Human "Analgesic" Action of d-Amphetamine, Amobarbital, Acetylsalicylic Acid and Acetophenetidin, in Combination. (20401)

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This new combination of drugs to be considered as analgesic evolved from 2 sets of pharmacological information. First, a mixture of amphetamine, aspirin and phenacetin, known as "Edrisal", has enjoyed widespread use as an analgesic since it was assayed and found effective by Burrill, Goetzl, and Ivy(1). This work, in turn, developed from the recognition that sympathomimetic drugs were capable of producing analgesic action(2). Second, the mood improvement following therapy with amphetamine is well established. Its combination with barbituric acid derivatives for the relief of anxiety and depression apparently originated with the work of Davidoff and Goodstone(3).

This report relates the experience obtained when the pain threshold elevating abilities of the following were compared on each of 16 normal human volunteers. A. d-amphetamine sulfate, 5 mg; amobarbital, 32 mg; acetylsalicylic acid, 162 mg, and acetophenetidin, 162 mg, hereafter called "Daprisal".* B. acetylsalicylic acid, 162 mg, and acetophenetidin, 162 mg. C. placebo. D. one experiment in which nothing was taken by the subjects, hereafter called the "dry-run".

Methods. To establish the experimental pain thresholds and compare the effects of the 4 treatments upon them, the method and discipline of Harris and Blockus(4) was employed. The thresholds of electrical elicitation of pain in a tooth pulp of each subject, were determined in triplicate 3 times at 15-minute intervals before medication; then 8 times at 20-minute intervals after medication. The subjects were selected because they had at least one metal restoration, which did not extend to touch soft tissue, in a vital tooth. Before every threshold determination, the tooth to be tested was carefully dried with 95% ethanol and, if necessary, kept dry by surrounding it with cotton rolls. Subjects were always in the post-cibal state. The medication program was determined in advance so that each treatment was given to every subject in such a way that each treatment occurred first, second, third and fourth, 4 different times. Further, the sequence of medications was arranged in 4 different patterns. Four envelopes were labeled for each subject and filled according to the above program before the experiment began. In this fashion, neither operator nor subjects knew the identity of medication at any time prior to the completion of the whole experiment. The occasion of the dry-run was an exception, of course. It should be stated that the 3 different forms taken by mouth were prepared as tablets that were identical in appearance.

Results. All readings taken were recorded in 4 tables, one for each treatment. An analysis of variance was performed on each of these 4 sets of data and are summarized in Table I.

Table I reveals that there was no significant variation between thresholds observed at 11 intervals over 3 hours (trials) during the dry-run or when aspirin-phenacetin was administered. However, the above variance was statistically significant ($P < 0.01$) when placebo or Daprisal was taken. The variances between trials in these latter 2 cases were broken down for more detailed analysis in Table I and showed that the post-medication thresholds were significantly higher than the pre-medication thresholds after Daprisal and placebo therapy ($P < 0.01$). There also was significant variation ($P < 0.01$) between post-medication thresholds after Daprisal but not after placebo.

To facilitate comparison of the time course of threshold changes after medication it is desirable to have a common base line. To do

* Trademark, Smith, Kline and French Laboratories, Philadelphia, Pa.

TABLE I. Summary of Analyses of Variance of Raw Data by Medications.

Medications	Source of variance	Degrees of freedom	Mean square	"F" ratio
Aspirin-phenacetin	Subjects	15	1032069	806.4 *
	Trials	10	1908	1.49
	Subjects × trials	150	1279	
Placebo	Subjects	15	1045701	412.22*
	Trials	10	11933	4.70*
	Subjects × trials	150	2536	
	Trials 1-3	2	5206	2.05
	" 4-11	7	1032	.40
	" 1-3 vs. 4-11	1	101695	40.08*
Daprisal	Subjects	15	1200360	253.54*
	Trials	10	51744	10.92*
	Subjects × trials	150	4734	
	Trials 1-3	2	2685	.56
	" 4-11	7	29478	6.22*
	" 1-3 vs. 4-11	1	276248	58.34*
Dry-run	Subjects	15	1161477	859.14*
	Trials	10	1383	1.02
	Subjects × trials	150	1351	

* = $P<0.01$.

TABLE II. Average Post-Medication Deviations from Pre-Medication Pain Thresholds for Each Drug and Control, Expressed in Microamperes.

	Minutes							
Medications	20	40	60	80	100	120	140	160
Aspirin-phenacetin	0.24	1.40	2.10	3.20	2.80	3.38	2.41	4.43
Placebo	5.93	6.18	4.51	3.49	5.44	6.87	5.30	4.79
Daprisal	0.52	6.78	8.07	9.31	11.52	14.26	16.17	20.12
Dry-run	0.68	0.46	−0.56	0.12	1.37	0.66	0.74	0.44

this, the average pre-medication threshold was calculated for each subject each time he served, and each of his post-medication changes from his pre-medication average was recorded. This procedure gave 4 new tables with one reading for each post-medication interval for each subject. These data are summarized in Table II and graphically presented in Fig. 1. To determine the significance of the differences between treatment effects, an analysis of variance was performed simultaneously on the data of all 4 of these tables. This analysis is summarized in Table III.

It is readily seen that there was significance ($P < 0.01$) to the difference between post-medication changes in thresholds attributable to treatments. Detailed analysis of treatment variance indicates that the changes in threshold following Daprisal are significantly greater than after the other 3 treatments and that there is no significant difference between the effects upon threshold of Aspirin and phenacetin, placebo, and a dry-run. The significance of variance between trials is attributed to the continually increasing elevation of the threshold after Daprisal which had not leveled off 160 minutes after administration.

A third analysis of variance was run on all of the original data simultaneously to evaluate the variation between the readings taken in triplicate. The "F" ratio for this variance was negligible (0.001).

Discussion. In this laboratory and elsewhere, experience with electrical excitation of the tooth pulp has consistently failed to demonstrate significant elevation of the pain threshold by non-narcotic drugs.

Daprisal, however, is the first non-narcotic ever tested in this laboratory which caused a statistically significant elevation of the threshold to experimentally induced pain in human subjects.

It is to be noted that the above conclusion is based on the conservative analysis compar-

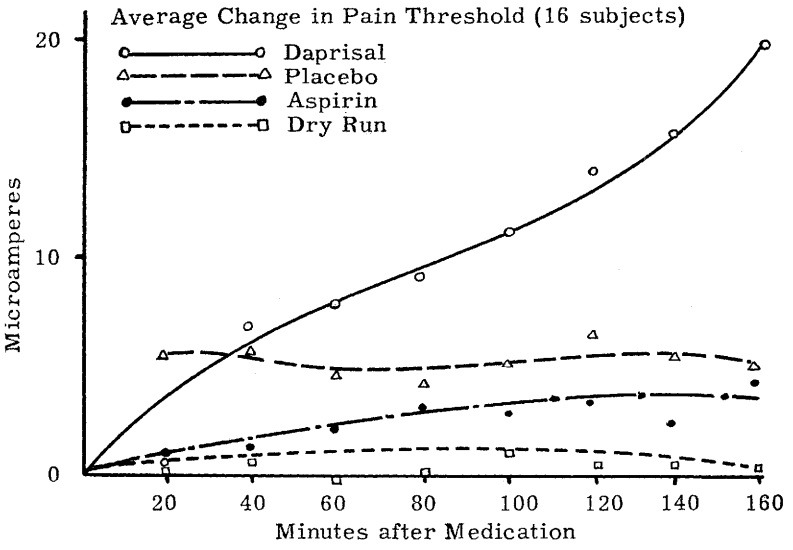

FIG. 1.

ing *all* post-medication readings rather than only maximal readings. Stated differently, the *average* threshold after Daprisal was significantly higher than were the *average* thresholds after aspirin-phenacetin, placebos, and no medication.

That the post-medication thresholds were higher than the pre-medication thresholds after placebos, is not readily explained and has not happened uniformly in our experience. Even in this respect, there was no significant variance between post-medication thresholds after placebos while the thresholds continued to rise significantly during the entire time after Daprisal had been given.

Worth mentioning was that not one of the 16 subjects noted any stimulation or depression after any of the drugs given. It was with some surprise that sleeplessness was not reported by anyone, although 5 mg of d-amphetamine was given, in combination, at 7:30 p.m. in every instance of its use.

Limited clinical experience in our hands tends to confirm the experimental finding that this unique drug combination is indeed analgesic. In several clinical cases, pain unrelieved by large quantities of salicylic acid derivatives was relieved by a single Daprisal tablet but not by a placebo. The mechanism by which compounds impotent as analgesics individually, become a potent analgesic when combined, is not sufficiently understood at this time to justify discussion.

Summary. Four treatments were compared on each of 16 human subjects for their ability to elevate the threshold to experimentally in-

TABLE III. Summary of Analysis of Variance of Post-Medication Deviations from Pre-Medication Averages by Subjects, Treatments and Consecutive Observations (Trials).

Source	Degrees of freedom	Mean square	"F" ratio
Treatments	3	440274.3	6.09*
Subjects	15	100054.1	1.38
Treatments × subjects	45	72245.2	
Trials	7	36461.4	5.94*
Error	441	6128.9	
Breakdown of treatments			
Daprisal vs. others	1	1065604.7	14.75*
Others	2	127609.1	1.76

* = $P<0.01$.

duced pain of the tooth pulp, by the method and discipline of Harris and Blockus. Rigorous elimination of bias was exercised. The treatments were: A. d-amphetamine, 5 mg; amobarbital, 32 mg; acetylsalicylic acid, 162 mg; acetophenetidin, 162 mg; B. acetylsalicylic acid, 162 mg; acetophenetidin, 162 mg; C. placebo; D. no medication, *i.e.*, a dry-run. The threshold of experimentally induced pain was elevated more significantly during the 2½ hours after the amphetamine mixture than after the other 3 treatments.

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Received June 8, 1953. P.S.E.B.M., 1953, v83.

Demyelination in Lambs from Ewes which Feed on Seaweeds. (20402)

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A nervous disorder in newborn and young lambs has been known to occur since the middle of the last century on many farms in Iceland *i.e.* farms near the coast where the sheep graze on seaweeds during the winter. Ewes are most prone to give birth to affected lambs when they eat much seaweed during the last half of the gestation period.

Many of the farmers along the coast graze their sheep on seaweeds in order to save hay. The daily intake of seaweeds per animal may become quite high (6 to 10 kg). Sheep seem to prefer certain species of seaweed such as *Rhodymenia palmata* and *Alaria esculenta* but where these species are scarce they consume other species too. The disease is rare on farms off the coast. Its incidence varies considerably from year to year on the same farm. On many farms the *mortality* may vary annually from 1% to 50% of the lambs born on the farm, but occasionally the losses may be as high as 80% to 90%. On some farms the disorder occurs every year, on other farms, even in the same area, the disorder seems to occur for one or 2 years after the herd has been free from the disorder for a number of years. Ewes which have given birth to affected lambs one year may produce either affected or healthy lambs the following year. This disorder is not so widespread now as it was 20-30 years ago, probably because the ewes are now fed much more hay during the gestation period, and on many farms the ewes are kept away from the seaside altogether during the last half of pregnancy. When the hay crop is poor for one year large losses among the lambs still occur. Older ewes seem to be more prone to give birth to affected lambs than young ewes, but ewes at any age may give birth to affected lambs.

The symptoms are usually essentially similar, but vary considerably in severity. The most prominent and common symptom is incoordination of movement, in many cases the lambs are unable to rise and stand, but lie helpless, some may be able to rise, but walk with much difficulty and collapse almost immediately, others walk with a staggering gait. Mild cases show only weakness of the hind quarters, especially when hustled. Many lambs are blind. The body temperature is normal. Most cases are fatal, but those lambs which do not show symptoms until some weeks after birth, often survive and if bred later, they may give birth to healthy lambs.

The macroscopic pathological lesions seem to be confined to the nervous system, particularly the cerebrum. In approximately one-half of the cases which we have examined, macroscopic lesions were present. In the most typical cases the convolutions of the cerebrum were flattened and poorly defined, on palpation fluctuation could easily be felt on the hemispheres and the cerebral cortex was in