recognition of the months of the year was retained for a longer period, and when she was presented at a clinical meeting on 23 June—she said the month was "June" adding "this will be near the end of it". When she could be persuaded to do so, she copied simple diagrams accurately. It was noted that she placed her cards correctly when playing patience. She never lost her way in a hospital block of many wards and corridors, but she was not aware of the name of the building nor of its function. She distinguished her right hand from her left and showed no dressing apraxia.

She recognized but was unable to name the members of her own family. She referred to them as "my son and two daughters and the lassie who has just got here you see"—this last phase categorizing her daughter-in-law who had lived abroad before her marriage. Her conversation indicated that she recollected events of strong personal significance in the present and recent past, i.e., her domestic activities, the activities of her children in so far as they impinged on her own, the circumstances of her son's second marriage and of her husband's death. She tended to dwell more on the recent than on the remote past, but if distant events were recalled to her, e.g., the deaths of her parents, she could elaborate the relevant details. She seemed aware of the chronological sequence of events, which she recalled spontaneously or by direction. Temporal association could act as a stimulus to recall. For example, in a conversation about her son's second wife, she was asked "Has she any children?" and she replied, "No, it was only in December (i.e., four months earlier) that he married her", adding, "It was the year before that that my man was dead". Here the stimulus word was December since her husband had in fact died the December before. Her total response to the foregoing question furthermore proved the retention of some degree of reasoning ability. She had no recollection of events outwith the personal and concrete. She showed some degree of insight in that she often ejaculated "I have got so stupid I cannot mind (*anglice*—remember) things at all", but she had no realization of her total situation.

Subsequent Course: Within a year, the generalized hyperalgesia had ceased to be evident. She developed a gorilla gait with bowed trunk and limply hanging arms. Her vocabulary became progressively more impoverished. Finally, with no intervening phase of dysarthria or paraphasia, she passed into a state of relative mutism, repeating infrequently a few phrases culled from her conversation with her husband (quoted above). Mental and physical activities coincidentally declined, and during the last nine months of life she lay in bed inattentive, but was rarely incontinent.

She died suddenly on 30 December, 1951.

Necropsy Findings: Both main branches of the pulmonary artery were occluded by partially coiled ante-mortem thrombus which had had its origin in the left femoral vein. There was early, incomplete infarction of both lungs. The coronary arteries and aorta showed moderately severe atheroma.

THE BRAIN showed slight generalized atrophy of the whole of both cerebral hemispheres, but in addition there was a lobar atrophy of both temporal lobes and of the left frontal lobe. This wasting was most marked in the left temporal lobe where the anterior two-thirds of the superior, middle and inferior temporal gyri and the anterior 2·5 cms. of the hippocampal gyrus were considerably shrunken and firmer than normal. The fusiform gyrus was intact. In the right temporal lobe the atrophy was less marked and involved only the anterior one-third of the middle and inferior temporal and fusiform gyri. The left frontal atrophy was confined to the anterior two-thirds of the lobe. The leptomeninges covering these affected lobes were thickened and slightly wrinkled, but elsewhere over the surface of the hemispheres they appeared healthy. The arteries at the base of the brain showed patchy atheroma. No abnormality of the cerebellum or brainstem was seen.

Section of the brain confirmed the lobar atrophy and showed that in the left temporal lobe the gvri were reduced to thin lamellae. The anterior part of each insula shared in this atrophy. No obvious involvement of the basal ganglia could be seen. There was a marked compensatory dilatation of both lateral ventricles which was most marked in the left anterior and posterior horns. The third ventricle too was dilated.

Microscopic Observations: In the left temporal lobe there was widespread atrophy of both cortex and convolutional white matter. The neuronal loss affected all layers of the cortex. Surviving nerve cells appeared atrophic and degenerate but there was no ballooning of nerve cells; and no argyrophilic inclusions, tangles or senile plaques

were seen. There was evidence of loss of myelin from both cortex and white matter and in response to this a quite marked gliosis had occurred. The leptomeninges showed very slight fibrous thickening.

The changes in the right temporal lobe and in the left frontal lobe were similar to those in the left temporal lobe but were less severe.

Sections examined from parietal and occipital lobes showed simply the mild changes expected to accompany moderately severe, generalized cerebral atherosclerosis.

In the basal ganglia there were a few small glial scars related to the vascular disease. In the midbrain too there was evidence of atherosclerosis but there was no demyelination of frontopontile or temporopontile tracts. A small quantity of free melanin pigment indicated minimal nerve cell loss from the substantia nigra.

In all sections there was evidence of moderately severe atherosclerosis. The arterioles appeared healthy.

Case 2

Summary: At the age of 50, an unmarried female school teacher was observed to show increasing egocentricity, lack of inhibition and narrowing and rigidity of her interests and activities. Five years later, aphasic defects became obvious, her practical performance deterioriated, but memory and orientation were not notably impaired and she was able to live alone without domestic help until her admission to hospital twelve years after the first appearance of personality changes. Examination revealed a generalized hyperalgesia. Death occurred two years after admission, being preceded by a terminal phase of mutism and immobility.

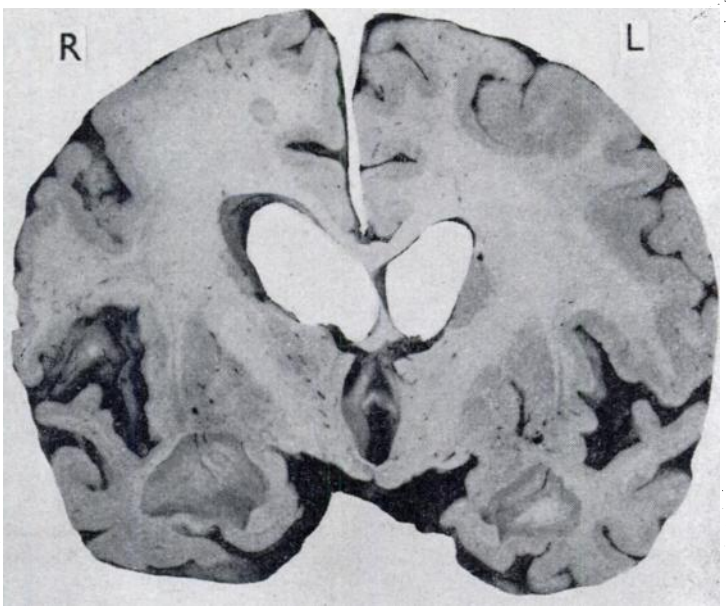

FIG. 2. (*Case 2*)
Coronal section cerebrum showing severe symmetrical atrophy especially of temporal lobes. Also compensatory hydrocephalus.

Miss S. V. P., aged 62, a retired teacher of needlework, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on 26 September, 1950.

Family History: The paternal grandmother and a paternal aunt suffered from a memory defect for a few years prior to their deaths in the ninth decade of life, and another paternal aunt had a child who was a mongolian idiot. There was no other relevant family history.

Previous History and Personality: She had no nervous traits as a child. At the age of 19, she became highly-strung and excessively concerned for her own personal safety. There were periods of a few days when she lay in bed trembling. From these symptoms, she recovered spontaneously when she was 24. At 27, she gained a teaching diploma in needlework, then taught in primary schools, and retained her last post from the age of 38 until she retired at 60. She had lived alone since 1941.

She was described as being very variable in temperament, but, on the whole, popular, competent and extraverted.

Medical History: Radium menopause at 32, followed by flushings and severe headaches until the onset of her mental illness at 50. At 50, she was struck on the right eye and nose with a shuttlecock, and the region was, for a time, swollen. At 60, she fell and struck her head, but did not lose consciousness.

Present Illness:

(a) *Phase 1—age 50–57*. Her relatives, who dated her illness from the badminton accident, first observed that, instead of wearing a dressing over the injured part of her face, she carried an umbrella to protect it from the sun. She became progressively more self-centred in her outlook and her activities became more stereotyped. She developed a rather silly, flat laugh. Her memory showed occasional lapses. For example, she forgot entirely about a letter she had sent to her relatives. Towards the end of this period she was occasionally unable to recall the names of things she used in her work, such as scissors and thimbles.

(b) *Phase 2—age 57–62*. During this period, her speech showed the greatest decline. She increasingly forgot the names of people and things, but was able to converse by substituting generic terms such as "thing", "man", "woman", or different but related words such as "school" for any building, "letter" for "key", "bread" for "cakes", "water" for "ink". Sometimes she transposed genders and family relationships. She understood progressively less of what was said to her. She gave up reading newspapers and writing letters, and communicated entirely by telephone. (She was thus able to manipulate the dialling system.) She lost her ability to calculate, required help with her accounts, and would hand banknotes trustingly to tram conductors and shop assistants. She remembered recent personal events with only occasional minor lapses, but became completely ignorant of current affairs in the outside world. She perseverated in her speech, and would repeat the same ideas over and over again. She was able to identify by sight her friends, places in the neighbourhood, and playing cards. She remembered important dates and anniversaries, but, at the beginning of Summer Time in the year of admission, arrived at church an hour late. Her spatial orientation remained good with only occasional lapses. Latterly she did not usually identify her friends and relatives at once, unless she had reason to expect to meet them, when she would greet them without hesitation. Sometimes, however, she revealed by her conversation that she was confusing her hearer's identity, e.g., she mistook her niece for her aunt, and the minister for her brother. Not normally tidy, she became obsessionally so. Nevertheless, her standard of needlework and her housework deteriorated. She would put sugar on ham and eggs and tea in the soup. She formed the habit of lifting the kettle from the fire with a large cloth which frequently caught alight, and she persisted in this despite the repeated warnings of her friends. She could not learn new procedures, but managed to do her routine shopping. Her dress became slovenly and dirty. She fell asleep frequently and slept soundly. She made no attempt to understand anything not directly related to her own narrow objectives, but understood fairly well the processes of shopping and obtaining her pension. She developed a habit of talking loudly in public about her personal affairs to anyone who would listen. She bought bizarre articles, for instance, a bright red coat for herself and a handbag for her nephew on his marriage. Obstinacy, suspicion and caution became more and more prominent, and she would lock the door of her living room, as well as her front door, before settling down for her weekly game of rummy with her friends. At public meetings, e.g., in Church or at school, she became readily excited and irritable. She knew when to seek help with her letters and accounts, and frequently remarked: "Och! I'm going daft." She remained active and was able to look after herself although living alone, until only six weeks before admission.

Examination on Admission: She was short, stocky and grey-haired, with a rubicund, cheerful countenance. Her personal habits were of a good level. Although she took no

part in the work of the ward, she attended Occupational Therapy Class. She showed pressure of speech and perseveration. Her affect was one of mild euphoria, characterized by a frequent rather silly laugh. This would be interrupted by a fleeting irritability. Her conversation was a series of random and reiterated explanations of her personal affairs, with interpolated comments on where she slept, when she expected her brother's visits, etc. By far her most striking disability lay in the sphere of speech and it was of such degree that only close attention and practice enabled the examiner to converse with her at all, although her articulation was quite clear. In expressive speech, she was able to use adjectives and verbs, e.g., "particular" and "retire", with more accuracy and facility than nouns and pronouns. She was either unable to find words at all, or used wrong but related or generic terms. "Glasses" or "tea" sometimes meant "money", "school" meant "house". She frequently used "man" for "woman", "she" for "he", and "father" for "brother". When tested with simple objects, she usually refused to name them at all. If told the name, she usually repeated it, but was unable to name it again a few seconds later. Her errors were inconstant, she did not have fixed words which "stood for" others, and she sometimes used the correct words. Similarly, she understood the spoken word erratically and with difficulty. A sample of her speech is as follows:

"I'm S. V. P. and I live along at the school (at my home) but here I've been writing something over there (embroidering a cloth at the Occupational Therapy Class) . . . Yesterday I was doing that thing (embroidering that cloth) . . . I want to wash that thing (the cloth). I want to have it done. You see my brother's coming tomorrow and I might go away. I live alone at my own house which is a great big place, up and down (upstairs and down) with a garden. I'll have to go and do that letter (embroidery)." She refused to read continuous print, but if a page were handed to her upside down she invariably turned it the correct way. When encouraged to spell out words, she seldom named the letters correctly, and when given the alphabet in jumbled order, she read it out in the correct order, pointing to each successive letter as if she were reading it correctly. She could write her name, but very inaccurately. She quickly lost interest in testing, but never showed a catastrophic response to failure. Instead she would rationalize, saying, "I live alone and I never bothered; I need my glasses; etc.", or admit frankly "I don't remember the names of things", or look crestfallen and push the test away with the phrase: "Och! I'm daft." She never confabulated. She was surprisingly well orientated. She quickly knew her way accurately about the ward. Two weeks after admission, she took two doctors, without hesitation, by what was, for her, an unusual tram route, and thereafter through a complex maze of suburban streets, to her home. She pointed out places on the way, and, although she could not name them, usually showed that she understood what they were. She once referred to "being put away here". Two weeks after admission, she referred to being here two weeks. She frequently indicated that she had left school two years before, which was correct. She referred correctly, but in her aphasic way, to events of the previous day, and was aware when Saturday (her brother's day for visiting) came round. She regularly went to the table at the correct times, in anticipation of meals. She knew her own identity, recognized the doctors, her visitors, and numerous neighbours during her visit home, but the only names she ever mentioned were her own, her brother's and her niece's. Her memory was difficult to test, and her response was erratic: she remembered events in her past life, recent events in the ward, and her visit home, but on one occasion she carefully put her spectacles and handkerchief under a pillow, and immediately proceeded to look for them elsewhere. Hearing and vision were obviously not grossly impaired. She refused to name colours, and, in her embroidery, consistently failed to change colours when this was obviously required. When shown various objects and pictures, she never named them, but often picked out minor details or indicated one of their uses; e.g., when shown a watch with the hands set at eight o'clock, she said, "I need my glasses. I can't see it. I live alone. It's eight o'clock, isn't it?" She could count as far as twenty, identify the numbers of tram cars, and reckon days and weeks, but was unable to do other simple calculations. When shown half-a-crown, she said "Oh yes, that's two, is it, or is it two and a half?" She could construct a triangle and make a poor copy of a five-pointed star with matches. Her embroidery (a professional skill) was slow and of a very poor standard, but she was able to follow the pattern correctly. She could put on her clothes and gloves correctly, but if the examiner pointed to his own thumb, she would grasp her little finger. Her social sense and judgment were impaired, so that for the most part she accepted uncritically her position in hospital and would think nothing of announcing publicly her intention of visiting the W.C.

Physical Examination: Neurological examination showed a slight tremor of the left hand, tigroid retinae and a well-marked hyperalgesia to painful stimuli over the whole skin surface. B.P. 150/110. Apart from moderate obesity, no other abnormality was found on routine physical examination. Blood W.R. was negative. Lumbar puncture provided a clear, colourless fluid under 60 mm. of pressure, with a free rise and fall under jugular compression to 150 mm.; 2 cells per cu. mm.; 50 mgm. Protein per 100 mil., a trace of globulin; 66 mgm. Sugar per 100 mil.; negative W.R.; and colloidal gold curve 0000000000. Straight X-rays of skull revealed no abnormality. E.E.G. was somewhat spoiled by movement artefacts, but showed no definite abnormality.

Progress: For the first eight months, no major change in her mental condition occurred. Her right shoulder became lower, so that her trunk was bent over sideways, and her steps became short and shuffling, with a side-to-side rolling gait. During this period she frequently referred to the expedition to her home. During the next six months she showed a marked deterioration in all spheres and at the end of this time she was completely bed-ridden. All proprioceptive reflexes were exaggerated, she had bilateral ankle-clonus and an occasional coarse rhythmical munching movement of the jaws, and a perpetual fingering of the mouth and nose. She was able to feed but not dress herself, was regularly incontinent of urine and also occasionally of faeces. She showed little interest in her surroundings and was unable to co-operate in any examination. Perseveration became very marked, and her aphasia prevented almost all communication, although articulation was hardly impaired at all. She was able to perform only very familiar actions. At the end of the next twelve months, she had paresis of both limbs on the right side and a generalized muscular rigidity of Parkinsonian type. She was now quite mute. Babinski's, Oppenheim's and Meyer's signs were all negative. On 21 December, 1952, she developed crops of blisters. She become comatose on 30 December, 1952, and died on 31 December, 1952.

Necropsy Findings: There were multiple bedsores. There was a well-established brochopneumonic consolidation of both lungs.

THE BRAIN showed moderately severe generalized atrophy with a severe lobar atrophy of both frontal and both temporal lobes. The leptomeninges were not thickened. The vessels over the surfaces of the hemispheres were healthy and the arteries at the base of the brain showed only a slight diffuse thickening of their walls and no evidence of atheroma. No abnormality of midbrain, pons or medulla or cerebellum was seen.

Serial coronal sectioning of the hemispheres showed that the wasting was most marked in the left temporal lobe, and that although the superior, middle and inferior temporal gyri and fusiform gyri were grossly shrunken, the hippocampal gyrus was intact. In the right temporal lobe the inferior temporal and fusiform gyri were severely affected but the superior and middle temporal gyri were also atrophied. The wasting of both frontal lobes was particularly well marked on the orbital surfaces. The anterior half of each insula was wasted and the caudate nuclei appeared slightly smaller than usual. There was marked compensatory dilatation of both lateral ventricles which was most marked in the body and temporal horn on the left side. The third ventricle shared in the dilatation.

Microscopic Observations: In the severely wasted temporal gyri there was a profound loss of nerve cells from the cortex and surviving cells were degenerate and contained a large amount of lipofuscin pigment. There were no ballooned cells and silver stains failed to demonstrate intra-cytoplasmic inclusions, tangles or senile plaques. The convolutional white matter was shrunken and there was considerable thinning of myelin. This atrophy was associated with marked astrocytic increase and glial formation but there was no microglial activity. The leptomeninges showed slight fibrous thickening with histiocytic infiltration of the subarachnoid space. In the less severely wasted temporal gyri the changes were similar but less marked.

The atrophy in the frontal lobes affected both grey and white matter. The cortex was narrower than usual and the nerve cell loss was more marked in the outer laminae so that the pyramidal cells appeared more superficial than usual. There were no ballooned cells or argyrophilic inclusions.

No significant abnormality of the occipital lobes could be seen.

The basal ganglia appeared normal and showed no obvious nerve cell loss or gliosis. The section from the midbrain showed no appreciable reduction in the number of cells in the substantia nigra but the presence of histiocytes containing melanin

indicated that degeneration of occasional cells had occurred. There was no evidence of demyelination in the cerebral peduncles.

In all sections the arteries appeared healthy but some of the arterioles showed slight hyaline thickening of their walls.

Case 3

Summary: At the age of 54, a married woman formerly noted for unusual energy and social poise became lazy, quarrelsome and tactless. Five years later, she complained of generalized bodily pain, and coincidentally was observed to have difficulty in finding words and performing complex tasks. From this time onwards her vocabulary became more impoverished, her interests more restricted and her programme of domestic tasks simpler and more stereotyped. Her topographical sense remained relatively intact. In her unaccompanied expeditions to shops, the cinema and her club, she was observed to adhere to a rigid timetable. On admission to hospital, nine years after the onset of symptoms, it was noted that she winced when pressure was applied to any part of her body. After a year, she slowly sank into a state of inertia and mutism which continued until her death three years and four months from the date of admission.

The duration of the illness was approximately twelve years.

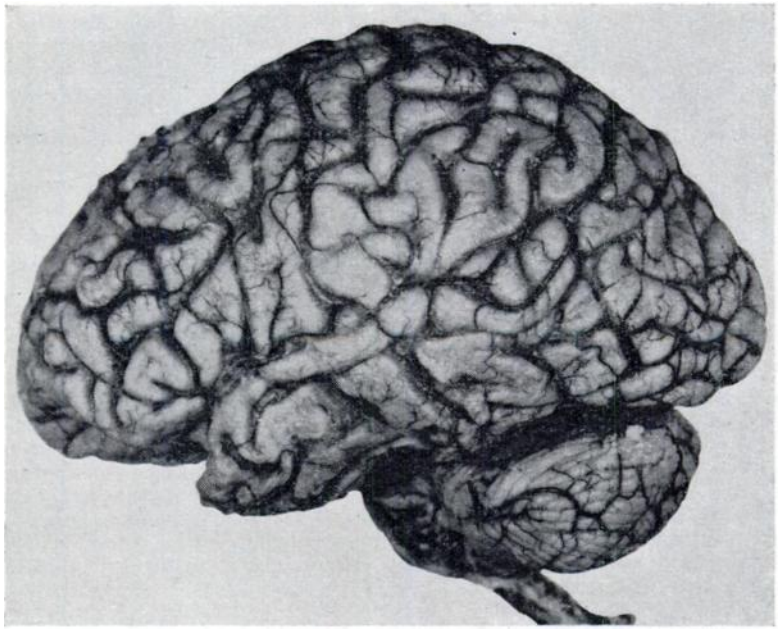

FIG. 3. (*Case 3*)
Lateral aspect of brain showing severe atrophy frontal and temporal lobes.

Mrs. Edith M. R., a housewife, aet. 63, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on 14 April, 1952.

Previous History: Family history was negative, apart from a record of explosive temper in the maternal line. In a motor accident at the age of 21, the patient was thrown against the windscreen sustaining a deep laceration between her eyebrows which left a permanent scar. While in Salonika during the 1914-18 war, she suffered from recurrent malaria. Following her marriage in 1920, she spent the next twenty-two years in Malaya, where she enjoyed excellent health. She had a family of two sons and a daughter, of whom one son was killed in flying operations in 1940. Her husband described her as quick-tempered, somewhat obstinate "but always amenable to reason". Possessed of abundant energy and initiative, she was a talented singer, a good dancer, an expert bridge player, an amusing conversationalist and led a full and busy social life.

History of Illness:

Phase 1—? 1943-1948.

(a) *Personality Changes*: Unusual wartime circumstances made it difficult to date the onset. In 1942, the patient along with her daughter, aet. 12, was evacuated by sea from Malaya and after spending some time in South Africa arrived in Scotland in late 1943. Her sister, who had last seen her on leave four years earlier, noted a definite change in her personality. She was lazy and unmethodical, egocentric and querulous, always complaining that "no one seemed to appreciate her". She was incredibly stupid in the handling of her daughter, whom she had pushed into a state of open rebellion. The two years she spent with her sister were rendered difficult for the latter because of the patient's constant squabbles with her daughter and her tactless remarks to friends. On her husband's return from Malaya in 1945, she moved to a house of her own, but her attempts to establish her accustomed social life ended in failure. Friends ceased attending her dinners and bridge parties, and it was later learned that they had been embarrassed by her recounting of intimate details and her constant derogatory references to her husband and family.

(b) *Phase 2—1948-1952* (Admission to hospital): She complained of generalized bodily pain and was treated for rheumatism at various clinics without relief. Her husband now noted that she had difficulty in recognizing acquaintances, in naming common objects and in carrying out complex domestic tasks—for instance, she was seen to refer to a cookery book when concocting well-known recipes. Somewhat later she began to cheat at bridge and on a shopping expedition stole a box of chocolates from a shop counter, showing no concern at the subsequent expostulations. (During the next four years, she was apprehended five times for similar blatant shop-lifting.) In 1951, it was discovered that she had withdrawn £500 from the bank, which she had spent in addition to her considerable housekeeping allowance. The bank manager related an incident when he had refused to cash her cheque, explaining to her that her account was overdrawn. She listened and appeared to understand, but immediately his back was turned, presented her cheque again at another counter where it was cashed by an unsuspecting teller. After this incident, her husband paid all the household accounts and she was allocated a small weekly allowance, which she often squandered in a single purchase of cakes or jig-saw puzzles. Her vocabulary became increasingly restricted but her conversation continued voluble, being liberally interlarded with stereotyped phrases. In 1950, her letters were reported as unintelligible by their recipients, and her husband persuaded her to write at his dictation. She ceased opening letters addressed to her, but continued to borrow and read library books. Her domestic efficiency now showed still further decline. She drew together rents in household linen instead of darning them: she used a simple floor sweeper instead of her electric vacuum cleaner. When preparing meals, she utilized tinned soups and ready-made puddings. As the main dish she invariably served fried mince and sausages. She kept the soup hot by placing it in plates in the oven, and could not be dissuaded from this practice when it was repeatedly pointed out to her that the resultant pellicle formation rendered the soup unpalatable. She adhered to a rigid time-table in performing her household tasks. A like rigidity was evident in her programme of social activities—visits to friends, expeditions to shops, the cinema and her club being relegated to specified days of each week. At her club, she invariably ordered two whiskies and soda and never exceeded this number. She had no difficulty in route finding, knew the destinations of trams and buses and negotiated traffic without mishap. Every Saturday she went with her husband to watch her favourite football team, and her running commentary indicated that she followed the moves in the game. She enjoyed variety shows but no longer understood a straight play. She could assemble 200 piece jig-saw puzzles and could take part in simple games like three-handed bridge and ludo. She knew the time of day, could compute periods of time and remembered family anniversaries. Although her memory for events and people was capricious, and she frequently mislaid articles, her conduct and conversation indicated that she retained day to day events of personal significance. She rarely referred to events in the past. Her general mood was one of euphoria, unless her comfort was menaced or her wishes disregarded. Flashes of irritability and explosive temper would then occur. She had no social inhibitions and would complain loudly of anybody or anything arousing her displeasure.

Physical Symptom of Pain: Reports on the patient's attendances at a Rheumatic Diseases Clinic in 1948-50 describe her complaint of "aching pains all over, mostly

affecting the shoulders and neck" and state that all treatment proved ineffective. It was recorded on one occasion that "her response to any sort of examination is grossly exaggerated". In 1950, she was seen by a psychiatrist (Dr. A. B. Hegarty) and later by a neurologist (Dr. K. Hermann), both of whom demonstrated organic intellectual deterioration which they considered was based on either Alzheimer's disease or Pick's disease. The neurological report records that the patient showed "marked spontaneous pain in the right limbs with no restriction of passive joint movement and no tenderness of the muscles" and stresses her lack of co-operation in the various examination procedures, e.g., sensory examination. On the physical side, no definite neurological abnormalities were elicited.

Physical Examination: The patient was an obese, well-preserved woman of middle-age. B.P. 143/78. No abnormality was found on clinical examination apart from a generalized hyperalgesia. Pinprick or pressure applied to all areas of the body evoked an exaggerated response. This response showed some day to day fluctuation in that it ranged from mere facial expressions of discomfort to vocal expressions of pain accompanied by gestures of withdrawal. Blood W.R. was negative. Lumbar puncture (which did not require, as in Case 1, a general anaesthetic) provided a clear colourless fluid under normal pressure: 6 cells per cu. mm.; 48 mgs. Protein per 100 mil.; 70 mgs. Sugar; 760 mgs. Chloride; Negative W.R. and Colloidal Gold Curve 0011100000.

E.E.G. Findings: An E.E.G. record taken on 3.12.53 showed only symmetrical stable alpha rhythm (8–10 c/sec.) and traces of low voltage 4–7 c/sec. activity in the parietal, occipital and temporal areas.

No recognizable activity was recorded from frontal areas.

A second routine record taken on 27.5.54 showed no new features. Further recording after the administration of 3 grs. "Seconal" showed symmetrical fast activity with a predominantly frontal distribution due to the barbiturate, and symmetrical sleep changes and aroused responses.

Mental Examination: The patient appeared most contented when allowed to remain in bed. There she occupied herself in assembling one or other of her 200-piece jig saw puzzles, in whistling a tune, or merely in following with her eyes the actions of persons in her vicinity. She required coercion to get up, but having done so carried through an elaborate toilet ritual, which included the application of cosmetics. She tended to be restless when ambulant, exploring corridors and side rooms and demanding of members of the staff (whom she seemed able to differentiate from patients) that she be allowed to go home. On occasions, she sat down at the piano and played a few simple melodies, or standing upright accurately hummed a tune, the while keeping time by slapping her thighs or tapping her feet. She showed a lack of social inhibition in that she would undress and talk loudly about her excretory functions when strangers were in the ward.

During interview, she kept up a constant flow of conversation, showing no defect of articulation or syntax. Despite an obvious gross reduction in her vocabulary—particularly in respect of substantives—her conversation showed no hesitation, since she utilized periphrases to convey her meaning, and interpolated a number of constantly recurring stereotyped phrases. Her conversation was also liberally sprinkled with superlatives and terms of endearment—"I think it's really wonderful, marvellous, to be doing this thing, darling. No, I can't remember words at all, but I'm really disgusted because I used to. I'm not joking, but I'm really disgusted. Yes, it's awfully bonny, but I can't remember words." While obviously unable to comprehend abstract terms and ideas she understood the gist of most of the simple questions addressed to her and a knowledge of her previous life history enabled her examiners to understand what her periphrasic sentences were intended to convey. Her attention was not always easy to obtain and testing of her various faculties had to be carried out mainly through the medium of conversation. Shown simple objects she would wave them away with some such remark as "It's awfully bonny, I cannot remember words", but might follow this up by a further comment which showed that she had a clear idea of the function of the object. Shown a pipe, she said, "Oh, my husband does that", shown a florin, she exclaimed "you are lucky, I haven't any money", and when the coin was presented later, she said "that's a two" (shillings). It was noticed that although she failed in nomenclature, she often gave numbers correctly, e.g., shown a picture of twelve marbles, she counted them accurately but was unable to name them; shown a watch, she said swiftly, "eight" which was the time registered on the watch face. She tended to confuse genders and relationships. Asked about her brother, she replied by referring to her sons. "Well,

there was two, and funnily enough the older one was gone (killed) and really it was very bad. *She* was gone, it's really disgusting because he was awfully bonny and really very tall and I think 18 (actual age of elder son when killed in action). It was really very bad luck."

She read a series of name cards with only one or two mis-pronouncements. (She handled the cards expertly, putting each one at the back of the pack after she had read out the printed word.) She refused to read a passage from a book, and similarly refused to write to dictation. On one occasion she agreed to write her name. She wrote "Edith" then paused and enquired "my husband's one, I've forgotten?" On being told her surname, she wrote it accurately.

She refused to draw or copy designs but her ability to complete patterns was illustrated in her assembly of jig-saw puzzles. She first selected pieces of the same colour, then separated out the straightsided pieces which formed the outline, after which she set to work to build up the picture. Her topographical sense remained relatively intact in that she never lost her way in ward block of many rooms and corridors. An attempt to assess her topographical sense outwith hospital was less successful than a similar attempt with Case 2. It was not feasible to take her to her home, so she was taken to her club in a motor car by a different route from that of her former approach. She failed to recognize landmarks or the club building, but once inside she found her way by scrutinizing the printed signs. She conversed about the type of meals and drinks she used to have in the club and said "my husband and I are always there on Friday, Saturday and sometimes Wednesday" (which was correct). She behaved normally when crossing streets and on one occasion seized hold of one of her escorts when he stepped off the kerb in front of an oncoming vehicle.

In conversation, she used the adverbs of place, e.g., "up" and "down" correctly. Referring to her house, she said "There are six of them" (a terrace of six houses): "they are all lovely, big, proper upstairs and downstairs. I do it awful nice. Get lunch for Sandy and my husband, then I wash the kitchen all over and when finished and all the things, I go upstairs and tidy, put on a proper thing and do my hair."

She knew the days of the week but not the month or year. She could assess the time of day and compute the number of days since her husband's last visit. She could assess in weeks the duration of her stay in hospital, describing this as "more than three", or "more than ten" and so on until twelve weeks were reached, after which her response became erratic.

Her memory could only be assessed from her behaviour and conversation. She was able to find her own clothes, although she did not always hang them in the same place. She spoke of her escorted visit to her club a month after it had taken place. While she had obvious memory impairment yet she was able to supply many details about her family, her house and her social interests. It was notable that she frequently interpolated numbers into her conversation, as if to compensate for her verbal impoverishment. "Funnily enough on Saturday we go to the Empire at 8.40. I love it, I'm not joking. But on Sunday at 6.30, the nice place, the proper thing—different ones." (This last sentence referred to her husband's habit of taking her to a different church every Sunday evening.) Again, in anticipating her husband's visit, she invariably mentioned both the day and hour of his arrival—"my husband will be coming on Saturday at 2.30 or 3". She often spoke of her life in Malaya, of her evacuation therefrom and temporary separation from her husband— "Funnily enough I went out and went to that place (South Africa). Lucky because my husband did things for all the different ones, for all those other men. It was bad luck. I went away down (to South Africa). Then I went away here. He (her husband) was coming along. It was very lucky." She rarely referred to the remote past or to her childhood.

Her mood was euphoric with episodic brief outbursts of irritation during which she might attempt to slap persons in her vicinity. Apart from her reiteration of her inability to remember words, she made no remark to indicate her realization of her situation.

Subsequent Course: After a year, she sank into a state of relative inertia and immobility, responding to greeting by mumbling a few stereotyped phrases, i.e., "I'm really disgusted, I never realized. Along in that place, dear, with all the proper bonny things." The generalized hyperalgesia was no longer apparent. Within eighteen months of admission, she was bedridden and doubly incontinent. She now stuttered when enunciating her few stereotyped phrases. In the last six months of life she was completely mute. She exhibited a mask-like facies, a waxy rigidity of all limbs and a grasp reflex.

Death occurred on 17 August, 1956, following bronchopneumonia.

Necropsy Findings: The lungs showed areas of bronchopneumonic consolidation. There were multiple bedsores about the sacrum, buttocks and heels.

THE BRAIN weighed 1,140 gms. There was severe, bilaterally symmetrical atrophy of both temporal lobes affecting particularly the middle and inferior temporal gyri and the fusiform gyri, but also the superior temporal and hippocampal gyri. The wasted gyri were abnormally firm in consistency, showed slight yellowish brown discoloration and sharp angulations in place of the usual rounded contours. The intervening sulci were widened and deepened and cerebrospinal fluid had accumulated deep to the thickened arachnoid bridging these gyri. There was also a symmetrical, but only moderately severe atrophy of both frontal lobes and slight atrophy of both parietal and both occipital lobes. No abnormality of the brainstem or cerebellum was seen. The arteries forming the Circle of Willis showed moderately severe atheromatous thickening of their walls.

Serial coronal sectioning of the cerebral hemispheres confirmed the severe temporal lobe atrophy. This affected both grey and white matter and in the convolutional white matter of the middle and inferior temporal gyri of each lobe there was a minute vacuolation. In addition, the anterior insula of each hemisphere showed severe wasting. In the frontal lobes the cortex was thinner than normal and there was an obvious diminution in the bulk of the central white matter. The basal ganglia, and in particular the caudate nuclei, appeared to participate in this atrophy. There was a marked compensatory dilation of all compartments of both lateral ventricles, especially of the body of the left lateral ventricle and of both temporal horns, and of the third ventricle.

Microscopic Observations: In the cortex of the atrophic temporal lobes there was almost complete loss of nerve cells and all trace of the normal architecture and lamination had been lost. The few remaining nerve cells were found mainly in the inner half of the cortex and these showed chromatolysis or shrinkage and nuclear pyknosis. There were no ballooned nerve cells and sections stained by the von Braunmuhl technique failed to demonstrate argyrophilic, intra-cytoplasmic inclusions, neurofibrillary tangles or senile plaques. Throughout the cortex, but mainly at the cortical margins, there was widespread proliferation of astrocytes forming a fibrillary meshwork. The response of the microglia and oligodendroglia was poor. In the white matter there was extensive loss of myelin with status spongiosis, and the fibrillary gliosis was isomorphous in character. There were numerous corpora amylaceae. The leptomeninges showed slight fibrous thickening with a histiocytic infiltration of the subarachnoid space.

Similar changes were observed in sections from the frontal lobes but the residual nerve cells and fibres were more numerous than in the temporal lobes, and some trace of cortical lamination remained. No ballooned cells, argyrophilic inclusions, neurofibrillary tangles or senile plaques were seen. Apart from marginal fibrillary gliosis, astrocytosis was not marked and there was only slight thinning of myelin.

In the parietal and occipital lobes there was only minimal loss of ganglion cells and no appreciable demyelination.

There was possibly some slight loss of nerve cells from the caudate nucleus and putumen of each hemisphere but no obvious demyelination or gliosis. There was no recognizable outfall of nerve cells from the thalamus but many of the cells contained a large amount of lipofuscin and showed chromatolysis. An occasional cell was undergoing neuronophagia. No other abnormality was seen.

In the midbrain there was slight loss of nerve cells from the substantia nigra with scattering of melanin pigment in surrounding tissues and slight gliosis. In each cerebral peduncle there was obvious demyelination and gliosis in the frontopontile and temporopontile pathways.

No cerebellar abnormality was seen.

In all sections the arteries showed moderately severe atheroma but there was only minimal thickening of the arterioles.

SURVEY OF CLINICAL FEATURES

Family History: There was no history of Pick's disease in the forebears or collaterals. These cases, therefore, fail to corroborate the hypothesis of genetic transmission. (Grünthal, 1930; Sjögren, Sjögren and Lindgren, 1952.)

Previous Injuries and Illnesses: Case 2 had what was probably a mild depressive illness in her twenties, and at the time the first changes in personality were noted was struck in the face with a shuttlecock. Case 3 sustained a moderately severe head injury at the age of 21, and suffered from recurrent malaria in her middle twenties.

Age of Onset was during the sixth decade.

Duration of Disease varied from eight to fourteen years. It was notable that none of the patients required hospital supervision until a late stage of the illness.

Course of Disease seemed to fall naturally into three phases, as described by Schneider (1929). In our three cases these could be summarized as follows:
(a) A first stage, characterized by personality change and impaired judgment.
(b) A second stage, characterized by the appearance of localizing signs (e.g., aphasia) on a background of progressive mental deterioration.
(c) A terminal stage of mutism and extreme hebetude.

It seems important to stress that in this syndrome of slowly progressive mental deterioration, in which the evolution of symptoms followed a strikingly similar course from case to case, we found that the details of the history provided even greater diagnostic help than the examination findings for these last naturally depend on the stage at which the patient is first seen. It is even conceivable that the wide variation in symptomatology of reported cases of Pick's disease may be attributable in part to an understandable tendency on the part of authors to emphasize the "cross section" findings at clinical examination rather than the longitudinal survey of these personality and intellectual deficits, which by their cumulative effect on behaviour finally bring the patient under observation. Therefore, in the discussion which follows, we have made no arbitrary division between the facts reported by the relatives and those noted after the patient's admission to hospital. In our tabulation of symptoms, we have allowed ourselves one chronological inconsistency: discussion of the somewhat complex personality changes appears at the end of this section, although these were the first manifestations of the disease process.

1. PHYSICAL SIGNS

(a) *Pain*: In all three patients, mild pressure applied to any part of the body appeared to cause pain, while deep pressure and minor painful stimuli, such as pinprick or venepuncture, called forth vocal and facial expressions denoting acute pain. These findings were corroborated by the nursing staff during routine nursing attention. This generalized hyperalgesia was most pronounced in Case 1 whose relatives had noted it some four years before her admission to hospital. In Case 2, a single woman living alone, the onset of this phenomenon could not be assessed, while in Case 3, it was so inextricably linked with her complaint of "rheumatic" pain that her relatives had not at any time distinguished it as a separate entity. Conversely, at no time while they were under our observation, could we convince ourselves that these patients suffered from spontaneously erupting pain. Their attitude at rest did not denote suffering. The previous histories of cases 1 and 3 indicated, however, that such "spontaneous" pain had been a feature of an earlier phase

of the illness. In course of time, the generalized hyperalgesia so strikingly evident at the time of their admission gradually disappeared and could no longer be elicited at the end of a year's hospitalization.

Occasional fleeting reference is made to pain as a symptom in the clinical records of reported cases of Pick's disease. Reich (1905, 1907), in a very detailed account of a male patient with Pick's disease, states that the relatives reported his having excruciating pains some years before admission to hospital. Schneider (1929) states that one of his patients complained of pain in the left arm for which no physical cause could be found. Bouton (1940) mentions pain as a symptom in two of his four cases of Pick's disease. In the first, a complaint of right-sided pain was ascribed to the condition of cholelithiasis found at necropsy. The second patient, a man of 61, was assumed to be suffering from somatic delusions, because in addition to frontal and occipital headache, he complained of a "pricking sensation in his skin, and of pain about the waistline and lower back". Reporting a series of eight cases, Schenk (1951) describes one in which the symptom of pain closely resembles that which we observed. The patient, a woman of 57, had a history of rheumatism of several years duration, and when she came under care in hospital it was recorded that "elle se plaint de douleurs au moindre contact".

The bizarre pain reactions of our three patients call to mind the "thalamic over-reaction" phenomenon of excruciating pain arising spontaneously and/or as an exaggerated response to stimulus. Accepted as generally denoting a vascular lesion in or adjacent to the thalamus, this phenomenon is said to follow, albeit more rarely, other types of lesion in this area. No such vascular lesion was demonstrated post mortem in our three cases. Moreover, when sections of the thalamus were examined with particular care, as in Case 3, no significant abnormality was found. While it is part of traditional neurological belief that excessive response to painful stimuli and severe "spontaneous" pain betoken a thalamic lesion, there are nevertheless cases on record to show that this so-called "thalamic over-reaction" phenomenon can occur with cortical lesions. Marshall (1951), writing on sensory disturbances in cortical wounds with special reference to pain, describes two cases of hyperalgesia following cortical wounding and refers to similar observations made by Kleist (1922) on head wounds of the 1914-1918 war. He also cites reports by Guillain and Bertrand (1932) and Davison and Schick (1935) which showed that spontaneous pain and hyperpathia have been found in association with cortical lesions without involvement of the thalamus. One of us (Robertson, 1953) has witnessed hyperalgesia in association with a subdural haematoma overlying the right frontal lobe.

It is possible that this symptom occurs more frequently in Pick's disease than the published cases would suggest. It is easy to see how it could be overshadowed by the general mental devastation. Alternatively, our observation that the hyperalgesia disappeared within a year of hospitalization argues that this symptom may only be elicitable during a particular phase of the disease.

(b) *Obesity*: All three patients showed a moderate obesity, and, perhaps more strikingly, retained this obesity as the disease progressed.

(c) *Hypersomnia*: Cases 1 and 2 exhibited hypersomnia before admission to hospital, and in the latter stages of their illness, all three slept soundly throughout the night and for long periods during the day. Nocturnal restlessness was never noted.

(d) *Other Physical Signs*: Case 1 developed a "gorilla" gait with bowed trunk and arms hanging limply by her side. Case 2 developed a lopsided posture—with trunk inclined to the right, a shuffling gait, exaggerated proprioceptive reflexes and munching movements of the jaws. Finally, she became bedridden with right-sided paresis and generalized muscular rigidity, but without definite pyramidal signs. Case 3 latterly developed a mask-like facies and mild dysarthria, in that she stuttered over the first syllables of her few remaining utterances. (Case 3 was the only patient to exhibit even a mild degree of dysarthria, and this as a terminal phenomenon.) Anomalies of gait, posture and muscular tonus are frequently reported in Pick's disease (Thorpe, (1932), Caron (1934), Ferraro and Jervis (1936), Becker (1948)), but their late appearance in the course of the disease, their variability, and their frequent occurrence in other types of presenile and senile dementias decreases their value as an aid to the diagnosis of Pick's disease.

2. APHASIA

This appeared five or six years after the personality changes, presented initially as a defect in noun-finding ("she forgot the names of things") and steadily progressed to a gross reduction in all elements of speech with a concomitant decreased understanding of the conversation of others. To compensate for their amnesia for words, these patients (a) employed circumlocutions, (b) used generic terms such as "thing", "man", "woman", (c) made one word convey several shades of meaning. (Case 3 used "lucky" not merely to mean "fortunate" but to denote anything considered good, valuable, useful or attractive), (d) selected from their restricted vocabulary substitute words, where the underlying association was not immediately apparent, (Case 2 used "glasses" for "money" presumably because both words denoted objects of extreme personal value). All three patients confused words denoting gender and family relationships. On occasion, they employed surprisingly elaborate adjectives and adverbs. They made accurate use of numbers and also of simple adverbs of place, e.g., "up" and "down". Increasing familiarity with their individual vocabularies and turns of phrase enabled the examiner to acquire considerable information from their spontaneous conversation whereas direct question and answer methods were less productive. This was not wholly attributable to their diminished comprehension. These patients showed a marked disinclination to listen to questions, particularly those questions which did not touch on their immediate personal concerns. In spontaneous conversation they appeared to have a clear mental image of what they wanted to express and made strenuous efforts to mobilize their limited vocabulary to this end. They rarely resorted to pantomime. They showed no dysarthria or paraphasia. Perseveration was marked. Case 1 at every interview introduced an anecdote relating to her recently dead husband. Cases 2 and 3 repeated similar anecdotes and in addition had a collection of standard phrases which they interpolated into every conversation. (A tape recording of the conversation of Case 3 strikingly illustrated her frequent reiteration of three phrases—"I'm not joking"—"I'm really disgusted"—"it's awfully lucky").

Reading and writing abilities were difficult to assess because of marked disinclination to submit to testing. All signed their names on admission, but could seldom be persuaded to do so thereafter. Cases 1 and 3 read printed name cards with occasional mispronouncement. Case 1 studied magazines with such earnestness that she gave the impression of acquiring information from either typescript or illustrations. Case 2 had given up reading newspapers

many years previously and seemed genuinely unable to read name cards. All patients recognized numbers, and Case 2 when taken on an expedition to her home, identified tram cars by their numbers. Case 3, when taken on a similar expedition to her club, recognized the various rooms by their printed signs, e.g., "Lounge", "Dining Room". It seemed therefore that the stimulus of practical necessity could evoke recognition of symbolical visual signs until a late stage of the disease.

When in the course of time these patients passed into their final stage of hebetude, the transition from spontaneous speech to relative mutism was accomplished swiftly with no intervening paraphasia or dysarthria. In this final stage, an external stimulus in the form of human greeting could still elicit remnants of their former conversation, such fragmentary phrases being repeated in a mechanical way as though a memory echo of former statements. (Case 3 murmured disjointedly "I'm really disgusted—I never realized—along in that place, dear, with all the proper bonny things".)

It is perhaps worth noting here that Cases 1 and 3, both of whom had musical training, retained a sense of rhythm and melody until a late stage of the illness.

Published cases of Pick's disease in the English and American literature contain few detailed analyses of the speech disturbance exhibited, and the comment generally made by the authors is that all types of aphasia are to be found (Thorpe (1932), Kahn and Thomson (1934), Ferraro and Jervis (1936), Nichols and Weigner (1938)). More elaborate studies have been carried out by Continental writers, influenced presumably by Pick's original emphasis on aphasia, and these have been analysed by Caron (1934). Caron catalogues such characteristic features as loss of memory for words, compensatory periphrases, preservation of syntax, normal articulation, and absence of paraphasia or jargon. He refers to the extreme reduction in speech in the final stage and to the iterative phenomena: "certain memories are conserved and reiterated monotonously." He quotes Stertz (1926) for the observation that these last always require an external stimulus for their production (as in our three cases) but he himself does not consider that this rule invariably applies. He emphasizes the patients' disinclination to submit to formal testing, and says that this trait has been noted by many observers.

The iterative phenomena call for further comment. That some or other type of perseverated utterance occurs frequently in Pick's disease is generally agreed (Kinnier Wilson, 1940), and is cited, even by those authors who otherwise make little detailed analysis of the aphasia, as a valuable diagnostic sign. It is understandable that the patient's repetition of stereotyped phrases should compel the attention of the observer, particularly when these appear in florid form, as in Case 3, of our series. Nevertheless, such iterative phenomena, whether taking the form of echolalia, pallilalia or verbigeration, occur in many types of cerebral lesion and we do not consider that they should be given predominance over the other aphasic features in conferring the diagnosis of Pick's disease. The aphasic features minutely described by certain Continental authors, e.g., Rosenfeld (1909), Stertz (1926) and Schneider (1927) and cited in Caron's monograph closely resemble those observed in our three cases. Such features conform, in general, to the type of aphasia designated "nominal" or "amnestic". Writers in the past, including Pick himself, have held that amnestic aphasia denotes a temporal lobe lesion; but it has also been reported to result from focal lesions in the parietal lobe (Head, 1920; Nielsen, 1946). To explain the remarkable uniformity of the aphasic

picture in our three cases, it seems permissible to incriminate both the disease process itself and also the cerebral areas on which its effects are exercised. It could then be postulated that a specific disease process with a predilection for the temporo-frontal lobes is responsible for the uniform type of aphasia in the cases of Pick's disease here described.

3. Spatial Manipulation and Temporal Orientation

Since all three patients suffered from a slowly progressive dementing syndrome, their concepts of space and time were inevitably impaired. Nevertheless, they showed a conspicuous absence of many of those spatial and temporal defects which have been investigated and enumerated in lesions of the parietal lobe (Critchley, 1953). In order to demonstrate this, we have followed as far as it was possible to do so, Critchley's list of these diverse "interdimensional spatial manipulations" the successful performance of which seems to depend on intact functioning of the parietal lobe.

A topographical sense was relatively intact until a late stage of the disease. Before their admission to hospital, all three patients journeyed unaccompanied through a large and busy city, and these journeys might involve boarding a series of buses and trams. They quickly orientated themselves in a hospital block of many wards and corridors and retained this ability as long as they were ambulant. Their capacity to perform certain relatively complex tasks, e.g., cooking and mending, showed that they were able to construct and manipulate objects, admittedly with impaired finesse. All three were still playing card games at home. (Case 1—Patience, Case 2—Rummy, Case 3—Bridge), although it was known that their proficiency had declined. In hospital it was noted that Case 2 could follow embroidery patterns while Case 3 completed 200-piece jig-saw puzzles with speed and dexterity. They were usually able to point to parts of the body on command, and showed no defect of laterality. No "dressing apraxia" was demonstrated during their first year in hospital; none required help in feeding or washing, and Case 3 could apply cosmetics effectively. All three patients could tell the time on a clock face. Cases 2 and 3 used the adverbs of place, "up" and "down" correctly.

If under the heading of spatial manipulation we include, as does Critchley (1953) "the conception of time or order or sequence", then it can be added here that all three patients must have had a clear conception of the links in a chronological sequence, otherwise they would not have been able to carry out their rigid programme of activities. In other words, they were able to build up chains of associations, the separate items of which were linked by their purely temporal connections. Their preservation of other aspects of temporal awareness may be tabulated as follows: (a) Cases 1 and 3 could assess the time of day without reference to a clock, (b) Cases 2 and 3 could gauge the passage of time in that they assessed their length of stay in hospital in the appropriate number of weeks. This illustrates how some aspects of temporal orientation are dependent on at least a primitive numerical sense. (It was notable that all three patients frequently interpolated numbers into their conversation—possibly to compensate for their verbal impoverishment—and Cases 1 and 3 could give the ages of their three children even when unable to remember their Christian names.)

The functions which we have included under the somewhat clumsy title of "spatial manipulation and temporal orientation" are frequently ignored in published cases of Pick's disease. Certain authors refer briefly (without

adducing examples) to the patients' defects in these spheres. Caron (1934), for instance, states that orientation is impaired early in the disease. Kinnier Wilson (1940) gives a similar opinion: "onset is as a rule insidious, among the first symptoms being a poor memory and a tendency to confusion in respect of space and time." Conversely, Ferraro and Jervis (1936) state that orientation was fairly well preserved in their case. Mayer-Gross, Slater and Roth (1954) in their textbook say that "the dementia progresses rapidly with increasing disorientation and loss of contact with the surroundings", but later, in discussing the differential diagnosis of Pick's disease and Alzheimer's disease, they add, "on the whole the picture in Alzheimer tends to be dominated by parietal lobe symptoms and in Pick by frontal lobe symptoms". Admittedly, it is only during the last two decades that attention has been focused on these spatial and temporal defects which are found in association with parietal lobe lesions (Russell Brain (1941), Critchley (1953)), so that now there is a general awareness of what constitutes the so-called parietal lobe syndrome. It may be that this relatively recent elucidation of parietal lobe symptomatology explains why so little reference was made to these aspects of Pick's disease by earlier writers. Certainly in our three cases the absence of such "parietal lobe signs" was one of the most striking features to emerge at examination and seemed to us to carry the strongest diagnostic presumption that the cerebral lesion, in its initial stages at least, involved the anterior part of the brain.

4. Memory

The rigid timetable of activities carried out by all three patients in the period preceding hospitalization indicated at one and the same time an impairment of memory functions and the ability to compensate for such impairment. Their spontaneous conversation in hospital revealed that they remembered personal experiences in the immediate and recent past. They rarely alluded to their childhood or the remote past, thus presenting a striking contrast with patients suffering from senile dementia. Specific questions designed to test recall of this or that event met with an inconstant response, but here again the response was more likely to be accurate when the question concerned events of recent or contemporary interest. They displayed no interest and made no response when questioned about those outstanding world events which form the basis of routine memory tests.

Various writers have emphasized the relatively good retention of memory functions in the first two stages of Pick's disease (Kahn and Thompson (1934) Nichols and Weigner (1938) and Malamud and Boyd (1940)). Memory comprehends many components, the analysis and synthesis of which have been but imperfectly explored. It may be that the ability to orient oneself in space and time represents a special aspect of memory, and in this our patients were not notably deficient. It has to be borne in mind that our patients suffered from a severe degree of amnestic aphasia which must affect memory in its higher conceptual aspects, and in addition renders difficult the testing of memory functions since the patient is not always able to understand the import of questions. This latter fact does not always seem to be taken into consideration by the authors of many of the reported cases of Pick's disease, who cite the responses to verbal questions as evidence of gross memory defects. In assessing the degree of memory impairment in aphasic patients, a careful study of their behaviour before and during hospitalization is essential. The evidence supplied by the behaviour and restricted speech of our patients indicated that

they recollected many of the simple and concrete facts of their daily existence, that they were able to fit these into a chronological sequence and were able to anticipate the immediate future.

5. PERSONALITY CHANGES

(a) "*Selfishness*": One of the earliest changes noted in the histories was *a restriction of the field of interest to immediate personal concerns*, variously interpreted by the relatives as "selfishness", "egocentricity", or even "apathy" and "laziness". Inquiry showed that "apathy" and "laziness" referred to diminished performance of communal tasks or duties towards others. By contrast, the patients continued to pursue their own individual aims with accustomed and even accentuated vigour. They displayed a notable self-sufficiency, and were able to provide for their material wants and indulge in favourite pastimes until a late stage of the disease. This was most strikingly illustrated in Case 2, a single woman, who carried on an active, if somewhat erratic, existence, without external care or supervision until her admission to hospital.

(b) "*Rigidity*" (*stereotypy*) *and* "*obstinacy*" (*perseveration*). At a somewhat later stage, certain qualities described by the onlookers as "rigidity" and "obstinacy" made their appearance.

(i) "*Rigidity*" (*Stereotypy*): All three patients gradually evolved an unvarying programme of activities. They adhered to a strict routine in their performance of domestic tasks, and allocated their various social and shopping expeditions to certain fixed days of the week. Case 3 went out every day, and her husband could always foretell the object of each daily excursion. Case 1 collected her pension and carried out certain errands on the same days of each week. Case 2 lived alone and was not subject to the same observation as the others, but her rigid adherence to a timetable was illustrated in her domestic tasks and by her turning up at church one hour late after the introduction of Summer Time. This rigidity was illustrated also in minor actions (sometimes with laudable results, since Case 3 invariably bought herself two whiskies when visiting her club, and was never known to exceed this number).

(ii) "*Obstinacy*" (*perseveration*): Closely related and yet dissimilar, was a quality usually described as "obstinacy". Once these patients started an action, they could not be deflected from their individual mode of terminating it. Case 1 continued to scatter crumbs for the birds in the garden although she knew that she was expected to use a recently erected bird-tray. Case 3 acquired the habit of placing plates of soup in the oven to heat, and could not be dissuaded from this although it was pointed out that the resultant pellicle rendered the soup unpalatable. The complex patterns of some of these perseverating actions concealed their essentially compulsive nature. Observers therefore often assumed that the patients' exasperating persistence indicated wilful malice.

(c) "*Restlessness*": This trend was never reported by relatives, but was a notable feature of the patients' conduct for a time after admission to hospital. Cases 1 and 2 rummaged endlessly in the drawers and lockers, withdrawing and examining articles of clothing. Case 3 perambulated the corridors, peering into all rooms encountered on her route, and spent long

periods beating time to a whistled tune by tapping her feet and slapping her thighs.

(d) "*Social Judgment*": There was a general blunting of social judgment, tact, self-criticism and self-restraint. All the patients discussed personal and intimate matters with strangers. Case 3 had indulged in persistent shoplifting for some years prior to admission; and Case 1, during the funeral service for her husband, was pre-occupied with a search for some of his personal belongings. None of the patients appeared to be influenced by the opinions and reactions of others, whether censure or praise, and pursued their simple aims unhindered by any but physical obstacles.

(e) "*Mood*": None of the patients was ever observed to weep and none ever displayed any sign of sadness or distress. The predominant emotional colouring in Case 1 was stolid placidity, in Cases 2 and 3 bland, facile euphoria, interrupted on occasion by fleeting irritability and aggression. Bereavements were dismissed with perfunctory expressions of grief. Case I said of her husband: "I was awful vexed when I lost him", and Case 3 said of her son's death: "It was really very bad luck." These expressions could not be entirely attributed to reduced vocabulary, for the patients were able at this time to give forceful, if periphasic, expression of opinion on matters which aroused their interest, and the matter-of-fact form of their statements on their bereavements was matched by their matter-of-fact manner in making them.

(f) *Reaction to Testing*: A striking feature was the *disinclination to co-operate in formal testing.* In this the patients differed markedly from others with a like degree of organic deterioration. Only rarely would they attempt the tests presented to them, and if the examiner insisted they became querulous. They never showed the "catastrophic reaction" of emotional distress in response to failure at a task. They rarely confabulated. Sometimes they used inappropriate facile excuses to explain their inability to perform a task, e.g., "I need my glasses, you see I live alone" (Case 2).

Comment on Personality Changes: It is generally agreed that emotional and personality changes dominate the clinical picture in the early stages of Pick's disease. It seems unlikely, however, that these changes in the sphere of so-called "personality" are entirely independent of intellectual deterioration. Primary emotional changes, caused directly by cerebral damage, are no doubt present; but we believe that the results of these changes become elaborated and extended because of a compelling need of the organism to compensate for failing intellectual powers. In the early stages of such an illness the intellectual deficits can still be covered up in various ways, and it is the resulting compensatory, "personality" changes that are reported by witnesses. For example, the "selfishness" of our patients seemed to imply not only a *lack of emotional interest in other people*, but also a *narrowing of their defective powers of attention to those stimuli subserving their own most essential needs.* Such canalization of interest enabled them to lead a relatively independent existence despite their failing capacities. Their *stereotypy* and *perseveration* can be understood in a similar way. It is not difficult to accept that *a simple rigid outlook may result from primary emotional blunting.* In addition, however, these patients were being left with progressively less

mental equipment for dealing with their environment. They were therefore compelled to *sacrifice their flexibility and adaptability in order to simplify their needs and activities*, thus keeping the pattern of their lives within the scope of their reduced abilities. These features recall some of the "adjustments" of behaviour in brain lesions described by Goldstein (1936, 1940), who believes that they occur automatically, when the total situation of the organism demands them, without training, conscious striving, or even awareness, on the part of the individual.

Some of the personality changes which we have enumerated have been mentioned already in published cases of Pick's disease, although the descriptive term utilized may not be the same. The terms "emotional apathy" and "indifference", used by certain writers, seem to refer to the quality which we designated "selfishness". The stereotypy of behaviour which was such a prominent feature in all our cases does not appear to have been emphasized as a pathognomonic trait, except by Nichols and Weigner (1938), who mention that their patient "became stereotyped in the discharge of her household duties, preparing the same meal day after day". The peculiar reaction of these patients to formal testing has been noted by several writers. Caron (1934) and Ferraro and Jervis (1936) have commented on the difficulty in holding the attention of patients with Pick's disease. Stertz (1926) speaks of "their profound aversion to respond by speech . . . their absolute refusal to name, to repeat and to write". Stertz considered that this was dependent on a primary inertia, but Pick (quoted by Caron) believed that it arose from the patients' realization of their own defects. We believe that this reaction is but another facet of the trait we have previously designated "selfishness". As such it may be held to depend on both (a) a primary emotional change and (b) an attempt of the organism to compensate for failing intellectual powers by ignoring all extraneous stimuli which do not subserve material needs.

Pathological Findings

The pathological changes in all three cases were basically the same. All showed a severe symmetrical atrophy of the temporal lobes (although minor differences existed on the degree of involvement of the individual temporal gyri). All showed a less severe and less uniform atrophy of the frontal lobes. The parietal and occipital lobes seemed scarcely affected by the disease process. Microscopically the salient feature was an outfall of ganglion cells from atrophic gyri. No neurofibrillary tangles, no argyrophilic inclusions and no ballooning of nerve cells were found. Argyrophilic plaques were also absent.

Conclusions

These cases presented a picture in which there was undoubtedly a generalized mental deterioration, but in which certain faculties stood out for their relatively good retention, alongside a very pronounced loss of others.

By far the greatest impairment was seen in the speech functions (all three patients exhibited a uniform type of amnestic aphasia), and in what may be termed the sphere of personality, i.e., mental functions that are known to become impaired in lesions of the temporal and frontal lobes. These patients lived in the present; they concentrated their energies and attention on their own persons, interests and needs; and they very early showed a marked falling off in altruistic identification, social responsiveness and inhibition.

The relatively good retention of memory in Pick's disease has been frequently commented on, but the comparative preservation of abilities which have come to be associated with the parietal lobes (awareness, understanding and manipulation of spatial and temporal relationships) has, we consider, been insufficiently emphasized in the past.

The physical signs common to all the cases were generalized hyperalgesia, somnolence, obesity and—in the final stages—anomalies of posture and muscular tonus. Of these, hyperalgesia, because of its rarity in neurological syndromes generally, was regarded as an important diagnostic sign.

A fairly constant pathological background was found to underlie this remarkably uniform clinical picture.

In order to arrive at a diagnosis, a detailed history of the development of the illness was found to be as important as repeated mental examinations. It is suggested that, with this proviso, it is not difficult to differentiate this variant of Pick's Disease from other dementias of the presenile period.

Summary

Three cases of Pick's disease, confirmed at autopsy, are reported.

A hypothesis regarding the differentiation of this condition from other pre-senile dementias on clinical grounds alone was made during the study of the first case; and this hypothesis was tested and verified when the other two cases were encountered.

The clinical features are discussed, and special reference is made to a generalized hyperalgesia displayed by all three patients.

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References

Becker, P. E., *Der Nervenarzt*, 1948, **19**, 355.
Bouton, S. M., *J. Nerv. Ment. Dis.*, 1940, **91**, 9.
Brain, W. R., *Brain*, 1941, **64**, 43.
Caron, M., *Etude de Clinique de la Maladie de Pick*, 1934. Paris:
Critchley, M., *The Parietal Lobes*, 1953. London: Edward Arnold & Co.
Davison, C., and Schick, W., *Arch. Neurol. Psychiat.*, 1935, **34**, 1204.
Ferraro, A., and Jervis, G. A., *Arch. Neurol. Psychiat.*, 1936, **36**, 79.
Goldstein, K., *The Organism*, 1936, New York:
Idem, After-Effects of Brain Injuries in War. Their Evaluation and Treatment. London: Heinemann.
Grünthal, E., *Z. ges. Neurol. Psychiat.*, 1930, **129**, 350.
Guillain, G., and Bertrand, I., *Ann. Med.*, 1932, **31**, 35.
Head, H., *Aphasia and Kindred Disorders of Speech* (2 vols.), 1920. Cambridge:
Kahn, E., and Thompson, L. J., *Amer. J. Psychiat.*, 1933-34, **13**, 937.
Kleist, K., In *Handbuch der ärztlichen Erfahrungen im Weltkriege*, ed. O. von Schjerning. 1922, **4**. Leipzig.
Malamud, N., and Boyd, D. A., *Arch. Neurol. Psychiat.*, 1940, **43**, 210.
Marshall, J., *Journ. Neur. Neurosurg. et Psychiat.*, 1951, **51**, 187.
Mayer-Gross, W., Slater, E., and Roth, M., *Clinical Psychiatry*, 1954. London: Cassell.
Nichols, I. C., and Weigner, W. C., *Brain*, 1938, **61**, 237.
Nielsen, J. M., *Agnosia, Apraxia, Aphasia*, 1946. New York: Paul B. Hoeber.
Pick, A., *Monatsch. Psychiat. Neurol.*, 1904, **16**, 378.
Reich, F., *Allg. Z. Psychiat.*, 1905, **62**, 835.
Iden, ibid., 1907, **64**, 835.
Robertson, E. E., *Brit. Med. J.*, 1953, *i*, 291.
Rosenfeld, E., *Journ. Psychol. Neurol.*, 1909, **14**, 115.
Schenk, V. W. D., *Ann. Med. Psych.*, 1951, **1**, 574.
Schneider, C., *Monatschr. Psychiat. Neurol.*, 1927, **65**, 230.
Idem, Z. ges. Neurol. Psychiat., 1929, **120**, 340.
Sjögren, T., Sjögren, H., and Lindgren, A. G. H., *Acta Psychiat. Kbh.*, Suppl. 82. 1952.
Stertz, A., *Z. ges. Neurol. Psychiat.*, 1926, **101**, 729.
Thorpe, F. T., *J. Ment. Sci.*, 1932, **78**, 302.
Wilson, S. A. K., *Neurology*, 1940. London: Edward Arnold & Co.