

Improved Brachial Plexus Blockade with Bupivacaine Hydrochloride and Carbonated Lidocaine

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Statistical norms were sought for the latency and duration of supraclavicular brachial block in 183 patients, using 1 per cent lidocaine hydrochloride, 1 per cent mepivacaine hydrochloride, 1 and 2 per cent carbonated lidocaine, and 0.25 per cent bupivacaine. Cutaneous areas subserved by the median nerve were slowest to become anesthetized. Carbonated lidocaine, 2 per cent, had the shortest latency (6.8 ± 2.97 min) and the shortest duration (153 min). Bupivacaine with epinephrine, 1/200,000, had the longest latency (23.02 ± 7.67 min), and the longest mean duration (630 min); bupivacaine without epinephrine lasted almost as long. A mixture of 1 per cent carbonated lidocaine and 0.25 per cent bupivacaine combined rapid onset (6.65 ± 2.24 min) with moderately long duration (453 min). The durations of action of lidocaine and mepivacaine were not influenced by age. However, the duration of action of bupivacaine was positively correlated with advancing age, and this relationship was enhanced by the presence of 1/200,000 epinephrine. (Key words: Brachial plexus; Conduction anesthesia; Carbonated lidocaine; Bupivacaine; Aging and local anesthetic agent.)

THE ROLE of regional anesthesia in clinical practice is limited by the capabilities of the local anesthetic drugs obtainable for everyday use. Two practical disadvantages are inherent in the agents currently available. First, the drugs take a considerable time to work, and require an interval of 10–20 minutes between

injection and development of satisfactory anesthesia. Second, the duration of anesthesia is limited to a period of two to four hours, and this may be inadequate for protracted operations, unless continuous catheter techniques are used.

Two new compounds show promise of answering the temporal shortcomings of regional anesthesia, one by shortening latency to within clinically acceptable standards, and the other by prolonging duration beyond the limits of surgical requirements.

The first of these compounds, carbonated lidocaine, is one of the class of carbonated salts of local anesthetic bases, prepared with high P_{CO_2} 's that has been under laboratory and clinical trial in our department since 1965. We have shown greatly increased speed and intensity of blockade using these agents in epidural analgesia.¹⁻³ The physical basis for the efficacy of the carbonated local anesthetics is still under investigation, but it is probably related to enhanced pH gradients across cell membranes caused by diffusion of the dissolved carbon dioxide, with a resulting "cation-trap" effect.⁴

The second agent is bupivacaine, the butyl homologue of mepivacaine, which has a longer duration of action than other local anesthetics in clinical use.⁵

The capabilities of both of these agents have been well established in epidural anesthesia, in terms of latency, dose requirements, duration, and quality of blockade.^{2, 6, 7} From these clinical studies it is clear that in the epidural space bupivacaine does not provide the dramatically prolonged duration that had been observed by Telivuo in his original series of intercostal blocks.⁵ This wide discrepancy in the behavior of a new anesthetic agent at different injection sites made it appear necessary

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TABLE 1. Brachial Plexus Blockade: Latency for Complete Analgesia of Hand and Forearm, and Duration of Action in 180 Patients

	Analgesic Solution	n	Dose of Local Anesthetic (mg)	Latency of Onset			Duration (Min)	
				Mean Total Latency (Min)	± SD	Upper 90 Per Cent Confidence Limit of Mean (Min)	Mean	Range
Group 1	1 per cent lidocaine HCl	27	500	14.07	3.76	20.39	296	140-235
Group 2	1 per cent carbonated lidocaine	28	500	8.21	2.83	12.96	167	100-230
Group 3	2 per cent carbonated lidocaine	28	500	6.8	2.97	11.63	153	120-225
Group 4	1 per cent mepivacaine HCl	25	500	14.84	6.22	25.27	245	175-300
Group 5	0.25 per cent plain bupivacaine HCl	27	125	21.31	5.20	30.03	575	180-815
Group 6	0.25 per cent bupivacaine + epinephrine	27	125	23.02	7.67	35.92	630	360-900
Group 7	1 per cent carbonated lidocaine and 0.25 per cent bupivacaine + epinephrine	18	300 + 75	6.65	2.24	8.98	453	270-555

to re-examine both of the new compounds in a peripheral-nerve-block situation that would lend itself to quantitative methods of comparison. Brachial plexus block by the supraclavicular route was chosen as a suitable comparative technique, since the presence of a well-recognizable bony landmark would lessen the variables arising from inconstant anatomic placement of the injected solutions.

Methods

Supraclavicular brachial plexus anesthesia was studied in 183 uncomplicated cases in which the patients did not have systemic disease and were to undergo operations on an upper limb. The patients ranged in age from 15 to 86 years. The classic anterior approach was employed, using the first rib as a bony landmark. Each patient received one of the seven solutions shown in table 1. All solutions except that given to Group 5 (plain 0.25 per cent bupivacaine) contained freshly-added epinephrine, 1/200,000. The mean ages in the seven groups were similar, ranging from 39 to 45 years.

The volume injected in each group was chosen so that the dose of local anesthetic would be within acceptably safe limits, and equivalent in potency and toxicity to the doses of the other agents (e.g., 125 mg of bupi-

vacaine was considered to be comparable to 500 mg of lidocaine or mepivacaine). An exception was made in Group 7, where the equivalent toxicity of the mixture of these two local anesthetics in 30 ml was slightly greater than toxicity in the other groups: this slight increase of total dose was justified on the grounds of the very low blood concentrations reported by Reynolds and Taylor after bupivacaine administration.⁸ Double-blind techniques of comparison were not feasible, since carbonated solutions are easily recognizable by their bubbles, so no attempt was made to conceal the identity of any agent used.

Patients were allotted to the various groups according to the probable duration of the operation, the time available for induction of anesthesia, and the time of day. Carbonated lidocaine was chosen for relatively short operations, and mepivacaine and bupivacaine for long procedures. Operations scheduled early in the day were given priority in the bupivacaine series. This degree of selection did not appear to introduce any undesirable statistical bias into the subsequent analysis of results.

Onset and regression of anesthesia were determined by pin-prick. Onset was measured from commencement of injection of the anesthetic solution. The times of onset in the cutaneous nerves of the hand and forearm were

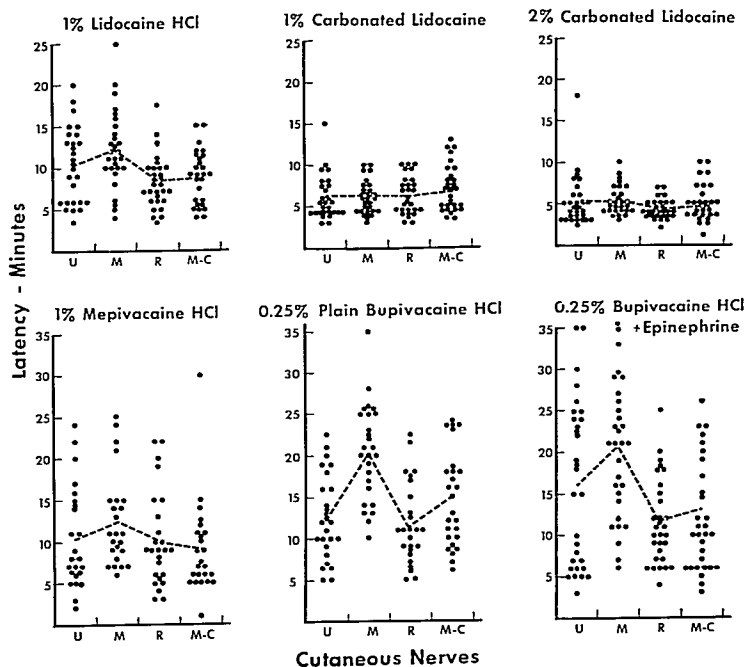


FIG. 1. Latency of onset of supraclavicular brachial plexus blockade in cutaneous nerves of the hand and forearm in 180 cases. All solutions except plain bupivacaine contained 1/200,000 epinephrine. U = ulnar; M = median; R = radial; M-C = Musculocutaneous (lateral antebrachial cutaneous); — = mean of individual data points.

plotted on a sensory-nerve diagram in each case. The following onset times were retrieved for statistical comparison: 1) ulnar nerve; 2) median nerve; 3) radial nerve; 4) lateral antebrachial cutaneous nerve (lateral cutaneous nerve of the forearm); 5) all cutaneous areas of the hand and forearm (total time for analgesia to develop). Duration of anesthesia was taken as the time from complete development of analgesia until the first return of pin-prick sensation in any cutaneous area of the hand or forearm, or to the first awareness of pain, whichever occurred sooner.

Attempts to assess the onset and quality of motor block proved inexact in our hands and were abandoned.

Data for onset and duration of analgesia were entered on IBM cards and submitted to the following computerized analyses: 1) means and standard deviations for onset times in individual cutaneous nerves, and for times to achievement of total analgesia in all areas; 2) linear regression for duration of analgesia against age, with the standard deviations and 90 per cent confidence limits to the regression lines.

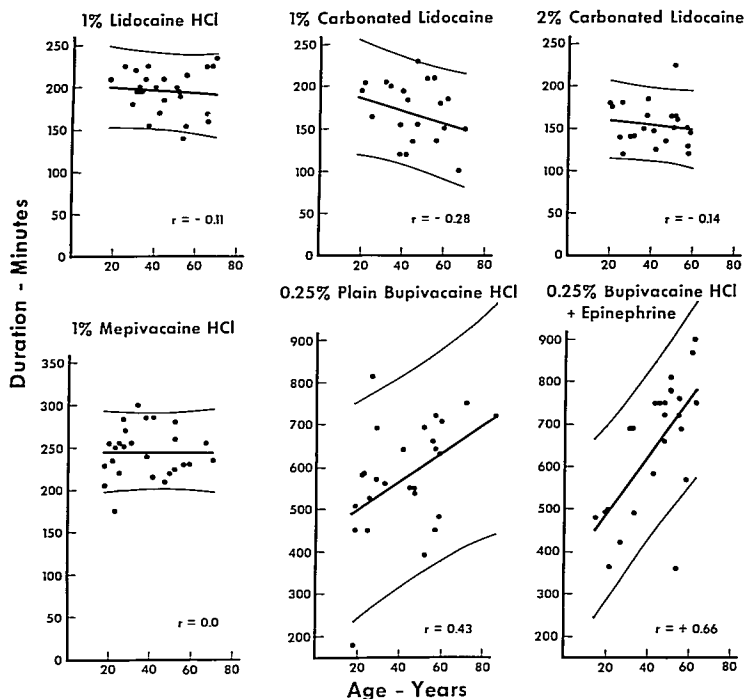


Fig. 2. Duration of brachial plexus blockade plotted against age in 183 cases, showing means and 90 per cent confidence limits ($SD \times 1.68$). r = correlation coefficient between age and duration in each group. All solutions except plain bupivacaine contained 1/200,000 epinephrine.

Results

Anesthesia was successful in all patients except three in the series which received bupivacaine with epinephrine; in these patients analgesia was patchy and incomplete. The three failures were excluded from subsequent calculations, and data from the remaining 27 cases of this group were subjected to statistical analysis.

ONSET (LATENCY OF ANALGESIA)

The onset times for the seven test solutions are shown as scattergrams in figure 1 and figure 3. The times to achievement of complete analgesia in the cutaneous distribution of the ulnar, median, radial, and lateral antebrachial cutaneous nerves are plotted as individual data points. The mean times to onset of analgesia in the four cutaneous areas are shown as

dotted lines drawn through the data points. The time lapse from the commencement of injection to development of complete analgesia in all cutaneous areas of the hand and forearm is shown in table 1. The upper 90 per cent confidence limits for the agents in table 1 show the waiting times that may be anticipated before satisfactory analgesia of the entire hand and forearm can be assured in nine of ten cases.

The latencies from time of injection to development of analgesia varied widely among the different solutions (fig. 1). There were also differences among the latencies of the four cutaneous areas tested. The hydrochloride solutions showed a tendency for slower onset in the distribution of the median nerve than in the other areas. This slow onset was most commonly found in the palm of the

hand and in the index and middle fingers, that is, in the palmar cutaneous distribution of the seventh cervical nerve.

One per cent mepivacaine and lidocaine hydrochloride are almost identical in their mean latency profiles, but 0.25 per cent bupivacaine is generally very slow to produce full analgesia, and its latency is more unpredictable, with an upper 90 per cent confidence limit of about 36 minutes. The mean latency profile of bupivacaine in figure 1 shows the most exaggerated delay in the median nerve distribution of all the test solutions: the difference between the median-nerve onset times and the radial and lateral antebrachial cutaneous latencies is highly significant ($P < 0.01$).

The carbonated solutions had markedly shorter times to onset than the hydrochloride solutions, and the salient of delay in the dis-

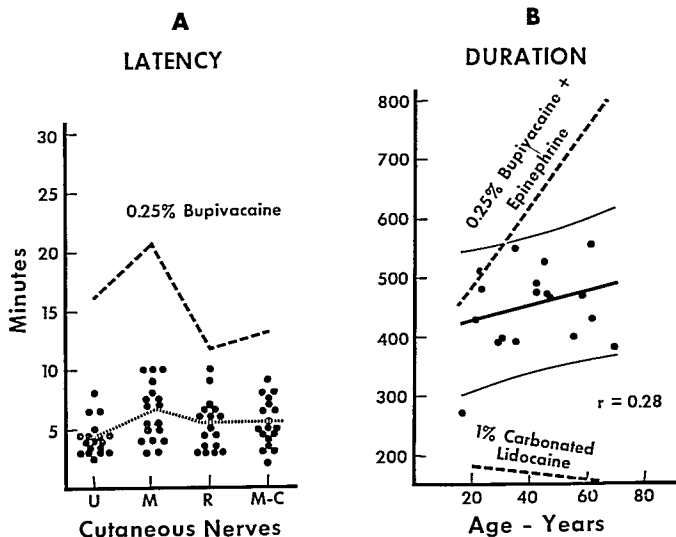


FIG. 3. A, Latency of onset, and B, duration of action of supraclavicular brachial plexus blockade in 18 cases, using 30 ml of 1 per cent carbonated lidocaine +0.25 per cent bupivacaine HCl +1/200,000 epinephrine. Mean latency for 0.25 per cent bupivacaine, and mean duration for individual solutions of 0.25 per cent bupivacaine and 1 per cent carbonated lidocaine are shown for comparison.

tribution of the median nerve is practically eliminated, so that the mean latency profiles become almost straight lines.

The most commonly used agents, lidocaine and mepivacaine hydrochloride, involve mean waiting times of 14-15 minutes. The upper 90 per cent confidence limit extends a further 6 minutes beyond the mean for lidocaine hydrochloride, and 10 minutes beyond the mean for mepivacaine. In other words, of ten patients receiving lidocaine hydrochloride we may expect to find one who will take longer than 20 minutes to develop full analgesia, and with mepivacaine we may expect to find one of ten who will take longer than 25 minutes. With 0.25 per cent bupivacaine the upper 90 per cent confidence limit extends even further, to a possible waiting time of 30 minutes for the plain solution and 36 minutes for bupivacaine with epinephrine.

By contrast, the three groups receiving the carbonated lidocaine solutions had upper 90 per cent confidence limits in the range of only 10-13 minutes, or about half the waiting time that must be anticipated for any of the orthodox hydrochloride solutions.

DURATION OF ACTION

The individual data for durations of action of the seven solutions in relation to age are shown as scattergrams in figure 2 and figure 3. Calculated mean regression lines and 90 per cent confidence limits for each population are superimposed on the data.

The durations of action of the seven groups vary over a wide range and are in the sequence: 2 per cent CO₂-lidocaine < 1 per cent CO₂-lidocaine < 1 per cent lidocaine HCl < 1 per cent mepivacaine < 1 per cent CO₂-lidocaine + 0.25 per cent bupivacaine < 0.25 per cent plain bupivacaine < 0.25 per cent bupivacaine + epinephrine.

Figure 2 shows that 0.25 per cent bupivacaine has a much longer action than any of the other test solutions, with a mean duration of 630 minutes at 40 years of age. However, there was also a wide variation around the mean between 360 and 900 minutes. Two per cent CO₂-lidocaine had a shorter duration than 1 per cent CO₂-lidocaine, but this difference probably resulted from the smaller volume of solution used in the former group.

Durations were shortened in the test groups where volumes were reduced in order to avoid toxic overdose; that is, 2 per cent CO₂-lidocaine, where the volume was only 25 ml, and the mixture of 1 per cent CO₂-lidocaine and 0.25 per cent bupivacaine, where the volume was 30 ml.

AGE

Advancing age had little or no effect on the duration of action of any analgesic agent tested except bupivacaine. Mepivacaine and lidocaine in both hydrochloride and carbonated forms have correlation coefficients close to zero, or even slightly negative. Bupivacaine, 0.25 per cent, is the only agent in this series that showed a positive correlation between duration of action and advancing age, the relationship being weak for the plain solution ($r=0.43$), and somewhat stronger for the epinephrine solution ($r=0.66$).

PREDICTABILITY

Mepivacaine is the most predictable agent in this series, with a standard deviation that is only 9 per cent of the mean duration, while 0.25 per cent bupivacaine has the widest variation, with a standard deviation that is about 25 per cent of the mean.

The duration of action of 0.25 per cent bupivacaine with epinephrine also has a large standard deviation, and because of the correlation with age the degrees of predictability vary. Duration is shortest and least predictable at the lower age limit, where the standard deviation is 29 per cent of the mean duration of 455 minutes at 15 years. The regression line rises steeply, however, and by 62 years the mean duration has increased to 770 minutes; although the standard deviation is almost unchanged, at this stage it is only 16.4 per cent of the mean.

The addition of epinephrine to 0.25 per cent bupivacaine makes very little difference to duration below the age of 30 years, but above this age the difference between the plain and the epinephrine solutions becomes more marked, and by 60 years the mean duration of action of the epinephrine solution is 20 per cent longer than that of the plain solution; by this point the influence of age has made the difference statistically significant. From figure

2 it can be seen that with advancing age bupivacaine has a duration that is more predictable than is apparent from the data in table 1. When the influence of age is taken into account, predictability is increased, and both predictability and duration are further heightened by the vasoconstrictive effects of epinephrine.

Discussion

Brachial plexus anesthesia has been studied exhaustively,⁹⁻¹¹ and the present investigation was originally designed to answer one question only: are there any practical advantages to using short-onset and long-acting agents for this type of anesthesia?

The results show that indeed there are distinct advantages, and that there are also certain disadvantages, but that the latter can be avoided. The waiting time for full anesthesia with carbonated lidocaine was 42 per cent shorter than when the hydrochloride salt was used. This finding is less dramatic than the 72 per cent shortening reported by Schulte-Steinberg and colleagues.¹¹ The difference between the two studies may be referable to different criteria of measurement, but nevertheless, in practical terms, either figure represents a major saving of time in a busy clinical situation.

To offset the advantage of faster onset, the duration of action of carbonated lidocaine was about 12 per cent shorter than that of the hydrochloride solution ($P < 0.015$), as well as being somewhat less predictable (see fig. 2). This shortening of duration had not been observed by Schulte-Steinberg *et al.*, nor had one of us found any comparable shortening when carbonated lidocaine was used in epidural analgesia.²

As might be expected, the volume of solution appeared to have a slight effect on duration. Thus, the duration of action of 500 mg lidocaine given as 25 ml of 2 per cent carbonated lidocaine was 10.5 per cent shorter than that of 50 ml of the 1 per cent carbonated solution, but this difference was not significant ($0.1 > P > 0.05$).

The duration of action of a bupivacaine injection appears to relate directly to its distance from the spinal cord. The outstanding persistence of bupivacaine in peripheral nerve blocks contrasts with its relatively unimpres-

sive duration in subarachnoid analgesia⁶ and its only slightly better performance in epidural analgesia. In this series, the duration of action of bupivacaine lay in the range of 6-15 hours; that is, about three times the duration obtained in a previous epidural study where analgesia began to regress after only 3½ hours.⁷

The clinical behavior of a local anesthetic is determined by its physicochemical properties. Bupivacaine has a greater affinity for negatively-charged protein receptor sites than other local anesthetic agents, and at a plasma concentration of 1 µg/ml the degree of protein-binding is about 96.5 per cent, as opposed to 75 per cent for lidocaine.^{8,12} This high affinity for proteins probably accounts for the difference between the durations of its action in the subarachnoid and epidural spaces, where duration is relatively short, and in peripheral nerves, where it is very long. In the latter situation there are many connective-tissue coverings, rich in protein, while in the former there are few. Moreover, with increasing age the character of the extraneural tissue changes, and at the same time the quantity increases.¹³ Thus, more binding sites are likely to become available with advancing age, trapping the local anesthetic molecules in the vicinity of the injection area and providing a biologically enhanced depot for slow protracted diffusion into the target nerves.

Unfortunately, once again a disadvantage accompanies a desirable attribute: the long duration of action of bupivacaine is bought at the expense of a proportionately long latency, which makes the agent rather unsuitable for routine use in a busy clinical environment. In this series the properties of bupivacaine exerted definite practical constraints on the collection of accurate data. The high probability of a slow onset demanded induction of anesthesia 35-40 minutes before the scheduled time of operation, while the long duration required that anesthesia be started early in the day, so that recovery of sensation could be observed before the patient had been settled for the night. In practice this meant that cases for study could not be scheduled first on the list, nor could they be started much later than 9 o'clock in the morning.

We have confirmed an observation of Harley and Gjessing that the palmar distribution of

the median nerve (C7) is slow to develop analgesia.¹⁰ From figure 1 it can be seen that this tendency was present in all the test groups. It was barely perceptible with the carbonated solutions, more evident with mepivacaine and lidocaine, and most apparent with 0.25 per cent bupivacaine, where the difference between the onset time for the median nerve and the neighboring nerves was statistically significant. This delay at C7 is reminiscent of a similar salient of delay seen in the fifth lumbar and first sacral distribution of the lower limb after lumbar epidural blockade, where the salient was abolished by using carbonated lidocaine, and exaggerated by bupivacaine.^{2,7} The cause of the delay in these two situations is speculative, but it probably was related to the thickness of the nerve coverings in the segments concerned and to the large numbers of sensory fibers subserving these cutaneous areas of the hand and the lower limb.

Our observations of duration of action in relation to age were unexpected (see fig. 2). Eriksson has shown that the duration of action of prilocaïne in finger blocks becomes progressively longer with advancing age, and he suggested that this was due to progressively diminishing blood flow with age.¹⁴ On the basis of Eriksson's data, we had expected to find a similar relationship in all our test solutions, although Telivuo and Pertala had found no correlation between age and duration in a series of intercostal blocks with bupivacaine.¹⁵ However, in this series, with the exception of bupivacaine, there was either no correlation or a slight, insignificant correlation with age (fig. 2).

In the case of bupivacaine with epinephrine, there was a highly significant correlation between age and duration ($P < 0.001$). Failure to appreciate this relationship has led to the belief that the duration of action of bupivacaine is as unpredictable as its latency. Figure 2 shows that this is not so. It is true that the predictability of duration is poor in young subjects, where the scatter of points about the mean is so wide that the standard deviation is more than a quarter of the mean, but by 62 years the duration has almost doubled, and the standard deviation has become less than a sixth of the mean.

The results in Group 7, with a mixture of 1 per cent CO₂-lidocaine and 0.25 per cent bupivacaine, show that the disadvantage of one drug can be masked by the advantage of the other. The clinical capabilities of this mixture exceed those of the other test solutions: there is a very fast onset time of less than 7 minutes and a mean duration of more than 7 hours. In our opinion this is an ideal combination for brachial plexus anesthesia.

Although no signs of toxicity were observed with the mixed agents in this series, the principle of mixing local anesthetic drugs may be questionable, since the toxicity of the two agents may be additive and may become dangerous if large volumes are injected. Carbonation of a long-acting drug such as bupivacaine would be an alternative way to produce a single agent with the combined virtues of prolonged duration of action and fast onset. Previous experience with prilocaïne showed that carbonation of this rather slow-acting agent increased the speed of onset to a marked degree.¹ It is suggested that the possibility of carbonating other slow-onset, long-acting agents should be considered in the future.

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Neonatology

ARTERIAL OXYGEN TENSION AND RETINAL VASOCONSTRICTION

Seventy infants who received oxygen therapy had measurements of arterial oxygen tension and acid-base balance and eye examinations during oxygen administration in an attempt to correlate the level of the arterial blood gases with the appearance of retinal-vessel changes. Eighteen of the infants had retinal-vessel alterations when the arterial oxygen tension was between 100 and 400 mm Hg. Hypercapnia, which increased cerebral blood flow as contrasted to the vasoconstrictive effect of oxygen, did not affect the retinal vessels. Changes in hydrogen ion concentration had no effect. The critical arterial oxygen tension for the appearance of irreversible retinal vascular changes is ill-defined, but data from this study suggest that a P_{O_2} in excess of 100 mm Hg may damage the immature retina. However, there is no uniform level at which retrolental fibroplasia will develop. The risk of retinal vascular changes increases with increasing P_{O_2} . Three infants whose gestational ages were 37 weeks or more developed retrolental vasoconstriction, which casts doubt on the notion that the retinal effect of oxygen is limited to low-birth-weight or markedly premature infants. Conversely, the inverse relationship between the risk of retrolental fibroplasia and the birth weight of the infant is supported by this study. P_{aO_2} should be kept at or below 100 mm Hg, particularly when mechanical ventilation of apneic infants is necessary. The authors indicate that the umbilical-artery-blood P_{O_2} value will not show the presence of a right-to-left ductus arteriosus shunt, which will lower the sampled P_{O_2} but result in a high P_{O_2} in blood going to the cerebral vessels. (Aranda, J. V., and others: *Arterial Oxygen Tension and Retinal Vasoconstriction of Newborn Infants*, *Amer. J. Dis. Child.* 122: 189-194, 1971.)