John Snow’s leadership in epidemiology as well as anaesthesia resulted from his research as much as his clinical practice. In anaesthesia, Snow’s research concerned the regulation of concentrations of volatile agents and the development of efficient inhalers; the uptake and elimination of volatile agents; the use of anaesthetic gas; carbon dioxide metabolism and respiration; and metabolism in anaesthesia and the theories of anaesthesia. In epidemiology, Snow investigated the relationship of water supplies to mortality in cholera during the London epidemic in 1854, which led him to formulate an original and valid theory of the transmission of cholera. Snow’s research, which has received less attention than anecdotes concerning his career (e.g., his anaesthetizing Queen Victoria and urging removal of the handle of a contaminated water pump), was always directed towards solving specific problems. The significance of his research is evident in its leading not only to improvements in health care but also to the evolution of anaesthesia and epidemiology as professional disciplines.

John Snow (1813–1858) (Figure 1) achieved fame and leadership in two different fields—anaesthesia and epidemiology. A busy practitioner, his fame and leadership derive largely from the value of his research in these two disciplines. His research, however, is generally less well known than the highlights of his life and career (Table 1) and those episodes in his life that are the stuff of legend rather than the substance of research. Thus he is remembered for administering chloroform to Queen Victoria (hence the term à la reine) rather than for carrying out research that laid the basis of understanding of the nature of anaesthesia and for urging the removal of the handle of a pump of a contaminated well in Broad Street, London (admittedly a symbolic act) rather than for conducting a complex epidemiological investigation of the cholera epidemic in London in 1854.

Snow’s research is worth study for several reasons. First, his research advanced immeasurably the evolution of anaesthesia in its early years. He initiated its transition from a rag-and-bottle craft to a specialty based on scientific knowledge. Likewise, as member of the London Epidemiological Society, he was one of a handful of...
TABLE 1: Highlights of the life and career of John Snow (1813-1858)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1813</td>
<td>Born, York, England</td>
</tr>
<tr>
<td>1837</td>
<td>Apprenticed as William Haldane, Newcastle-on-Tyne</td>
</tr>
<tr>
<td>1841</td>
<td>Attended cholera victims, Kingsnorth</td>
</tr>
<tr>
<td>1850</td>
<td>Walked to London, viaing Wales and Bath en route</td>
</tr>
<tr>
<td>1851</td>
<td>Student of anatomy at Humanean School of Medicine</td>
</tr>
<tr>
<td>1852</td>
<td>Studied at Westminster Hospital</td>
</tr>
<tr>
<td>1853</td>
<td>Passed examinations for MBBS and LSA</td>
</tr>
<tr>
<td>1854</td>
<td>Set up general practice in Soho, London</td>
</tr>
<tr>
<td>1857</td>
<td>Graduated MB, BS (London)</td>
</tr>
<tr>
<td>1858</td>
<td>Obtained higher degree of MD-London</td>
</tr>
<tr>
<td>1859</td>
<td>Established ethical rules</td>
</tr>
<tr>
<td>1860</td>
<td>Anaesthetist, St. George's Hospital</td>
</tr>
<tr>
<td>1861</td>
<td>Anaesthetist, St. George's Hospital</td>
</tr>
<tr>
<td>1862</td>
<td>Published On Ether</td>
</tr>
<tr>
<td>1863</td>
<td>Conducted chloroform ether</td>
</tr>
<tr>
<td>1865</td>
<td>Published On the Mode of Communication of Chlores</td>
</tr>
<tr>
<td>1865</td>
<td>Established Queen Victoria at birth of Prince Leopold</td>
</tr>
<tr>
<td>1866</td>
<td>Urged removal of handle of cholera-contaminated water pump in Broad</td>
</tr>
<tr>
<td></td>
<td>(now Brunswick) Street London, and conducted into epidemiologic investigation of the London epidemic.</td>
</tr>
<tr>
<td>1867</td>
<td>Published 2nd edition of monograph on cholera</td>
</tr>
<tr>
<td>1868</td>
<td>Anaesthetist Queen Victoria at birth of Princess Beatrice</td>
</tr>
<tr>
<td>1869 (June 16)</td>
<td>Died, London</td>
</tr>
</tbody>
</table>

*There are numerous accounts of Snow’s life and work in the literature of anaesthesia, epidemiology and general practice. The biographic accounts are short sketches. The only contemporary accounts are those by W. B. Richardson, on which many later accounts are based. Among other accounts are those by Gowers (1934), Key (1946), Hopkin (1958), Cementwright (1958), Edwards (1959), Brown (1964) and Thomas (1969).*

Snow not only was observant but also understood a basic aspect of respiration. He understood the physiology of respiration long before he began his research into anaesthesia. Two topics that interested him in these early years (1837-1847) were the toxicity of carbon dioxide and asphyxia.
CARBON DIOXIDE TOXICITY

On December 1, 1838, at a meeting of the Westminster Medical Society, Snow asked Dr. Golding Bird to explain a statement he had made at the previous meeting. When Dr. Bird had said that from eight to ten per cent of carbonic acid in the atmosphere would be fatal to life, was he referring to an adulteration of the atmosphere by the addition of that quantity of carbonic acid, or the deterioration of the atmosphere by its decomposition, as by the burning of a charcoal stove? Snow pointed out that, in the latter case, the fatal effects of varied air would be attributed to the resulting deficiency of oxygen. According to the London Medical Gazette, Snow, in researching this question, "had mixed certain gases, and had respired with impunity as much as 40 of carbonic acid, when the proportion of oxygen was increased in an equal degree." These experiments led him to conclude that "the absence of oxygen, not the presence of carbonic acid, or any other gas, was the usual cause of death in cases of asphyxia from deteriorated atmosphere." 11

This topic was debated in the Westminster Medical Society over the next few months. By the end of March 1839, however, Snow had become convinced that carbon dioxide exerted a deleterious effect "independent of the diminution of oxygen consequent on its inhalation." He described some experiments he had performed on small animals and birds designed to determine the effects of breathing "Lucifer" atmospheres consisting of different proportions of air, oxygen, and carbon dioxide. 12

Snow thought this topic "of great importance" and evidently preserved the records of his experiments, for it was seven years later when finally he published the results of these 18 experiments. 13 His work yielded two conclusions: first, that "5 or 6 per cent of carbonic acid cannot exist in the air without danger to life, and that less than half this amount will soon be fatal"; and, second, that "illness and subsequent death (accut) after removal (from) an atmosphere deteriorated by removal of part of its oxygen, whilst no carbonic acid was present." 14 Snow, who was adept at chemistry and had been schooled in the country that had given birth to such eminent chemists as Robert Boyle, Henry Cavendish, Joseph Priestley, Humphrey Davy, Michael Faraday, and John Dalton, paid particular attention to the absorption of carbon dioxide. He wrote that in some of these experiments "the small quantity of carbonic acid given off from the lungs of the [experimental] animal was absorbed by lime water." In discussing his results, Snow referred to the suggestion of a Professor Graham that the carbon dioxide remaining after explosion of fire-damp (i.e., chiefly methane) in coal mines be removed "by means of inhaling the air through a cushion filled with a mixture of slaked lime and powdered sulphate of soda." Snow remembered this suggestion when he came to conduct experiments on rebreathe the atmosphere of a few years later. 15

ASPHYXIA AND RESUSCITATION

Asphyxia and resuscitation also prepared Snow's mind for his later work on anaesthesia. He discussed this topic first at a meeting of the Westminster Medical Society on October 16, 1841. 16 Much of his paper, which was published later in the year, 17 concerned asphyxia in life, stillborn, but his discussion on respiration in interest was interesting because it reflects his knowledge of respiratory physiology as it stood in the middle of the 19th century. The main object of the paper was a discussion of neonatal asphyxia, which Snow related, affected "a large proportion" of the five per cent of infants that were delivered stillborn.

Snow's chief reason for discussing this topic was to describe an apparatus designed to resuscitate asphyxiated stillborn infants; his paper is of interest because it illustrates his interest in pursuing a research interest that proved relevant to his ready understanding of anaesthesia a little later. In 1838, a Snow noted, a Mr. Read had demonstrated "a syringe for exhausting the lungs by the mouth, the nostrils in the mean time being held, when, on removing the pressure, air from the nostrils, the chest expanded again by the natural elasticity and resiliency of the ribs, muscles of respiration, and pulmonary tissue. . . . " This apparatus he evidently designed for use in adults, but Snow pondered whether it could be adapted to the "resuscitation" of stillborn infants. However, what seemed to be "insurmountable difficulties"—the emptiness and lack of resiliency of neonatal lungs, for example—prevented Snow from following up this idea. But in 1841 he did ask Mr. Read to "make a little instrument on exactly the same plan, adapted to the size of new-born children." This he has done, in the following form and operation:

It consists of two syringes, one of which, by a tube adapted to the mouth, and closing it, withdraws air from the lungs, and the other syringe returns the same quantity of fresh air through a tube fitted to the nostrils. The two pistons are held in the same hand, and lifted up and pressed down together, the cylinders becoming fixed side by side, and each having two valves. When the pistons are raised, one cylinder becomes filled with air from the lungs, and the other with fresh air from the atmosphere, which can be warmed on its way by passing through a tube and metal coil placed in hot water. When the pistons are depressed, the latter cylinder is emptied into the lungs, and the
day, soon adopted the more appropriate of these respi-
rate techniques to the treatment of cardiovascular
stores during anesthesia.

The regulation of concentrations of volatile agents and
the development of efficient inhalers.

Low n a month after ether had been introduced into
medical practice in England, Snow realized that the
earliest anaesthetic inhalers were defective and unrea-
lable. These consisted of glass vessels containing sponges.
He commented on these crude devices as follows:

Both glass and sponge being very indelicate
conductors of ether, the interior of the inhalers
became very much reduced in temperature, the
evaporation of ether was very much checked, and
the patient breathed air much colder than the
freezing point of water, and containing very little
of the vapour of ether. On this account, and
through other defects in the inhalers, the patient
was often very long in becoming insensible, and,
in not a few cases, he did not become affected
beyond a degree of excitement and incurability. 21

The earliest inhalers, instead of facilitating inspiration,
were obstructed. Respiration was obstructed by the
sponges, the ether itself, valves that were too small and,
particularly, breathing tubes that were too narrow. As Snow wrote
of this mechanical problem, "there is reason to believe
that, in many instances, this was the cause of failure, and
that in others the insensibility, when produced, was partly
due to asphyxia. 22

But there was a second problem: "the medical practi-
tioner," he wrote in March 1847, "ought to be acquainted
with the strength of the various compounds, and... to
be able to regulate their potency. 23 Many factors had to be
considered with a compound like ether: its proportion
in the air, its solubility and absorption in the blood,
the balance between inhalation and exhalation of it, and
the ambient temperature. Snow had concluded that "by
regulating the temperature of the air whilst it is exposed
to the ether, we should have the means of ascertaining
and adjusting the quantity of vapor that will be contained in
it..." This was one of Snow's great contributions: he
applied the results of his research on the vaporization of ether
at different temperatures to the designs of an inhaler
so that the concentration that was being delivered at any
one moment could be determined quite easily. (The
accuracy of Snow's calculation is discussed in the Appendix.)

The practical import was obvious: since the early
inhalers "did not allow of any regulation of temperature
but were always used at that of the apartment, whatever it might be, and this afforded no index to the quantity of vapour taken up . . . ." what was needed was an inhaler designed to take the ambient temperature into account. Then anaesthetists would be able to "determine the proportion of ether to air, and by measuring the ether consumed in an operation, the quantity of air, as well as of vapour, breathed per minute, or throughout the inhalation . . . ." He then continued:

All that was required to regulate the temperature of both the ether and the air, and consequently, of the resulting mixture, was to bring them into proximity with substances having a good capacity for, and a good power of conducting, caloric. The first we have in water, and the second is in the metal itself; by placing the ether in a metal vessel, and that vessel in a basin of water brought to the desired temperature by mixing cold and warm water together, the object was attained. Two or three plints of water supply the caloric abstracted in the evaporation of an ounce or two of ether without being much reduced in temperature; and as the water never requires to be many degrees either above or below the heat of the apartment, its temperature is but little altered by the surrounding air during the short time of an operation.20

Snow brought a scientific approach to the administration of ether; he put it on a quantitative footing.

He extended quantification to the design of the inhaler itself. His first model (Figure 2), which he demonstrated to the Westminster Medical Society on January 23, 1847, took the form of "a round tin box, two inches [5 cm] in diameter and four or five inches [10 or 12.5 cm] in diameter.21 This was modified during the summer of 1847 to become the better known box-like inhaler, the size of a half octavo volume.22 It consisted of two main portions (Figure 3). In one, a circular ether chamber six inches (15 cm) in diameter and one and a quarter inches (0.62 cm) in depth contained a spiral baffle plate soldered to the floor and extending to one-sixteenth of an inch (0.16 cm) from the floor. The other half held the water, at a temperature of
A metal tube over the perimeter of the ether chamber led to the facepiece. Snow gave much thought to the dimensions of the inhaler. "The dimensions of the ether chamber," he wrote, "are not a matter of indifference." The chamber had to be shallow enough to allow the air passing through it to be brought into contact with the surface of the ether, yet not so shallow as to reduce, during vigorous inspiration, splashing of ether into the breathing tube. The calibre of the breathing tube was critical also: "It ought to be so capacious as to offer no impediment to the most rapid inspiration; and to meet his requirements it must be wider than the nauclea, to compensate for the resistance arising from the friction of the air against the interior of the tube." It is, therefore, three-quarters of an inch (1.87 cm), in internal diameter.  

If he had done with ether, Snow studied the influence of the ambient temperature on the concentration of chloroform-inhaled and performed experiments to determine the quantity of chloroform vapour that would be taken up by 100 ml of air at different temperatures.  

Now then, no time to design an inhaler for the administration of chloroform. This was smaller than the ether inhaler and more portable (Figure 4). It comprised two metal cylinders. On the upper surface of the inner one a perforated disc allowed air to pass into the cylinder, which served as an evaporating chamber. Inside the inner cylinder was screwed a frame with four stiff wires that supported two casts of "bibulous paper" (i.e., blotting paper), at the bottom of which four notches allowed air to become saturated with chloroform vapour and to pass upwards and onto the breathing tube. The space between the inner and the outer cylinder contained water, the temperature of which never exceeded 60°F (15.5°C).  

Other types of apparatus for the administration of chloroform did not account for factors affecting vaporization, particularly variations in temperature, and Snow warned the ignoring the effect of the ambient temperature could mean that a high concentration might be unknowingly delivered by the anaesthetist. Snow pointed out that "if...a person inhales chloroform from a handkerchief or an inhaler, in such a way that the air he breathes shall be half-saturated with the vapour, then supposing the temperature of the apparatus, the handkerchief, etc., to be 50° (100°F), the air he breathes will contain 4 per cent; but if the temperature be 70° (21.1°C), the air will contain 9.5 per cent of the vapour."

Snow was critical of the Scandinavian method of administering chloroform - an initial dose of "two or three drachms" split on the handkerchief or lint "and more added from time to time" - because the concentration of chloroform could not be regulated accurately.

Solving the fundamental problem of how to control the *one fluid drachm (or dram) is equivalent to 3.698 ml.*
The clinical staging of the depth of anaesthesia

Snow opened his monograph on ether by stating that “the point requiring most skill and care in the administration of the vapour or ether is, undoubtedly, to determine when has been carried far enough.” Others, besides Stewart, e.g., Pholstery and Freuden and Nottger in France, were interested in gauging the depth of anaesthesia by classifying the effects of ether into stages, 8 to 12 degrees, but Snow, characteristically, went further and supported his clinical observations and classification of the depth of anaesthesia into five degrees (i.e., stages) by 73 experimental work also.

Much of his most important research on the depth of anaesthesia was described from 1848 to 1851 in a series of 16 papers... one of the classics of the literature of anaesthesia. In the first paper he wrote that he had "found a plan of determining more exactly the proportion of ether and of other volatile substances present in the blood in the different degrees of narcosis. It consists in ascertaining the smallest quantity of vapour, in proportion to the air, that would produce a given effect. He intended to do this by weighing the smallest quantity of the volatile agent in a bottle and introducing it into a small animal or bird into a jar and waiting until the effect of the vapour no longer increased.

Over the years Snow performed no fewer than 14 experiments as part of his research "On Narcosis by the Inhalation of Vapours." From these he learned the effects of anaesthesia on animals and the concentration of volatile agents in the blood that produced different degrees of anaesthesia. From the results of these and other experiments he extrapolated the calculations to estimate the quantity of the blood averaged 30 pounds. This quantity would contain 26.85 pounds of carbon, which would produce 410 fluid ounces. ThisBeing reduced to mililiters and multiplied by 0.0000044, or i 12 minims as the whole quantity in the blood. More than this was used in practice, Snow noted, because some of it reached no further than the upper airway. But he found that if he put 12 minims into a "bladder" and breathed it over and over again ("in the manner of taking nitrous oxide") it sufficed to produce anaesthesia to the second degree (in which "the mental functions are impaired, but not necessarily suspended"). To induce the third degree (in which surgical operations were best performed) about 18 minims would be absorbed; to induce the fourth degree (when the breathing is stertorous, the pupils dilated, the muscles completely relaxed and the patient "perfectly insensible"), 24 minims; while to induce respiratory arrest (the fifth degree), about 36 minims would be absorbed.

*One minim, or 1/60 of a fluid dram, is equivalent to 0.016 ml.

![Image](image-url)
Snow, therefore, quantified the degrees of anaesthetic power. Although in practice he relied on the clinical signs, he drew from his research how much ether or chloroform he would require for an anaesthetic and how much a patient would have absorbed at a particular depth of anaesthesia.

The scope of volatile agents

The efficiency of ether and chloroform was immediately apparent, but it soon became clear that neither agent was ideal. So Snow began to search for the "perfect" anaesthetic. He also sought a "perfect" local anaesthetic, at that time excluding freezings mixtures, but the lack of success in this effort led him to abandon it in order to concentrate on the search for a perfect narcotic vapour. As Richardson notes, "his grand search was for a narcotic vapour which, having the physical properties and practicability of chloroform, should, in its physiological effects, resemble ether but not producing, by any accident of administration, paralyse of the heart; he was looking for an anaesthetic which might be inhaled with absolute safety, and which would destroy common sensation without destroying consciousness." His studies performed from 1848 to 1851 were conducted with this in mind. Although he never found the perfect anaesthetic among the eight volatile agents he studied (ether, chloroform, ethyl nitrate, carbon disulphide, benzin, ethanomethane, ethyl bromide, and 1,2-dichloroethane), he did learn a very great deal about these substances and about the nature of anaesthesia.

Indeed, this research enabled him to formulate "Snow's rule." He wrote as follows:

"We find that the quantity of each substance in the blood, in corresponding degrees of narcosis, bears a certain proportion to what the blood would dissolve — a proportion that is almost exactly the same for all of them, with a slight exception in the case of benzoin, which I believe is more apparent than real. The actual quantity of the different substances in the blood, however, differs widely, being influenced by their solubility. When the amount of saturation of the blood is the same, then it follows that the quantity of vapour required to produce the effect must increase with the solubility, and the effect produced by a given quantity must be in the inverse ratio of their solubility..."

He found that this rule held good for all the substances and, in addition, for carbon bichloride: ethyl iodide, ethyl oxide acetate, methyl oxide nitrate, pyrocyanic spirit, iodine and alcohol. This "general law," Snow said, did not apply to all narcotics, but only those producing effects "analogous to what are produced by ether, and having... a similar mode of action." He went on to explain: "I am not able at present to define them better than by calling them, that group of narcotics whose strength is inversely as their solubility in water (and consequently in the blood)." He headed that "in estimating their strength, when inhaled in the ordinary way, another element has to be taken into account, viz., their volatility, for that influences the quantity that would be inhaled." Interestingly, he arranged all the volatile substances he mentioned in two series: "in the first column, in the inverse order of their solubility, which is the direct order of their actual potency; and in the second column, in the order in which they stand after their volatility is taken into the account, which is the order of their potency when mixed with air till it is saturated at any constant temperature."

This series of studies did not include studies of another volatile agent, amylene. He conducted other experiments on this, as well as on amyl chloride, and was associated with two deaths in Snow's hands — a more unusual occurrence and in contrast to his experience with chloroform, from which he himself never had a fatality directly resulting from its use in the entire decade of his experience with it.

Elimination of volatile agents, carbon dioxide nasoabdominal and rebreathing

Snow was convinced with the "speedy subsidence" of the anaesthetic state as well as its onset. Having, in 1847, "asserted that the vapour of ether was given out again from the lungs unchanged," he conducted experiments to determine whether preventing removal of volatile agents during expiration would prolong their effects. Snow in fact formulated the concept of rebreathing in a closed circuit using the principle of carbon dioxide resorption; he did so 65 years before Dennis Jackson described his research into carbon dioxide resorption.

Passages from a paper: he wrote in 1850 provide the details of this research.

I have assumed from the first that the speedy subsidence of the narcotic caused by chloroform and ether, in comparison with that from alcohol and other narcotics, depends on the volatility of the former substances, which allows of their ready exit by the expired air. It was previously estimated, for instance, that twenty-four minutes of chloroform are contained in the blood of an adult of average size in a state of very complete insensibility, this being about one-twentieth part as much as the blood would dissolve. The inhalation being now discontinued,
the fresh air which reaches the air cells will
abstract from the blood nearly one-twenty-eighth
part as much as it can hold in suspension at the
temperature of 100° (38° C) and in each hundred
cubic inches of air which saturated at 100°,
contains 45.3 cubic inches of vapour of chloro-
form, 4.35 - 28 — 1.94 cubic inches; or 1.48
minutes, will be the quantity removed by the first
hundred cubic inches of air which reaches the air
cells. It has been shown that about half the
inspired air goes as far as the air-cells; and
supposing the patient to be breathing 400 cubic
inches in the minute, 200 cubic inches would act
in the removal of the vapour. In this manner it
would take two minutes and a half to reduce the
quantity of chloroform from 24 to 18 minutes
... after which the effects would diminish more
slowly... it follows as a necessary consequence
of this mode of exertion of a vapour that, if
its exhalation by the breath could in any way be
stopped, its narcotic effect ought to be much
prolonged. 1

Having formulated the hypothesis, Snow sought to test it
To do this he designed three experiments. They showed
that "such is the case."

What Snow did was as follows. First, he introduced some
750 cubic inches of oxygen into an impermeable
balloon attached to his ether inhaler. He put four ounces of
"solution of potassa" into the inhaler, to the other
opening of which was attached a tube connected to a
valveless face mask. After inhaling as much chloroform
as he himself could take "without being rendered uncon-
scious," he breathed the oxygen from and to the balloon
and over the potash solution. This process of rebreathing
he continued for ten minutes, "during which time the
feeling of narcosis subsided very little." He noted that
the feeling of narcosis passed off "very slowly after-
wards, about half an hour elapsing before it was quite
gone." On a second occasion he used the same quantity of
oxygen and potash solution but placed 15 minims of
chloroform in the spiral inhaler, in a small glass vessel,
which prevented its mixing with the potash. He breathed
as in the first experiment and found that he could do so for
15 minutes; the effects of the chloroform were induced in
the first three minutes, producing "narcosis" but not
unconsciousness. He discontinued the experiments "on account of a feeling of want of breath," the effects of the
chloroform did not pass off for another half-hour. In the

*The active ingredient of this solution, as far as Snow was
concerned, was potassium hydroxide.

third experiment he used two and a half drachms of ether,
and finding that he could breathe the oxygen for 20 minutes.
He observed that "the effects of the small quantity of
chloroform and ether inhaled in these experiments would
have passed off in three or four minutes," if the exhale
vapour had been allowed to diffuse itself in the air in the
usual way. He had shown that his hypothesis was sound.

He did not, however, evidently yet his idea into practice.
Remarkably, Snow was able to measure the amount of
carbon dioxide exhaled before he breathed chloroform
and while he breathed it. In experiment 67 of his
narcosis series of studies, for example, he determined
that 42 grams of carbon dioxide were absorbed by the
potash while he was breathing oxygen for ten minutes
before he breathed the chloroform but just 33 grams of
carbon dioxide after inhaling the chloroform. 2 He also
found that the production of carbon dioxide was reduced
from 4.20 to 3.30 grams.

Metabolism in anaesthesia and the theory of anaesthesia
The absorption of carbon dioxide to prolong the effects of
ether and chloroform was only one aspect of Snow's
overall interest in carbon dioxide excretion. This was a
distinct phase of his research — a separate branch of his
inquiry into the action of narcotic vapours — and much of
the concluding paper in his series "On Narcosis by the
Inhalation of Vapours" in 1851 3 concerned his measure-

*One gram is equivalent to 0.065 grain.
The diminution of the amount of carbonic acid gas extracted by the lungs under the influence of chloroform, ether, and alcohol, shows that the processes of oxidation going on in the body are lessened. In the amount of carbonic acid given off has a pretty close relation to the quantity of oxygen consumed.

Chloroform, ether, and similar substances, when present in the blood in certain quantities, have the effect of limiting those combustion processes between the oxygen of the arterial blood and the tissues of the body which are essential to sensation, volition, and, in short, all the animal functions. The substances modify, and in larger quantities arrest the animal functions, in the same way, and by the same power, that they modify and arrest combustion, the slow oxidation of phosphorus, and other kinds of oxidation unaffected with the living body, when they are mixed in certain quantities with the atmospheric air.

This explanation is probably applicable to the action of all narcotics whatever, but is here applied only in the class considered in these papers, namely the volatile narcotic substances not containing nitrogen, or those substances whose power was found to be in the inverse ratio of their solubility in water and the serum of the blood.

Snow thought that this concept of the mechanism of anesthesia was the best observation he had ever made. Certainly it was important in his day, for some of Snow's contemporaries, in contrast to Snow, equated anesthesia with apoplexy. As early as February 1847 Snow showed that "apoplexy was a very different state from that produced by ether," for he had found that the effects of ether in air were no different from those of ether in oxygen. Snow thought that his concept of anesthesia would not be lost as "historical truth," and it is by no means obvious that we have yet advanced far beyond Snow regarding a firm and clear understanding of the mechanism of anesthesia. Faced with complex mechanisms that are difficult to understand and explain, we frequently turn to analogical expression — which is precisely what Snow did, as his friend Benjamin Ward Richardson told:

Playing a taper, lasting one of our experiments, in a box through which vaporiform was diffused, and watching the declining flame, he once said: "There, now, is all that occurs in narcosis; but to
Snow's research on cholera.

Ether and chloroform were tangible substances about which, in part due to Snow's efforts, there was, soon after their introduction as anesthetics, a good deal of chemical knowledge and an increasing body of physiological understanding. The cholera virbus, however, had neither been seen nor studied, and speculation rather than knowledge determined the action of physicians and public health authorities. Snow's research on cholera led to a new understanding of the disease and of its presentation. With this new understanding, too, came an easing of some of society's fears about the disease and some of the social tensions that the dread disease induced.51 What Snow achieved in his epidemiological research on cholera was to construct a useful paradigm for the understanding of cholera. He helped to bring intellectual order out of emotional chaos.

Snow's approach to research on cholera was not dissimilar to his approach to research in anesthesi. He began by making clinical observations; with these he formulated a hypothesis; to prove or disprove it he conducted what became a classic epidemiological investigation; a theory then resulted.

Snow's observations were based on his own experience, on the experiences of others and on extensive reading of the medical literature. The starting point was his own experience of cholera; gained in 1831 when, as an apothecary, he attended victims of cholera among miners in Killingworth, in the north of England. After seeing more of cholera in later years he came to make two important conclusions and an important deduction.52 First, in contrast to most of his contemporaries, he concluded that cholera is a local affection of the alimentary canal and that it is communicable from one person to another. Next, 34 years before Koch demonstrated the existence of the cholera vibrio in 1883, Snow made an astute deduction based on his observations:

...the disease must be caused by something which passes from the mucous membrane of the alimentary canal of one patient to that of the other, which it can only do by being swallowed.

Later, he emphasized that "the morbific matter of cholera, having the property of reproducing its own kind, must necessarily have some sort of structure, most likely that of a cell"53 (italics added).

Snow noticed that lack of personal hygiene and overcrowding were associated with cholera. But, Snow argued, "there is often a way open for it to extend itself more widely, and that is by the mixture of the cholera evacuations with the water used for drinking and culinary purposes, either by permuting the ground and getting them into wells, or by running along channels and sewers into the rivers."54

Snow thus concluded that cholera was a water-borne infection. But, in the prevailing climate of thought that favoured a miasmatic rather than a contagion cause of cholera, if Snow was to convince anyone that he was correct, he had to prove the soundness of the theory that he had arrived at in the fall of 1848 and published first in 1849.

To put his theory to the test, Snow had to wait until 1854. In that year, London witnessed "the most terrible outbreak of cholera which ever occurred in this kingdom [of Great Britain]."55 The epidemic occurred on Broad
The second phase of the investigation was much more far-reaching. In conducting it, Snow was at his most thorough, conscientious and single-minded. West Snow, "I resolved to spare no exertion which might be necessary to ascertain the exact effect of the water supply on the progress of the epidemic." He obtained the addresses of persons who had died of cholera in some districts in London where the water pipes, though conveying water supplies by two different companies, happened to be "intermingled" as they passed to their destinations. Then he checked the mortality rate associated with residence in the houses against the source of the water supplied to them. One source of supply originated in an unpolluted part of the river Thames, the other, in a polluted part. He did the bulk of this research largely single-handed; he explained this by saying, "I was desirous of making the investigation myself, in order that I might have the most satisfactory proof of the truth or fallacy of the doctrine which I had been advocating for five years." A remarkable feature of the investigation was its
extent. It was in experimenting "on the grandest scale": No fewer than three hundred thousand people of both sexes, of every age and occupation, and of every rank and station, from gentle folks down to the very poor, were divided into two groups without their choice, and, in most cases, without their knowledge: one group being supplied with water containing the sewage of London, and assigned it, whatever might have come from the cholera patients, the other group having water quite free from such impurity.60

The essence of Snow's findings was this: in the first seven weeks of the epidemic, the mortality for persons living as the houses supplied with the polluted water was 8.5 times higher than for persons living in the houses supplied with the untreated water.61 Later analysis of 21 subdivisits supported this: for the same period, the mortality ratio averaged 7.1.62

Snow had done what no one else had done: quantitate the effect of cholera-contaminated water. Thereafter, the tide of opinion turned. One person who changed his mind about the value of Snow's work was Sir John Simon, the first Medical Officer of Health for the City of London, Medical Officer to the General Board of Health and Medical Officer of the Privy Council. Although for many years Simon never shared Snow's opinion that cholera was spread by water, he did come to write in 1880 this of Snow's conce: "(though now more than 30 years old, [he] may probably still be counted the most important truth yet acquired by medical science for the prevention of epidemics of cholera."

Although there were flaws in Snow's research,63 it has deservedly been regarded as "a neatly perfect model" of epidemiological analysis and his argument as having "the pertinence of a masterpiece."64 These flaws included the lack of proof that the Broad Street pump was actually contaminated, the absence of explanation for the rise and fall of the epidemic though the water supply had remained unchanged, the lack of information about the numbers of persons living in each of the houses in the various districts, use of a rather primitive chemical test to differentiate the two water supplies and the degree of elevation of one related to the water supply.65 This research on cholera, conducted on "the grandest scale," yielded results that, too, were of the grandest scale. Acceptance of Snow's theory meant that cholera could now be prevented. And, after 1866, cholera returned to Snow's own country no more. Snow's work came to benefit countless persons. Recognizing this, Henry Whitehead, formerly a cow worker with Snow, praised Snow as being "as great a benefactor... to the human race... as appeared in the nineteenth century."66

Snow's research on other topics

Snow was licensed to practice medicine in 1858, at the age of 25, when he passed the examination of the Society of Apothecaries. A year earlier, when still a student, he had joined the Westminster Medical Society in London (later, the Medical Society of London), and regular attendance at its weekly meetings provided him with his postgraduate education. His participation in the Society's meetings enabled him to identify problems on which, interested as he was in research, he could cut his teeth. As he matured and as he worked towards his MD degree (obtained in 1844), the wide variety of topics discussed by the Society's members gave him much food for thought.

In the years before he concentrated on anaesthesia and cholera, Snow spoke on a number of topics as meetings of the Westminster Medical Society and he conducted research on some of them. In addition to neuralgias and carbon dioxide toxicity, the topics most interested Snow in his early years constituted a diverse group indeed: arsenic-containing colicides;67 injection of antivenin and antitoxin;68 posttraumatic anasthesia;69 distortion of the chest and spine in children caused by enlargement of the abdomen;70 hemorrhage in the capillary blood vessels;71 inflammation;72 lead carbonate poisoning;73 haemorrhagic stomatitis;74 strangulation of the ileum;75 and urinary calculi.76 Later papers concerned infection of medications,77 purpura haemorrhagica;78 moriarty in different occupations79 and the adulteration of bread as a cause of rickets.80 None of his research on these topics is of particular importance yet it constitutes another facet of his work that impels one to conclude that Snow was a complete physician. These topics interested him in a general practitioner but they reveal him in our eyes as a physician who had broad interests in not only medical problems but social problems: as a physician who not only read widely but wrote on numerous topics of current interest; as a physician who was both curious and observant; and as a physician who was also a medical scientist with original ideas—ideas that, as his papers on environmental topics shared, are relevant today.

These aspects of Snow's interests are pertinent that add color and variety to this remarkable physician's career. But, in the context of research, they also illustrate that traits as Snow's character that fitted him for research. He recognized a problem, sought ways of investigating it and then drew conclusions relating to current practice. Snow always wished to study a topic that interested him by doing the work himself, in part no doubt because he knew that the work would thus be done thoroughly. As 81

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medical student at the proprietary school of unaniuits in
former Windsor Street in London (associated with
the name of William Hunter)\(^1\), he determined that the
practice of using aconite acid to pre-serve cadavers was
indeed dangerous; he reported that he "made a careful
evaluation of the subject..." a phrase that was character-
able of him even as it was later when he studied the
London cholera epidemic of 1852.\(^2\) He left no stone
untoured.

Discussion
In John Snow, life was short but his work was long indeed.
In his life lasted only 45 years, his career as a physician,
only two decades; his concern with the epidemiology of
cholera, only 11 years; and his research in anaesthesia,
between five years; yet in so short a career Snow conducted
research that greatly expanded the evolution of two
aspects of medicine. What is the significance of his
research?

Snow's research has exerted its effect principally on the
thinking and practice in the two fields of medicine that
concerned him most—anaesthesia and epidemiology.

His research in anaesthesia was conducted during the
first decade of this new discipline's development. The
decade began with ether and chloroform being adminis-
tered by means of crude equipment and by individuals
who were not trained for the task, but it ended with these
agents being accurately administered from relatively
sophisticated equipment by, in England at least, physi-
cians who derived from, and gave to, anaesthesia a
rapidly developing sense of professionalism. The decade
opened it complete absence of theoretical and
practical knowledge of anaesthesia; it closed with a
considerable body of knowledge being available to those
who administered anaesthesia. The decade started with
anaesthesia regarded as a craft based on empirical
techniques; it finished with anaesthesia, certainly in
England, as a medical discipline founded on scientific
knowledge and principles. Much of all this was largely the
outcome of the work of one man—John Snow. He
provided a paradigm for the understanding and practice
of this new field of medical practice, even though it
was some years before his influence was fully felt and
appreciated.

In integrating research with clinical practice, Snow set
an example for other 19th century English anaesthesiologists
to follow. But Snow himself was following the path taken
in the late 18th century in England by a group of men
who practiced "pneumatic medicine"—Henry Cavendish,
Joseph Priestley, James Watt, Joseph Wedgwood, Rich-
dard Pearson, Theobald Beddoes, and Humphrey Davy.\(^3\)

These men, familiar with the new chemistry that was
directed to elucidating and making use of gases like
oxygen, carbon dioxide, nitrous oxide and ether, stimu-
lated interest in chemistry and familiarity with crude
inhalation equipment. Snow grew up when the work of
these men was still relatively new. Snow, too, was only
15 years younger than Henry Hill Hickman, who was
publishing his experiments on carbon dioxide in the late
1830's.\(^4\)\(^5\) When Snow had already set his sights on
anaesthesia as a career, Snow, of course, conducted his
research after anaesthesia has finally been introduced into
clinical practice, but he did so with a clear sense of the
objectives of clinically oriented research, and it is because
of this that his research gave direction to the new
discipline of anaesthesia.
The most far-reaching influence of Snow's work in
anaesthesia was its effect in professionalizing anaesthe-
sia. This influence was summarized by Mosin in his John
Snow Memorial Lecture for 1964 in the following terms:

Snow was not the first or the last to have an insatiable
mind. Nor was he the first or last by ascetism of body to
live when a new door of knowledge is opened. He was, however, one
of those rare men able to discern clearly between the value
and importance of normal dexterity in medicine, however ad-
vanced it may be and however much application and devel-
oped of it may need; and those intellectual processes of
mind given to us few which can recognize the dependence
of craft on continually expanding medical scientific knowl-
dge. For without an appreciation of this, any numerous
performed by the hand is of no more significance or capacity of
use in an expanding medical science than is the student and most elements
of man in a primitive stage.\(^6\)

Part of the legacy of Snow's work, then, is the way
anaesthesia evolved as a professional specialty.
Snow's work has exerted an influence partly through
his writings. Although many of his publications were
based on research, he wrote nothing without directing into
his fellow anaesthetists, so that they might be able to
apply the results of his research in their everyday practice.
Snow wrote a monograph on ether and a textbook on
chloroform and other anaesthetics, together with many
journal articles on anaesthesia-related subjects. Their
volume and their quality placed Snow at an unrivaled
position in his day as the doyen of English anaesthesiologists;
his writings and his precepts profoundly influenced his
fellows anaesthetists. The teachings embodied in his
writings have also influenced works of anaesthetists
who came long after him. His writings publicized a
number of fundamental anaesthetic problems. It was
Snow who formulated the rule relating solubility and
potency; who pointed out the effect of temperature on
vaporization of volatile agents; who conducted the first pharmacological experiments on the action of anesthetic agents; who conceived the idea of carbon dioxide absorp-
tion in a closed-circuit apparatus; and who stressed the need to understand the physicochemical and physiological principles underlying the anesthetic state and determin-
ing its safety. For Snow, research and clinical practice went hand in hand; but his research ultimately was the servant of clinical practice and so the resulting knowledge formed the matrix of anaesthesia. Each stage of a modern vaporizer, for example, is an unspoken testament to Snow's contributions to anaesthesia. The knowledge his research yielded entered the unwritten lore of anaesthesia, just as the knowledge of grammar enters the unwritten lore of speech yet is seldom overtly recognized for what it is.

Snow's research on cholera was designed to solve different problems from those of anaesthesia, but its influence too has been far-reaching. An immediate effect was to provide mid-Victorians with a sound paradigm for the understanding of cholera. The significance of his research lay in its originality; the reviewer of his critical work on cholera wrote of Snow's theory of the transmis-
sion of cholera that it presented "an entirely novel view of the node in which it may become diffused." Snow's view prevailed, and so countless thousands of people have unknowingly benefited, for Snow's research meant that they never contracted cholera.

Snow's research on cholera exerted an influence through its writings, too. Snow's epidemiological method has inspired epidemiologists, even up to the present day, and many current texts on epidemiology cite Snow's research on cholera as a model of epidemiological investigation. Although modern epidemiologists vary in the emphasis they place on Snow's work and in their interpretation of his work in relation to modern concepts of epidemiology,19-20 a representative opinion is that "John Snow's contribution was to evolve an elegant, internally and externally consistent theory which concerned the mechanisms and processes involved in every aspect of the subject he had chosen to study."21

Finally, Snow's ideas, embodied in his writings, on cholera as on anaesthesia, contrast to be of relevance. Snow is one of those figures who are historically significant because the ideas carry their meaning across the years. Kendall has suggested a test for the significance of ideas of historical figures: "read some of the papers of the great men of the past and see whether you don't come out with some few ideas bearing on your own work."22 This light, Snow's research is as significant in direct proportion to the number of those who have read his writings in the past, who read them today and who will read them in the future.

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Résumé
La direction de John Snow en épidaenologie et en anesthésie est le résultat de sa recherche ainsi que de sa pratique clinique. En anesthésie l'investigation de Snow était concernée par la concentration des agents volatiles et le développement des inhalateurs effectifs: l'exhalation et l'élimination des agents volatiles; les phases de l'anesthésie; le métabolisme des agents anesthésiques et la ventilation respiratoire des gaz; le métabolisme de l'anesthésique et la théorie d'anesthésie. En épidaenologie, Snow a investiguée la relation entre l'appréciation de l'eau et la mortalité à Londres pendant l'épidémie de choléra en 1854, ce qui a aidé à formuler une théorie critique et originale sur la transmission du choléra. L'investigation de Snow a repoussé un point d'attention sur les agents qui servaient à sa carrière et le rôle du choléra dans la vie quotidienne et social. La signification de son investigation est évidente dans sa direction, non seulement dans les soins de la santé mais aussi dans l'évolution de l'anesthésie et de l'épidémiologie comme disciplines professionnelles.

Appendix
Accuracy of Snow's calculations on the volume of ether vapour taken up by 100 cubic inches of air at different temperatures.
In his major text On Chloriform and Other Anaesthetics: Their Action and Administration, Snow stated that at 40°F (4.4°C) 100 cubic inches of a saturated mixture of ether vapour and air would contain 27 cubic inches of ether vapour; he tabulated the proportion of volumes at other temperatures also (pp. 347–48). To answer this question, the volume of ether vapour in 100 cubic inches of air at 40°F has been calculated using data from the CRC Handbook of Chemistry and Physics 167th edition, ed. R. C. Weast, Boca Raton. CRC Press, 1989, as follows:
1 Calculated vapor pressure of ether at 40°F (4.4°C) = 0.002 torr (a standard atmosphere of 760 torr or 1 standard atmosphere). This is 25.5 per cent of the pressure, or 48.4 per cent of the ether vapor.
2 Ayarm's law of partial volumes indicates that the vapor, which is separable from the total volume, would occupy 25.5 per cent of the volume, or, in this case, 25.5 cubic inches of the 100 cubic inch basis.

This volume differs very little from...
Snow's calculated volume. The difference of 1.5 cubic
meters can be explained on the basis that the ether Snow
used was likely not to have been completely pure. He
claimed that its specific gravity was 0.73 at 60° F (15.5° C)
and its boiling point, 98° F (36.8° C); today, the specific
gravity of ether is put at 0.7138 grams per ml and the
boiling point at 34.5° C.

Surprisingly, Snow, along with others, believed that
nitrogen contained two atoms, and that the atomic
weight of carbon was six. These errors multiplied each
other, so that if Snow's own calculations were based
on such beliefs no error resulted.