The History of Anesthesiology

Reprint Series: Part Nine

PEDIATRIC ANESTHESIA

Illustrated above is the title page of the 1512 edition of Eucharius Roesslin's "The Rosegarden of Pregnant Women and the Midwives," one of the most famous works on midwifery, with sections on the management and feeding of infants and of diseases of children.

The History of Anesthesiology

Reprint Series: Part Nine

PEDIATRIC ANESTHESIA

The development of interest and ultimate specialization in pediatric anesthesia came soon after the practice of anesthesia achieved professional status in the forties and fifties. Professionalism is a calling in which one professes to have acquired some special knowledge used by way of instructing, guiding, or advising others — or of serving them in some art. In addition to mere specialization, professionalism in medicine entails study, with consequent progress, recruitment of others, integration with other branches of medicine and devotion to the kinds of investigation that solve problems within a particular field of endeavor. The pioneers in pediatric anesthesia fitted into this mold and they promptly defined the differences among infants, children and adults in regard to physiologic function and response to anesthetics. As a result surgeons were able to perform more complicated operations on the very small or otherwise very ill child, with diminishing morbidity and mortality. The textbooks of those times illustrate nicely the metamorphosis of pediatric anesthesia: Clement A. Smith on the Physiology of the Newborn Infant (1945), M. Digby Leigh and M. Kathleen Belton on Pediatric Anesthesia (1948), and Robert M. Smith's Anesthesia for Infants and Children (1959).

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SELECTED PAPERS ON PEDIATRIC ANESTHESIA

With Annotations

1. Ayre P: Anesthesia for hare-lip and cleft palate operations on babies. *Brit J Surg* 25: 131-132, 1937.
   This system eliminated rebreathing, the expiratory valve and other obstructions to normal respiration, and permitted a high gas flow of ether vapour in oxygen.

2. Waters RM: Pain relief for children. *Amer J Surg* 39: 470-475, 1938.
   Waters emphasized the need for adequate psychological preparation of the child and the effect of good premedication on consequent anesthetic requirement.

3. Barcroft J: The onset of respiration at birth. *Lancet* 2: 117-121, Aug 1, 1942.
   The result of many researches on sheep, this report focuses on the transition between intrauterine and terrestrial life insofar as respiration and circulation are concerned.

4. Bigler JA, McQuiston WO: Body temperatures during anesthesia in infants and children. *JAMA* 146: 551-556, 1951.
   Herein is stressed the need for temperature control in the child — the first intentional use of cooling in modern inhalation anesthesia.

5. Deming M van N: Agents and techniques for induction of anesthesia in infants and young children. *Curr Res Anesth Analg* 31: 113-119, 1952.
   By means of measurement of cyclopropane concentrations in blood this paper pointed out the higher requirement for anesthetics in infants, later confirmed by MAC determinations.

6. Eckenhoff JE: Relationships of anesthesia to postoperative personality changes in children. *Amer J Dis Child* 86: 587-591, 1953.
Although others had called attention to the effects of hospitalization on the child, this paper attempted to relate long-term deleterious psychological effects on the child, to anesthetic management.

7. Smith RM: The prevention of tracheitis in children following endoctracheal anesthesia. *Curr Res Anesth Analg* 32: 102-112, 1953.
As there was initially much opposition to tracheal intubation, this paper stressed the importance of careful technique and sterile apparatus in the prevention of post-intubation sequelae.

8. Holliday MA, Segar WE: The maintenance need for water in parenteral therapy. *Pediatrics* 19: 823-832, 1957.
This report still provides the basis for pediatric fluid therapy despite wide differences of opinion.

Suggestions for selection of articles in this compilation were generously offered by:
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ANÆSTHESIA FOR HARE-LIP AND CLEFT PALATE OPERATIONS ON BABIES

By PHILIP AYRE

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THE anæsthesia employed for hare-lip and cleft palate operations at the Babies' Hospital, Newcastle upon Tyne, may be divided into two phases—the nitrous-oxide–oxygen phase and the oxygen-ether phase. In all cases the babies were intubated by the endotracheal technique of Dr. Magill, wide-bore rubber catheters being inserted through the mouth into the trachea just beyond the laryngeal opening. No especial difficulty was experienced in carrying out this procedure, except that on a few occasions the catheter entered a bronchus; this was manifested clinically by laboured respiration and jerky movements of the diaphragm. On slightly withdrawing the catheter, the breathing became normal.

After prolonged trial, we found that, while nitrous-oxide–oxygen anæsthesia afforded excellent results in adult patients, certain grave disadvantages presented themselves when the same anæsthetic was administered to infants. In the first place, the anoxæmia caused by nitrous oxide—and any proportion of oxygen below 20 per cent represents some degree of sub-oxygenation—appeared to be much more deleterious to babies than to adult patients. In the second place, it was extremely difficult to adjust the amount of re-breathing to the small proportions suitable for a baby. No matter how small the re-breathing bag, there was always too much 'dead space', so that the respiratory exchange rapidly became hampered by the accumulation of excess products of respiration.

As a result of anoxæmia and excessive re-breathing, the condition of many babies showed marked deterioration within a short space of time. Rapid, 'snatching' respirations, accompanied by greyish pallor and sweating, presented anything but a satisfactory picture of anæsthesia; while vascular oozing obscured the area of operation and made the surgeon's task more difficult. In most cases so high a proportion of oxygen had to be administered in order to keep the baby a good colour, that quite large amounts of ether were needed to maintain adequate anæsthesia; so that the description 'nitrous-oxide–oxygen anæsthesia' became farcical.

In an endeavour to remedy the above distressing state of affairs (and spurred on by the caustic criticism of a candid surgeon!), the writer sought to devise a method by which the endotracheal technique could still be utilized without the drawbacks associated with nitrous oxide and excessive re-breathing. The following method is simple in the extreme, and has proved highly satisfactory during the last eighteen months at the Babies' Hospital.

Briefly, the apparatus consists of a T-piece which is connected by a short piece of rubber tubing and a Magill angle-piece to a wide-bore Magill rubber catheter previously inserted into the trachea (*Figs.* 101, 102). Through one limb of the T-piece oxygen and ether vapour is delivered from a Boyle or other continuous-flow apparatus. The other limb remains open to the outside air; for convenience, a short piece of tubing may be attached and allowed to hang down beneath the operating towels. A strand of fine gauze, fixed with adhesive strapping close to the open end of the latter tubing, will wave to and fro with the patient's respirations, thus serving as a useful indicator to the anæsthetist. *Fig.* 103 shows the special T-piece described above, which may be obtained in two sizes.*

The advantages of this technique are as follows :—

1. The baby inhales fresh air and oxygen under as nearly normal physiological conditions as possible. The system is open to the outside air, without the intervention of a re-breathing bag, expiratory valve, or other obstruction to normal respiration. Sufficient ether vapour is added to the oxygen to maintain adequate anæsthesia, the baby being kept just short of 'gagging'. Deep anæsthesia is neither necessary nor desirable.

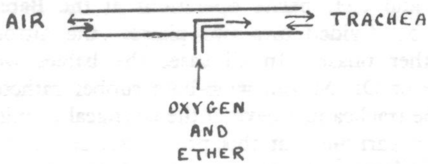

Fig. 101.—Diagrammatic representation of T-piece.

Fig. 102.—Photograph taken at conclusion of operation for hare-lip. The endotracheal tube is still in position. The T-piece has been adapted from a Clausen-Evans pharyngeal air-way.

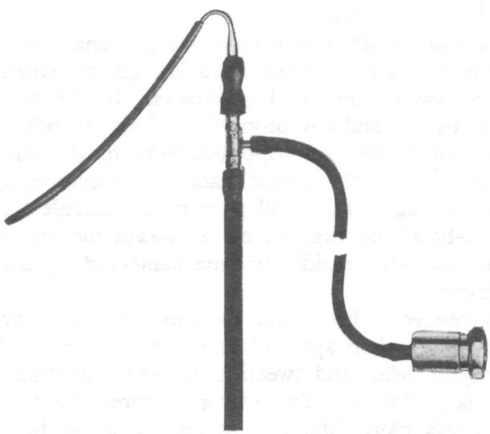

Fig. 103.—The author's T-piece connected up to the endotracheal tube.

2. The 'dead space' is reduced to negligible proportions, while the continuous flow of oxygen at the rate of from 1½ to 3 litres a minute flushes out the lungs, and effectually prevents undue accumulation of respired products.

The excellent colour and quiet, natural breathing of the babies have convinced us that oxygen and ether vapour, administered by the T-piece method, is the anæsthetic of choice for all hare-lip and cleft palate operations on babies and young children. Not only is the general condition of the patient very satisfactory throughout operations lasting from 30 minutes to 1½ hours, but the post-operative convalescence is remarkably smooth and free from anxiety. Last, but by no means least, comparative peace now reigns in an operating theatre formerly the scene of many sanguinary battles !

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Ralph M Waters

PAIN RELIEF FOR CHILDREN*

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THE suppression of pain and the production of anesthesia both depend upon a depression of the excitability of cell protoplasm in portions of the central nervous system. Susceptibility to drug depression decreases as this excitability of the nervous tissue increases, and vice versa. As we shall see, various factors may alter excitability in either direction. The first of these to consider is age. From birth until puberty the sensitivity of the child's nerve cells to afferent stimuli is a rapidly but inconstantly changing factor. To this circumstance may be attributed much of the difficulty which is encountered in the choice and dosage of drugs for the relief of pain or for anesthesia in children.

Guedel has suggested a parallelism between metabolic activity, as expressed in calories per hour per square meter of body surface, and cell excitability or what he calls reflex irritability. As irritability of the cells of the central nervous system increases, or decreases, the character of resulting efferent stimuli will cause a corresponding change in metabolic activity. He suggests plotting normal metabolic activity as the ordinate and age as the abscissa to form the curve reproduced in Figure 1. He postulates a practical parallelism between this curve and a hypothetical one for reflex excitability or that quality which we aim to depress with such drugs as the opiates or the anesthetics. Experience testifies to the value of his suggestion.

The rapid changes occurring in early life, roughly represented in Figure 1, are probably dependent upon: (a) rate of growth; and (b) beginning endocrine activity. Obviously the curve will not be the same for all children of the same age. If the factors on which the rapid changes depend are kept in mind, an imaginary curve for each child may be visualized. This composite curve is raised or lowered by many factors concurrently influencing patients in need of pain relief. In a given case all the factors influencing the curve representing metabolic rate and reflex excitability, upward as well as downward, must be taken into consideration, along with age and weight, before appropriate therapy can be chosen.

In Table I are tabulated five of the commonest influences affecting children. It will be noticed that all five circumstances, and others less commonly, may alter the normal curve (Fig. 1) either upward or downward.

TABLE I

Hypersthenicity Healthy Strong Active	1. Strength	Hyposthenicity Debilitating illness Burns Chronic osteomyelitis
Acute fever	2. Temperature	Hypopyrexia Long exhaustive fever
Fear Anger Irritability (crying) Worry	3. Emotional state	Sunny disposition Cooperative type Lethargic
Pain Uncomfortable or wet bed Impure atmosphere Hunger Full bladder	4. Bodily comfort	"Bliss" (bodily state just before rising) Ideal nursing care Perfect hospital environment
e.g. Hyperthyroidism ?	5. Endocrine activity	e.g. Hypothyroidism Obesity ?

The five factors in the central column influence Guedel's curves. A few disturbances of these factors which elevate the curves are shown in the column on the left, and some which depress the curves are on the right. A child in whom factors on the left predominate will tolerate a larger dose of depressant medication, while one in whom factors on the right predominate will require a correspondingly smaller dose.

* From the Department of Anesthesia, University of Wisconsin Medical School.

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To visualize the individual curve for a child of five suffering from acute appendicitis, we might proceed as follows: Metabolic activity in a normal child is usually at a peak at the age of five or six. Since this increase is doubtless due to rapid growth, we will inquire if our sick youngster is in a period of increasing stature and weight, or at a standstill, making a mental note that the curve is likely to be influenced upward or downward accordingly. Reference to Table I helps further to individualize the curve. If the youngster is exceptionally strong and active, if high fever is present, and if he is frightened and in severe pain, the drug dosage necessary to make the child comfortable or to place him in a state in which he can be easily anesthetized, may approach that commonly administered to an adult. On the other hand, careful consideration of the right hand column in Table I is necessary. If one happens to be dealing, not with a hypersthenic child but with a hyposthenic, malnourished weakling, this factor in itself may more than counterbalance the augmentation due to fever, fear and pain. The dose necessary to comfort such a child may be only a small fraction of that necessary in the previous instance. If thoughtful consideration can be given each case, a proper choice of drugs in suitable doses to meet the needs of each individual can be selected.

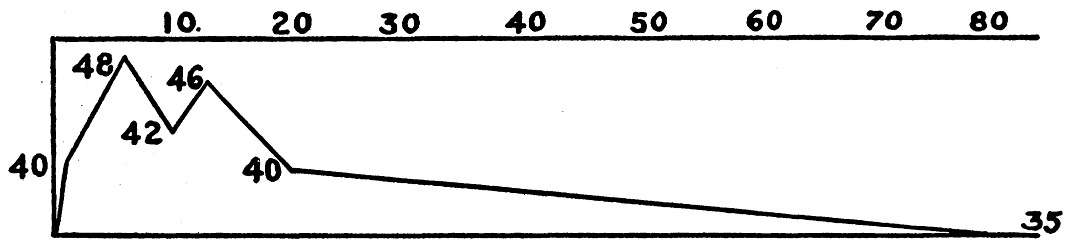

Fig. I. Curve of the normal metabolic rate throughout life, estimated in calories per hour per square meter of body surface. The curves of oxygen demand and reflex irritability are exactly parallel. (From Guedel's Inhalation Anesthesia, Macmillan Co., 1937.)

DRUGS

In general, there are two classes of nonvolatile sedative drugs which are used to make patients comfortable or to prepare them for inhalation anesthesia. Both probably tend to subdue afferent stimuli. One group, composed of such drugs as scopolamine and barbituric acid derivatives, does not, in moderate dosage, allay pain, but rather effects a psychic depression or an approach to normal sleep. These drugs seem to depress the curves when elevated by the emotional state. Coal tar derivatives may be applicable in case the rise is due to fever. The physician should never lose sight of the fact that nonmedical treatment, such as a comfortable bed, hygienic atmosphere free from carbon dioxide and with ample oxygen, elimination of mental irritation, etc., decreases the need for sedation with this group of drugs. The other group of agents is well represented by the opium derivatives. Their primary effect is to depress cell irritability. They oppose the upward trend of the curves resulting from hypersthenicity and pain, and possibly from other factors. It is important to remember that such drugs tend to depress respiration. Overdose can often be avoided by considering the right hand column of Table I or the individual characteristics of patients which tend to depress the normal curves.

A rational combination of drugs chosen from both groups, according to the apparent needs of the individual patient at the time of administration is desirable. Conversely, the use of a much greater dose of one drug from the second group may cause alarming respiratory depression without procuring either adequate pain relief or psychic sedation. Experience has led us to a somewhat routine choice of one drug from each group, varying the individual dosage of each drug according to the principles suggested above. We feel that thorough familiarity with the action of one representative of each group has brought better results than constant changing from one drug to another in the group. A defense of our choice of scopolamine and morphine may be in order. Later, some detail of the manner of administration to children will be afforded.

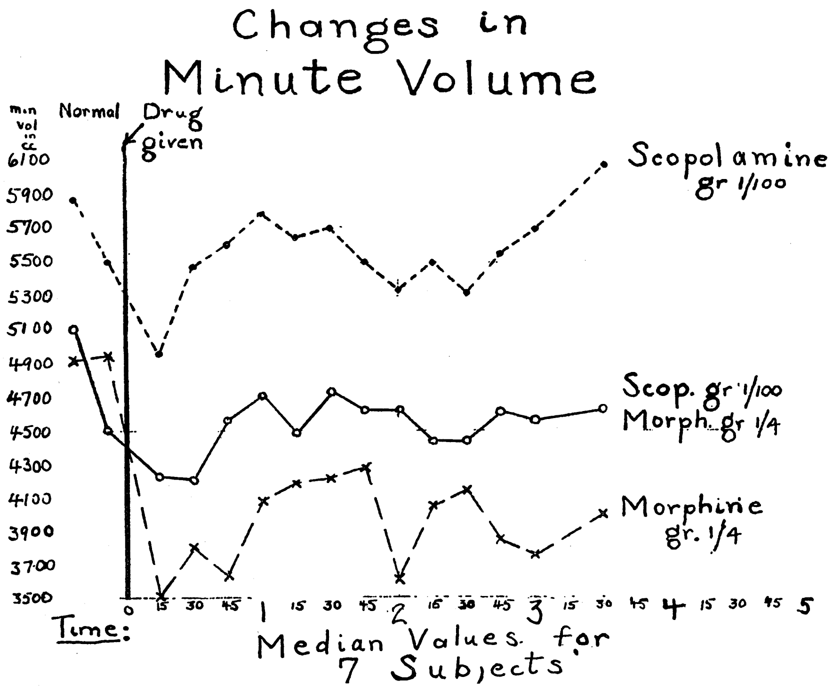

FIG. 2. Composite graphs of median values of minute-volume respiratory exchange in seven normal adults to whom were administered: (1) morphine ¼ gr.; (2) scopolamine 1/100 gr.; and (3) the two drugs combined. Note the maximum depression in the first half-hour period. Also the slight depression of respiration when both drugs were administered simultaneously.

Morphine is one derivative of opium which has been more generally used than any other. The supply is always available and its stability reliable. Deterioration is very infrequent. Activity of one lot as compared with another is always the same. Idiosyncrasy to its effects is extremely rare. Its choice, therefore, needs little defense.

Scopolamine, on the other hand, is unstable in storage and some members of the profession are less familiar with its actions. The effect of scopolamine as a psychic sedative, however, is so perfect as to warrant acquiring familiarity with its effects. Insistance on the use of a fresh product from a reliable manufacturer will usually assure a satisfactory supply. If unfavorable reactions, resulting in talkativeness and restlessness, or rarely, fever, occur frequently, the whole shipment from which the doses came should be destroyed and a fresh supply substituted. Although sneezing and semi-permanent loss of memory have been described as effects of aged scopolamine,* these manifestations have not been noted in our more recent experience covering over 25,000 administrations to adults and children during the past fifteen years. During this time, the supply has been carefully supervised. Practical experience supports the belief that morphine is more stable in tablet form, whereas scopolamine keeps better in solution. Respiratory depression is not a scopolamine effect, but rather is due to other concurrent medication. A flushed face and neck are usual and must be disregarded. Extreme

* WATERS, R. M. Toxic by-effects of the atropin group. *Am. J. Surg.*, 36: 119 (Oct.) 1922.

restlessness and delirium are sometimes a result of oxygen want secondary to respiratory depression from morphine, although attributed to scopolamine. A few patients have shown an anaphylactoid reaction. One such occurrence of alarming severity has been seen in an eighteen year old boy who had both a local and general reaction. Intradermal injection of an infinitesimal amount of scopolamine later resulted in a reddened area of considerable extent. A similar sensitivity to morphine has been described. With reasonable precautions to assure a fresh and reliable supply of scopolamine, we have found a combination of morphine and scopolamine, when administered hypodermically both for the relief of pain and for pre-anesthetic sedation, very effective.

Experimental as well as clinical experience has convinced us that these two drugs administered together give a much more satisfactory result than either alone. The undesirable effects of morphine (respiratory depression, prostration, and nausea) are less frequent and less marked when the dose is combined with scopolamine. Likewise the undesirable effects of scopolamine (restlessness, talkativeness, uncoöperativeness*) are seldom seen after the combined medication. The graphs in Figure 2 (based on a paper to be published at a later date) represent the individual and combined effects of scopolamine and morphine on the minute-volume respiratory exchange of normal adults. The tendency will be seen in these graphs for the two drugs to "balance" each other in their effect on pulmonary ventilation. Such experimental evidence agrees closely with our clinical observations over a period of many years. Administration by hypodermic injection has assured that the total dose was absorbed, whereas oral and rectal medication is uncertain. In our experience, it has not been difficult to teach nurses to prepare and administer these drugs without danger or annoyance to the child. A majority of individuals require a ratio of twenty-five parts of morphine to one part of scopolamine. The hospital drug room usually contains tablets of 1/8 gr. of morphine (0.008 Gm.) and ampoules of 1/200 gr. of scopolamine (0.00032 Gm.). Smaller doses for young children and infants are prepared by dissolving these amounts together and discarding the portion of the solution not required. For example, if 1/32 gr. of morphine and 1/800 gr. of scopolamine are desired, a total solution of 4 c.c. is made and three-quarters of it discarded before administration.

We believe that the combination of these two drugs, if carefully individualized, can be administered to good advantage for pain relief in non-surgical and postoperative cases. A smaller dose of morphine with less respiratory depression will suffice, while good psychic sedation or even amnesia is secured. Split dosage, the second administration following at least one hour after the first, may be used whenever there is doubt regarding the amount required. One may thus take advantage of the opportunity to observe the physical signs produced by the first dose as a criterion on which to base the quantity of each drug used in the second. If myosis and respiratory depression follow the first dose, the second should consist of a larger amount of scopolamine and little or no morphine; whereas if midriasis, restlessness and extreme flushing of the face with fast respirations are present, morphine should predominate in the second dose. Enough morphine and scopolamine to make any child comfortable may thus be given safely. Leech* and others have attempted to tabulate dosage of these agents in children according to age. Such a scheme may prove useful to some. It is our belief, however, that careful individualization of choice of drugs as well as doses will develop in the physician a skill far

* On several occasions, excitation in adults from scopolamine has been abolished by the use of 1/40 to 1/60 gr. of apomorphine, as suggested by Wright. As little as 1/150 gr. to a child has been of benefit.

* Leech, B. C. Preanesthetic medication in children. *Anesth. & Analg.*, 14: 283 (Nov.-Dec.) 1935.

more satisfactory than any attempt at routinization.

ANESTHESIA

Premedication dosage, correctly estimated as to quantity and time of administration, can aid the anesthetist greatly, not only during induction of inhalation or block anesthesia, but also during maintenance and recovery. The time element is so important that both induction and maintenance can actually be made more difficult if it is disregarded. The time of administration of pre-anesthetic drugs, as well as the dose, is an integral part of the anesthetic procedure. Such therapy ordered by the surgeon without the knowledge and coöperation of the anesthetist is not only an example of discourtesy, but is positively dangerous to the patient. For the same reason, the changing of time schedules is fraught with danger if the interval between hypodermic premedication and anesthetic administration is unexpectedly increased or reduced. A desirable interval between such medication and the induction of anesthesia is one and one-half hours. This period of time is ample to produce whatever respiratory depression will result, and the anesthetist is protected from suddenly finding himself confronted with unexpected depression from the premedication at a time when similar depression is apt to occur due to accidental overdose during induction with a volatile agent.

If an approximation to basal metabolic activity and cell irritability could be secured in every child before entrance to the operating suite, the choice of agent and technique of administration to produce anesthesia would be simple. Our experience has shown that careful attention to individualization of dosage with morphine and scopolamine will usually accomplish such a result. When proper premedication cannot be accomplished, the individual variation of the curve to which we have already referred will serve as a guide in choosing from the available volatile and gaseous anesthetics the one best suited in potency. Further than this, the skill and experience of the anesthetist will determine his choice of anesthetic agent and technic. It is safer for him to adopt the method with which he is most skilful rather than to attempt to follow the rule of someone else.

A thorough appreciation of the danger of unduly disturbing the transport of oxygen and carbon dioxide is important. The child has a small respiratory tract. Extreme modification of carbon dioxide and oxygen transport can occur with the use of even a very small anesthetic mask. Valves that are easily operated by adults or a thickness of gauze that causes no appreciable resistance to the breathing of older patients may prove a serious load to the respiration of an infant. The frequency with which the illnesses of children are accompanied by chemical imbalance makes the slightest interference with the elimination of carbon dioxide, through increased dead space or obstruction to respiration, extremely hazardous. Not infrequently an ill-chosen technique or the careless adaptation of apparatus designed for adults to the use of infants and children, results in sufficient interference with carbon dioxide elimination to serve as the trigger which sets off a convulsive seizure. The utilization of carbon dioxide as a therapeutic agent in such an emergency has proved fatal. The technique of inhalation anesthesia in children should be aimed at providing an atmosphere of adequate tension of the anesthetic agent and of oxygen. Further than that, the effort should be to keep the ingredients of the anesthetic atmosphere as near those of normal air as possible.

When reliable inhalation anesthesia is available, we feel that the use of local or block anesthesia after the first three months of life is seldom justified. If technical facility in block anesthesia exceeds that with inhalation, no objection can be raised to its use. Morphine and scopolamine may be supplemented with tribromethanol by rectum to complete premedication. Its substitution for hypodermic dosage in certain terror-stricken youngsters is highly to be recommended. In general, however, none of the non-volatile agents should be used for complete anesthesia. Final "leveling off" to the necessary depression can be more safely conducted by one of the volatile or gaseous agents kept under second-to-second control through the respiratory tract. Thus will the attention of the anesthetist be more surely concentrated on the maintenance of a free airway, the normal transport of oxygen to the tissues of the body and the adequate elimination of carbon dioxide.

In Table II is shown the incidence of the use of pre-anesthetic medication in children at Wisconsin General Hospital during the past four years. The major number of such administrations to children occurred in the last half of the period. Increasing care in individualization of dosage has brought us to almost as routine a use of morphine and scopolamine in children over one year old as has long dominated our practice in adults. As greater attention is devoted to careful individualization, we believe that the benefit of these drugs can, with perfect safety, be extended to the first year of life.

TABLE II
THE INCIDENCE OF ANESTHETIC DRUG ADMINISTRATION AT THE WISCONSIN GENERAL HOSPITAL FROM 1933 TO 1936, INCLUSIVE, AND THE NUMBER OF CHILDREN IN THIS GROUP. THE PERCENTAGE OF CHILDREN RECEIVING HYPODERMIC MEDICATION BEFORE ANESTHESIA IS SHOWN

	Under 1 Yr. 275 Cases	1–10 Yrs. 2218 Cases	Total 2493 Cases
Some form of premedication.	143 52%	1867 84%	2008 80%
Premedication with morphine and scopolamine....	36 13%	1552 68%	1558 62%
Premedication with miscellaneous agents...........	107 39%	345 16%	452 18%

Total Administrations = 16,667
Administrations in Children under 11 yrs. = 2493 (14.9%)

SUMMARY

The rationale has been stated of basing depressant drug dosage in children upon the supposed parallel curves for cell irritability and metabolic activity rather than solely upon age and weight.

Satisfactory accomplishment of pain relief and of pre-anesthetic sedation with morphine and scopolamine has been described. Attention has been directed to the desirability of combining these two drugs in the proportion of twenty-five to one unless physical signs indicate a variation from this combination. Complete familiarity with a given combination of depressant drugs, and individualization of their dosage has afforded more satisfactory pain relief and pre-anesthetic sedation than attempts to change from one combination of drugs to another.

It is our belief that ninety minutes is the optimum interval between a pre-anesthetic hypodermic of morphine and scopolamine and the induction of inhalation anesthesia. The time interval between administration of premedication and induction of inhalation is as important as the dose of agent.

Disturbance of oxygen ingress to, and carbon dioxide egress from, the tissues of the body is a more likely fault of anesthesia than is an ill-advised choice of agent.

Careful supervision of respiration throughout the period of anesthetic drug action is essential.

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THE ONSET OF RESPIRATION AT BIRTH*

SIR JOSEPH BARCROFT, M.A. CAMB., F.R.S.

THE inspiratory effort is an event so dramatic as to have stamped itself on the imagination of the idealist as the earnest of a new vital principle; to the realist the first breath is the necessary initiation of life in a new environment. To quote the words of Dr. D. H. Barron: "When an animal is born and begins its struggle towards an independent existence, its first efforts are those of breathing. Breathing is living; the onset of respiration is the beginning of life." If I may figure the first breath as a chord struck on an instrument I may divide a consideration of the subject into some description of the instrument itself, and some investigation of the impact upon it.

In the human species a complete series of observations on the development of respiratory movement during the course of gestation would obviously be very difficult—nay, wellnigh impossible. Stray observations at present can only be made at cæsarean sections, and then often when the patient (and fœtus) are subject to a degree of anæsthesia which is prejudicial to the more delicate movements. The best course open to us is to make serial observations on other mammals, to judge what is so fundamental as to constitute a basis of development common to the higher mammals, to separate this from the differences in detail which may be seen from form to form, and to check up the result, so far as man is concerned, by comparison with such human observations as seem from the experimental point of view most unexceptionable.

As a base line no more appropriate animal is available than the sheep. Its gestation period, 5 months, though not so long as that of man, is long as compared with those of the smaller animals. Unlike the rat, the sheep does not run through the gamut of its intra-uterine development in 21 days, and as the phases of development do not crowd upon one another they are more easily discerned. Moreover, the sheep's fœtus is as large as the human one, and the sheep stands operation extremely well.

Can we, from a study of embryonic life, give even a halting sketch of the way in which the instrument of respiration has been elaborated? Mere inspection of embryonic movement at successive stages in the life of the mammalian fœtus tells us much—a body of information substantial enough to stand analysis. Movements of the respiratory type during fœtal life have been described by a number of observers, and in several forms of life. These observations have done less than they should to fire the imagination of workers, perhaps because they were not connected with any coherent idea of the general motility in the organism. Indeed it would scarcely be possible for them to be so connected without a systematic study of the whole relationship of respiratory movements to general motility, a study involving the observation of the fœtus at stated and suitable intervals during its growth.

With a sheep under spinal anæsthesia and immersed in a saline bath at body temperature the amniotic sac can be laid bare and the fœtus—at say 30 days—may be seen through the transparent walls. At that age the embryo is about the size of the thumb nail, and floats quite freely in the amniotic fluid, attached to the wall by the umbilical cord. Evidence of the heart beat may be seen in the cord, but apart from that no intrinsic movement of the embryo is to be discovered.

DEVELOPMENT OF MOVEMENT IN THE FŒTUS

The development of movement generally and respiratory movement in particular may be divided arbitrarily into four stages; the factors which dominate the successive stages, however, do not arise abruptly—the reverse is the case. Each stage as it develops imposes itself upon, rather than replaces its predecessors (fig. 1).

Stage 1: *Spasm.*—The first neuromuscular movement of which the sheep's fœtus is capable takes place about the 34th or 35th day: if the face of the embryo be tapped sharply between the eye and the mouth, the head gives a twitch, it is thrown back a little, and at the same time rotated, the nose being turned towards the side which was struck. There is only one point the striking of which evokes the movement; and only one movement evoked. Removal of the skin shows that the point struck is just over that to which the maxillary branch of the fifth cranial nerve has grown. The functionally effective central nervous system at that time thus consists in something very restricted—an afferent path (the maxillary branch of the fifth nerve), an efferent path, which includes the spinal accessory and upper cervical ventral nerve roots and a central connexion between the two (involving cells, presumably those in the recticulospinal tract, connected with the maxillary branch of the fifth).

As each day passes from the 35th onwards, this reflex spasm expands in various ways. (*a*) The movement can be evoked from the stimulation of other points. For instance, as the maxillary branch of the fifth nerve extends peripherally, the area stimulation of which evokes movement increases, and shortly involves the nose. The ophthalmic branch evokes a response and so on. (*b*) The muscles used in the spasm increase in number, and by the 38th day the diaphragm has become involved, but only as an item in a generalised movement; nevertheless it is the first movement of a respiratory muscle. Of two fœtuses observed on the 38th day, the diaphragm of one gave a single twitch on stimulation of the face, that of the other gave two successive twitches. This brings us to the second stage.

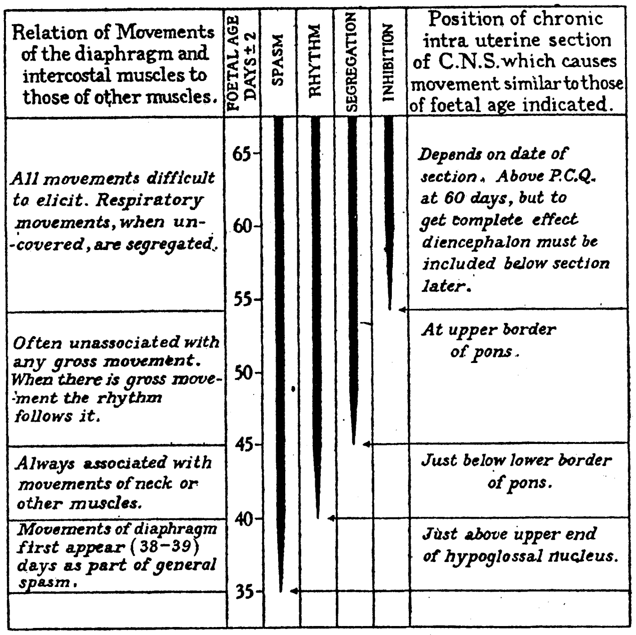

Fig. 1

The four stages of development of respiratory and general movement in the fœtus of the sheep.

Stage 2: *Rhythm.*—By about the 40th day the typical response of the fœtus to a stimulus such as tapping the nose is not merely a spasm but a rhythm of successive spasms. As day follows day, the number of spasms which constitute a single rhythmic discharge increases, and the rate also becomes quicker; starting at about 40 to the minute, it rises to over 60. It is in these days that the intercostal muscles are first seen to contract. Presumably they do not come into the picture as early as the diaphragm because the spinal centres for the intercostal nerves are lower down the cord than those of the phrenic nerves.

Stage 3: *Segregation.*—Even as early as the 38th day it was observed that the diaphragm might give two movements when the rest of the body only gave one. By the 42nd day careful observation shows that the first one or two spasms in a rhythmic response from the stimulation of the fifth nerve may invoke more muscles than do the subsequent spasms; the respiratory

1. Abstract of the Linacre lecture, delivered on May 6, at St. John's College, Cambridge.

muscles are those which continue longest. By the 45th day the response to stimulation consists of an initial movement of the body—a sort of writhe—involving the head, the trunk and the limbs, followed by what for want of a better term I may call an after-discharge. This after-discharge bears all the appearance of a respiratory rhythm. Let me define more clearly the time-relations between the initial somatic movement and the after-discharge, because the word "after" changes its meaning as gestation progresses. At first the movements of the diaphragm and chest muscles merely outlast those of the other parts of the body, but about the 45th day they do not seem to be set up till the generalised movement is over, later still there is a definite pause between the end of the writhe and the beginning of the rhythm. This pause increases in length as gestation proceeds.

Hitherto I have been speaking of what takes place as the result of stimulus to the face, but by 50 days movement can be elicited from stimulation of most parts of the body. The fact that the rhythm becomes more and more easy to elicit is connected probably with the great extension of the area which yields sensory impulses, both extraceptive and proprioceptive. By the 49th day the most trifling movement of the body seems to touch off the respiratory discharge; indeed it is difficult to hold the fœtus so still as to prevent the appearance of rhythmic movements of the chest. These rhythms therefore appear almost unconnected with somatic movement, and give the impression of being spontaneous. Yet it is noticeable that whenever a definite movement of the body sets up a rhythm, the frequency and the amplitude of the rhythm depend upon the strength of the movement. Before the 50th day asphyxia in the sense of occlusion of the cord is never found to initiate a respiratory rhythm. Therefore a connexion between the intensity of effort and the consequent respiratory response seems to be a fundamental property of the central nervous system, and is discernible before any regulation of respiration by carbonic acid or the like takes effect.

Stage 4: *Inhibition*.—Between the 50th and 60th days a great change takes place in the fœtus. On the 50th day it is "on a hair trigger." Slight indeed is the touch necessary to evoke a mobile response, and rhythmic movements of the chest come and go with little obvious cause; but by the 60th day the fœtus has become inert. Only slight and localised responses follow quite considerable stimuli. As compared with its condition 10 days earlier it gives the impression of being moribund. That it is not so may be proved by subjecting it to asphyxia or even to exposure. If the cord of a healthy but inert fœtus of say 65 days be occluded, the fœtus will throw off its inertia. The demonstration is dramatic if the fœtus be one of twins. The control will present all the appearance of being asleep, while that with the cord occluded will wake to activity. In essence it reverts to the condition at which we left it at 50 days though the detail of its movements has changed somewhat, being less crude than formerly. No further development in kind occurs before the birth of the fœtus. The stage is in fact set for the first breath, though only half the gestation period has elapsed.

OCCLUSION OF THE UMBILICAL CORD

As we have seen, it is not until inhibition is established that occlusion of the cord causes respiratory movements. If at 39 days the cord is occluded, the spasms characteristic of stage 1 disappear, and the fœtus is motionless. If at 42 days the cord is occluded, the characteristic rhythm disappears and is replaced by spasms—functionally the fœtus reverts to stage 1, and if the occlusion is persisted with ceases to move at all. If at 49 days the cord is occluded the characteristic segregation disappears, followed by disappearance of the rhythm, and then even of the spasm; and lastly, if at 65 days the cord be occluded, and the occlusion be persisted with, inhibition disappears, and respiratory rhythm duly segregated appears. The fœtus, in short, reverts from stage 4 to stage 3, and with further occlusion it passes through stage 2 and stage 1. One can only infer that occlusion depresses each mechanism, and that it depresses them in the reverse order from that in which they are developed. As the higher ones go, the lower ones are left at the mercy of such sensory stimuli as remain able to play upon them.

INTRA-UTERINE BRAIN SECTION AND RESPIRATORY MOVEMENT

A classical method for the localisation of the important centres in the central nervous system is that of sectioning it in suitable places. This method has drawbacks, one being that much more is cut than is immediately relevant; another, in acute observations, is the difficulty of distinguishing what is due to passing trauma and what to severance of conduction paths. An effort is usually made to let the traumatic effects wear off by allowing some time to pass between the sectioning and the observation. With the fœtus this is impracticable. There appeared, however, to be the remote possibility of sectioning the C.N.S. in utero by an aseptic operation without impairing the healthy growth of the fœtus, and at some subsequent time, after Wallerian degeneration had taken place, of observing the fœtal movements.

This procedure in the hands of Barron proved entirely successful. The sections were made for the most part after the 60th day—that is, after inhibition had become established. The observations were made about a fortnight later. It proved desirable to carry out the experiment on twin-bearing ewes, so that there was always a control to the operated fœtus. After the section the fœtus grew at the normal rate, as judged by the age and weight curve, and by comparison with the twin control. Indeed one or two were allowed to go on to term and might with care have been brought up as lambs, had not the sections been so low as to preclude independent respiration.

1. If the section was across the medulla, but below the tip of the calamus scriptorius, the fœtus made no respiratory movements, therefore we obtained nothing of the effect described by Brown-Séquard and later by Langendorff and Wertheimer on embryo puppies.

2. If the hypoglossal nucleus was below the section, a single tap on the body usually resulted in two or three excursions of the diaphragm, never more. In this respect the foetus resembled those aged 38 and 39 days (stage 1) in which respiratory movements are first seen, except that in the 38–39 day fœtuses the movements could only be evoked from the face (because the sensory paths had not been functionally developed elsewhere) whereas in the older operated fœtus movements only followed stimulation of the body (because the fifth sensory tract was above the section).

3. Sections just behind the pons gave results similar to stage 2. Two fœtuses gave similar results. Respiratory movements occurred only on stimulation, and consisted not in two or three gasps, but in a rhythmic response of eight or nine, the fœtuses therefore resembled in their respiratory response those of 40 to 42 days. This extension of the rhythm seemed to be due to the influence of the part of the medulla above the upper end of the hypoglossal and below the entrance of the auditory nerve.

4. Section just anterior to upper border of pons gave results similar to stage 3. Two fœtuses were observed with this section, one as early as the 58th day, the second as late as the 132nd, in both cases the condition was the same, namely, one of almost continual respiratory movement, and that without any specific stimuli. These movements showed little connexion with others. The second fœtus was one of twins, and it is noteworthy that the unoperated twin exhibited the properties of a normal fœtus, its potential movement being profoundly inhibited. This section, then, throws back the fœtus to the condition of 50–55 days, when segregation of the respiratory from the somatic movements has gone far, but when inhibition is but little developed. We may assume therefore that the seat of inhibition is definitely in front of the pons.

5. Section above the posterior corpora quadrigemina. The seat of inhibition does not appear to be the same in all fœtuses studied; so far as our observations went it was lower down the brain in the younger fœtuses than the older ones. There seemed however to be two localities principally involved; the first was the lower part of the midbrain, the second the upper part of the diencephalon. A fœtus in which the section was made at 60 days just above the posterior corpora quadrigemina, and which was examined on the 68th day, was almost as completely inhibited as its twin, and quite unlike the fœtuses in which the section was just above the pons. On the other hand a number of fœtuses in which the sections had not been made until the 75th or 80th day showed that release was not complete so long as the

upper part of the diencephalon was attached. The cerebral hemispheres seemed to contribute nothing to the inhibition of the pontine and medullary mechanisms.

Analysis of the respiratory movements provided by chronic intrauterine section was therefore as follows:

Stage	Reproduced by section.
1.	Just above nucleus of nerve xii.
2.	„ below pons.
3.	„ above pons.
4.	„ above posterior corpora quadrigemina in fœtus up to 70 days. After 80 days higher up.

At birth the flooding of the central nervous system with sensations from without introduces a new factor. We have no quantitative records on the sensory side of what reaches the brain, either from the skin or from the joints and muscles which now have to bear the weight of the constituent parts of the newborn body; but we have a record of the effect of those sensations on the outflow from the C.N.S. The flood of sensory impulses which beats upon the brain when the embryo is thrust into its new environment must be taken as having a profound effect in raising the general sensitivity of the C.N.S.

THE RESPIRATORY MECHANISM AT BIRTH

The machinery of respiratory movement which started as part of the general reflex movement of the body was in its general features in being by the 60th day. It began with a reflex spasm of the body in which the diaphragm took part; it then became rhythmic, and respiratory movement became more and more detached from somatic movement. As the area of the body which could contribute to sensation enlarged, the concrete stimulus necessary to produce respiratory movement decreased. The whole mechanism, once it had been perfected, came under the influence of inhibition but could always be evoked by stimulation.

From this time onwards the issue as to whether the fœtus did, or did not, exhibit respiratory movements depended on whether stimulation or inhibition had the upper hand. In the uterus inhibition held the field. At birth two things happen. First, inhibition is depressed by asphyxia, for which reason alone the fœtus would tend to revert to its early practice of making respiratory efforts. Secondly, the brain emerges from a sensory vacuum and is bombarded with volleys of sensation, which raise the general sensitivity. For this sensation to have its full effect, however, the brain must be well oxygenated.

Grant that whether the fœtus shows respiratory movements or not depends on the balance between inhibition and sensation, you cannot consider the problem merely as a subtraction sum and leave it there. You cannot simply say: "For normal intra-uterine conditions let us rate inhibition at 5 and sensation at 3; inhibition wins by 2 and this fœtus will not make respiratory movements. If I push inhibition down to 1, then sensation wins by 2 and respiratory movement begins; or if leaving inhibition at 5 I push sensation up to 7 then sensation wins again by 2 and respiration begins." That may be crudely true as far as it goes, but the conditions which the last two alternatives represent are not the same; afferent impulses work at different levels simultaneously, and anything which reduces them reduces them at the higher levels rather than the lower ones. Inhibition working at centres in the midbrain and higher up overrules sensation. If you reduce inhibition to zero and sensation to 2, those 2 are likely to come in at the low medullary level and you may expect a gasp (stage 1), the sort of thing which occurs with the section just above the hypoglossal nucleus. If, on the other hand, you secure the onset of respiration by leaving inhibition untouched and pushing up sensation, you may expect an orderly and controlled rhythm very similar to normal respiration.

Actually the matter may be put to the test: Afferent impulses may be controlled over a wide range, being reduced to a minimum by the use of a heavy dose of urethane,[1] and to a less extent by lighter doses, or increased by spraying a current of gas over the surface of the fœtus whilst withholding a general anæsthetic. In this way you can induce patterns of respiration corresponding to any of the stages which I have described (fig. 2).

Urethane, 1 g. per kg., is sufficient completely to anæsthetise the pregnant sheep. If this dose be given, the fœtus exposed by cæsarean section and the cord occluded, a long time will elapse—perhaps a minute, perhaps more than a minute—before any respiratory effort occurs; when it does the fœtus will give a gasp. After a long pause there may be another gasp and so on at intervals till a pattern of rhythmic respiration appears (fig. 2, III, rhythmic respiration occurred in about 4 min.). Urethane, 0·25 g. per kg., deprives the mother of the use of her legs, but leaves her sitting up. If then she is given a spinal anæsthetic, and if the fœtus be delivered, it will give a few gasps after which rhythmic respiration will shortly supervene (fig. 2, II, rhythmic respiration appeared in a little over a minute.) If no urethane be given and the cord be tied, there will probably be no gasps; rhythmic respiration will start at once, indeed so rapidly that you are in doubt whether it is not the mere handling of the fœtus that has produced the rhythm (fig. 2, I). Lastly, without any occlusion of the cord, respiration may be induced by such a process as the projection of a draught of air from a fan or gas cylinder on to the surface of the fœtus.

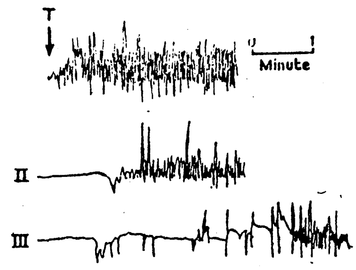

Fig. 2—Chart of intratracheal pressure at birth in 3 lambs. T, cord tied. I, no general anæsthetic. II, 0·25 g. of urethane per kg. III, 1 g. of urethane per kg.

The respiratory patterns which may be expected in sheep are as follows: (1) the simple spasm or gasp; (2) the spasm or gasp involving the respiratory muscles outlasted by a respiratory rhythm of shallower respirations; (3) rhythms of shallow respirations which come and go, possibly not preceded by any obvious spasm; (4) the establishment of almost continuous respiration of a normal character. Which appeared would depend on the stringency of the conditions to which the fœtus was subjected. The first would be that in which sensation was at its minimum and asphyxia at its maximum, the last at which sensation was at its maximum and asphyxia at its minimum. These are what on a basis of observations in the sheep we might expect to find in the child at birth.

So far as could be gleaned from mere observation the expected patterns appeared under the expected circumstances. A human fœtus delivered as the result of cæsarean section under a general anæsthetic (? chloroform), deep enough for the complete anæsthesia of the mother, gave a typical picture such as would be given by sheep under the same circumstances. It began life with a series of isolated gasps. The fourth pattern was shown by a baby who began to breathe as soon as his head (which was little if at all cyanosed) emerged and who continued right on. The intermediate patterns were also seen.

THE URGE TO BREATHE

Asphyxia.—When the umbilical cord is tied or the placental circulation fails, there are two chemical happenings. The oxygen supply is cut off, and the carbonic acid produced by the body in general and by the respiratory centres themselves in particular accumulates. Much effort has been spent upon the relative effects of oxygen want and carbonic acid excess on the respiratory centre, and most of it deals with an antithesis between the two. While it is right and necessary to make a correct analysis of the effects of each, too much has been made of the antithesis between them, and too little of the possibilities of their reinforcing one another. Certainly with regard to the effect of occlusion of the umbilical cord you cannot get the one without the other, and it would be highly desirable in addition to knowing what each achieves, to know also whether the whole is merely the sum of the parts, or whether the conjunction of the two amounts to more than a summation. But first arises the question: are there really two factors?

1. The experimental detail cited here must not be taken to be even an oblique criticism of the use of anæsthetics during delivery. Least of all of the trifling quantities often used as a routine measure. Any criticism of that sort would need to be considered with regard to the individual anæsthetic, the dose, and the numerous reasons for and against giving an anæsthetic.

First, has excessive CO_2 a stimulating effect upon the respiration of the fœtus? Snyder and Rosenfeld performed a large number of careful experiments chiefly on rabbits. They judged of the respiration of the fœtus from the movements which they saw through the uterine wall when the abdomen was open though they checked these up with movements of the abdominal wall in the intact rabbits. They state that in 24 experiments embracing 78 fœtuses, excessive CO_2 administered to the mothers produced stimulation of respiratory movements in 8, and had no effect on the other 16. On the other hand, once the fœtuses were born CO_2 exerted its normal stimulating effect. Their conclusion was that "the CO_2 response of the newborn is related to birth rather than to the stage of development." If the CO_2 in the fœtus is reduced, respiratory movements are depressed. I take their meaning to be that there is an optimum CO_2 level which is the level normally obtaining in the fœtus.

Eastman, Geiling and Lauder (1933) attempted an answer in another way. In a number of human deliveries they took samples of the blood from the umbilical cord when the fœtus gave its first breath. Applying the carbonic acid content found to the CO_2 dissociation curve of the same blood, they got results so various as to lead them to the conclusion that the onset of respiration was not a simple function of the CO_2 pressure. In 1938 I published observations on sheep under urethane in which I could induce no fœtal respiratory movements by the administration of CO_2 to the mother. On the other hand, there seems to be no doubt that CO_2 will induce, or at all events accentuate, respiratory movements under suitable circumstances. Windle (1940) and his colleagues obtained them in the cat at 44 days. Windle's figure shows that a cat fœtus which had been giving respiratory movements off and on at about 2 a minute had them increased up to 33 a minute by administration to the mother of oxygen containing 8% of CO_2. We have observed augmented respiratory movements in sheep where the mother had a spinal anæsthetic and in which the fœtuses therefore had no anæsthetic. The following seems to be typical:

"sheep, 83 days' pregnant, was given 10% CO_2 in air; this definitely increased the depth of the respiratory movements which by this time were frequent in any case, owing to exposure. Her breathing was much affected. The effect of nitrogen alone was much greater, making the fœtus kick about; this it did, even though the mother was not reacting greatly."

This experiment also seems aptly to describe our experiences with regard to oxygen-want. The point to emphasise is that respirations of rather a different type are associated with oxygen-want, they are often gasps and generally part of a more extensive muscular movement. Moreover, they can be elicited both in fœtuses free from urethane and in those which have had a heavy dose. It seems likely therefore that the gasp given by a fœtus in poor condition is liberated by oxygen-want, while in a lively fœtus both oxygen-want and CO_2 excess play a part when the cord is tied. Pending more information on this subject, however, it seems desirable to use the word asphyxia to denote that combination of oxygen want and CO_2 excess which is brought about by failure of the placental circulation. Certainly the oxygen level in the blood coming from the brain seems pretty accurately to define the limits of asphyxia necessary to invoke respiratory effort. This limit varies somewhat with the age of the fœtus but it may be said fairly exactly that if the blood in the sinuses coming away from its brain carries less than a quarter of its possible load of oxygen, a fœtus aged 90–120 days would show respiratory movements, and that this limit gradually sinks to 15% at term.

Sensation.—A catalogue of the forms of sensation which may conspire to initiate respiration at birth would include reactions to specific sensations as well as a general heightening of the sensibility of the nervous system caused by the establishment of general sensibility on a large scale. Moreover, cutting across such a classification would be the division of sensations into extraceptive and proprioceptive.

Among specific sensations acting outside the body pain (if such a word can be applied to the experiences of an organism so anoxæmic that it can have no real consciousness) can have a dramatic effect. There can be no more specific reaction than that of the gasp in a refractory rabbit's fœtus when the ear is firmly pinched. Among specific stimuli from the inside of the body the rise of blood-pressure associated with the cutting off of the placental circulation can possibly be a factor in the initiation of respiration at birth. It is not a necessary factor, since examples are on record of animals in which pinching the cord has induced gasping in the absence of hypertension. On the other hand in sheep fœtuses in good condition slowing in the pulse appears within 5 sec. of the rise of pressure caused by the occlusion of the cord; this phenomenon is abolished by section of the vagi and it would seem likely to be a reflex due to stimulation of the aorta or carotid sinus mechanisms or both. If so, the possible reactions of these same mechanisms on the respiratory centre cannot be excluded.

Among internal sensory impulses those carried by the vagus first occur to the mind; but of course the volley of afferent impulses brought to the brain along the vagus is initiated by the expansion of the chest, and whereas these afferent muscular proprioceptive impulses are all-important after the first inspiration, they can scarcely be regarded as a factor in launching the first breath. Apart from such specific sensations the general flood of stimuli from the skin and probably from the muscles and the joints are of first importance, for we must remember that at birth not only is the surface of the fœtus exposed to cold and to contact with surrounding objects, but removal of the embryo from its aqueous environments subjects it to the strains put upon it by its own weight. No analysis has been made of these varying sensations, but, their accumulated effect is shown by the degree of muscular tone which they invoke. A fœtus with its placental circulation intact alternately taken out of and replaced in its bath of saline, exhibits muscular tone to the point of shivering when it is taken out of the bath and relaxation when it is replaced.

In the course of a long series of experiments I naturally have been confronted with a number of fœtuses which showed little inclination to breathe even when the cord was ligated. In such cases I have found myself implementing the principle set forth above—namely, the initiation of the greatest number of afferent impulses, especially from the sensory endings of the fifth cranial nerve, and their combination with an oxygen supply so copious that when a gasp does take place the blood may acquire as much oxygen as possible, and thus render the brain more receptive to the next sensory volley. In practice this amounts to the direction of the stream of oxygen from a cylinder on to the fœtus more especially on to its face, nose, and mouth, once the air passages have been rid of mucus. I use the word "stream" not "trickle," because the current of oxygen should stimulate as large a surface as possible, and the atmosphere round the mouth and nose should be rich in that gas. The stream of oxygen should, in fact, be as vigorous as is deemed compatible with the welfare of the fœtus always bearing in mind that, unless a fœtus breathes it has no welfare. I mention this procedure because I have been occasionally surprised by the dramatic success which has followed it.

Remembering that the newborn fœtus has had no respiratory exchange for some time and is therefore overloaded with carbonic acid, I can see little point in adding that gas to the oxygen at this stage, though a certain admixture of nitrogen may be desirable to prevent the lungs collapsing completely should the interval between the gasps be long enough for the complete absorption of the oxygen inhaled. At a later stage, when the respiratory rhythm has been established, CO_2 in the oxygen is desirable.

Such then is the picture that I draw of the onset of respiration at birth. Perhaps it is too much to claim even that it is a picture; rather I regard it as a blocking out of one, for a lifetime might be spent in filling in the details.

I wish to thank Mr. W. S. Mansfield and the Cambridge University Farm staff, for providing suitable ewes; and the LCC officials and the staff of the British Postgraduate Medical School who gave me the opportunity to test whether correspondence existed with human cases.

References at foot of next page

TERMINAL ILEOSTOMY IN ULCERATIVE COLITIS

RODNEY MAINGOT, F.R.C.S.
SENIOR SURGEON TO THE SOUTHEND GENERAL HOSPITAL AND TO THE ROYAL WATERLOO HOSPITAL

MANY patients suffering from idiopathic ulcerative colitis respond satisfactorily to a well-planned and prolonged course of medical treatment. No specific therapy has yet been devised, and the success of any particular remedy, such as sulphapyridine, sulphaguanidine (Stickney et al. 1942), Bargen's serum (Bargen 1936) or antidysenteric serum (Bargen et al. 1930), is no proof of its specificity. The indications for operation are difficult to define, because the disease is so protean in its manifestations and in the way it responds to orthodox and other types of treatment. Nevertheless, it would be accepted by most that surgery is called for where efficient medical treatment has failed to bring about a cure or to produce relief of symptoms; also where certain complications have occurred, such as subacute perforation or abscess, fistula, sinuses, obstruction, massive hæmorrhage or polyposis, or the possibility of malignancy cannot be excluded. In the first group are included all those cases which prove intractable to continuous medical treatment conducted under the best conditions in hospital or nursing institution for a period of about six months, and those chronic ambulatory cases which are totally incapacitated for as long as three months or more in each year.

OPERATIVE METHODS

Surgical treatment may conveniently be divided into the following.

Methods employed for the purpose of irrigating the large bowel—(a) appendicostomy; (b) valvular cæcostomy.

Methods directed to exclusion of the colon from the passage of fæces by means of ileostomy: (a) simple loop ileostomy; (b) terminal (transverse) ileostomy, either end or single-barrelled ileostomy (Rankin 1935) or implantation of the proximal and distal limbs of the divided ileum into separate incisions in the abdominal wall (Cattell 1939).

Ileostomy followed by colectomy with anastomosis of the ileum into the lowest portion of the pelvic colon or into the remaining rectal pouch.

Ileostomy followed by total excision of the colon, rectum and anus.

Ileostomy followed by restoration of the intestinal continuity—i.e., by end-to-end or side-to-side ileo-ileostomy or ileo-cæcostomy.

Until recent years appendicostomy has had numerous supporters and there are reports of many cases treated by this method which have apparently responded satisfactorily. But in my opinion—and I was at one time an ardent supporter of this operation—there is no convincing evidence that cases thus treated fare better than with efficient medical treatment alone. Valvular cæcostomy possesses no distinct advantage over appendicostomy except perhaps that it is easier to perform. Neither of these operations places the large bowel at rest, nor does either of them allow the colon to be irrigated in a manner that is unquestionably better than by washing out from below. Hurst (1940) and others have shown by simple radiological experiments that the cæcum can always be reached by introducing a pint and a half of opaque medium per anum and that the colon, especially when it is abnormally irritated, as it is in ulcerative colitis, can be completely evacuated by this means. There is consequently no advantage in injecting fluid from above. Many authorities have in addition questioned the value of colonic irrigations and instillations in the management of this disease. They have brought forward evidence to show that washing out the large bowel with weak astringent lotions, tap water, salt solution, 0·8% sulphanilamide in physiological saline, &c., has yielded just as disappointing results as instillations of warm olive oil or crude cod-liver oil with its rich vitamin-A content, whether these were injected through an appendicostomy opening or per rectum. In the majority of cases these injections or instillations instead of alleviating symptoms or hastening the reparative processes in the gut wall seem to aggravate the condition, to induce colicky pains, to cause unnecessary suffering and to increase the number of daily bowel evacuations. Cave and Nickel (1940), drawing from their wide experience, state that "Appendicostomy, cæcostomy and, except for certain cases, colostomy have been discarded as ineffectual surgical measures, and have in the past and do at present complicate further surgery when undertaken."

Ileostomy is the operation of choice. There are many types of ileostomy, but in a general way it may be stated that loop ileostomy is chosen when the patient has been exsanguinated by repeated severe hæmorrhages or when in the rare fulminating case toxæmia is pronounced. Loop ileostomy is a simple emergency measure which is associated with a high mortality, for it is indicated as a last resort in patients who are desperately ill and in whom medical treatment after a reasonable trial has led to no improvement. It needs courage to operate on such cases which are extremely exsanguinated or toxæmic, but I have on occasion seen amazing improvement follow within a few days, and eventually complete recovery. The operation is performed through a small right gridiron incision under local anæsthesia (Maingot 1940). The lowest loop of ileum is picked up, drawn through the wound, anchored in position, and then decompressed with a rubber catheter. It takes but a few minutes to perform, but in a large percentage of cases the patient dies from toxic absorption.

The single-loop method of Rankin, which is the simplest of the elective ileostomies, is nowadays rarely undertaken. By this plan the terminal ileum is withdrawn through a McBurney or low transrectal incision, the intestine is crushed with enterotomes, divided with a cautery, and after the distal end has been oversewn and inverted with purse-string sutures of silk it is dropped back into the peritoneal cavity and the operation is completed by closing the wound around the protruding limb of intestine, into which a rubber tube is passed and secured to permit of immediate drainage of the bowel. The main objections to this procedure are that the distal stump of ileum may blow out, leak or perforate and thus give rise to a virulent spreading peritonitis if for one reason or another the intracolonic pressure remains unduly raised in the immediate post-operative period, as may, for instance, obtain in the case of a stricture of the large bowel, and if at some future date the operation of restitutio ad integrum is contemplated it is more difficult to apply the criteria of cure than if both ends of the divided ileum were on the surface of the abdomen. When therefore an elective ileostomy is called for it is better to divide the ileum about 6–8 inches from the ileocæcal junction and to implant the proximal and distal limbs of the intestine into separate incisions in the abdominal wall after the technique advocated and so successfully practised by Cattell. A detailed account of this operation is presented in the case-report which follows.

In most instances the ileostomy will be permanent. It will, of course, be permanent after total colectomy which is performed in two or three stages, where the patient refuses any further operative interference, or where partial or total colectomy or restoration of intestinal continuity is for one reason or another deemed inadvisable or too hazardous.

If the disease appears to be strictly limited to the distal half of the colon and proves recalcitrant to medical therapy, colostomy of the end type (Devine 1935) with interruption of the continuity of the bowel can be carried out in the transverse colon, and the distal half of the bowel be resected after it has been defunctioned for several weeks. The colostomy is well tolerated and easy to manage, easier in fact than ileostomy, and the late results in these localised cases of the left colon are on the whole satisfactory. In about 80% the disease starts in the rectum or pelvic colon and progresses in

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BODY TEMPERATURES DURING ANESTHESIA IN INFANTS AND CHILDREN

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Fever, convulsions and death following surgery on children is a sequence of complications that has long been dreaded by surgeons and anesthesiologists. Dr. Isabella C. Herb [1] pointed out in "Abt's Pediatrics" in 1925 that operating room temperatures should be between 65 and 70 F., and that temperatures above this are exhausting to the patient. Although the staff at The Children's Memorial Hospital was conscious of this danger, our only preventive measures were the usual ones—such as light draping, cancelling of elective surgery on excessively hot days and ice packs following surgery if the temperature was noticeably elevated at the conclusion of surgery.

In the summer of 1947 we were suddenly jolted out of our complacency by two deaths due to postoperative hyperthermia.

REPORT OF CASES

CASE 1.—T. M., 1 year of age, was operated on for correction of webbed fingers. The day before surgery his temperature was 100.4 F. rectally. No reason for this slight elevation could be found. His rectal temperature the next day before going to the operating room was 98.8 F. The anesthesia was started at 9:35 a. m., and the operation was completed at 1 p. m. Ethyl chloride induction, followed by open drop ether, was used for the anesthesia. During surgery the anesthetist reported that the

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The water mattress was made by the Davol Rubber Company, Providence, R. I.

The thermo-electric clinical thermometer was made by the Central Scientific Company of Chicago.

From The Children's Memorial Hospital, Chicago, and the Ortho S. A. Sprague Memorial Institute Laboratories, Chicago.

1. Abt, I. A.: Abt's Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, chap. 160, p. 602.

child was not doing well. The pulse and respiration rates were rapid, and there was profuse perspiration. Oxygen and intravenous fluids were administered. Following surgery the child was placed in an oxygen tent, the temperature in the tent being 76 F. The body was very hot, and the feet were cold. The pulse rate was 150 to 200, and the respiratory rate was 48 to 80 per minute. Death occurred at 2:45 p. m., when the rectal temperature was 108.5 F. At autopsy there was edema and congestion of the brain and leptomeninges, petechial hemorrhages throughout the brain and miliary tuberculosis only of the lungs, liver and spleen. The impression of the main cause of death was heat stroke.

CASE 2.—D. D., the second patient, was first operated on for a tracheo-esophageal fistula at the age of 3 days. The proximal end of the esophagus was brought out through the neck. The lower end was ligated, and a gastrostomy was done. On his last admission, at the age of just past 1 year, his temperature had fluctuated from 97.8 to 100.6 F. rectally. Anesthesia for anastomosis of the esophagus to the fundus of the stomach placed in front of the thorax was started at 1:35 p. m., and the operation was completed at 6:25 p. m. Anesthesia consisted of cyclopropane with oxygen administered by the to-and-fro technique. An adequate airway and gaseous exchange were difficult to maintain. At the end of the operation the temperature was 101.4 F. rectally, the pulse rate was 106, and the respiratory rate was 108. Three hours later the temperature was 108 + F. rectally. In spite of the patient being in an oxygen tent and ice packs, death occurred 12 hours later. Preoperative medication consisted of morphine, 1/32 grain, and atropine sulfate, 1/300 grain. At postmortem the essential observations were cerebral edema and congestion of the lungs, liver and adrenals.

Personal communications from other physicians in the Chicago area revealed other similar deaths of children in whom hyperpyrexia was developing during or following surgery. Although there have been some studies of temperatures during anesthesia, the significance of fever and its control has not been sufficiently emphasized. Knight [2] reported in 1942 that hyperpyrexia is of frequent occurrence during prolonged operative procedures, and that it has a deleterious effect on the recovery period. He believed that the closed system of administering anesthetic gases tends to raise the patient's temperature. He developed a gas cooler to control the rise in body temperatures. Burstein and

2. Knight, R. T.: Elevation Of Body Temperature During Anesthesia and Its Control, Anesth. & Analg. **21**: 117-119 (March-April) 1942.

Mark[3] state that in the closed system the carbon dioxide absorber, especially of the to-and-fro variety, tends to warm the breathing mixture. They reduced the heat by using ice bags on the upper end of the to-and-fro cannister and the face mask. By this method the rise in body and skin temperature is minimized. Without ice bags and with a room temperature of 85 F. the rebreathing atmosphere rises to between 104 and 113 F. With ice bag technique the gas temperatures were between 83 and 87 F.

We were unable to adequately control the body temperatures in children by cooling the gases in a to-and-fro absorption system. We have had no experience with gases cooled with the circle technique.

PROCEDURE

Rectal temperatures taken at the termination of surgery revealed that the majority of the children undergoing surgery had some elevation of temperature. It seemed desirable that continuous temperature recordings should be made. Consultation by Dr. Bigler with Dr. Marshall N. States and Dr. Harris M. Sullivan of the Central Scientific Co., of Chicago, resulted in their construction of a thermo-electric clinical thermometer that was safe to use when explosive anesthetic agents were being administered.

The apparatus consists essentially of a thermocouple, one junction of which is held at a constant temperature in a constant temperature well, the other junction being an integral part of the rectal insert. The thermocouple current is read on the scale of a galvanometer that is calibrated in degrees. The instrument is completely electronic, and there are no sparking points.

Until the spring of 1948 we were concerned chiefly with the causes and prevention of hyperthermia. The advisability of producing hypothermia for the purpose of decreasing the oxygen demand during operation on "blue babies" was discussed. Perusal of the voluminous

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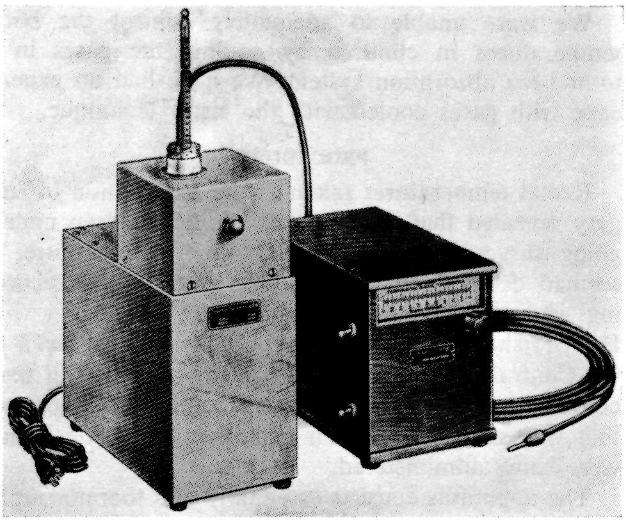
3. Burstein, C. L., and Mark, L. C.: Control Of Temperature Of Inspired Atmosphere In Absorption Technic, Anesthesiology **9**: 197 (March) 1948.

medical literature on cold therapy, the effects of cold and local refrigeration anesthesia, led us to believe that hypothermia may be produced safely in adults, but we were unable to find any reports of the deliberate production of hypothermia in critically ill children. In fact, the literature abounds with reports on the conservation of body temperatures in children undergoing surgical procedures. However, because of the acute need of increasing the arterial oxygen or of lowering the oxygen



Thermo-electric clinical thermometer with constant temperature well, galvanometer scaled for reading degree of temperature and rectal insert.

demand in patients with critical hypoxemia, we decided to resort to hypothermia.

CASE 3.—Thomas O., aged 3 months and 25 days, was admitted to the hospital in May of 1948 with marked cyanosis. He had begun to have spells of cyanosis at the age of 2 months. During these attacks, which lasted for about 30 minutes, he became semicomatose and blue-black in color.

It was the unanimous opinion of the cardiologists, surgeons and anesthesiologist that the infant would probably die on the operating table. But it was obvious that he was doomed without surgery. Therefore, it was decided to attempt an anastomosis.

Morphine, $\frac{1}{60}$ grain, and atropine, $\frac{1}{300}$ grain, were administered one hour before the operation. Cyclopropane was administered by the to-and-fro technique, and the infant was surrounded with ice bags. His temperature was lowered until it registered 96 F. rectally. Very little cyclopropane was needed for maintenance of the anesthesia. In fact, for more than 90 minutes the cyclopropane valve was shut off. On the completion of an anastomosis between the aorta and the pulmonary artery hot water bottles were applied. When the rectal temperature reached 96.7 F. the patient began to react, and cyclopropane was again administered for closure of the incision. The patient was awake when he left the operating room. The total anesthesia time was three hours.

Convalescence: After 24 hours the infant was removed from his oxygen tent. Phleboclysis was discontinued, and he was given a full formula by bottle. He was discharged on the fourteenth postoperative day after an uneventful recovery.

RESULTS

The normal rectal temperatures of infants and children are approximately one degree higher than the mouth temperatures. In our tables, for convenience, we used rectal temperatures of from 99 to 100 F. as normal and placed all temperatures in units of one degree. Two hundred and fifteen patients between 4 days and 13 years of age who underwent surgery were studied. Eight patients had a temperature of from 100 to 101 F. on arrival in the operating room.

CONTROL GROUP

The control group consisted of 89 patients who had no cooling and 22 patients who were cooled with ice bags after alarming fever had developed. Hence, it is obvious that in these 101 children the number in whom extremely high temperatures were developing would be more than the number indicated in chart 1. It is also probable that some temperatures would have exceeded 104 F. had not ice bags been used before the termination of surgery. Twelve of the 22 patients were in such critical condition that ice bags were used before their temperatures reached 102 F. We did not feel justified in jeopardizing any child for the purpose of a statistical study.

As can be seen in chart 1, 62.3 per cent of the children in the control group suffered temperatures above 100 F. Seven of these 63 children suffered temperatures of between 103 and 104 F., 15 of between 102 and 103 F. and 17 of between 101 and 102 F.

Of the 22 patients on whom ice bags were used, eight became normal or subnormal before surgery was completed. Of these, the temperatures were from 99 to

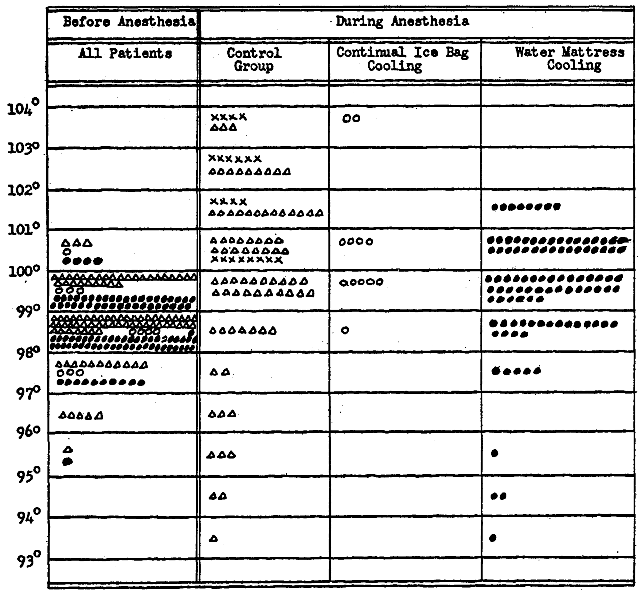


Chart. 1.—Highest temperatures recorded during anesthesia, with the explanation of symbols as follows: triangle, patient in whom no cooling method was employed; "x," patient in whom ice bags were used after rise in body temperature; open circle, patient in whom ice bag cooling was used continually, and closed circle, patient in whom water mattress cooling was employed.

100 F. in three, 98 to 99 F. in three, 97 to 98 F. in one and 96 to 97 F. in one. The remaining 14 patients continued to have fever at the close of the operation.

In 41 patients with fever no ice bag cooling was used. Only five of these had a normal temperature, and one had a temperature of from 98 to 99 F. at the end of surgery. The other 35 continued to have fever. Although ice bag cooling of the patient was of some help, it was not as helpful as expected.

The normal and subnormal temperatures recorded in chart 1 were the highest temperatures recorded during surgery. Of those below 97 F., all but one were in infants under 6 months of age (chart 3). The exception was under 1 year of age. Of the 38 patients without some fever, only 20 were within the normal 99 to 100 F. range.

In this control group there was a spread of temperatures of from 93 to 104 F., or of 11 degrees.

ICE BAG COOLING

During the hot summer months ice bags were used on a number of surgical patients in an attempt to control the temperatures during surgery. This not only was disturbing during the operation but also was not particularly effective in controlling the fever in some patients. Twelve patients had ice bags packed around the body from the start of anesthesia. Of these, six (50 per cent) developed fever, two of from 103 to 104 F. and four of from 100 to 101 F. Of these six patients, body temperature was above normal at the end of surgery in four, normal in one and subnormal in one. Of the six with no fever, one was normal, two were from 97 to 98 F., and three were from 96 to 97 degrees F. at the termination of surgery. In two of the latter hot water bottles were substituted for the ice bags during surgery.

Because of this experience with ice bags, the development of a more easily controlled technique seemed advisable. A rubber mattress, measuring 19 by 24 inches, was constructed for us by the Davol Rubber Co. This mattress is compartmented in order to give it stability when it contains water. Inlet and outlet tubing at opposite corners facilitate the regulation of the mattress temperature by introduction of hot or cold water.

WATER MATTRESS GROUP

The water mattress was filled and in place on the operating table under the sheet. Each child was placed on the mattress before the induction of the anesthesia and surgical preparation. The temperature of the water in the mattress varied from tap water of 60 to 70 F. to ice water of 40 to 50 F. The temperature of the water was varied according to the age of the child, the room temperature and the degree of cooling desired by the anesthesist. For patients under 1 year of age ice water was not necessary at any time.

The water mattress was used with 102 patients. In 40 (39.2 per cent) the temperature rose above 100 F. rectally (chart 1). There were no patients with a fever over 102 F., in contrast to 24 in the control and ice bag groups. In only eight were the temperatures 101 to 102 F., and in 32 the temperatures were 100 to 101 F. The temperature was normal before the end of surgery in 25 of the 40 patients. It was below 100 F. in 15 minutes in two patients, in 30 minutes in 10, in 45 minutes in two, in 60 minutes in five, in 75 minutes in five and in two hours in one. Of these 25 patients, the temperature before the end of surgery was 99 to 100 F. in 17, 98 to 99 F. in three, 97 to 98 F. in three, 96 to 97 F. in one and 94 to 95 F. in one. In three the cool water was replaced with warm water when the temperatures became subnormal.

Of the 63 cases with their highest temperatures normal or subnormal, as indicated in chart 1, those below 97 F. all occurred in infants under 1 year of age. Temperatures of from 97 to 100 F. were about equally distributed in the age groups over 1 year of age. Hot water replaced the cool water when the temperature became subnormal in 17 instances. In the mattress-cooled group the variation in temperatures was 11 degrees, but the fevers were not as high, and more cases fell within the normal or slightly subnormal range.

TEMPERATURES BEFORE SURGERY

In only eight patients was there an elevation of temperature before surgery. In one patient ice bags were used from the beginning of the anesthesia. The temperature was 101 F. before surgery and gradually came down to 100.4 F. in two hours at the end of the operation. Three patients with temperatures of

100.2, 100.6 and 101 F. had no cooling, and at the end of surgery, one and one-half to two hours later, they had fevers of 101.6, 101.5 and 103.4 F. The remaining three patients were cooled with the water mattress. The temperature before surgery was 100.2 F. in two patients and 100.8 F. in the third, but at the end of 45 minutes two were normal, and the third was 100.6 F. at the end of surgery, one hour and 40 minutes later.

ONSET OF FEVER

A temperature of over 100 F. was present in 109 of the 215 patients studied. In chart 2 the time of onset of the fever after the beginning of surgery is divided into 15 minute periods for the first hour and

	No Cooling	Part Time Cooling	Continual Ice Bags	Cold Water Mattress
0 - 15 minutes	△△△△△△△△△△ △△△△△△△△△△△△	××××××××××× ×××	oo	●●●●●●●●●●●●●● ●●●●●●●●●●●●●● ●●●
15 - 30 minutes	△△△△△△	××××××××××	oo	●●●●●●●●●●●●
30 - 45 minutes	△		oo	●
45 - 60 minutes	△△△△			●
1 - 2 hours	△△△△△△△			
2 - 3 hours	△△			
3 - 4 hours				●

Chart 2.—Time of onset of fever after start of anesthesia (only temperatures above 100 F. recorded), with the explanation of symbols as follows: triangle, patient in whom no cooling method was employed; "x," patient in whom part time cooling was used; open circle, patient cooled through the continual use of ice bags, and closed circle, patient in whom water mattress cooling was employed.

then into hourly periods thereafter. In 63 patients (57.8 per cent) the temperature began to rise above normal in the first 15 minutes, while 27 (24.7 per cent) did so in the next 15 minutes. This means that 82.5 per cent of the febrile patients began to develop a temperature within the first 30 minutes. It is apparent that something besides the actual surgery must influence the temperature.

PREOPERATIVE MEDICATION

In all but a few of the very young infants some preoperative medication was used. In patients a few weeks to a few months of age small doses of atropine were administered preoperatively. Between 1 year and 5 years of age the majority of the children received both morphine and atropine, while most of the children 5 years of age and older received morphine and scopolamine hydrobromide as preoperative sedation. Although it is generally believed that the belladonna group of drugs may cause fever, no relationship between these drugs and fever could be shown in this series. The old belief that morphine will tend to prevent fever [1] may be correct, but it did not prevent fever in over 50 per cent of the patients studied.

ANESTHESIA

The majority of the 215 patients studied were thoracotomies, usually for correction of a congenital heart lesion. These patients were almost routinely anesthetized with cyclopropane administered by a to-and-fro technique through an endotracheal tube. This may have had an influence on our observations; however, open drop ether, with and without oxygen insufflation under the mask, semiclosed, circle absorption and pharyngeal insufflation techniques were all used in various other types of surgery, and no definite influence on temperature elevation could be shown due to the method of administration.

AGE OF THE PATIENTS

The patients varied in age from 3 days to 13 years. The age of the patient had a very definite influence on the temperature during surgery. Below 6 months of age the infant tends to develop hypothermia—only one patient in this group had a temperature above 100 F. Between 6 months and 1 year of age, half the patients developed hyperpyrexia while one-half developed hypothermia. From 1 year to 13 years of age the children in the control group had an average temperature of 101 to 102 F., while the cooled group showed an average temperature of 100 F. The temperatures of all patients are shown in chart 3.

MONTH OF YEAR

There was very little difference between the number of patients with fever during the winter months and the number with fever during the hot summer months.

Temperatures above normal were about equally divided between all months of the year, with the exception that the majority of fevers above 102 F. occurred between April and September. This same relationship holds true when one considers the operating room temperatures. We do not have air conditioning, and the temperature of the operating room varied from 69 to 88 F. Although there was a rise in temperature in some

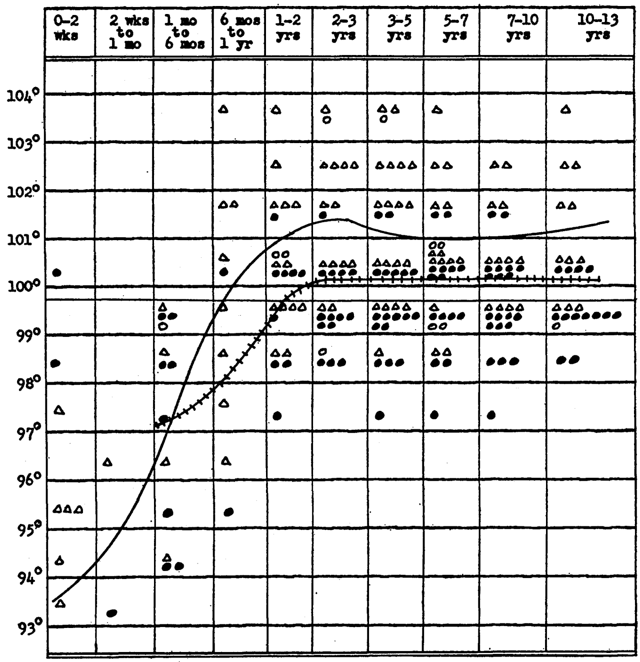


Chart 3.—Height of temperature during anesthesia relative to patient's age, with the explanation of symbols as follows: triangle, patient in whom no cooling method was employed; open circle, patient in whom ice bag cooling was used, and closed circle, patient in whom water mattress cooling was employed.

patients throughout this whole range, the majority occurred when room temperatures were between 76 and 82 F. The temperature about the patient must have been higher at all times due to the necessary draping (kept as light as possible), the number of people around the table and the operating room lights.

LENGTH OF SURGERY

In the group of patients studied each anesthesia lasted from 30 minutes to five hours. It can be seen in chart 2 that 82 per cent had a rise in temperature within the first 30 minutes. In most instances this will increase during the surgical procedure if cooling is not used.

RELATION TO TYPE OF SURGERY

As our thermo-electric thermometer was set up in only one of the operating rooms, the cases studied were rather selective. There were 154 cases, including great vessel surgery, anastomosis of the aorta and pulmonary arteries, division of patent ductus and excision of coarctation of the aorta. In 55 of these cases there was either no cooling or only ice bags about the patient after the temperature began to rise. In this group 41 (74.5 per cent) had fever above 100 F. Of the 11 patients who were packed in ice bags during the whole operation, six (54.5 per cent) had a temperature above 100 F. Of the 88 cases in which the cold water mattress was used, 37 (43.2 per cent) had some fever.

There were 11 cases of primary or secondary surgery of tracheo-esophageal fistulas. As would be expected when considering the age of these patients, only one suffered a temperature above 100 F. Mediastinal tumors and lobectomies made up 10 cases. Of the six patients without cooling, four suffered some fever, while the four who were cooled with the mattress maintained temperatures within normal limits.

Seventeen abdominal surgery cases included bowel surgery, abdominal and kidney tumors and bile duct atresia. Eight of 12 patients in the control group and two of five patients in the mattress-cooled group had some fever. There were four patients with inguinal herniorraphies in the noncooled group, all of whom had temperatures above 100 F.

In the control group there were 12 cases of surgery on bones and tendons, with fever in three patients, and one of three patients on whom skin grafts were applied had a fever. Of the remaining 16 miscellaneous patients, all in the control group, only one had fever.

TEMPERATURES AFTER SURGERY

It is always difficult to find the cause of postoperative fever and hence to rationalize on the relationship of temperatures during anesthesia and postoperatively. When no fever was present during anesthesia there was no significant difference in the number of children with fever within 72 hours postoperatively, whether cooled or not cooled. The average for each group was close to 50 per cent. The temperatures were 100 to 101 F. in 74 per cent, 101 to 102 F. in 20 per cent and 102 to 103 F. in 6 per cent.

In the control group of children with fever during anesthesia 77.5 per cent still had fever at the end of surgery, but only 50 per cent continued to have fever for 48 to 72 hours. In the mattress-cooled group the corresponding figures were 37.5 per cent and 42.5 per cent. There is little difference in the effect of cooling during anesthesia with respect to fever 48 to 72 hours postoperatively. Temperatures of over 101 F. were present in 42 per cent of the control group and 34 per cent of the water mattress group. All patients with anesthesia temperatures of 100 F. at the end of surgery had postoperative fever. This was generally higher in the noncooled group—one rising as high as 106 F.

There were 12 deaths in this group of 215 children. Four deaths occurred in cases of congenital tracheo-esophageal fistulas. Two of these were operated on at the age of 3 days (temperature of both being from 97 to 98 F.), one at the age of 4 days (temperature from 93.6 to 95 F.) and one 6 days old (temperature of 94.8 and 96 F.). All were in the control group; all had pulmonary infection before surgery, and all died shortly after the operation except one patient who died on the fourth day. Seven deaths occurred in the group with congenital malformations of the heart and one in the group with a double aortic arch. The temperatures were 91.8 to 95.6 F., age 7 months; 92 to 100 F., age 3 months; 92.8 to 94.6 F., age 6 months; 97.4 to 100.6 F., age 1½ years; 98 to 98.2 F., age 2¼ years; 98.4 to 98.6 F., age 2 months and 100 to 100.8

F., age 2 years. The two patients with temperatures over 100 F. were in the control group, and the rest were in the cool water mattress group. All died within 14 hours postoperatively, with the exception of two who lived two and six days respectively. None of these children were good surgical risks, and it was believed that the temperature during surgery had nothing to do with their deaths.

The postoperative course of the mattress group was generally better than that of the control group. All four patients with prolonged and unexplained fever were in the control group having fever during anesthesia. Major postoperative complications were about equally divided between the two groups and were usually related to the preoperative condition or to the immediate surgery. Major postoperative pulmonary infection occurred with approximately the same frequency whether or not the children were cooled during surgery. However, this series is too small to have statistical value on this point.

ANESTHETIST AND SURGEON

It is the opinion of both the technician anesthetists and the physician anesthetists who administer the anesthesia at The Children's Memorial Hospital that appreciably less anesthetic agent is required when the temperatures are subnormal. During surgery on "blue babies" subnormal temperatures seem to have a beneficial effect on the heart action. Exploratory operations on "blue babies" in which no anastomosis was possible had a mortality of 54.4 per cent in the uncooled group and a mortality of 14.4 per cent in the cooled group. Although the total number of these exploratory operations was only 18, the 40 per cent difference in mortality is probably significant.

The surgeons doing most of the operations have become very dependent on the information and control offered by the thermo-electric thermometer. Respirations and heart action are slower, and there is not as much perspiration and fluid loss. Hyperthermia can easily be recognized and controlled.

COMMENT

What the optimal temperature during surgery should be requires more study. From our own experience we feel that subnormal temperatures of between 95 and 97 F. are very satisfactory in selected cases. Burstein and Mark [3] state that without a temperature above normal the respiratory efforts remain effortless and of normal pattern. There is less laryngeal spasm, sweating is abolished and the pulse and blood pressure tend to remain normal. Crossman and Allen,[4] in writing on the treatment of shock by the reduction of body temperature, state that this causes a reduction of exudation and probably of toxin formation, a more liberal blood supply to the vital organs by constriction of the peripheral vessels and relief of anoxia by reduction of total metabolism. Temple Fay, in discussing the above paper, states that temperatures of 92 to 94 F. can be maintained for several days without ill effect. As body temperature is reduced to subnormal, more oxygen is had in solution in the blood, body tissue fluids and the cells themselves. Cellular metabolism is reduced, and therefore less oxygen is required. It has been found that for every degree of temperature change there is a change in metabolism of 7 per cent.

In reporting his experiments on the effects of hyperthermia and hypothermia in dogs, Prec et al.[5] reports that in the former there is increased oxygen consumption, reduced cardiac output and increased arteriovenous oxygen differential. The heart rate is increased, and the right auricular pressure falls. There is an increased demand by the tissues and vascular bed for blood. This, coupled with the reduced cardiac output, will lead to collapse unless vasoconstriction occurs. In hypothermia there is a decrease in oxygen consumption, respiratory and cardiac rates, and the blood pressure and the cardiac output fall.

Most of the above observations were true in our patients, as evidenced by less anesthesia, slower pulse

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4. Crossman, L. W., and Allen, F. M.: Shock and Refrigeration, J. A. M. A. **130**: 185-189 (Jan. 26) 1946.

5. Prec, O.; Rosenman, R.; Braun, K.; Rodbard, S., and Katz, L. N.: The Cardiovascular Effects Of Acutely Induced Hypothermia, J. Clin. Investigation **28**: 293 (March) 1949.

and respirations, less perspiration and what appeared to us to be a better recovery period.

CONCLUSIONS

1. Temperatures of infants and children during surgery vary widely and should be carefully watched.

2. Infants under 6 months of age tend to develop subnormal temperatures during surgery, which so far we have not found harmful.

3. Fever during surgery developed in over 62 per cent of the children studied in this series between the ages of 6 months and 13 years when not cooled.

4. A cold water mattress is more efficient than ice bags in preventing fever.

5. Subnormal temperatures seem to be beneficial in certain selected cases.

6. Techniques, presently being perfected, for the simultaneous recording of heart rate, blood pressure, electrocardiograms, electroencephalograms and arterial oxygen saturation should be combined with temperature studies in children to give us added information on the effects of hyperthermia and hypothermia.

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Agents and Techniques for Induction of Anesthesia in Infants and Young Children.*

Margery van N. Deming, M.D., Philadelphia, Pa.
Departments of Surgery and Anesthesia of the Children's Hospital

INDUCTION OF ANESTHESIA in infants and small children is approached with greater certainty if one is aware of the fundamental physiologic functions which are peculiar to this age group. Maintenance of normal respiratory and circulatory functions during induction is a major factor in success of the subsequent anesthetic period and in the general well being of the infant. In addition, the central nervous system is incomplete functionally at birth, and this alters somewhat the infant's response to anesthetic agents. Differences occur between adult and infant in circulatory, respiratory, and central nervous systems which are of importance in the choice of agents and technique for induction. These differences are most pronounced in the newborn, and persist to some degree throughout infancy and childhood.

The normal respiratory pattern of the newborn at rest is characterized by rapid, regular respirations interrupted by an occasional deep breath. The average tidal volume is 20.5 cc. per minute with an average rate of 28.5 per minute.[1] Rapid rates of 80 to 90 per minute may occur in the normal infant, but are maintained only for one or two minutes. Since one third of the tidal volume represents dead space air, it is obvious that such rapid, shallow respirations are inefficient. If such rates persist it may result in both peripheral and central respiratory exhaustion and inadequate gas exchange.

Oxygen consumption in young infants is almost twice that of adults or 7 cc. per kilogram body weight per minute, and therefore hypoxia may occur with relatively little change in effective tidal volume. Rapid, shallow respirations, partial respiratory obstruction and dead space in anesthetic apparatus may cause insidious onset of hypoxia in spite of adequate oxygen content in the anesthetic mixture. Tidal volume increases with added weight more rapidly than respiratory rate decreases, resulting in progressively larger minute volume. The oxygen consumption also increases, reaching a peak of 10 cc. per kilogram of body weight per minute, between 3 and 5 years of age.[2]

Small infants have extremely active laryngeal reflexes, a natural condition for those obliged to live on liquids. Only in grave illnesses, certain neurologic conditions, extreme hypoxia and profound anesthesia are these reflexes greatly depressed or abolished. All too frequently severe laryngospasm occurs during induction of anesthesia from irritating anesthetic mixtures, secretions in the upper respiratory tract, vomitus and excessive carbon dioxide in the inspired gas. In presence of laryngospasm, all voluntary efforts may fail to move any

*Presented before the Twenty-Fifth Annual Congress of Anesthetists, Joint Session of the International Anesthesia Research Society and the International College of Anesthetists, Miami Beach, Fla., October 30-November 2, 1950.

air past the cords without help of positive pressure synchronous with inspiratory efforts, or until severe hypoxia finally relaxes the spasm. Also peculiar to infants is aspiration of gas into the stomach[3] during inspiratory efforts, often resulting in distention from accumulation of large amounts of air and anesthetic agents in the stomach. Upper respiratory obstruction from any cause increases the amount of distention from this source, and may be sufficient to impair respiration and circulation. Pallor or cyanosis, grunting respirations and decided hypotension may be present when the gastric dilatation is severe. Prompt recovery follows relief of distention, accomplished by passing a small catheter into the stomach.

Greater fluctuations of circulatory function occur in the normal infant than in the adult. The resting newborn has blood pressure of 80 to 90 systolic, 50 to 60 diastolic and pulse rate of 130 to 140 per minute.[3] Any spontaneous or stimulated activity normally increases blood pressure and pulse rate. Blood pressure may reach 160 to 165/90 to 100 and pulse 160 to 170 per minute. Return to resting state is rapid when activity ceases. During induction of anesthesia blood pressure and pulse rate usually rise, and increase is greater if there is a pronounced excitement stage, respiratory obstruction or hypoxia. Severe hypotension, with or without bradycardia, may occur during induction when respirations are assisted too vigorously, anesthesia is deepened too rapidly, anesthesia is carried into too deep a plane, and often following inductions with intravenous pentothal sodium. This cardiovascular depression responds readily to adequate oxygenation and ventilation for a few minutes. Despite wide variation in normal circulatory response, infants and small children seem far less susceptible to circulatory accidents than are adults.

Respiratory difficulties are more frequent in pediatric anesthesia than are severe circulatory disturbances. Hypoxia, secondary to respiratory complications is fairly well tolerated for short periods, but clinical evidence of central nervous system damage will be present if it persists longer than three or four minutes. Cessation of circulation with ischemia in addition to hypoxia produces irreparable damage to the central nervous system in a matter of seconds.

Infants and newborns have variable tolerance of hypoxia. Long accepted opinion that this age group could withstand prolonged or severe hypoxia without sequelae is no longer tenable. Although some may survive a period of severe hypoxia with no immediately apparent evidence of cerebral damage, others with clinically less severe hypoxia show signs of permanent loss of brain substance and disturbed cerebral deprivation. To avoid the possible tragic consequences of hypoxia, the oxygen content of the anesthetic mixture and respiratory function must always be kept adequate, especially during induction when disturbances in respiration are most frequent.

The variability of the infant's response to oxygen deprivation as well as to anesthetic agents is due in part to incomplete development of the central nervous system. Anatomically, its formation is not complete until eighteen months, and functionally its capacity should increase throughout childhood. Due to minimal function of cortical and some subcortical centers, stages and planes of anesthesia as seen in older children and adults are ill defined and difficult to interpret in infants. Depression of subcortical centers apparently requires higher blood stream concentration of anesthetic agents than is necessary to depress cortical centers, especially when barbiturates or cyclopropane is used.

Arterial blood samples were taken from infants and adults under cyclopropane anesthesia and analyzed by the manometric method of Arcutt and Waters for comparison of cyclopropane concentration. The first group of 10 infants, under 18 months, had all received preanesthetic medication, had spontaneous respirations throughout anesthesia and were considered in first plane of third stage. Arterial blood gas analysis after inductions revealed an average concentration of cyclopropane of 18.1 mg. per cent (range 11.5 to 27.7 mg. per cent). A second group of 10 infants, from 18 months to 5 years, was studied under conditions similar to the first group. Average concentration of cyclopropane in arterial blood in this group was 13.6 mg. per cent (range 9.2 to 17.5 mg. per cent). Arterial blood samples taken from adults who had received preanesthetic medication and cyclopropane anesthesia until respirations were depressed had an average concentration of 11.9 mg. per cent cyclopropane (range 6.8 to 13.8 mg. per cent). Although concentration of cyclopropane in arterial blood required for anesthesia in infants is increased, it is probable that there is no comparable elevation of lethal concentration, thus decreasing the margin of safety. No studies have been done on infants under barbiturate or ether anesthesia, but the clinical impressions is that they require relatively more of these agents than do adults.

Older infants and young children have inadequate emotional development to adjust easily to loss of security caused by separation from home and family. Emotional instability is frequent. The young child is little concerned with the nature of the operation but he is deeply concerned about the prospect of being rendered unconscious. From 1 to 4 years, children are particularly susceptible to psychiatric complications from an unpleasant encounter with anesthesia.[4] Although in large measure this problem is best handled by judicious preanesthetic sedation, even adequate sedation may be nullified by unskilled and stormy induction. Normal emotional growth may be seriously disturbed by fears, obsessions, or regressive or social behavior subsequent to traumatic induction.

Armed with knowledge of the more outstanding physiologic peculiarities of infants and young children, better selection of agents and techniques can be made. Induction should be brief, not too unpleasant, and accompanied by minimal disturbances of respiratory, circulatory and central nervous systems. For convenience, agents and techniques for induction will be discussed first, for newborn and young infant from birth to 2 months; second, for the infant of 2 months to 2 years; and third, for the young child of 2 to 6 years.

Among the newborn, general anesthesia is probably most often induced by open drop method with ether or vinethene-ether sequence. This technique requires considerable patience for breath holding, laryngospasm and rapid, shallow respirations frequently prolong induction. Every mask increases dead space many times, so that there is always danger of carbon dioxide accumulation and diminished oxygen tension unless oxygen is delivered under the mask. In spite of adequate preanesthetic medication and oxygen supply, respirations may be rapid and gas exchange insufficient. Excessive secretions may partially occlude the airway, and may not, because of character of the respirations, cause noisy breathing. This method, with its all inherent difficulties, is relatively safe and is satisfactory for some procedures.

Recently, suitable equipment has become available for administration of anesthesia to infants by semiclosed techniques. This permits less irritating gaseous agents to be used for induction and better control of oxygen content in the anesthetic mixture. A small mask and reservoir bag of 500 or 1000 cc. capacity with flow rates of 1 to 1.5 liters per minute can be used safely with or without a 90 Gm. soda lime, to-and-fro canister for induction. The excess gas is permitted to escape around the mask, helping to diminish the effect of the mask dead space. The reservoir bag is filled with nitrous oxide or helium and oxygen 75:25, and as soon as the mask is adjusted on the infant, the helium or nitrous oxide is discontinued and cyclopropane begun. During the early part of induction cyclopropane concentration of about 35 per cent of total gas flow is often required. Subsequent concentrations vary with response of the patient. Ether may be added if desired. With semiclosed technique there is little disturbance in character and rate of respiration. At first sign of inadequate gas exchange, manual assistance to respiration can be given.

Since density of these anesthetic mixtures is considerably greater than air, more muscular effort is required by the infant to move the gas through small upper respiratory passages. Some of this wasted energy can be preserved to the infant by using helium to reduce density of the mixture, thereby diminishing respiratory effort necessary to produce satisfactory gas exchange. This is important primarily in the severely ill, feeble or premature infant whose energy must be carefully hoarded if survival is to be expected.

Many surgical procedures in the newborn period, requiring general anesthesia, are for correction of serious congenital anomalies, which untreated are incompatible with life of any great length. For these infants tracheal intubation is often essential for safe maintenance of anesthesia. It may be done by either direct or indirect method when anesthesia is at least in lower second plane of third stage. Intubation attempted in lighter anesthesia is often technically more difficult and may be followed by severe bronchospasm. When bronchospasm follows too early intubation, it is extremely resistant to therapy, and an alarming degree of cyanosis may persist for several minutes. Oxygen administered by rhythmic positive pressure is probably the most effective therapeutic measure for this unfortunate complication.

Induction of anesthesia with cyclopropane has narrower margin of safety than induction with open drop ether. Nevertheless, in skilled hands, this hazard is more than outweighed by benefit to the patient of slower respiratory rate, ready control of, or assistance to, respiration, and more accurate regulation of oxygen supply.

Infants from 2 months to 2 years are more easily managed during induction. Laryngeal irritability decreases throughout this period. Increasing tidal volume lessens the relative importance of dead space of anesthetic apparatus. Open anesthesia is probably most commonly used for this age group. With a small mask, no excessive padding and a truly open technique, it is safe and satisfactory. Induction may be started with vinethene or ethyl chloride to shorten the excitement stage and facilitate the introduction of ether. Of the two agents, vinethene is slightly more irritating, increases the amount of secretions in the upper respiratory tract and may be accompanied by muscular twitching in light anesthesia. Ethyl chloride is a potent agent and causes little increase of upper respiratory secretions. It has the potential hazards of liver damage associated with all halogenated anesthetic agents. Neither this complication nor circulatory collapse described as occurring with ethyl chloride has been observed in more than 2500 inductions.

Respiratory disturbances are the most common complication during open drop inductions. Partial respiratory obstruction, breath holding, larynogospasm or apnea may occur at any time and may result in greater or less degree of hypoxia. To increase the safety of the method, no open drop anesthesia should be started unless some means of administering positive pressure oxygen is at hand and ready for use.

Much of the struggling and crying which accompany open drop anesthesia can be avoided by using semiclosed technique with nitrous oxide or cyclopropane and oxygen. This method is particularly suited to management of the restless, anxious or poorly sedated infant. Early, a high flow of 2 to 4 liters per minute of nitrous oxide-oxygen 75:25, is used so that the mask need not be lightly applied to the face. As analgesia develops the mask is adjusted to diminish leaks, nitrous oxide is discontinued and cyclopropane or ether is added to deepen anesthesia. Method of maintenance can be suited to the patient and the contemplated operation. Semiclosed induction has the advantage of slower respiratory rate, less tachycardia, less secretions in the upper respiratory tract and ready control of ventilation and oxygenation.

For the toxic infant with high fever, who must be anesthetized, pentothal sodium is usually selected as agent for induction. This short-acting barbiturate is of value, first, because it tends to prevent generalized convulsions which are more prone to occur in the toxic infant, and second, because it tends to reduce or prevent further rise in body temperature. The intravenous dose is 12.5 to 100 mg. of a 2.5 per cent solution of pentothal. If no intravenous solution is running, and the veins are difficult to find, pentothal may be given by rectum 10 mg. per pound of body weight in 30 to 50 cc. of water. No special preparation of the bowel is necessary, and the effect is adequate in fifteen to twenty minutes. When pentothal has been used during induction, semi-closed nitrous oxide-oxygen-cyclopropane sequence is used to avoid laryngospasm, which frequently occurs when volatile agents are employed.

Induction of anesthesia in the young child from 2 to 6 years can be done by almost any method used for adult anesthesia. Children of this age are easily frightened and memory of unpleasant experiences is vivid. For this reason open drop inductions are usually avoided. Open drop can be carried out satisfactorily for both anesthesiologist and surgeon, but seldom is it so skillfully given that the child does not object or remember the experience with dread. Induction with nitrous oxide-oxygen or cyclopropane-oxygen by the semi-closed or closed method causes little disturbance to the patient, and often the child will cooperate by holding the mask. A child who receives this type of induction rarely fusses if a second anesthesia is necessary.

Pentothal sodium is used intravenously in doses of 100 to 250 mg., especially if an intravenous drip is already running when the child comes to the operating room. (Care must be taken to avoid laryngospasm following pentothal if open drop anesthesia is selected for maintenance of anesthesia.) Induction of general anesthesia with pentothal is almost always preferable for the young child whose body temperature is elevated or who has a history of convulsive seizures.

Basal narcosis is reserved for those children in whom there is special indication for this type of sedation. For the apprehensive fearful child with previous unpleasant encounter with anesthesia and for the child whose overanxious parents have communicated their anxiety to him, basal narcosis is ideal. Forty-five minutes after pre-anesthetic sedation and fifteen minutes before moving to the operating room, pentothal in the dose of 10 mg. per pound of body weight is given rectally. This generally produces light sleep or at least complete amnesia for transfer of the patient and subsequent anesthetic procedures. Tidal volume is slightly depressed in about 10 per cent of these children, but no major respiratory complications have occurred to date with this technique.

In general, it may be stated that the less traumatic the induction of anesthesia is for the child, the greater is the anesthesiologist's contribution to the general well being of the pediatric surgical patient and the better will be his rapport with the child's parents, his surgeon, and his pediatrician.

Summary

1. Some of the more important differences between infants and adults in physiology of the respiratory, circulatory and central nervous systems, have been described.

2. Importance of avoiding hypoxia in the young child is stressed.

3. Advantages of a semiclosed induction, with cyclopropane-oxygen-nitrous oxide, are discussed.

4. Utility of pentothal sodium, intravenously or rectally, is stated.

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RELATIONSHIP OF ANESTHESIA TO POSTOPERATIVE PERSONALITY CHANGES IN CHILDREN

JAMES E. ECKENHOFF, M.D.
PHILADELPHIA

SOME POSSIBLE deleterious effects of hospitalization and surgical operations on the personalities of children have been described.[1] However, apparently there has been no attempt to relate the experiences of the induction period of anesthesia to the development of undesirable personality changes afterward. It is difficult to establish precise relationships, because the experiences of hospitalization, anesthetization, and operation are not easily separated. A recent study of the effect preanesthetic medication has upon the course of anesthesia [2] has led to an investigation of possible relationship between anesthesia and personality changes.

Over an 18-month period, questionnaires were mailed to the parents of all children admitted to the Hospital of the University of Pennsylvania for an otolaryngological operation. Answers were sought to the following questions: 1. Is your child a bed-wetter; since operation does he wet the bed or wet it more frequently? 2. Does your child have night cries or terrors; since operation does he have night terrors or have them more frequently? 3. Is your child subject to temper tantrums; since operation do they occur or occur more frequently? 4. Has your child become afraid of meeting strangers since operation? 5. Has your child been afraid to have his face covered since operation? 6. Has your child become afraid of new odors since operation? 7. How did you prepare your child for hospitalization and operation?

Two months after the operation, letters containing the above questions were mailed to 1,008 parents. Replies were received from 612, or 61% of the total. Parents of children 12 years or older apparently were less interested in the study, since only 39% of this group replied. If this group is deleted from the study, the replies to the questionnaire would constitute 65%. Pertinent factors in groups answering or not replying appear to be homogenous in all respects, i. e., ward or private status, age, anesthetic agent employed, number of unsatisfactory inductions of anesthesia, and training status of the anesthetist. The results of the survey may be considered as truly representative for the entire group. The effects of preanesthetic medication upon the child scheduled for operation will not be considered here, since they have already been discussed.[2] In this study, preanesthetic medication

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From the Department of Anesthesiology, Hospital of the University of Pennsylvania, and The Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.

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consisted of pentobarbital and scopolamine and usually morphine in dosage ranges recommended by Leigh and Belton.[3] Anesthesia was administered by resident or staff anesthetists, medical students, or interns under supervision. The anesthetist assigned had been asked to make detailed remarks concerning the condition of the child prior to induction and the course during induction and maintenance of anesthesia. Completed questionnaires were correlated with the anesthetic records of the children concerned.

RESULTS

Seventeen per cent of the replies indicated a personality alteration which might be traced to anesthesia and/or the hospital experience. Thirty-two per cent of the changes reported were in the form of night cries or terrors, appearing either for the first time or becoming worse after hospitalization. Temper tantrums comprised 26% of the changes; fear phenomena (afraid of darkness, unaccustomed odors, strangers, or of having face covered) constituted 23%; and the remainder (19%) pertained to bed-wetting.

Incidence of Postoperative Personality Changes in Children

	Age, Yr.									
% Changes	2	3	4	5	6	7	8	9	10	11+
50.............	..	..	..	..	..	..	..	..	..	..
	..	..	..	..	..	..	..	..	..	..
	..	..	..	..	..	..	..	..	..	..
40.............	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
30.............	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
	X	X	X	..	..	X	..	..	..	..
20.............	X	X	X	..	..	X	..	..	..	..
	X	X	X	..	X	X	..	..	..	..
	X	X	X	X	X	X	X	..	X	..
10.............	X	X	X	X	X	X	X	..	X	..
	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X
0.............	..	..	..	..	..	..	..	..	..	..

The incidence of personality change was highest in the youngest children and was as clear-cut as in the report of Levy.[1b] The data are presented in the accompanying Table.

It can be seen that there was a relationship among age, reaction to the induction of anesthesia, and personality changes. With unsatisfactory inductions (crying, struggling, vomiting, and early obstruction), the probability of undesirable personality change was greater in young children than if induction were smooth. In relation to those inductions classified as being unsatisfactory, 57% of 3-year-olds had personality changes; 38% of 4-year-olds; 32% of 6-year-olds, and 14% of 8-year-olds. In children over the age of 8 years with unsatisfactory inductions, personality alterations averaged 8%, differing little from those of like age with satisfactory inductions. Reactions were surprisingly constant in the 3- to 8-year-olds with a smooth induction of anesthesia, the average incidence being 16% and the range 13 to 19%.

3. Leigh, M. D., and Belton, M. K.: Premedication in Infants and Children, Anesthesiology **7**:611-615, 1946.

The percentage of personality changes was approximately the same with all induction agents (cyclopropane, ethylchloride, and vinyl ether [Vinethene]), varying between 13 and 17%. A surprising finding, however, was that of 25 complaints related to bed-wetting, 23 were in patients given vinyl ether and only 2 with other agents.[4] On a percentage basis, bed-wetting was five times more common after administration of vinyl ether for induction of anesthesia. This finding is all the more interesting since there was no remarkable difference in other changes compared to the anesthetic agent administered.

In nine children, an incidental finding was that of convulsions or convulsive movements occurring during induction of anesthesia. Convulsions were seen in eight patients receiving vinyl ether or in whom a change to ethyl ether from vinyl ether had just been made. The ninth child was one subject to epileptic convulsions and in whom operation had twice been cancelled in other hospitals because of seizures occurring during the induction phase of anesthesia. On the third occasion (included in this series) anesthesia was induced with cyclopropane; a convulsion occurred two minutes after induction and lasted 45 seconds. The operation was completed without further incident. Vinyl ether was administered to 608 patients, and ethyl chloride, cyclopropane-nitrous oxide, or thiopental to the remaining 400.

The following are examples of statements found on returned questionnaires. The first three relate to preanesthetic medication.

CASE 1. (H. D., age 4 years, tonsillectomy).—"My only cause for complaint was that his sedative was not given to him soon enough before he was taken to the operating room, and the child was terrified."

CASE 2. (H. S., age 5 years, tonsillectomy).—"Due to the excellent way in which the operation was handled, my child has nothing but a pleasant recollection of his operation. I feel that was entirely due to the drug that was given him before he went to the operating room. My other child was given nothing before the ether, and was taken on an adult stretcher, and as a result is scared to death of hospitals. I firmly believe that if all children were given some drug to quiet them and make them good and drowsy, they would accept the anesthetic more readily."

CASE 3. (L. C., age 4 years, dilatation for posterior choanal atresia).—"I have noticed changes in her play. Everything is an operating room table, and she is always operating and giving needles to her dolls, her brothers, sisters and playmates. She is always pretending that she is giving ether, and I have to hide my needles or she is taking them and sticking everyone. My daughter knew what an operation meant, as she had had three operations on her elbow in the past 2 years, and two on her nose in 2 months. When it came time for her operation on her nose, we explained what was to be done and that afterward she might have a tube up her nose, but that the operation was to make her breathe normally again. I told her I would be there when she went to the operating room. She was very good and very interested in each phase of being prepared at the hospital.

"The first operation was in September and everything went smoothly. She was asleep when they took her to surgery. In the second operation which occurred in November, she was not medicated until about 5 minutes before they took her to surgery, and she left screaming in terror which I know was bad for her emotionally. It left a definite mark on her afterwards. She was afraid and did not want anyone to touch her afterward, and I even had trouble for awhile changing her tube at home. She would go into screaming tantrums. The first time she did just beautifully, and I had no trouble with her at home.

"My daughter may need another operation on her nose soon again, and before I allow it, I am going to make it understood with my doctor that she is to be medicated in time beforehand. . . ."

4. Agents employed for induction of anesthesia in the 612 patients were as follows: vinyl ether-ethyl ether, 363; nitrous oxide and/or cyclopropane-ethyl ether, 138; ethyl chloride-ethyl ether, 101; thiopental-nitrous oxide or thiopental-ethyl ether, 10.

A fourth case concerns the importance of relationships between anesthetist and patient.

CASE 4. (G. H., age 6 years, tonsillectomy).—"He was quite brave about the whole thing and the only thing he ever mentions about his trip to the hospital is the praise he received from the doctor when he blew up the balloon. I imagine this occurred when he was getting the ether, but he keeps telling us how the doctor told him that he was one of the best youngsters he ever saw at blowing up the balloon."

The final two cases are indicative of lack of proper preparation for the experience of hospitalization and operation.

CASE 5. (B. O., age 4 years, tonsillectomy).—"I told her she was going to the hospital to see the newborn babies. After she was in the hospital she was told the truth."

The postoperative personality changes consisted of increased frequency of night terrors and temper tantrums and fear of strangers.

CASE 6. (G. F., age 3 years, tonsillectomy).—"When I took her to get her tonsils out, I told her she was going to play with all the little girls and see the babies. She thought that was wonderful. Since the operation she just cries all the time and is a very restless sleeper and cries in her sleep. I want to bring her back for a check-up on her nerves, but just can't do it because she screams and carries on high and says, 'Don't leave me there Mommie.' She thinks right away they are going to keep her. . . ."

COMMENT

One cannot blame all personality defects or abnormalities on unfortunate experiences with hospitals. However, this and other studies suggest that such experiences may be important. The better the child's home preparation for his experience of hospitalization and operation, the lower should be the incidence of postoperative personality changes. Many doctors do not advise parents as to how best to prepare children. Adults view these matters through their own eyes, forgetting the child's outlook and making little effort at preparations. Some parents apparently believe that the best way to handle the situation is to tell falsehoods. On a few occasions in the operating room, we have been confronted by children demanding the ice cream promised to be awaiting them.

Our experience indicates that it is important for physicians to advise parents about psychological preparation of the child. Helpful suggestions may be written with other preoperative instructions so that parents can refer to something rather than rely on memory. In the returned questionnaires, there were some descriptions of excellent preoperative preparation, but too few to allow correlation between preparation and personality changes. It would indicate, however, that with the proper stimulus from the physician, the number of adequate preparations could be increased.

A previous report has demonstrated a clear-cut relationship between the type of preanesthetic medication and the incidence of crying prior to induction of anesthesia. It was shown that 35 to 40% of children 5 years of age or less who received only atropine or scopolamine cried. Induction of anesthesia was always classified as unsatisfactory under those circumstances. It was further shown that the use of a barbiturate with the belladonna drug, plus careful attention to the time of administration of the drugs, significantly reduced the incidence of crying. In this respect it was reasoned that the crying child might be the one in whom personality changes were most likely to develop. The data presented herein indicate such reasoning was correct. Careful attention to preanesthetic medication could materially reduce undesirable sequelae. It is of interest, nevertheless, that in 16% of young children with satisfactory induction of anesthesia personality changes developed. Presumably, the numbers in this group could be reduced by more attention to home preparation, efforts at improved relationships between hospital personnel, parents, doctors, and patient, and possibly more careful attention to preanesthetic medication. Obviously, skill of administration of anesthetics remains of prime importance. Some children had satisfactory inductions of anesthesia, but their medication had been given too late or too early. It is possible that suppressed fears could have resulted in subsequent personality conflicts, even though the children appeared cooperative, and induction was smooth.

The clinical impression has been expressed that vinyl ether anesthesia is associated with a higher incidence of bed-wetting and appearance of undesirable personality changes. We could establish no unusual relationships for the latter, but the association with bed-wetting was obvious and striking. The explanation for this response is not apparent.

The incidental observation that eight anesthetic convulsions occurred in 621 anesthesias where vinyl ether was used for induction closely parallels the data of the previous report,[2] wherein there were nine convulsions in 674 anesthesias during which vinyl ether was employed. The phenomena of muscular activity with vinyl ether has been reported in animals, but the explanation is not clear. These convulsions all responded to ventilation of the lungs with oxygen, though cyanosis before the convulsions was not always detectable. However, the latter does not rule out anoxia as having been present. If one were to assume that oxygen lack were the prime factor, the incidence of convulsions should have been the same with all agents. Because of the response to oxygen it may be advisable always to give oxygen simultaneously with vinyl ether. This matter is now being investigated.

From the foregoing two paragraphs, one cannot help but speculate on the significance of vinyl ether being associated with a high incidence of enuresis and with convulsions occurring more commonly than with any other anesthetic agent studied. This warrants further consideration.

The results of this investigation have stimulated interest for a thorough study of the problem. Obviously, a questionnaire survey is inferior to interviewing parents and direct observation of children before and after anesthesia. This report is therefore submitted as a compilation of preliminary observations. An attempt will be made to begin a long-term study utilizing the services of social workers and psychiatrists, as well as anesthetists. Likewise, the investigation will be broadened to include children for all types of surgery and not those for otolaryngological operations only.

SUMMARY

The results are presented of an investigation correlating the preparation and induction of anesthesia with personality changes in 612 children who underwent otolaryngological operations. It has been observed that 17% of the children had personality changes that might be attributed in part to inadequate preanesthetic or anesthetic management; that the younger the child, the more likely the development of personality changes; that unsatisfactory preanesthetic medication and induction of anesthesia is associated with a high incidence of personality changes in young children, and that bed wetting occurs five times more commonly after the use of vinyl ether (Vinethene) than after other techniques.

Miss Angela Verratti, R.N., assisted in obtaining the material for this report.

28th CONGRESS OF ANESTHETISTS, QUEBEC, P. Q., CANADA
OCTOBER 26-29, 1953

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The Prevention of Tracheitis in Children Following Endotracheal Anesthesia.*

Robert M. Smith, M.D., Boston, Mass.
Anesthesiologist, The Children's Medical Center

AMONG INFANTS and children there has been a comparatively high incidence of laryngeal irritation and tracheal edema following endotracheal anesthesia. Many cases have been reported that have required tracheotomy,[1,2,3,4] and several have ended fatally.[5,6,7] It is evident that the child's larynx will not tolerate rough or unclean technique. The tissues of the child's glottis are loose and have a decided tendency toward the development of edema. The increased susceptibility to infection is evident in the high incidence of severe laryngotracheitis that occurs among children as a primary disease, and that can kill a normal child in the course of a few hours.

As a result of the higher incidence of tracheitis among children two untenable views have developed: the first, that we should refrain from the use of endotracheal anesthesia; the second, that tracheitis is an unavoidable occurrence in pediatric anesthesia, which should not deter us from its general use. A far more reasonable view would be that we retain the use of this invaluable technique, but that we refine our methods by the use of special precautions, and eliminate those errors that might lead to the development of tracheal irritation. As Gillies[8] warned us two years ago, endotrachael anesthesia is too valuable a method to be jeopardized by abuse.

There are a number of technical errors which the anesthetist may commit that may lead to the development of tracheitis. Mechanical injury by the use of excessive force has frequently been blamed. There is justification for such indictment, for there are several mistakes that lead to the use of force. This is but one factor. Another is chemical irritation which occasionally causes inflammation of the tracheal mucosa with serious results.

Perhaps the greatest neglect in the technique of intubation has been in the matter of cleanliness. Soiled endotrachael tubes may carry a wide variety of organisms into the trachea and rub them against the delicate mucosal tissues for periods of several hours. Ether anesthesia, drying of the membranes, and other operative factors further decrease the patient's resistance to infection, and facilitate the entrance of organisms. Contamination certainly must be considered a real hazard in endotracheal intubation.

Occasionally the infant's larynx will be able to withstand trauma that is done with a clean instrument. A clean cut heals quickly. Or the infant's trachea may even be able to resist definite contamination

*Presented before the Twenty-Seventh Congress of Anesthetists, Annual Meeting of the Members of the International Anesthesia Research Society and the International College of Anesthetists, Virginia Beach, Va., September 22-25, 1952.

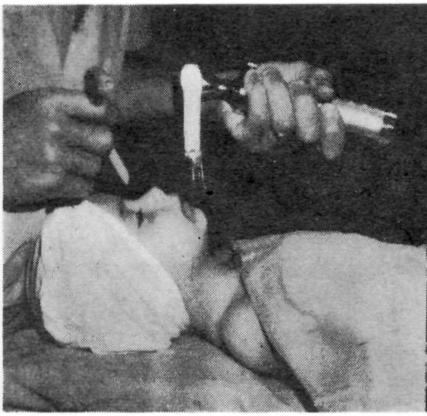

Fig. 1. Incorrect use of large heavy laryngoscope.

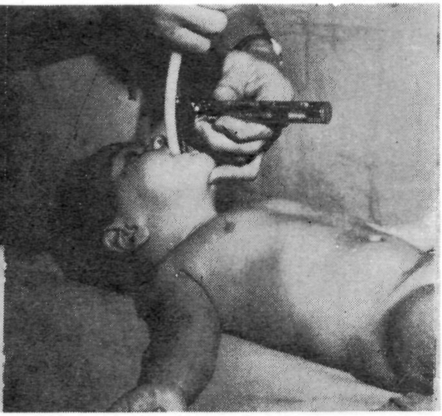

Fig. 2. Incorrect use of excessively large endotracheal tube.

alone, providing that there is no associated laceration or injury that will serve as a portal of entry. Undoubtedly the greatest danger lies in the combination of trauma and contamination. The anesthetist who lacerates the glottis, and then rubs a dirty tube across the wound has committed a serious offense.

Although endotracheal intubation is practiced many times daily by most anesthetists, and the steps are indeed elementary, certain errors are committed with discouraging frequency. For this reason one feels justified in reviewing briefly the mistakes which must be avoided if we are to reduce the incidence of tracheitis.

I. Mechanical Trauma

1. The use of large, heavy laryngoscopes. Too often the anesthetist uses laryngoscopes that are poorly suited to children. Heavy

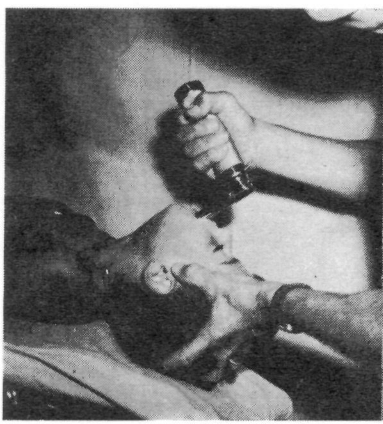

Fig. 3. Incorrect use of force with laryngoscope.

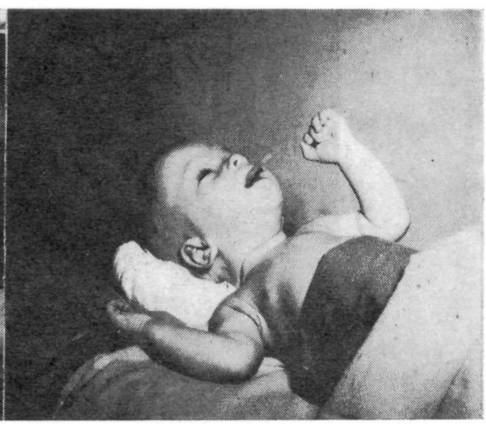

Fig. 4. Spasm due to intubation before patient is relaxed.

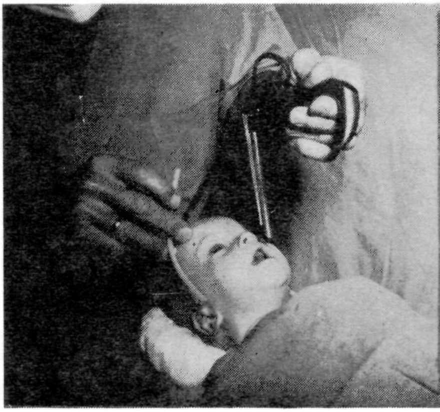

Fig. 5. Correct use of anterior commissure laryngoscope.

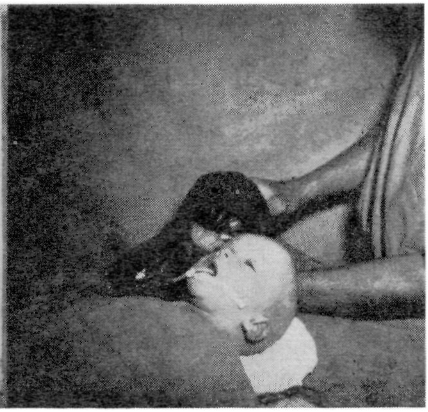

Fig. 6. Insecurely fixed endotracheal tube which irritates cords.

scopes with large handles are clumsy and difficult to use with deftness (fig. 1). Trauma may best be avoided here by the use of light, easily handled laryngoscopes that may be held in the fingertips, not grabbed in the fist. Instruments with blades that are either short or wide invite ploughing and prying to force a way down the pharynx. The structure of the child's pharynx calls for a blade that is long and narrow such as that of the Flagg model, in preference to the heavy, blunt Guedel type. The practice of trying to use adult sized laryngoscopes for children is certainly to be condemned.

2. The use of large endotracheal tubes. Endotracheal tubes of excessive caliber require forceful passage which may stretch or tear the vocal cords (fig. 2). During the course of the operation continued pressure due to large tubes, or overdistended cuffs may lead to irrita-

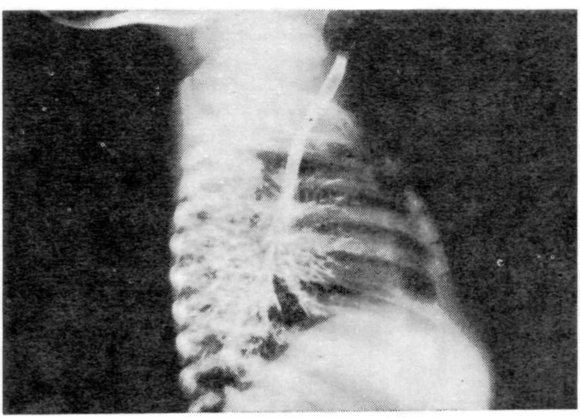

Fig. 7. Tracheogram showing normal 30 degrees forward slant of trachea.

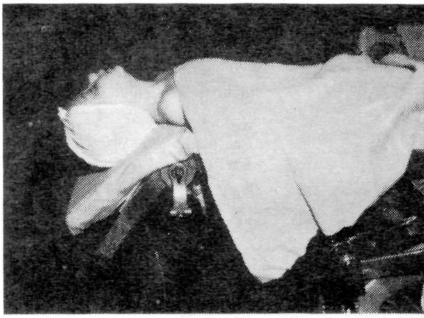

Fig. 8. Incorrect position for intubation. Hyperextension of neck causes angulation of airway at larynx. (See fig. 10).

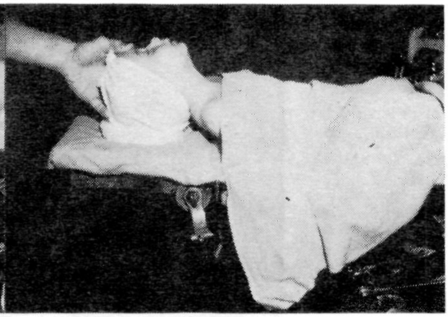

Fig. 9. Correct position for intubation. Head raised, neck flexed at 45 degrees, bringing upper airway in alignment with forward slant of trachea. (See fig. 11).

tion, edema, or even sloughing of tissues. Flagg [1] and Beecher[9] [10] have repeatedly warned us of this danger. Etsten[11] and Green[12] have found membranes of sloughed material blocking the trachea following endotracheal anesthesia. These membranes may be attributed to continued irritation or pressure of the tube against the trachea. Care should be taken to use tubes that may be passed easily and which will not invite irritation regardless of the duration of the operation.

3. Unnecessary roughness. Even when equipped with proper instruments, the anesthetist may use inexcusable force and roughness (fig. 3). Hurry, impatience, or ignorance of pediatric anatomy may result in feverish prodding at structures that could be gently lifted aside. Hurried motions are dangerous, and must be avoided at the time of intubation. Intubation by nasal route, and blind intubation may be especially traumatic in the hands of the average anesthetist, and are to be reserved for specially indicated cases.

4. Intubation while the patient is inadequately relaxed (fig. 4). Intubation during a light plane of anesthesia may cause spasm of the

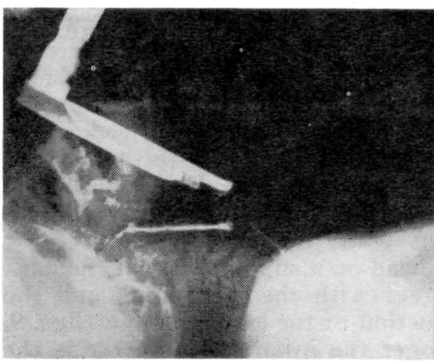

Fig. 10. Passage of laryngoscope with neck extended, showing angulation at larynx.

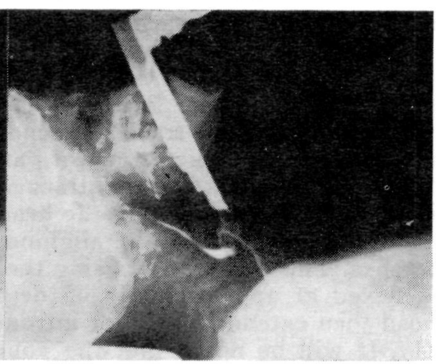

Fig. 11. Passage of laryngoscope with head raised, neck flexed, showing continuous curve of upper and lower airway.

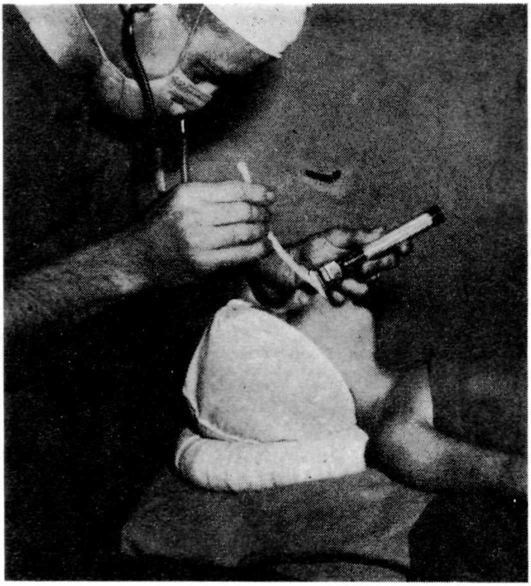

Fig. 12. Correct technique for endotracheal intubation: a light laryngoscope gently held, a small tube, the patient relaxed, and head elevated. Stethoscope will be used to check position of tube.

glottis. If this occurs prior to the passage of the endotracheal tube, excessive force will be required to insert the tube, while if the glottis closes down on the tube after passage, coughing and bucking may ensue. Such spasmodic movements cause traumatic grinding of the tube against vocal cords and tracheal muscosa. Similar damage may occur at the end of operations if patients are allowed to awaken while endotracheal tubes are still in place. Spasm and coughing may be dangerous at this time.

5. Faulty positioning of the head. Hyperextension of the head and neck angulates the trachea at the larynx, and renders intubation considerably more difficult (figs. 8, 10). Efforts to overcome this malposition easily lead to the use of excessive manipulation of the blade of the laryngoscope. Better understanding of anatomic relationship will aid here. As the trachea ascends through the chest and neck of the erect patient, it makes a forward angle of 30 degrees with the vertical (fig. 7). Consequently, endotracheal intubation may be accomplished most easily by positioning the head so that the upper airway (mouth and pharynx) will be in alignment with the forward slant of the trachea. This is done by raising the head on a support so that the neck is flexed at approximately 45 degrees with the horizontal, and the head then extended fully for introduction of the laryngoscope (figs. 9, 11). It will be noted that the younger the infant, the shorter is the neck in relation to the body and head. It is increasingly important to

elevate the heads of smaller patients for intubation. With such positioning it is gratifying how easy intubation becomes.

6. Difficult intubation due to anatomic abnormalities. Special problems arise when patients with decidedly malformed heads, mouths, or cervical structures require intubation. Hydrocephalic patients are frequently encountered in pediatric anesthesia. Here special pains must be taken in positioning and instrumentation. In some instances intubation which has been virtually impossible with standard laryngoscopes has been accomplished with the anterior commissure scope of the bronchoscopist (fig. 5). This instrument has a slender, tubular blade with a pointed tip, and if carefully used may be of real assistance to the anesthetist.

7. Continued motion of the tube during anesthesia. If there is motion of the endotracheal tube, considerable irritation of the cords or tracheal mucosa may result. Such motion may be the fault of an unstable type of apparatus which drags on the tube. This will happen with a heavy to-and-fro soda lima canister if it is insecurely fixed (fig. 6). The other principal cause of continued motion is a gasping or tugging type of respiration which, with each respiration, saws the tube back and forth across the vocal cords. Quiet respiration is essential for this reason. Saklad[13] has called attention to the damage that may be done by the hard tip of a curved tube during anesthesia, and pointed out that this could be avoided by use of doubly curved tubes, or tubes,

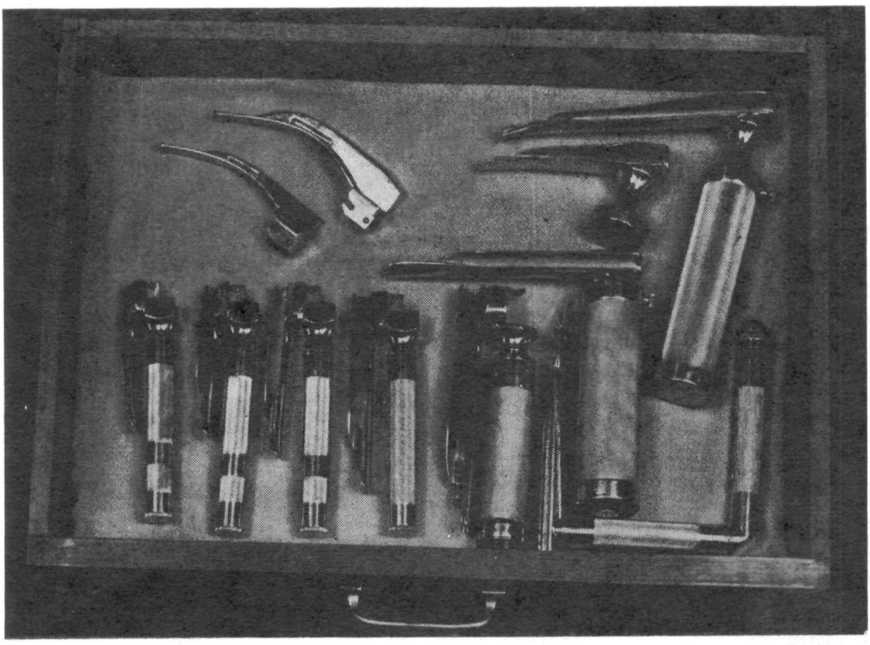

Fig. 13. Laryngoscopes for pediatric use are cleaned and maintained in drawer of special cabinet.

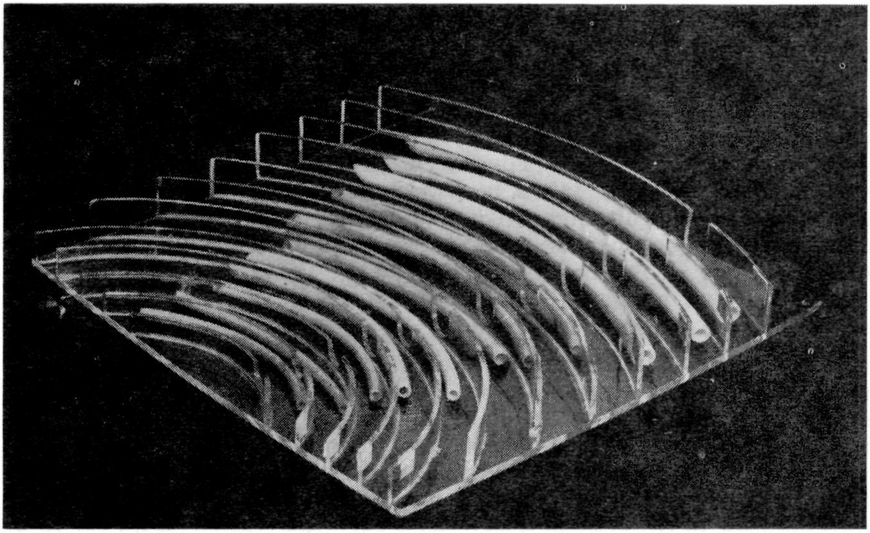

Fig. 14. Lucite® tray for endotracheal tubes of different sizes.

such as the Portex plastic type, that become pliable at body temperature.

8. Drying of the mucosa by continuous flow of oxygen. This may occur in nonrebreathing or insufflation types of anesthesia, where continuous high rate flows of oxygen are directed against tracheal walls. It would be preferable to humidify such flows by passage through water. This may be done by placing water in the ether vaporiser and bubbling oxygen through the water.

II. Chemical Trauma

Of less frequent occurrence is the injury that comes from chemical irritation. Inadequate rinsing may leave an excess of sterilizing solution on endotracheal tubes. Lubricating ointments,[14] and especially those with anesthetic properties, [5] have been found to cause sensitivity reactions in the form of edema and tracheitis. Two such reactions occurred in my experience. During the last five years no lubricant has been used in the great majority of our cases. Endotracheal tubes are merely dipped in water immediately before passage.

III. Contamination

Occasionally tracheitis will develop after intubation which has been completely atraumatic. In these cases it seems reasonable to suspect that the irritation is due to introduction of foreign organisms. Such contamination may occur as a result of any of the following errors in technique.

1. Inadequate cleansing of endotracheal tubes, laryngoscopes, and suction catheters. Organisms may be transmitted from patient to

patient if equipment is not thoroughly washed. Tubes should be autoclaved or soaked in sterilizing solution.

2. Improper storage after cleansing. Endotracheal tubes will become soiled if they are left where they are exposed to air currents, handling, or contact with unclean objects. If loosely carried in pockets or anesthesia kits they may acquire a wide variety of organisms.

3. Contamination of tubes immediately before use. Careless handling of tubes at time of use nullifies previous cleansing. Anesthetists have been known to give rectal anesthetics, then without washing their hands, induce and intubate their patients.

5. Use of contaminated lubricants. Organisms have been cultured from standard lubricants. It is important to use lubricants that are bacteriostatic (xylocaine®), or that are packaged antiseptically.

6. Intubation in the presence of upper respiratory infection or pharyngitis. If this is done, one faces the risk of adding irritation to inflammation already present. Pharyngitis may well be taken as a contraindication to endotracheal anesthesia.

For the past six years at the Children's Medical Center special care has been used in the cleaning, storing, and handling of endo-

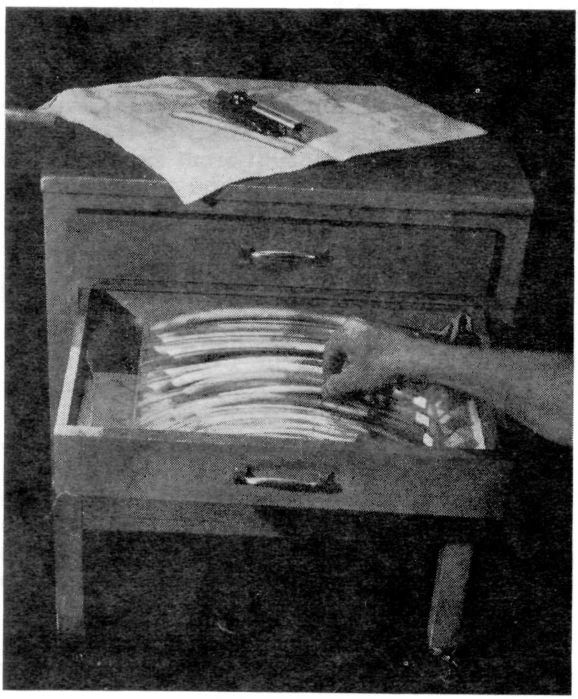

Fig. 15. Prior to use, laryngoscope and endotracheal tube are selected and placed in a clean towel to avoid gross contamination.

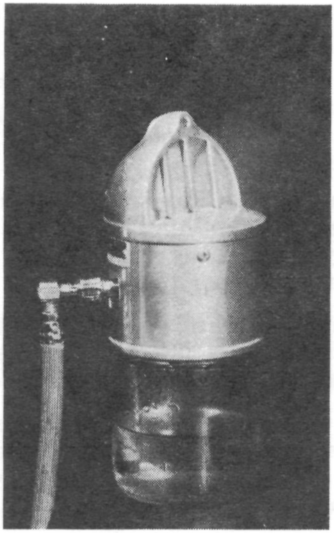

Fig. 16. Mistogen humidifier.

tracheal equipment. This program consists in initial washing with soap and water, soaking in alcohol or zephiran,® (1:1000 aqueous solution), rinsing thoroughly in water, then storing endotracheal tubes and laryngoscopes in a cabinet where they are not touched until time for use. Laryngoscopes are kept in top drawer (fig. 13), while endotracheal tubes are stored in second drawer in a lucite® tray (fig. 14) which is partitioned off to separate tubes of different sizes. Prior to use, endotracheal tubes are picked up by their "outer" ends and placed with the laryngoscope on a clean towel, in which they are carried until actual intubation is performed (fig. 15). The lower, or tracheal end of the tubes is not handled. No pretense is made to maintain true surgical sterility; however, cultures have shown that endotracheal tubes may remain sterile for seventy-two hours under this technique.

Prevention of tracheitis may be carried into the postoperative period. Patients should be watched for early signs of tracheal irritation, and upon the appearance of harsh cough, stridor, or retraction they should be given antibiotic therapy and placed in an oxygen tent with high humidity. For humidification we have developed a portable vaporizer called the Mistogen®*[15] (figs. 16, 17), which is run by oxygen and vaporizes a cool, fine, nonwetting mist with particle size of 1 to 3 micra. This may be placed in any small oxygen tent or incubator. With this treatment tracheal irritation may be quickly relieved, and progression of the complication may be arrested.

It is felt that this program has been worth while. Over 3,000 children have received endotracheal anesthesia at this hospital during the

*May be purchased from Production Foundry Corp., 2700 Magnolia Avenue, Oakland, California.

TABLE 1
Follow-up of 560 Children After Endotracheal Intubation

April 1 - September 1, 1952

Age	Under 1 Mo.	1 Mo. - 1 Yr.	1 - 10 Yr.	10 - 21 Yr.	Total
No. of cases	16	97	329	118	560
Hoarseness	0	3	33	7	43
Cough	0	2	24	6	32
Sore throat	—	—	9	5	14
Retraction	0	3	3	0	6
Treated with humidity	0	5	7	2	14
Tracheotomized					0

past six years and none has required tracheotomy or has had any permanent or fatal complication of intubation. Papper[14] has recently attested the use of similar precautions.

A special follow-up study was made of all patients who had endotracheal anesthesia during the five months period from April 1 to September 1, 1952 (table 1). In this period 560 children were intubated. They were checked at four hours and twenty-four hours after operation in order to assess both early and delayed symptoms of irritation (table 1).

Hoarseness was noted most frequently, occurring in 43 cases, or in approximately 1 out of 12 patients. Fortunately this was of transitory nature and unaccompanied by signs of obstruction or inflammation and was regarded as having little significance. It might be interpreted as being due to lag in the recovery of cord motion, after the cords had been immobilized over a prolonged period of time. Sore throat occurred in 14 patients. In some instances this was undoubt-

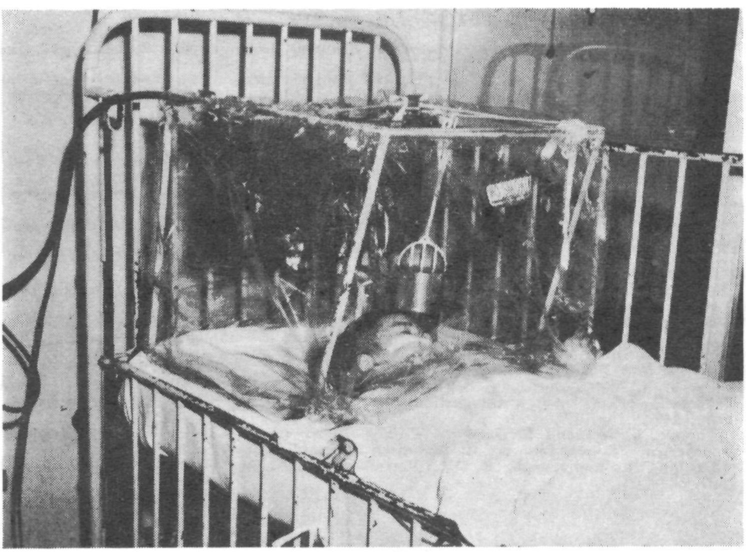

Fig. 17. Use of oxygen and humidity in treatment of early tracheitis.

edly due to trauma at intubation, but in others to the presence of Levin tubes, or nearby operative sites. This figure is not a fair one, for the younger patients could not complain of their discomfort.

The appearance of suprasternal or subcostal retraction was taken as a sign of real respiratory obstruction and undeniable cord irritation. Retraction occurred in 6 patients postoperatively. Three of these had had preoperative strictures or anomalies of the trachea. All 6 were relieved by the above treatment. No patient in this series required tracheotomy, and in none was there any lasting effect of intubation such as scarring, granulomata, or continued hoarseness. This series appears sufficiently large to show that endotracheal anesthesia, if carried out with gentleness and cleanliness, is a relatively safe procedure.

Summary

1. An endeavor should be made to reduce the incidence of tracheitis which follows endotracheal intubation in pediatric anesthesia.

2. The incidence of tracheitis may be reduced to a minimum by avoiding mechanical force, chemical irritation and contamination in intubation and by treatment with antibiotics, oxygen, and humidity at the appearance or signs of tracheal irritation.

3. A humidifier is described which may be used for this purpose.

4. A follow-up study is reported of 560 children who received endotracheal anesthesia.

Acknowledgment is made to Miss Jean Lootz, R.N., for assistance in obtaining data.

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THE MAINTENANCE NEED FOR WATER IN PARENTERAL FLUID THERAPY

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ONE OF THE MAJOR objectives of parenteral fluid therapy is provision of water to meet physiologic losses. These losses, the insensible and urinary losses, have been extensively studied and defined for infants and adults. It is established from these studies that both insensible loss of water and urinary water loss roughly parallel energy metabolism and do not parallel body mass (weight). Therefore, any values which are applicable to all ages must be derived from some function of energy metabolism.

Initially, and to a large extent even today, needs for water have been determined on the basis of weight in infants and on the basis of total amounts in adults. Although this serves well for infants and adults, the hapless individual between these two groups receives, at best, a rough estimate of his requirement for water.

Darrow and Pratt[1] have referred water needs directly to energy expenditure, computed from a set of tables[2] utilizing 100 calories as a basis of reference. This latter figure is well chosen since it is equivalent to 1 kg in the infant and ready transfer of familiar numbers is possible. However, the necessity for using a table and for making computations has probably served as a barrier to its widespread acceptance.

Crawford and his associates[3] have referred needs for water, and a variety of drug dosages as well, to a unit of surface area (S.A.) since surface area closely parallels basal energy metabolism. In this system surface area is computed from a height-weight nomogram.

Wallace[4] has recently devised a scheme for computing requirement for calories per kilogram from a simple formula relating calories per kilogram to age.

The following scheme was devised to permit an estimate of total expenditure of energy from weight alone using a relationship between weight and expenditure of energy that may be easily remembered (Fig. 1). The lower line in Figure 1 defines basal caloric expenditure at the various weight levels and the upper line defines estimated caloric expenditure for normal activity.[5] The line in between indicates the calculated expenditure of energy for hospitalized patients. It is calculated from the simple equations illustrated below the graph and is necessarily arbitrary. The course of the calculated line for infants implies that hospitalized infants are more active and more nearly approach normal expenditure than is the case with adults. Hospitalized children and adults are assumed to have an energy expenditure roughly midway between basal and normal levels. Using this system, expenditure of energy ranges from 100 to 3000 calories. Table I illustrates the weight comparable to each of these 100-calorie increments.

Since losses of water are a function of expenditure of energy, needs for water must be computed from some function of energy metabolism. In Table II requirements for water at various weights are compared using the different systems referred to previously. Close agreement of needs for water as determined by the various methods is apparent. There is one exception which merits comment. In computing needs for water per unit of surface area, the values in the 6 to 15 kg range are significantly less than the others calculated in

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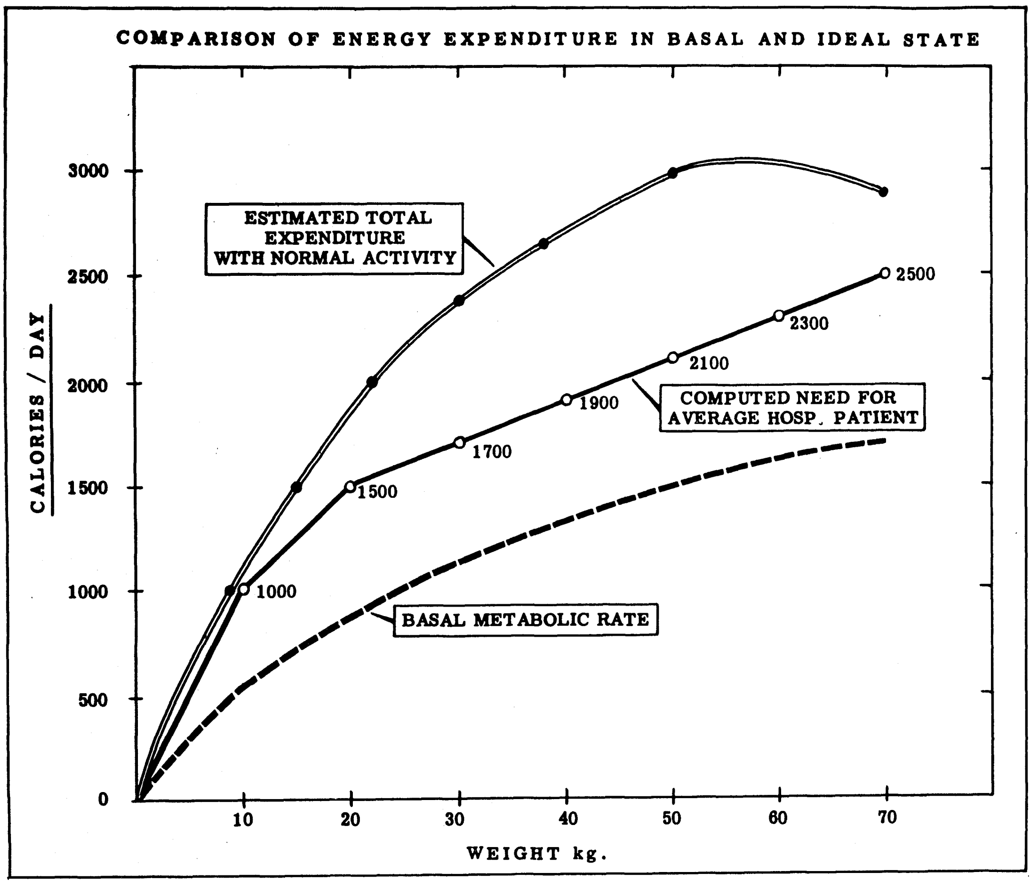

FIG. 1. The upper and lower lines were plotted from data of Talbot.[5] Weights at the 50th percentile level were selected for converting calories at various ages to calories related to weight. The computed line was derived from the following equations:

1. 0-10 kg—100 cal/kg.
2. 10-20 kg—1000 cal + 50 cal/kg for each kg over 10 kg.
3. 20 kg and up—1500 cal + 20 cal/kg for each kg over 20 kg.

that range, a finding related to the fact that energy expenditure, either basal or total, is higher per unit of surface area for the child of intermediate weight than for the small infant or for the adult. An increase of about 50% in needs for water per unit of surface area for this group would make them comparable to the other groups. With this exception, the four systems give similar results.

The higher figure in the adult range computed from the system of Darrow and Pratt results from the use of a constant percentage of basal metabolism as an estimate of activity. As noted by Darrow and Pratt, a lower percentage would more probably describe the actual activity of hospitalized adults. Accordingly, a figure comparable to the others would be obtained if this adjustment is made.

It may be appropriate to examine the two major components of loss of water, urinary and insensible, in terms of their relation to these systems.

INSENSIBLE WATER LOSS

With respect to insensible loss of water, Newburgh and Johnston[6] and Levine and Wheatley[7] have demonstrated that, for all ages, insensible loss of water in the resting state in a comfortable environment is a constant function of basal energy expenditure. The figures average 45 ml of water expended for each 100 cal of energy. At

TABLE I

EXPENDITURE OF ENERGY AND ITS RELATION TO WEIGHT

Expenditure of Energy (cal)	*Weight of Body (kg)*	*Expenditure at Energy (cal)*	*Weight of Body (kg)*
100	1	1600	25
200	2	1700	30
300	3	1800	35
400	4	1900	40
500	5	2000	45 (average adult female)
600	6	2100	50
700	7	2200	55
800	8	2300	60
900	9	2400	65
1000	10	2500	70 (average adult male)
1100	12	2600	75
1200	14	2700	80
1300	16	2800	85
1400	18	2900	90
1500	20	3000	95

The figure of 2000 cal may be arbitrarily assigned to the average female adult. Although this correlates with a weight less than the average for adult females, it takes into account the lower metabolic rate per unit weight of females as well as the smaller weight of females in comparison to males. A suggested average for adult males is 2500 cal. Significant deviation in size could dictate appropriate deviations from this figure.

this level 25% of the total expenditure of energy is dissipated by insensible loss of water. With increased activity, adults continued to dissipate 25% of their total expenditure of heat by insensible loss of water; but with increased activity, infants showed a marked increase in insensible loss of water per 100 cal of total expenditure. The insensible loss of water rose from 45 to 90 ml/100 cal. Under these conditions 50% of the total expenditure of energy is dissipated by insensible loss of water.[7]

In hospitalized patients, insensible loss of water was estimated by Heeley and Talbot[8] to be 930 ml/m^2 for all ages compared to 750 ml/m^2 for adults in the basal state as reported by Newburgh and associates.[9] Heeley and Talbot further showed that insensible loss of water per unit of surface area was greatest in infancy and diminished with age. By recalculating these data, using the reported weights of the subjects, to express insensible loss of water in terms of estimated expenditure of energy, an average of 50 ml/100 cal/day is obtained.

Comparing the above data in terms of surface area for the various age groups to the average for the entire group, the per-

TABLE II

NEEDS FOR WATER IN RESPECT TO WEIGHT COMPUTED FROM VARIOUS SYSTEMS (*ml/24 hr*)

Method of Estimation	*Weight*						
	3 kg	*6 kg*	*10 kg*	*15 kg*	*20 kg*	*30 kg*	*60 kg*
Cal.*	300	600	1000	1250	1500	1700	2300
S.A.† (Crawford *et al.*[3])	300	450	660	900	1200	1500	2550
Cal.** (Darrow *et al.*[1])	240	600	975	1290	1530	1950	3000
Cal.‡ (Wallace[4])	300	600	1000	1360	1640	2100	2400

* Needs for water estimated to be 100 ml/100 cal—see text.

† Needs for water estimated to be 1500 ml/m^2 for each weight computed and assuming 50th percentile height for that weight.

** Needs for water estimated to be 120 ml/100 cal as given by the author. Basal calories from the table of Talbot.[5] Activity assumed to be 30%, specific dynamic action 15%, and growth 5%. This results in a 50% increase over basal rate. (For adults a total increase of 30% is more likely.)

‡ Needs for water estimated to be 100 ml/100 cal as given by the author. Caloric need estimated as follows: cal/kg = 100 (3 × age in years). Total calories then equal weight × calculated calories per kilogram.

TABLE III

RELATION OF INSENSIBLE LOSS OF WATER TO SURFACE AREA AND TO ESTIMATED CALORIC EXPENDITURE FOR VARIOUS AGE GROUPS

Age Groups	*ml/m²*	*ml/100 cal**	*Per Cent Deviation of Each Age Group from Mean for All Ages†*	
			ml/m²	*ml/100 cal*
0– 3 yr	1150	59	124	118
3– 8 yr	950	49	102	102
8–16 yr	700	45	75	90
All ages	930	50	—	—

* Data of Heeley and Talbot[8] recalculated from weight, estimated caloric expenditure and observed insensible loss.
† Mean for all ages taken as 100% and mean for each age group expressed as per cent of this figure.

centage deviation of each of the various age groups from the over-all average may be calculated. Repeating the same calculation using the data expressed in terms of 100 cal of estimated expenditure, a similar but less marked influence of growth is demonstrated (Table III). Using surface area as the standard reference, infants have a 24% increase over the group average. Using estimated expenditure of energy as the standard reference, the increase is 18%. Similarly, values for adults by the first system are 25% below average for the group and by the second are 10% below. Therefore, 50 ml/100 cal/day represents a figure that approximates insensible loss of water for all ages. This figure agrees well with previously reported estimates.[1]

URINARY WATER LOSS

The problem of urinary water loss is best considered in terms of total excretion of solutes. The excretion of water is largely a function of the amount of solute requiring excretion and of the factors which control the concentration at which the solute is to be excreted.

These factors have been discussed in detail by Gamble,[10] Welt,[11] and Talbot.[12] Under usual conditions, solute concentrations may be varied from a low of 75 mOsm/l to a high of 1200 mOsm/l so that each milliosmol may be excreted in as much as 13.5 ml of water or as little as 0.8 ml, and the concentration is determined within these limits by the intake of water. In disease states requiring parenteral fluid therapy the limits of concentration may be considerably narrowed. In addition, the intake of water is no longer controlled by the patient in response to his own stimuli and, finally, administration of drugs as well as other stimuli may influence factors controlling excretion of water, i.e., secretion of antidiuretic hormone, independent of water intake. Accordingly, a definition of the average solute load during parenteral fluid therapy, along with some knowledge of its range, is essential in ascertaining the volume of water needed. It is furthermore desirable to consider those factors which might influence excretion of water other than intake of water and load of solutes. Such considerations would assist in ascertaining the safest concentration range and the factors which may dictate exception to the average figure for water needs.

A theoretic approach to the problem of requirements for water, in terms of excretion of solutes, during parenteral fluid therapy has been applied by Gamble *et al.*[10] and Talbot *et al.*[12] using data obtained from adults receiving glucose. In Table IV rates of excretion of solutes are illustrated for infants receiving glucose and water.[13] Two infants were shifted from a cow's milk feeding to the glucose and water feeding for a 5-day period. Later glucose and water were administered to these infants for 10 days. The data depict the average excretion of

TABLE IV

AVERAGE DAILY EXCRETION OF SOLUTES ON VARIOUS REGIMENS

Subjects	*Regimen*	*Day of Study*	*mOsm/100 cal/day*
Infants	Glucose	1	24.2
Infants	Glucose	2–5	14.5
Infants	Glucose	6–10	10.3
Adults	Glucose	Adjusted*	12.5
Infant	Human milk	Adjusted	11.0
Infant	Cow's milk	Adjusted	41.0
Adult	Average diet (1200 mOsm/day)	Adjusted	48.0

* Observation made when diet had been constant so that excretion of solutes was relatively constant.

solutes for the first day while receiving glucose and water and the average excretion of solutes during the second to fifth days. In the two experiments extended to 10 days, the daily excretion of solute for days 6 to 10 is presented and illustrates a gradual decline in excretion of solutes. Days 2 to 5 are selected as most representative of the rate of excretion of solutes during parenteral fluid therapy. Days 6 to 10 appear to represent the irreducible minimum. The figures compare well with the data of Gamble and Butler[14] in which excretion of solutes for an adult, receiving only glucose and water, was measured, when the latter was also expressed in terms of mOsm/100 cal/day. The adult was estimated to have a caloric expenditure of 2500 cal.

It is of interest to note that infants receiving human milk had a solute excretion of the same magnitude. Figures for excretion of solutes are also given for infants receiving a standard cow's milk feeding. These illustrate the greater solute excretion that results from the high protein and electrolyte intake of cow's milk. If the average diet of the adult results in the excretion of 1200 mOsm/day, the excretion of solutes expressed per 100 cal per day (48 mOsm) approximates that of the infant receiving cow's milk (41 mOsm).

The figures of greater importance in this table, however, refer to the average excretion of solutes of infants and adults receiving glucose and water. Days 2 to 5 simulate the circumstances of parenteral fluid therapy with respect to energy metabolism. The average figure for this period is 15 mOsm/100 cal/day. Normally, in parenteral fluid therapy, extra electrolyte is included which will provide an excess of from 3 to 7 mEq of cation per 100 cal per day. This leads to an addition of 6 to 14 mOsm/100 cal/day to the total excretion of solutes. Using the mean of these figures, 10 mOsm/100 cal/day, the total daily excretion of solutes then averages 25 mOsm/100 cal (15 mOsm/100 cal from energy metabolism + 10 mOsm/100 cal extra electrolyte). From Table IV the minimal excretion of solutes that would be encountered is 10 mOsm/100 cal/day. Maximum excretion of solutes would be 40 mOsm/100 cal/day in instances of rational parenteral fluid therapy except where clinical evidence indicates higher excretion, e.g., diabetes mellitus.

In circumstances encountered in most instances of parenteral fluid therapy, glomerular filtration rate is not greatly reduced and rate of excretion of solutes is not greatly increased. In these circumstances the limit of dilution with maximum water loading is approximately 75 mOsm/l, representing a fourfold dilution from the concentration of solutes in glomerular filtrate, 300 mOsm/l. If the minimum solute load, 10 mOsm, is excreted at only a twofold dilution, 150 mOsm/l, 66.7 ml of urine ($10/150 \times 1000 = 66.7$ ml) would be required. This would seem to represent an attainable minimum for concentration of solutes of most patients.

Conversely, except with solute diuresis of unusual degree, solutes may be concentrated in the urine of normal subjects to 1200 mOsm/l, a fourfold concentration of glomerular filtrate.

Taking a twofold concentration, 600 mOsm/l, as the maximum safe concentration to expect of patients receiving parenteral fluid therapy, the maximum solute load of 40 mOsm/100 cal/day excreted at this concentration would require 66.7 ml (40/600 × 1000 = 66.7). The minimum solute load excreted at 150 mOsm/l requires the same volume of water as the maximum solute load excreted at 600 mOsm/l. This of course derives from the fact that the high concentration of solutes is four times the low and the maximum solute load is four times the minimum. The average solute load, 25 mOsm/l excreted in 66.7 ml of water would be excreted at a concentration of 375 mOsm/l (25/66.7 × 1000 = 375 mOsm/l). Providing 66.7 ml of water for renal excretion for patients receiving parenteral fluid therapy permits the predicted solute loads of 10 to 40 mOsm/100 cal/day to be excreted between the concentrations of 150 and 600 mOsm/l, and the average solute load of 25 mOsm/100 cal/day to be excreted at a concentration of 375 mOsm/l.

To test this concept, the concentration of solutes in the urine was determined in infants, children and adults who had been receiving parenteral fluid therapy for at least 12 hours. The subjects were on various hospital services and their intake of fluid was dictated by the individual service. A random, untimed specimen of urine was obtained. Urine was collected and preserved with thymol. Concentration of solutes was determined in a Fiske osmometer and concentration of creatinine by the method of Folin and Wu.[15]

The data, with respect to concentration of solutes, are represented in Figure 2 in the form of a frequency distribution. This figure is subdivided into three categories arbitrarily defined, as indicated, to represent values pertaining to infants, children and adults. Concentrations of solutes were

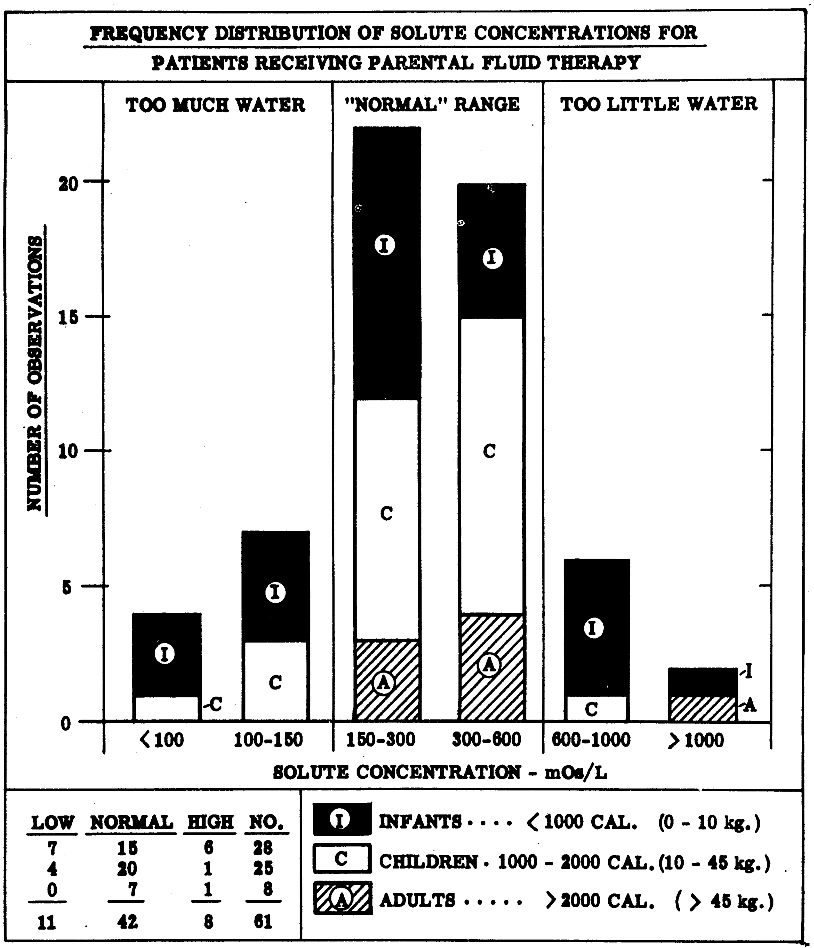

FIG. 2.

within the "normal" range in the urine of seven of the eight adults. Concentrations in 4 of the 25 children were low, and only one was high. The concentrations in 13 of the 28 infants were outside the "normal" range. The deviations from "normal" could arise either from erroneous sampling due to variability in rate of administration of fluid, from solute excretions outside the estimated limits, or from improper administration of water. A sampling error of this type is least likely to occur in the infants in whom therapy was generally provided at a constant rate over the 24-hour period.

Since the deviations were greatest in infants, efforts were made to estimate the quantity of solutes excreted during a 24-hour period, thus providing a means of comparing the theoretically estimated values for excretion of solutes to observed values. From a measurement of the daily excretion of creatinine, the expected daily excretion of solutes was computed. A sample calculation is illustrated in Table V. The daily excretion of creatinine was determined in unpublished observations on infants receiving either glucose or human milk and found to be 10.7 mg/kg/day.[13] This figure agrees well with the figure of Marples and Levine[16] for infants receiving diets low in protein (11.6 mg/kg/day). The rate of excretion of solutes computed in this manner averaged 19.5 mOsm/kg/day. In the present system, this would be 19.5 mOsm/100 cal/day since, for the infants included, an infant weighing 1 kg expends 100 cal. A range of 9.9 to 39 mOsm/100 cal/day was observed. This coincides quite well with the theoretic calculations concerning excretion of solutes. The validity of such calculations is admittedly doubtful, for excretion of creatinine from hour to hour and from infant to infant is constant only within broad limits. Furthermore, excretion of creatinine has not been observed under the circumstances of parenteral fluid therapy. In spite of these limitations, we infer from the data that excretion of solutes falls roughly within the theoretically determined limits. If this is the case, it is then necessary to conclude that administration of water was improper in a significant number of infants.

In the case of children and adults, a similar calculation to determine the rate of excretion of solutes was not possible since excretion of creatinine in the child and adult varies even more than it does in the infant, at least in relation to weight or any function of energy metabolism predicted from weight.[17]

The data does imply that the amount of fluid actually given the individuals studied did not consistently permit excretion of solutes within a safe concentration range as it imposed demands on dilution and concentration of solutes which might well exceed individual capability.

As excretion of water is a slow, continuing process, the desirability of regulating the rate of administration of fluids in order that large loads of water are not given in short periods of time should be mentioned. An example might serve to illustrate this point. An infant weighing 3 kg is assumed to have a total daily need for water of

TABLE V

AN EXAMPLE ILLUSTRATING METHOD OF CALCULATION OF TOTAL DAILY EXCRETION OF SOLUTES

Daily excretion of creatinine = 10.7 mg/kg/day (assumed—see text)

Concentration of solutes = 550 mOsm/l (by determination)

Concentration of creatinine = 301 mg/l (by determination)

$$\frac{\text{Conc. solute}}{\text{Conc. creatinine}} = \frac{550}{301} = 1.82 \text{ mOsm/mg creatinine excreted}$$

Solute excretion = 10.7 mg creatinine/kg/day × 1.82 mOsm/mg creatinine = 19.5 mOsm/kg/day

1 kg in this range = 100 calories

Solute excretion = 19.5 mOsm/100 cal/day

300 ml (100 ml/100 cal) and a total daily excretion of solutes of 75 mOsm (25 mOsm/100 cal). The rate of excretion of solutes would then be about 3 mOsm/hr. At maximal urinary dilution (75 mOsm/l) the maximal rate of excretion of water would be 40 ml/hr (13.3 ml/mOsm). Should half the daily need for water, 150 ml, be given in a 1-hour period, the excretion could then be but 40 ml. The insensible loss of water in that hour would account for an additional 6 ml. The balance, 104 ml, would be retained. The total quantity of water in the body is estimated to be 1800 ml (60% of the body weight). The addition of 104 ml of water would represent a dilution of body fluid of nearly 6% and would result in a drop of approximately 8 mEq in the concentration of sodium in the serum. Such an abrupt decrease in concentration of sodium is sufficient to produce symptoms. Furthermore, under stimulus for maximal excretion of water the administered water would be excreted in a 4-hour period and, unless this were taken into account, a period of relative water deficit would then ensue.

Daily administration of water is then best provided continuously, but certainly it should be provided over a period of at least 12 hours. This is especially true in the infant. The significant number of infants excreting urine at concentrations less than 100 mOsm/l indicates that the above considerations are often ignored. Excessive amounts of glucose and water are frequently given to "maintain an infusion." The inherent danger of such practices is evident from the foregoing consideration.

Equally apparent is the fact that insufficient amounts of water were provided in 6 of the 28 infants, and a fairly extreme degree of concentration of solutes in the urine resulted. Such circumstances, obviously, may lead to production of significant deficits of water and to dehydration.

In summary, the losses of water of an individual consist of the insensible loss and the urinary loss, stool losses being negligible. From the considerations given here, the average figure for total loss of water is 116.7 ml/100 cal/day. It is fair to assume that the water of oxidation will provide nearly 16.7 ml.[10] The balance, 100 ml/100 cal/day, must be provided parenterally. Fortuitously then, average needs for water expressed in milliliters equals estimated energy expenditure in calories.

MAINTENANCE ELECTROLYTE NEEDS

With respect to maintenance needs for electrolyte, less precise data are available, and figures considerably in excess of the minimum requirements are readily handled. This fact is apparent in comparing the electrolyte intake of infants receiving human milk and cow's milk. The intake of electrolytes in relation to the intake of calories for babies receiving each type of milk is indicated in Table VI. Also presented are the figures recommended by Darrow[1] for infants and adults, and by Welt[11] for adults, recalculated in terms of 100 cal. Close agreement of the various systems is evident. It is also apparent that these values fall between the intakes provided by human milk and cow's milk and should therefore be acceptable as maintenance needs for electrolyte.

TABLE VI

INTAKE OF ELECTROLYTES PROVIDED PER ESTIMATED 100 CALORIES ON VARIOUS REGIMENS

Regimen	*mEq/100 cal/day*		
	Na	*Cl*	*K*
Human milk*	1.0	1.2	2.0
Cow's milk	3.5	4.5	6.0
Recommended†	3.0	2.0	2.0
Recommended (Darrow)	3.0	2.0	3.0
Recommended adult**	3.0	3.0	1.0

* Computed assuming an intake of 150 ml/100 cal/day which provides 100 cal.

† May be added to glucose and water using 3 ml of molar sodium lactate and 1 ml of 2 molar potassium chloride for each 100 ml of maintenance fluid.

** Adult values from Welt [11] Administration of 500 ml of normal saline per day provides 75 mEq of sodium and chloride total. Potassium administration of 30 mEq/day is recommended. The figures per 100 cal are calculated assuming adult calorie expenditure to be 2500 cal/day.

CONCLUSION

In presenting a simple and arbitrary scheme for computing calories from weight, it is recognized that significant deviations from this relation exist. Excessive obesity, the declining metabolism of the aged, and the increased metabolism of patients with infection, all may require modifications of the scheme. Infants during the first 10 days of life, have a metabolic rate 20 to 30% less than that cited here. As with any method, an understanding of the limitations of and exceptions to the system are required. Even more essential is the clinical judgment to modify the system as circumstances dictate.

With respect to the general applicability of the average figures for water intake per 100 calories, it is evident that specific clinical situations dictate alterations. Hyperventilation may double the insensible losses of water, and glycosuria or excessive excretion of nitrogen may double renal losses of water. Obviously, in anuria losses of water are decreased and administered fluids should replace only the insensible loss of water plus the measured volume of urine excreted. Simple observations of the clinical status may dictate a modification from the average values of this or any other system. Finally, it should be emphasized that these figures provide only maintenance needs for water. It is beyond the scope of this paper to consider repair of deficits or replacement of continuing abnormal losses of water. These must be considered separately and must be added to the needs for maintenance.

SUMMARY

It is generally agreed that the maintenance requirements for water of individuals is determined by their caloric expenditure. By means of the following formulae, the caloric expenditure of hospitalized patients can be determined from weight alone. For weights ranging from 0 to 10 kg, the caloric expenditure is 100 cal/kg/day; from 10 to 20 kg the caloric expenditure is 1000 cal plus 50 cal/kg for each kilogram of body weight more than 10; over 20 kg the caloric expenditure is 1500 cal plus 20 cal/kg for each kilogram more than 20.

Maintenance requirements for water depend upon insensible loss of water and renal loss. An allowance of 50 ml/100 cal/day will replace insensible loss of water, and 66.7 ml/100 cal/day will replace the average renal loss so that the total requirement is 116.7 ml/100 cal/day. As water of oxidation will supply approximately 16.7 ml/100 cal/day, the remaining 100 ml/100 cal/day must be supplied to meet the remaining water losses of patients on parenteral fluid therapy. Possible exceptions to this figure are discussed.

Maintenance requirements of sodium, chloride and potassium are 3.0, 2.0 and 2.0 mEq/100 cal/day, respectively.

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SUMMARIO IN INTERLINGUA

Le Requirimentos de Mantenentia de Aqua in Patientes sub Therapia a Fluido Parenteral

Es acceptate in general que le requirimentos de mantenentia de aqua es determinate per le expension caloric del individuo. Per medio del sequente systema, il es possibile determinar le expension caloric de patientes hospitalisate super le base de solmente lor pesos. Pro pesos ab 0 a 10 kg, le expension caloric es 100 cal per kg per die; ab 10 a 20 kg, le expension caloric es 1000 cal plus 50 cal per kg pro omne kg de peso corporee supra 10 kg; supra 20 kg, le expension caloric es 1500 cal plus 20 cal per kg pro omne kg de peso corporee supra 20 kg. Le resultatos obtenite per iste methodo de calculation es ben de accordo con le recommendationes de alteros que es basate super systemas plus complexe.

Le requirimentos de mantenentia de aqua depende del insensibile perdita de aqua e del perdita renal de aqua. Un margine de 50 ml per 100 cal per die suffice a reimplaciar le insensibile perdita de aqua, e 66,7 ml per 100 cal per die reimplacia le perdita renal medie de aqua. Ergo le total requirimento de aqua es 116,7 ml per 100 cal per die. Proque aqua de oxydation provide circa 16,7 ml per 100 cal per die, le remanente 100 ml per 100 cal per die debe esser administrate pro coperir le remanente perditas de aqua in patientes sub therapia a fluido parenteral. Deviationes possibile ab iste valores es discutite.

Le requirimentos de mantenentia de natrium, chlorido, e kalium es 3,0, 2,0, e 2,0 mEq per 100 cal per die, respectivemente.

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