A minority of those not using oral contraception may not have been sufficiently gifted to employ such medication without difficulty, but no marked differences were found in median intelligence scores between the two groups. The possibility that the group of women who received oral contraceptives during the post-partum period chose this method just because they, to a greater extent than the others, had experienced increased psychiatric symptoms during the *early* post-partum period is judged to be unlikely. The only factor which seems able to account for the differences found in psychiatric symptoms, especially neurasthenic and depressive ones, and in weight gain, is that one of the groups used oral contraceptives while the other did not. Unfortunately, the material is not sufficiently large to enable a closer analysis to be made *within* the oral contraception group of what further factors lead to an impairment in some women. No increase of anxiety-tension symptoms was found in the material, but this does not necessarily imply that such symptoms did not increase in certain cases. On the contrary, it is possible that such an increase occurred but was balanced out by a group of women who had anxiety symptoms before medication which decreased owing to the greater security provided by the contraceptive.

The results obtained suggest that there is a causal connexion between use of oral contraceptives and an increase of psychiatric symptoms in a number of women. Since the pattern of symptoms is selective, comprising mainly those of a neurasthenic or depressive type, and since no differences in total psychiatric morbidity existed in the material before or during pregnancy, the side-effects found may to a large extent be ascribed to hormonal factors. The results of this investigation cover only the first four months of medication. We are unable to judge whether or not the observed changes persist over a longer period of treatment. The results from other studies (Nilsson *et al.*, 1967; Nilsson and Sölvell, 1967) do, however, suggest that psychiatric symptoms occur primarily in the initial

stages of medication. It is difficult to explain why the frequency of side-effects seems to decrease with increasing observation time. One important factor is probably that a large number of women who experience such symptoms discontinue treatment at an early stage and have therefore dropped out of later investigations.

Summary

In a prospective psychiatric and psychological investigation of 165 women during pregnancy and the post-partum period it has been possible to compare 54 women who were prescribed oral contraceptives during the post-partum period with 104 women who used other contraceptive methods. There were no differences between the two groups in respect of psychiatric symptoms and psychological or social factors before medication—that is, before and during pregnancy. During the post-partum period a significantly higher frequency of psychiatric symptoms was found in the oral contraceptive group as regards both the total number of psychiatric symptoms and individual symptoms of a neurasthenic and depressive nature. These side-effects may be causally related to the tablet medication and can presumably be ascribed to hormonal factors.

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REFERENCES

- Hauser, G. A., and Schubiger, V. (1965). *Arch. Gynäk.*, **202**, 175.
Kane, F. J., jun., Daly, R. J., Ewing, J. A., and Keeler, M. H. (1967). *Brit. J. Psychiat.*, **113**, 265.
Marke, S., and Nyman, G. E. (1961). *Socialmed. T.*, **38**, 315.
Nilsson, A., Jacobson, L., and Ingemansson, C.-A. (1967). *Acta obstet. gynec. scand.*, **46**, 537.
Nilsson, L., and Sölvell, L. (1967). *Acta obstet. gynec. scand.*, **46**, Suppl. No. 8.
Westrin, P. A. (1967). *WIT III. Manual*. Stockholm.

Infective Endocarditis in Three Patients with Hypertrophic Obstructive Cardiomyopathy

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Infective endocarditis is a little-known complication of hypertrophic obstructive cardiomyopathy, though it may not be uncommon.

Boiteau and Allenstein (1961) described two cases, one of which had evidence of healed endocarditis on the mitral valve at necropsy. Soulie *et al.* (1962) and Linhart and Taylor (1966) reported two further cases. Franks and Braunwald (1968) have recorded three other well-documented cases. In one of these the aortic valve was seen at operation to have been the site of the infection. The same authors describe one probable and two possible further cases of endocarditis in patients with this condition.

To these cases we add three of our own seen at Hammersmith Hospital between 1959 and 1967.

Hypertrophic obstructive cardiomyopathy is now a well-recognized clinical entity. As it is known to be a disorder of the myocardium the possible development of infective endo-

carditis may not readily be considered, and no such cases have yet been recorded in the British literature. Our purpose is to emphasize the risk of this complication, to discuss the reasons for the susceptibility of patients with this form of cardiomyopathy to infective endocarditis, and to stress the necessity for preventive measures.

Case 1

The patient was 39 years old when he first presented in 1964. He was a battery manufacturer who for the previous five years had suffered from angina of effort and dyspnoea on exertion.

He had florid clinical signs of hypertrophic obstructive cardiomyopathy with jerky pulses, a double apical impulse, and a late-onset systolic murmur at the apex, which radiated to the axilla and to the left sternal border. The blood pressure was 110/60. His electrocardiogram showed left ventricular hypertrophy with an intraventricular conduction defect (Fig. 1), and on chest radiography the left ventricle was seen to be prominent (Fig. 2).

Left ventricular catheterization showed an intraventricular gradient of 127 mm. Hg. Furthermore, on left ventricular angiography the left ventricle had the typical appearance of severe hypertrophic obstructive cardiomyopathy with over-complete systolic emptying, a

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systolic constriction between the anterior cusp of the mitral valve and the ventricular septum, and moderately severe mitral incompetence (Figs. 3 and 4).

Ventriculomyotomy to relieve the left ventricular obstruction was advised, being carried out by Professor H. H. Bentall in January 1965. After operation the exercise tolerance improved and there was no further angina.

In April 1967 he was readmitted with sudden diplopia. He had felt generally unwell for a period of three months with profuse night sweats. These symptoms dated from some dental fillings which had unfortunately been undertaken without antibiotic cover.

He was ill, febrile, with finger-clubbing, Osler's nodes, a palpable spleen, and a left-sided third cranial nerve palsy. The sedimentation rate was 108 mm. in the first hour, but haemoglobin and white blood count were normal. As he had already received three short courses of penicillin before his admission to Hammersmith, each of which had been followed by transient remission of his symptoms, it was hardly surprising that six consecutive blood cultures were sterile.

The clinical diagnosis of infective endocarditis due to a penicillin-sensitive organism and complicated by a cerebral embolus

seemed certain, and he was treated for six weeks with high dosage of penicillin and streptomycin. He rapidly became afebrile, and at the time of discharge he was well, showed no sign of cardiac deterioration, and the sedimentation rate had dropped to 12 mm. The third-nerve palsy remained.

Six weeks later, after a sudden episode of severe headache with transient loss of consciousness, he was again admitted; this time he was dysphasic, photophobic, and had a right-sided hemiparesis.

Carotid angiography showed a bilocular aneurysm situated on the left middle cerebral artery (Fig. 5). This was exposed and wrapped by Mr. Valentine Logue, who found the aneurysm surrounded by much friable granulation tissue which bound it to the surrounding blood vessels and brain. These features, together with the site and bilocular shape of the aneurysm, strongly suggested that it was of mycotic origin. Unfortunately the patient died 10 days postoperatively.

At necropsy the heart weighed 655 g. There was gross asymmetrical left ventricular hypertrophy typical of hypertrophic obstructive cardiomyopathy and the interventricular septum measured 38 mm. in thickness in the region of the left ventricular outflow tract.

The mitral valve contained two small apertures on its anterior leaflet, with a vegetation 3 mm. in diameter on the atrial surface and some cusp thickening. Histology of this vegetation revealed that it consisted predominantly of fibrin, though there was also

FIG. 1.—Electrocardiograms of Cases 1, 2, and 3. Case 1: Mean QRS axis -30° , left ventricular hypertrophy, and intraventricular conduction defect. Case 2: Mean QRS axis -10° , complete left bundle-branch block. Case 3: Mean QRS axis -25° , left ventricular disorder.

FIG. 2.—Case 1. Postero-anterior chest x-ray films showing prominence of the left ventricle.

FIG. 3.—Case 1. Frontal view of retrograde left ventricular angiogram mid-systolic frame, showing greatly increased left ventricular muscle thickness. End systolic pictures (not presented here) showed over-complete emptying.

FIG. 4.—Case 1. Lateral view of same ventricular angiogram as in Fig. 3, showing fully open aortic valve, constriction between the anterior cusp of the mitral valve and the ventricular septum, the so-called "pinch-cock" mechanism (arrowed), and mitral regurgitation.

widespread cellular infiltration composed of histiocytes and chronic inflammatory cells.

No causative agent was found and the infection appeared to have been cured.

Microscopy of the myocardium showed bizarre-shaped muscle fibres with irregular nuclei, and fine patchy replacement fibrosis with much interruption of the muscle fibres.

The wall of the left middle cerebral artery had disappeared in a mass of blood clot and neutrophils. The appearance was that of a mycotic aneurysm.

Case 2

A 49-year-old woman was first seen at Hammersmith in 1959 with six months' history of syncopal attacks on exertion, some recent

FIG. 5.—Case 1. Lateral view of carotid angiogram showing carotid siphon. The arrow points at the bilocular aneurysm situated on the left middle cerebral artery.

FIG. 6.—Case 2. Postero-anterior chest x-ray film showing marked increase in heart size with left and right atrial enlargement. There is no dilatation of the aorta or valve calcification.

dyspnoea, and angina of effort. Her pulse was quick-rising. There was a left ventricular heave at the apex, a systolic thrill, and an ejection systolic murmur at the left sternal edge which was conducted to the neck and axilla. Blood pressure was normal (180/70).

Electrocardiogram showed complete left bundle-branch block (Fig. 1). On chest x-ray examination there was cardiac enlargement but no aortic valve calcification. A grossly thickened left ventricular muscle wall without cavity dilatation was found at angiocardiology. A diagnosis of hypertrophic obstructive cardiomyopathy was made.

In 1962 she reappeared with some peripheral oedema and raised jugular venous pressure. A double left ventricular impulse with a late-onset systolic murmur at the apex was now recognized. The chest x-ray film showed considerable cardiomegaly (Fig. 6). Retrograde left ventricular angiography revealed marked mitral regurgitation, but the aortic valve appeared normal. Simultaneous left ventricular and left brachial artery records showed a resting gradient of 63 mm. Hg. This was just before physiological or drug manipulation of the gradient became recognized as an important part of the assessment of these patients, and as the obstruction did not seem to be severe enough surgery was not advocated. The patient was therefore discharged, but only to be readmitted three months later at another hospital, febrile and confused, having felt unwell during the previous week.

Her temperature was 102.6° F. (39.2° C.), she had a tachycardia, and developed splinter haemorrhages. The white blood count was 10,000, with 92% polymorphs and a shift to the left. Blood culture yielded a growth of pneumococci, but she had no signs of pneumonia and the lungs were clear radiologically. A diagnosis of infective endocarditis was made.

A few days later she unexpectedly collapsed and died. Permission for a post-mortem examination was not obtained.

Case 3

A part-time staff nurse was 59 years old when admitted to the Central Middlesex Hospital with a recent onset of angina of effort. For three years she had noticed exertional dyspnoea. Ten years previously a systolic murmur had been detected and interpreted as probably due to a ventricular septal defect. She was a married woman with one son. There was no heart disease in the family, and, like the previous two patients, she had no knowledge of rheumatic fever in childhood or adolescence.

On admission she was running a low-grade temperature, and on two separate occasions *Staphylococcus albus* was isolated from her blood. She was, and had been, edentulous for a number of

FIG. 7.—Case 3. Postero-anterior chest x-ray film showing marked increase in heart size with left and right atrial enlargement. There is no dilatation of the aorta or valve calcification.

years. The haemoglobin and white blood count were normal, but the sedimentation rate was 41 mm. in the first hour. A diagnosis of infective endocarditis was made and she was given cloxacillin for six weeks. The underlying heart condition was thought to be non-rheumatic mitral regurgitation probably associated with hypertrophic cardiomyopathy, and she was transferred to Hammersmith Hospital for further investigation. She was now afebrile with no signs of residual infection. The arterial pulses were brisk and a late-onset systolic murmur was heard at the apex. The blood pressure was 120/80. The sedimentation rate was 28 mm., white blood count 6,000, and haemoglobin 10.6 g./100 ml. Electrocardiograms showed a left ventricular disorder (Fig. 1). Marked cardiac enlargement was noted on the chest x-ray film (Fig. 7).

Inhalation of amyl nitrite caused considerable accentuation of her murmur, while administration of phenylephrine reduced its intensity, squatting abolished it, and following the release of strain after the Valsalva manoeuvre it almost completely vanished. These responses are typical of hypertrophic obstructive cardiomyopathy, and occur in no other known heart condition (Oakley *et al.*, 1967).

Haemodynamic study revealed no resting interventricular gradient, but the left ventricular end systolic volume was greatly reduced and there was some mitral regurgitation. There was also left atrial enlargement and appreciable hypertrophy of the free wall of the left ventricle and particularly of the interventricular septum and papillary muscles. Drug studies were not carried out because she had some angina during the study and also because the diagnosis and future treatment were already clear.

Discussion

These three patients all had clinical, angiographic, and haemodynamic evidence of hypertrophic obstructive cardiomyopathy, and the diagnosis was not thought to be in doubt in any of them.

Diagnosis of the endocarditis was certain in the first patients, in whom the negative blood cultures were explained by the antecedent administration of antibiotics. The infection was temporally related to dental manipulation, and death eventually resulted from a ruptured mycotic aneurysm. Histology of the mycotic aneurysm within the cerebral vessel and of the mitral valve confirmed the infective origin.

In Cases 2 and 3 necropsy proof is lacking. In the second patient the illness was short, and was interrupted by sudden death as occurs in this disease. The third patient was edentulous and the organism *Staph. albus*, so the portal of entry of the blood-stream infection was probably not from her mouth. In such patients infective endocarditis is rarely caused by *Streptococcus viridans*. The insidious onset and indolent nature of the third patient's illness fits in well with the coagulase-negative staphylococcus which was cultured. In both these cases there was good circumstantial evidence of infective endocarditis.

The possible sites of origin of infective endocarditis in hypertrophic obstructive cardiomyopathy are on the mitral valve or its jet lesion (the site of impingement of a high-velocity jet), or, alternatively, at the site of the interventricular gradient or on its jet lesion on the aortic valve. Our first two patients had left ventricular outflow gradients demonstrated at the time of study, and all three were shown to have mitral regurgitation of varying degrees at angiography. We now believe that most if not all patients with hypertrophic obstructive cardiomyopathy have some mitral regurgitation (Oakley *et al.*, 1967). Slight mitral incompetence is well known to be peculiarly at risk from infective endocarditis, the predisposing feature probably being the high-pressure jet into a low-pressure chamber (Rodbard, 1963).

The second possible nidus for infection seems to be less probable because the interventricular gradient is often both small and intermittent in hypertrophic obstructive cardiomyopathy. A high-velocity jet would be a feature in only the minority of patients with a very big gradient. This was only the case in our first patient, but at necropsy the site of infection

was found to have been on the mitral valve. In both our other patients mitral reflux was demonstrated, but one had only a moderate resting gradient and the other had no resting left ventricular outflow gradient. Though Franks and Braunwald (1968) suggested that the site of infection is probably on the leaflets of the aortic valve, it seems to us more likely that the mitral valve may be a more common site of infection in hypertrophic obstructive cardiomyopathy. The aortic valve may also be at risk in patients with severe left ventricular outflow tract obstruction.

Table I shows an analysis of the sites of infection and the evidence of mitral incompetence in a review of up-to-date recorded cases of infective endocarditis in patients with hypertrophic obstructive cardiomyopathy. Out of a total of 13 recorded cases the site of infection is known with certainty in only three. Two were on the mitral valve—our own Case 1 and one of Boiteau and Allenstein's two cases. The other was on the aortic valve as described by Franks and Braunwald (1968). In the other cases the sites of infection were not determined (Table I).

TABLE I

Authors	Total No. of Subacute Bacterial Endocarditis	Site of Infection	
		Known	Unknown
Boiteau and Allenstein (1961) ..	2		2
Soulie <i>et al.</i> (1962) ..	1		1
Linhart and Taylor (1966) ..	1		1
Franks and Braunwald (1968) ..	6	1 aortic valve	5
Present series ..	3	1 mitral valve	2

In Table II factors known to have engendered the infection were examined. Out of the 13 cases three were precipitated by dental extractions, one followed a therapeutic abortion, and one a cardiac catheterization, and in eight cases no known antecedents were recognized. Table III analyses the organisms isolated from the blood cultures of these cases. Of the nine cases with positive cultures, six were caused by *Str. viridans*, one by pneumococci, and one by staphylococci. One organism (Franks and Braunwald (1968)) was not identified.

TABLE II.—Factors Precipitating Endocarditis

Authors	Dental	Other	Not Known
Boiteau and Allenstein (1961) ..	1	Therapeutic abortion	
Soulie <i>et al.</i> (1962) ..			1
Linhart and Taylor (1966) ..	1		
Franks and Braunwald (1968) ..		After cardiac catheterization	5
Present series ..	1		2

TABLE III.—Organisms Grown from Blood Cultures

Authors	<i>Str. viridans</i>	Others	None
Boiteau and Allenstein (1961) ..	2		
Soulie <i>et al.</i> (1962) ..	1		
Linhart and Taylor (1966) ..	1		
Franks and Braunwald (1968) ..	2	1	3
Present series ..		1 Staphylococci, 1 Pneumococci	1

Because hypertrophic obstructive cardiomyopathy is known as a disorder of cardiac muscle without structural deformity of valve cusps, bacterial endocarditis may not readily be considered in the diagnosis of a patient with this disorder. The purpose of this report is to emphasize the fact that these patients are not only at risk but that the risk may be particularly high, both because of the frequency of mild mitral incompetence in hypertrophic obstructive cardiomyopathy and because the disorder is most commonly seen in young adults possessing their own teeth. Careful antibiotic prophylaxis for dental procedures and the need to report unexplained febrile illness must therefore be stressed to such patients.

Summary

Three cases of infective endocarditis occurring in patients with hypertrophic obstructive cardiomyopathy are described. One of these patients died as a result of a ruptured mycotic aneurysm. An analysis of the current literature with particular reference to the site, the precipitating causes, and the type of infecting organism in this condition is presented. It appears that the site of predilection of the infection may be the mitral valve. The commonest recognized organism remains *Streptococcus viridans*. The need for vigilance and adequate prophylactic precautions is stressed.

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report Case 2. We wish to thank Professor V. Logue, of the National Hospital for Nervous Diseases, for permission to use his operative notes, as well as Dr. R. O. Barnard, National Hospital for Nervous Diseases, and Dr. E. G. J. Olsen, Hammersmith Hospital, for their histological reports. We also thank the departments of radiology and photography at Hammersmith Hospital.

REFERENCES

- Boiteau, G. M., and Allenstein, B. J. (1961). *Amer. J. Cardiol.*, 8, 614.
 Frank, S., and Braunwald, E. (1968). Idiopathic Hypertrophic Subacute Stenosis. A clinical analysis of 126 patients, with emphasis on the natural history. To be published.
 Linhart, J. W., and Taylor, W. J. (1966). *Circulation*, 34, 595.
 Oakley, C. M., Raftery, E. B., Brockington, I. F., Steiner, R. E., and Goodwin, J. F. (1967). *Brit. Heart J.*, 49, 629.
 Rodbard, S. (1963). *Circulation*, 27, 18.
 Soulie, P., Joly, F., and Carlotti, J. (1962). *Acta cardiol. (Brux.)*, 17, 335.

Recovery from Acute Renal Failure Due to "Irreversible" Glomerular Disease*

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[WITH SPECIAL PLATE FACING PAGE 467]

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Patients with acute glomerular disease who develop sufficient uraemia to require dialysis rarely recover, particularly if there are fibrinoid necrosis of glomerular capillaries and obliteration of Bowman's space by epithelial crescents, and especially if the patient is an adult (Merrill, 1957; Brun *et al.*, 1958; Hutt *et al.*, 1958; Alwall *et al.*, 1958; Parsons and McCracken, 1959; Schreiner, 1960; Berlyne and Baker, 1964; Harrison *et al.*, 1964; Lee *et al.*, 1966; Forland *et al.*, 1966). But recovery is not so uncommon as to justify the opinion, which prevails in most renal units, that prolonged oliguria and biopsy evidence of severe proliferative glomerulonephritis indicate irreversible disease with an inevitably fatal outcome which does not merit repeated dialysis.

In our opinion it is often unwise to abandon hope for a useful recovery of renal function on the grounds that the histological lesions in a renal biopsy specimen appear to be severe and irreversible, and in support of this view we report here the clinical course and renal histology of four patients.

Case 1

A 14-year-old schoolboy developed oedema of the face, pain in the ankles and elbows, and generalized abdominal tenderness with diarrhoea on 15 February 1963, the day after the onset of a sore throat and cervical lymphadenopathy. On the third day of his illness he was admitted to another hospital, where the blood urea was found to be 130 mg./100 ml. He passed no urine at that hospital and was transferred to Hammersmith Hospital on 21 February, at which time his blood pressure was 120/70 and there was slight sacral oedema. The haemoglobin was 11.3 g./100 ml.; the plasma electrolyte concentrations were sodium 128, potassium 6.6, chloride 88, and bicarbonate 15 mEq/l.; and the blood urea was 385 mg./100 ml. The plasma globulin was increased to 4.5 g./100 ml., largely as a result of an increase in γ -globulin, and the plasma albumin was 2.8 g./100 ml. The antistreptolysin titre was 800 Todd units/ml. (normal less than 200 units/ml.) and there was a marked reduction in serum complement.

Five haemodialyses were required before the blood urea concentration ceased to rise (Fig. 1). Prednisolone 60 mg. daily was given from 15 March and was reduced to 20 mg. daily by 17 April, when he left Hammersmith Hospital. A percutaneous renal biopsy on 18 March showed six severely affected glomeruli, all with proliferative and exudative changes (Special Plate, Fig. 1). A crescent was present in one glomerulus and fibrinoid necrosis in another, two arterioles showed fibrinoid necrosis, and in one there was an associated polymorph reaction in the wall. In the less affected glomeruli the lesion appeared to be focal. Tubular atrophy was marked—some residual tubules were dilated and contained blood and protein casts. There was interstitial fibrosis with foci of plasma cells, eosinophils, and polymorphs. The histological diagnosis was acute glomerulonephritis, perhaps as a manifestation of polyarteritis.

FIG. 1.—Clinical course of Case 1.

For 28 days the daily urine output never exceeded 400 ml. When haemodialysis was no longer required for the control of uraemia he became hypertensive. After he was discharged back to the referring hospital he made a very slow recovery and was not finally discharged home until December 1963. Treatment with prednisone was continued for a further three months. In June 1964 the blood pressure was 130/90 with treatment, the blood urea was 65 mg./100 ml., and the serum proteins were normal; there was only slight proteinuria. He returned to school until early in 1965, when hypertension, oedema, and uraemia became uncontrolled, and he died in

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