ENCEPHALOPATHY AND FATTY DEGENERATION OF THE VISCERA
A DISEASE ENTITY IN CHILDHOOD

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THIS report describes the clinical and pathological features of a group of twenty-one children admitted to the Royal Alexandra Hospital for Children between March, 1951, and March, 1962, who appear to have had an illness which, we believe, represents a clinicopathological entity. We shall refer to this condition as fatty degeneration of the viscera, of unknown cause.

The outstanding clinical features were profoundly disturbed consciousness, fever, convulsions, vomiting, disturbed respiratory rhythm, altered muscle-tone, and altered reflexes. The onset was usually associated with cough, rhinorrhœa, sore throat, or earache. There was often hypoglycæmia and a low cerebrospinal fluid (C.S.F.) glucose, and the serum glutamic-oxalacetic acid transaminase (S.G.O.T.) and serum glutamic-pyruvic acid transaminase (S.G.P.T.) levels were increased in each of the seven patients in whom they were measured.

Seventeen of the children died, and at necropsy remarkably uniform pathological changes were found. To the unaided eye, these were expressed as cerebral swelling, a slightly enlarged, firm, and uniformly bright-yellow liver, and pallor and slight widening of the renal cortex.

Clinical Features

The series consisted of fourteen girls and seven boys. The youngest was 5 months old, and the eldest $8^1/_2$ years. Fourteen of the twenty-one were aged 2 years or less, and the other 7 were over 5 years.

The frequency of the main clinical features and the laboratory findings is shown in the tables.‡ There was usually an initial period of malaise, often with cough, sore throat, earache, or rhinorrhœa, and the children did not seem very ill. Usually after 1 to 3 days, but varying occasionally to 2 or 3 weeks, there was fairly abrupt clinical deterioration, the most worrying changes being persistent severe vomiting and the onset of stupor or coma, sometimes followed by convulsions. In ten of the fourteen children who had upper-respiratory tract symptoms, there was a short period of apparent recovery before symptoms returned and the more serious phase of the illness supervened.

In nearly half the group there was wild delirium, with screaming, intense irritability, and violent movements, during the period when consciousness was deteriorating, and in several of the other children an unusual degree of restlessness was noted.

On admission to hospital, all but two of the patients were already stuporose or comatose. Eight exhibited, at some time afterwards, the delirium described above. Usually one or more of the features that we have learnt to regard as characteristic, such as hyperpnœa or a low C.S.F. glucose, was present at or shortly after admission, and others appeared over the ensuing 12 or 24 hours.

Every patient had profoundly disturbed consciousness, and seventeen had seizures. The types of convulsion varied, and some patients had more than one sort of fit at different times. Focal twitching and tetanic spasms were seen most often, and in three patients, one of whom had opisthotonus, the spasms were sufficiently like tetanus for this diagnosis to be considered. Convulsions were often difficult to control; in ten of the seventeen patients who had fits these lasted more than 3 hours, and in four they were terminated only by death.

Vomiting was another constant symptom, and in most patients it was severe. Eleven patients vomited black or dark-brown material. It was notable that vomiting invariably ceased or became much less frequent shortly after admission, that is, a few hours after the onset of stupor or coma.

The respiratory rhythm was noted to be abnormal in twenty cases, and most exhibited changing patterns of breathing. Hyperpnœa and irregular respirations were the commonest abnormalities noted, but shallow or rapid breathing also occurred, and one patient, who became apnœic, remained alive for 26 hours with assisted respiration.

The liver was palpable in twelve, and in seven it seemed, on repeated examination, to have become larger than on admission. In six the liver was thought to be abnormally firm, and this was, in our experience, a more helpful finding than apparent enlargement.

Muscle-tone and tendon-reflexes tended to be changeable. Increased or variable tone and tendon-reflexes were found in sixteen. The plantar responses were abnormal or equivocal in about half of the group, and they were often variable from time to time in the same patient. The pupils became dilated or unresponsive to light, or both, in ten patients. In only one patient were the pupils unequal.

A characteristic posture was observed—the elbows flexed, the legs extended, and the hands clenched—and some or all of these features were noted in seven patients. This finding, in common with hyperpnœa, firmness or enlargement of the liver, and changes in the muscle-tone and tendon-reflexes, was more often recorded in the more recently admitted cases, when clinicians at the hospital had become familiar with the condition.

In twelve patients ketones were found on urine analysis, or there was a ketonic odour on the breath. Every patient except one had fever while in hospital, but this was not

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Beuren, A. J., Apitz, J., Harmjanz, D. (1962) *Circulation*, **26**, 1235.
Dawson, I. M. P., Craig, W. S., Perera, F. J. C. (1954) *Arch. Dis. Childh.* **29**, 475.
Fanconi, G., Girardet, P., Schlesinger, B. E., Butler, N. R., Black, J. A. (1952) *Helv. pædiat. Acta*, **7**, 314.
Fletcher, R. F. (1957) *Arch. Dis. Childh.* **32**, 245.
Joseph, M. C., Parrott, D. (1958) *ibid.* **33**, 385.
Mitchell, R. G. (1960) *ibid.* **35**, 383.
Rashkind, W. J., Golinko, R., Arcasoy, M. (1961) *J. Pediat.* **58**, 464.
Rinvik, B. (1957) *Ann. Pædiat. Fenn.* **3**, 464.
Russell, A., Young, W. F. (1954) *Proc. R. Soc. Med.* **47**, 1036.
Schlesinger, B. E., Butler, N. R., Black, J. A. (1956) *Brit. med. J.* i, 127.
Williams, J. C., Barratt-Boyes, B. G., Lowe, J. B. (1961) *Circulation*, **24**, 1311.

usually present on admission. Five patients appeared to have abdominal pain at some stage of the illness. In each case this was brief.

Four patients had a rash. In three this was a non-specific erythematous eruption of short duration, but in the fourth patient it was an unusual and striking feature of the illness. The rash had started on the front of the neck and had become generalised. The lesions were discrete pink papules which became excoriated and crusted. On admission after the rash had appeared, a diagnosis of varicella with encephalitis was made. The patient died, and at necropsy the typical changes of fatty degeneration of the viscera were found. The skin lesions were histologically quite unlike those of varicella, being strictly circumscribed foci showing necrosis of the epidermis and the full thickness of the dermis, with some leucocytic infiltration and the formation of micro-abscesses at the edges of the lesions.

Seventeen of the twenty-one patients died, the average time of survival after admission being 27 hours, and the longest survival $2^1/_2$ days. Vomiting invariably subsided shortly after admission, but the disturbance of consciousness did not improve, and, together with disturbed respiratory rhythm, convulsions, or peripheral circulatory failure, or a combination of these, this dominated the clinical picture until death.

Four patients survived the illness. Each of them was given intravenous glucose by infusion and two received hydrocortisone intravenously as well, one was given insulin and glucose, and one was given both hydrocortisone and insulin. In each case consciousness was normal by about 24 hours after improvement was first detected. Within a day or so of regaining consciousness each of the patients had returned to apparently normal health and remained well thereafter.

Laboratory Investigations

The following are the investigations which often gave abnormal results (see also table III):

The *C.S.F.-sugar concentration* was estimated either qualitatively or quantitatively. The qualitative test was performed by boiling equal quantities of C.S.F. and Benedict's solution. Where no reduction occurred, this is reported as " negative ", and the result is considered to represent a value for C.S.F. sugar of less than 25 mg. per 100 ml. The C.S.F.-sugar concentration was estimated before intravenous glucose was administered, in nineteen patients. In thirteen of these the concentration was reduced, although in two this was only detected in a second specimen of C.S.F., the first being normal.

The *blood-sugar level* was estimated before glucose was administered in nine patients. It was less than 50 mg. per 100 ml. in six, 62 mg. per 100 ml. in one, 195 mg. per 100 ml. in another, and normal on 2 occasions in one other. In the patient whose blood-sugar level was 62 mg. per 100 ml., the C.S.F. had given a negative qualitative test for sugar.

The *blood-urea* exceeded 40 mg. per 100 ml. in nine of the twelve patients in whom it was measured. Five of these were clinically dehydrated, and two were considered not to be dehydrated. In one patient the blood-urea was 64 mg. per 100 ml. on admission, and it rose to 180 mg. per 100 ml. next day, although signs of dehydration had not worsened and they were never of more than mild to moderate severity.

The *S.G.O.T.* was estimated in seven patients, and it was raised in each case. Initial levels varied between 106 and 1170 Karmen units per ml. per minute.

The *S.G.P.T.* was estimated in four patients, and it was initially raised in all to between 155 and 1200 Karmen units per ml. per minute.

The *prothrombin-index* was estimated in four, and it was low in each of these.

Neutrophil leucocytosis was commonly observed.

Electroencephalography was performed in six cases, and gross generalised abnormalities were found in each. Repeated tracings were made in two patients who survived, and a return to normal was observed.

Chromatography of the urinary aminoacids was performed in six instances. The pattern in one case was normal, and the other five showed a generalised increase in the concentration of aminoacids.

Blood-cultures were performed twice, and there was no growth of organisms in either case.

Clinical Diagnosis

In a number of patients admitted with stupor or coma, with or without fits, and with a history of vomiting, it has been possible to make an antemortem diagnosis of fatty degeneration of the viscera. The most helpful diagnostic findings in such patients have been hypoglycæmia, with no immediate response to intravenous glucose, low C.S.F. sugar, hyperpnœa, increased or variable muscle-tone and reflexes, firmness of the liver, and raised serum-transaminase levels. A history of unusually severe vomiting, progressing to a stage in which black vomitus has run effortlessly from the mouth of the stuporose patient, has sometimes suggested the diagnosis.

Pathological Features

Irrespective of the period of survival from the time of onset of serious symptoms, the gross and microscopic pathological changes found in the seventeen cases which came to necropsy was, apart from some minor variations, identical from case to case.

Gross Changes

The brain was always swollen, and this swelling was sufficient to produce obvious flattening of the cerebral convolutions, but it never reached a degree sufficient to produce herniation of tissue, and only rarely was any flattening of the pons and medulla or coning of the cerebellum apparent. The cut surfaces were pale and moist. The liver was slightly enlarged, and it felt unduly firm, and the capsular and cut surfaces were uniformly bright yellow. The kidneys had a slightly widened cortex which was pale, with a faint yellow tinge. The upper-respiratory tract was not inflamed, and there were no pulmonary pathological changes apart from a little œdema in some cases. The heart was usually dilated, and in a few instances the myocardium, when viewed from the endocardial surface, had a faint yellow tinge. In the majority of cases the stomach contained a small quantity of dark fluid coloured by altered blood, and in a few there were multiple superficial erosions.

Microscopy Appearances

The cerebral changes, which were in no sense specific, were principally located in the cerebral cortex, but they were not restricted to any specific area nor to any one lamina of cortical cells. Cortical neurones showed one of two changes: in one form the cell was considerably swollen; in the other the cell was shrunken and deeply staining. Cells of both types were intimately mingled, though in some areas several microscopic fields were composed almost exclusively of one or the other type. The striking feature of the enlarged cells was the pallor of the cell body which, in the paraffin sections, appeared empty or contained a few coarse refractive granules; in frozen sections a few cells of this type were found to contain a number of sudanophilic granules. Fat droplets were also seen in a few of the capillary endothelial cells in these sections, but fat emboli were not found in the vessels. In the deeply staining cells the cell body and the nucleus were contracted; the cytoplasm was opaque, and the nucleus was dense with a hazy outline and no visible nucleolus. In occasional cases eosinophilic necrosis of

the cortical neurones was found, sometimes in a laminar distribution—a pathological change which is often discovered in patients who die in convulsive states from many causes.

In all regions of the brain the astrocytes and oligoglia were greatly swollen, though the cell bodies did not contain fatty droplets. There was no proliferation of the microglia and no evidence of any inflammatory reaction in the meninges or cerebral tissue, and the myelin was well preserved in all regions.

In the tissues other than neural, the changes were those of fatty degeneration which affected the liver and kidneys in all cases and the myocardium and pancreatic acinar cells to a limited extent in a few. Frozen sections were made of these two latter organs, however, only when the examination of paraffin sections suggested the possibility of fatty change, and so minor degrees of fat accumulation could have been present more often than the record suggests.

In the liver it is the uniformity and completeness of the fatty change that is such a striking feature; every cell in every lobule is packed with fatty droplets. In addition, many cells contain a few optically empty vacuoles, even where the frozen sections were made from material embedded in gelatin, suggesting that these empty spaces may represent unstainable material rather than vacuoles from which the fat had been dislodged during processing. Despite this extensive fatty change, there was no necrosis either of zonal distribution or of individual cells, nor were mitotic figures or binucleate liver cells present as indirect evidence of prior cellular dissolution.

There were two cases which, though resembling the group in all other aspects, did show some variation in the liver. In both the liver felt a little softer than normal rather than unduly firm, and in one case it was slightly reduced in size. In addition to the uniform fatty change both these cases showed a narrow zone about the portal tracts of cellular necrosis, and in one (the case in which the liver size was a little reduced) there was an accumulation of inflammatory cells, which were principally lymphocytes and plasma-cells, but with occasional polymorphs in the portal tracts.

In the majority of cases portions of liver were placed in an alcoholic fixative during necropsy and stained for glycogen. Very little glycogen, and certainly no glycogen in excess, was found in any of these sections. Because of the uncertainty which still remains regarding the estimation of glycogen in necropsy material, however, this aspect will be mentioned again when the biopsy specimens are discussed.

In the kidney fatty degeneration was obvious in the proximal convoluted tubules and in the loops of Henle; occasional droplets of fat were present in only a few cells of the distal tubules. The glomeruli, vessels, and interstitial tissues were entirely normal. Apart from the fatty change found in the myocardium and pancreas (already remarked upon), histological study of the other organs, including the endocrine glands, revealed no pathological changes.

In the specimens from liver biopsies performed during the active stage of the illness in two patients, the changes in the liver cells were identical with those seen at necropsy in all cases. The biopsy specimens differed from the necropsy material only in that glycogen could be demonstrated in the cells in amounts considered to be within the normal range. In one case the S.G.O.T. level had fallen from 1200 to 530 Karmen units at the time of the first biopsy. The biopsy was repeated in this patient 3 weeks later, when the S.G.O.T. level had fallen to 37 Karmen units and the patient was clinically well. In this second biopsy specimen the liver tissue was histologically normal in every respect.

Treatment

It cannot be proved that any form of treatment has altered the outcome. We have gained an impression, however, that the continuous infusion of glucose and the concomitant use of a corticosteroid improved the chances of survival. It was a feature of the illness that a single dose of glucose by intravenous injection did not bring about the expected improvement in the hypoglycæmic patients. When glucose was given by infusion the results bore some relation to the rate of administration and to whether hydrocortisone was given as well. Five children received glucose by infusion at a rate less than 2·5 g. hourly, and no improvement was seen. Among six who were given larger doses of glucose, without corticosteroids, there was one survivor. Seven children were given glucose infusions at rates greater than 2·5 g. hourly, together with hydrocortisone in high dosage, and of these three survived. Since we had become accustomed to regarding the outlook as almost hopeless, this has created a fairly strong impression that the treatment had some bearing on the outcome.

Insulin was sometimes given with the idea of enhancing the utilisation of the infused glucose. Two of the four children who survived received soluble insulin.

Discussion

When the first patient of the series was admitted to hospital in 1951, he was thought to be suffering from encephalitis or septicæmia. When a full necropsy study had been completed it was evident that neither of these diagnoses was likely. However, the possibility of an unusual degree of neuronal swelling and fatty degeneration of the liver and kidneys as the result of septicæmia or even viræmia by an unidentified organism was not considered to be disproved. While accepting the non-specific character of the pathological changes when viewed separately and out of context with the history, the impression remained that this was an unusual case, that the pathological findings were unexplained, and that no exactly similar case had come to necropsy in this hospital in the preceding 10 years.

Some 2 years elapsed before the second patient presented, and from this case and the next organs were submitted for toxicological examination. It was not possible to guide the toxicologist in his investigations further than to suggest a routine study for the more commonly encountered poisons, especially those likely to produce fatty degeneration without cellular necrosis as the only definable microscopic pathological change. These studies were unfruitful; but no exhaustive toxicological analysis has ever been undertaken.

As further patients presented with similar clinical features, and the pathological pattern remained constant regardless of the duration of the illness preceding death, we became increasingly convinced that we were dealing with a clinicopathological entity, and one sufficiently distinctive to allow a presumptive clinical diagnosis to be made sometimes. We are not, of necessity, entirely convinced that the ætiology is identical in every case.

When seven patients had been seen, a retrospective investigation was made of the illness in the five most recent cases, through the cooperation of the Institute of Child Health in Sydney. A medical officer of the Institute visited the homes of the children concerned. His investigation included a history-taking of any illness in the family at about the time the patient became ill, a general review of the patient's immediate environment, and a searching inquiry as to possible access to drugs and poisons.

More recently a further study of this type was conducted by the department of public health in the State of New South Wales. The visits and interviews were more closely related to the patient's illness. In addition to the more general inquiries made in the first survey special attention was paid to the possible ingestion or inhalation of carbon tetrachloride or trichlorethylene, and in view of

the hyperpyrexia in some patients, of dinitrate cresol or dinitrate orthocresol (the pesticides used against red-spider infestations). This survey, like the first, failed to provide evidence of access to any likely poison or to show any relation to concurrent illness in parents or siblings.

Few conditions resemble the fatty-degeneration syndrome at all closely. There is a strong similarity to the case described by Curry et al. (1962) in an 8-year-old boy, who died after being ill for 6 days. His illness began with vomiting, abdominal pain, and screaming fits, and then passed into stupor. When admitted to hospital 6 hours before he died, he had a C.S.F.-glucose level of 15 mg. per 100 ml. and a blood-sugar level of 75 mg. per 100 ml. No other investigations were contributory, and serum-enzyme studies were not recorded. At necropsy his body was slightly jaundiced, the liver was intensely yellow, and severe fatty change was found in the liver microscopically. Fatty change was also found in the heart-muscle and kidneys. Thorough toxicological examination failed to reveal any toxic substances. This case-report is of special interest because the urine contained an abnormal substance which proved to be a pteridine. Whether this substance was also responsible for the bright-yellow colour of the liver seen in our series has not been investigated.

The vomiting sickness of Jamaica bears certain resemblances to this fatty-degeneration syndrome. This illness is peculiar to Jamaica, and there is a diminishing incidence after the age of 10. The onset is sudden, with violent vomiting followed by drowsiness and coma, and the mortality-rate is high though variable (Hill, 1952). Fatty change of the liver, kidneys, and other organs is a prominent feature, but the widespread œdema of connective tissues, swelling and hyperæmia of the lymph-nodes, and necrosis of liver, kidney, and pancreatic cells are all features which do not appear in the necropsy material in our series, and we have been unable to reveal a likely source for a vegetable poison such as that believed to cause the vomiting sickness of Jamaica.

Cases similar to those recorded here have occurred in other Australian States. To our knowledge these patients have not been reported as a group, although some of the children with acute encephalopathy described by Anderson (1963), seem to have had illnesses very like the one we have described. Anderson attributed the changes outside the nervous system to secondary nutritional effects in a primarily neurological disorder, rather than an integral part of the overall disease process.

We have recorded the details of this series because we are convinced that they form a group different from those children in whom fatty changes, especially in the liver, are a secondary manifestation of a variety of diseases. We hope that the experience of others may help to suggest an answer to the problems of ætiology, prevention, and treatment.

Summary

The clinical and pathological features have been described in twenty-one children with encephalopathy and fatty degeneration of the liver, kidneys, and sometimes other organs.

It is suggested that the illness of these children represents a clinicopathological entity of unknown ætiology.

REFERENCES

Anderson, R. McD. (1963) *Med. J. Aust.* i, 573.
Curry, A. S., Guttman, H. A. N., Price, D. E. (1962) *Lancet*, i, 885.
Hill, K. R. (1952) *W. Indian med. J.* **1**, 243.

BONE RESORPTION AND OSTEOPOROSIS

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BONE is a living tissue which is constantly being laid down and resorbed throughout life—more rapidly in the young than in the elderly. When the resorption outstrips the laying down of new bone, osteoporosis develops. This word " osteoporosis " simply means that there is less bone than one would normally expect; it is not a description of a specific disorder. From the age of about 30 onwards the amount of bone normally decreases.

The first difficulty has always been to decide where the difference lies between normal and abnormal bone resorption, and the second to decide whether there is, in fact, any such definite border, even though gross resorption is clearly abnormal.

In an attempt to clarify the picture, this subject of osteoporosis will be considered within the whole context of bone deposition and removal. Looked at in this way it can be shown that the various types of osteoporosis manifest themselves as a consequence of a certain type of cell behaviour. When many cells display this activity there is clear-cut osteoporosis; when few cells are active there is borderline osteoporosis which may produce no clinical manifestations. Here two types of osteoporosis will be described: localised " disuse osteoporosis "; and the type whose cause is as yet unknown, and which commonly leads to fractures in the elderly—more particularly in elderly women. Clinically this is the most important type, because of the large number of people affected.

Bone Deposition and Removal

The mechanism of bone formation is quite different from that of calcification. From many careful observations recorded in the second half of the 19th century and the early years of the present century it became known that the necessary conditions for ossification were the presence of calcified tissue (formed normally or abnormally) and the penetration of blood-vessels. Thomas [29] had shown that calcareous foci were gradually eroded by proliferating blood-capillaries, and that as a result of an unknown stimulus (believed to be the presence of the calcium salts) some of the mesothelial cells of the new blood-vessels assumed the role of osteoblasts, and thus originated bone. In his description of a bone—complete with marrow cavity—formed within an artery wall, Bunting [6] stated that lamellar bone " contains numerous typical bone corpuscles, and is penetrated at its thickest portion by a capillary vessel surrounded by a layer of cells resembling osteoblasts closely applied to the wall of bone, the whole appearing to represent a Harversian canal ".

During the past ten years Trueta and his co-workers [38 39 41–44 46] have carefully re-examined the mechanism, making use of additional techniques now available. They have provided convincing evidence that the osteoblasts which lay down bone are members of a series of related cells derived from the cells of the sinusoid vessel walls (vessel-wall cell—intermediate cell—osteoblast—osteocyte) and joined together as a syncytium—thus, all the cells in the group are joined to one another through their cell processes (figs. 1–3). In developing bone, the matrix produced by osteoblasts is laid down on calcified cartilage; thereafter it is laid down on previously existing bone.

Normal resorption takes place along the surfaces of the bone, and osteoclast formation is frequently observed.