Papers and Originals

Complicated Rheumatoid Disease*

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Rheumatoid arthritis is a disease not only of bone, ligament, and joint, but also of the patient as a whole. It has not only articular manifestations; but general ones also, so that loss of weight, anaemia, and low-grade ill-health are very much a part of the clinical picture. How often have we heard a patient say, "My arthritis is better than it was, doctor, but I feel worse in myself," or vice versa. Along with this prolonged disorder of body goes, inevitably, psychic (or spiritual) distress. A prolonged painful illness will find the weak spots in anyone's psychic armour, so that depression and anxiety are an everyday and regular part of the disease in many, if not most, cases. Suffering may occasionally make saints; more often it makes tense short-tempered sinners.

Grace Stuart, herself a sufferer from rheumatoid arthritis, in her book *The Private World of Pain* quotes the late Reverend Dick Sheppard as saying to Laurence Housman, "I like pain: it brings me nearer to my Master." But later, racked with more severe and continuous pain, he wrote in a moment of despondency to his friend, "I do not love suffering, so you must not worry about me in that way. I dislike all that talk about how lovely it is to suffer. I think it is a rotten process which has nothing whatsoever to do with God. . . . I know it may do me good—that is, if I take it decently, but I know it is as likely to embitter mankind as to convert him." And Somerset Maugham: "I know that suffering did not ennoble, it degraded. It made men selfish, mean, petty, and suspicious. It absorbed them in small things. It did not make them more than men; it made them less than men." Nevertheless, after 20 years of close contact with the rheumatoid sufferer, I have seen many more saints than sinners emerge from their suffering, and I am daily amazed at the fortitude with which these patients accept their daily painful and unpleasant lot. This, then, is our first aspect of the complicated picture of rheumatoid arthritis; the patient's emotional reaction to a prolonged, painful, and at times seemingly hopelessly progressive disease.

The physician who sets out to treat this condition must put time aside to deal with the patient's individual problems and must blend sympathy and practical and timely advice with intelligent use of analgesics and occasionally psychotropic drugs. In many patients this aspect is the greater one and the more important. I have said on many occasions previously that therapy in rheumatoid arthritis is not so much a treatment as a way of life. The sufferer may often be lucky and have a natural remission from disease activity, but equally often she continues to have daily pain, weakness, and stiffness for many years. Almost all this time is spent at home, the patient and her disease being far from physician and physiotherapist. She is alone with her arthritis in her private world of pain. Over 90% of a rheumatoid sufferer's life is touched only by her physician's advice and his drugs, and in some cases by the results of orthopaedic surgery. There have been a hundred

cures for rheumatoid arthritis; there are, in fact, none. But there are today many ways of controlling symptoms which were unknown to our predecessors, and Nature will sometimes effect a cure if we give her the chance by reasonable, sane, and unbiased advice.

The Rheumatoid Nodule

The rheumatoid nodule is not a complication, but is the characteristic basic lesion, the gumma as it were of the disorder, and when nodules are present the sheep-cell-agglutination test is almost invariably positive in high titre. Nodular rheumatoid disease is usually the classical more severe form, more prone to the complications under discussion, and carrying a more serious prognosis than non-nodular disease. But the nodules themselves lead to trouble, for they may break down and become infected, leading to chronic ulcers and sinuses; and as they occur typically over the bony points pelvic and spinal pressure-points may be involved, creating a difficult nursing problem in the bed- or chair-fast patient. These nodules, when they occur below the elbow, may cause periosteal changes visible in x-ray films (Kreel and Urquhart, 1963), and may be an inconvenience to the patient if they break down and become ulcerated, but they are of slight inconvenience as compared with buttock or sacral nodules. These may range in size from an orange pip to the orange itself, and if they break down may lead to deep sloughs and large raw areas which call for skin-grafting. Such chronic ulcers over pressure-points of the pelvis may become chronically infected and contribute to a fatal outcome.

Surgery should be minimal, apart from debridement and grafting, as the areas often heal poorly. Nodules over the ears and shoulders may prevent sleep because of pain from pressure on pillows. Wherever it may be, a rheumatoid nodule may break down. This may be in response to local trauma or may occur spontaneously; sometimes two or more nodules may break down at the same time, suggesting a general systemic effect. Vaughan-Jackson (1962) has drawn attention to attrition ruptures of extensor tendons of the hands, the tendon sawing itself in two by friction on ulnar styloid process; but nodules may occur in tendons and rupture well away from any point of attrition.

Some patients suffering from severe classical rheumatoid disease with much-advanced irreversible changes in bone and joint have no nodules; others have literally hundreds of nodules scattered all over the body, with new ones appearing in crops. Of these two types it is the nodular patient who appears to fare worst.

Polyarteritis

The sufferer from severe rheumatoid arthritis has often several rheumatoid nodules visible over bony prominences and a strongly positive sheep-cell-agglutination test. This patient

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has a less favourable prognosis than his fellow-sufferer without these features, more particularly as he is more likely to show changes of a rheumatoid polyarteritis, with visible vascular symptoms referable to different viscera. Over the past 15 years, since corticosteroid therapy came into its own, I have seen an increasing number of patients with rheumatoid arthritis complicated by necrotizing arteritis, and my impression is that, now that high-dosage corticosteroid therapy is much less popular, this polyarteritic rheumatoid picture is also much less common. Nevertheless, widespread polyarteritis may occur as part of the rheumatoid picture in patients who have never received corticosteroids. It is my own personal theory that this complicated polyarteritic picture is more common in patients on corticosteroids because of the fluctuating suppressive effect of the drug, sudden diminution and stopping of dosage being so often followed by an exacerbation of rheumatoid disease and appearance of polyarteritic features with considerable systemic upset. On a constant dosage of corticosteroid I have also seen arteritis follow exacerbation of disease as a result of trauma or infection when steroid dosage was not increased to meet the crisis, and I have been tempted to suggest that periods of inadequate dosage may lead to exacerbations of a mild diffuse arteritis which without steroid therapy would probably never have shown itself.

Kemper, Baggenstoss, and Slocumb (1957) reported that of 52 rheumatoid patients studied at necropsy 38 had received no corticosteroids: none of these developed generalized lesions of polyarteritis, whereas 4 out of 14 treated with corticosteroids did so. These workers believed that vascular changes in rheumatoid arthritis fell into three groups: (1) perivascular or adventitial accumulation of leucocytes, plasma, or other cells, with no necrosis; (2) subacute arteritis with histiocytic and lymphocytic infiltration through all layers of the vessel wall, with no necrosis, but possibly with swelling of collagen and some exudation of fibrin; and (3) lesions of acute arteritis with cellular infiltration and necrosis of vessel wall—that is, a necrotizing angiitis. They thought that in certain patients group 3 changes could be precipitated by corticosteroid therapy, and from my own experience I think they are probably right. Schmid, Cooper, Ziff, and McEwen (1961) have reported similar findings and conclusions.

The arteritis of rheumatoid disease may cause ugly and eventually fatal changes: gangrene of toes and feet; mesenteric infarction; rupture of small aneurysms in kidney, spleen, or gut; and perforation of small intestine. Though arterial changes can be demonstrated in the fingers not infrequently by angiography (Laws, Lillie, and Scott, 1963; Laws, 1965), Bywaters and Scott (1965) make the point that they have never observed histological necrotizing arteritis in the finger vessels, though it may occur in non-rheumatoid (idiopathic) polyarteritis nodosa. Brachial arteriograms in the two conditions are also said to be different (Laws *et al.*, 1963). It is important when dealing with rheumatoid patients to realize that odd pains in abdomen, chest, and elsewhere can be due to serious arteritic manifestations of the rheumatoid disease process.

Rheumatoid Neuropathy

Like polyarteritis, in rheumatoid disease neuropathic changes, though rare, appear to be more common in patients with nodules and a strongly positive sheep-cell-agglutination test. Both neuropathy and polyarteritis are relatively more common in the male. It may well be that the neuropathy is usually due to, and is part of, the polyarteritic process, but Golding and I (Hart and Golding, 1960) have made a case for this not being the entire answer. In a patient with extensive neuropathic change we could find at necropsy little evidence of involvement of vasa nervorum, and the usual symmetrical involvement of feet more than hands, sensory more than motor, is different from the essentially asymmetrical motor neuropathy

in primary polyarteritis nodosa. In the neuropathy of diabetes mellitus involvement of vasa nervorum was first held to be the main cause, but in the light of further study this has been abandoned as only one relevant factor. In our opinion, although arteritis may be the cause in many cases, it does not adequately explain all. Our more severe cases had been on corticosteroid therapy, though 12 out of 42 cases reported had never received this treatment. We see far fewer cases now that large-dose corticosteroid therapy has been abandoned—by large I mean more than 8 mg. of prednisolone daily or its equivalent. Ferguson and Slocumb (1961) also found the disorder more common in patients showing signs of hypercortisonism. Rare as rheumatoid neuropathy may be, Pallis and Scott (1965) have reported 30 cases, and Bennett and Scott (1965) have drawn attention to the fact that autonomic nerves may be involved. It is resistant to all forms of therapy. If severe and extensive it carries a bad prognosis.

Compression Neuropathies

It is not unusual for rheumatoid arthritis to present as a carpal-tunnel median-nerve compression syndrome, the patient complaining of nocturnal burning and tingling in the arms. There are usually other features of rheumatoid arthritis present to suggest the diagnosis, but these are often overlooked at the time, and operation is performed, often successfully, to relieve the pressure. Similar compression of the ulnar nerve at the elbow by the rheumatoid inflammatory mass may occur, necessitating freeing of the nerve and transplanting it anteriorly.

We have reported (Hart and Golding, 1960) a case where ulnar-nerve compression was caused by a thickened arcuate ligament between the two heads of flexor carpi ulnaris, the near-by rheumatoid changes in the elbow causing no direct pressure: the condition was immediately relieved by simple division of the ligament. This had been well described by Osborne (1957) in his original account of the condition, and he has since (Osborne, 1959) given an excellent account of the various ways in which this nerve may be affected. The most dangerous of neurological complications in rheumatoid arthritis, however, is spontaneous atlanto-axial dislocation, with the risk of compression of the cord on the odontoid process and symptoms varying from pain in the upper part of the neck to complete quadriplegia. Sharp and Purser (1961) concluded as a result of their studies that over the age of 45 years a separation of more than 3 mm. of the odontoid process from the anterior arch of the atlas on a conventional lateral film is usually abnormal, and that x-ray films taken of the neck in extension and flexion may give the diagnosis. Treatment with supports may be necessary, and sometimes occipito-cervical fusion, the indication for operation being the presence of neurological signs. In some cases, as in a boy under our care, the odontoid process becomes eroded completely away. When this happens cord compression is less likely to occur.

Rheumatoid Lung

A rich literature has sprung up under this heading, and those of us who are seeing large numbers of rheumatoid sufferers every week wonder how many we are missing; for it seems to be the rarest of rheumatoid involvements. Where we have found fibrosis or pleural effusions there has usually been another more likely explanation, as in a case Mackenzie and I reported some years ago (Hart and Mackenzie, 1955). Aronoff, Bywaters, and Fearnley (1955) also commented on the relative rarity of such lesions. Nevertheless, lung and pleural lesions do occur in the following forms: (1) pleural lesions, (2) diffuse interstitial pulmonary fibrosis, (3) rheumatoid pneumoconiosis (Caplan's syndrome), (4) lung nodules, and (5) combinations of 1-4.

1. We have seen pleural nodules on two occasions masquerading as apical bronchial carcinomata, the solid lesion removed

at operation proving to be a large rheumatoid nodule, in one case causing pain by pressing on and eroding adjacent ribs, x-ray films strongly suggesting an invasive lesion. Both were advanced cases of nodular rheumatoid disease. In neither was there evidence of neoplasia or any other pathological condition. Pleural effusions have been reported as part of the rheumatoid disease process (Emerson, 1956; Horler and Thompson, 1959).

2. Occasionally, usually in males, a diffuse fibrosis develops in rheumatoid cases with a positive sheep-cell-agglutination test, where there seems to be no other cause; but we find it rare, unlike Malcolm Thompson in Newcastle (Thompson and Leathart, 1965), who sees it more frequently, again usually in males. According to the *British Medical Journal* (1965) the process, thought to be autoimmune in nature, starts as an inflammation in the alveolar walls with infiltration of lymphocytes and plasma cells. Turner-Warwick and Doniach (1965), in a study of 48 patients with interstitial pulmonary fibrosis, found that 14 had rheumatoid arthritis, all with rheumatoid factor in their serum. No specific lung autoantibodies were found.

3. The large rounded nodules reported by Caplan in coal-miners have since been described in workers with asbestos, iron, and silica. Miall (1955) found no higher incidence of rheumatoid arthritis in coal-miners than in others. It is possible that any irritant dust has a different action in the rheumatoid sufferer's tissues from that in others.

4. Nodules in the substance of the lung are rare.

Crico-arytenoid Involvement

Involvement of the crico-arytenoid joint is one of the more unpleasant events in the life of the rheumatoid (Copeman, 1957; Baker and Bywaters, 1957). Happily it is rare in its advanced and obvious form. The cords cannot be fully abducted because of involvement of the crico-arytenoid joint, and the patient experiences dyspnoea or stridor on exertion, hoarseness, and inability to raise the voice. Pain radiating to the ears may occur, and fullness in the throat when swallowing or speaking. During bouts of infection of the upper respiratory tract these symptoms become rapidly worse, and a tracheostomy may be urgently necessary. It is probably much more common than we think, because only the advanced cases with severe symptoms are diagnosed. On laryngoscopy there may be oedema and redness and reduced mobility of joint and cord. Bienenstock Ehrlich, and Freyberg (1963) found crico-arytenoid involvement in seven out of eight necropsies on rheumatoid sufferers and made two good points: (1) that it should be thought of more frequently—17 out of 64 randomly selected rheumatoids had symptoms considered to be due to this complication in their series; and (2) that sedatives should never be used in such cases, as they may dangerously depress respiration.

Scleromalacia Perforans

In our experience chronic uveitis is no more common in rheumatoid arthritis than in the population at large, unlike Reiter's disease and ankylosing spondylitis, where it is much more frequent. Scleromalacia is rheumatoid nodulation occurring in the sclera—a rheumatoid nodular scleritis. This may leave the sclera atrophic and blue-looking or may perforate the eye, with complete and permanent loss of vision. Happily it is a rare complication.

Cardiac Lesions

The lone aortic reflex seen occasionally in ankylosing spondylitis and Reiter's disease may also occur in rheumatoid

arthritis, though very rarely (Zvaifler and Weintraub, 1963): three of the five patients (two men and three women) reported had nodular episcleritis or scleromalacia perforans also (Weintraub and Zvaifler, 1962). At necropsy two of these patients had rheumatoid granulomata similar to rheumatoid nodules in the myocardium, with evidence of aortitis and dilatation of the aortic root. The condition tends to be milder clinically with rheumatoid arthritis than with ankylosing spondylitis.

Swelling of the Calf

A not uncommon complication of rheumatoid arthritis is sudden development of swelling of the leg below the knee. This usually occurs when there is considerable arthritic involvement of the joint with effusion. The swelling may prove to be due to:

(a) Venous thrombosis, predisposed to by slowing of venous return at the affected joint, or

(b) rupture of the knee-joint, the joint fluid setting up an inflammatory reaction as it escapes into the tissues of the calf. Pressures within the knee rise considerably when the joint is tightly flexed, particularly when the patient does a "full knees bend," Dixon and Grant (1964) raising intra-articular pressures in normal knees from 30 to 1,000 mm. Hg by this manoeuvre. Rupture of the synovial cavity may closely resemble venous thrombosis of the calf, and both may give a positive Homan sign; there is little doubt that in the past some cases of the former have been misdiagnosed as the latter. Arthrographic studies by Tait, Bach, and Dixon (1965) have shown that the rupture occurs at the back of the knee between the insertions of the semimembranosus and semitendinosus muscles medially, and the medial head of the quadriceps laterally, most of the fluid tracking down beneath the deep fascia and dispersing among the muscles of the calf, only a small amount of fluid passing superficially. A large swelling in the knee or semimembranosus bursa which suddenly lessens or disappears at the time of the appearance of an inflamed swollen calf should suggest the diagnosis. Correct diagnosis is essential, as the treatment of the two conditions is entirely different, the ruptured knee needing rest and possibly splintage, but not anticoagulants.

Less dramatic swelling may occur in the calf or below other affected joints, such as shoulder or elbow. It would seem that the synovium of a joint or bursa may either proliferate downwards, to appear as a cystic swelling below the joint, or it may rupture silently with little and mild inflammatory reaction, to appear as a cystic swelling, in the calf, arm, or forearm. A synovial sac involved by the rheumatoid disease process may proliferate wildly and appear in places well beyond its usual anatomical site, and the fluid within it, if rupture occurs, seems, unlike normal joint fluid, to be productive of acute pain and inflammatory changes.

Amyloidosis

Amyloid, as Kenney and Calkins (1965) succinctly remark, remains uncertain in its composition, unknown in its pathogenesis, and resistant to treatment. The previous differentiation into "primary" and "secondary" falls down frequently on clinical grounds, primary disease not always being a localized or discrete entity and the two often overlapping in sites of distribution, and chemical tests fail in general to show essential differences. The incidence in rheumatoid arthritis varies with the enthusiasm in looking for it, and ranges from 5 to 60%; Fearnley and Lackner (1955), using a modified congo-red test, found 8 cases among 183 patients studied in one year.

Extensive replacement of renal parenchyma by amyloid may persist with only slight proteinuria for several years before nephrosis or renal failure occurs. Renal-vein thrombosis may occur as a complication, revealing itself either as acute renal failure or as slow development of the nephrotic syndrome (Barclay, Cameron, and Loughridge, 1960).

Amyloidosis in rheumatoid disease occurs usually in the more advanced case which has been active for many years, and it is usually fatal within five years of diagnosis. Kidney biopsy gave the highest yield of positive results, 87%, in the 10-year study of Blum and Sohar (1962), rectal mucosa coming second with 75%; gingival biopsy was positive in only 20% of cases. In our unit we use rectal biopsy as being the best-tolerated investigation of a condition which has no effective therapy, and this we do only if persistent proteinuria or rising blood urea makes this diagnosis seem likely.

Secondary Infection

Rheumatoid arthritics are often ill, debilitated persons, and their tissues have a diminished resistance to infection. This is seen in its extreme form in Felty's syndrome, where the low white blood cell count predisposes to infection. Such cases often respond dramatically to splenectomy, as in two of our cases reported by Gibberd, Gilbertson, and Jepson (1965). Kellgren, Ball, Fairbrother, and Barnes (1958) have drawn attention to the frequency with which pyarthrosis occurs in chronically inflamed rheumatoid joints, and this we have often seen. It is a safe rule to regard all solitary joint exacerbations in rheumatoid disease as possibly due to infection or local injury rather than primary exacerbation of the disease process. Aspiration will reveal pus in the former, possibly a haemarthrosis in the latter. Although infections of joint, perinephric regions, and subcutaneous tissues appear to be more common in corticosteroid-treated patients, these complications occur not uncommonly in rheumatoids not so treated, and pyaemia and septicaemia should be suspected, and blood cultures taken, if persistent fever appears for no reason in a debilitated rheumatoid sufferer. Septic complications are not always accompanied by a leucocytosis, and blood counts are not always helpful.

Bone Fractures

Though it is not unusual to see fractures of vertebrae and ribs in patients rendered Cushingoid by prolonged corticosteroid therapy, fractures of these and of long bones may occur where such therapy has never been given. I was called to one patient's home because the arthritis in his elbow, as he thought, had flared up: in fact, when stretching to undo his back braces button he had snapped radius and ulna 2 in. (5 cm.) below the elbow. Another man deceived me into thinking he had acute gout, as the leg just above the ankle was swollen, red and shiny, and intensely painful, preventing him from walking. It had come on rapidly, like gout, in the small hours, but was due to a fracture of tibia and fibula occurring as he stepped from his bed on to the floor to visit the lavatory. Such minor traumata are all that is necessary in advanced cases with bones porotic from prolonged disease and restricted mobility. I had a most unusual case under my care last October in St. Stephen's Hospital. A woman of 50 with rheumatoid arthritis of only moderate degree and activity, without any major injury, split her pelvis through ilium and ramus. She attended hospital only because walking caused pain in the affected side of the pelvis. Such lesions occur extremely rarely in normal people, and I know of no other similar case.

Relation of Rheumatoid Arthritis to Systemic Lupus Erythematosus

I have been dealing so far with systemic features of an essentially arthropathic disorder. Where does rheumatoid arthritis stop and systemic lupus start? It is tempting to regard both as variations on one autoimmune theme, S.L.E. being considered, as it were, a malignant or systemic variety of rheumatoid arthritis. The danger of this theory lies in its

therapeutic implications. It has taken us many years to realize that high dosage in long-term suppressive therapy in rheumatoid arthritis starts at 6–8 mg. daily, and that complications inevitably will follow at higher dose levels. If rheumatoid arthritis blends into S.L.E., then low-dose therapy should logically run on into higher dosage according to severity of symptoms and the efficiency of their suppression by corticosteroids. This, in my opinion, is a dangerous conception and a false one. Treatment of a potentially fatal condition such as S.L.E. should be considered quite apart from rheumatoid arthritis, or dangerous complications will occur if both are treated on like lines.

Several workers (Goldfine, Stevens, Masi, and Shulman, 1965; Hazevoet and Kievits, 1966) have made the point that patients with rheumatoid disease with L.E. cells present in their circulating blood fare no differently from cases without such cells, so far as prognosis, complications, and treatment are concerned. Though cases do occur which seem to lie between the two conditions, unless the very definite diagnosis of S.L.E. is made treatment should be kept at safer conservative levels. To treat rheumatoid arthritis as systemic lupus is to court disaster.

Drug Complications

The commonest of complications in rheumatoid arthritis are the drug-induced ones: dyspepsia from aspirin or phenylbutazone, Cushing's syndrome from cortisone or its analogues, headaches from indomethacin, and so on. But this is a subject on its own, which will not be discussed. Suffice it to say that in the long years of corticosteroid overdosage as many patients suffered from drugs as from disease, and even today overtones and complications of therapy colour the clinical picture of most severe cases of rheumatoid arthritis one sees.

Summary

In rheumatoid arthritis we have a disorder which continues for many years; which affects body and soul, and does not stop at the bones and joints. These patients are systemically ill as well as arthritic. Nevertheless, to merge rheumatoid disease on autoimmune grounds into the picture of other connective-tissue disorders, such as systemic lupus erythematosus, is to turn the calendar back to the days of corticosteroid overdosage. I only hope Dr. Wilfred Edgecombe would have approved the message. I think he would.

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Syndrome of Encephalopathy and Fatty Degeneration of Viscera in New Zealand Children

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In 1963 a new syndrome was described in Australian children based on the association of severe fatty degeneration of the liver with acute encephalopathy (Reye *et al.*, 1963). Twenty-one children in Sydney had an acute illness with profound disturbance of consciousness progressing to coma, and, in the majority, to death within two and a half days of admission to hospital. Prodromal respiratory symptoms, persistent severe vomiting, disturbed respiratory rhythm, convulsions, altered reflexes and muscle tone, and hypoglycaemia were often present. Pronounced cerebral swelling and fatty changes in the kidneys were additional findings at necropsy.

In the correspondence which followed this first description similar cases were reported from England, Scotland, South Africa, and Czechoslovakia (Elliott *et al.*, 1963; Maloney, 1963; Utian and Wagner, 1963; Stejskal and Kluska, 1964). Though this disease appears to be widely distributed the cause is unknown.

Since 1959 at least nine children in Auckland have died of a similar disease. The purpose of this report is to present the clinical and pathological features of these nine patients, to compare them with those previously described, and to consider possible aetiological factors. Three further cases of illnesses which possibly represent variations from the typical disease pattern are described.

Typical Cases (Nos. 1-9)

Six cases were seen in 1959 and 1960, and one in each of the years 1962 to 1964. Ages ranged from 4½ months to 6½ years. Seven were less than 2 years old. There were seven boys and two girls. Four were European, three Polynesian, and two part-Polynesian and part-European. All children had grown and developed normally. Two were siblings—brothers aged 1½ and 6½ years—whose illnesses occurred nine months apart. Otherwise there was no known contact between cases, no recent or past history of similar illnesses in the families, nor of other concurrent family illnesses. There was no particular seasonal incidence and no concentration of cases in one locality.

The major clinical, biochemical, and pathological findings are summarized in Table I and details of individual patients are presented in Table II.

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Clinical

Coma was the major concern in all patients, and eight of the nine were unconscious or stuporous on admission to hospital. Most of them had prodromal symptoms. Six had a history suggestive of a trivial infection of the upper respiratory tract, usually with coryza and cough, beginning four to seven days previously. Repeated vomiting was a more dramatic symptom in six children, preceding the onset of coma by intervals of three days to a few hours. Though this vomiting was severe there was no haematemesis. It was accompanied by increasing drowsiness until coma ensued, without prior convulsions. Two children were irritable during the period of loss of consciousness, but only one had bouts of screaming and violent movements similar to the wild delirium occurring in nearly half the cases described by Reye *et al.* (1963). Three children did not vomit. Two of these were the siblings who were found unconscious in bed in the morning, no previous symptoms having been noted. The third child had been admitted to hospital after a convulsion which appeared to be febrile in type. He had pharyngitis and otitis media, which settled promptly after treatment with tetracycline; but on the fifth day, after being anorexic for the previous 20 hours, he was found unconscious.

Seven patients had deep stertorous "acidotic" respirations shortly after the onset of coma. There was no evidence of shock, blood-pressures were normal, and there was minimal tachycardia. Only one child had a temperature above 38.5° C. Six children had evidence of otitis media or pharyngitis. The only other findings of note at the initial examinations were a petechial rash on the abdomen and limbs of one child and moderate enlargement of the liver in another. There was no jaundice.

TABLE I.—*Syndrome of Encephalopathy and Fatty Degeneration of the Viscera*

	Essential Features	Usually Accompanied by	Less Frequently Present
Clinical	Acute severe progressive disturbance of cerebral function?	Coryza and cough. Vomiting. Hyperpnoea. Leucocytosis. Hypoglycaemia. "Acidosis"	
Biochemical		Fatty change in renal tubules. Reactive changes in lymphoid tissue	Ketosis. Rising blood urea
Pathological	Intense diffuse fatty change in liver. Cerebral swelling. Absence of specific findings		Fatty infiltration of myocardium. Gastro-intestinal haemorrhage