Left Ventricular Oxygen Consumption, Blood Flow, and Performance in Mitral Stenosis

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Previous investigations in animals have shown the relative importance of the various components of cardiac effort: heart rate,1,2 arterial pressure,3-6 cardiac output,3-5 rate of pressure development,7-8 and the "tension-time index"9 as hemodynamic determinants of coronary blood flow and myocardial oxygen consumption. Particular emphasis has been placed on the importance of arterial pressure and various pressure-heart rate indices.9-11 These studies have provided valuable insight into the determinants of myocardial oxygen usage. However, information obtained during the study of acute dog preparations, altered by anesthesia and surgery, is not necessarily applicable to normal human cardiac function or to chronic disease in man. Studies in human subjects investigating the determinants of coronary flow and myocardial oxygen consumption during rest and exercise have been limited to a description of myocardial energy requirements and oxygen delivery in patients with minimal heart disease,12 congestive heart failure,13 and hyperlipemia.14

The restrictions imposed by mitral stenosis on the left ventricular response to effort provide a unique opportunity to study the determinants of coronary flow and myocardial oxygen usage in man. Not only is the response of cardiac output limited in many cases, but this limitation, associated with peripheral vasodilatation in the exercising extremities, leads to a decrease in arterial pressure (exertional hypotension) in a significant number of patients.15 These phenomena permit an evaluation of the influence of pressure and pressure change that is not possible in other subjects. For these reasons, the hemodynamic determinants of coronary blood flow and myocardial oxygen usage were studied in a series of patients with mitral stenosis.

Materials and Methods

Nineteen patients under 50 years of age with mitral stenosis were studied. All had pure mitral stenosis without evidence of mitral regurgitation or aortic valve disease. None had a history of chest pain or an electrocardiogram suggestive of coronary artery disease. Moderately severe to severe mitral stenosis was demonstrated in all patients at cardiac catheterization and confirmed at surgery.

Patients were studied in the fasting state following mild barbiturate sedation. A double-lumen catheter was placed in the pulmonary capillary wedge position and pulmonary artery through a right antecubital vein. The coronary sinus was entered through a left antecubital vein. The left ventricle and aortic root were catheterized in a retrograde fashion through percutaneous puncture or arteriotomy of brachial or femoral arteries.

Steady-state measurements of coronary blood flow, cardiac output, and systemic and pulmonary arterial pressures were made at rest and during supine exercise on a bicycle ergometer. Coronary blood flow was measured by the nitrous oxide desaturation technic,16 with use of a partition coefficient between blood and myocardium of 1.1.17 Cardiac output was measured by the Fick method. Blood gases were analyzed by the technic of Van Slyke and Nell18 on specimens.
obtained from the coronary sinus, pulmonary artery, and aorta during the sixth minute of nitrous oxide desaturation. Expired air, which was analyzed for oxygen by the Scholander apparatus or the Beckman oxygen analyzer, was collected in a Tissot spirometer during the fifth to seventh minutes of nitrous oxide desaturation in the resting study, and during the sixth minute of desaturation in the exercising study. Pressures were measured with Statham strain-gauges, recorded by an Electronics for Medicine recorder, and calibrated directly with a mercury manometer. The reference level for zero pressure was half way from the manubrium to the table top. Immediately before and after each measurement of coronary blood flow, arterial and coronary sinus blood specimens were obtained for the determination of lactate and pyruvate.

Myocardial oxygen consumption (\(\text{MVO}_2\)) expressed as mL/100 Gm. LV/min., was calculated as the product of coronary arteriovenous oxygen difference and coronary blood flow (CBF), expressed as mL/100 Gm. LV/minute. Excess lactate was calculated according to the Huckabee formula. The product of heart rate and the planimetrically integrated systolic arterial pressure, the pressure-time per minute (PTM), expressed as mm. Hg second/minute, was obtained from recordings at paper speeds of 100 or 200 mm./second. Internal myocardial efficiency was calculated as the ratio of PTM to \(\text{MVO}_2\), as suggested by Sarnoff and co-workers.

The data in seven patients were incomplete due to unsatisfactory CBF determinations, displacement of the coronary sinus catheter during exercise, or an unsteady state as determined by comparison of heart rates and pressures recorded before, during, and after each CBF. In 12 patients, six men and six women, the data were complete at rest and during exercise. A group of CBF studies in normal subjects during rest and exercise previously reported from this laboratory was used as controls. Comparisons were made of the relative degree of exercise achieved, as well as of any differences occurring in basic coronary and systemic flow patterns between this group of normal subjects and patients with mitral stenosis. Since pressure records in the normal subjects were obtained at appreciably lower sensitivities and at slow paper speeds on a direct-writing recorder, comparison of PTM data was not considered valid.

Statistical analyses were performed with conventional methods for small samples. Differences were evaluated by Student's t test. Correlations were measured with the correlation coefficient \(r\). Since myocardial oxygen requirements not connected with effort but needed for maintenance of the architectural integrity of the heart are unknown, and may vary from patient to patient, particular emphasis was placed on the analysis of changes, from rest to exercise, in CBF, \(\text{MVO}_2\), and the various components of cardiac effort.

**Results**

The results appear in table 1.

**Coronary and Systemic Hemodynamics at Rest**

At rest, patients with mitral stenosis had a mean total body oxygen consumption, heart rate, and mean aortic pressure that did not differ significantly from normal subjects. Despite a lower cardiac index \((p < 0.05)\) and left ventricular minute work \((p < 0.05)\), CBF, \(\text{MVO}_2\), and coronary vascular resistances did not differ from normal. Myocardial oxygen extraction was increased \((p < 0.02)\) due to a slightly lower mean CBF and slightly higher \(\text{MVO}_2\). Total peripheral resistance was above normal \((p < 0.02)\).

**Coronary and Systemic Hemodynamics during Exercise**

During exercise, at a level of total body oxygen consumption not significantly different from that achieved by the normal subjects, patients with mitral stenosis had a faster heart rate \((p < 0.02)\), lower cardiac index \((p < 0.01)\), and lower left ventricular minute work \((p < 0.01)\), but higher peripheral resistance \((p < 0.02)\) than did normal subjects. Four patients with mitral stenosis responded to exercise with a fall in mean arterial pressure, while the remaining eight had a pressure increment not different from normal. Patients with mitral stenosis were therefore separated into subgroups on the basis of the direction of change of mean aortic pressure during exercise (group A = pressure increment, group B = pressure decrement). No significant differences between group A and group B were present in either the systemic or coronary hemodynamic patterns at rest (table 2). During exercise, group A increased left ventricular PTM and minute work, while the hypotension occurring in group B resulted in a reduced PTM and unchanged minute work (table 2). Moreover, coronary hemodynamics were strikingly differ-
Table 1

Effects of Exercise in Mitral Stenosis

<table>
<thead>
<tr>
<th>Subject, age, sex</th>
<th>Body surface area, M.²</th>
<th>CBF ml./100Gm. LV/min.</th>
<th>MVO₂</th>
<th>C(A-V)O₂, vol. %</th>
<th>Total body VO₂, ml./min.</th>
<th>Cardiac index, L. /min. /M.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.B., 27, M</td>
<td>1.67</td>
<td>87*</td>
<td>10.2</td>
<td>11.6</td>
<td>222</td>
<td>3.02</td>
</tr>
<tr>
<td>J.M., 49, M</td>
<td>1.62</td>
<td>56</td>
<td>6.2</td>
<td>11.2</td>
<td>259</td>
<td>2.39</td>
</tr>
<tr>
<td>M.S., 24, F</td>
<td>1.86</td>
<td>88</td>
<td>8.6</td>
<td>9.8</td>
<td>216</td>
<td>3.23</td>
</tr>
<tr>
<td>S.T., 36, M</td>
<td>1.74</td>
<td>90</td>
<td>10.1</td>
<td>11.3</td>
<td>176</td>
<td>1.77</td>
</tr>
<tr>
<td>F.M., 42, F</td>
<td>1.42</td>
<td>71</td>
<td>8.0</td>
<td>11.2</td>
<td>214</td>
<td>2.18</td>
</tr>
<tr>
<td>F.S., 43, F</td>
<td>1.78</td>
<td>75</td>
<td>9.1</td>
<td>12.1</td>
<td>278</td>
<td>3.39</td>
</tr>
<tr>
<td>I.F., 30, F</td>
<td>1.29</td>
<td>59</td>
<td>6.4</td>
<td>10.8</td>
<td>177</td>
<td>2.25</td>
</tr>
<tr>
<td>J.R., 40, M</td>
<td>1.66</td>
<td>83</td>
<td>12.6</td>
<td>15.2</td>
<td>349</td>
<td>3.45</td>
</tr>
<tr>
<td>J.D., 36, M</td>
<td>1.79</td>
<td>74</td>
<td>9.5</td>
<td>12.9</td>
<td>222</td>
<td>2.21</td>
</tr>
<tr>
<td>B.P., 45, M</td>
<td>1.71</td>
<td>89</td>
<td>10.7</td>
<td>12.0</td>
<td>225</td>
<td>2.99</td>
</tr>
<tr>
<td>D.I., 47, F</td>
<td>1.92</td>
<td>81</td>
<td>9.8</td>
<td>12.1</td>
<td>251</td>
<td>2.42</td>
</tr>
<tr>
<td>M.L., 31, F</td>
<td>1.43</td>
<td>86</td>
<td>11.5</td>
<td>13.4</td>
<td>197</td>
<td>3.13</td>
</tr>
</tbody>
</table>

Mitrake stenosis
- Mean resting values
- Mean exercising values

Normal subjects
- Mean resting values
- Mean exercising values

Significance of differences (mitral stenosis vs. normal subjects)
- Rest
- Exercise

*Resting values.
**Exercising values.
†C(A-V)O₂, coronary arteriovenous O₂ difference.
§LVEDP, left-ventricular end-diastolic pressure.
¶Patients with atrial fibrillation. All other patients were in regular sinus rhythm.
*NS, not statistically significant.

All other abbreviations are as given in the Materials and Methods section of the paper.

ent (table 2, figs. 1-4). When arterial pressure and the PTM rose, CBF and MVO₂ increased, and coronary vascular resistance fell in a manner not significantly different from that of normal subjects. In contrast, a decrease in arterial pressure or PTM was associated with a fall in CBF, while MVO₂ decreased or was unchanged at the expense of an increased myocardial oxygen extraction. With exertional hypotension, coronary resistance rose, despite a fall in total peripheral resistance, suggesting vasoconstriction.
Determinants of Coronary Blood Flow and Myocardial Oxygen Consumption

Changes in CBF correlated well with changes in mean aortic pressure ($r = 0.93$, $p < 0.001$), and in PTM ($r = 0.81$, $p < 0.001$), but poorly and insignificantly ($p < 0.01$) with changes in cardiac index ($r = 0.34$) and left ventricular work ($r = 0.54$).

Under the circumstances of bidirectional change in perfusion pressure in these patients, changes in CBF correlated poorly with changes in MVO$_2$ ($r = 0.26$, $p > 0.10$), since a fall in CBF was accompanied by increased oxygen extraction resulting in little change in MVO$_2$. However, absolute values for CBF correlated well with MVO$_2$ at rest ($r = 0.81$, $p < 0.01$) and during exercise ($r = 0.78$, $p < 0.01$).

MVO$_2$ was most influenced by PTM (at rest, $r = 0.66$, $p < 0.01$; during exercise $r = 0.75$, $p < 0.01$; and for the change from rest to exercise, $r = 0.88$, $p < 0.001$, fig. 3). Although

| Heart rate, beats/min. | Mean arterial pressure, mm. Hg | LVEDP, mm. Hg | PTM, mm. Hg/sec./min. | LV work, Kg.-M./min. | Total peripheral resistance, mm. Hg | Coronary resistance index, mm. Hg | Mitral valve area, cm.$^2$
|------------------------|-------------------------------|----------------|------------------------|---------------------|-----------------------------|-----------------------------|----------------
| 78                     | 87                            | 10             | 1957                   | 6.29                | 1381                        | 1.00                        | 0.8
| 107                    | 94                            | 6              | 2719                   | 8.09                | 1255                        | 0.66                        | 0.5
| 72;                   | 93                            | 11             | 1704                   | 4.52                | 1923                        | 1.66                        | 1.17
| 144                   | 96                            | 10             | 2293                   | 4.23                | 2270                        | 1.17                        | 1.02
| 74                     | 90                            | 9              | 2424                   | 6.97                | 1200                        | 0.75                        | 1.2
| 135                   | 94                            | 11             | 2641                   | 13.81               | 642                          | 0.99                        | 0.4
| 87                     | 81                            | 9              | 1631                   | 3.58                | 2104                        | 0.99                        | 0.6
| 120                   | 86                            | 7              | 1889                   | 9.49                | 895                          | 0.77                        | 0.6
| 86;                   | 75                            | 6              | 1504                   | 3.34                | 1935                        | 1.06                        | 0.86
| 132                   | 80                            | 6              | 1928                   | 3.60                | 2040                        | 1.35                        | 1.3
| 96;                   | 108                           | 12             | 2918                   | 9.36                | 1430                        | 1.44                        | 1.3
| 120                   | 111                           |                | 3510                   | 12.07               | 1172                        | 0.93                        | 0.9
| 73                     | 67                            | 8              | 1530                   | 2.83                | 1876                        | 1.15                        | 0.4
| 130                   | 84                            |                | 2556                   | 5.97                | 1357                        | 0.66                        | 0.9
| 93                     | 115                           | 7              | 2923                   | 9.43                | 1608                        | 1.39                        | 0.9
| 190                   | 122                           |                | 3737                   | 12.89               | 1326                        | 1.20                        | 0.9
| 68                     | 85                            | 9              | 1999                   | 4.83                | 1715                        | 1.15                        | 0.9
| 144                   | 72                            | 6              | 1658                   | 3.94                | 1514                        | 1.33                        | 0.9
| 84                     | 85                            | 11             | 2367                   | 6.23                | 1331                        | 0.96                        | 0.9
| 103                   | 75                            | 7              | 2111                   | 6.58                | 982                          | 1.12                        | 0.6
| 70;                   | 93                            | 11             | 2417                   | 6.21                | 1600                        | 1.15                        | 1.45
| 90                     | 87                            | 12             | 2253                   | 7.14                | 1231                        | 1.15                        | 1.3
| 65                     | 99                            | 5              | 2572                   | 6.44                | 1633                        | 1.16                        | 1.3
| 92                     | 92                            |                | 1880                   | 6.07                | 1434                        | 1.01                        | 0.8
| 79                     | 90                            | 9              | 2162                   | 5.84                | 1645                        | 1.17                        | 0.99
| 126                   | 91                            | 8              | 2431                   | 7.82                | 1343                        | 0.99                        | NS
| 77                     | 92                            |                | 7.46                   |                     | 1347                        | 1.14                        | NS
| 98                     | 99                            |                | 12.58                  |                     | 907                          | 0.90                        | NS

NS $p < 0.02$ NS $p < 0.01$ NS $p < 0.02$ NS

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Table 2

Effects of Exercise in Patients with Mitral Stenosis with and without Exertional Hypotension

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean resting values</th>
<th>Mean exercising values</th>
<th>Mean change from rest to exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body O₂ consumption</td>
<td>236</td>
<td>223</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.71</td>
<td>2.69</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>82</td>
<td>72</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>90</td>
<td>91</td>
<td>NS</td>
</tr>
<tr>
<td>LV work</td>
<td>5.8</td>
<td>5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>1682</td>
<td>1570</td>
<td>NS</td>
</tr>
<tr>
<td>PTM</td>
<td>2074</td>
<td>2339</td>
<td>NS</td>
</tr>
<tr>
<td>CBF</td>
<td>11.7</td>
<td>12.6</td>
<td>NS</td>
</tr>
<tr>
<td>C(A-V)O₂</td>
<td>8.9</td>
<td>10.4</td>
<td>NS</td>
</tr>
<tr>
<td>MVO₂</td>
<td>1.21</td>
<td>1.11</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group A patients had a rise in pressure during exercise, and group B patients had exertional hypotension. All abbreviations and units of measurements as in table 1.

Discussion

The wide range of cardiac outputs, systemic pressures, and heart rates observed in the patients with mitral stenosis proved useful in the experimental tests. The data in these patients indicated that when left atrial pressures and heart rates were elevated (table 1), atrial flutter was observed in four patients. The data in these patients did not appear to be different from those with a regular sinus rhythm or from those with atrial fibrillation.

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Figure 1
The relationship between the changes in coronary blood flow and mean aortic pressure produced by exercise.

Figure 2
The relationship between the changes in myocardial oxygen consumption and mean aortic pressure produced by exercise.

Figure 3
The relationship between the changes in coronary blood flow and pressure-time per minute produced by exercise.

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evaluating the varying metabolic requirements of these several components of cardiac effort. Despite the restriction imposed by mitral stenosis on resting cardiac output and external work, CBF did not differ from that of normal subjects who had insignificantly different aortic pressures and heart rates. During exercise, regardless of the ability of individual patients to increase external work or cardiac output, CBF and MVO$_2$ rose when a pressor response occurred and did not differ from normal. Moreover, a fall in arterial pressure resulted in a reduced CBF regardless of changes in external work or output. Thus, in this chronic valve disease, changes in CBF are relatively independent of changes in cardiac output and work. In fact, the data demonstrate the dependence of changes in CBF on changes in perfusion pressure ($r = 0.93$). When a fall in perfusion pressure occurred, oxygen requirements were supplied only through increased myocardial oxygen extraction, since CBF decreased. This confirms the work of Alella and co-workers, who demonstrated in dogs that coronary flow increased with increases in aortic pressure in those situations where oxygen consumption was unchanged. In the same study, a two-fold increase in cardiac output did not alter coronary flow when aortic pressure was held constant.

Despite a cardiac output below normal at rest and a smaller increment during effort, resting MVO$_2$ did not differ from normal and changes in MVO$_2$ during exercise followed alterations in the systemic pressure but not in the cardiac output. Correlation of output with MVO$_2$ was poor. This is in agreement with Alella and co-workers, who found in dog experiments that the regression coefficient associating output with MVO$_2$ was not significantly different from zero. Left ventricular work was also limited by a reduced cardiac output at rest; exercising work was affected by a restriction in output in most patients and by a reduction in pressure in four patients. Since MVO$_2$ followed only pressure

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**Figure 4**

*The relationship between the changes in myocardial oxygen consumption and pressure-time per minute produced by exercise.*

**Figure 5**

*The effect of exercise on the internal myocardial efficiency. The ratio of pressure-time per minute to myocardial oxygen consumption is used to express internal myocardial efficiency. The closed circles connected by thin lines represent the ratios at rest and during exercise for each patient with mitral stenosis. The open circles connected by the heavy line are the mean values for the entire group and those connected by the dashed line are the mean values for subjects with minimal heart disease as reported by Gorlin et al.*

*FRANK ET AL.*
and not the cardiac output, correlation coefficients relating oxygen consumption to external work were poor. Wiggers and Katz, 22 Katz et al., 10 and Alella et al. 3 have previously pointed out in dog studies that work represents only the dynamic effort of the ventricle while static effort, the build-up and maintenance of tension in the ventricle, is more costly in terms of energy expenditure.

The factor that takes account of both the static and dynamic components of effort is the total systolic wall tension. However, calculation of total wall tension in the ventricle requires a knowledge of both the dimensions and the pressure of the chamber, since the relationship between pressure and total myocardial force changes with alteration in size and shape. Measurements of both left ventricular volumes and myocardial oxygen consumption in the same human subjects have not yet been reported, and previous studies as well as the present one are, therefore, not entirely complete. However, in the absence of a knowledge of ventricular dimensions, PTM proved to be the most important determinant of MVO₂. Increments in PTM were uniformly accompanied by comparable increments in MVO₂ while a decrease in PTM resulted in a reduced MVO₂ (r = 0.88). If during supine exercise, no significant change in ventricular volume occurs, the volume factor would be the same in both states and is excluded by an analysis of differences as reported in this study.

Rodbard and co-workers 23 had predicted that the reduced left ventricular filling in mitral stenosis would be expected to shorten the radius and lower the total tension and thus the oxygen requirements of the myocardium. Studies in this laboratory have shown that the end-diastolic volume of the left ventricle at rest is indeed smaller in patients with mitral stenosis than in normal subjects and changes little during exercise. Therefore the total wall tension for a given pressure would be less than normal. However, despite the shortened radius, MVO₂/100 Gm. LV/minute was within normal limits. It is possible that, while MVO₂/100 Gm. LV/minute is normal, the total MVO₂ is, in fact, reduced by reason of a reduced muscle mass. Alternatively, as Gauer 24 has predicted, a given stroke output may, in a small heart, be ejected at a lower myocardial efficiency, owing to greater fiber shortening with enhanced internal frictional loss of energy. In our patients with mitral stenosis, however, the combination of a reduced stroke volume and a reduced end-diastolic volume resulted in a percentage shortening from initial fiber length not significantly different from that of normal subjects studied in this laboratory (normal = 19.6 ± 3.7 per cent; mitral stenosis = 16.5 ± 3.8 per cent, p > 0.10). In all probability, therefore, the mass of the left ventricle in mitral stenosis is reduced.

Aortic pressure, uncorrected for systolic time, correlated better with oxygen usage than would have been anticipated from recent dog studies. 11 However, Lorber 25 has reported similar results in situations where diastolic filling was held constant. The restriction to diastolic filling in mitral stenosis might reproduce this situation. In addition, Katz and Feinberg 10 have shown that changes in pressure prove to be a better index of changes in tension at rapid heart rates. Patients with mitral stenosis in this study had a significantly greater heart rate response to effort than did normal subjects.

The internal efficiency of left ventricular pressure development, expressed as the ratio PTM/MVO₂, was not significantly different in mitral stenosis at rest from values reported in patients with normal left ventricles. 12 However, the mechanism of tension development during exercise was different. Patients with mitral stenosis sustain a reduction in pressure-time/beat with an excessive heart rate response. Normal subjects increase pressure-time/beat with a lesser rate increase. Thus the efficiency of pressure development rises with effort in normal subjects but falls in patients with mitral stenosis, in the absence of an increase in anaerobic metabolism. These observations in intact man indicate that, with total tension per minute constant, the more frequent development of a lower myo-
cardial tension requires more energy than the less frequent development of a higher tension.

Summary

The restriction imposed by mitral stenosis on the cardiac output response to exercise provides a unique opportunity in man to evaluate determinants of coronary flow and myocardial oxygen consumption, since one or several variables may be limited. Coronary and systemic hemodynamic patterns were therefore evaluated in 12 patients with mitral stenosis and compared with normal subjects.

While cardiac output and left ventricular work were lower than normal at rest, coronary flow and myocardial oxygen consumption did not differ from normal. During exercise, despite subnormal cardiac output and left ventricular work responses, coronary blood flow and myocardial oxygen consumption increased normally in the group of patients in whom arterial pressure rose. However, coronary flow fell in four patients who experienced exertional hypotension, while myocardial oxygen consumption was reduced or unchanged. In both groups, myocardial oxygen extraction was above normal at rest and rose further during exercise. Changes in myocardial oxygen consumption followed alterations in the pressure-time index, but the excessive heart rate response to exercise resulted in a greater oxygen expenditure per unit of tension developed per beat than that found in normal subjects.

It is concluded that the primary determinant of coronary blood flow in mitral stenosis is the arterial perfusion pressure while myocardial oxygen consumption is primarily dependent on the pressure-time index. In addition, heart rates inappropriately high for a given state result in energy expenditures above that required for maintenance of pressure and cardiac output.

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References


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How Medicine Became a Science

In the latter part of the eighteenth century real scientific progress bearing on medicine was made in several directions, in chemistry, in physics and in pathology. Scheele, Black and Priestley contributed to the foundation of modern chemistry but it was Lavoisier who first looked on chemistry with the modern eye. He it was who first dissolved the mists of vague speculation and saw the true meaning of chemical reaction. His Réflexions sur le Phlogistique (1783) and particularly his Traité Élémentaire de Chimie (1789) mark the birth of modern chemistry. Lavoisier based his views upon the secure foundation of experiment and observation, and he had a firm opinion that his views would be ultimately adopted. His words are noteworthy—

"I do not expect that my ideas will be adopted at once; the human mind inclines to one way of thinking and those who have looked at nature from a certain point of view during a part of their lives adopt new ideas only with difficulty; it is for time, therefore, to confirm or reject the opinions that I have advanced."

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