focus should doubtless be treated—not necessarily by ablation of the organ concerned—but the evidence of its existence must be strong, and our promises as to the remote results of its treatment cautious.

Conclusion

It is not, however, my intention to weary you with a long catalogue of the mistakes which all of us make and which, if sown on fertile ground, are the seeds which grow into the tree of experience and, in the fullness of time, reward us with the fruit of knowledge and wisdom. My purpose in bringing to your notice these few practical illustrations of common fallacies has rather been to point, the moral and adorn the tale of the main purpose of my discourse. And this has been to urge that in our attitude to the methods we use in diagnosis and the measures we adopt in treatment we should beware equally of an excess of empiricism as of an exaggerated rationalism.

NON-SPIROCHAETAL INFECTIOUS JAUNDICE

BY

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An outbreak of infectious jaundice among the inmates of Stoke Park Colony during 1935 gave an opportunity for the study of this disease. In England the view most commonly accepted is that infectious jaundice occurs in two forms: (1) Weil's disease, a grave form which is spirochaetal in origin; and (2) epidemic catarrhal jaundice, mild in type, of which the causative organism is unknown. The ordinary sporadic form of catarrhal jaundice is regarded as a separate disease, due to an ascending cholangitis, in which exposure to cold and errors of diet play a large part as predisposing causes.

Miller¹ summarizes a more modern viewpoint when he writes:

"The old view that so-called catarrhal jaundice is due to an ascending infection of the ducts from gastro-duodenitis falls more and more into disfavour. The alternative hypothesis is that it is a hepatitis due to some unknown infection occurring sporadically or in epidemics. Viewed thus it is seen to have an incubation period of fourteen to twenty-eight days, an autumnal seasonal incidence, an age incidence from 5 to 10 years especially, and to have the power of conferring a lasting immunity from fresh attacks. The type of child with 'cyclical vomiting' seems particularly liable to this disease, and adults show much more immunity against it than children."

Hampson,² whose work Miller is discussing, points out that "epidemic catarrhal jaundice" is a bad term, and prefers "epidemic infective jaundice."

Hurst and Simpson³ consider that two separate conditions are commonly diagnosed as catarrhal jaundice. In the first there is gastro-duodenal catarrh with obstruction of the ducts, and the initial symptoms of gastritis are followed by jaundice. In the second there is a mild subacute hepatic necrosis in which jaundice is the first symptom, followed by symptoms of general toxæmia; the liver is tender and slightly enlarged, and the spleen is always palpable. In France catarrhal jaundice is regarded as a manifestation of infectious jaundice. Widal and Abrami⁴ state that "infectious jaundice occurs in three forms . . . catarrhal jaundice, benign infectious jaundice, and malignant jaundice."

Weil's disease, or malignant jaundice, is accepted as being due to infection by the spirochaete or *Leptospira icterohaemorrhagiae* of Inada and Ido. The spirochaete

That we should appreciate the value of proven facts and apply to them the highest standard of proof that we can attain. That scepticism is necessary in embracing new ideas, though it is not necessary for us to go so far as Montaigne, who wrote, "I feel we should say most times: There is no such thing." That we must never be impervious to new ideas, and if only we will say "There may be no such thing" we shall avoid the pitfalls into which credulity may lead us.

The Hippocratic aphorism which has served me as a text concludes with the observation that judgement is difficult. The late Lord Dewar once remarked that an optimist was one who made of every difficulty an opportunity; and a pessimist one who made of every opportunity a difficulty. Let us then be optimists, and strive to achieve that balanced judgement which alone can enable us to distinguish fact from fallacy and guide us into the path of wisdom.

may be demonstrated in urine or blood; the disease may be reproduced in guinea-pigs by injection of the same material, or agglutination reactions may give positive results even with dilutions of 1 in 1,000,000.

Some Views on the Causative Organism

The causative organism of "catarrhal" jaundice, sporadic or epidemic, has not been established. These epidemics are regarded by some writers as being due to a mild form of spirochaetal infection. Montford,⁵ describing an outbreak in North Leicestershire, refers to two epidemics, among others, in which a spirochaete was found, and states "the symptomatology in these and other British epidemics did not greatly vary, and it would seem that such epidemics are manifestations of the one disease, although a spirochaete or other organism could not be constantly demonstrated." Pettit⁶ mentions the many pathogenic spirochaetes which resemble *Spirochaeta icterohaemorrhagiae*, particularly *S. hebdomadis*, *S. pettiti*, *S. pseudo-icterogenes*, etc. He quotes Saesilo, who, working in Amsterdam, found that of nine cultures obtained from rats in the town seven showed typical *Spirochaeta icterohaemorrhagiae*; the other two gave serological reactions identical with those of another spirochaete which causes the spirochaetal fever of Déli. Pettit suggests from this that there may be a second spirochaetal disease in Europe in which the symptoms are less severe than in Weil's disease. This may explain the findings of Elliott and Beattie⁷ in the Selkirkshire epidemic, in which eight urines out of ten showed some form of spirochaete and only one a typical leptospira. In no case was animal inoculation successful in this outbreak.

Benign infectious jaundice occurs sometimes in association with infections of the coli-typhoid group. Boyd⁸ states "cholangitis may occasionally be a cause of transient jaundice. It is probable that the cases of epidemic catarrhal jaundice are of this nature, possibly due to the paratyphoid group of bacteria." Widal and Abrami mention many investigations into the cause of jaundice in which agglutination reactions, blood culture, or examination of the faeces revealed typhoid, paratyphoid, or *B. coli* infections. They give the following examples:

Sacquépée and Fras,⁹ Audibert,¹⁰ and many others obtained positive typhoid agglutinations in cases of jaundice. Netter and Ribadeau-Dumas,¹¹ Sacquépée and Fras, and Demanche¹² obtained positive paratyphoid agglutinations in similar cases. Typhoid bacilli in the stools of jaundiced patients have been demonstrated by Sacquépée and Fras, and Etienne.¹³ Positive blood cultures were obtained in cases of sporadic jaundice by Delachanal and Savy¹⁴ (typhoid), Lemierre¹⁵ (paratyphoid B), Widal, Lemierre, and Bénard¹⁶ (para. *B. coli*). Positive blood cultures of paratyphoid B were obtained in epidemic jaundice by Sarrailhé¹⁷ in the Dardanelles and by Cantacuzène¹⁸ in Rumania. Both obtained strong positive agglutination reactions, and both further confirmed the causative organism. Volunteers were given cultures of the paratyphoid B by the mouth; they were isolated, and all developed jaundice,

On the other hand Martin obtained entirely negative results in the Dardanelles epidemic. Sisto,¹⁹ examining the faeces in 100 cases of jaundice, obtained paratyphoid B in three cases only, and these gave negative agglutination reactions. Garnier and Reilly²⁰ investigated more than one thousand cases of jaundice; in only 0.5 per cent. did the coli-typhoid group appear to be the cause of the disease. Widal and Abrami describe an interesting case of jaundice in which blood culture showed *Staphylococcus aureus*. At necropsy the condition was proved to be spirochaetal jaundice. They point out, therefore, that the organisms discovered in cases of jaundice may be only "microbes de sortie" thrown out in the course of an unknown infection.

In two of Montford's series of forty-five cases the urine was examined bacteriologically. Both specimens showed large numbers of Gram-negative bacilli resembling *B. coli* in their behaviour, but some of which at least were regarded as *B. proteus*. Poulton²¹ describes a case of infectious jaundice which developed epididymo-orchitis as a complication. Investigations for spirochaetes were negative, but the urine contained *B. coli*. It was suggested that both the jaundice and the epididymitis were the result of *B. coli* infection.

In Bashford's²² series of forty-eight cases the urine and faeces were examined in four cases with negative results, except that in two of them the faeces showed the same serological type of Morgan's bacillus. The sera from six of his cases agglutinated the same type of Morgan's bacillus, but Bashford points out that ten out of twenty normal blood sera give the same agglutination reaction.

Present Investigation

In the Stoke Park series of sixty-five cases specimens of blood, urine, and faeces were sent to Professor Walker Hall of the Department of Preventive Medicine of the University of Bristol. Six blood sera showed no agglutination with an emulsion of *Leptospira icterohaemorrhagiae* in dilutions of 1 in 10 to 1 in 30,000. Eight further specimens of blood were investigated by: (1) culture; (2) examination for spirochaetes; (3) injection into guinea-pigs; and (4) agglutination against typhoid "H" and "O," paratyphoid A and B, *Br. abortus*, and all the *Salmonella* group. All these investigations gave entirely negative results.

Eight catheter specimens of urine were similarly investigated by: (1) culture; (2) examination for spirochaetes; and (3) injection into guinea-pigs. One specimen gave a culture of *B. coli anaerogenes*; otherwise all the investigations were negative. Four specimens of faeces were examined bacteriologically for typhoid "H" and "O," paratyphoid A and B and others of the *Salmonella* group, *Br. abortus*, and *B. flexneri* with negative results. There grew out a strain of slow-fermenting *B. coli*, but this on injection into a rat did not cause any untoward symptoms.

Out of the total of sixty-five cases twenty-seven occurred in patients under the age of 10 and forty-seven in patients under the age of 15. Only six patients were over the age of 25, and these were aged 26, 31, 33, 34, 35, and 40 respectively. In addition, two female members of the staff developed jaundice at this time, and are not included in these figures.

Symptoms and Physical Signs

It is perhaps worth while noting the symptoms and physical signs for comparison with other epidemics. In some of the older patients the initial complaints were of sore throat and headache, and the tonsils were enlarged and inflamed. It was noticeable in these patients that the period between the onset of symptoms and the development of jaundice was longer than in the majority of patients. Glover and Wilson²³ describe the occurrence of tonsillitis early in the epidemic. They took swabs

from the throats of ten patients, but these showed nothing abnormal. Beauchamp²⁴ reports three interesting cases of jaundice affecting members of one family. In each case the illness began with a sore throat, followed two days later by the appearance of bile in the urine; two days later still each patient became jaundiced. The incubation period was twenty days.

These and other observations may go to show that a nasopharyngeal infection is at least one means of entry of the causative organism or virus. But in the majority of patients there was no history or evidence of a sore throat. Of the two members of the staff who developed jaundice one complained of severe sore throat with a sudden onset, the other of pelvic pain with an insidious onset. In the older children and adults the commonest initial symptoms were those of "feeling sick," "feeling cold," headache, and abdominal pain. Vomiting was not a prominent symptom. The site of the abdominal pain was over the liver, around the umbilicus, or in the right iliac fossa. Hamilton Fairley,²⁵ describing the physical signs in his series of cases of Weil's disease, mentions generalized tenderness most marked in the right iliac fossa, and points out that in early cases before jaundice develops a diagnosis of acute appendicitis may be made. In the Stoke Park series the tenderness was generally over the enlarged liver, but three cases showed this tenderness in the right iliac fossa. One patient, the first of the series, had such marked tenderness with a rising pulse rate a week after the appearance of jaundice that he was transferred to a general hospital, where appendicectomy was performed.

Among the younger children a constant feature during the height of the epidemic (when contacts were examined daily) was conjunctival injection occurring as the earliest physical sign. This was noticed at about the same time as the first refusal of food, before the initial rise of temperature, and several days before the appearance of jaundice. It was of value in early diagnosis and segregation.

Kramer,²⁶ quoted by J. D. Rolleston,²⁷ describes a group of forty-five cases of Weil's disease in Rotterdam, none of which developed jaundice. In this group the principal symptoms were conjunctival and episcleral injection and pains in the muscles. Pettit states:

"At the beginning of spirochaetosis the principal vessels of the conjunctiva show dilatation; furthermore, small subconjunctival haemorrhages sometimes occur. This congestion is frequent enough to constitute a significant physical sign."

Weekes and Firket, quoted by Pettit, noted this pre-icteric conjunctival hyperaemia in twenty-nine out of fifty patients who later developed spirochaetal jaundice. Morgan and Brown²⁸ also noted this sign as occurring frequently in the 1925 epidemic of "catarrhal jaundice" described by them.

Pettit also quotes a case of typical "catarrhal" jaundice which proved to be spirochaetal on animal inoculation. In this case thirty-two days elapsed before the guinea-pig (injected with blood) developed jaundice.

Spread by Contact Infection

In recent epidemics most observers support the view of spread by contact infection. Bashford could find no common responsible factor in the epidemic described by him, but points out that person-to-person spread, although the most probable explanation, could only be the result of the most casual contact in his cases. Elliott and Beattie support the same view and quote Hindle and Brown, and Mackie and McLachlan, whose conclusion was the same. Wilson and Glover state that the evidence appears strongly to suggest that transmission was usually by nasopharyngeal droplet infection, and that it was favoured by intimate contact, especially in sleeping quarters. The contrary view is still given in some textbooks; Strümpell and Seyfarth²⁹ state:

"Fairly extensive epidemics of (catarrhal) jaundice have repeatedly been observed in barracks, prisons, isolated places, etc., and can only be explained on the assumption of a local source of infection. Strümpell once observed a mild epidemic of jaundice in numerous members of a student community, and in this case the beer was to blame."

At Stoke Park the prominent symptoms among the younger children were gastro-intestinal, and it was among these that the epidemic started. A primary alimentary infection cannot be excluded among these children, especially as fifty-five of the sixty-five patients who developed the disease received their food from a common kitchen. But although the first three blocks affected were supplied by the same kitchen, cases did not occur in all three blocks simultaneously, the epidemic ceasing in one block before another became involved. As the epidemic progressed a contact spread became increasingly obvious. Even the early history is suggestive. One boy, "A," developed jaundice in the North Block on December 24th, and another, "B," developed jaundice in Ivy Lodge on December 25th. Both cases were diagnosed as of catarrhal jaundice, and both children were admitted to hospital. The boy "A" returned to the North Block on December 31st. During January there were eighteen cases of jaundice in this block. The boy "B" did not return to his block until January 25th. There were no cases of jaundice in Ivy Lodge in January, the second case developing there twenty-six days after the return of the boy "B." Twelve cases of jaundice subsequently occurred in this block.

At Hanham Hall, five miles from the Colony, a girl developed jaundice following the return of patients from the Colony Hospital. These patients had not suffered from jaundice, and were not nursed in the same ward as cases of jaundice. This first case of jaundice was removed from Hanham Hall at once. Two more patients developed the disease twenty-five and twenty-seven days later respectively. These and other observations give an incubation period (to the appearance of jaundice) in adults and older children of about twenty-six days. Among the very young patients the incubation period appeared to be shorter—from fifteen to twenty-one days. Six cases in the present series showed no jaundice of conjunctiva or skin, although bile was present in the urine and the liver was enlarged. Such patients, if not ill, would act as "carriers," and contact spread could not be traced. This is probably the explanation of isolated instances with an apparent incubation period of forty days or longer. The outbreak in Ivy Lodge following the return of the boy "B" thirty-one days after jaundice suggests that a long isolation period is necessary.

Twenty-eight patients showed no pre-icteric stage, and thirty-one showed a pre-icteric febrile period varying from one to eleven days. Every intermediate day between these figures was represented. Six patients did not develop jaundice. Forty patients showed an initial rise of temperature, which was 103° or over in six cases. The stools were usually paler than normal for twenty-four hours, but typical clay-coloured stools were uncommon. Jaundice was present for more than one week in sixteen cases and for more than two weeks in four. The liver was enlarged in forty-one cases and greatly enlarged (three fingers below the costal margin) in five. The spleen was enlarged in ten cases. Bile was present in the urine in all cases, the longest period being eighteen days. In one case bile was present in the urine for five days, and reappeared for a further two days after being absent for a week. One patient, a boy aged 8½ years, developed two distinct attacks. On the first occasion he was jaundiced for a week. Thirty-four days after bile had disappeared from the urine he developed a more severe attack, which lasted over three weeks. The child had remained during the thirty-four days in a ward with other cases of jaundice. Albumin was present in the urine in eleven cases, the longest period being eight days. Renal casts were not seen.

An Accompanying Acidosis

In the 1925 epidemic in the Midlands, described by Morgan and Brown, vomiting was a constant feature. Its severity and frequency was out of all proportion to the mildness of the attack. The cause of the vomiting was attributed to

a duodenitis around the opening of the bile duct. Twenty urines were examined in this epidemic, of which eight gave a positive acetone reaction. Of these twenty urines ten were examined after the tenth day of the disease. Morgan and Brown considered the vomiting to be the cause of the acidosis. One patient in Morgan's series, a girl aged 11 years, died. On section the liver was pale and fatty, and microscopical examination showed that the cells were distended with fat, especially round the periphery of the lobule. Actual necrosis of the liver cells was not observed. Macleod³⁰ points out that "in cyclical vomiting in man considerable quantities of fat may be present in the liver within a very short period of time after the onset of the condition."

In twenty-six cases at Stoke Park the urine was tested daily for acetone from the onset of the disease, and positive tests were obtained in twenty-four. Only three of these patients had vomited. In twenty cases acetone was present on the first day of the disease in large amount, but this gradually decreased each day until about the fifth or sixth day, when the test was negative. Hampson considered that the disease was particularly likely to attack those children who suffered from "cyclical vomiting," and these findings at first appear to support this view. But five of the patients giving positive results were adults (aged 26, 31, 33, 34, and 40), and another explanation seems necessary in their case. Fever is excluded as a cause of the acidosis, as in eleven out of the twenty cases showing acetone on the first day the temperature was never above normal. Vomiting is excluded, since only three of these patients had vomited. Starvation, even if complete, requires several days to produce acidosis in adults, and a large quantity of acetone bodies in the urine was demonstrated on the first day of the disease. The most likely explanation is that acidosis arises as a consequence of a maladjustment between the metabolisms of fat and carbohydrate, and that this maladjustment is caused by a hepatitis. A similar acidosis occurs in anaesthetic poisoning.

The recognition of this primary acidosis, largely overshadowed as it is by jaundice, is of importance in treatment. Fats need not be prohibited (especially uncooked fats, as in butter and milk) if a sufficiently large carbohydrate intake is assured. In the early stages of the disease large amounts of glucose should be given, in fluid form if necessary, combined with alkalis. If bronchitis is present expectorant mixtures containing ammonium chloride or similar substances are to be avoided. Early treatment by alkalis and glucose appeared to shorten the duration of the jaundice. Signs of acidosis disappeared in twenty-four hours. The alkali dosage should be sufficient to render the urine alkaline quickly. In practice the albuminuria when present was found to disappear rapidly with this treatment.

One patient developed a heavy morbilliform rash, which lasted two days, at the onset of jaundice. Montford describes one similar case and Glover and Wilson describe one resembling German measles, and mention rashes in two or three cases. Morgan and Brown describe one case. Epistaxis was present in five cases, occurring in each instance the day before the appearance of jaundice. One member of the staff also complained of epistaxis the day before jaundice appeared. Some degree of bronchitis was common in the early stages among the younger children.

Nervous symptoms were rare, but one patient developed symptoms better described as "mental." A medium-grade feeble-minded woman, aged 33, became depressed during the first week of an attack of jaundice. This was followed by alternating states of depression and elation, a condition of affairs which lasted three weeks. When elated she was frequently violent to staff and patients. There were fairly well-systematized delusions. Recovery was rapid, and the patient professes to have no memory of her misbehaviour. The case is the more unusual as the patient is well known as a stable defective who gives no trouble.

Two patients who were previously apparently healthy (aged 17 and 11 years) died two and four months respectively after jaundice. In both cases death was due to an acute generalized tuberculosis. The first patient, while still jaundiced, developed an acute generalized bronchitis, which subsequently proved to be tuberculous. The second developed tuberculous adenitis of the neck within three weeks of jaundice.

Summary and Conclusions

Non-spirochaetal infectious jaundice is to be regarded as a general infection in which symptoms of disorganized liver function predominate. These symptoms are due to two main causes: first a maladjustment between the metabolisms of fat and carbohydrate causing acidosis; and secondly an escape of bile into the blood stream causing jaundice, bilirubinuria, a tendency to haemorrhages, etc. Jaundice of skin and conjunctiva is not invariable, and was not present in about 8 per cent. of the present series. Enlargement of the liver is common, occurring in 63 per cent. of cases, and is probably due to a deposit of fat in the liver cells. The spleen was enlarged in 15 per cent. of cases, and 17 per cent. showed albuminuria.

The causative organism or virus is unknown. Guinea-pigs do not appear to be susceptible to the disease. The evidence is in favour of a primary nasopharyngeal infection in some cases. Second attacks are rare, but do occur. The symptomatology differs from that of Weil's disease in degree only. In epidemics, Weil's disease should be excluded as soon as possible.

Every case of "catarrhal" jaundice in children should be isolated for a period of at least four weeks. Any case may be the starting-point of an epidemic. In institutions observation of contacts (particularly with reference to the urine) and quarantine for a similar period should be enforced.

Treatment should be directed principally against the acidosis.

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HUMAN TUBERCULOSIS OF BOVINE ORIGIN IN STAFFORDSHIRE

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A recent publication by one of us (A. S. G., 1934)¹ on the incidence in England and Scotland of human and bovine tubercle bacilli in tuberculous meningitis included six cases of this disease from Staffordshire. Of these six cases, three proved to be bovine, two human, and one an anomalous dysgonic strain, which is still under investigation. The bovine ratio in this small series prompted a further and more extended inquiry so as to include all forms of human tuberculosis in this county.

During the period from January, 1934, to June, 1935, we have examined bacteriologically six cases of cervical gland, twenty-nine cases of bone and joint, twelve cases of meningeal, two cases of renal, and 230 cases of pulmonary tuberculosis. The original material—aspirated pus, cerebro-spinal fluid, urine—of the non-pulmonary cases was in each instance injected subcutaneously in the thigh of a guinea-pig at the County Bacteriological Laboratory, Stafford.

Each guinea-pig was killed when its inguinal glands were sufficiently enlarged, and was carefully examined to make sure that there were no lesions other than those which were obviously artificially induced. In none of the animals was there any sign or suspicion of spontaneous tuberculosis, which, in fact, has never been observed among the guinea-pigs in this laboratory. One of the inguinal glands adjacent to the seat of injection was excised with sterile precautions and sent to the Field Laboratories, Cambridge, where the tubercle bacilli were cultivated and typed by one of us. The original material of the pulmonary cases was sputum, and from it cultures were obtained in the laboratory at Stafford, either directly with the aid of KOH (5 per cent.), or through the guinea-pig (three instances).

The results in the different forms of tuberculosis are stated separately.

Non-pulmonary Forms of Tuberculosis

Cervical Gland Tuberculosis.—The six cases were in persons aged 1½, 2, 12, 17, 22, and 23 years respectively, of whom three were males and three females. In the child of 12 cervical adenitis had been present since the age of 4 years, and the culture was obtained from a gland which began to enlarge three months ago. In the three older persons the duration of the adenitis ranged from about one up to three years. The tubercle bacilli obtained in culture from each patient exhibited the characters of dysgonic bacilli of the bovine type and were fully virulent for the rabbit. Six rabbits inoculated subcutaneously with these strains died in from twenty-eight to seventy-one days (average 37.9 days) of general tuberculosis typical of infections with bovine tubercle bacilli.

Bone and Joint Tuberculosis.—The twenty-nine cases comprised fourteen of the hip-joint, nine of the spine, and one each of a finger, a rib, a humerus, a sternum, and a knee- and an ankle-joint. The cultures from nineteen cases were culturally of the human type (eighteen eugonic and one dysgonic). The remaining ten cases—namely, five of the fourteen hip-joints, two of the nine spines, and the finger, rib, and humerus—yielded cultures