THE PHYSIOLOGICAL BASIS FOR SUPPLEMENTAL OXYGEN IN THE NEWBORN*

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INTRODUCTION

RECENT SURVEYS[1, 2] have clearly shown that one of the most important immediate causes of neonatal mortality is hypoxia, both prenatal and postnatal, chiefly in small premature infants. Prevention and treatment of antenatal hypoxia is an obstetric problem and beyond the scope of this paper. Postnatally hypoxia is associated with respiratory distress syndromes which include hyaline membrane disease, primary atelectasis, immaturity of the lung, aspiration of amniotic fluid, massive pulmonary hæmorrhage, neonatal pneumonia and spontaneous pneumothorax together with mixed syndromes of these conditions. It has been shown that 35-50% of total neonatal mortality is associated with these syndromes.[1, 2]

Towbin[3] has recently re-emphasized the importance of perinatal hypoxia in morbidity and mortality from cerebral damage. While hypoxia has been closely correlated clinically with such damage, there is at present no correlation of the objectively measured duration and extent of postnatal arterial oxygen desaturation with cerebral damage as shown in the various types of cerebral palsy.

Supplemental oxygen is the obvious essential treatment of hypoxia, but administration needs to be controlled by measurement of blood oxygen to ensure adequate relief. Small premature infants pose an additional problem in that over-oxygenation may result in blindness due to retrolental fibroplasia (RLF).[4-12] This results from the susceptibility of the vessels in the incompletely vascularized retina to constriction and obliteration by hyperoxia with subsequent fibroblastic overgrowth on return to normal oxygen levels. This condition largely though not exclusively affects infants below 3½ lb. (1590 g.) birth weight, corresponding roughly to a gestational age of 30 weeks or less.

Control is therefore necessary to avoid the dangers both of hypoxia and hyperoxia. To control supplemental oxygen without measuring the level of blood oxygen is akin to controlling insulin administration without measuring the level of blood sugar. It can be done but it is less than satisfactory in the acute case.

In order to help the physician to deal adequately with this problem of control, an attempt is made in this paper to relate knowledge of respiratory physiology to newborn infants, especially in regard to oxygen absorption. A review is given of processes by which oxygen enters the blood in the lung and thence reaches the tissues from the arterial blood.

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The Normal Processes of Respiration

Respiration in regard to oxygenating function can be divided into two stages, the first comprising those processes by which oxygen is absorbed into the blood through the lungs and the second those in which oxygen is made available to the tissues by arterial blood.

First Stage of Respiration (Absorption in the Lungs)

The lung processes in the first stage can be divided into tidal ventilation, distribution of inspired gases to the alveoli (or alveolar ventilation); diffusion across the alveolo-capillary membrane, and circulation of blood through the alveolar capillaries (Fig. 1).

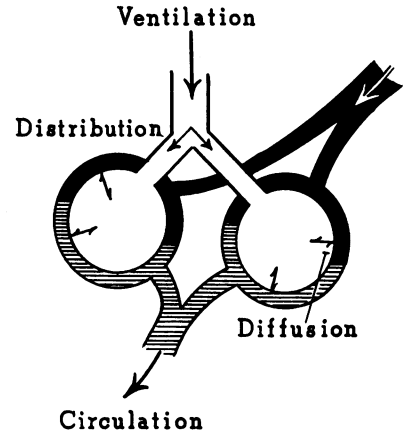

Fig. 1.—After Comroe, J. H., Jr. *et al.* in *The Lung,* Year Book Publishers Inc., Chicago (1955). The four processes concerned in the passage of oxygen from the atmosphere into the pulmonary blood.

In the normal individual, blood at the end of a pulmonary capillary will have reached equilibrium in regard to partial pressure of oxygen (PO_2)* with the gas in the alveolus at approximately 104 mm. Hg. Minor unevenness of distribution of inspired air will result in some alveoli being hypoventilated or unventilated. This, in effect, raises the total pulmonary dead space. Blood circulating round such alveoli will be exposed to less than the normal 104 mm. Hg partial pressure of oxygen (PO_2), and when this poorly oxygenated blood mixes with the pulmonary outflow the mean partial pressure of oxygen (PO_2) will be lowered to 95 mm. Hg (equivalent to 97.1% arterial oxygen saturation—SaO_2). This amounts to an alveolar-arterial oxygen pressure gradient of 9 mm. Hg. These relationships are illustrated diagrammatically in Fig. 2.

In respiratory distress in the newborn, recent work suggests that there is an increase in the physio-

*The physiological symbols used throughout this paper are those suggested by a group of respiratory physiologists meeting under the chairmanship of Pappenheimer and published in *Fed. Proc.*, 9: 602, 1950.
PaO_2 = partial pressure of oxygen in arterial blood. PO_2 = partial pressure of oxygen. PAO_2 = partial pressure of oxygen in the alveolus. SaO_2 = arterial oxygen saturation. DO_2 = oxygen diffusing capacity.

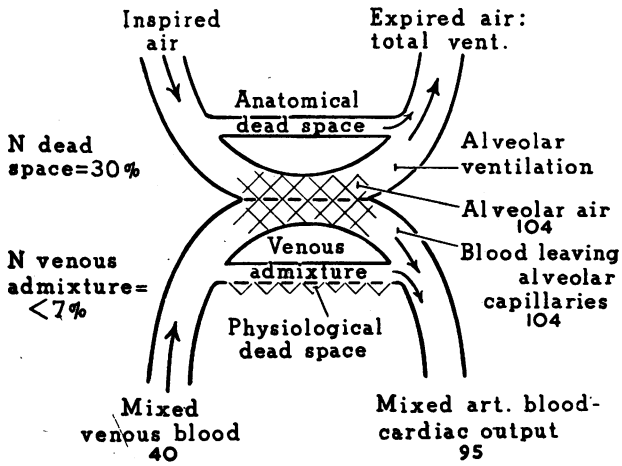

Fig. 2.—Illustrating blood/gas relationships. The figures refer to PO_2 in mm. Hg (modified from Riley, R. L. and Cournand, A., *J. Appl. Physiol.*, 1: 825, 1949). This figure is discussed in the text.

logical dead space up to twofold.[13] This may be compensated by an increase in minute volume due to tachypnœa, the tidal volume varying little. In this case, alveolar ventilation (VA) remains approximately normal and the normal alveolo-raised alveolar-arterial oxygen gradient in proportion to the severity of the pathological changes in the lung. The extent by which diffusion difficulty and the exercise of respiratory effort could raise the alveolar-arterial oxygen pressure gradient can be appreciated by reference to the theoretically derived saturation-tension curves in Fig. 3 which are displaced to the right of the normal curve in proportion to the degree of intrapulmonary shunt and diffusion difficulty.[14]

Second Stage of Respiration (Transfer of Oxygen to the Tissues from Arterial Blood)

This depends on the availability of oxygen in arterial blood and an adequate peripheral circulation. Availability is determined by the shape of the oxygen hæmoglobin dissociation curve, where degree of saturation is related to partial pressure of oxygen (PO_2) (Fig. 4).

The normal partial pressure of oxygen in arterial blood (PaO_2) is 95 mm. Hg. If on the one hand a rise in the percentage of inhaled oxygen results in a rise in partial pressure of oxygen in arterial blood (PaO_2), the premature infant will—at a

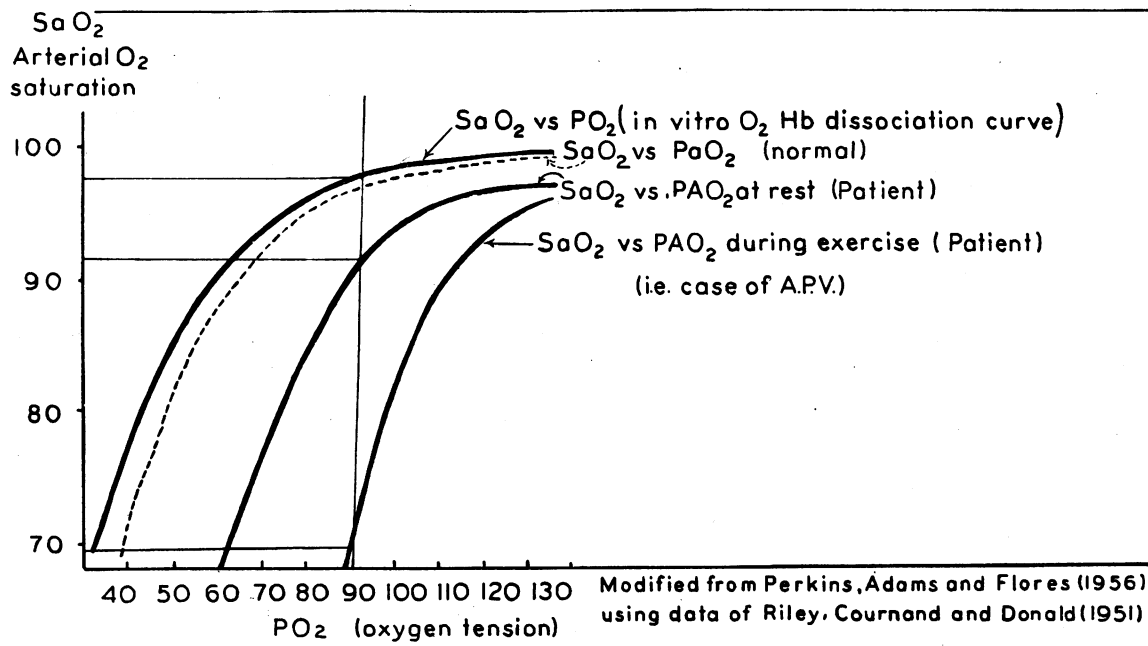

Fig. 3.—Theoretical saturation/tension curves to illustrate the separate components making up the total alveolar-arterial gradient for PO_2. The distance on the abscissa between a given point on a curve and the iso-saturation point on the *in vitro* O_2 Hb-dissociation represents the alveolar-arterial gradient. It will be noted that exercise in a patient with a limited DO_2 displaces the curve to the right in such a way that, at a PO_2 of 88 mm. Hg, the SaO_2 is only 69% compared with the resting SaO_2 of 92% at the same PO_2 of 88 mm. After Perkins *et al.*, 1956.[14] (A.P.V. = abnormal pulmonary ventilation.)

capillary pressure gradient is maintained. If, through exhaustion or obstruction to air flow, minute volume cannot be increased, blood gas homœostasis will fail and an increased alveolo-arterial pressure gradient results.

This gradient may be further raised by concomitant diffusion difficulty. This difficulty is aggravated by the increased diffusion necessary to supply more oxygen demanded by the increased respiratory work of dsypnœa. The net result is a certain level for a certain time—run the risk of developing retrolental fibroplasia (RLF). Recent work[12, 15] suggests that 35-40% oxygen for two to seven days is critical. Douglas and Edholm[16] have shown in adults that an arterial oxygen saturation of 99.5% corresponds to an alveolar partial pressure of oxygen of 212.9 ± 7.7 mm. Hg. Assuming an alveolar arterial pressure gradient of 10 mm. Hg, this would result in an arterial oxygen tension of approximately 200 mm. Hg. Reference to Fig. 4

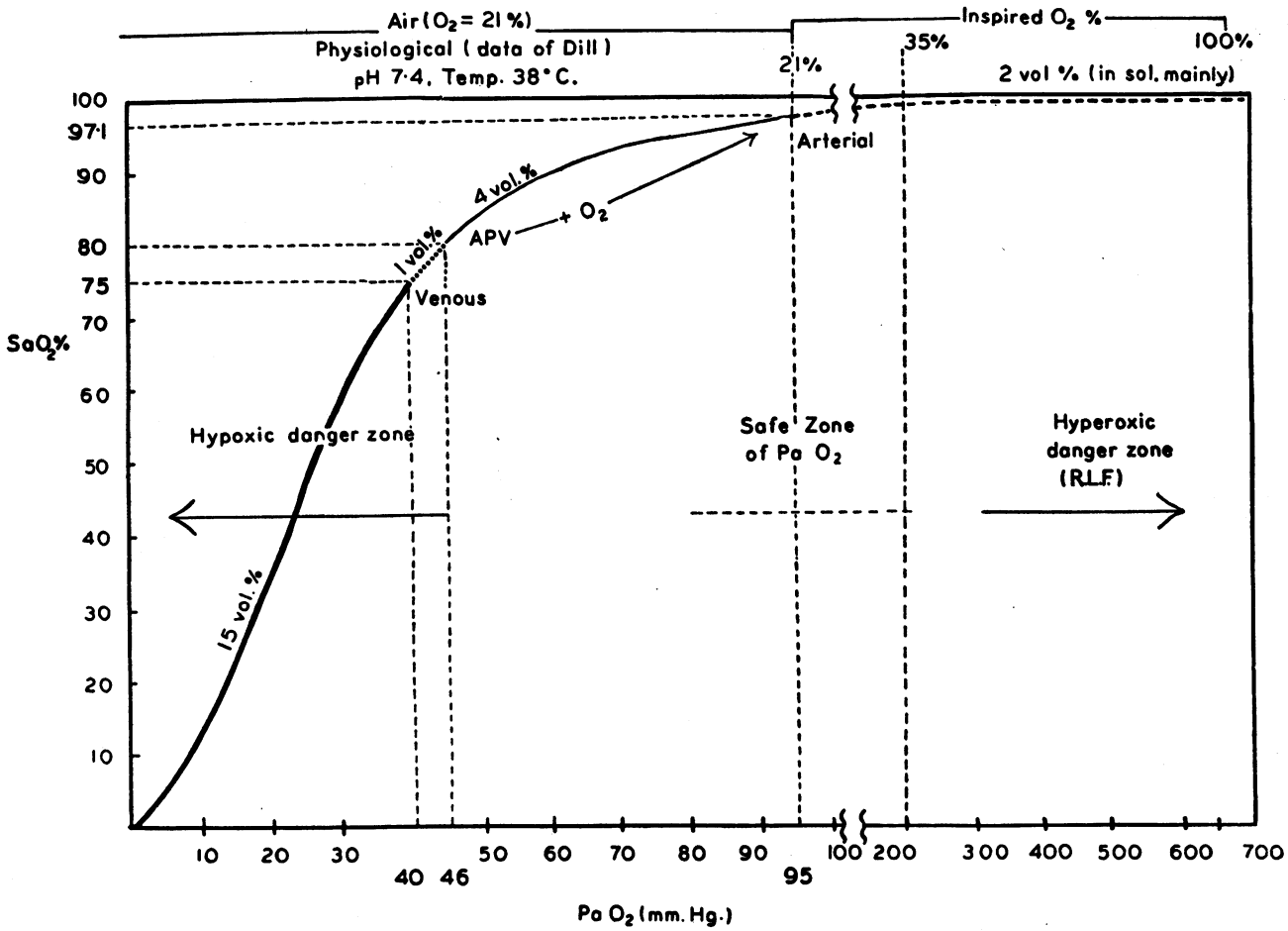

Fig. 4.—The oxygen hæmoglobin dissociation curve extended to cover the range of PaO_2 encountered with supplemental oxygen up to 100% at a pressure of one atmosphere. The volumes % of oxygen available between different arterial partial pressures of oxygen are indicated on the curve. The effect of supplemental oxygen in restoring a case of abnormal pulmonary ventilation to the physiological safe zone of PaO_2 is also indicated. Note that the scale of the abscissa changes above 100 mm. Hg. This diagram is further discussed in the text. (A.P.V. = abnormal pulmonary ventilation.)

will show that 40% of inspired oxygen, in the absence of a defect in absorption, will result in a partial pressure of oxygen in arterial blood (PaO_2) of about 240 mm. Hg or about 2½ times the normal figure. It is this high partial pressure of oxygen in arterial blood (PaO_2) which is responsible for initiating the vasoconstrictive and vaso-obliterative changes of retrolental fibroplasia (RLF). A partial pressure of oxygen in arterial blood (PaO_2) of around 240 mm. Hg and above is therefore dangerous.

On the other hand, in a hypothetical case of a newborn infant with an oxygen absorption defect breathing air, the arterial oxygen saturation (SaO_2) might be reduced relatively slightly to, say, 80%. At this arterial oxygen saturation (SaO_2) the partial pressure of oxygen in arterial blood (PaO_2) is about half of normal and is almost at the "venous" point on the dissociation curve.

Reference to Fig. 4 shows that there is a pressure head of oxygen of only 6 mm. Hg available over the normal "venous" point on the dissociation curve corresponding to the availability of only 1 vol. % oxygen. Compare this with a pressure head of 55 mm. Hg and 5 vol. % oxygen available at a normal 97.1% arterial oxygen saturation (SaO_2). There is, therefore, a danger of hypoxic tissue damage, though other factors such as tissue tolerance to hypoxia, increased oxygen extraction by the tissue due to a low tissue partial pressure of oxygen (PO_2), volume of local blood flow and oxygen carrying capacity of the blood[17] affect the final outcome. Of course many cases of respiratory distress may have an arterial oxygen saturation (SaO_2) well below 80% with a consequently greater danger of tissue hypoxia.

The aim of supplemental oxygen therapy in respiratory distress should therefore be the restoration of partial pressure of arterial oxygen (PaO_2) to the "safe" area around 95 mm. Hg, corresponding to an arterial oxygen saturation (SaO_2) around 95-97%. If oxygen is given in a concentration just sufficient to achieve this, the dangers of both hypoxia and hyperoxia (RLF) will be avoided no matter what the percentage of inspired oxygen may be.

The problem is to recognize in the patient the danger areas of partial pressure of oxygen in arterial blood (PaO_2) to both sides of physiological norm. There is as yet no satisfactory direct method of estimating partial pressure of oxygen in arterial

blood (PaO_2) *in vivo*, though the oxygen polarograph is promising.[18]

At present most clinicians rely on a combination of physical signs and symptoms, of which the most important is probably cyanosis, to indicate that the infant may be in the hypoxic danger zone. The hyperoxic danger zone is avoided empirically by limiting the duration of therapy to less than seven days and the percentage of oxygen to below 40, on the basis of the previously observed fall in incidence of retrolental fibroplasia (RLF) resulting.[19] This policy has been shown to be without adverse effect on neonatal survival or growth and development[19, 20] and is largely effective in eliminating retrolental fibroplasia (RLF). There is probably little danger of transgressing the upper hyperoxic danger zone with adequate control of oxygen percentage around 35%* but this may not be true of the lower hypoxic zone for two reasons.

Firstly, it has been shown that the ability to recognize cyanosis clinically varies from person to person and even in the same person at different times.[22] In addition to this personal factor there are the well-known pitfalls in regard to total hæmoglobin content and sluggish peripheral circulation, especially pertinent in the newborn. Thus the most generally accepted clinical indication for supplemental oxygen is fallible. Cyanosis, moreover, even if recognized, can only be very grossly correlated visually with arterial oxygen saturation (SaO_2).

Secondly, some cases with severe defect in the absorption of oxygen in the lungs may require a percentage of oxygen considerably above the usually safe upper limit of 35-40% to achieve a partial pressure of oxygen (PaO_2) within the safe zone.[23] Thus, some cases, even with 35% supplemental oxygen, may remain in the hypoxic danger zone.

The numbers in this latter category are unknown, but it is possible that an occasional case may require a very high percentage of oxygen if not pure oxygen to achieve a partial pressure of oxygen in arterial blood (PaO_2) within the safe zone. From what has been said above there is theoretically no danger of hyperoxic retinal vascular changes provided the oxygen is limited to the minimum necessary by oximetric control of arterial oxygen saturation (SaO_2).† All such problem cases should probably have the benefit of special control techniques, which would involve frequent monitoring of the infant's inhaled oxygen concentration and arterial oxygen level.

It is possible that some of these infants who remain cyanosed neonatally in spite of high inspired oxygen concentrations may have a central right-to-left shunt through patent fetal passages (ductus arteriosus, foramen ovale) because of the effect of hypoxia in raising further the already high pulmonary artery pressures of the newborn.[26] It follows from what has been said earlier that the partial pressure of oxygen in arterial blood in such cases will remain low and there is therefore no danger of retrolental fibroplasia.

*It is still not uncommon to hear oxygen prescribed in terms of flow in l./min. rather than in precisely controlled percentage. This is an extremely dangerous practice in view of the high concentration attainable in modern incubators with low rates of flow.[21]

†Respiratory epithelial damage may occur in the 70 to 100% range if such atmospheres are maintained for longer than four hours in the normal adult.[24] If there is already pulmonary damage, the resulting œdema appears to protect the respiratory epithelium from further hyperoxic damage, and high concentrations of oxygen can probably safely be given.[25]

SUMMARY AND CONCLUSIONS

Supplemental oxygen is of prime importance in reducing the neonatal mortality and morbidity due to hypoxia, but a surfeit for the premature infant may entail blindness due to retrolental fibroplasia. The physician's problem is to avoid this surfeit while supplying enough oxygen to overcome the barrier to absorption posed by the immature or diseased lung.

A review is given of the processes by which oxygen enters the blood in the lung and thence reaches the tissues from the arterial blood. This suggests therapeutic principles and control techniques to guide the physician where the closest clinical observation may be fallacious.

If any improvement is to be made in morbidity and mortality from neonatal hypoxia and hyperoxia, it will be necessary to recognize by objective measurement the special problems posed by the disordered respiratory mechanism.

Since oxygenation of the tissues by arterial blood is one of the fundamental functions of repiration, it is suggested that objective measurement of the degree of oxygenation of arterial blood is one of the essential adjuncts to the treatment of cases in this special group with supplemental oxygen.

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RÉSUMÉ

Un apport supplémentaire d'oxygène est d'importance primordiale dans l'abaissement de la mortalité et de la morbidité causées par l'hypoxémie du nouveau-né, mais un excédent peut causer la cécité chez les prématurés en déclanchant la fibroplasie rétrolentaire. Le problème se pose dans la détermination de la quantité d'oxygène qui doit être suffisante pour surmonter l'obstacle que présente le poumon pathologique ou prématuré et qui doit cependant rester en deça de la concentration nocive pour l'œil. L'auteur offre un rappel des processus par lesquels l'oxygène pénètre dans la circulation par les poumons et de là atteint les tissus par l'entremise du sang artériel. D'après ces données, il suggère certains principes thérapeutiques ainsi que des moyens de contrôle technique qui peuvent aider le médecin dans la conduite du traitement là où les observations cliniques même les plus perspicaces pourraient être erronées. La nécessité de reconnaître par des moyens objectifs les problèmes spécialisés que représentent les troubles du mécanisme respiratoire est à la base de tout progrès dans le domaine de l'administration de l'oxygène. Puisque l'oxygénation des tissus par l'hématose constitue une des fonctions fondamentales de la respiration, l'auteur suggère que la détermination objective du taux d'oxygène dans le sang artériel forme le pivot de l'oxygénothérapie.

A SURVEY OF BURNS AT THE VANCOUVER GENERAL HOSPITAL FROM 1946 TO 1955

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VARIOUS EXCELLENT PROGRAMS for management of burns have been well described and documented over the last ten years.[2-3] It is our purpose to indicate the results that follow the many different interpretations and applications of these in a large open hospital.

The burns have been grouped as superficial or deep, indicating partial-thickness or full-thickness skin destruction respectively; mixed types of burns have been placed in the latter group. During the period from 1946-1955, 780 patients with burns (528 superficial and 252 deep) were admitted at periods varying from a few minutes to several months after the injury. Early in the series it was common to receive a patient burned three weeks or more previously; this was usually due to failure to recognize the depth of the burn until the necrotic skin separated. Now there is a general appreciation of the characteristics of a deep burn; the patient usually arrives within the first few days and it is rare to get an old untreated burn.

Fig. 1 illustrates a progressive decline in the admission of patients with superficial burns. This is attributed to wider knowledge of the recognition of the degrees of burns by the profession, and to the onset of the British Columbia Hospital Insurance Scheme in 1947, with an associated rise in population which resulted in a scarcity of hospital beds making admission of patients with this degree of burn difficult. Since only extensive superficial burns require hospital care, this decline has saved money and no one has suffered unduly. Although the incidence of burn admissions has not increased, there has been a decrease in the ratio of superficial/deep from 4:1 to 2:1 for the same reasons. Additionally, skin grafting on the smaller burns is now being more widely performed in hospitals throughout the province, whereas formerly such cases were transferred. Now it is usually the extensive burns that are sent in.

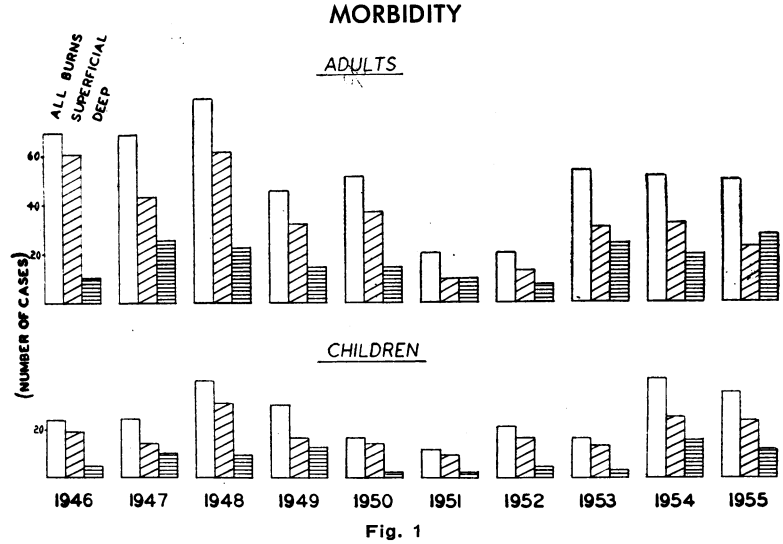

Fig. 1

The causes were as follows: flame—314, scalds—237, chemical—36, electrical—27, direct heat—117, not stated—49. As expected, flames and scalds were the most common, the former more frequently causing a deep burn and the latter a superficial burn. There is a greater incidence of scalds in children; these were largely due to home accidents. Flame burns on this coast frequently resulted from

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