Papers and Originals**CARDIOLOGICAL PROBLEMS IN YOUNGER WOMEN: INCLUDING THOSE OF PREGNANCY AND THE PUERPERIUM***

BY

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Women are endowed with certain advantages. They face fewer hazards than the male, whom they tend to outlive. In infancy and childhood mortality among boys is greater than in girls, and in middle life ischaemic heart disease takes a much greater toll among men. The Registrar-General's figures tell us, for instance, that in the five-year period 1953-7 the mortality from coronary artery disease in the age-group 55-59 years was four and a half times higher for men than for women. Age and sex may thus influence the development and progression of vascular disease. Life expectancy for the female now exceeds that of the male by a greater number of years than ever before. Hence a closer study of the "feminine" response to long-term cardiovascular damage ought to increase our understanding of the basic processes involved.

I. CORONARY ARTERY DISEASE

The clinical manifestations of obliterative coronary disease are unequally distributed between the sexes—a fact to which Heberden (1802) drew attention in his original account of angina pectoris and which has been confirmed many times since. For all types of ischaemic heart disease the male:female ratio over the past 20 years has been estimated to range from 2.4:1 to 4:1 (Oliver and Boyd, 1959). In a consecutive series restricted to patients with acute myocardial infarction under my personal care in the ten-year period 1949-59, there were 569 men and 293 women—a ratio of 1.9 to 1.

The disproportion between the sexes is most pronounced in the younger age-groups, in which the men far outnumber the women. Oliver's (1958) analysis of 1,000 consecutive patients suffering from coronary artery disease is shown in Table I. Under age 35 the

TABLE I.—*Influence of Age on Sex Ratio in Clinical Coronary Disease. 1,000 Consecutive Patients. (After Oliver, 1958)*

Age in Years	Men	Women	Ratio Males : Females
Under 35	19	1	19 : 1
35-39	44	3	15 : 1
40-49	188	26	7 : 1
50-59	256	53	5 : 1
60-69	195	86	2 : 1
70 and over ..	68	61	1 : 1
Total	770	230	3.4 : 1

ratio is 19 males to 1 female. By the time age 70 is reached the sexes are equally affected. In women the reproductive years are accompanied by a reduced liability to obliterative coronary disease. Endocrine

factors may thus have a protective or retarding influence on the development of obliterative coronary disease in women or, conversely, promote or accelerate the production of coronary atherosclerosis in men.

The part played by the female sex hormones can be deduced from the fact that younger women who have had both ovaries removed are more prone to develop ischaemic heart disease prematurely than a comparable group characterized by unilateral ovariectomy (Griffith, 1956; Oliver and Boyd, 1959). Pathological support for this conclusion is given in the works of Wuest *et al.* (1953) and Rivin and Dimitroff (1954), who found more advanced atheroma than anticipated in women after bilateral ovariectomy; conversely, Hawke (1950) observed coronary atherosclerosis less often in eunuchs than in normal men of similar age. The involutionary changes of the menopause—naturally or artificially induced—are accompanied by an increase in blood lipids and an abrupt increase in the incidence of ischaemic heart disease. It is now well known that in humans oral oestrogens lower plasma cholesterol and β -lipoprotein cholesterol (Barr, 1953; Oliver and Boyd, 1954, 1956).

Elevated serum cholesterol levels precede the clinical development of coronary heart disease, and individuals with high blood lipid levels have a greater risk of developing coronary disease (Dawber *et al.*, 1957; Kannel *et al.*, 1961). The association of hypercholesterolaemia with coronary artery disease is therefore close, though not necessarily one of cause and effect. It is disappointing to know from the carefully controlled five-year study of Oliver and Boyd (1961) that oestrogen administration sufficient to maintain a significant reduction of the serum cholesterol levels did not influence the morbidity and mortality of a group of men surviving a single acute myocardial infarction—a therapeutic failure that must be a stimulus to further endeavour. Ovarian and other hormones, used singly or in combination before the development of irreversible vascular damage, may well prove more effective in the future. Coronary disease is almost certainly the end-product of multiple interacting factors—an endocrine imbalance, a disturbance of fat metabolism—with heredity, hypertension, occupation, and other features playing a subsidiary part. The failure to produce clinical benefit by the use of oestrogens alone, despite a significant reduction in the blood lipids, is perhaps not so surprising.

Sex may influence the clinical presentation of coronary artery disease. Kannel *et al.* (1961) conclude that in women coronary disease presents predominantly as angina without infarction, whereas in men acute infarction or sudden death is commonly the first indication, angina pectoris being less frequent as the primary indication of obliterative atherosclerosis.

*Some of the material on which this paper is based was first incorporated in the Lock Lecture of the Royal Faculty of Physicians and Surgeons of Glasgow on February 21, 1962, and later expanded to form the Margaret Orford Lecture to the College of Physicians, Surgeons, and Gynaecologists of South Africa, given on March 29, 1962.

Sudden and unexpected death is four times as common in men as in women. Thus the evidence implicating the endocrine system, derived originally from the relative immunity of younger women to coronary disease, is now so strong that any hypothesis advanced to account for the aetiology of coronary atherosclerosis must include the role of the sex hormones.

Coronary Heart Disease in Young Women

The rarity of ischaemic heart disease in younger women is illustrated by the fact that James *et al.* (1955) found only five patients under 40 years of age among 146 women suffering from acute myocardial infarction. Similarly, Weinred *et al.* (1957) noted an incidence of only 2.3% in women under 40 among a series of 219 with acute infarction. My colleague Dr. Michael Oliver, in a group of 50 women under the age of 45 with ischaemic heart disease, found that half had sustained acute infarcts, the remainder having angina of effort. Hypertension was the commonest causal factor, occurring in 21 instances. Ten patients experienced a premature spontaneous menopause. Six of the 50 women had had bilateral ovariectomy or radium therapy some years previously. Anaemia (Hb less than 75%) was observed in ten, diabetes in three, myxoedema in one, and facial hirsutism in four. Fourteen of the series had hypercholesterolaemia—that is, a blood cholesterol in excess of 275 mg./100 ml.—in eight it was post-menopausal, and in the remaining six it was regarded as being familial and idiopathic.

Pregnancy and Coronary Disease

Coronary heart disease is seldom recognized during pregnancy. Watson *et al.* (1960) reported two cases occurring in young women, one aged 22 having a major anterior infarct two weeks before term, and the other, aged only 17, having a posterior infarct six days after delivery. Neither had hypertension, severe anaemia, diabetes mellitus, or other metabolic disorder. These authors collected from the literature only 26 well-authenticated examples. If a disturbance of the lipid pattern was the dominant factor in the aetiology of coronary atherosclerosis, examples of ischaemic heart disease would be anticipated with much greater frequency during pregnancy. The total blood cholesterol in normal pregnancy increases considerably and the lipoproteins alter in distribution to resemble that found in men with ischaemic heart disease. This biochemical disturbance is temporary and does not in itself predispose to ischaemic heart disease, though there is a suggestion that women with the largest families are probably more prone to coronary artery disease in later life than those who have borne only one or two children (Winkelstein *et al.*, 1958).

II. HYPERTENSION

That age influences blood-pressure levels in healthy people is fully accepted, though sex differences have not been so clearly appreciated until recently. Master *et al.* (1952) examined the readings in 15,706 healthy people of both sexes from youth to old age. As shown in Fig. 1, the average systolic pressure in men shows a smooth rise from age 20 to 50—a rise in fact of 7 mm. (123 to 130 mm.). After age 50 the rise is accelerated—rising 12 mm. (130 to 142 mm.) between 50 and 65 years. It is

clear from Fig. 1 that up to age 45 the systolic pressure in women is less than in men of corresponding age—the difference between the sexes at ages 25 to 29 years amounting to 8 mm. By the time age 45 is reached the pressures have equalized and thereafter on the average the systolic readings in women are a few millimetres higher than in the male. In the diastolic levels the sex differences are similar but less marked—the readings in women being 3 to 4 mm. lower than in men. By age 50 the discrepancy between the sexes disappears. The

FIG. 1.—Mean systolic and diastolic pressures on a sex basis by age-groups. Up to age 45 the systolic pressures in women is a few mm. Hg less than in men. In the diastolic levels the sex differences are similar but less impressive. By age 50 the discrepancy between the sexes disappears. (After Master *et al.*, 1950.)

explanation for this sex difference is not known, but, as in coronary artery disease, it is reasonable to suggest that endocrine factors must play a part. The involutional changes of the menopause coincide with a gradual readjustment of pressure in the female, the reading thereafter being similar in healthy members of both sexes.

Under 25 years of age the incidence of hypertension in males exceeds that in women (Alvarez, 1923; Symonds, 1923; Boynton and Todd, 1947); whereas after age 40 hypertension occurs more frequently in the female (Schwab and Schulze, 1931; Wetherby, 1932; Master *et al.*, 1943). As an explanation for this sex difference, it may be suggested that, with age 40 as the dividing line, ovarian involution predisposes to both atherosclerosis and hypertension in those with a hereditary or other trait. Infections of the urinary tract are certainly more common in the female. Similarly, pregnancy toxæmias in young women are known to contribute to the prevalence of hypertensive vascular disease in later life.

Middle-aged women tolerate high blood-pressure better than men (Woolsey, 1957; Simpson and Gilchrist, 1958). The mortality rate after 10 years of hypertension is probably twice as high in men as in women (Blackford and Wilkindon, 1932). Furthermore, the male is more prone to malignant hypertension (Page, 1939). Rasmussen and Bøe (1945) found that deaths from heart failure and from cerebral vascular accidents were more frequent in men than in women. There is thus good evidence that the vascular system of women is more tolerant to the sustained burden of hypertension than that of men, in whom the disease runs on the average a shorter and severer course.

Pregnancy in Relation to Blood-pressure

Despite the adverse influence of hypertension on mother and foetus, there are comparatively few critical studies of the behaviour of the blood-pressure in healthy women throughout normal pregnancy. Blood-pressure in the healthy is constantly varying in response to all manner of external and internal influences. Its limits and its range are difficult to define. Nevertheless, some useful studies have been made. Hare and Karn (1929) showed that about mid-term the systolic pressure drops by 4 to 6 mm. below the normal non-pregnant level. Thereafter it increases gradually as the pregnancy advances. The diastolic pressure follows a similar course though the mid-term dip is less sharply defined. Both the systolic and diastolic readings tend to rise by 5 or 6 mm. in the last 10 weeks. Fig. 2 is constructed from the

FIG. 2.—Mean of blood-pressure readings recorded throughout pregnancy in 150 normal women. (Constructed from data of Dieckman and Kramer, 1952.)

data of Dieckmann and Kramer (1952). It shows the mean of the pressure readings recorded throughout pregnancy in 150 normal women.

Physicians in the medical wards pay little heed to the small increases in pressure which the obstetricians rightly view with such misgivings. The views expressed by Browne (1947), that in pregnancy any rise of blood-pressure above 120/70 must be regarded with suspicion, have received striking support in recent years. The incidence of pre-eclamptic toxæmia in women with pressures between 120/70 and 140/90 before the 15th week rises to 39% as term approaches. This compares with a 1.8% incidence in strictly normotensive women (McClure Browne, 1958, 1961). Minor elevations of pressure early in pregnancy denote distinct maternal and foetal risks.

It is therefore true to conclude that while the non-pregnant woman is for the most part particularly tolerant of continued hypertension—much more so than the male—her relative immunity is not maintained throughout pregnancy—in fact, she becomes temporarily hypersensitive. Minor fluctuations of pressure are then of the greatest significance to her.

III. RHEUMATIC HEART DISEASE

It is generally agreed that rheumatic infection (rheumatic fever, subacute rheumatism) is a little more apt to attack females than males (Coombs, 1924). This has been attributed to the preponderance of girls affected by chorea (Cohn and Lingg, 1943). Otherwise the incidence in childhood is about the same between the sexes. On the other hand, some years later, when valvular lesions have become well established and easy of recognition, females with rheumatic heart disease show a distinct preponderance. Thus Olesen (1955) found among 271 patients with predominant mitral stenosis a male:female ratio of 1:2.5. Jones (1933) recorded a ratio of 1:2.8, Biörck *et al.* (1955) 1:4.4, and in a recent series of mine the ratio was 1:5 in favour of the female. Nevertheless, Wood (1956) points out that the ratio for pure isolated valvular lesions is much in favour of the male, his figures being 4:1 for mitral stenosis and 3:1 for mitral incompetence—a remarkable sex discrepancy considering the dominance of valvular disease in the female.

Pregnancy and Rheumatic Heart Disease

Of the different varieties of heart disease encountered among pregnant women, rheumatic valvular damage accounts for 94%. The present analysis is based on the experience of all varieties of heart disease encountered at the antenatal department of the Simpson Pavilion of the Royal Infirmary during the past 33 years.

Careful supervision of cardiac patients throughout pregnancy has proved rewarding. Our current mortality rate among cardiac women is 0.4%—that is, more than 15 times less than it was 30 years ago, when the rate was 6.3% (see Table II). Over the same period the total

TABLE II.—Mortality Among Pregnant Cardiac Patients Attending the Simpson Pavilion of the Royal Infirmary, Edinburgh, in Five-year Periods since 1928

Years	Total Cardiac Cases	Total Cardiac Deaths	Maternal Mortality %
1928–32	203	13	6.3
1933–37	228	17	7.5
1938–42	266	9	3.4
1943–47	401	7	1.7
1948–52	425	6	1.4
1953–57	335	4	1.2
1958–60*	257	1	0.4

* A three-year period.

maternal mortality has fallen from 1.11% (203 deaths among 18,359 admissions) to 0.04% (representing 6 deaths in 14,540 admissions)—that is, nearly 30 times less than 30 years ago. In other words the decrease in cardiac deaths has not kept pace with the tremendous reduction in maternal mortality as a whole.

The cardiac woman starts her pregnancy at a disadvantage as compared with her healthy sister. Her capacity for exertion tends to deteriorate as the pregnancy advances. The major hazards confronting these women are (1) congestive heart failure, running a subacute or chronic course, and (2) pulmonary oedema, acute in onset, often unanticipated and frequently fatal. The objective in the antenatal care of these cardiac patients is a sustained endeavour to avoid these serious complications.

Rheumatic heart disease runs its course and sooner or later takes its inevitable toll. Nevertheless, the complete elimination of cardiac deaths from the reproductive

phase is not beyond achievement. The better care of cardiac women—valvotomy before conception in certain instances, sterilization in others in whom structural damage is far advanced, and as a last resort interruption of pregnancy in the early weeks for the ill-advised and grossly incapacitated cardiac women—can all contribute to the avoidance of needless fatalities. The recognition that rheumatic heart disease is not acceptable as an indication for caesarean section has been the means of saving many lives (Haig and Gilchrist, 1948-9; Bunim and Rubricius, 1948). More than any other measure, the full use of antenatal beds by these cardiac patients, often for months at a time, can yield benefits unsuspected 20 or 30 years ago and bring safely to term many whose lives are for a time grossly imperilled.

Problem of Acute Pulmonary Oedema

The pattern of heart failure encountered in pregnancy has gradually undergone a change during the past 30 years. For instance, in the 20-year period 1928-47 congestive heart failure accounted for 61% of the 46 deaths and acute pulmonary oedema for 13%, whereas in the next 13 years (1948-60) only 8% of the 12 deaths were attributed to congestive failure. On the other hand, 67% of the deaths resulted from acute pulmonary oedema in this period (Table III). Among pregnant

TABLE III.—*Mortality Rate and Causes of Death Over Two Consecutive Periods—1928-47 and 1948-60. A Fourfold Decrease in Cardiac Mortality in the Second Period is Accompanied by a Relative Increase in Deaths from Acute Pulmonary Oedema with a Decrease in Deaths from Congestive Heart Failure*

	First Period 1928-47	Second Period 1948-60
Total cardiac cases	1,098	1,017
Deaths	46	12
Mortality rate	4.2%	1.2%
Causes of death:		
Congestive heart failure	28 (61%)	1 (8%)
Subacute bacterial endocarditis	7 (16%)	1 (8%)
Acute pulmonary oedema	6 (13%)	8 (67%)
Miscellaneous	5 (10%)	2 (17%)

cardiac patients congestive failure now takes a milder form; it is more readily controlled and probably less ominous than it was 20 or 30 years ago. Among the 1,017 cardiac patients observed during 1948-60, acute pulmonary oedema had an incidence of 4.3% as compared with a rate of 7.3% for congestive failure (Table IV). Although about half as common as con-

TABLE IV.—*Contrasting Acute Pulmonary Oedema with Congestive Heart Failure in Their Incidence and Mortality Among 1,017 Cardiac Women During Pregnancy in the Period 1948-60*

	Acute Pulmonary Oedema	Congestive Heart Failure
Cases	44	74
Incidence	4.3%	7.3%
Deaths	8*	1
Mortality rate	18.2%	1.7%
Overall mortality for 1,017 cardiac cases	0.8%	0.1%

* Includes one death one month post partum.

gestive failure, acute pulmonary oedema has a mortality rate more than 10 times as great (18.2% as against 1.7%).

The serious significance of acute pulmonary oedema to the pregnant woman has been particularly emphasized by Bramwell and Jones (1944) and Bramwell (1953), who pointed out its association with the severest grades of mitral stenosis. Morgan Jones (1959) has noted that

congestive heart failure is most prone to occur in women greatly handicapped before pregnancy with large hearts and considerable myocardial damage. By contrast, women who develop acute pulmonary oedema may be otherwise symptomless. Their hearts are usually small and the grade of mitral stenosis is often severe without appreciable myocardial damage. Attacks often occur suddenly, usually after the first trimester, and are more common as term approaches. Tachycardia, hydraemia, some unusual exertion, an emotional upset, an upper respiratory infection, fatigue, and sleeplessness are the common precipitating factors.

Prevention depends on ample hours of rest and sleep, diuretics to control blood volume, and digitalis to reduce tachycardia and improve ventricular output. For the attack itself the essentials are morphine subcutaneously, digoxin intravenously, and mersalyl intramuscularly. Most of these patients will require to be confined to bed for the remainder of pregnancy. Some will require valvotomy.

For many years the classification of cardiac patients according to their exertional capacity from grade 1 (freedom from symptoms) to grade 4 (symptoms persisting at rest in bed—for example, congestive heart failure), with intermediate groups grade 2 (exertional intolerance slight) and grade 3 (exertional intolerance moderate), has provided a useful scale on which to build an immediate prognosis. The woman's capacity for exertion commonly tends to deteriorate by a grade or more as the pregnancy advances. Thus by a study of her symptoms early in pregnancy the likelihood of the development of congestive heart failure about the time of delivery can often be predicted; acute pulmonary oedema is less easily anticipated; too often it occurs unexpectedly. Other well-recognized factors in determining the course of events during pregnancy are the age of the patient and her exertional tolerance in a preceding pregnancy. With each year over age 30 the greater is the likelihood of cardiac difficulties. The woman classified in grade 3 or 4 in one pregnancy is likely to be similarly handicapped in the next, and, if previously grade 1 or 2, deterioration by a grade or more in the succeeding pregnancy is common.

In the assessment of the immediate prognosis more emphasis requires to be placed on the extent of the local valvular damage. When the heart is small, the stenosis severe, and pulmonary hypertension considerable, the risk of acute pulmonary oedema is all the greater, even in spite of a satisfactory exertional tolerance in the early months of pregnancy. In these circumstances, when mitral stenosis is the dominant lesion, valvotomy within the first half of pregnancy may prove a more certain means of avoiding this serious complication than medical measures alone. The prevention of acute pulmonary oedema is the major problem in current obstetric cardiology.

Problem of Mitral Valvotomy in Relation to Pregnancy

The surgical relief of mitral stenosis is a palliative procedure. Successful division of the commissures reduces valvular obstruction to a greater or less degree, but rigidity and thickening of the cusps persist. Hence symptoms are relieved to a variable extent. Restenosis is common.

Mitral valvotomy performed apart from pregnancy carries a mortality rate which increases progressively

with the patient's age and pre-operative exertional tolerance. Mr. Andrew Logan's 10-year experience for both sexes is shown in Table V. After age 30 the immediate operative mortality increases sharply. As shown in Table VI, the operative risk is greatly

TABLE V.—*Influence of Age on Operative Mortality After Mitral Valvotomy. Mr. Andrew Logan's Series, 1951-60*

Age in Years	Cases	Deaths	Mortality (%)
0-19	12	0	0
20-29	97	1	1.0
30-39	180	8	4.4
40 and over ..	113	7	6.2
Total	402	16	4.0

TABLE VI.—*Operative Mortality Among Both Sexes After Mitral Valvotomy in Relation to Patient's Preceding Exertional Tolerance. Exertional Grades 1 and 2 Carry an Operative Mortality of 1 to 2% or Less, Whereas in Grades 3 and 4 it May Rise to Approximately 5 and 20%*

Author	Total Cases	Exertional Grade			
		1	2	3	4
Bailey and Bolton (1956)	1,000	3%	3%	10%	18%
Ellis <i>et al.</i> (1959) ..	1-100	—	14%	—	32%
	101-500	—	4%	—	24%
Learoyd, <i>et al.</i> (1960)	501-1,000	—	0.8%	—	19%
	400	—	2.5%	6.4%	25%
Average		1%	2.0%	5%	20%

influenced by the patient's exertional grade. The mortality for both sexes ranges from about 1% or less in grade 1 patients to about 20% in grade 4. Grade 2 and grade 3 carry a mortality rate of approximately 2% and 5% respectively. To perform valvotomy in the presence of congestive failure invites disaster—only one in four or five will survive. The operation has a considerable morbidity even in well-chosen patients. The technique may falter, free regurgitation may result from a torn cusp, an embolus is occasionally detached or auricular fibrillation initiated. Minor degrees of congestive heart failure are commonly observed within 10 to 14 days of surgery.

Opinions differ regarding the advisability of valvotomy for mitral stenosis during pregnancy. There are those (Mendelson, 1955; Marshall and Pantridge, 1957; Bridgen, 1961) who believe that the surgical indications are essentially the same as in the non-pregnant; others contend that operation, performed when the severer grades of cardiac disability threaten, does not eliminate the hazards to which mother and infant are then exposed, but may in fact increase the risk unnecessarily (Burwell, 1954).

Our conservative approach can be justified on the basis of the progressive reduction in maternal cardiac mortality observed during the past 20 years, the rate now standing at a figure less than the overall operative mortality for mitral valvotomy in the non-pregnant. Soulié *et al.* (1961), reporting nine successful cases of mitral valvotomy during pregnancy, have collected 180 further instances, with 10 operative fatalities, giving a mortality rate of 5.3%. On a statistical basis it is difficult to dismiss lightly the sum of the combined mortality rates for maternity, for mitral stenosis, and for valvotomy, which these women face. Yet statistics are not in themselves the whole answer.

The success of the strictly medical approach depends primarily on the full co-operation of the patient, the availability of suitable in-patient accommodation, and

her willingness to occupy a hospital bed perhaps for six months if necessary. Not every mother is prepared to make such a sacrifice. Experience emphasizes the contribution which skilled regulation of day-to-day therapy—diuretics, digitalis, salt restriction—coupled with expert nursing and obstetrical care constantly at hand, can make in difficult circumstances.

Valvotomy Before Pregnancy

Valvotomy performed before pregnancy avoids an additional burden for the pregnant woman and allows the selection of optimum conditions for surgery. Moreover, the degree of stenosis can be more accurately assessed in the non-pregnant, who are unencumbered by compensatory mechanisms—increased blood volume and blood flow—which can distort, exaggerate, and sometimes mask the usual signs of valvular disease. Kaufman and Ruble (1958) report 96 pregnancies occurring after mitral commissurotomy with no maternal and only one foetal death.

Fifty-four women in our series have had successful valvotomies performed for mitral stenosis shortly after pregnancy. A subsequent pregnancy has occurred in 28 of these patients. In five the disability in the pre-valvotomy pregnancy was slight (grades 1 and 2); in 23 it was considerable (grades 3 and 4). The course of the post-valvotomy pregnancies in the 23 women who had been grade 3 or grade 4 was closely related to their ages at the time of the subsequent pregnancy. Their response is shown in Table VII. Of the 15 patients

TABLE VII.—*Exertional Grade of 23 Patients in Two Consecutive Pregnancies, a Mitral Valvotomy Intervening in Each Instance. Valvotomy was Performed After a Pregnancy in Which 18 Women Had Been Classed as Grade 3 and 5 Women as Grade 4. Of the 15 Patients Under 30 years in Post-valvotomy Pregnancy, 14 Were Upgraded, Whereas of 8 Women Aged 30 and Over only 1 was Substantially Improved in the Subsequent Pregnancy. My Colleague, Dr. Robert Marquis, has kindly supplied the details incorporated in this Table*

Pregnancy	No. of Patients	Exertional Grade			
		1	2	3	4
Pre-valvotomy ..	23	0	0	18	5
Post-valvotomy:					
Under 30 years ..	15	3	11	1	0
30 years and over ..	8	0	1	4	3
Total	23	3	12	5	3

under 30 years, 14 were upgraded in the post-valvotomy pregnancy, whereas of eight women 30 years and over at the time of the post-valvotomy pregnancy only one patient was upgraded, and this in spite of the fact that two of the women who developed gross congestive failure (grade 4) had both had surgically very satisfactory valvotomies without the production of mitral incompetence. This is a small number from which to draw conclusions, but the findings are impressive. Of 23 patients considerably disabled in one pregnancy 15 (65%) were upgraded in the subsequent post-valvotomy pregnancy—a substantial achievement contrary to past experience and directly attributable to successful surgery.

An earlier study of two consecutive pregnancies in 169 patients in whom a valvotomy did not intervene (Haig and Gilchrist, 1948-9) led to the conclusion that the woman who attains grade 3 or 4 in one pregnancy will do so again in the next and that even in the milder grades some deterioration can be anticipated in a subsequent pregnancy. A well-timed valvotomy can break this sequence, and perhaps allow a woman to have a

child for whom the burden might otherwise be too great. The benefits of valvotomy are often of limited duration, and as increasing age is an adverse factor for the cardiac woman, pregnancy, after a successful operation, should not be long delayed.

Valvotomy During Pregnancy

In the past eight years, only 11 of 592 patients have had valvotomies performed during pregnancy. In the selection of patients for this procedure the major consideration is the severity of symptoms in relation to the period of gestation.

(1) *In the first 20 weeks*

Although patients in grade 1 or 2 at this stage ought to tolerate surgery well the operative mortality—approaching 2% in the non-pregnant—exceeds that experienced among pregnant cardiacs in the same grade under strict medical control and selection. Nevertheless, if physical signs are gross, if the patient's age is 30 years or more, and if her full co-operation cannot be anticipated throughout the remainder of her pregnancy, there is a reasonable justification for recommending valvotomy in the first four months, the earlier the better. Five of our patients, none more seriously handicapped than grade 2, had valvotomies before the 16th week, four being submitted to surgery before the diagnosis of pregnancy had been established. All did well.

Seen in the first 12 to 14 weeks, the patient considerably handicapped (grade 3 to 4) presents a more controversial problem. There are a number of alternatives to choose from. With strict medical management, complete bed rest, and full co-operation many of these women will respond to treatment and go to term successfully, surmounting the undoubted risk of congestive failure. If mitral stenosis dominates, valvotomy can be performed at a selected time after delivery. Alternatively, the physician may feel happier if the patient whose heart has been brought under control by intensive medical measures by the third or fourth month will consent to a prompt therapeutic interruption and a valvotomy some months later. The primiparous patient may well be reluctant to accept this advice—in which case, after a good response to intensive treatment, a mitral valvotomy performed before mid-term can be justified on the grounds that the risk of surgery at that time in a patient previously classified as grade 3 or 4 is distinctly less than the expected mortality rate for a patient with intractable heart failure at term. If congestive failure persists or grows worse as pregnancy advances, despite intensive medical and nursing care, there is nothing to be gained by surgery.

(2) *The second 20 weeks*

The load imposed by surgery by the time mid-term is reached is considerable. Patients in grades 1 and 2 at 20 weeks seldom, if ever, justify surgery unless acute pulmonary oedema threatens, but patients presenting as grade 3 to 4 at this stage of gestation are a source of much misgiving, particularly those in frank congestive failure. With continuous bed rest and thorough treatment, the subsequent mortality among those in grades 3 and 4 at this stage of pregnancy should be less than half the surgical mortality rate of 5 to 20% for the same grade of effort intolerance among the non-pregnant. Many make steady progress under intensive therapy and go to term successfully. If they do not improve, the outlook

as pregnancy advances becomes increasingly poor. Faced with this dilemma after mid-term, the surgeon will best adhere to the working rule, "When in doubt don't interfere." An exception might be congestive heart failure commencing after the 20th week but brought under sufficiently good control within the following week or two to permit a valvotomy, or, secondly, a history of recent acute pulmonary oedema at this stage of pregnancy. As this complication itself carries a mortality rate approaching 20%, mitral valvotomy could then be justified, even later in pregnancy, provided energetic medical measures had previously been instituted with some success.

In the last two months of pregnancy valvotomy should be avoided. One of our patients came into this category. She was first seen at 26 weeks in grade 4 and at once admitted to hospital. She had advanced mitral stenosis and well-marked pulmonary hypertension. Valvotomy at 33 weeks was judged the lesser evil. Her death at age 30 from a torn cusp with resulting acute pulmonary oedema was the immediate outcome of the valvotomy—the only cardiac death among 257 patients in the three-year period 1958–60.

The abandonment of caesarean section has resulted in a striking reduction in mortality rate in the severer grades of heart failure, and by the avoidance of valvotomy in the last two months the fatalities should continue to decrease. For the cardiac patient late pregnancy is no time for major surgery. The prospects of a further improvement in the management of these patients are good, provided more have valvotomy before pregnancy, and provided intervention is kept to a minimum after mid-term.

CARDIOMYOPATHY OF PREGNANCY AND THE PUERPERIUM

A small proportion of women with apparently healthy hearts develop in the later months of pregnancy or early in the puerperium a degree of cardiac distress which occasionally advances to congestive heart failure. Originally described by Meigs (1848), the older literature has been reviewed by Jensen (1938) and the more recent by Becker and Taube (1962).

Current experience suggests that at least two entities may be included under the vague title of cardiomyopathy of pregnancy. A number of patients present as congestive heart failure, presumably the result of an acute myocarditis of doubtful aetiology. For instance, Haig and I (Haig and Gilchrist, 1948–9), amongst a series of 352 cardiac women re-examined 1 to 10 years after their last confinement, encountered seven patients in whom no sign of heart disease could be detected, yet each of these women had suffered from congestive heart failure necessitating in-patient treatment during her preceding pregnancy. None had shown evidence of anaemia, fever, kidney disease, hypertension, pre-eclamptic toxæmia, or nutritional deficiency during the pregnancy; in two, caesarean section had been judged advisable on account of the cardiac incapacity. All were over 30 years of age; all but one gave a history of rheumatic fever long before pregnancy. Some years after delivery careful and repeated examinations, including radiology and electrocardiography, revealed no evidence of valvular or other damage. All were symptom-free, fit, and well. Recovery was complete. An active myocarditis of unknown aetiology occurring in pregnancy, leading to

congestive failure but capable of complete resolution, appears to be a genuine but uncommon entity.

In a second group, angina and tachycardia are the dominant features, congestive failure being exceptional. Patients are occasionally encountered in whom symptoms of fatigue, palpitation, dyspnoea, and angina of effort date back precisely to a pregnancy some months or years earlier. In this group of patients the cardiac disability tends to persist. For instance, Mrs. A. (No. 4362) was 28 years old during her pregnancy when symptoms started and left bundle-branch block was found. That was 20 years ago. She still has tachycardia and angina. Of six patients included under this heading only one (Mrs. L., No. 9149) developed a transient congestive failure. This occurred at age 25 in the puerperium of her third pregnancy. It was attributed to a succession of pulmonary infarcts. During the pregnancy she complained of palpitation and dyspnoea. Her symptoms persist four years later and she still has tachycardia, a gallop rhythm, some exertional pain, and dyspnoea. The resemblance to coronary disease is close, but the continuous tachycardia and the invariable dyspnoea in greater or less degree are very characteristic of a myopathy.

Detailed clinical and pathological descriptions will be found in the papers of Gouley *et al.* (1937), Hull and Hafkesbring (1937), and Hull and Hidden (1938). Post-mortem examinations have been reported in 15 instances (Meadows, 1957; Benchimol *et al.*, 1959; Rosen, 1959; Tweed, 1960; Becker and Taube, 1962). Opinion favours a degenerative rather than an inflammatory lesion, largely subendothelial in distribution and accompanied by superimposed ventricular thrombosis. Similar changes have been found in a variety of myopathies and appear distinct from the diffuse inflammatory reaction usually associated with an idiopathic myocarditis.

The evidence that this form of heart disease is a specific entity, directly related to pregnancy, is not conclusive. Similar findings have been recorded in males (Gouley *et al.*, 1937), and have been said to occur apart from pregnancy. Hypersensitivity, including possible reactions to the products of conception, has been suggested as an aetiological factor by Becker and Taube (1962), and the recent demonstration of trophoblastic tissue in the maternal blood during pregnancy might lend support to this possibility (Douglas *et al.*, 1959). Vascular lesions in the subendocardial plexus might thus be interpreted as a non-specific reaction of a hypersensitive state. Alternatively, a biochemical disturbance, analogous in its consequences to the cardiac damage produced by serotonin, may yet be incriminated in some of these patients.

On clinical grounds it is unlikely that either manifestation—the acute myocarditis or the chronic subendocardial fibrosis—should be regarded as specific entities peculiar to pregnancy or the puerperium. Knowledge is scanty regarding these uncommon forms of heart disease (Brigden, 1957), but it seems more reasonable to suppose that pregnancy is not the primary cause, but merely an event accompanied by active myocardial disease and a greater or less degree of cardiac incapacity.

SUMMARY

Sex and age have a remarkable influence on the development and progression of certain cardiovascular diseases.

Women of child-bearing age, for instance, are relatively immune to angina pectoris and acute myocardial infarction. Endocrine factors may thus exert a protective influence in the female, or, conversely, promote the development and progression of coronary artery disease in the male.

Thus any hypothesis advanced to account for the aetiology of obliterative coronary atherosclerosis must include the role of the sex hormones.

Blood-pressure is also influenced by age and by sex, the readings in healthy women up to middle life being on the average a few mm. Hg lower than in men of corresponding age. Over 40 years of age persistent hypertension is more common and better tolerated in the female.

In pregnancy she loses this immunity and becomes temporarily hypersensitive. Pressure rises of a few mm. Hg then denote distinct maternal and foetal risks.

Rheumatic heart disease is more common in women. It gives rise to special problems during pregnancy.

The major hazards confronting these cardiac patients are (1) a gradual deterioration to congestive heart failure before delivery, and (2) acute pulmonary oedema, often unanticipated and frequently fatal.

In pregnancy, acute pulmonary oedema is now relatively more frequent as a cause of death. It has a mortality rate approaching 20%. Its prevention is the major problem in current obstetric cardiology.

Strict medical supervision of cardiac women throughout pregnancy has proved rewarding. Our current mortality rate is 0.4%—15 times less than it was 30 years ago.

Valvotomy before conception in certain instances, sterilization in others in whom structural damage is far advanced, the recognition that rheumatic heart disease is not an indication for caesarean section, can all contribute to the avoidance of needless fatalities.

Mitral valvotomy is seldom essential during pregnancy. It can be justified in the earlier months when congestive heart failure threatens or when acute pulmonary oedema is anticipated. Late pregnancy is no time for major surgery.

The term "cardiomyopathy of pregnancy" includes a number of different entities. In one group congestive heart failure, presumably attributable to an acute myocarditis, is the dominant feature. Recovery can be complete and lasting. In a second group the leading features are dyspnoea, tachycardia, and angina of effort. In this instance the cardiac disability can persist for many years and prove refractory to treatment.

I express my indebtedness to my colleagues, Dr. Robert Marquis and Dr. Michael Oliver, on whose co-operation I have come to count and whose experience has been freely placed at my disposal. Mr. Andrew Logan has kindly supplied me with the details of his operative mortality in our patients with mitral stenosis.

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TREATMENT OF PRURITUS OF OBSTRUCTIVE JAUNDICE WITH CHOLESTYRAMINE

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Retained bile salts have for long been incriminated as the cause of the severe itching suffered by patients with obstructive jaundice. However, even using modern biochemical methods, a good correlation has not been shown between blood bile-salt levels and pruritus (Carey, 1958; Osborn *et al.*, 1959). In 1947 Varco noted that pruritus could be relieved in patients with partial biliary obstruction by intermittent external biliary drainage. This effect was presumably by preventing the little bile that could be excreted from being reabsorbed: the enterohepatic circulation was thus broken. The resin cholestyramine is said to bind bile salts in the intestine, so eliminating them in the faeces (Fig. 1) (Carey, 1960; Carey and Williams, 1961; Van Itallie *et al.*, 1961), and has been shown to stop the itching of obstructive jaundice (Carey and Williams, 1961). The present work reports the use of this material in 10 patients with pruritus due to obstructive jaundice; in addition to serum lipid fractions, faecal fat has been estimated.

FIG. 1.—Diagram showing the postulated mechanism by which cholestyramine removes bile acid in faeces, so blocking their enterohepatic circulation.

Material and Methods

The 10 patients treated were suffering from chronic obstructive jaundice (nine from primary biliary cirrhosis and one from congenital intrahepatic atresia) of at least one and half years' duration and were in a steady clinical state. All the patients were spontaneously complaining of itching, and scratch marks were present on the skin. The itching was graded clinically as mild, moderate, or severe. During the study the patients received a constant dietary intake of fat, carbohydrate, and protein.

Blood samples were obtained fasting and analyses were done in duplicate. Serum was analysed by the following methods: bile acids (Carey, 1958), cholesterol (Sperry and Webb, 1950), phospholipid (Allen, 1940), total lipids (Albrink, 1959). Triglycerides were calculated by subtracting phospholipids and cholesterol esters from the total lipids. Serum bilirubin and other routine liver-