Attempts have been made to explain Hill's sign on the basis of flow phenomena. Friedberg (1956) writes: "Since the femoral artery is in a direct line with the aortic stream, while the brachial issues from the aorta at a right angle, the femoral artery receives not only the pressure head but also the velocity head of the aortic stream . . . in aortic insufficiency the velocity head is considerable, there is a pronounced excess of pressure on the femoral as compared with the brachial artery." Sodeman (1961) offers essentially the same hypothesis to explain differences in arm and leg systolic and diastolic pressures thought to exist in normals. He states that leg systolic pressure is commonly 20–30 mm. Hg higher and leg diastolic pressure is 10 mm. Hg or more higher than arm pressure. Such arm-leg pressure differences cannot be confirmed by intra-arterial measurements; therefore explanations of this sort must be viewed with scepticism.

There is also reason to question seriously the validity of results derived from cuff measurements correlating arm and leg pressure differences to severity of aortic insufficiency (Frank *et al.*, 1964), degree of cardiac decompensation in aortic insufficiency (Pont *et al.*, 1953), or distinction of functional from organic aortic insufficiency (Loewenberg, 1940). Intra-arterial studies do not confirm any of these impressions, and suggest that virtually no differences in arm and leg blood-pressures exist in supine persons with aortic insufficiency or in normal controls.

A clinical sign based upon indirect cuff blood-pressure measurements should withstand the comparison test of direct measurement. In this study such discrepancies between direct and indirect pressures were encountered that the leg cuff was finally abandoned. A cuff that fits poorly or is too narrow can give pressure readings that are too high. This is especially true when using the leg cuff, where variations in the consistency of the large fat-and-muscle mass create a need for variable amounts of pressure to compress a relatively deep artery of large calibre (Trout *et al.*, 1956). Most available leg cuffs fit the conical shape of the thigh poorly, and contribute to artifact by actually compressing only a narrow band of tissue. In addition, auscultation or palpation of leg arteries is often difficult. All of the various factors mentioned probably contribute to the inaccuracy of indirect leg-pressure measurement.

The problem of when to use a cuff on the lower limbs is a practical one. Existing leg cuffs are inaccurate. Perhaps their use should be abandoned until a better cuff is designed,

in order to avoid being misled. Palpation of the femoral artery affords a quick and easy appraisal of the situation, and can give valuable clues to the existence of aortic coarctation or aorto-iliac stenosis. When doubt exists, direct arterial puncture can give accurate data safely and easily. If strain gauges and a multichannel recorder are not readily available for intra-arterial measurements, an inexpensive device such as that described by de Bono (1963) can be employed.

Summary

Disproportionate femoral systolic hypertension in aortic insufficiency (Hill's sign) is based upon values obtained by indirect cuff determinations made in the arms and legs. Direct arterial punctures, using strain gauges and a multichannel recorder, in 20 persons with aortic insufficiency compared with 50 controls failed to reveal the presence of this sign. As in the normal supine controls, blood-pressures in the arms and legs in aortic insufficiency were found to be virtually the same. Various explanations for Hill's sign were discussed and found to be inadequate. It is suggested that until a better leg cuff is devised diagnostic problems should be resolved by intra-arterial punctures of the femoral arteries.

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Jaundice in Severe Infections

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"Many systemic infections produce structural and functional changes in the liver which occasionally are accompanied by jaundice. Fortunately, these are seldom of sufficient severity to alter the course of the underlying disease or to require special treatment. It is important to note, however, that unless their relationship to infection is recognized they may lead to serious diagnostic errors. Jaundice is particularly likely to be misleading, since it may be misinterpreted as a sign of primary hepatic or biliary tract disease and thus divert attention from the underlying infection and lead to inappropriate treatment"

(Klatskin, 1963). Diagnostic errors of this kind are especially likely if the jaundice is "obstructive" in its biochemical pattern. We wish to report a group of five patients in whom the jaundice of severe infection showed many "obstructive" features. In four of them the nature of the infection was obscure when jaundice appeared, the patients presenting with fever of unknown origin.

Case 1

A Jamaican housewife aged 35 gave a history of generalized abdominal pain with fever for a month before admission. The pain began suddenly, was at first colicky in nature, and had radiated

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through to the back. For one week before admission she vomited frequently and had occasional diarrhoea. There was no relevant past or family history. At the time of admission she was apyrexial and deeply jaundiced. The abdomen was tender and without palpable viscera or masses. There were no abnormal signs in other systems. During the next six days she developed a fever up to 101° F. (38.3° C.) and a tender suprapubic mass. Laparotomy revealed a large right-sided tubo-ovarian abscess, which was drained. The liver, gall-bladder, and bile-ducts were normal, as was an operative cholangiogram. Liver biopsy was carried out. The patient recovered uneventfully, the jaundice disappeared, and she has since remained well.

The results of investigations are shown in the Table. Blood cultures were negative, but pus from the tubo-ovarian abscess gave a pure growth of *Streptococcus pyogenes*.

The liver biopsy was reported upon by Dr. J. S. Murrell. "The liver architecture is normal and there is no evidence of parenchymatous disease. Mild bile retention with some plugging of canaliculi is present in the peripheral part of the lobules. A slight increase in round cells is evident in the portal tracts. There is no evidence of bile retention or of bile-duct proliferation distal to the lobules—that is, in the portal tracts. These changes indicate a degree of intrahepatic biliary obstruction. Another feature is marked proliferation of Kupffer cells, and these are seen to contain iron pigment. These findings suggest past episodes of haemolysis." In relation to this last point, the blood showed no reticulocytosis throughout the illness and her haemoglobin was of normal adult type.

Case 2

An English housewife and part-time machinist aged 54 was admitted after 24 hours' colicky abdominal pain which had radiated to the right side. She had vomited frequently and also complained of frequency of micturition. For many years she had suffered epigastric discomfort after food, often waking at night. There was slight tenderness in the right iliac fossa on examination and a temperature of 102° F. (38.9° C.) but no other abnormal signs. Twenty-four hours later the temperature has risen to 105° F. (40.6° C.) and there was no abdominal tenderness. Five days after admission she became jaundiced, with a just palpable liver, and for a period of one day was tender in the epigastrium. For three weeks she remained pyrexial, with rigors, jaundice, and an enlarged non-tender liver. Intensive investigations, including intravenous cholangiography and gastrograffin series, did not elucidate the diagnosis. The results of relevant investigations are shown in the Table. Empirical treatment with chloramphenicol and novobiocin was ineffective. Nearly a month after admission a typical appendix abscess developed, this diagnosis being sustained at operation when the appendix was removed and the abscess drained. Blood cultures initiated during the pre-operative period grew *Bacteroides*. The post-operative course was prolonged, residual

intra-abdominal abscesses requiring surgical drainage on four occasions. After a long convalescence she eventually recovered completely.

Case 3

An Indian businessman aged 54 was returning by air from a visit to the U.S.A., when he felt unwell. Shortly after arriving at his home in London he had a rigor and was admitted to hospital. On admission his temperature was 103.8° F. (39.9° C.) without localizing symptoms and there were no abnormal physical signs. Subsequently he had a remittent fever up to 104° F. (40° C.). Intensive investigation failed to elucidate the diagnosis. One week after admission he became jaundiced, the abdomen was distended without tenderness, and the presence of ascites was suspected. Results of relevant investigations are shown in the Table. Penicillin and streptomycin therapy was started, but next day his condition deteriorated rapidly, with peripheral circulatory failure, and he died.

Necropsy revealed a right-sided subphrenic abscess and small bilateral perinephric abscesses. There was no demonstrable hepatic or biliary disease.

Blood cultures initiated before death gave a growth of *Str. pyogenes*, the same organism being recovered from the perinephric abscesses.

Case 4

An unmarried English nursing sister aged 45 went on holiday to Egypt. Two weeks after her return she became ill with generalized aching pains, severe backache, and vomiting. She improved transiently, but after a remission lasting about one week the same symptoms returned in more severe form accompanied by high fever. Three days after the onset of the fever she developed severe diarrhoea, and two days later was admitted to hospital. There was no relevant past or family history.

On examination her temperature was 102.7° F. (39.3° C.), basal rales were present in both lungs, and the liver was enlarged 1½ in. (4 cm.) below the right costal margin. Initially her temperature settled, but she remained ill and became jaundiced. Five days after admission she deteriorated, developing meningism and evidence of incipient circulatory failure. Intensive investigation had failed to arrive at a diagnosis, the only positive findings being patchy basal shadowing on chest x-ray examination and a trace of protein and slight excess of white and red cells in a clean specimen of urine which grew a *Proteus* species on culture. Blood cultures began shortly after admission were subsequently positive for *Proteus*, and she was treated with streptomycin, chloramphenicol, hydrocortisone, and fluids by intravenous infusion. Recovery was complete. Follow-up bacteriological examination of the urine was negative and intravenous pyelography failed to reveal a lesion in the urinary tract. The biochemical features of the jaundice are recorded in the Table.

Results of Investigations

Case No.	Urine		Blood										Site of Infection	Blood Culture	Abscess Culture
	Bilirubin	Urobilinogen	Total Bilirubin (mg./100 ml.)	Conjugated Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K.A. units/100 ml.)	S.G. O.T. (units/ml.)	S.G. P.T. (units/ml.)	Thymol Turbidity (units)	Urea (mg./100 ml.)	Amylase (units/100 ml.)	Total W.B.C./c.mm.	Neutrophils/c.mm.			
1	+	+	23.2 12.2* 1.8†	15.2 8.1*	11	24	30	2.8	< 200	< 200	28,000 42,000	26,000 38,500	Tubo-ovarian abscess	Negative	<i>Str. pyogenes</i>
2	+	—	3.5		11	48	23	Not done	57, 42	210	11,300 (on admission) 5,000 (2 days after admission) 23,000 (1 day pre-op)	9,800 4,500	Appendix abscess	<i>Bacteroides</i>	Various
3	+	—	5.4		17	42	16	1.5	180 (one day before death)		20,400 26,400	18,400 25,000	Subphrenic and perinephric abscesses	<i>Str. pyogenes</i>	<i>Str. pyogenes</i>
4	+	—	3.1		22	88	34	4.2	70, 30		15,200 23,000	13,800 20,700	Acute pyelonephritis	<i>Proteus</i>	<i>Proteus</i> (urine)
5	+	—	10.4	7.6	26	64	34	1.4			16,400	13,300	Pelvic abscess	Not done	<i>E. coli</i>

* One day post-operatively. † 11 days post-operatively.

Case 5

A man of 43 was admitted with the syndrome of acute appendicitis of 24 hours' duration. There was no relevant past medical history. Shortly after his admission an acutely inflamed appendix was removed without incident. During the post-operative period he developed a pelvic abscess, and six days after operation the urine was noted to be bile-stained and the patient slightly jaundiced. A swab of the discharge from the wound grew *Escherichia coli*, a *Proteus* species, and *Clostridium welchii* on culture. The jaundice deepened and persisted in all for some 10 days. A residual abscess in the left iliac fossa required drainage four weeks after the appendicectomy. The patient left hospital well six weeks after admission. The biochemical findings relevant to the jaundice are shown in the Table.

Discussion

In addition to the biochemical pattern of their jaundice, these patients presented several features in common. They all suffered from bacterial infections, with a severe general illness accompanied by high fever and neutrophilia. Two cases had their origin in appendicitis, one patient had a tubo-ovarian abscess, one had perinephric and subphrenic abscesses in association with streptococcal septicaemia, and in the remaining patient the only identifiable focus was a urinary infection. The bacteria involved were *Str. pyogenes* in two patients, one of whom had a positive blood culture, *Bacteroides* in one with positive blood culture, *Proteus* in one with positive blood culture, and mixed flora including *E. coli* in one (blood culture not done). Only in Case 5 did jaundice develop at a time when the diagnosis of the causal infection was already established; Case 1 presented with fever of uncertain origin accompanied by jaundice from the beginning, while Cases 2, 3, and 4 presented with fever only, jaundice developing several days after admission.

Jaundice can be due to excessive haemolysis, defective uptake of bilirubin by the liver, defective conjugation by glucuronyl transferase, or defective excretion of conjugated bilirubin, which may be intrahepatic or extrahepatic in origin. The biochemical picture in these cases was one of defective excretion of conjugated bilirubin—that is, that of "obstructive jaundice." There was no evidence of haemolysis. The urine contained bilirubin but no urobilinogen except on one occasion in Case 1, when both bilirubin and urobilinogen were present. The alanine transaminase and the thymol turbidity were normal, and the aspartate transaminase was normal or slightly or moderately raised. The serum alkaline phosphatase values were normal or only slightly raised, but this finding is not incompatible with a diagnosis of cholestatic jaundice. For example, the alkaline phosphatase is not increased at the onset of the obstructive phase of infective hepatitis, and it is not increased in steroid jaundice (Foss and Simpson, 1959). Extra-hepatic biliary obstruction was excluded by operation or necropsy in the first three cases, and there was no clinical reason to suspect it in the other two. None of the patients had received a hepatotoxic drug; in particular, no drug known to cause intrahepatic cholestasis had been administered to any of them. The evidence thus suggests that in these patients severe sepsis was accompanied by intrahepatic cholestasis.

Jaundice in association with severe infection has long been recognized. In some infections, such as *Cl. welchii* septicaemia, the jaundice is haemolytic in nature, while in others a mixed biochemical pattern is found. A predominantly cholestatic

pattern has been reported in neonates suffering from severe *E. coli* infections, often with acute pyelonephritis (Bernstein and Brown, 1962; Hargreaves, 1964). In the cases reported by Hargreaves there was no evidence of extrahepatic biliary obstruction and the liver was normal at necropsy. Jaundice has also been recorded in association with *Str. pyogenes* infection in scarlet fever (Fishbein, 1962), but in these patients the thymol turbidity was raised. Cholestatic jaundice as an association of sepsis in adults does not seem to be generally recognized. If a patient with fever of unknown origin develops jaundice which is "obstructive" in type a diagnosis of cholangitis secondary to extrahepatic biliary obstruction is apt to be made. The cases described show that such a diagnosis may be wrong. Case 1 provides the most vivid example; this patient became very deeply jaundiced; the jaundice was "obstructive" in pattern, but laparotomy and operative cholangiography showed the bile-ducts and gall-bladder to be completely normal.

The mechanisms responsible for jaundice in these patients are uncertain. A gross condition, such as liver abscesses or portal pylephlebitis, was excluded by the operative or necropsy findings in Cases 1, 2, and 3, and was highly unlikely on clinical grounds in Case 4. Case 5 might have suffered an episode of portal pylephlebitis. The liver biopsy in Case 1 did show bile retention, but whether these histological changes are responsible for the cholestatic jaundice or are themselves secondary to disturbances at cellular level is uncertain. The excretory path of conjugated bilirubin has not been fully determined but is known to be susceptible to various factors, as is the conjugating mechanism. The excretion of conjugated bilirubin is reduced in newborn guinea-pigs (Schenker, 1963); this may be the cause of an apparently obstructive jaundice in haemolytic diseases of the newborn (Oppé and Valaes, 1959). Certain drugs—for example, bunamiodyl (Billing, Maggiore, and Cartter, 1963) and novobiocin (Hargreaves and Lathe, 1963)—depress the excretion of conjugated bilirubin, probably by acting on the excretory mechanism. It is possible that the excretory mechanism is susceptible to a number of bacterial toxins, which may thus be capable of producing intrahepatic cholestasis.

Summary

Five patients who developed jaundice of cholestatic type in the course of severe bacterial infections are described.

If this type of jaundice occurs during an infection presenting as a fever of uncertain cause, it is tempting to conclude that the patient has biliary obstruction, and this may not be so.

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