CYANOSIS IN THE EARLY HISTORY OF ANAESTHESIA

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On May 1st, 1847 Gideon Mantell of Lewes, surgeon and amateur geologist, discoverer of the iguanodon and other dinosaur fossils, recorded in his journal:

'Went to Bartholomew's Hospital, and witnessed two operations under the influence of ether: the first I have seen. The loss of sensibility in both instances was complete, no consciousness of the operation. But the effect on the system was appalling, though transient.'

What he meant can be gathered from a letter written by Dr Charles Locock of Hertford Street, London, to his friend James Young Simpson, some three months after the introduction of ether:

'Many thanks for your pamphlet on the ether inhalation, with which I have been much interested. People here and in Paris are getting frightened about it, as the arterial blood becomes black under its influence...'

Disturbing reports had appeared almost from the outset. At Guy's Hospital a patient's face had been much congested and at St Thomas's there was so much coughing and turgidity of the face that the operation had been abandoned. At St Bartholomew's a patient's breathing was once or twice laborious, the abdomen heaving a great deal, the face, and even the whole surface of the skin, somewhat purple the greater part of the time. And as regards Mr Tomes's celebrated case of lithotomy at the Middlesex:

'...after breathing deeply and tranquilly for about two minutes, his countenance became livid...'

Present-day anaesthetists will have no doubt that what was observed was cyanosis resulting from respiratory obstruction, yet such an explanation does not feature in any of the early accounts. Rather it appears that a chemical cause was being proposed. Dr James Pring of Weston-super-Mare wrote of the state of uncertainty among the profession about the propriety of using ether. French physiologists had described a dark, fluid state of blood in etherised animals, and a similar state had been seen repeatedly in this country by surgeons operating on patients under the influence of ether. The arterial blood exhibited the same change. The question was whether the change was due to a deficiency of oxygen, or whether it was an independent chemical change, in which case it would occur equally in blood removed from the body. To test this thesis he had collected two samples of arterial blood from a sheep, one of which had been mixed with a small quantity of washed ether. Within three minutes the etherised blood was almost black, and the coagulum was much softer than usual, while the unexposed blood remained florid, and coagulated normally. The experiment had been repeated with oxygen added to the ether bottle; the oxygen had neither prevented the colour
change, nor could the blackened blood be restored by oxygen. The conclusion was that the change was purely chemical. Whether to continue to use ether, in the face of this evidence, was for the surgeons to decide.\textsuperscript{7}

Dr Pickford of Brighton, an early exponent of bashing the media, went even further.\textsuperscript{8} The public had been led by the daily press to expect perfect immunity from pain, without fear of any ill effects or consequences, but he wished to undeceive the public. What of the pulse, respiration, and countenance, during the state of insensibility? The circulation becomes first rapid then slow and feeble; the respiration laboured and stertorous, the countenance livid, the lips and tongue are blue, the pupils dilated ... the muscles universally relaxed, the functions of the brain and nervous system suspended .... and the patient, to all intents and purposes, was a senseless corpse. The condition had been compared by some to drunkenness, by others to asphyxia, or to apoplexy of the congestive form. But etherisation was more alarming and dangerous than any of these: there was a chemical and vital alteration in the constitution of the blood itself. Ether robs the blood of its oxygen, intensely blackens it by the solution of its corpuscles and their contained haemoglobin, chemically deprives it of its powers of coagulation, and renders it unfit for the purposes of life. A black vitiated blood circulates through the system, analogous in many particulars to that in putrid and malignant fevers. This impaired condition of the blood is not even partially corrected until atmospheric air has been breathed for some time, and sufficient lymph corpuscles have found their way into the circulation to replace those destroyed by the ether.\textsuperscript{*} The ether has dissolved the blood corpuscles, and permitted its contained haemoglobin to escape. Under the microscope numerous remains of the capsules of corpuscles could be seen.

**Conflicting reports on cyanosis**

In the face of all this, it is remarkable how little the bluish discoloration of the skin or the blood features in the early books on etherisation. Robinson, reporting on some 120 operations, mentions only one patient whose face was much congested, another who turned very red, or rather purple in the face, one with congestion of the face and head, the colour being somewhat livid, and one where the symptoms of congestion of the brain were so apparent that it was thought more prudent to delay the operation.\textsuperscript{9} Two of these cases appear to be identical with ones mentioned above. Robinson must have been aware that there was concern, because he quotes Boott reporting the observation of the surgeon, Mr Hale Thomson that, in his operations, under the full effect of ether, the arterial blood presented its usual appearance, nor was there any reason to suspect asphyxia.\textsuperscript{10}

\textsuperscript{*} Pickford supposed that red blood corpuscles were produced from the lymph corpuscles, an idea going back at least to Boerhaave, for whom one of the functions of the lungs was sanguification, the red cells being produced by the squeezing together of five or six lymph corpuscles as they passed through the lung capillaries. This shows how out of touch he was with contemporary physiology, which held that the red cells were produced in the spleen. The bone marrow was not recognised as the site of haemopoiesis until twenty years later.
John Snow, too, minimised its significance in his first treatises.\textsuperscript{11,12} Neither mention the word cyanosis, neither contain any indication of the recognition of respiratory obstruction. In fact, Snow was at pains to point out that in his patients:

'The blood that flows in operations is not much altered in colour ... the patient's lips remain unchanged in hue ... only when the patient has been holding his breath, or coughing, have I observed the arterial blood to be a dark colour; and I consider that those writers who have described it as being, usually or always, of a venous appearance, must have used inhalers that did not allow a proper supply of air. The blood always coagulates on the floor of the operating theatre, and the black blood which flows during an amputation when the tourniquet is applied, constantly becomes afterwards red on the surface from exposure to the air.'

Any problems with respiration were attributed only to the unsuitability of the apparatus. Snow repeatedly emphasised the importance of wide bore tubing and low resistance to breathing. Also, he was concerned to refute the suggestion, implicit in the comments quoted, that ether alters the blood chemically, and interferes with coagulation.

If one read only Snow's own writings, one would conclude that his patients were rarely if ever cyanosed. Only once does he refer, and in general terms, to one or two patients whose faces became purple, but should this occur: 'there need be no alarm'. The face-piece may be removed if thought proper, but breathing always becomes extremely regular when the next degree is attained.\textsuperscript{13} However, from early 1847, the \textit{Lancet} published eye-witness accounts of the operating lists under general anaesthesia at the London teaching hospitals, and it is instructive to compare these descriptions of the same cases with those that Snow published later in his book. For example, on 28 January at St George's Hospital, Snow is described as having anaesthetised a little boy with a long sequestrum in the tibia. The account continues: '... inhaled - operation commenced after one and a half minutes - inhalation stopped a minute later just as his face was becoming rather purple, and the pulse feeble.'\textsuperscript{14} Snow's own account makes no mention of cyanosis.\textsuperscript{15} Then, on 11 February, he anaesthetised a woman with malignant disease of the breast. The account in the \textit{Lancet} reads as follows:

'The woman inhaled for four minutes, when it was ascertained by Dr Snow that the cap which admits air to the ether was not removed and, consequently, she got no ether, and but little air. This was remedied, and she had the disadvantage of beginning the inhalation of the ether rather out of breath. It excited some coughing, and in three or four minutes the face was becoming purple, and the pulse feeble and quick, and the features rather distorted. The inhalation was accordingly discontinued, and the operation commenced.'

She had inhaled sufficient ether to render her analgesic, so although she struggled, she afterwards denied having felt any pain. But in Snow's own account there is again no mention of the initial hypoxia, nor of cyanosis, only of coughing, which he attributed to existing bronchitis.\textsuperscript{16} It is disconcerting to find that one's hero at times made the same mistakes as the rest of us.
We read of cyanosis in other accounts also. In a case of bilateral amputation at the London Hospital after a train accident, described as 'the most formidable operation as yet performed ... under the influence of ether' it is said that: 'The blood in the small arteries was much darker than usual, so that it was really difficult to distinguish it from venous blood.'\(^1\) Of Mr Nunn's fatal case in Colchester, the account reads:

"After having inhaled the ether for eight minutes, the patient became fully under its influence, even to the extent of stertorous breathing, and the face and lips presented a livid hue."\(^1\)

The disquiet continued. John Denham, in 1849, reporting on the use of chloroform in labour paints a:

'...fearful picture of the evils likely to arise from its use ... apoplectic stertor, convulsions, partial paralysis ... the blood blackened, the brain poisoned, and other still more formidable consequences, are among the number of dangers mentioned as liable to be induced by the state of anaesthesia.'\(^1\)

Edward Murphy, in 1850, also remarked on the dark colour of the blood:

'It may be chloroform - it may be the imperfect oxydation of the blood - that produces the alteration; whichever is true, the question is well worthy of an attentive examination.'\(^1\)

**Theories of cyanosis**

Of the observers cited, only Murphy and Pring suggested that hypoxaemia might be a factor, and researchers into the history of medicine of the first half of the nineteenth century may come to share the view that there were two populations of doctors at large, the younger moderns, who knew what we would regard as the 'right' answers, and the older traditionalists, who clung to the 'elements of medicine' of the eighteenth century. The physiology textbooks of the early part of the nineteenth century reveal conflicting ideas about the process and functions of respiration, and the cause and significance of the colour difference between arterial and venous blood. This uncertainty includes the remnants of earlier beliefs, chemical, physical and mechanical, which ramify throughout the whole of the succession of systems of medicine.

Before Harvey, the difference in appearance of arterial and venous blood was attributed to the presence in the former of a bright red, thinner blood, together with the higher type of pneuma, the vital spirit.\(^1\) Harvey himself denied that there was any difference in colour between venous and arterial blood, and for this he was criticised as an inaccurate observer by Cohen.\(^1\)
Keilin more perceptively pointed out that it was in support of his revolutionary thesis that it was the same blood that circulated from the veins to the arteries and round again that he had to deny even a difference in colour. \(^{33}\)**

Harvey's discovery, with its implicit erasure of those aspects of Galenic physiology that centred round the heart, raised questions about the lung function, the purpose of respiration, and the source of body heat, and these were addressed by the "remarkable group of investigators who centred round Robert Boyle, and became the original members of the Royal Society.

The first recorded observations of the change of colour that blood undergoes when exposed to air was published by the anatomist Carlo Fracassati of Bologna in 1665. It was a classical observation that when blood was collected in a bowl it formed a clot with a red surface above, and darker parts below. This was seen as the sedimentation of its constituents, the light spiritual part uppermost, the humours below, with the heaviest, the black melancholy humour, at the bottom. But Fracassati showed that if the clot was turned over, its dark undersurface on exposure to air soon became a florid red. This observation upturned classical physiology. It was quickly picked up and confirmed by Robert Boyle (1627-1691) and by Robert Hooke (1635-1703), who noted also that when the red surface was progressively sliced off, the exposed dark beneath soon became florid.

The in vivo site of this colour change was demonstrated by Richard Lower (1631-1691) on the open thorax of a dog. Lower's suggestion that the change of colour was due to absorption of particles from the air was elaborated by John Mayow (1641-1679) who, in his *Tractatus Quinque* identified them as 'nitro-aerial' and attributed to them several of the properties that today are associated with oxygen.

However, this was only one of several explanations of the colour change, which can be classified as chemical, physical and mechanical. The chemical suggested that combination with certain aerial particles caused the change of colour; the physical and mechanical, that the churning and moulding that the cells underwent during their passage through the lungs caused a change in their shape that caused them to reflect light more brightly. So, while it might be thought that Mayow had put respiratory physiology on the right path, the mechanical physiology associated especially with Boerhaave delayed progress by the best part of a century. Haller, in the middle of the eighteenth century, actually denied that the blood changed colour at all during its passage through the lungs.

So chemistry took a back seat until the elaboration of the lime-water test and the demonstration by Joseph Black in 1756 that fixed air, or carbon dioxide, is given out during exhalation. This was soon followed by the confirmation by the Italian anatomist, Giovanni Cigna, that blood did change colour, and that the change depended on contact with air. Lavoisier's experiments with the ice calorimeter established that oxygen is consumed, and related it to the amount of heat generated. Thus respiration became equated with combustion, in this case the combustion of waste carbon compounds, and the question then arose, where did this process take place? Two theories were proposed.

While some suggested that it took place throughout the body, ideas about the constitution of the organs and tissues were not far advanced, and the favoured site, supported by Lavoisier among others, was the lungs. This would account for the generation of body heat, but if waste carbon compounds were being combusted in the lungs, it followed that since all the oxygen being inhaled would be used up in the production of an equal volume of carbon dioxide that would be breathed out, neither gas should be found in the blood in the systemic circulation nor was it, until some fifty years later. So the darker colour of venous blood was explained by the accumulation in it of carbon which, as everyone knew, was black.

The second theory, associated with Lagrange and Hassenfratz, proposed that the reaction took place in the periphery. The demonstration of tissue respiration by Spallanzani at the beginning of the nineteenth century gave support to this, and by the 1820s the idea that the reaction took place in the peripheral capillaries was strongly gaining ground.

**A change in nomenclature**

Cyanosis is as old as haemoglobin, and much older than man. It is a state that we all pass through at each end of our lives. It used to be, and perhaps still is, one of the clinical signs that medical students are early on taught to look out for, so the absence of the word 'cyanosis' in any of Snow's writings was surprising. In the Oxford English Dictionary I was astonished to find that the first recorded use of the word was in 1834, in a book by John Mason Good, *The Study of Medicine*. Good, who based his work on the nosology of Cullen, itself inspired by the botanical classification of Linnaeus, listed Cyanee or Cyanosis, or Blue skin, as the third species of the Genus Exangi, of the Order Dysthetica, of the Class Haematica. His and other contemporary medical textbooks attributed cyanosis solely to congenital heart disease, and specifically to a patent foramen ovale. The first and second species of the genus were aneurysm and varix, and the connection between the three was that in all of them there is turbulent blood flow. Only slowly from the 1840s on, did the connection between cyanosis, other categories of heart disease, and pulmonary disease, become recognised.

Of course, the earlier word for blueness of the blood was lividity, but lividity appears to have carried a sinister connotation: it was associated with terminal conditions, and was hardly regarded as a readily reversible state, especially with no oxygen cylinder at the head of the bed. I think the question of why Davy's suggestion regarding the use of nitrous oxide as a pain relieving agent was not taken up may be answered, in part at least, by the contemporary view of lividity. In March 1800, in the company of Astley Cooper and others at a meeting of the Askesian Society, William Allen, lecturer in chemistry at Guy's Hospital (later of Allen and
Hanbury's), inhaled what he called gaseous oxide of azote (nitrous oxide) and recorded in his diary that: 'The company said that my eyes were fixed, face purple, veins in the head very large, apoplectic stertor. They were all much alarmed, but I suffered no pain and in a short time came to myself. But a purple face, apoplectic stertor and dilated head veins were the signs of a stroke; and also current at that time and for the next thirty years, was the belief that blue or venous blood was poisonous to those tissues accustomed to being perfused with arterial blood. So, although Allen came to no harm, it is not surprising that the experiments were abandoned.

We know from his writings that John Snow kept himself fully aware of the latest developments in physiology. At the beginning of Part 17 of his series of publications On Narcotism by the Inhalation of Vapours, he surveyed contemporary theories about the chemistry of respiration and its site in the body, and referred to the researches of W F Edwards, and of H G Magnus who, in 1837, demonstrated the presence of oxygen and carbon dioxide in the peripheral blood. Snow dismissed the lungs as the site of formation of carbon dioxide, and believed that the reaction took place in the capillaries of the systemic circulation. Also, the phenomena of asphyxia, previously attributed to an excess of carbon in the blood, were now known to be caused by want of oxygen in the arterial circulation. In the same series of essays Snow had clearly distinguished between anaesthesia and asphyxia, so he obviously felt no reason to be concerned by the fears raised by Drs Pring and Pickford. Also, as against his confessed disposition not to allow an occasional risk to stand in the way of ready applicability, his experience with cyanosed patients who recovered and appeared none the worse for it, would soon have deprived the condition of its anxieties.

Would it have been easy to detect slight cyanosis in Snow's time? Artificial lighting was generally by candle or gas, both of which shift the colour temperature towards the red end of the spectrum, so it is reasonable to excuse failure to detect slight cyanosis, unless operating in daylight. However, we know that operations were usually performed about mid-day, and that operating theatres were lit by skylight. Also, of course, there was no shortage of accounts of cyanosis being observed.

Landmark publications after Snow's death were by Stokes, who described the absorption spectra of oxygenated and reduced haemoglobin, and Pfluger, who showed that the respiratory reactions take place not in the capillaries but in the tissues. In 1923, Lundsgaard and Van Slyke established that blood appears cyanosed when it contains 5g of reduced haemoglobin, and that this is an absolute figure.

For how long was cyanosis a feature of clinical anaesthesia? Those who have read Hewitt's Anaesthetics and their Administration have noted that he describes two types of anaesthesia, simple and complex. Complex anaesthesia was what occurred in practice, and consisted of simple anaesthesia plus a varying degree of asphyxia, evidenced by cyanosis. Nitrous oxide anaesthesia was always expected to be accompanied by cyanosis until a general practitioner dental anaesthetist, Dr Tom, of Cheltenham, in an influential paper published in 1956, described his technique which was 'revolutionary' in that it postulated using a high percentage of oxygen (20%) with nitrous oxide.
It is startling to realise that it is now perfectly possible for a well-taught and well-supervised trainee to spend a subsequent clinical lifetime without ever seeing a single instance of anaesthetic-induced cyanosis. With careful practice, the blue of cyanosis could be as archaic a condition as the green of chlorosis had become fifty years ago.

Summary

By a simple change of nomenclature in the 1830s, when Snow was a student, cyanosis as we understand it today, became a new concept. Its predecessor, lividity, was a fearsome condition, generally terminal. Growing understanding of the physiology of cyanosis, and experience of managing it in relation to anaesthesia, dispelled those fears. Putting it another way, familiarity bred contempt, so that when nitrous oxide was reintroduced in the 1860s, although there were further expressions of alarm about the cyanosis that inevitably came with it, notably from Clover and Benjamin Ward Richardson, these were not sufficient to prevent cyanosis from becoming, for many years, a tolerated concomitant of general anaesthesia.
References

3-6 Lancet 1847; i: 78,79,105,132.
10 ibid 12.
13 Snow J. op. cit. 1847; 37.
14 Lancet 1847; i: 158.
15-16 Snow J. op. cit. 1847; 56, 58.
17-18 Lancet 1847; i: 238, 343.
19 Denham J. A Report Upon the Use of Chloroform in Fifty-Six Cases of Labour Occurring in the Dublin Lying-In Hospital. Dublin: Hodges and Smith, 1849. (also published in the Dublin Quarterly Journal of Medical Science August 1849.)
26 Snow J. op.cit. 1858; xxxv.