SOME GENERAL CONSIDERATIONS IN EVALUATING LOCAL ANESTHETIC SOLUTIONS IN PATIENTS *

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To persons who have been working in the field of local anesthesia for any length of time, or who have attempted to survey the literature published in the last fifty years, it seems that progress has become slow and that the achievements of the last two decades are of relatively minor importance. There has been no strikingly original development in local anesthetics since the first years of the century, when procaine was introduced, and it was discovered that epinephrine could be advantageously added as a vasoconstrictor. Since then the alterations in practice brought about by research have been those secured through changes in the degrees of potency or modification along special lines, but none of which has represented an innovation which was a sharp break with the past. This emphasizes the fact that we appear to have attained a static condition in the development of local anesthetic agents, where there may be anticipated quantitative improvements rather than major qualitative inventions which would start us off in an entirely new direction.

It would be extremely perilous to prophesy that there shall not be developed any qualitatively different anesthetic materials in the future, but nevertheless, the results of forty years of very intensive research at least indicate that this major invention is not going to be arrived at easily. Until a genius comes along with a bold new idea, which breaks open an entirely new field of study, the best that the rest of us can do is to try to improve our knowledge along more obvious lines to the utmost degree. This means that there must be a refinement of technics and procedures from the quantitative standpoint, so that we may select the best of a series of closely related products, or may avoid failing to recognize an additional 10 per cent or 15 per cent in some useful property which the coarser objective methods of an earlier generation would have missed.

With the emphasis thus placed on refinement in methods of study of local anesthetic agents, it becomes necessary to evaluate critically procedures for studying these remedies so that those working in this field may

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make their observations in such a way as to give them maximum value. To the trained pharmacologist or statistician working in the field of biological evaluation, the methods and principles to be employed are well understood. However, to the clinician who does not have occasion to use these frequently, there may be some point in discussing certain phases of these procedures, that he may know the general organization a study should have if it is to yield maximum value.

THE VALIDITY OF INDIVIDUAL OBSERVATIONS

It is a truism, so well recognized that it is startling to see it so often neglected, that no conclusions can be drawn which are more reliable than the data from which they arise. It is not possible to make careless, incomplete, or inaccurate observations, and from these by some statistical sleight of hand draw accurate conclusions as to what actually took place. In the field of clinical local anesthesia this problem of getting accurate observations is complicated by a factor which is frequently overlooked. This is that there is no objective way of measuring whether sensation is absent or not, that can be applied readily in patients. In each case the interpretation as to the degree of anesthesia depends on the judgment of the patient or operator. Therefore, the data are subjective in origin, no matter how objective might be later interpretations of them when they are arranged in carefully organized numerical tables.

The subjective factor is unusually important in this field because there is no clearly recognized end point which is so sharp as to leave no doubt as to whether anesthesia is present or absent. If there is a complete block of the nerve, so that there is no sensation to even the strongest stimulus, or if there is exquisite tenderness or pain, then there can be no doubt as to how the response should be classified. However, in that very broad intermediate zone of partial depression of nerve function, the decision as to whether complete anesthesia is present depends upon many factors inherent in the individual, or related to the surrounding circumstances. This is well illustrated in the observations of individual variations described by Crile in his studies on anociassociation.

Two of the extraneous variables are the intensity and frequency of the stimulus, which are difficult to control or to measure quantitatively. Another factor, which is not often consciously considered, is the inherent sensitivity of the part in question. It is well known that the various portions of the body have very different thresholds to pain as well as other sensations. The conjunctivae of the eye and urethra are much more sensitive than the mucous membranes of the mouth. A stimulus insufficient to arouse sensation in the partially anesthetized mouth would give rise to acute discomfort on these other membranes, if they were only anesthetized to an equal degree.

How important these are may be illustrated with some data from the experience of one of us (T) in trying to evaluate topical anesthetics to be used in oral surgery (1). In this particular series of studies, alleged local anesthetic solutions were used in pairs in the mouth of each patient in a dental surgical clinic. They were applied identically, one on each side of the mouth, at the same time, and a record made at the time of application as to whether, in the opinion of the surgeon and the patient, anesthesia was absent, was partial or was, perhaps, so complete that there was no sensation at all. These solutions were labelled by numbers only, and in many of the pairs of bottles there was included, as one member of the pair, normal salt solution or dilute alcohol, which had been aromatized and colored so as to resemble a true topical anesthetic. The solutions were frequently changed and were supplied under many different numbers and combinations so that all the subjective factors were balanced out as well as can be done in clinical studies. The surgeons knew at no time the true composition of the solutions under test. The data secured have been summarized in part in table 1.

TABLE 1

Comparative Local Anesthetic Efficiency of Control and Anesthetic Solutions Applied Topically to the Gums and Oral Mucosa

Solution	No. of Cases	Degree of Local Anesthesia		
		Complete %	Partial %	None %
Physiological Salt Solution	576	11	32	57
Alcohol 10%	201	16	28	56
Alcohol 95%	156	37	41	22
Procaine HCl 20%	37	19	38	43
Cocaine HCl 1%	40	15	75	10
Phenol 5% in H_2O	38	32	44	24
Benzocaine 10% in 70% alcohol	61	59	39	2

It can be seen that in 11 per cent of the patients treated with physiological salt solution, there was, in the opinion of the doctor and the patient, complete anesthesia. An additional 32 per cent believed that partial anesthesia was present, making a total of 43 per cent of patients in whom the suggestion that a topical anesthetic had been applied was enough to secure the subjective impression of anesthesia from a completely bland and ineffective agent. With 10 per cent alcohol, which also is probably not at all anesthetic, almost identical values were secured. In other words, the mucosa of the mouth is so insensitive that almost one-half the patients and operators believed some anesthesia had been produced when there was no true anesthetic effect. Obviously, therefore, a much less intense anesthesia would be required in the mouth for topical effects than would be needed in some organ that was highly sensitive.

It might be of interest to point out that in these studies, which involved about forty different materials, procaine, even in the strongest strength which could be tested, was quite ineffective as a topical anesthetic, a finding which is in accord with general experience, and that cocaine was rather poor, because the conditions required prompt anesthesia, while cocaine acted relatively slowly. The best topical anesthetic in this series was benzocaine, which produced anesthesia in all but 2 per cent of the patients. It was used as an alcoholic solution, which caused some difficulty, since alcohol in the 70 per cent strength needed is somewhat caustic to the oral mucosa when applied on cotton pledgets. Later observations not included in the present data have shown that excellent anesthesia from benzocaine can be secured by using the same 10 per cent strength in propylene glycol without causing chemical burns of the tissue.

METHODS OF HANDLING DATA

After the individual observations of the local anesthetic responses have been made, there still remains the problem of how to group and evaluate the recorded information so as to extract the greatest information. If the data have consisted of observations in which the frequencies of certain types of response are recorded in terms of the volumes of solution administered, or some similar numerical classification, it is often useful to average the values in each particular group and to plot these on some form of graph paper. When this is done on paper ruled with the usual arithmetical scale, the data almost invariably assume an S-shaped curve which is more or less regular, depending upon the amount of data secured and the accuracy of the estimates of the responses. For many purposes such a curve is highly informative. However, it suffers from one serious defect, which is that values have to be secured on each part of the curve, in order to permit conclusions in that area of the dose-response relationship. This is because with a curve the position of the line cannot be fixed accurately except between points relatively close together, and practically not at all by extrapolation beyond the zone of observation.

It has been found that such curves will almost always be transformed into a straight line if the values are plotted as probits or their equivalents on probability paper. The advantage of such a transformation is that, if necessary, a straight line may be drawn from determinations of only two points, thereby permitting fairly reliable inferences as to the expected degree of response from doses not used and even at the extremes of the curve where it would be practically impossible to obtain sufficient observations for safe conclusions.

An example of how this may operate is shown in the hypothetical curve of figure 1, in which there are plotted on the left the concentrations required to produce anesthesia in various percentages of cases in a given series. It can be seen that anesthesia would be produced in 50 per cent of the cases from an injection of 40 mg. However, using the straight line relationship, we can predict that there would be 0.01 per cent, or 1 patient out of every 10,000, who would be anesthetized by only

13 mg., and that there also would be 1 out of every 10,000 who would not be anesthetized by 120 mg.

Obviously, such a curve permits us to obtain some idea as to what incidence of abnormal or "idiosyncratic" responses might be anticipated in a series of adequate magnitude. It is not always certain that the extrapolation can be carried to the extreme indicated here, since in some sets of data the curve may break at some point and a new straight line with a different slope be established. However, when this occurs, it is the result of an intervention in the phenomenon of some different mechanism, and therefore, oftentimes by itself reveals some important phase of the action which might otherwise be overlooked.

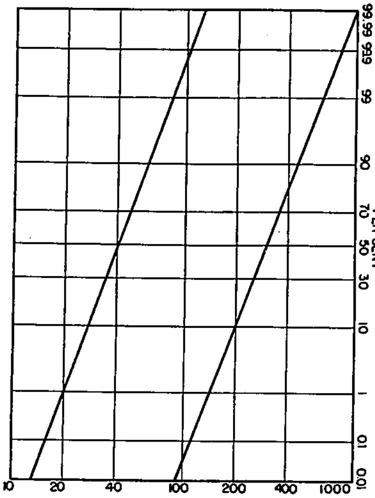

FIG. 1. The influence of dosage in mg. on the percentage showing anesthesia (left) and dying (right) from a hypothetical local anesthetic.

Inspection of the figure indicates that the slope of the curve is a matter of great importance. If the slope is steep, the concentrations required to produce a given action fall within a narrow range. This enables the surgeon to be more sure as to the amount needed for anesthesia. However, where the slope is flat, anesthesia would be produced in some patients at concentrations much less than is required by the majority, and, conversely, there will be increased numbers of patients where anesthesia fails even though the concentration is many times that adequate for the majority.

With such flat slopes the danger of getting toxic and dangerous reactions is intensified. This is illustrated in the same figure by the curve on the right where there is plotted the hypothetical mortality curve of the same anesthetic for various doses, assuming a margin of safety similar to that of the common local anesthetics. It can be seen that there is an overlapping of the curves so that the dose of 100 mg., which would be required to assure anesthesia in 999 out of 1,000 patients, might cause a fatality if not antidoted in about 1 out of 3,000 patients. It is in the overlapping zones of these two curves that we find the occasional patient who dies from a concentration of a local anesthetic which is well tolerated and used with satisfaction in the vast majority of individuals. Obviously, we do not have to create special theories of "idiosyncrasy," "thymic states" and related hypothetical situations to explain such occasional unexpected adverse effects. The simple laws of probability, and distribution of reactivities according to well established biological principles, is explanation enough.

From this viewpoint it can be seen that the older terminology of "maximum tolerated dose" or "minimum fatal dose" has no precise meaning, because there is no such thing as a minimum fatal dose or a maximum tolerated dose. There are simply doses which have fixed probabilities of producing stated effects in certain proportions of cases. These older terms should be discarded because they tend to give one a wholly fallacious sense of quantitative accuracy. When it is stated that the margin of safety between the effective anesthetic dose and the minimum fatal dose is 10 times, there is omitted the crucial information as to whether the slopes of the curves between dose and anesthesia and fatalities are so flat that there will be an appreciable chance of either anesthesia not being secured from highly safe doses or fatalities being encountered from surely effective ones; or as in the ideal case, whether the curves may be so steep that there is no significant overlapping.

In our opinion, there has not been adequate consideration of the slopes of the curves of response of various anesthetic drugs. It has not been established, for instance, whether the slopes for anesthetic potency are the same as for toxicity. It is probable that even for compounds of identical potency at the 50 per cent point there may be differences in the slopes of their dosage-action curves which would make the one with the steepest curve preferable for use. It remains to be established whether the curves expressing various aspects of the response to any given anesthetic are parallel.

In some types of data, the information is not secured in the form of frequencies of a given response, but rather in terms of a measure of the amount required to achieve a certain end point in a certain number of animals. The former type of data is like that of pitching a coin where you either have a head or a tail, but never anything in between; whereas the latter is like the titration of a solution, where you measure the exact value on the particular material in question. For these latter "graded responses" the number of subjects required to establish the average value with accuracy is much less than for the "frequency response" type of data. This is illustrated in table 2 where the mortality of procaine determined in the two different ways is tabulated. It can be seen that by using only 5 or 6 animals in the graded response type of determination, an accuracy of the estimate was secured of 7 and 11 per cent respectively, whereas when the frequency type of data was secured, from 28 to 155 animals were required to secure data of about the same order of accuracy. It is general experience that about 10 times as many observations are needed in the frequency type of determination, to establish a value with a given degree of accuracy, as is required when graded responses may be used. Therefore, it is of great value in local anesthetic studies to make the observations of the graded response type, if at all possible.

TABLE 2

COMPARISON OF THE NUMBER OF ANIMALS NEEDED FOR ACCURACY IN DETERMINING THE LETHAL DOSE OF PROCAINE BY THE GRADED RESPONSE AND FREQUENCY DISTRIBUTION TYPE OF PROCEDURES

Type of Procedure	Nature of Test	No. Animals Used	$LD_{50} \pm s.e.$	Variance %	Reference
Graded Response	Intravenous cat procaine	5	30.9± 2.3	7.4	(2)
	Intravenous cat procaine plus epinephrine	6	64.3± 7.4	11.5	(2)
Frequency Response	Rats intraperitoneal	125	257. ± 8.0	3.1	(2)
	Rats intraperitoneal	28	269. ± 5.8	2.2	(3)
	Rats intravenous	155	38.3± 1.6	4.2	(3)
	Mice intravenous	100	56.9± 1.5	2.6	(3)
	Mice intraperitoneal	120	124. ± 7.1	5.7	(3)
	Mice subcutaneous	36	339. ±42.4	12.5	(3)

BALANCED DESIGN OF EXPERIMENT

When studies are being carried out on clinical material, many factors enter which cannot be controlled and which may modify the observed response in a manner not representative of general experience. Such things as season of the year, sex and age of the patient, the experience of the operator, and other elements which do not require enumeration, oftentimes serve to make one series of observations not comparable to those of a second series set up as a control. To avoid this it is very important deliberately to arrange balance in the design of the experiment, so that each factor which cannot be directly controlled is balanced out by seeing that it occurs with equal frequency in each series. The easiest way this can be accomplished is to have the procedure carried out on the same patients with the two solutions under test at one time, or by splitting them into groups in which the sequence can be reversed for balance. In this way any shift in the skill of the operators, seasonal changes or related phenomena will balance out, and their effects cancel. It is, of course, not always possible to get an ideal balance in the design, because it is seldom that patients have multiple identical operations, or ones so similar that one can be considered a control on the other in the same patient. However, attempts along these lines can be made in such types of operations as bilateral hernioplasties, tonsillectomies and in oral surgery. The more closely a complete balance in the design is attained, the greater will be the reliability of any conclusions that may be drawn and the smaller the number of patients required. In the experimental laboratory this balance is not so difficult, since there the animals and the experimental procedures are under more complete control.

INFLUENCE OF AGE

In carrying out studies on local anesthetic procedures one of the variables constantly present is differences in the ages of the patients. It is a matter of considerable importance in trying to evaluate data either to assure oneself that the age distribution is identical in the experimental and control groups or else to determine that the age distribution does not modify the responses being studied. We have recently had the opportunity to analyze the results of a "blind-test" study of the effects of 13 local anesthetic solutions used for oral surgical procedures in about 4,000 patients. These solutions were either well known preparations or proposed modifications of current formulae. These data are being presented elsewhere from the standpoint of the effects of the various solutions, so that this phase of that study need not be discussed here (4). The data, however, offered the opportunity of segregating the patients according to various other physiological criteria to determine whether any of these could be used to predict the type of response to be anticipated from the anesthetic. The patients were totally unselected and, therefore, accurately represented a cross section of patients requiring surgical procedures on the mouth, face and jaws.

When these data were classified according to age, there were 3,735 patients in whom age data were available, of whom 46 per cent were males. The volumes of solution used in the various age groups were substantially the same, within the limits of error of estimation, or the differences were so small as to have no biological significance, as was true also of the average times of onset of anesthesia. Various disease conditions were present in a portion of these patients, and the categories of cardiovascular and kidney disease increased progressively with age, as would be anticipated. The age group of 1 to 9 years included only 14 individuals who, having mainly deciduous teeth, were not comparable to the rest of the series.

TABLE 3

INFLUENCE OF AGE ON RESPONSE TO LOCAL ANESTHETIC PROCEDURE

Age	No. of Cases	Average Duration Minutes	Grade of Anesthesia	Patient Reaction Per Cent		Amount Excessive Bleeding During Operation Per Cent	Blood Pressure Mm.		Pulse Rate per minute	
			Some Pain Per Cent	Calm and Cooperative	Very Difficult		Before Injection	After Injection	Before Injection	After Injection
1– 9	14	142.8±41.48	21.4±10.96	33.3±13.60	25.0±12.50	25.0±21.65	101.0±8.34 / 53.8±2.18	102.0±2.78 / 52.5±2.47	101.8±6.27	98.8±7.06
10–19	472	148.6± 6.47	7.9± 1.21	33.9± 2.23	15.3± 1.71	7.4± 1.77	112.1±0.76 / 61.5±0.95	114.7±0.94 / 64.2±0.72	95.3±0.92	97.6±1.00
20–29	407	163.6± 9.66	6.6± 1.23	36.9± 2.48	14.6± 1.81	6.4± 1.46	115.2±0.74 / 69.9±0.62	119.8±0.88 / 69.4±0.70	92.9±0.78	95.0±0.89
30–39	660	161.5± 8.66	8.9± 1.09	37.6± 1.88	13.4± 1.34	13.1± 1.47	121.8±0.79 / 74.1±0.59	120.2±0.88 / 75.9±0.61	94.0±0.41	96.3±0.71
40–49	972	156.9±16.32	5.6± 0.74	47.9± 1.67	12.2± 1.09	16.9± 1.25	131.3±0.81 / 79.1±0.97	139.7±0.93 / 80.6±0.51	92.0±0.45	94.9±0.53
50–59	816	182.7±15.47	6.5± 0.87	54.3± 1.76	10.4± 1.08	20.2± 1.42	143.2±1.02 / 82.1±0.55	151.7±1.08 / 83.4±0.52	91.8±0.51	94.7±0.58
60–69	338	172.8±38.44	5.2± 1.19	64.3± 2.68	8.0± 1.52	23.2± 2.35	151.8±1.19 / 82.2±0.99	160.8±1.88 / 83.9±0.99	87.6±2.47	91.0±0.93
70–89	56	—	1.8± 1.82	69.8± 6.31	3.8± 2.63	16.1± 4.91	156.4±4.52 / 80.4±2.14	166.7±4.62 / 84.6±2.84	83.9±2.03	88.2±2.33
Combined Results	3735	158.3± 8.37	6.8± 0.41	46.3± 0.85	12.2± 0.56	16.1± 0.67	131.2±0.45 / 76.5±0.29	138.8±0.50 / 78.0±0.28	92.2±0.25	94.9±0.29

In table 3 we have summarized the significant findings concerning which some comment may be made. Inspection of this table will reveal that the degree of anesthesia produced throughout the various age groups was similar within the limits of indicated variation. The possible exception to this was in the highest age group, of those above 70 years, in whom 96 per cent of the operations were completely painless after only a single injection. Because of the special nature of any operative procedures which might be carried out in this group, who were to a very considerable extent edentulous, it does not seem likely that this represents any true deviation in sensitivity to the anesthetics. The duration of anesthesia averaged one hundred fifty-eight minutes for the entire series. It can be seen that there is an apparent tendency for short anesthesia in the low age groups and long duration in the older individuals. Because of the high variability between individuals, these differences are not established to as high a degree of reliability as could be desired, but there are indications that longer anesthesia is apt to be associated with increased age.

Another feature of the response in which age might enter is in the emotional reaction to the operation. Inspection of the table shows that only about one-third of the youngest patients were calm and cooperative during the operation, as compared to more than two-thirds who caused no such difficulty in the oldest age group. Patients who were very difficult to handle were encountered only one-third as frequently in the older patients as in the very young ones. These differences were progressive with age and reflect the better emotional poise and self-control which is developed with advancing years. This is an item of some importance to a surgeon, since it indicates the frequency with which difficulties should be anticipated in maintaining the patient's cooperation during the operations.

The amount of bleeding observed in these patients was recorded both during the operation and postoperatively, according to the categories of none, slight, moderate, and excessive. For the sake of brevity, only excessive bleeders during the operation have been tabulated in table 3. Excluding the 1 to 9 year group, it can be seen that excessive bleeding progressively increased with age until finally in the 60 to 69 year group there was difficulty in about one-fourth the patients from this source as compared to only 7 per cent of the young group. Inspection of the blood pressure measurements on these individuals reveals that the systolic and diastolic pressures recorded before injection increased with age, as has been frequently demonstrated in other types of observations previously. Therefore, it may be that the increased susceptibility to hemorrhage in the older group was associated with the higher levels of arterial pressure. It will be noted that the changes in systolic blood pressure during the anesthetic procedure were greater in the older individuals than in the young groups, but that no such difference was observed in diastolic pressure. The differences here are fairly small, but again they seem to be progressive with age in a way which could scarcely be ascribed to chance variation. Conversely the normal pulse rate decreased progressively with age, but the change in the pulse rate due to the injection was the same for all age groups.

It would seem that from the standpoint of age, the most significant feature is that it exerts considerable influence upon the degree of co-operation to be secured from the patient, and on the amount of bleeding to be anticipated. The other effects are so small as to be of no practical importance.

EFFECTS OF DISEASE STATES ON RESPONSE

Another problem on which information can be obtained from these data is whether patients with existing disease states represented bad operative risks. The patients were classified by the examining doctors or nurse as being either normal or having (1) cardiovascular disease, (2) kidney disease, (3) pulmonary disease, (4) diabetes, (5) neuro-muscular disease, (6) pregnancy, or (7) other disease states not included in the above. In table 4 are summarized the positive correlations found between the various disease states and the responses being recorded. The obvious correlations such as sex and age to pregnancy, etc., have not been included in this table, as a means of conserving space.

The completeness of anesthesia was substantially the same in all the groups of patients, indicating that none of the disease states encountered here predisposed the patient to a poor response to the anesthetic agent in terms of degree of anesthesia produced. The onset and duration of anesthesia were the same for all groups. Those individuals with neuromuscular disease proved to be most uncooperative, whereas pregnancy was associated with unusually good cooperation. The other disease states did not seem to modify in any significant way the degree of cooperation to be secured from the patient.

Excessive bleeding during the operation was seen particularly in the cardiovascular and neuromuscular disease groups and was significantly diminished in the pregnancy and pulmonary disease classifications. Since the cardiovascular group contained many hypertensives, the increased bleeding here may well be explained on that basis. There is no ready explanation, however, for the increased incidence of excessive bleeding in the patients suffering from nervous disorders.

The systolic and diastolic blood pressures were high in the cardiovascular group and were moderately raised in the renal and diabetic classifications. Pregnancy seemed to be associated with a low blood pressure, both systolic and diastolic, of considerable magnitude possibly due to youth. However, inspection of the average blood pressure levels after the injection of the anesthetic reveals that all of these various groups responded with an increase in blood pressure, both systolic and diastolic, of about the same magnitudes, the exception being pregnancy, where there were few patients recorded, and where the changes were

TABLE 4

INFLUENCE OF EXISTING DISEASE STATES ON RESPONSE TO LOCAL ANESTHETIC PROCEDURE

History	No. of Cases	Some Pain During Operation Per Cent	Patient Reaction Per Cent		Excessive Bleeding During Operation Per Cent	Blood Pressure Mm.		Pulse Rate per minute	
			Calm and Cooperative	Very Difficult		Before Injection	After Injection	Before Injection	After Injection
Negative or Normal	2082	6.8±0.50	47.4± 1.00	11.3±0.63	15.9±0.82	127.4±0.48 / 75.4±0.29	134.6±0.56 / 76.2±0.31	91.8±0.30	94.3±0.34
Heart or Circulatory Disease	485	7.6±1.19	42.2± 2.33	16.4±1.74	19.0±1.86	154.2±1.78 / 87.6±0.99	162.2±1.86 / 88.5±1.44	93.6±0.70	97.1±0.80
Kidney Disease	122	4.7±1.90	42.4± 4.51	16.1±3.38	16.0±3.57	140.9±3.29 / 81.6±1.69	151.2±3.58 / 83.6±1.51	91.3±1.43	94.1±1.61
Pulmonary Disease	57	3.5±2.44	42.0± 6.74	14.8±4.84	10.7±4.14	129.6±4.00 / 73.4±2.13	130.5±4.45 / 77.2±2.34	97.1±2.13	102.5±2.51
Diabetes	59	3.3±2.31	44.4± 6.78	13.0±4.59	13.2±4.66	143.0±3.27 / 81.8±1.49	152.7±3.29 / 82.2±1.87	94.9±2.12	95.9±2.19
Nerve Disease	132	8.0±2.35	31.7± 4.20	22.8±3.76	19.7±3.63	132.8±2.87 / 78.1±1.22	144.3±2.32 / 79.9±1.27	92.4±1.29	96.4±0.87
Pregnancy	15	0.0	33.3±12.17	6.7±6.45	8.3±7.06	113.3±4.49 / 67.7±4.30	116.4±5.03 / 67.1±3.91	102.1±3.45	105.3±4.89
Other	249	6.3±1.54	46.5± 3.29	17.0±2.07	11.4±2.14	133.1±2.06 / 77.0±1.06	141.5±2.25 / 78.7±1.06	92.8±0.96	96.2±1.14
Combined Results	3801	6.7±0.40	45.8± 0.83	12.9±0.57	16.0±0.66	132.3±0.49 / 77.5±0.28	140.0±0.54 / 78.5±0.32	92.3±0.25	95.1±0.28

minimal. Therefore, there is no reason for the surgeon to fear that the presence of these disease states might be associated with a tendency for undue cardiovascular responses, at least insofar as the present type of injections are concerned.

INFLUENCE OF SYSTOLIC BLOOD PRESSURE

Another criterion which might be applied to a patient is that of blood pressure, since it is possible that an unusual level of systolic or diastolic blood pressures may be associated with aberrant responses to the anesthetic. In table 5 are summarized the data according to systolic blood pressure groupings.

It was found that there was no correlation between the systolic pressure and the volume of solution required, the degree of anesthesia produced or its time of onset. As was to be expected, the average ages of the patients were greater in the groups with higher average levels of systolic pressure. The duration of anesthesia as recorded was rather variable because of the difficulty of keeping the patients under continuous observation until complete return of sensation had occurred. However, the data seem to suggest that the duration diminished in the groups of higher systolic pressure, indicating perhaps some difference here from normal individuals.

Patients who were difficult to handle apparently were more numerous in the elevated systolic pressure groups than in the normal individuals. It may very well be that we have a causal relationship here, since the emotional condition which would produce poor cooperation with the surgeon might well increase systolic blood pressure at the same time. It would appear there were increased possibilities that persons with high blood pressure levels would prove more difficult to handle than the patients in the normal pressure range. Excessive bleeding also was considerably more frequent as the systolic blood pressure level rose. In the individuals with the lowest pressures only 6.3 per cent were recorded as giving excessive bleedings, whereas in the highest pressure group there were 40 per cent of such cases reported. Obviously, there would appear to be a direct relationship between the systolic blood pressure level and the amount of difficulty to be anticipated in controlling the bleeding during the operation.

A question which is of immediate interest to a surgeon is whether a high blood pressure level indicates that he is going to have a greater than normal pressor response to the anesthetic to contend with. There is a certain fear that undue cardiovascular responses should be expected from persons with high blood pressure. However, inspection of the data in table 5 shows that after the injections the increases in both systolic and diastolic blood pressures were no greater in the hypertensive group of patients than in the normal individuals. In other words, the circulation of a hypertensive individual does not tend to give an exaggerated response to a pressor substance or stimulus. This fact is of

TABLE 5

INFLUENCE OF SYSTOLIC BLOOD PRESSURE ON RESPONSE TO LOCAL ANESTHETIC PROCEDURE

Systolic Pressure Mm.	No. of Cases	Average Age	Average Duration Minutes	Patient Reaction Per Cent	Excessive Bleeding During Operation Per Cent	Blood Pressure Mm.		Pulse Rate per minute	
				Very Difficult		Diastolic Before Injection	Systolic-Diastolic After Injection	Before Injection	After Injection
70- 99	95	30.3±1.74	158.7±15.81	16.3±3.85	6.3±3.04	59.5±0.82	102.6±2.02 / 62.1±1.22	88.8±1.40	87.8±1.78
100-109	350	33.9±0.73	168.8±12.88	10.1±1.65	9.3±1.73	65.8±0.51	113.6±1.10 / 68.3±0.59	88.4±0.73	90.4±0.81
110-119	550	35.5±0.61	182.0±11.21	14.1±1.52	12.4±1.55	72.2±0.40	122.7±0.54 / 73.8±0.48	89.5±0.59	92.0±0.69
120-129	676	39.3±0.53	144.7±11.88	10.7±1.21	14.9±1.44	76.3±0.36	130.8±0.53 / 77.2±0.44	92.0±0.53	94.6±0.63
130-139	522	44.0±0.60	187.1±20.96	12.1±1.43	17.1±1.71	80.1±0.45	139.3±0.65 / 79.7±0.52	92.8±0.63	95.5±0.69
140-149	420	48.0±0.60	211.7±25.68	10.0±1.50	16.1±1.84	83.9±0.50	149.8±0.73 / 85.3±0.60	93.5±0.73	96.8±0.83
150-159	253	50.6±0.73	141.0±33.70	19.8±2.58	18.3±2.45	87.9±0.67	160.0±1.09 / 88.4±0.79	96.2±1.08	100.2±1.17

TABLE 5—*Continued*

Systolic Pressure Mm.	No. of Cases	Average Age	Average Duration Minutes	Patient Reaction Per Cent	Excessive Bleeding During Operation Per Cent	Blood Pressure Mm.		Pulse Rate per minute	
				Very Difficult		Diastolic Before Injection	Systolic-Diastolic After Injection	Before Injection	After Injection
160–169	184	53.0±0.71	139.0±41.63	10.0±2.24	21.9±3.10	89.3±0.79	170.8±1.11 / 89.9±0.87	93.0±1.17	96.7±1.27
170–179	90	54.9±1.05	120.0± 0.00	19.1±4.14	23.3±4.46	94.0±1.41	179.6±1.70 / 96.0±1.26	95.8±1.81	99.5±1.87
180–189	92	54.8±0.99	—	18.4±4.16	28.9±4.78	99.7±1.45	192.8±1.70 / 103.9±1.82	93.8±1.51	95.9±1.67
190–209	87	56.5±1.04	119.3±44.56	17.7±4.29	22.6±4.56	102.8±3.10	204.8±2.27 / 106.6±1.62	96.8±1.56	99.0±1.88
210–229	52	56.0±1.49	—	15.7±5.10	17.7±5.34	114.7±2.43	221.2±3.03 / 109.0±3.82	94.2±2.28	98.7±2.66
Over 229	30	57.9±1.48	—	17.9±7.24	40.0±8.94	128.8±4.74	239.3±4.57 / 110.2±2.98	98.3±3.01	103.9±3.71
Combined Results	3401	42.9±0.26	170.8± 5.40	12.0±0.59	16.2±0.73	80.0±0.27	142.2±0.51 / 81.1±0.28	92.2±0.25	94.9±0.20

some interest, not only in understanding local anesthetic procedures, but also in the consideration of the basic causes of clinical hypertension. The pulse rates tended to be faster in patients with elevated systolic pressures than in normal. Again, however, there was no evidence, as is shown in the table, that any groups of these patients had greater pulse changes than those at other systolic pressure levels.

INFLUENCE OF DIASTOLIC BLOOD PRESSURE

The diastolic blood pressure groupings are summarized in table 6. Omitted from this table as from the others are the tabulations of volumes of solutions, completeness of anesthesia, onset times and other observations made in which there were no significant findings as related to the criterion under examination.

As was to be anticipated, the average age was higher in those individuals of the greater diastolic pressures. The duration of anesthesia seemed to be greatest in those having normal diastolic pressures and to be possibly slightly shorter in those of either unusually low or unusually high diastolic readings. However, because the number of patients on whom adequate data were available is not as large for this part of the observations as could be desired, the standard error figures recorded are so high as to make conclusions hazardous. Excessive bleeding was infrequent in those with low diastolic pressures, and seemed to increase as the pressure rose. This parallels the effects of systolic pressure, so that it cannot be determined whether either or both of these were the causative factor leading to excessive bleeding, or whether they were all dependent on some underlying cause. Those individuals with high diastolic pressures also had high systolic pressures, as was to be expected. However, the data in the table show that high levels of diastolic pressure before the operation were apparently not associated with any unusual increases in systolic pressure during the operation. As a matter of fact, there is an indication that at the higher levels of diastolic pressure there was a tendency for the diastolic readings to be diminished slightly after the anesthetic injection rather than to be raised, as was the case at sub-normal diastolic levels. There were associated with increased diastolic pressures before the injections were made, increased pulse rates. However, the pulse rate changes are so small that from the data it cannot be concluded that any unusual pulse rate change was associated with any pre-existing level of diastolic pressure.

INFLUENCE OF PULSE RATE

The pulse rate is another measure of the cardiovascular condition which can be readily observed before the operation and which might, therefore, be of interest as a means of predicting the type of response to be secured. It was found, however, that the volumes of solution required, the degree, onset and duration of anesthesia were not correlated with the initial pulse rates. However, a striking relationship was found

INFLUENCE OF DIASTOLIC BLOOD PRESSURE ON RESPONSE TO LOCAL ANESTHETIC PROCEDURE

Diastolic Pressure Mm.	No. of Cases	Average Age	Average Duration Minutes	Excessive Bleeding During Operation Per Cent	Blood Pressure—Mm.		Pulse Rate per minute	
					Systolic Before Injection	Systolic-Diastolic After Injection	Before Injection	After Injection
20– 49	31	29.8±5.92	149.0±21.78	8.0±5.47	108.2±2.83	119.8±2.73 / 61.6±2.50	89.0±2.83	92.4±6.85
50– 59	179	31.2±1.26	150.9±16.38	7.2±2.18	108.9±0.99	117.7±2.13 / 59.7±1.64	89.6±1.03	91.8±1.18
60– 69	496	36.5±0.71	170.3±12.27	10.5±1.49	116.3±0.69	123.7±0.91 / 68.7±0.46	90.1±0.65	90.7±0.71
70– 79	895	41.8±0.50	158.6±11.61	14.8±1.26	125.1±0.54	132.4±0.68 / 75.7±0.33	90.4±0.47	93.0±0.54
80– 89	935	44.1±0.45	190.5±11.84	17.2±1.29	135.0±0.60	142.1±0.74 / 82.0±0.34	93.4±0.49	96.4±0.55
90– 99	516	47.8±0.56	195.3±19.65	20.3±1.81	148.2±0.96	155.6±1.11 / 90.4±0.52	93.8±0.66	96.8±0.76
100–109	197	50.4±0.71	167.1±31.60	18.3±2.81	166.0±1.84	175.8±2.04 / 100.8±0.82	95.7±1.05	100.4±1.21
110–119	75	53.1±1.18	115.3±32.52	31.5±5.45	185.1±3.05	192.7±3.63 / 109.9±1.27	93.6±1.89	98.8±2.29
120–129	47	54.6±1.42	—	19.6±5.87	203.3±3.83	210.9±4.50 / 117.8±1.92	97.1±2.21	100.1±2.42
Over 120	30	51.7±2.05	—	27.6±8.30	217.8±4.77	225.2±4.89 / 131.8±2.41	98.3±2.45	104.8±3.38
Combined Results	3401	42.9±0.26	170.9± 5.87	16.2±0.68	134.5±0.46	142.1±0.52 / 80.9±0.29	92.2±0.25	94.8±0.30

TABLE 7

INFLUENCE OF PULSE RATE ON RESPONSE TO LOCAL ANESTHETIC PROCEDURE

Pulse Rate	No. of Cases	Patient Reaction—Per Cent		Excessive Bleeding During Operation Per Cent	Blood Pressure—Mm.		Pulse Rate per minute
		Calm and Cooperative	Very Difficult		Before Injection	After Injection	After Injection
Under 60	7	66.7±19.24	16.7±15.23	28.6±17.08	153.7±21.88 / 76.6± 8.27	167.1±20.28 / 81.1± 7.17	66.0±5.07
60- 64	49	68.1± 6.83	10.6± 4.51	14.3± 5.41	134.6± 1.30 / 78.8± 2.30	142.4± 4.63 / 80.7± 2.47	72.6±1.58
65- 69	98	67.7± 4.85	6.5± 2.52	15.4± 4.11	126.9± 2.04 / 73.8± 1.45	134.2± 2.35 / 76.6± 1.36	72.6±0.88
70- 74	168	65.0± 3.81	6.4± 1.95	12.1± 2.76	127.5± 1.86 / 76.6± 1.09	134.9± 1.83 / 78.4± 1.09	77.7±0.73
75- 79	185	67.6± 3.56	6.9± 1.93	18.0± 3.04	130.5± 1.81 / 77.6± 0.93	137.8± 2.13 / 77.9± 1.11	81.6±0.82
80- 84	732	58.5± 1.86	7.9± 1.02	15.6± 1.41	132.2± 0.97 / 78.7± 0.57	139.3± 1.06 / 79.9± 0.58	86.6±0.38
85- 89	388	57.2± 2.61	11.6± 1.69	16.8± 1.99	130.4± 1.31 / 78.7± 0.77	138.6± 1.47 / 80.9± 0.79	91.0±0.53
90- 94	350	46.6± 2.70	7.9± 1.46	14.4± 1.96	133.9± 1.52 / 80.2± 0.87	142.0± 1.55 / 80.9± 0.91	94.8±0.59
95- 99	307	43.2± 2.92	12.7± 1.95	16.4± 2.24	139.4± 1.70 / 82.6± 0.85	148.3± 2.01 / 84.0± 0.97	98.1±0.62
100-104	574	32.5± 2.00	13.0± 1.43	16.9± 1.63	136.6± 1.13 / 81.6± 0.67	143.5± 1.23 / 82.0± 0.68	102.6±0.55

TABLE 7—Continued

Pulse Rate	No. of Cases	Patient Reaction—Per Cent		Excessive Bleeding During Operation Per Cent	Blood Pressure—Mm.		Pulse Rate per minute
		Calm and Cooperative	Very Difficult		Before Injection	After Injection	After Injection
105-109	144	26.1± 3.81	20.9± 3.54	17.6± 3.33	138.9± 2.24 / 81.7± 1.43	146.5± 2.41 / 82.8± 1.50	108.4±1.02
110-114	124	14.5± 3.27	22.2± 3.84	23.7± 3.90	142.0± 2.46 / 85.5± 1.41	149.0± 2.77 / 86.9± 2.01	111.9±1.21
115-119	61	29.5± 5.79	19.7± 5.09	8.8± 3.77	140.0± 3.50 / 79.7± 1.68	144.7± 4.03 / 78.0± 1.93	113.3±1.76
120-124	125	13.8± 3.11	26.0± 3.95	12.9± 3.12	139.2± 2.76 / 81.7± 1.47	146.4± 2.98 / 82.5± 1.50	119.3±1.14
125-129	21	0.0	71.4± 9.86	15.0± 7.98	144.2± 4.98 / 85.3± 2.87	155.5± 5.70 / 87.4± 2.52	124.9±3.02
130-134	24	17.4± 7.90	43.5±10.34	28.6± 9.86	158.5± 7.35 / 87.0± 3.94	165.7± 8.17 / 85.5± 3.87	131.3±2.57
135-139	10	0.0	60.0±15.49	40.0±15.49	136.2± 5.68 / 81.6± 5.62	140.8± 7.06 / 79.6± 5.98	123.8±6.06
140-144	18	0.0	72.2±10.56	5.6± 5.42	146.6± 7.23 / 85.7± 3.04	155.8± 7.33 / 86.3± 3.95	139.3±3.51
Over 144	6	0.0	83.3±15.23	16.7±15.23	139.3±11.87 / 78.3± 4.77	154.7± 9.47 / 75.0± 6.69	138.7±6.34
Combined Results	3391	46.0± 0.81	12.8± 0.60	16.3± 0.68	134.6± 0.47 / 80.1± 0.51	142.1± 0.52 / 81.1± 0.28	94.9±0.29

between the initial pulse rate and degree of cooperation of the patient (table 7). Those individuals with slow pulse rates were in general highly cooperative and gave little difficulty during the operation. However, those with excessively fast pulses gave increased incidences of difficult handling, which were of such high frequency, as a matter of fact, that the observation of a fast pulse in a patient before operation should lead the surgeon to take special precautions to maintain calm and to avoid exciting the individual in question.

Excessive bleeding was not associated with any particular level of pulse rate, so that in this there is a difference from the other two cardiovascular measurements of systolic and diastolic pressures. Inspection of the table shows that patients with high pulse rates had no higher initial pressures, either systolic or diastolic, than the normal individuals, nor did they show any unusual pressor responses. Under these conditions it is seen that the pulse rate could not serve to predict those individuals who would have an unusual rise of blood pressure from the injection of the anesthetic. The pulse rate tended to increase after the injection in those individuals who had low initial pulses and to decrease slightly in those whose pulse was very high at first. Inasmuch as the tendency is for the pulse to return to the normal, when it is either unduly high or low, it is apparent that the changes in direction of response observed here are those which would be anticipated quite independently of any anesthetic procedure.

SUMMARY AND CONCLUSIONS

There have been summarized in this presentation some of the more important variables which should be considered in undertaking a study of local anesthetic procedures, or in evaluating the probability of securing under any given set of circumstances an abnormal or atypical response. It is obvious that in setting up such a study those extraneous factors which have here been demonstrated to play a role should be so distributed that they do not distort the average results and lead to fallacious conclusions.

There is a crying need for extensive quantitative critical and objective studies of the effects of local anesthetics in human subjects. It is only by consideration of the contributory factors discussed here that such studies may achieve a degree of reliability which will afford a safe basis for therapeutic innovations. It should be pointed out that without such human studies proposed changes in local anesthesia are apt to be of uncertain value. Animal studies can be done with a degree of control and with a multiplication of experimental subjects which permits almost any desired degree of accuracy. However, these animal tests are often of limited usefulness in deciding whether one local anesthetic is superior to another in practice because of the small differences involved. In attempting to carry over the results of the animal experiments to the human organism, the unjustified assumption has to be made that the human responds quantitatively the same as the animals. This is true usually for the quality of response, but is much less apt to be so for the degree of the response. Therefore, since we are now searching for, and are willing to utilize, even minor degrees of improvment in local anesthetic materials, it is obvious that only human tests can prove conclusively the existence of these alleged improvements for patients. Because clinical investigations of the magnitude required are so difficult to conduct, it is doubly important that they be planned so as to yield the maximum information by fully taking into account all the vital contributory factors enumerated herein.

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examinations in the past in *Physics and Chemistry:*

1. What effect on narcotic potency occurs when halogens are added to a narcotic drug? What effect on narcotic potency occurs when more hydroxyl radicals are added to hydrocarbons?
2. What principle in physics is involved that makes respiration more satisfactory during an attack of bronchial asthma if a mixture of helium 80 per cent and oxygen 20 per cent is inhaled by the patient than if air is inhaled?
3. What are some of the dangerous impurities or degeneration products (if any) which might be found in cyclopropane, (old) ether, chloroform, paraldehyde, ethylene, ethyl chloride? What might be their effects if administered to a patient?