Generalization from Pain of Various Types and Diverse Origins

Abstract. Pain that arises from very different pathological origins responds in a quantitative fashion to a given dose of a given narcotic, but this is not true when the pain has been contrived by experimental means, in man, with customary techniques.

Among the problems in the study of pain is the question of whether observations made on one kind of pain from one source are comparable to observations made on another kind of pain from another source. There are two great sources of pain, experimental and pathological. If generalization is possible, one should be able to show that study of pain of various types from widely differing origins leads to the same results. An admirable opportunity to make such an examination is presented in the work of two groups of investigators—the Harvard group who for years have studied the acute pain arising from surgical wounds and the Sloan-Kettering group who have studied, also for years, the chronic pain of malignant disease. It is possible to find a significant common factor for study in the two groups: it is the relationship between a given dose of morphine or other analgesic agent and the pain relief produced by it, expressed in quantitative terms.

Specific data from the two groups are given in Table 1.

If this level of excellent agreement had occurred once only, one might have supposed that this was merely happy coincidence, even though extraordinary. The fact is, such agreements between these two laboratories (and among others as well) have, over the years, been common, notwithstanding the fact that the two groups have studied pain of very different origins. A recent example of agreement, arrived at through a somewhat different approach from that described above, is the following, a comparison of the work of Seed, Wallenstein, Houde, and Bellville (*1*), on dihydrocodeine with the work of Gravenstein, Smith, Sphire, Isaacs, and Beecher (*2*).

Seed *et al.* took the difference between the pain relief effected by each dose of dihydrocodeine and that effected by the standard 10-mg dose of morphine as a measure of analgesic effect. Thus, one can calculate a straight-line log dose-effect curve, using the method of least squares. They did this, with suitable weighing of the effect at each dose in accordance with the number of patients involved, and the following equation was obtained

$$Y = 50.32 \log X - 89.32$$

where Y is percentage difference between the effects of the given doses and X is the dose of dihydrocodeine in milligrams. When Y is zero, X is 59.6 mg. Since the Harvard group's maximum dose was 45 mg this calculation represents an extension of their data.

The Sloan-Kettering group approached the problem in a second way. This time they studied the effects of the different doses of morphine versus the effect of the standard 10-mg dose of morphine in the data of Keats, Beecher, and Mosteller (*3*) and derived the following equation,

$$Y = 57.55 \log X - 58.99$$

Using this equation and the similar one for dihydrocodeine, they calculated equivalent analgesic doses. They found 18.76 percent less pain relief for 5 mg of morphine than for 10 mg. From the equation for dihydrocodeine it was calculated that 25.2 mg of dihydrocodeine would produce the same degree of analgesia as 5 mg of morphine, and for 10 mg of morphine the equivalent dose of dihydrocodeine would be 50.4 mg. The Harvard group's finding that 59.6 to 50.4 mg of dihydrocodeine (the value depends on the method of calculation employed) produces the same degree of analgesia as 10 mg of morphine is in remarkable agreement with the value of 53 mg obtained by the Sloan-Kettering group when they studied peak effects during the first or second hour, as the Harvard group had done.

But in the case of experimental pain the situation is different. The current lack of such reproducibility of result in experimentally produced pain in man (animals are another matter) is striking. Some 15 groups of investigators (see *4*) have failed to demonstrate that the experimental pain threshold in man varies dependably with even large doses of morphine or other analgesic agents, whereas small doses of morphine will relieve the pain of a great wound or extensive disease.

Clearly, there is an important difference between the two types of pain, experimental and pathological, in terms of response to analgesia. There is some evidence at hand about what this difference is: true anxiety or fear appears to be missing in experimental pain. When anxiety or fear has been injected into the experimental pain situation, evidence has been obtained that experimental pain then responds to morphine as pathological pain does [see Malmo and Shagass (*5*) and Hill *et al.* (*6*)].

Other factors may be found to account for the difficulties encountered in the use of experimental pain in man to appraise analgesic agents (experimental pain is very useful in studies with animals). In our own unpublished work with experimental pain produced by tourniquet, where pain intensity grows slowly (as contrasted with the sudden stab of pain produced by most experimental methods), we have found promising leads to suggest that experimental pain slowly produced *may* be useful in appraising analgesic agents. (There may of course be an anxiety factor here; the matter needs further study.) Houde (*7*) has suggested that in most studies of experimental pain possibly too much reliance has been placed on mechanical contrivances, gages, and so on, and that perhaps it would be better to rely more completely on patients' statements. This is, of course, what is done in appraising pathological pain.

One must conclude that there is a difference between the two types of pain in man, as generally produced to date. Whether this difference is qualitative or quantitative (one suspects that it is the latter) is beside the immediate point. There is reason to believe that pain of both experimental and pathological origin consists of two components—(i) the original sensation and (ii) the psychic reaction or processing component—and that the second is dominant in pathological pain, whereas the first is dominant in experimental pain.

There is such uniformity of response to analgesic agents of pathological pains of widely differing origin in man that one can utilize this response to quantify analgesic agents, as Keats, Beecher, and Mosteller (*3*) showed in comparing one series of "unknown" morphine solutions with another series of unknown morphine solutions. While this demonstration in one laboratory is of interest, interest is greatly broadened by the demonstration, discussed here, of quantitative reproducibility in two laboratories dealing with pathological pain of very different origins.

These findings lead to the following conclusions. (i) Pain arising from widely different pathological sources responds in a remarkably precise, quantitative fashion to a given dose of a given narcotic. (ii) No such demonstration has yet been made in man for experimental pain as commonly produced; why this is so requires further study. (iii) Cautious

Table 1. Pain relief effected in man by parenteral injection of 10 mg of morphine and by a placebo. The studies of Lasagna and Beecher (*8*) were of postoperative wound pain; the study of Houde and Wallenstein (*9*) was of chronic pain from cancer.

Study	No. of patients	Percent relieved by	
		Morphine	Placebo
Lasagna and Beecher			
1952	66	65.8	39.0*
1953	56	69.3	
Houde and Wallenstein			
1952–53	57	65.0	42.0

* Averaged placebo data from Lasagna, Mosteller, von Felsinger, and Beecher (*10*).

generalization concerning pathological pain from study of specific pathological pain is permissible. (iv) No such generalization from experimental pain in man to pathological pain in man is as yet permissible. There is some acceptable evidence that the response is comparable when a powerful anxiety component has been introduced into the experimental pain situation. How broad the limits of usefulness of this finding may be is yet to be shown. Other, as yet unknown, factors may be pertinent.

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Maximal Photosynthetic Rates in Nature

Abstract. It seems likely that turbulence under natural conditions, both aquatic and terrestrial, is higher than it is in the bottles or leaf chambers used when photosynthesis is measured experimentally. Most of the maximal photosynthetic rates reported in the literature are probably lower than those which occur in nature.

Most previous estimates of photosynthetic yield in aquatic habitats have been based on experiments involving enclosure of phytoplankton communities in clear and dark bottles and exposure of these communities to light of various intensities by suspension at different depths in a lake. The data so obtained are considered representative of the photosynthetic activity of the phytoplankton under natural conditions, and these data are inserted in equations containing factors for light penetration, day length, and phytoplankton abundance (*1*) to provide estimates of yield per unit of water surface. The average hourly yield obtained when the exposure period was long (8 hours or more) was lower than that obtained in exposures of a few hours' duration (*2*), and yields obtained when bottles were agitated exceeded those in quiet bottles (*3*). Doty (*3*) considered the quiet bottle a closer approach to natural conditions than the agitated bottles, and most of the studies in the literature are based on data from quiet bottles. It seems likely, however, that confinement of a phytoplankton community in bottles represents a significant departure from the natural condition and may have a considerable influence on photosynthetic rate. During the summer of 1958, a study (*4*) was carried on in western Lake Erie in which photosynthesis was measured under completely natural conditions and the observed rates were compared with data from parallel experiments in which clear and dark bottles were utilized.

The clear- and dark-bottle experiments were conducted as described in previous papers (*1, 2*). Phytoplankton communities at natural densities were confined in clear and dark bottles, suspended at various depths (0 to 3 m) at 0.5-m intervals, and exposed for 3 hours. The difference in *p*H (*4*) in the clear and dark bottles was used to determine CO_2 absorption by reference to a differential titration curve for the natural water (*2*).

The measurements made under completely natural conditions were made by sampling at approximately 4-hour intervals. Samples were taken from five depths (0.1, 1, 3, 5, and 8 m) at a station in the channel between South Bass and Middle Bass islands where the water was 9 m deep. The samples were returned to the laboratory for *p*H determination, and the change in *p*H during a given time interval was used to compute the change in CO_2 concentration. Table 1 shows an example of the data obtained and of computed values for the CO_2 change for the water column.

In this study no corrections were applied for CO_2 exchange between air and water. The surface water usually was slightly supersaturated in the morning and undersaturated in the afternoon. Bohr (*6*) has shown that when water is stirred vigorously the rate constant for CO_2 transport across the gas-liquid boundary layers is about 2×10^{-3} cm/sec. Thus, the maximal rate of CO_2 entry would be of the order of 9 mmole/m² per 12 hours (*7*) if free CO_2 concentration in water were zero. But the actual free CO_2 concentration is not zero, and the water is not stirred so vigorously as in Bohr's experiments. The CO_2 equilibrium between air and water was usually reached during the morning hours (the average time of this occurrence was 0800), so the net diurnal CO_2 exchange must have been in the direction of CO_2 absorption from the atmosphere, and neglecting this process makes our estimates of photosynthesis too low. It seems likely that the error is less than 2 percent.

The computations in Table 2 also assume that the *p*H changes due to the influx of different water between sampling times will not introduce a systematic error. Random errors will, of course, be introduced by this factor, so the rate computed from a single day's work may be too large or too small, depending on whether the change of water masses increased or decreased the *p*H value. In the average from several days' work, however, such random errors will cancel out. Values for individual days ranged from 0 to 620 mmole/m² day.

Students of photosynthesis have usually considered two quantities, (i) total or gross photosynthesis and (ii) apparent photosynthesis (that is, photosynthesis in excess of the respiratory processes of the plants which carry on the photosynthetic activity). When one is measuring CO_2 change in a natural aquatic environment, a third quantity must be considered—namely, net photosynthesis (that is, photosynthesis in excess of the respiratory contributions of the entire aquatic community). Computations like those in Table 1 represent diurnal net photosynthesis. Because the nocturnal CO_2 production is practically equal to the diurnal CO_2 uptake (the *p*H value at 0630, for example, shows no consistent trend from day to day), we can obtain an approximate estimate of the gross

Table 1. Carbon dioxide change as computed from *p*H change under completely natural conditions.

Depth (m)	*p*H		ΔCO_2 (mmole/m³)	Cubic meters* represented in water column	ΔCO_2 for entire water column (mmole/m²)
	Time				
	0600	1100			
0.1	8.24	8.42	24	1	24
1.0	8.23	8.40	24	1	24
3.0	8.21	8.35	19	2	38
5.0	8.20	8.31	15	2	30
8.0	8.19	8.28	12	3	36
Total					152

* The first two samples are considered representative of the first two meters; the 3- and 5-m samples, of the next 2-m intervals, respectively; the 8-m sample, of the last three meters in the water column.