CONCERNING THE PATHOLOGY AND ETIOLOGY OF THE INFECTIOUS JAUNDICE COMMON AT THE DARDANELLES, 1915.

BY

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DURING the autumn of 1915 troops at Gallipoli, and to a lesser extent in Egypt, suffered from a nearly non-fatal form of infectious jaundice, usually without complete obstruction to the entry of bile into the intestine, and not associated with any tendency to haemorrhages. It appeared to be markedly infectious; some units had 25 per cent. of their strength affected, and many cases occurred amongst patients in hospital for other complaints.

The first case occurred in the French lines about August 10th; during September the epidemic spread slowly until the end of that month, when it rapidly extended, reaching its maximum in October. During November it rapidly declined, and was practically over by the end of the year.

The following is an account of a case of moderate severity. All variations between this and mild jaundice without any obvious signs of illness were common.

The onset is characterized by lassitude, loss of appetite, headache, and often suffusion of conjunctivae. It is ushered in with a brief period of pyrexia, temperature 101–102°, and generally some pain in the upper abdomen. The liver becomes slightly enlarged, can be felt below the ribs, and is tender to the touch. The spleen is sometimes enlarged, but not tender.

Although the temperature may have returned to normal, these symptoms continue for three to five days, when jaundice occurs and lasts one to two weeks, or longer. The urine is bile-stained and the pulse often slow whilst jaundice is present.

By the time that jaundice is developed the patients generally feel better, but weakness continues, with rapid pulse and breathlessness on the least exertion.

Seven to ten days after the onset of the disease a distinct increase in the area of cardiac dullness may be made out.* Slight albuminuria is not uncommon.

Convalescence is slow and the patient is not good for much for a month or longer.

According to the accounts of the disease published by Sarrailhé and Clunet (1916), Willcox (1916), and by Hurst (1916), the gall bladder is often, or generally, palpable and tender. Specific enlargement of the gall bladder was not discoverable in the cases I saw, nor was this the case in the experience of my colleagues. Sarrailhé and Clunet also record two cases of "ictère grave" which developed in forty-eight hours with high temperature, speedy collapse, purpura, haemorrhages, and death. They do not mention the existence of nephritis in these.

In opening the discussion on cases of jaundice at Alexandria in November, 1915, Professor Kartulis gave a brief survey of the varieties met with in Egypt and the Levant. He described two types of epidemic jaundice as not uncommon. The first is a severe disease of sudden onset with rigor, high temperature, intense headache, vomiting, and prostration. The liver becomes enlarged and tender, and the urine contains albumin and casts. On the fourth or fifth day jaundice appears. Epistaxis, haematuria, and petechial haemorrhages are characteristic features. The urine diminishes in amount and the patient becomes unconscious or delirious. Death occurs in 30 per cent. or upwards of the cases from uraemia, haemorrhages, or secondary infections. Convalescence is very prolonged.

The milder type described by Professor Kartulis resembles the disease encountered at Gallipoli as described above, but in the Egyptian cases nephritis, epistaxis, and petechial haemorrhages would appear to be usual symptoms.

Professor Kartulis had by means of various microscopical and bacteriological methods searched for the pathogenic agent in both classes of infectious jaundice, but hitherto in vain. He suggests that it must be invisible, like that of yellow fever.

The severe form resembles very closely the infectious jaundice prevalent in certain coal mines in Japan which, towards the end of 1914, was shown by Inada, Ido, Hoki, Kaneko, and Ito (1916) to be caused by a spirochaete. They accordingly named the microbe *Spirochaeta icterohaemorrhagiae*, and the disease spirochaetosis icterohaemorrhagica. Later Ido, Hoki, Ito, and Wani (1916) found the spirochaete in 39 per cent. of the rats in the mines, and they suggest that the miners became infected from these rodents.

Spirochaetosis icterohaemorrhagica has been also described by Hübener and Reiter (1916), Gwyn and Ower (1916), Stokes and Ryle (1916), and Martin and Pettit (1916), as occurring in the German, British, and French trenches.

In the spirochaetal disease, in addition to hepatitis and jaundice, haemorrhages and an acute nephritis occur. It has a mortality of 20 to 30 per cent., and is apparently dependent upon man's association with rats for its propagation. As described above, the Gallipoli disease was much milder, was apparently more infectious, and there was no reason to suppose that rats contributed to its dissemination. Nevertheless certain striking analogies occur, and the milder types of cases described by Kartulis show many characters intermediate between our comparatively mild disease and spirochaetosis icterohaemorrhagica.

SEARCH FOR THE CAUSE OF THE DISEASE.

At Lemnos in the autumn of 1915 I was not in a position to make animal experiments. I hunted for parasites in the blood of early cases, using dark-ground illumination with fresh films and also preparations stained with Giemsa's stain, but without success. I also made blood cultures in eighteen cases, but the only positive result was that I once isolated *B. typhosus*. This patient subsequently went through an ordinary attack of typhoid fever.

The experience of Captain Campbell (1916) at Cape Helles was similar. He made sixty-four blood cultures in non-febrile cases of jaundice and obtained negative results. On the other hand, from nine blood cultures of cases running a continuous temperature he recovered paratyphoid bacilli. In five instances the organism was *B. paratyphosus* B.

Sarrailhé and Clunet had, I understood, found an organism resembling *B. paratyphosus* in the blood in a number of cases of jaundice at Cape Helles, and were of opinion that the jaundice was merely a manifestation of paratyphoid fever. I therefore tested the serums of 37 cases two or three weeks subsequent to the onset of an attack of jaundice. Fifteen of the cases had had continuous fever for some time. Out of the 15 the serums of 7 agglutinated *B. paratyphosus* A and 2 *B. paratyphosus* B. The serums of the remaining 22 cases which had had no continuous fever gave no agglutination with either of the paratyphoid bacilli in a dilution of 1 in 50.

As both jaundice and paratyphoid fevers, especially paratyphoid A, were very common at the Dardanelles during October and November, 1915, it is not unreasonable to suppose that in some instances the two diseases were superimposed. As previously mentioned, a number of patients contracted jaundice in the hospital. In some cases the jaundice may have supervened as a complication of paratyphoid, cholecystitis being a not uncommon sequela of this disease. Jaundice, however, is rare.

Another line of inquiry was undertaken at Major Hurst's suggestion, and with his help. Having with him an Einhorn's evacuator, Major Hurst persuaded patients to swallow it, and, when it had passed on into the duodenum, aspirated a few cubic centimetres of the duodenal contents, which were submitted to bacteriological examination forthwith. Duodenal samples from 8 cases of jaundice and from 4 normal individuals, including Major Hurst and myself, were examined; 0.02 c.cm. of the material was plated out upon MacConkey's bile salt agar, and also upon ordinary nutrient agar. Specimens of the different types of colonies were picked off, sown upon agar slopes, and subsequently investigated. The investigation of the cultures was carried out by my colleague, Sister F. S. Williams, for which, and for much other help with the

* This was first pointed out by Lieutenant-Colonel Willcox.

observations in this inquiry, I am deeply grateful. The results were as follows:

Three of the plates were sterile—two jaundice and one control.
Nine of the plates grew organisms varying from 10 to 300 per plate.
Five types of bacilli were isolated.
Four types of cocci were isolated.

Only one type of microbe was universally present, and accounted for the great majority of the colonies. This was a small, non-motile, Gram-negative bacillus, which fermented no sugar, and did not form indol. This bacillus was present in all six of the plates from jaundice cases which grew anything at all, and three of the controls. It is apparently a non-motile member of the *faecalis alcaligenes* group common in the upper part of the alimentary canal. On first culture some of these colonies were much denser than others, but on subculture this difference tended to disappear.

The remaining types of bacilli were also all Gram-negative. Their characteristics are given below. Two of these types occurred in Case V, one in Case II, and one in Case VIII.

TYPES OF MICROBE CULTIVATED FROM DUODENUM.

Bacilli.

Appearance of Colony.	Appearance of Bacillus.	Fermentation of Sugars.					Indol.
		Lactose.	Glucose.	Mannite.	Dulcite.	Saccharose.	
A. Translucent	Short non-motile	A	A	A	0	0	0
B. Translucent	Short motile	0	0	A	0	0	0
C. Dense white	Short motile	A G	A G	A G	0	A G	0
D. Dense white	Short motile	0	A	A	0	0	0

Cocci.

The cocci were all Gram-positive with a tendency to form diplococci; two types occurred in Case IV, one in Case II, and one in Case V.

Appearance of Colony.	Appearance of Microbe.	Fermentation of Sugars.					Indol.
		Lactose.	Glucose.	Mannite.	Dulcite.	Saccharose.	
A. Dense white ...	—	0	0	0	0	0	0
B. Small glistening	—	0	A	0	0	0	0
C. White	—	0	A	0	0	A	0
D. Large yellowish	—	A	A	A	0	A	0

The only organism showing any general association with jaundice was the bacillus of the *faecalis alcaligenes* group and that was equally abundant in the controls. The other microbes were distributed haphazard, so that the results lend no support to the view that the jaundice is due to a microbial infection of the duodenum extending up the bile ducts.

MORBID ANATOMY.

As mentioned above, jaundice at Gallipoli was rarely fatal. Three cases died in No. 3 Australian General Hospital, in whom jaundice was still present at the time of death. In two of these the cause of death was cardiac syncope occurring some weeks after the onset of the illness, in the other jaundice supervened during an attack of paratyphoid B fever. *Post-mortem* examinations were made upon these cases by my colleague Major Upjohn, but as in two patients death occurred during convalescence, and in the case of the third the jaundice might have been a complication of his paratyphoid fever, one cannot expect to derive therefrom much information as to the essential pathology of the disease.

The following is a brief epitome of the notes made by Major Upjohn at the autopsies.

CASE I.

A young Maori admitted October 3rd, 1915, with fever, diarrhoea, abdominal pain, and vomiting. Symptoms maintained until October 10th, 1915, when he became delirious and violent, and died on October 11th. Slight jaundice developed a few days before death.

Post mortem: Heart and lungs normal; spleen enlarged. Liver enlarged, yellow, tough; excess of fibrous stroma. Gall bladder full of bile, which could, however, be slowly emptied into the duodenum by slight pressure. Small intestine injected, especially Peyer's patches in lower portion, no ulceration. Brain normal. *B. paratyphosus* B was recovered from the spleen and gall bladder.

CASE II.

Pte. C., aged 41, admitted October 25th, 1915, with slight rise of temperature, pain and tenderness over liver, jaundice, and great lassitude. On November 7th he was convalescing slowly, still weak and breathless. On November 21st he died suddenly during slight exertion.

Post mortem: Mildly jaundiced. Heart dilated, flabby, muscle light in colour. Liver usual size and consistency; olive brown in colour, gall bladder empty. Spleen normal size and appearance. Intestines normal. Spleen and bile sterile.

CASE III.

Pte. McP., aged 35, suffered from jaundice some weeks previously. Admitted from a convalescent dépôt, where he had been taken suddenly ill with rapid pulse and breathlessness, and pain in right hypochondrium. He died four hours after admission.

Post mortem: Heart dilated and flabby, muscle pale. Liver large, greenish, friable; gall bladder contained a small amount of bile. Spleen enlarged, soft. Kidneys pale, enlarged, and friable. Bile and spleen sterile.

Morbid Histology of the Liver.

The histological changes in the liver of both the cases which died some weeks after the onset of the jaundice attack were similar. Sections stained with logwood and viewed with the naked eye or a hand lens presented a marbled appearance, the outer portion of the lobules being stained, the inner colourless. Small deeply-staining areas where compensatory hypertrophy of liver tissue had occurred were scattered throughout the sections.

In each portal area there was small celled infiltration, with young fibrous tissue, and large cells full of pigment granules. The epithelium cells of the small bile ducts were proliferated, and many of the ducts appeared not to be patent. Deposits of the same pigment granules existed between the cells.

The outer half of the liver cells of the lobule appeared normal, but the inner half were more or less damaged. The cells adjacent to the intralobular veins were necrosed and indistinguishable as liver cells; more peripherally they were vacuolated. They did not contain fat. Amongst the degenerated cells were a number containing pigment granules. The distribution of this pathological change was not uniform, some groups of lobules being more severely affected than others. There was no dilatation of the blood capillaries. No bacteria were seen.

Small portions of the liver of both patients were treated by Levaditi's silver method for demonstrating spirochaetes. In neither case was there any suggestion of their presence.

The gist of the above results was communicated at the discussion on jaundice at the Anzac Medical Association, Cairo, on February 6th, 1916. At that time it did not seem worth while putting them on record, as I expected to encounter the disease again in Egypt the next autumn, and to be able to carry out experiments on animals. The disease did not, however, reappear among troops in epidemic form during 1916, so that I had no chance of completing the inquiry.

My object in recording them at this juncture is two-fold. First, the information may direct future investigators along more fruitful lines of inquiry; and secondly, because in the meantime conclusions regarding the etiology and pathology of the disease have been published which seem to be open to question.

MM. Sarrailhé and Clunet (1916), the pathologists to the French force at Cape Helles, conclude that the epidemic jaundice at Gallipoli was merely a manifestation of paratyphoid A fever. These gentlemen were in the habit of making blood cultures of suspected cases of enteric, and up to the end of August they recovered only *B. paratyphosus* B and *B. typhosus*. At this time they noticed a clinical modification of the (enterica) epidemic. Cases of gastric derangement with fever became less numerous and less severe, many were accompanied by "extension to the biliary passages," and numerous cases of jaundice occurred. Coincident with this modification in clinical type the

nature of the microbes isolated by blood culture changed. The organisms they now recovered corresponded in general characters to paratyphoid bacilli, but would not agglutinate with either their paratyphoid A or paratyphoid B serums from the Pasteur Institute. They provisionally regarded it as a new type, *B. paratyphosus* "D" (= Dardanelles). They state that from nearly all their cases of jaundice, and from those of "gastric derangement with fever" during the jaundice epidemic they found no longer *B. typhosus* and *B. paratyphosus* B, but this atypical variety.

In a later paper (1916) the authors report the result of the examination of ninety-four of the aberrant strains at the Pasteur Institute. Eighty-four strains were declared to be *B. paratyphosus* A, six *B. paratyphosus* B, and four *B. typhosus*. However, MM. Sarrailhé and Clunet see no reason to modify their opinion that "camp jaundice is merely a hepatic manifestation of the paratyphoid epidemic."

The main epidemiological features described by MM. Sarrailhé and Clunet as occurring in the French lines were repeated at Lemnos, but the same close relationship between jaundice and paratyphoid A was not observed either clinically or in the bacteriological laboratories.

Captain Archibald and his colleagues (1916) at Mudros East found that in September and October the incidence of paratyphoid B steadily rose and was the prevailing type, but about the middle of November the number of cases of paratyphoid A shot up, while that of paratyphoid B rapidly fell, the typhoid cases, as before, remaining low. Our experience at No. 3 Australian General Hospital at Mudros West indicates a more gradual and later change of type. During October, November, and December the number of bacteriologically diagnosed cases of paratyphoid A was 83, 76, and 45; of paratyphoid B 34, 40, and 18 respectively, but after the third week in December only paratyphoid A was met with. Jaundice was first observed in September. In October the number of cases admitted rapidly increased. During the later weeks of October and early weeks of November it was extremely common amongst troops and hospital personnel stationed at Mudros, and numbers of patients contracted the disease in the hospital.

Judged by admissions to No. 3 Australian General Hospital, the epidemic of paratyphoid A was in full swing when jaundice appeared. Some patients suffering from the former undoubtedly had jaundice, but the same was the case with patients suffering from typhoid, paratyphoid B, and dysentery, and the impression made upon us was that we were in the presence of two widespread epidemics, one of which was occasionally superimposed upon the other. The same conclusion was arrived at by Lieutenant Campbell (1916) from his experience at Cape Helles.

The experience of MM. Sarrailhé and Clunet was evidently different from ours, and it is difficult to disprove their contention. I can only point out that the prevalent type of jaundice at No. 3 Australian General Hospital, which is described at the commencement of this paper, was not accompanied by a continuous fever, and that paratyphoid bacilli were not recovered from such cases, nor did their serums agglutinate *B. paratyphosus* A or B, although the strains of both of these organisms which we employed were readily clumped by the serums of patients suffering from these diseases. Instances such as they record did occur, but can, I submit, be more reasonably interpreted as double infections. Paratyphoid fever has been abundantly studied in different parts of the world since its first differentiation by Achard and Bensaude in 1896, but jaundice is surely a rare symptom, for I cannot discover a single recorded instance of its occurrence in the literature.

Another account of the disease given by Major Hurst (1916) seems to me to accept too readily one possible view of its pathology. According to this observer the jaundice is caused by an extension of a catarrhal process from the duodenum, and the enlargement of the liver "must be due to a general infection secondary to that of the alimentary canal." I am not clear exactly what Major Hurst had in mind in framing the first part of the sentence, but the latter portion is unmistakable. However, Major Hurst is evidently not entirely satisfied with this view, for on p. 106 he admits that it is uncertain whether the primary infection is duodenal or through the blood.

Willcox (1916) also inclines to the opinion that the epidemic jaundice of campaigns starts as a gastro-intestinal infection, and that cholangitis follows from spread from the duodenum. This view leads both Willcox and Hurst to the conclusion that infection is conveyed by the alimentary tract.

It is with trepidation that I enter the arena against Lieutenant-Colonel Willcox and Major Hurst when the combat is over matters largely clinical, but it seems to me unfortunate that, in the absence of definite knowledge of the etiology of the disease, these gentlemen should thus light-heartedly throw the weight of their authority in favour of one possible interpretation of its pathology and method of spread. I submit that the picture presented by the infectious jaundice at Gallipoli, and the morbid anatomy, meagre as it is, are more consistent with the view that we are dealing with a hepatitis following a systemic infection than with that of a catarrhal jaundice from plugging of the bile ducts from extension of an inflammatory process from the duodenum.

The reasons which influence me in arriving at this conclusion are briefly:

1. The illness is ushered in by a febrile attack like influenza, but usually of shorter duration.
2. Jaundice does not occur for some days, and is preceded by swelling and tenderness of the liver.
3. Bile is rarely completely prevented from entering the intestine.
4. The spleen is often enlarged.
5. Albuminuria is not uncommon.
6. Notwithstanding the comparatively slight initial illness the existence of a serious toxaemia is indicated by lassitude, which endures for some weeks, and evidence of myocardial poisoning.
7. Histological evidence of necrosis of liver cells and inflammation around the portal areas.

SUMMARY AND CONCLUSIONS.

1. No parasites were discovered in blood films taken during the disease.
2. Blood cultures were sterile unless the jaundice supervened during an attack of typhoid or paratyphoid.
3. The observations made at No. 3 Australian General Hospital at Mudros do not support the conclusion of MM. Sarrailhé and Clunet at Cape Helles that the jaundice was merely a manifestation of paratyphoid fever.
4. Bacteriological analysis of duodenal contents removed from patients affords no justification for the view that the jaundice was due to a bacterial infection spreading up the bile ducts.
5. The livers of two patients who succumbed during the convalescent stage of jaundice showed microscopical evidence of hepatitis with necrosis of liver cells.
6. It is pointed out that the infectious jaundice of Gallipoli, although much milder, presents analogies to the severer form spirochaetosis icterohaemorrhagica, and it is contended that the symptomatology and morbid histology are consistent with the view that it is primarily a systemic infection.

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