PAIN RELIEF WITH HYPNOTIC DOSES OF BARBITURATES AND A HYPOTHESIS[1]

ARTHUR S. KEATS AND HENRY K. BEECHER

Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts

Received for publication April 5, 1950

Several independent observers have reported the failure of barbiturates to protect significantly against the perception of pain produced experimentally (Wolff *et al.*, 1941; Andrews and Workman, 1941; Smith *et al.*, 1943; Wolfe and MacDonald, 1944; Hart and Weaver, 1948). Their findings provide the basis for the current teaching that barbiturates in small dose have little or no analgesic power. This view stands in contrast to our experience with barbiturates in the treatment of *existing* pain, both acute and chronic.

As early as the Cocoanut Grove disaster, Beecher (1943) observed that hypnotic doses of barbiturates appeared to be useful in relieving the pain of badly injured patients. These random observations in wounded men were confirmed during the recent war (Beecher, 1946) and these necessarily uncontrolled findings led to the present controlled study. The data obtained demonstrate the analgesic power of a small (hypnotic) dose of pentobarbital sodium when used in treating pain from natural causes. Early in these observations it appeared probable that there is an effect of barbiturates on "pathological" pain which does not become apparent in studies of experimentally produced pain. This concept suggested interesting implications as to the factors involved in human pain as well as to the mode of action of barbiturates. These matters will be discussed in terms of our data.

METHOD. *Subjects.* The pain of postoperative patients provided material for this study. The method of study is based on the principles established by Denton and Beecher (1949a). We wish to re-emphasize the importance of measuring analgesic power in subjects with pain from disease or surgery. In our experience experimentally produced pain in man has little value in the assay of analgesic power.

All patients from the routine operative lists of the surgical services were potential subjects for this study if they fulfilled the following requirements: (1) The surgery performed was of a major type in which sufficient trauma was produced to give rise to persistent severe postoperative pain. (2) No contraindications to morphine or barbiturates were present. (3) The patient was sufficiently intelligent, oriented and without language barrier to give reliable information.

To insure that the potential subjects were in a clear mental state and free of the effects of the general anesthetic, they were not studied until 7:30 a.m. of the first postoperative day. From then until 6:00 p.m. constituted the experimental period. Where a spinal anesthetic was used, the patients were observed only to 6:00 p.m. on the day of operation.

Procedure. When any such patient developed steady (i.e., constantly present) wound pain of severe or of great, but "bearable," intensity he was used as a test subject. Pain

[1] This work was carried out under grants from the United States Public Health Service, RG 301, and from the United States Army, W-49-007-MD-371.

on motion, so frequent in postoperative patients, was not used since the barbiturate we planned to use might produce decreased body activity and apparent relief for this reason. "Gas pains" and other intermittent pains were not suitable for use because they often subsided spontaneously. Forty per cent of the patients followed developed pain of the proper type and degree and thus became eligible for use as subjects.

When suitable pain developed and its exact nature was recorded, the subject was given intravenously the first drug of a series (morphine, barbiturate or saline) and the degree of pain relief evaluated 30 minutes later. This interval was considered sufficient to insure peak drug effect as well as adjustment by the subject to these effects. If little or no relief was obtained, the second drug was given intravenously (approximately forty minutes after the first dose) and again evaluated in 30 minutes. If this also failed, the third and final drug was similarly given and evaluated. If pain relief was obtained after any dose, the subject was followed until his pain returned to approximately the original level and the series of administrations continued in the manner described. Not every subject received all three drugs since, in many, no pain returned within the experimental period after the first or second administration. In others the recurrent pain was milder or of different type and therefore was not adequate for further testing. Three subjects refused further medication after the first or second of a series lest they become "dope addicts".

Drugs and Order of Administration. The three drugs used were saline, pentobarbital sodium, and morphine sulfate. All were given on the basis of mgm. per 70 kgm. of body weight except saline, which was consistently given as 1.0 ml. All drugs were given intravenously because this route offered the advantages of: (a) elimination of absorption variables, (b) rapid achievement of peak drug effect, enabling rapid evaluation before previous pain experience was forgotten, and (c) shortening of the period of drug action so that more drugs could be evaluated during the experimental period.

Pentobarbital sodium was selected as the barbiturate for use in this study primarily because it is short lasting, is representative of most barbiturates in action, and has been widely used in neurophysiological experimentation. Eight mgm. of morphine per 70 kgm. were chosen because it is a small intravenous dose which would relieve postoperative pain in about 90 per cent of unselected trials (Denton and Beecher, 1949b). Drugs were given intravenously over about one minute and during administration a neutral effect was maintained with no suggestion as to resultant relief or no relief, other than that which was implicit in the act of medicating the subject.

Five groups of subjects were studied in the above manner, differing from each other in the dose and order of administration. They were: (a) pentobarbital sodium (60 mgm./70 kgm.) followed by morphine 8 mgm./70 kgm.) in 30 subjects; (b) saline followed by pentobarbital sodium (60 mgm./70 kgm.) followed by morphine in 31 subjects; (c) saline followed by pentobarbital sodium (90 mgm./70 kgm.) followed by morphine in 31 subjects; (d) morphine followed by pentobarbital sodium (90 mgm./70 kgm.) followed by saline in 34 subjects; (e) five subjects at each of the six possible orders of administration of saline, pentobarbital sodium (90), and morphine, all having the full series of three doses each (total 30 subjects). While achieving this balanced design of six possible orders, we used an additional 22 subjects in whom incomplete sets of doses (less than three) were obtained.

Evaluation of Relief. With only a few exceptions all evaluations of the degree of pain relief were made by trained technicians, who were unaware of the nature or dose of the drugs being given. They were never present during the administration of the drugs. It is just as important for the observer as for the patient to be in ignorance of the agent under consideration. Criteria for evaluation were rigidly established and all technicians were indoctrinated with the same standards. Evaluations therefore were impartial. The technicians interviewed the subjects fifteen minutes and 30 minutes after the injection. The 30-minute evaluation was considered final and was the basis for our tabulations.

Criteria of Relief. Soon after initiation of this study, it was observed that in a sizeable number of subjects following doses of morphine and more especially pentobarbital, the decision as to the presence or absence of pain relief was exceedingly difficult. Two types

of puzzling reactions were observed. One was in those subjects who claimed that their pain had not, or only slightly, changed and yet who did not want further medication. They appeared perfectly comfortable, content, and divorced from any "painful" experience in contrast to their predose state. Despite the fact that their pain was said to be still present, we could not believe that further medication was indicated. The converse was found in those subjects who claimed that the pain was "quite a bit better", and yet, who continued to be restless, tense, unhappy, bothered greatly by minor ailments (position, tubes), and generally uncomfortable. Here it was impossible to believe that the medication had been very successful, despite the relief of pain. The patient was not content. Therefore all doses were evaluated both for pain relief and for comfort. Thus four categories of response were observed, viz: (a) no comfort, no pain relief, (b) no comfort, pain relief, (c) comfort, no pain relief, and (d) comfort, pain relief. The latter two categories of response were considered to represent the therapeutic or desired effect, both from the physician's and the patient's viewpoint. Further justification for the use of these criteria will shortly become apparent.

Pain relief was judged present when "all" or "most" or "more than half" of the pain was gone at 30 minutes. "Slightly better", "a little better" or "less than half gone" were judged as no pain relief. The presence or absence of comfort can best be described as an estimation of the over-all status of the subject following medication and by his satisfaction with the results of the medication. Since all subjects were uncomfortable before the drug was given by reason of their pain at least, this evaluation was not difficult. Primary emphasis in evaluation was placed on the subjective responses, but objective evidence was also considered. Whatever difficulties of criteria were encountered in any single subject, the errors made were consistent with all three drugs by reason of our experimental design.

The doses of pentobarbital used intravenously might be expected to produce such sleep as to suppress any complaints at all and preclude any reliable evaluation. This was rarely the case. Whereas wide variations among subjects were seen in the hypnotic effects of these dose levels, many did not sleep and almost all were readily rousable. At 30 minutes, they could give intelligent responses to the questions put to them. In fact, sleep occurred more frequently after morphine than after pentobarbital (although not so deep), presumably the result, in part, of relief of discomfort. Sleep in itself was not considered to indicate necessarily either comfort or pain relief and all subjects were awakened for interviews. In this way evaluation of effects of both morphine and pentobarbital were made *during* almost peak action of the drug and the errors of retrospective opinions (very unreliable in our experience) were eliminated. Sleep did not necessarily accompany relief since often pentobarbital produced deep sleep without either comfort or pain relief, according to the subjects' statements.

RESULTS. The initial group of 30 subjects was studied primarily to determine the degree and frequency of relief we might expect from the arbitrarily chosen pentobarbital dose level of 60 mgm. per 70 kgm. of body weight. At the same time it was important to estimate the number of subjects who would not be relieved even by morphine. Therefore in this initial group only two drugs were used, pentobarbital followed by morphine when no relief was obtained or when the pain had recurred. The results are shown in table 1 (Group I). The reasons for the greater number of subjects receiving pentobarbital than morphine were given above.

These results made it imperative that saline be treated similarly. In a second group of 31 subjects, saline was given initially, followed by pentobarbital and morphine. The results of this series (Group II) confirm the previous results.

In order to learn whether the therapeutic response obtained with pentobarbital

was a function of the drug or whether this response was a characteristic of certain subjects, we continued our study with a third group in which the pentobarbital was increased to 90 mgm. and the order of administration kept the same as in the second group. The data here (Group III) are equivocal in that they can support either conclusion. In spite of the increased dose, the percentage relief with pentobarbital remained the same as when 60 mgm. were used, implying that the response to barbiturate was a characteristic of the subject. However, the poor response to morphine in this group implies that the "total" pain of the group was more severe than in the other and since pentobarbital relief in this group more nearly approximated the morphine relief, it could be concluded that a higher therapeutic rate was achieved with the increased dosage. Clearly, it is essential that the effects of the drugs be studied in the same patient.

To determine which of the possibilities was correct, we studied a fourth group in which the dose levels remained the same but the order of administration was exactly reversed, morphine followed by pentobarbital and saline. The reversed order was introduced in order to assess simultaneously the influence of order of administration on the results obtained. These data (Group IV) seem to indicate both that the order of administration does somewhat influence the relief obtained and that a higher helping rate can be obtained with an increase in dose.

Since it was not feasible to repeat the above procedure with a group at each possible order of administration, a fifth group of 30 subjects was studied to obtain a balanced design of the six possible orders (i.e., ABC, ACB, BAC, BCA, CBA, CAB). Consecutive subjects were therefore committed to a definite order of administration before being seen and five subjects were obtained at each order possible. Subjects receiving less than the full series of doses (three) were not included in this group and each assigned permutation was completed before going to the next, according to a definite schedule. This design was used in order to eliminate as well as to investigate the effects of order of administration. This group (Group V) in itself significantly demonstrates that pentobarbital possesses greater therapeutic effectiveness than saline. The effects of order of administration are discussed below.

The last group (Group VI) is made up of those subjects not receiving the full complement of three doses in the balanced design group, mainly because their pain failed to return during the experimental period. These subjects are included as supplementary data. The high percentage relieved in this group with all drugs is noteworthy. It seems probable that the "total" pain of this group was less than it was in Group V. Certainly it was more easily and quickly overcome.

In the collection of these data, several incidental observations were made which are of interest: (a) Among all the pentobarbital doses given in the presence of pain, marked excitement was observed only once and moderate excitement twice (all in subjects under 60 years of age). (b) Age *per se* did not seem to increase the sensitivity to barbiturates. (c) Separate study of the subjects who obtained a therapeutic effect from pentobarbital did not reveal any obvious common characteristic (e.g., age, sex, temperament, operation, type of pain, etc.) and response to pentobarbital could not be predicted.

EVALUATION OF DATA. In the previous work with analgesics in postoperative pain, we observed that the order of pain experienced by these patients did not correlate to any valid degree with the age, sex, operation, disease, previous narcotic or surgical history, or the predictable personality of the patients. Large variations in pain experience were present among patients having the same operative procedures and we could not predict, within wide limits, which patients would experience the greatest pain postoperatively. It therefore seemed of the greatest importance in this study to control the many patient-to-patient variables. We have accomplished this by testing the three drugs in the same patient. Thus presumably, we have tested the drugs against approximately the same degree of pain while controlling the other patient-to-patient differences.

We also observed that the intensity of the pain experienced varies inversely with time following operation, reaching a peak when anesthesia effects become minimal and gradually tapering off from this point. Is this attributable to accommodation or to a real decrease in stimulus? Superimposed on this gradual waning there occur smaller spontaneous variations in the degree of pain in either direction.

That time itself is a great healer is clear from the existence of a large number of subjects of all groups in whom no pain returned after the first or second dose of a series (e.g., in obtaining the 30 subjects for Group V, all with complete dose series, 22 subjects were disqualified because of no return of pain). In the factorially designed experiment (Group V) we have the six permutations of administrations repeated five times each. If time itself were the important factor in the short interval of our experimental period, we would expect to find a gradually increasing number of subjects helped with the increasing number of administrations. Since in this group each drug was given the same number of times at each administration number (first, second, or third), the time effect is not confused with the specific drug effect. The tabulation of therapeutic effect according to administration number is given in table 2. If time were a major factor, we would expect a consistent increase in the number obtaining therapeutic effect across the + rows of the table. There is no such consistent result. Indeed even the total data which do suggest this slightly could easily be explained by a sampling error in one of the saline numbers.

Two other factors possibly influencing the percentage relieved are suggested by these data: (a) the cumulative effect of drugs successively administered and (b) the psychologic effect of the preceding medication in determining relief of the succeeding one, i.e., a relief dose is more likely than not to be followed by another relief dose whatever drug used. Contrasting the results of Groups III and IV certainly suggests that either or both of these factors could be operating. Any cumulative effects present in these data would tend to increase the therapeutic effect of the later doses and exaggerate the time factor. The time factor already has been shown with Group V to be of no consequence. In three out of the remaining four groups, or three-fourths of the data, the weakest drug was used first, and the most potent, last. Any cumulative effects would therefore appear only in the morphine relief. Since we are primarily interested in demonstrat-

ing the difference between saline and pentobarbital, any such cumulative effects need not concern us. Similarly in three-fourths of our data (Groups I to III) the psychological effect of the previous medication would only tend to decrease the number of relief doses with pentobarbital and morphine, since the weaker

TABLE 1

Therapeutic effectiveness of saline, pentobarbital, and morphine in small groups of subjects

DRUGS (IN ORDER OF ADMINISTRATION)	DOSE (MGM. PER 70 KGM.)	NO. OF SUBJECTS	RESPONSE				THERAPEUTIC DOSES (C AND D)	PER CENT RELIEVED
			(a) 0 comfort 0 relief	(b) 0 comfort + relief	(c) + comfort 0 relief	(d) + comfort + relief		
Group I								
Pentobarbital	60	30	16	1	6	7	13	43.3
Morphine	8	26	4		1	21	22	84.6
Group II								
Saline		31	27			4	4	12.9
Pentobarbital	60	25	14	2	4	5	9	36.0
Morphine	8	22	2	2	1	17	18	81.8
Group III								
Saline		31	25		1	5	6	19.4
Pentobarbital	90	27	17		3	7	10	37.0
Morphine	8	23	9	1	4	9	13	56.5
Group IV								
Morphine	8	34	6	1	2	25	27	79.4
Pentobarbital	90	20	7		2	11	13	65.0
Saline		15	11			4	4	26.7
Group V (Random administration)*								
Saline		30	24		1	5	6	20.0
Pentobarbital	90	30	13	2	1	14	15	50.0
Morphine	8	30	6	3		21	21	70.0
Group VI (Incomplete sets)*								
Saline		11	6			5	5	45.0
Pentobarbital	90	14	4			10	10	71.0
Morphine	8	8			1	7	8	100.0

* *See text under results.*

or weakest drug was used initially. There is no such problem in Group V by reason of the experimental design. If both these factors operate in these data, they would tend to negate each other and under any circumstances not favor the pentobarbital in 80 per cent of the data.

To analyze our data more critically, we elaborated several theories which could

possibly explain the results obtained in this study. We then set up mathematical models based on each of the theories to predict the results to be expected in this experiment. The theoretical values were then compared to the experimental values and the agreement provided an index of the validity of the theory.

Certain models leaned heavily on the psychological theory, i.e., the likelihood of obtaining a therapeutic effect from any drug is affected by the previous history of the successes and failures of the subject with previous drugs. Other models emphasized the pharmacological theory or very simply the concept that subjects have a differential sensitivity to drugs. The model which most consistently agreed with our results leaned heavily on pharmacological causes with little or no psychological component. This is precisely what would be expected if the differences in the drugs themselves were responsible for the observed differences

TABLE 2

Time effect (administration number) compared to therapeutic effect for random administration

(Group V)

DRUG		ADMINISTRATION NUMBER		
		1	2	3
Saline	+	1	1	4
	0	9	9	6
Pentobarbital (90)	+	5	4	6
	0	5	6	4
Morphine (8)	+	6	8	7
	0	4	2	3
Totals	+	12	13	17
	0	18	17	13

+ = Therapeutic effect.
0 = Non-therapeutic effect.

in therapeutic effect, and gives no good evidence in this experiment that the psychological effect of previous results with drugs is important here. Although this factor appears prominent in certain portions of our data (e.g., Group IV), it must operate with all three drugs, in all data to be valid. The models used will be presented elsewhere.

The disposition of subjects not receiving the complete series of doses presents a problem in data evaluation. Considering the differential sensitivity to drugs among subjects, all our subjects could be divided into an "easy-to-relieve" group (incomplete series of drugs because of no pain return) and a "hard-to-relieve" group (complete series of drugs). Two methods of presenting our data become possible. One is to pretend that since we have an "easy-to-relieve" group, all unadministered drugs would have helped all subjects in this group (generous estimate). The other is to tabulate the results of only those doses

actually administered (conservative estimate). These two methods err in opposite directions and a true value probably lies somewhere between. The second method was used in table 1. Table 3 presents both estimates of all the data collected and it is obvious that the helping rate of both 60 mgm. and 90 mgm. of pentobarbital is consistently and significantly better than saline and not as good as morphine.

If all "easy-to-relieve" subjects are excluded and only the "hard-to-relieve" are considered, the relative positions of the three drugs remain approximately the same (table 4). Group I was omitted because only two drugs were admin-

TABLE 3

Conservative and generous estimates of therapeutic effectiveness for the various drugs. The first value is the conservative, the second the generous

Obviously drugs administered first in the series have only a single estimate. The sample sizes in actual administrations have been given previously.

GROUP	PER CENT RELIEVED			
	Saline	Pentobarbital (60)	Pentobarbital (90)	Morphine (8)
I		43.3		84.6–86.7
II	12.9	36.0–44.8		81.8–86.2
III	19.4		37.0–45.2	56.5–67.7
IV	26.7–67.6		65.0–79.4	79.4
V, VI	26.8–42.3		56.8–63.5	76.3–82.7

TABLE 4

Estimate of therapeutic effectiveness of various drugs in "hard-to-relieve" subjects

GROUP	NO. OF SUBJECTS	PER CENT RELIEVED			
		Saline	Pentobarbital (60)	Pentobarbital (90)	Morphine
II	22	0	27		82
III	23	9		26	57
IV	15	27		53	53
V	30	20		50	70

istered. Pooling the results of the remaining four groups, it is obvious that even in "hard-to-relieve" subjects pentobarbital is consistently better than saline by 100 to 200 per cent.

A final method of data evaluation which would eliminate some variables cited above (e.g., time and psychologic effects) is the comparison of helping rates of the drugs according to their position in order of administration, i.e., comparing all first doses, etc. This tabulation is shown in table 5 and reaffirms both the relative positions of these drugs in therapeutic efficacy and the conclusions drawn from table 2. For the second administration both the conservative and generous estimates are given. No generous estimates are given for the third administration because they get ridiculously large since so many subjects dropped out.

We have tried by various methods to account for any factors, other than specific drug effects which might operate in these data and which possibly might have produced the results obtained. We have been unable to identify any such factors of significance. Therefore we conclude that the differences in helping rates observed are solely the result of the different drugs used. We are justified, then, in pooling our data and presenting the conservative helping rates in table 6. The statistical evaluation by the method of standard error of the difference between two proportions is similarly justified (table 7) (Hill, 1939).

TABLE 5

Estimates of therapeutic effectiveness of various drugs by comparison of results by order of administration

Both conservative and generous estimates are given for the second administration

GROUP	PER CENT RELIEVED		PER CENT RELIEVED		PER CENT RELIEVED		PER CENT RELIEVED	
	Saline	n*	Pent. 60	n*	Pent. 90	n*	Morphine	n*
First administration								
I			43	30				
II	13	31						
III	19	31						
IV							79	34
V, VI	17	18			57	21	69	13
Second administration								
I							85–87	26
II			36–45	25				
III					37–45	27		
IV					65–79	20		
V, VI	31–44	13			54–63	13	87–87	15
Third administration								
II							82	22
III							56	23
IV	27	15						
V, VI	40	10			60	10	70	10

* n = sample size, the number of real administrations.

It is clearly seen that both dose levels of pentobarbital produce a degree of relief that is significantly different from that of saline and not equal to morphine. We have not shown the effects of 60 mgm. of pentobarbital to be significantly different from 90 mgm. The increased percentage of relief with 90 mgm., the much larger proportion of both comfort and relief achieved by 90 mgm., and the greater proximity of pentobarbital (90) to morphine in individual groups certainly suggests that the effects observed are dependent on the dose rather than on a characteristic of a certain proportion of subjects studied. We have shown that the pain relieving rate of pentobarbital in the doses administered is about

TABLE 6

Conservative estimate of therapeutic effectiveness of various drugs in all groups combined

	DRUG			
	Saline	Pentobarbital	Pentobarbital	Morphine
	Dose			
	1.0 ml.	60 mgm./ 70 kgm.	90 mgm./ 70 kgm.	8 mgm./70 kgm.
No. of subjects	118	55	91	143
Response:				
(a) 0 Comfort, 0 Relief	93	30	41	27
(b) 0 Comfort, + Relief		3	2	7
(c) + Comfort, 0 Relief	2	10	6	9
(d) + Comfort, + Relief	23	12	42	100
Therapeutic doses (c and d above)	25	22	48	109
Per cent relieved	21.2	40.0	52.7	76.2

TABLE 7

Statistical reliability of differences in percentages of therapeutic effect obtained with various drugs

DRUGS COMPARED	PER CENT RELIEVED	$\%_1 - \%_2$	$SE_{(\%_1 - \%_2)}$*	$2 \times SE_{(\%_1 - \%_2)}$*
Pentobarbital (60)	40.0	18.8	7.6	15.2
Saline	21.2			
Pentobarbital (90)	52.7	31.5	6.4	12.8
Saline	21.2			
Pentobarbital (90)	52.7	12.7	8.4	16.8
Pentobarbital (60)	40.0			
Morphine	76.2	36.2	7.5	15.0
Pentobarbital (60)	40.0			
Morphine	76.2	23.5	5.8	11.6
Pentobarbital (90)	52.7			

* SE is standard error of the difference between the two percentages.

50 per cent, in contrast to rates of 75–80 per cent for morphine and 20 per cent for saline.

DISCUSSION. Impulses resulting from painful peripheral stimuli on reaching the thalamic nuclei are probably projected to the cortex via pathways still not

well defined (Greenblatt and Myerson, 1949). It is probable that in this projection these impulses or their spread are modified by reinforcing or inhibiting impulses from other areas of the nervous system, ultimately effected through the subcortical internuncials. The resultant modified impulses appear in consciousness as the complex symptom of pain.

Some of the complexities in studying and treating pain in man can be resolved by an appreciation of the contribution of both the original stimulus and the modification of this stimulus in making up the total picture of pain. Lacking more specific information we have categorically labeled these modifying influences as psychic and assume a wide range in the degree to which the psychic factor can operate in any individual. Support for this assumption is found in the observation that neurotic individuals differ markedly from normal individuals in their reaction to a painful stimulus, whereas their levels of pain perception are almost identical (Chapman *et al.*, 1946; Chapman *et al.*, 1947).

This approach to the pain experience makes it unreasonable to conclude that patients obtaining pain relief from placebos or saline do not have "real pain". It is likely that in such patients the psychic modification of pain stimuli is very great and that suggestion of relief alone is sufficient to block the thalamocortical spread of impulses by a purely cortical mechanism. Such a psychic mechanism is probably like that which operates in the blockage of the pain experience by hypnotism and similar to the suppression of pain from injury during athletic contests in which the excitement of the game has prevented awareness of the injury or its pain. The same holds during fighting, as pointed out previously (Beecher, 1946). It would seem from this that cortical impulses alone can interrupt the perception of pain stimuli. We venture to predict that the pain experience can be altered by any large quantity of afferent or sensory stimuli, however produced (mechanically, or by drugs, by environment, etc.). Indeed the euphoria-producing action of morphine has been suggested as responsible for much of its pain-relieving properties (Wolff *et al.*, 1940), presumably by alterations in the psychic factors operating. It is probable that such drugs as dextroamphetamine sulfate (Ivy *et al.*, 1944) and procaine intravenously (Graubard and Peterson, 1949) for which analgesic powers have been claimed, act through their abilities to produce psychic changes rather than any alteration in the actual pain stimulus. It is possible that any drug which will produce reasonably large changes in the psyche can be shown to possess some analgesic powers. These postulates are to be tested experimentally.

This approach also makes it understandable why different results can be obtained with the same drug when applied to existing pain on one hand and to the perception of experimentally inflicted pain on the other. The perception of inflicted pain represents the recognition of a threshold physical stimulus, whereas existing pain is the stimulus plus its associated psychic modification. It may be convenient and wise to consider the physical stimulus only as "pain" and the combination of physical and psychic modification as "suffering". In man we are concerned with "suffering"; in animals we are probably concerned primarily with "pain". Obviously man is the animal of necessity for the study of pain.

The recent experience with prefrontal lobotomy for the relief of intractable pain gives support to this concept of the pain experience. In this surgical procedure, no representative pain areas are excised, little cortex is destroyed, and yet by it many patients are divorced from their suffering, presumably by interruption of these same thalamo-cortical projections. Lobotomy patients sometimes admit that they still have their pain, but that "it does not bother" them (Dynes and Poppen, 1949). The concern, anxiety, and significance have been detached from their pre-lobotomy pain. This observation is akin to the experience of a large number of our subjects who, after receiving pentobarbital, were observed to be quite comfortable, but without any diminution in their awareness of pain (comfort without pain relief) and justifies the distinction between comfort and pain relief. The demonstration that lobotomized patients have no loss of ability to perceive pain and in fact have a lowered skin threshold to inflicted painful stimuli (Chapman, 1949) further emphasizes the importance of this separation of the pain stimulus and the psychic modification of the stimulus, and the separation of perception of inflicted pain stimuli and existing pain.

Beecher has suggested that pentobarbital relieves suffering in a way similar to that of lobotomy, by interruption of the previous spread of pain impulses from the thalamus to certain cortical areas, thus blocking or altering the psychic modification of these pain stimuli. There is some evidence that pentobarbital can prevent the spread of afferent impulses. Forbes (1922) proposed the now well accepted explanation of the spinal cord afterdischarge phenomenon as the consequence of long circuiting in the central nervous system of an afferent impulse after the original stimulus had ceased. Forbes, Cobb and Cattell (1923) found that spinal cord transection resulted in a great reduction in afterdischarge presumably as a result of *physical* curtailment of the internuncial reflex circuits. In studying the effect of various anesthetic agents on afterdischarge, Beecher, McDonough, and Forbes (1939) found that barbiturates, in contrast to ether, affected afterdischarge like spinal cord transection. Barbiturates reduced afterdischarge and by inference, the internuncial spread of afferent stimuli by *pharmacological* curtailment. That the action of barbiturates on the brain itself is in part the result of a depression of the internuncial spread of impulses is suggested by other recent evidence (Bremer, 1937; Swank and Watson, 1949). The barbiturates can be thought of as producing a temporary reversible lobotomy, a sort of pharmacological lobotomy, a reversible depression of the internuncial spread of pain impulses perhaps between the thalamus and the cortex. In 50 per cent of our subjects tested, pentobarbital would seem to have prevented or satisfactorily reduced the conscious perception of the psychic modification or emotional associations of pain stimuli, and prevented suffering.

It is not to be concluded from the observations made here that barbiturates alone can be substituted for morphine in the routine care of postoperative patients. Even when given intravenously to our selected groups, the degree, frequency, and duration of analgesia were significantly less than after morphine and the hypnosis greater. Undoubtedly in certain patients pentobarbital alone can be used to treat pain; in others it can be used advantageously as a supplement to a small dose of narcotic with increased comfort achieved. The significant ob-

servation is that half of our subjects while under the effects of pentobarbital either did not experience what is commonly called pain or were not discomforted by it.

The observations made in this study suggest that the fundamental differences between the two classes of substances, narcotics and hypnotics, are fewer than supposed. Narcotic agents have, of course, both analgesic and hypnotic powers. Hypnotic agents would seem to have the same.

It is hoped that the implications of this observation as to the mechanisms of pain and pain relief, and the mode of action of barbiturates will stimulate further inquiry.

SUMMARY

1. Hypnotic doses of pentobarbital sodium intravenously relieved what has been called postoperative pain in 50 per cent of patients, in contrast to 20 per cent with saline and 80 per cent with morphine (a total of 178 patients was studied).

2. The pain experience of man consists of both perception of painful stimuli and the psychic modification of these stimuli.

3. A hypothesis is presented to explain the analgesic properties of pentobarbital by depression of the internuncial spread of pain impulses in the brain and inhibition of the psychic phase of pain experience. An analogy to prefrontal lobotomy is drawn.

ACKNOWLEDGMENT. We are indebted to Dr. Frederick C. Mosteller, Associate Professor of Mathematical Statistics, Harvard University, for guidance in statistical matters.

REFERENCES

ANDREWS, H. L., AND WORKMAN, W.: THIS JOURNAL, **73:** 99,1941.
BEECHER, H. K.: Ann. Surg., **117:** 825, 1943.
BEECHER, H. K.: Ann Surg., **123:** 96, 1946.
BEECHER, H. K., MCDONOUGH, F. K., AND FORBES, A.: J. Neurophysiol., **2:** 81, 1939.
BREMER, F.: Compt. rend. Soc. de Biol., **124:** 848, 1937.
CHAPMAN, W. P.: J. A. M. A., **140:** 18, 1949.
CHAPMAN, W. P., COHEN, M. E., AND COBB, S.: J. Clin. Investigation, **25:** 890, 1946.
CHAPMAN, W. P., FINESINGER, J. E., JONES, C. M., AND COBB, S.: Arch. Neurol. and Psychiat., **57:** 321, 1947.
DENTON, J. E., AND BEECHER, H. K.: J. A. M. A., **141:** 1051, 1949a.
DENTON, J. E., AND BEECHER, H. K.: J. A. M. A., **141:** 1146, 1949b.
DYNES, J. B., AND POPPEN, J. L.: J. A. M. A., **140:** 15, 1949.
FORBES, A.: Physiol. Rev., **2:** 361, 1922.
FORBES, A., COBB, S., AND CATTELL, H.: Am. J. Physiol., **65:** 30, 1923.
GRAUBARD, D. J., AND PETERSON, M. C.: Anesthesiology, **10:** 175, 1949.
GREENBLATT, M., AND MYERSON, P. G.: New England J. Med., **240:** 1006, 1949.
HART, E. R., AND WEAVER, O. M.: Anesthesiology, **9:** 276, 1948.
HILL, A. B., Principles of Medical Statistics, The Lancet, Ltd. (London, 1939), Second Edition, p. 72.
IVY, A. C., GOETZL, F. R., AND BURRILL, D. Y.: War Med., **6:** 67, 1944.
SMITH, D. L., D'AMOUR, M. C., AND D'AMOUR, F. E.: THIS JOURNAL, **77:** 184, 1943.
SWANK, R. L., AND WATSON, C. W.: J. Neurophysiol., **12:** 137, 1949.
WOLFE, G., AND MACDONALD, A. D.: THIS JOURNAL, **80:** 300, 1944.
WOLFF, H. G., HARDY, J. D., AND GOODELL, H.: J. Clin. Investigation, **19:** 659, 1940.
WOLFF, H. G., HARDY, J. D., AND GOODELL, H.: J. Clin. Investigation, **20:** 63, 1941.