flow to the liver is an important factor causing alteration in the B.S.P. test in cases of acute myocardial infarction.

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A SYNDROME DUE TO THE BACTERIAL COLONIZATION OF SPITZ-HOLTER VALVES

A REVIEW OF FIVE CASES

BY

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The treatment of hydrocephalus has been advanced by the introduction of non-return valves that shunt the cerebrospinal fluid (C.S.F.) from the lateral ventricle of the brain to the superior vena cava. At this hospital the Spitz-Holter valve has been used, details of which are shown in Fig. 1. The complications of thrombosis and sepsis are each recognized to occur in approximately 10% of cases. Over 120 cases have been treated at this hospital (Cohen, 1961, unpublished), and in the group complicated by sepsis we have differentiated a new syndrome—persistent bacteraemia—which is characterized by persistent pyrexia, progressive anaemia, splenomegaly, and positive blood cultures. Previously these cases have been included with the septicaemias, and the attempted eradication of the infection by the use of systemic and intraventricular methicillin has been reported (Callaghan *et al.*, 1961). Five case histories of this syndrome and one of septicaemia are recorded.

Case 1

A male infant born on January 1, 1959, had an occipital encephalocele excised on February 24 and subsequently developed progressive hydrocephalus. A Spitz-Holter valve was inserted on April 4, but needed two revision operations before effective shunting was obtained. (The last operation was on August 2.)

In October the infant began to run a continuous temperature—range 99–102° F. (37.2–38.9° C.)—and on investigation was found to have a urinary infection due to *Proteus vulgaris*. This partially responded to sulphadiazine and

chloramphenicol (125 mg. q.d.s.), but during the next three months the infant became anaemic (Hb 47%) and needed two blood transfusions to correct this anaemia. As the symptoms persisted further investigations were carried out and *Pr. vulgaris* was then cultured from the blood. At this stage there was no evidence of infection around the valve. On December 12 the infant was put on kanamycin (100 mg. b.d.), which temporarily reduced the pyrexia, but still *Pr. vulgaris* was repeatedly cultured from the blood (Fig. 2). The C.S.F. obtained by direct ventricular puncture was sterile on two occasions. On January 7, 1960, the catheter was removed from the internal jugular vein and the C.S.F. allowed to drain externally into a container. This C.S.F. was found to be clear and colourless, contained 3 leucocytes per c.mm., yet culture produced a profuse growth of *Pr. vulgaris*. After diverting this infected C.S.F. from the blood-stream the temperature returned to normal and urine and blood cultures remained sterile from then on (Fig. 2). Thus it appeared that bacteraemia had been controlled.

On February 2 (almost one year after its insertion) the valve was removed and *Pr. vulgaris* isolated from all the component parts, indicating colonization of the valve by this organism. As the hydrocephalus was still progressive, ventricular drainage was instituted and C.S.F. draining externally by this method was sterile, confirming that it was the removed colonized valve that had been the source of the bacteraemia. A second valve was inserted on March 31, and this functioned satisfactorily. The child was discharged, but on June 13 he died because of an episode of raised intracranial pressure (16 months after the original operation).

At necropsy there was no evidence of infection, thrombosis, or embolism, but an enlarged spleen was found. This weighed 100 g. and showed marked lymphoid hyperplasia.

Case 2

A male infant born on March 8, 1960, had haemorrhagic disease of the newborn complicated by intraventricular haemorrhage. This led to progressive hydrocephalus and ventriculography demonstrated a basal cistern block. A Spitz-Holter valve was inserted on May 19.

Post-operatively his temperature slowly rose to 101° F. (38.3° C.) and then fluctuated between 97 and 99.5° F. (36.1 and 37.5° C.). On the tenth post-operative day the spleen became palpable and during the next three months enlarged to 2 in. (5 cm.) below the costal margin. Anaemia then slowly developed (Hb 55%) over the next six months, necessitating one blood transfusion. Coagulase-negative staphylococci were cultured from the blood on 15 occasions during the nine months that the bacteraemia was in existence. During this same period coagulase-positive staphylococci were isolated on three occasions, but this was not the organism primarily isolated (see Table).

FIG. 1.—Component parts of the Spitz-Holter valve: a proximal ventricular catheter (A); the valve (X) that shunts the C.S.F. from the lateral ventricle of the brain to the superior vena cava or right atrium via the internal jugular catheter (B). These parts are held together and in position by the black silk sutures (1 and 2).

In spite of intensive and prolonged attempts to eradicate the infection (including penicillin and sulphadiazine, tetracycline, and systemic methicillin for 150 days) the bacteraemia persisted. On March 10 the catheter was removed from the internal jugular vein and C.S.F. allowed to drain externally. This C.S.F. was clear and colourless, contained 9 leucocytes per c.mm., and culture produced a heavy growth of coagulase-negative staphylococci. At the same time C.S.F. obtained by direct ventricular puncture was clear and colourless, contained no cells, and was sterile. The spleen became smaller and after 10 days was no longer palpable, the blood cultures were sterile, and the temperature had returned to normal. The Spitz-Holter valve was removed on April 13, 1961 (11 months after its insertion), and coagulase-negative staphylococci were cultured from all the component parts.

Case 3

A male infant born on June 12, 1959, was noticed to have craniosynostosis. This was later complicated by progressive internal hydrocephalus which was confirmed by ventriculography. A Spitz-Holter valve was inserted on March 10, 1960.

The post-operative period was covered by antibiotics (penicillin and sulphadiazine for 10 days and tetracycline for 10 days), but the temperature rose to 102° F. (38.9° C.) and remained elevated—range 99–102° F. (37.2–38.9° C.). The infant then became anaemic (Hb 44%) and during the next six months needed seven blood transfusions to correct this progressive anaemia. The spleen then enlarged, and by the 12th post-operative week had reached 2 in. (5 cm.) below the costal margin. Coagulase-negative staphylococci were cultured from the blood on 28 occasions during the year that the bacteraemia was in existence, whereas coagulase-positive staphylococci were cultured only three times during the same period (see Table). The patient was given a 50-day course of methicillin by intramuscular and intraventricular injection with marked clinical improvement. The temperature returned to normal, the spleen became impalpable, and finally the blood cultures were sterile. When antibiotic treatment was discontinued he relapsed—the pyrexia recurred, he became anaemic again, and his spleen rapidly enlarged to 4 in. (10 cm.) below the costal margin. A bone-marrow puncture on October 12 showed a “cellular hyperplastic marrow with a shift to the left in the myeloid series.”

On October 27 the spleen was removed as it was thought to be the site of abscess formation and by virtue of its size to be causing features ascribed to “hypersplenism.” The spleen weighed 150 g. No abscesses were present, but a culture of the spleen grew coagulase-negative staphylococci. Histological examination revealed “considerable quantities of haemosiderin in the pulp and germ centres of the follicles, evidence of an actively progressive haemolytic process.” The splenectomy had had the desired effect of reducing the haemolysis, as he needed only one blood transfusion in the five months following this operation. As blood cultures still grew coagulase-negative staphylococci and the temperature remained elevated, the internal jugular catheter was exteriorized on March 14, 1961, and the C.S.F. allowed to drain externally. This was clear and colourless, contained 3 leucocytes per c.mm., yet culture grew coagulase-negative staphylococci, whereas C.S.F. obtained by direct ventricular puncture was sterile. The temperature then returned to normal and the blood cultures were sterile on two successive occasions.

The valve was removed on April 11 (13 months after its insertion); at operation there were no signs of infection around the valve, but on culture of all the component parts coagulase-negative staphylococci were grown, once again indicating colonization. As the hydrocephalus was still progressive a second valve was inserted on April 22, and the patient then progressed favourably and was discharged.

Case 4

A male infant born on December 12, 1959, developed progressive hydrocephalus after a meningitis due to *Escherichia coli*. Ventriculography demonstrated a basal cistern block. A Spitz-Holter valve was inserted on March 31, 1960, and post-operatively he developed a stitch abscess which cleared completely on local treatment.

Six weeks post-operatively the temperature began to rise—range 97–101° F. (36.1–38.3° C.)—and another abscess developed in the region of the upper end of the valve. This, too, healed on local treatment. The temperature, however, remained elevated and his spleen began to enlarge and was palpable 2 in. (5 cm.) below the costal margin. Coagulase-positive staphylococci were isolated from the blood on 10 occasions during the six months that the bacteraemia was in existence, and during the same period coagulase-negative staphylococci were isolated three times.

FIG. 2.—Case 1. Effects produced by the staged surgical procedure.

The patient then became anaemic (Hb 48%) and needed five blood transfusions during the next six months. Penicillin and sulphadiazine were then given, followed by chloramphenicol and oleandomycin. The temperature still remained elevated, so he too was put on a course of methicillin by intramuscular and intraventricular injection and then locally, but the bacteraemia persisted despite continuing methicillin for 110 days. On October 27 the valve was removed and coagulase-positive staphylococci were isolated from all the component parts. Since removal of the valve the fever has subsided, the spleen has been impalpable, and coagulase-positive staphylococci have not been cultured from the blood again.

Case 5

A female infant born on March 16, 1958, was noted to have progressive hydrocephalus at a few weeks of age. Ventriculography demonstrated a basal cistern block, and a Spitz-Holter valve was inserted on October 21.

Post-operatively the patient ran a temperature—range 98–101° F. (36.7–38.3° C.)—even though this period was covered by a course of penicillin and streptomycin. No cause for the temperature could be found, and blood cultures were sterile even though she was suspected of having a "bacteraemia." After a period of observation the temperature settled and she was discharged. Attendance at the follow-up clinics was very erratic, and 18 months later the patient was readmitted with a history of malaise, prolonged bouts of fever and several "blue attacks."

On examination the child was marasmic and pale, and her spleen was palpable 4 in. (10 cm.) below the costal margin. The temperature rose to 100° F. (37.8° C.) and the haemoglobin was 29%. Coagulase-negative staphylococci were isolated from the blood on 10 occasions after the bacteraemia had been proved, and during the same period coagulase-positive staphylococci were isolated twice. Once again attempts to control the bacteraemia by antibiotics failed (penicillin by intramuscular and intraventricular injection for 30 days, and methicillin by intramuscular and intraventricular injection for 50 days). The valve was removed on October 27, 1960, (two years after its insertion), and no signs of infection were seen at operation, although coagulase-negative staphylococci were cultured from all the component parts, once again indicating colonization by these organisms. After removal of the valve the child made a rapid recovery—the temperature and haemoglobin level remained normal, and blood cultures were repeatedly sterile. Fortunately, as in Case 4, the hydrocephalus had arrested.

Case of Septicaemia

In contrast with these five cases, the history of an infant who died of a fulminating septicaemia is recorded.

Case 6.—A premature male infant born on April 17, 1960, developed progressive hydrocephalus and had a Spitz-Holter valve inserted on July 28. The post-operative period was covered by a course of penicillin and sulphadiazine. The patient ran a temperature for three days, but this soon settled and he was discharged on the tenth day. Three days later he was readmitted in a critical condition. His temperature was 103° F. (39.4° C.) and a fluctuant swelling was found around the valve. He had signs of consolidation in the right upper lobe of the lung. Despite treatment he rapidly deteriorated and died the following day. At necropsy a large abscess was found around the valve, which appeared to be still functioning satisfactorily. There was adherent thrombus formation in the superior vena cava, and the lungs showed numerous areas of consolidation with early abscess formation and empyema. Coagulase-positive staphylococci were isolated from the lungs, pleura, spleen, and also from the blood taken just prior to his death.

Leucocytosis has not been a prominent feature in these cases, as more than 60% of the white-cell counts

performed were normal, and of those that were raised only one exceeded 20,000 white cells per c.mm. The platelets have appeared normal in all cases.

Clinical Manifestations

Case No.	Duration of Disease (Days)	Severity of Anaemia Indicated by		Spleen Size Below Costal Margin		Organisms Isolated (Frequency in parentheses)
		Lowest Hb %	No. of Blood Transfusions Over Six Months	in.	cm.	
1	120	47	4	0*		<i>Pr. vulgaris</i>
2	290	55	1	2	5	Coag.-neg. staph. (15) Coag.-pos. staph. (3)
3	360	44	7	4	10	Coag.-neg. staph. (28) Coag.-pos. staph. (3)
4	200	48	5	2	5	Coag.-pos. staph. (10) Coag.-neg. staph. (3)
5	730	29	6	4	10	Coag.-neg. staph. (10) Coag.-pos. staph. (2)
6	10	60	0	0		Coag.-pos. staph.

*In this patient the spleen was not noted to be enlarged during life but was so at necropsy.

Discussion

Sepsis in the scalp wound or contamination of the operation site may involve the component parts of the valve, and organisms will then be carried into the blood-stream by the flow of the C.S.F. The resulting condition depends to a large extent on the nature of the infecting organisms. If the organisms are of a relatively high degree of virulence (coagulase-positive staphylococci as in Case 6) then inflammation occurs around the valve and a septicaemia with embolic abscesses may ensue. If, however, the organisms are by comparison less virulent (*Pr. vulgaris* as in Case 1, coagulase-negative staphylococci as in Cases 2, 3, and 5) or are rendered so by antibiotics (coagulase-positive staphylococci as in Case 4), then obvious inflammation around the valve does not occur, but the organisms persist in the component parts, resulting in colonization. When this occurs in a functioning valve then sterile C.S.F. from the lateral ventricle is infected in its passage through the valve and is carried into the blood-stream, thereby causing the bacteraemia, which, when compared with the septicaemias, is mild and chronic. All these facts are borne out by the sequence of events in Case 1, which was the first where proof of the natural history of the syndrome was obtained.

This patient had all the signs of a persistent proteus bacteraemia. The valve was not clinically suspect as there was no inflammation around it and the C.S.F. obtained by direct ventricular puncture was sterile. The bacteraemia, however, was terminated by the exteriorization of the internal jugular catheter. In addition, the sterile C.S.F. from the lateral ventricle was persistently infected after passing through the valve (Fig. 2), thereby incriminating the valve. Final proof was obtained when the valve was removed, for, though there was no evidence of inflammation around the valve, the same organisms were cultured from all its component parts. Cases 2 and 3 behaved in a similar manner after the exteriorization procedure described, whereas in Cases 4 and 5 the bacteraemia was terminated by a one-stage removal of the valves. Therefore there exists the condition of colonization of the valve by these comparatively less virulent organisms, and if the valve is functioning it will give rise to a persistent bacteraemia.

The triad of persistent pyrexia, progressive anaemia, and splenomegaly can be explained by the continual contamination of the blood-stream by these organisms of relatively low virulence. This is in strong contrast with the history of the rapidly fatal septicaemia (Case 6) where the virulent coagulase-positive staphylococci produced an abscess around the valve and invaded the blood-stream, causing embolic abscesses in the lungs. Further support for the concept of persistent bacteraemia is that in none of the cases was there any evidence of embolic foci in lung, brain, kidney, bone-marrow, intestinal vessels, or skin.

The treatment of this condition has been described in a separate article (Callaghan *et al.*, 1961). Systemic and intraventricular methicillin did suppress the clinical signs, but relapse was immediate on discontinuing the drug. The only absolute cure was removal of the valve.

In the past few years much attention has been paid to the role of the staphylococcus in human disease. Generally speaking, the coagulase-positive strains have been clearly associated as human pathogens, whereas the coagulase-negative strains were usually regarded as contaminants when obtained in pure culture from the blood. Recently, however, evidence has accumulated to prove that the negative strains cannot always be so regarded (Fleming and Seal, 1955; *Lancet*, 1956, 1958; Smith *et al.*, 1958). The report of coagulase-negative staphylococcal endocarditis after mitral valvotomy has demonstrated the pathogenicity of this organism (Resnekov, 1959), while the natural history of the syndrome described here adds further evidence to this concept. Thus coagulase-negative staphylococci were repeatedly cultured from the blood of patients with the syndrome. After exteriorization of the internal jugular catheter the signs and symptoms all disappeared, the blood cultures became sterile, yet the C.S.F. draining externally still contained the coagulase-negative staphylococci. Finally, culture of the component parts of the valve after removal produced a pure growth of the coagulase-negative staphylococci.

The cases in this series all exhibited mixed infections with coagulase-negative and coagulase-positive staphylococci (see Table). In Cases 2, 3, and 5 the negative strain was the dominant and was cultured first in all three cases, whereas the positive strain was only occasionally cultured. In Case 4 the coagulase-positive strain was the dominant and was repeatedly cultured before the negative strain was isolated. The fact that mixed staphylococcal infections can occur was also noted by Resnekov (1959). He postulated that both organisms were present initially and that the coagulase-negative strains persisted because they were more resistant to antibiotic treatment. In three cases in this series, however, the coagulase-negative staphylococci were the first isolated, so that the full significance of mixed infection remains uncertain.

Summary

A new syndrome—persistent bacteraemia—occurring in cases of hydrocephalus treated by the insertion of a Spitz-Holter valve is described. It is due to colonization of the valve by organisms of relatively low virulence, and is characterized by persistent pyrexia, progressive anaemia, splenomegaly, and repeatedly positive blood cultures.

The coagulase-negative staphylococcus was the causal organism in three of the cases.

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PARAESTHESIA OF THE HAND IN PREGNANCY

BY

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Interest in paraesthesia of the hand during pregnancy has increased in recent years, probably as a result of the recognition of the carpal-tunnel syndrome. Wilkinson (1960) has produced some evidence that during pregnancy compression of the median nerve in the carpal tunnel is due to excessive fluid retention, and McCallum (1959) and Wood (1959) have successfully treated this condition with oral diuretics.

An investigation has been made into the cause of sensory disturbances in the hand during pregnancy and their relationship to excessive fluid retention. Twenty-three patients who attended the antenatal clinics of Queen Charlotte's Hospital during 1959 and 1960 and who complained of symptoms in the hand were selected for the study. Four patients with cramps in the fingers alone were excluded from the series.

Clinical Findings

The time of onset of symptoms varied from the 20th to the 38th week of pregnancy, and in two patients with the carpal-tunnel syndrome the symptoms began in the puerperium. Pain, numbness, and tingling were the most frequent symptoms, and their most common site corresponded with the distribution of the sensory branches of the median nerve (Table I).

Site	No. of Patients
Median-nerve distribution	12
Four fingers ± thumb	10
Inside of forearm and little finger	1

A diagnosis of the carpal-tunnel syndrome was made in 12 patients; the symptoms involved the sensory distribution of the median nerve to the hand and fingers in all cases, and pain was referred to the forearm in seven of them. Only 2 of the 12 patients had symptoms relating to all the branches of the median nerve in the hand. Sensation in the fingers was diminished in five patients and weakness of the hand was present in two. Wasting of the thenar eminence was detected in one patient.

Ten patients had symptoms in the four fingers of one or both hands, the thumb also being affected in eight