Hyperbaric Oxygen in Cardiovascular Disease

Potential Usages and Hazards

By HERBERT A. SALTZMAN, M.D.

CLINICAL interest in hyperbaric oxygenation is recent, but scientific curiosity about high-pressure environment dates back to ancient times. Alexander the Great of Macedonia was the earliest hyperbaric investigator of whom we have recorded evidence. He surveyed the ocean depths in a glass and animal skin diving-bell (fig. 1). Among his most remarkable observations was a fish of such extraordinary length that it required 3 days to swim by his viewing port. Certainly Alexander and his biographers were not given to understatement, a trait they may share with subsequent workers in this field. During the past two centuries, scientists in many countries have studied the biologic effects of increased environmental pressures with emphasis on the underwater civil and military applications of this knowledge. Sporadic efforts at treatment of various illnesses with compressed air alone have proved ineffectual and been abandoned with the exception of decompression sickness. More recently, however, Boerema and associates have introduced the hyperbaric chamber to the modern medical era by demonstrating enhanced oxygenation when increased atmospheric pressures are combined with the respiration of pure oxygen. Present-day medical chambers reflect this concept in their design and employment.

In the modern chamber alveolar oxygen tensions can be increased far beyond levels achieved by any other means. In practice, the patient respires pure oxygen from a mask or other appropriate delivery system while the chamber is pressurized with air. At several atmospheres of environmental pressure the

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Figure 1

Illustration according to a medieval French manuscript of Alexander the Great surveying the ocean from a diving bell. From a Thirteenth Century manuscript, courtesy of the New York Public Library.
HYPERBARIC OXYGEN

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oxygen molecules breathed are crowded together and exert a proportionally greater pressure upon the alveolar air spaces and pulmonary capillaries.\(^{5}\) With efficient respiratory gas exchange, pulmonary capillary blood will equilibrate to the same tension, thereby forcing larger amounts of oxygen into free solution in blood. If this increase in oxygen delivery can be translated into more effective oxygenation of tissues, hyperbaric oxygenation will have dramatic therapeutic application in certain cardiovascular diseases associated with organ hypoxia. Suitable examples include coronary heart disease, cerebral vascular insufficiency, arterial insufficiency of the extremities, and surgical procedures that require temporary interruption of the circulation. This review describes the known biomedical effects of hyperbaric oxygenation upon the circulation in health and in the presence of cardiovascular disease. In addition, the special problems associated with this modality are discussed briefly, so that the limitations of present-day therapy can be delineated more clearly.

Physiologic Effects

Environmental air contains 20.93 per cent oxygen with a resultant inspired air tension of 149 mm. Hg.\(^{6}\) Dilution of this gas in the lungs lowers the effective alveolar oxygen tension to 100-110 mm. Hg. Other factors normally present reduce the tension to 100 mm. Hg or less during the time equilibrated pulmonary capillary blood enters the systemic circulation. The amount of this slightly soluble gas which enters free solution obeys physical laws described by Henry and is proportional to the oxygen tension. Normally constituted blood will hold 0.0031 vol. per cent of oxygen for each mm. Hg tension exerted by that gas. Therefore, a 100-ml. aliquot of blood would hold 0.31 ml. of oxygen in free solution, if the oxygen tension were 100 mm. Hg. This volume is small by comparison to the much larger (20 ml.) amount carried in chemical combination with oxyhemoglobin; nevertheless the physiologic importance of freely dissolved oxygen is great. The number of oxygen molecules forced into solution can be increased readily by a factor of 5 with respiration of pure oxygen. Oxygenation can be increased still further by increasing the atmospheric pressure. At 3 atmospheres of absolute pressure, the alveolar oxygen tension exceeds 2,000 mm. Hg, and perfectly equilibrated pulmonary capillary blood would contain 6 vols. per cent of oxygen in free solution, an amount exceeding the over-all metabolic requirements. This oxygen content of blood has been experimentally determined in normal animals and man during exposure to increased atmospheric pressure.\(^{6-8}\) In most studies the measured values for arterial blood oxygen tension are similar to the findings in table 1. In general, the anticipated linear relationship to atmospheric pressure is demonstrated readily. Under the usual experimental conditions, however, observed values fail to equal the anticipated measurements for reasons that are not understood fully. The measured arterial blood oxygen tension approaches 1,700 rather than 2,000 mm. Hg at 3 atmospheres absolute, with approximately 5.0 vols. per cent of oxygen in free solution. That physically dissolved oxygen exceeds the over-all body metabolic requirements is confirmed by demonstration of 100 per cent oxygen saturation for venous blood hemoglobin. Under the same experimental conditions the right atrial blood oxygen tension exceeds 400 mm. Hg (table 1).

Certain vascular effects of hyperbaric oxygenation can be observed directly in the optic fundus in figure 1. Hyperbaric oxygenation produces two major changes in the retinal vessels when they are compared to air-breathing control.\(^{9}\) First, marked constriction occurs in both veins and arteries, and smaller vessels are no longer visible. The caliber of the retinal vessel decreases further as the oxygen tension rises. Secondly, the normal color difference between retinal venous and arterial blood is lost. The general nature of the vasoconstrictive phenomenon is indicated by the calculated rise of systemic vascular resistance in normal subjects exposed to hyperbaric oxygena-

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\(^{5}\) Tensions are calculated as the product of environmental dry pressure and gas concentration, i.e., \([\text{(}760 - \text{water vapor pressure} \frac{[47]}{\text{)*}} \times 0.2093 = 149]\).

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Hyperbaric peroxygenation. Several oxygenation. Hyperbaric increase type have determined to increase moderately in this experimental setting, and mean arterial blood pressure remains constant. As a result, measured heart work does not increase grossly.

The observed hyperoxygenation of venous blood suggests that tissues accumulate increased amounts of oxygen during hyperbaric exposure despite vasoconstriction and blood flow reduction. This oxygen storage effect, however, is not easily demonstrated. Miniature electrodes have been developed for insertion into tissue but seem influenced to an excessive degree by proximity to blood vessels or alterations in tissue pressure. Perhaps the most valid test of tissue oxygen uptake is to determine whether normal organ function can be prolonged if perfusion is temporarily interrupted. Several recent experiments of this type have demonstrated a measurable increase in tissue oxygen storage during hyperbaric oxygenation. For example, mean normal brain electrical activity persists for 20 seconds longer during induced circulatory arrest if the experimental animal has been hyperoxygenated at 3.04 atmospheres absolute. Hyperbaric oxygenation can be demonstrated to produce similar effects in normal man as well. With use of the eye as a test organ of convenience, temporary retinal ischemia is produced by application of pressure over the eyeball. In the absence of perfusion, vision is lost within a 10-second period during air breathing and returns promptly after release of the ischemic pressure. However, inhalation of 100 per cent oxygen increases the persistence of vision during ischemia to 50 seconds at 3.72 atmospheres absolute (fig. 2). Persistence correlates directly with the higher arterial blood oxygen tensions. In addition, this interval of retained vision can be extended further with the addition of carbon dioxide in small amounts to the inspired oxygen gas mixture. However, in another series of studies, Brown and associates have demonstrated only a modest increase in survival of a large series of dogs subjected to hyperbaric oxygenation prior to total arrest of the circulation by electronic fibrillation of the heart. Only five of 14 animals survived 15 minutes of total circulatory arrest after hyperoxygenation at 4 atmospheres absolute and hypothermia.

Three conclusions can be drawn from these several experimental observations. First, hyperbaric oxygenation does increase the deliv-

Table 1

Mean Blood-Oxygen Responses to Hyperbaric Oxygenation in Ten Normal Subjects

<table>
<thead>
<tr>
<th>Environmental pressure (atmospheres)</th>
<th>Inspired gas</th>
<th>Arterial blood</th>
<th>Venous blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pO2 (mm. Hg)</td>
<td>O2 (vol. %)</td>
</tr>
<tr>
<td>1</td>
<td>air</td>
<td>89 3.2*</td>
<td>19.1 0.32</td>
</tr>
<tr>
<td>1</td>
<td>100% O2</td>
<td>507 13.9</td>
<td>21.2 0.51</td>
</tr>
<tr>
<td>3.04</td>
<td>air</td>
<td>402 9.2</td>
<td>20.8 0.51</td>
</tr>
<tr>
<td>3.04</td>
<td>100% O2</td>
<td>1721 33.5</td>
<td>25.2 0.51</td>
</tr>
</tbody>
</table>

* 1 Standard error.

Table 2

Hemodynamic Effects of Hyperbaric Oxygenation in Ten Normal Subjects

<table>
<thead>
<tr>
<th>Environmental pressure (atmospheres)</th>
<th>Inspired gas</th>
<th>Cardiac output (L./min.)</th>
<th>Heart rate (beats/min.)</th>
<th>Mean blood pressure (mm. Hg)</th>
<th>Peripheral resistance (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>air</td>
<td>6.1 ± 0.38*</td>
<td>75 ± 2.5</td>
<td>89 ± 3.8</td>
<td>15.3 ± 1.14</td>
</tr>
<tr>
<td>1</td>
<td>100% O2</td>
<td>5.8 ± 0.35</td>
<td>71 ± 2.8</td>
<td>90 ± 2.8</td>
<td>16.0 ± 1.14</td>
</tr>
<tr>
<td>3.04</td>
<td>air</td>
<td>5.7 ± 0.25</td>
<td>68 ± 2.8</td>
<td>88 ± 3.5</td>
<td>15.8 ± 0.79</td>
</tr>
<tr>
<td>3.04</td>
<td>100% O2</td>
<td>5.3 ± 0.35</td>
<td>63 ± 2.8</td>
<td>92 ± 3.2</td>
<td>17.8 ± 1.20</td>
</tr>
</tbody>
</table>

* 1 Standard error.
ERY OF OXYGEN TO VULNERABLE TISSUES, AND THIS INCREASED OXYGEN SUPPLY CAN BE UTILIZED TO PROLONG ORGAN FUNCTION IN THE ABSENCE OF PERFUSION. SECONDLY, THIS OXYGEN-STORAGE EFFECT IS OF ITSELF LIMITED AND NOT LIKELY TO BE OF EXCEPTIONAL VALUE TO THE CARDIOVASCULAR AND NEUROSURGEON WITH PRESENT TECHNIQUES OF APPLICATION. THIRD, ORGAN FUNCTION FAILS PROMPTLY AND INEVITABLY IN THE TOTAL ABSENCE OF A CIRCULATION, SUPPORTING THEORETICAL CALCULATIONS AND EXPERIMENTAL OBSERVATIONS WHICH INDICATE THAT GAS DIFFUSES POORLY THROUGH NONVASCULAR TISSUE ROUTES.14

CLINICAL OBSERVATIONS OF HYPERBARIC OXYGENATION IN CARDIOVASCULAR DISEASE

The biologic effectiveness of hyperbaric oxygenation in the treatment of medical ischemic illness is limited clearly by factors not present in studies of normal subjects. Most important, normal tissue oxygen delivery requires an intact capillary circulation, and impaired organ perfusion is an inherent part of ischemic illness. Retinal vascular occlusive disease is an easily identified clinical problem of this type. In addition, function of the visual organ can be measured with precision. So far the favorable visual functional responses to hyperoxygenation have been real but small, and appear limited to the interface between perfused and nonperfused retinal tissue.15 Two patients with retinal occlusive vascular disease demonstrated small increases in visual field size as measured with a Goldman perimeter during oxygen breathing at 1 atmosphere absolute. Significant additional improvement did not occur during hyperbaric oxygenation, and visual field measurements returned to control values after termination of oxygen breathing. In a third patient, oxygen breathing at 3.04 atmospheres did not improve visual acuity which had been damaged by a retinal arterial embolism a few hours earlier. Nevertheless, vision returned completely 12 hours later after movement of the embolism peripherally. Negative observations of the latter type do not rule out totally a beneficial effect of hyperoxygenation, since edema resulting from hypoxia might not have resolved during a short period of treatment. On the other hand, a reduced circulation may sustain organ function only during hyperbaric oxygenation. As a possible example of this hypothesis Heyman16 has observed a remarkable restoration of neurologic function with hyperoxygenation in four of 12 patients with acute cerebral vascular accidents. In one of these instances, the improvement persisted after decompression. However, the over-all functional responses to short periods of hyperoxygenation has not been impressive in this

Figure 2

Photographs of optic fundus in a normal subject (left) breathing air at 1 atmosphere absolute, and (right) breathing 100 per cent oxygen at 3.04 atmospheres absolute. Note the marked decrease in size of all vessels during hyperbaric oxygenation.
group. An apparent excellent treatment response has been observed also in a youngster with purpura fulminans who developed profound peripheral ischemia, pain, and a blue-black discoloration of the distal extremities. Since the natural history of this illness is often one of gangrene, amputation, and loss of life, the child was exposed intermittently to a total of 40 hours of hyperoxygenation at 2 atmospheres of pressure, in an attempt to oxygenate the hypoxic tissues. During each treatment the ischemic areas changed in color from purple to red and pain decreased noticeably. This child recovered completely. In another instance, a 53-year-old woman sustained a second myocardial infarction with cardiac arrest and resuscitation followed by sustained hypotension and a chaotic heart rhythm which could not be reversed by pharmacologic means. After all therapy had failed, the patient was subjected to 18 hours of hyperbaric oxygenation at 2 atmospheres of absolute pressure. In the eighth hour the cardiac rhythm reverted to normal and remained stable thereafter. This patient has recovered also from her illness. However, large case series confirming the general significance of these individually favorable responses have not been forthcoming as yet.

The internist has been excited most by the potential of hyperoxygenation for the treatment of severe coronary heart disease. Only Cameron has reported a carefully compiled and controlled series thus far. He reports no difference in treatment results for 20 patients with acute myocardial infarcts who were exposed to 48 hours of hyperbaric oxygenation at 2 atmospheres absolute. Furthermore, the mortality of 30 per cent was identical to previous hospital experience. However, interpretation of this study is limited by technical problems of gas delivery and the statistical limitations of good-risk case evaluation. Of the six patients in the hyperoxygenated group who died, five manifested cardiogenic shock prior to treatment. Only one patient in the control group manifested circulatory collapse upon entering this series, suggesting some difference in the clinical severity of cases in the groups compared. Future studies of high-risk patients should provide a more precise answer to this important question.

The results of treatment for peripheral ischemic illness have been inconclusive. Ischemic pain disappears commonly but returns after completing treatment. However, hyperoxygenation therapy requires further evaluation as regards extension of exercise tolerance and healing of ulcers in ischemia.

Hyperbaric oxygenation offers great promise to the cardiovascular surgeon, particularly in the management of severe cyanotic congenital heart disease. These patients often have responded unfavorably to previously available therapy. An increase in oxygen tension and content during hyperbaric exposure should provide a greater tolerance to anesthesia and to circulatory arrest during surgical treatment of the cardiac abnormality. Bernhard has operated on 90 children with congenital cardiac malformations with the aid of hyperbaric oxygenation. The results are impressive, particularly in the cyanotic group, in which 18 of 25 children have responded favorably. Nevertheless, respiratory gas exchange becomes a very inefficient means of oxygenating blood in a child with a large extrapulmonary right-to-left shunt. Enormous tensions would be required to saturate arterial blood normally. For this reason, the physiologic advantages resulting from oxygen respiration alone may prove limited. However, the combination of hyperoxygenation, efficient extracorporeal heart-lung machines, and hypothermia may have extraordinary value and merits very active study.

Special Problems Inherent in the Clinical Application of Hyperbaric Oxygenation to be Considered Carefully by Interested Groups

Unfortunately, the structural and hardware requirements of a hyperbaric chamber do not conform to standard architectural experience. The builder and user must solve unfamiliar problems in design. As a result, the research hyperbaric facility becomes enormously expensive to construct and may approach a cost of $1,000 per square foot of net usable floor.
space. Much of this cost is inherent in the stringent safety requirements of an artificial environment and is not likely to be changed with experience. Furthermore, like the submarine, the hyperbaric chamber requires an experienced crew familiar with the intimate details of their ship and capable of reacting instantly and correctly to changing requirements. We have found that experienced Navy-trained divers are particularly valuable in meeting these needs. The well-designed chamber provides back-up systems for all essential operational components. A typical example is the problem of air supply for pressurization and ventilation should the compressors fail. An ideal solution is to maintain, at all times, an emergency 24-hour supply of air in high-pressure storage flasks.

Fire is the most serious consequence of technical failure. The problem is particularly acute here because there is no possible rapid escape from the interior of a pressurized chamber. The gaseous environment, instrumentation, and limited volume exaggerate the hazard, and fatal accidents due to fire have occurred in nonclinical facilities. The advent of therapeutic chambers has made a solution to the problem more difficult, since the circumstances of treatment may preclude attempts at movement of either the patient or attending personnel. We have attempted to solve our problem by eliminating all possible fire hazards and by providing a specific means of control if all precautions fail. The Duke Chamber contains no sparking electric motors. Air-powered motors drive the internal air conditioner and even turn the tonometer on the waterbath. The uniforms worn by personnel and all of the surgical drapes are impregnated with a special fire retardant. Although the chamber is pressurized and ventilated with air, enrichment of the internal environment with oxygen or anesthetic gas would be hazardous. For this reason, and in order to facilitate collection for measurement, expired air of oxygen-breathing patients and animals is vented through a special exhaust device directly to the exterior. A special partitioning valve system had to be designed in order to perform this task without producing on the one hand a serious expiratory load resistance or on the other hand exposing the lungs of the patient to the large intolerable pressure gradient across the chamber wall. \(^{22}\) If a fire were to occur despite all precautions, a fire sprinkler system has been provided which incorporates sufficient pressure produced by a booster pump to overcome the resistance of a high atmospheric pressure within the chamber.

The research chamber must be engineered to permit quantitative measurement if results of treatment are to be evaluated properly. Every physiologic measurement made during a hyperbaric exposure requires a special engineering solution. For example, blood samples collected at 3 atmospheres will bubble and hemolyze if transferred outside the chamber for measurement. Therefore, equipment should be placed in the chamber for measurement of gas tension at the pressure of sample collection.

A patient subjected to a protracted hyperbaric exposure is isolated to a large extent from many of the hospital facilities that would be available ordinarily if a clinical requirement arose. Therefore, the operational chamber should contain essential emergency drugs and supplies, including tracheotomy and cut-down trays. Adequate nursing help and both integral operating and x-ray facilities should be incorporated, whenever possible, in future clinical hyperbaric chamber construction. If an acute surgical requirement were to occur during hyperoxygenation, the ability to move the patient to an operating room and perform the necessary surgical therapy without decompression would offer obvious advantages.

Another problem peculiar to hyperbaric exposure is decompression illness or "bends." A bends incidence of 2 to 6 per cent is found in standard references. \(^3\) This figure is unacceptable in a medical environment. Unfortunately, the differing biologic characteristics of medical personnel as compared to selected healthy young divers, and the present biomedical emphasis on prolonged shallow subsurface dives, increases the likelihood of in-
adequate nitrogen elimination when standard decompression tables are used. Three transient visual manifestations of dysbarism occurred in our first 1,500 personnel dives. 

However, the respiration of pure oxygen during the final minutes of an air decompression schedule accelerates nitrogen elimination and decreases the likelihood of nitrogen bubble formation during decompression. Clinically significant symptoms have occurred only once in our personnel since oxygen breathing has been incorporated into our decompression routine. Fortunately, the patient has the largest margin of protection under these circumstances, since he will wash out much of his tissue nitrogen while respiring pure oxygen during treatment. In any case, if a serious bend occurs, equipment and personnel should be prepared for prompt recompression.

In future exposures the use of exotic gas mixtures with differing tissue solubility and clearance characteristics will require more sophisticated decompression schedules. Exotic gases will be used for the patient, in order to avoid prolonged exposure of pulmonary tissue to pure oxygen, and for personnel so that they may function efficiently at greater environmental pressures. At the present time, the narcotic effects of nitrogen limit air-breathing personnel to an exposure of 4 atmospheres or 45 p.s.i.g, if they hope to function at a near optimum level. This measurable narcotic phenomenon is particularly serious if technically difficult procedures, such as cardiovascular surgery, are planned.

Major respiratory gas-delivery problems have occurred in severely ill, dyspneic, and only partially oriented patients. Unfortunately, control of the airway by intubation has served these patients poorly. Pulmonary work and respiratory distress increase substantially as a result of an increased respiratory gas density during hyperbaric exposure. Airway intubation aggravates respiratory distress because of the inevitable reduction in size of airway lumen. This effect can be demonstrated readily in normal subjects by introducing tracheotomy fittings into a respiratory assembly and measuring pulmonary ventilatory and mechanical performance. In addition to an increase of pulmonary work, airway resistance rises and flow rates decrease, as would be anticipated.

The most serious unsolved problem for the hyperbaric therapist is oxygen toxicity. Extreme hyperoxia can produce acute central nervous system symptoms and signs that terminate in convulsions and death. This form of oxygen toxicity is easily managed in man by discontinuing oxygen breathing promptly, but limits seriously the duration of safe exposure at oxygen pressures greater than 2.5 atmospheres absolute. Furthermore, patients may develop oxygen convulsions more readily than normal subjects. For example, a patient with sickle-cell disease in crisis convulsed after only 12 minutes of oxygen breathing, with a measured arterial blood oxygen tension of less than 60 mm. Hg (equivalent to a 2.5 atmosphere exposure).

A much more serious form of oxygen toxicity occurs in the lungs with excessive exposure to hyperbaric oxygenation. Characteristic irreversible findings of bronchopneumonia, congestion, and fibrinoid hyaline membrane formation appear with subsequent failure of respiratory gas exchange. This process terminates ultimately in death. However, an uninterrupted exposure of 3 to 5 hours does not produce symptoms of respiratory toxicity at inspired oxygen pressures of less than 3 atmospheres and forms the basis of most current treatment schedules.

A unique form of acidosis develops during hyperbaric oxygenation with displacement of acid into plasma, which would otherwise be bound isohydrically to the large venous pool of reduced hemoglobin. This phenomenon is caused by the less efficient buffering action of oxygenated venous hemoglobin. The extent of acidosis is small and limited to the venous circulation in normal animals and man with a pCO₂ rise of 5 or 6 mm. Hg and pH fall of 0.01 unit. However, animals subjected to hyperbaric oxygenation after surgical creation of a large venoarterial shunt demonstrated a very severe systemic acidosis, despite vigorous respirator-controlled ventilation. In this

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setting, the loss of a large fraction of the reduced hemoglobin acid buffer, the increased production of carbon dioxide, and the inefficient pulmonary clearance of carbon dioxide in the presence of a venoarterial shunt bypassing the lung, act synergistically, and carbonic acidosis results. This acidotic phenomenon becomes important clinically when children with cyanotic congenital heart disease are exposed to hyperbaric oxygenation.

Hyperbaric oxygenation has been shown by Mengel and associates to affect the red blood-cell population of animals with the appearance of hemolysis. Hemolysis is exaggerated by dietary depletion of antioxidants, such as vitamin E, and appears to be largely inhibited by supplemental feeding of animals with the same antioxidant. Significant hemolytic changes in patients, however, are rare. The relation of these observations to the clinical and pathologic manifestations of oxygen toxicity noted in the central nervous system and lungs is not clear as yet. If similar biochemical mechanisms are involved, current studies of factors producing hemolysis may provide information leading to more effective control of oxygen toxicity hazards in many organs.

Summary

In summary, hyperbaric oxygenation produces remarkable physiologic increases in oxygen transport to body tissues. However, potential benefit from hyperoxegenation in the treatment of ischemic disease appears dependent upon the presence of a partially intact capillary circulation. Improved means for prevention of oxygen toxicity and better techniques of oxygen delivery to specific sites are required, if hyperbaric oxygenation is to fulfill present hopes for therapeutic application.

References

2. Beebe, W.: Half Mile Down. New York, Duell, Sloan and Pearce, 1934, Figure 5 opposite p. 32.
How Medicine Became a Science

The latter part of the seventeenth century was dominated by the intelligence of Newton, whose influence on medicine was indirect. The influence of Newton was still strong at Cambridge when Stephen Hales arrived there, and it is likely that the same influence may have been at work to induce Francis Hauksbee to support Cheselden’s lectures on anatomy by teaching his students the mechanics of the human body. The latter part of the seventeenth century saw a large field opened for observation by the development of the microscope. Working with simple apparatus Hooke, Malpighi and Leeuwenhoek gave accurate descriptions of many minute objects. Leeuwenhoek pictured some micro-organisms which have in modern times been identified as common bacteria of the mouth. In the same period Robert Boyle’s chemical researches showed that air was necessary for animal life, and a few years later Lower and Mayow showed that it was a special part of the air which was essential for respiration; unfortunately the definite discovery of oxygen was not to be made for another century.—ZACHARY COPE, KT. Some Famous General Practitioners and other Medical Historical Essays. London, Pitman Medical Publishing Co., Ltd., 1961, p. 187.
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