

## Sodium Lactate Infusions and Panic Attacks: A Review and Critique

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Response to sodium lactate infusions has been proposed as an experimental model and a biologic marker for panic attacks. Several authors have claimed that patients suffering from panic attacks, but not normal controls, "panic" in response to lactate. A careful review of methods and results of 13 studies, however, reveals serious methodologic problems, lack of specificity and sensitivity, and a failure to consider cognitive variables. When baseline differences are ruled out, the responses of patients and controls may not differ. So far, response to lactate cannot be interpreted as a model and marker for panic attacks and does not provide evidence for their underlying biologic distinctness from other types of anxiety. Known biologic mechanisms do not sufficiently explain the effects of lactate. Instead, an interaction of peripheral physiologic changes, past experience, environmental cues, and their appraisal as threatening or dangerous seems to be a more appropriate model.

In the field of anxiety research much attention has recently focused on panic disorder (1–6). New data emphasize the seriousness of the condition. Coryell et al. (7) found significantly lower long-term recovery rates in patients with panic disorder than in patients with primary unipolar depression. The same research group, in a 40-year retrospective follow-up, found excess mortality in patients with panic attacks similar to that of patients with affective disorder, with higher suicide rates and more cardiovascular deaths in male patients than expected for the general population (8).

Several authors see panic disorder as clearly distinct from other anxiety and phobic disorders (1, 2, 9–13). They also give panic attacks central importance in the etiology and course of agoraphobia and propose to include agoraphobia in the diagnostic category of Panic Disorder as currently defined in DSM-III (14). Klein (15) argues that panic attacks are primary to agoraphobia and that therefore the diagnosis should be "panic disorder with or without agoraphobia" rather than "agoraphobia with or without panic attacks." In the same vein, Sheehan and Sheehan (11–13) divide all anxiety and phobic disorders into two groups labeled "endogenous" vs. "exogenous" anxiety. The major defining criterion for "endogenous anxiety" is the occurrence of panic attacks (11–13, 16, 17).

This situation is largely responsible for the recurrence of interest in the effects of sodium lactate infusions, interest that had temporarily vanished after Pitts and McClure's original explanation for its panic-

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inducing effects had been rejected (18–24). Recently, Klein and his colleagues in a number of publications stated that they have confirmed Pitts and McClure's (25) finding that lactate infusions provoke panic attacks in most panic patients<sup>1</sup> but in very few control subjects (26–36). Currently several other centers are working in this area (37–41). Contemporary researchers focus more narrowly on Panic Disorder instead of considering sodium lactate as the biochemical substrate of anxiety in general (42).

Two major applications of lactate infusions have been proposed. First, they are seen as an experimental laboratory model for evoking and studying panic attacks similar or even identical to those occurring spontaneously. This model could be used to investigate the pathophysiology of panic attacks, the efficacy of treatments, and the homogeneity or heterogeneity of different anxiety disorders. Second, some authors propose that response to lactate infusions is a possible biologic marker for panic attacks, the crucial phenomenon of Panic Disorder or Agoraphobia with Panic Attacks: "Biological evidence of the distinctness of panic disorders from other anxiety disorders comes primarily from lactate challenge tests" (10, p. 4). And Carr and Sheehan (43, cf. 3) conclude that the results of lactate infusion studies suggest "that panic disorder is a biological disease" (p. 100).

In order to determine whether response to lactate infusions is suitable for these purposes, we evaluate the current status of the research on the effects of lactate in-

fusions. Specifically, we deal with the following questions:

1. To what degree do lactate and placebo infusions induce panic in patients with anxiety disorders and in controls?
2. What are the specific subjective, psychophysiologic, and biochemical effects of lactate infusions, and are there differences between groups in these effects?
3. Are the differences between patients and controls quantitative or qualitative in nature?
4. How similar are the effects of lactate infusions to naturally occurring panic attacks?
5. Do baseline levels of anxiety and arousal affect response to lactate?
6. What are the causal or mediating mechanisms by which lactate induces these effects?

A careful review of methods and results of the 13 lactate infusion studies published so far suggests that the answers to these questions, although not incompatible with a biologic model of Panic Disorder, do not provide confirmation of it. Substantial methodologic problems, the omission of cognitive variables, and lack of specificity and sensitivity of the response to lactate infusion limit its interpretation as model and marker for panic attacks.

## METHODOLOGIC OVERVIEW

Nine of the thirteen published studies that we found compared their sample of panic patients to a clinical or nonclinical control group. Four studies did not use comparison groups. Twelve studies used one of the two following designs. A com-

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<sup>1</sup>In this article the term "panic patients" is used to refer to patients that fulfill DSM-III criteria for Panic Disorder or Agoraphobia with Panic Attacks.

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bination of both designs was used by the 13th study (39–41):

*Design A: Different infusions on separate days.* Subjects received several different infusions (lactate, saline, lactate plus calcium, etc.) in separate sessions. In these studies, subjects and experimenters or observers were generally “blind” to which solution was being given on a specific day (25, 38, 44–47). Thus, these studies generally were double blind.

*Design B: Sequential infusions on the same day.* Subjects received placebo infusions followed by lactate within one experimental session. In these studies, subjects were not “blind” to which substances they would receive, but only to when the infusion of lactate would begin (26–31, 33–35, 37, 48, 49). However, since experimenters knew when the infusions changed, these studies were only single blind with regard to the onset of the lactate infusion.

The methodologic procedures and quality of the studies with and without comparison groups is described in Tables 1 and 2 in terms of generally acknowledged parameters of empirical clinical research and parameters specific to lactate infusions. Any methodologic criticism not apparent in these columns is listed in the last column under “other criticism.”

The most important methodologic criticisms can be summarized as follows:

Many studies fail to report essential information. Patients, controls, matching procedures, settings, instructions, and assessment of dependent variables, especially psychophysiologic variables, are rarely described in sufficient detail. Furthermore, results are often reported incompletely and only qualitatively.

Most studies had inadequate criteria for panic attacks. None used objective cri-

teria, and several did not explicitly specify criteria. This is especially relevant in single-blind studies where non-blind observers or the experimenters themselves determined whether or not panic attacks occurred.

Many studies used insufficient dependent measures, for example, only self-reported somatic symptoms or a single global assessment of the number of subjects experiencing panic attacks. Most studies did not present data on subjective anxiety or did not use standard measures of anxiety. Psychophysiologic and biochemical measures were obtained rarely, and no behavioral measures were reported. Most studies did not take the time-course of the events into consideration (no frequent or continuous assessment).

Control strategies were generally inadequate. Different infusion rates for control and lactate infusions, and the presence of too many nonblind observers endanger the single blind. Most studies did not control sufficiently for demand characteristics and expectancy biases. Some even induced different expectations in their experimental groups by giving them different information before the infusions.

In spite of these limitations, the results of these studies contain worthwhile information about clinical anxiety. Most of the studies share positive methodologic features such as the use of a control infusion, testing patients who met the established DSM-III criteria for Panic Disorder or Agoraphobia with Panic Attacks, single- or double-blind control strategies, and use of the same lactate dose range [with two minor exceptions—Rainey et al. (39–41) and Lapierre et al. (38); cf. Table 1]. Converging evidence from these studies may present

TABLE 1. Overview of Studies with Comparison Groups\*

Study	Infusions	Characteristics and Expectancy Biases	Patients	Subjects Controls	Matching	Criteria for Panic Attacks	Dependent Measures	Other Criticisms
<i>Design A: Different Infusions on Separate Days</i>								
Pitts and McClure (25)	a) 20' 1/2 sl b) same + CaCl <sub>2</sub> c) 20' glucose in NaCl	Double-blind, one blind observer present, no information about instructions	N = 14, equivalent to PD and AG	N = 10, adequate exclusion criteria	Adequate	Specific list of somatic symptoms, unspecified "mental fear"	Symptom SR list, observer C and SR severity ratings	C
Fink et al. (44)	Same as Pitts and McClure (25)	Same as Pitts and McClure (25)	N = 5 "anxiety patients"	N = 4 "controls"	?	Presumably same as Pitts and McClure (25)	Presumably same as above, unspecified EEG variables	A, C
Bonn et al. (45, 46)	a) 20' 1/1 sl b) same amount of NaCl (in nonrandom order)	No information provided about blindness, presence of experimenters, instructions, etc.	N = 24 "anxiety patients"	N = 9 "normals"	?	Same as Pitts and McClure (25)	Symptom and anxiety SR, HR, RR, EMG, skin temperature, biochemical measures (lactate, phosphate, bicarbonate, calcium, cortisol, growth hormone)—all unspecified	A, B, unclear and incomplete presentation of procedures, subsamples, and results
Lapierre et al. (38)	a) 20' 1/1 sl b) 20' D5W	Double-blind, sufficient instructions, subjects alone	N = 23, PD and AG, N = 16, GAD	none	?	Patients pressed lever when panic occurred	Visual analog anxiety SR, lever pressing, symptom list, EEG, AEP, CNV, EOG, EMG, HR	B, unclear report of results, 500 ml limit for infusions

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Design B: Sequential Infusions on the Same Day					Number of subjects reporting only physiologic panic symptoms unspecified
Kelly et al. (48)	a) 10' saline (slow) b) 20' 1/2 sl	N = 20, equivalent to PD and AG	N = 10, adequate exclusion criteria	Adequate Same as Pitts and McClure (25)	Observer ratings and SR of anxiety and depression (3' intervals), symptom SR list: HR, FBF
Rifkin et al. (27)	a) 30' D <sub>5</sub> W (slow) b) 2' D <sub>5</sub> W (fast) c) 20' 1/2 sl	N = 9, PD	N = 7, adequate exclusion criteria	"Experimenter determined anxiety, agitation, restlessness, demand to stop"	No other than specified under criteria for panic
Appleby et al. (26)	a) 30' D <sub>5</sub> W (slow) b) 20' 1/2 sl	N = 25, PD and AG	N = 15, adequate exclusion criteria	? ? no sign. diff.	API, "numerous ratings", biochemical (norlepinephrine, cortisol, prolactin, testosterone), results for other measures not reported
Liebowitz et al. (28, 29, 31, 33)	a) 30' D <sub>5</sub> W (slow) b) 2' D <sub>5</sub> W (fast) c) 20' 1/2 sl	N = 43, PD and AG	N = 20, adequate exclusion criteria	"No objective criteria for panic attacks", "clinical observation, patient self-report"	Panic attack rating by apparently nonblind staff member, API (4 x), HR, BP, biochemical measures (5 x) (lactate, pyruvate, calcium, phosphate, prolactin, (nor)epinephrine, cortisol, venous CO <sub>2</sub> )

TABLE 1. (continued)

Control of Demand		Characteristics and Expectancy Biases			Patients	Subjects Controls	Matching	Criteria for Panic Attacks		Dependent Measures	Other Criticisms
Study	Infusions	Combination of Designs A and B: Comparison of Three Infusions, Each Preceded and Followed by Placebo Infusions			N = 11, PD N = 10	N = 10 ?		Unspecified anxiety and RDC panic symptoms	STAI and Hamilton anxiety scales (4 x), panic SR, blood gases and catecholamines (4 x), HR, RR, SCL, EMG, finger temperature	B, not completely overlapping samples reported in different papers, higher ratio of men in control group partly explains HR differences	
	a) 20' 1/1 sl b) 20' D <sub>5</sub> W c) 20' of 20g isoproterenol in D <sub>5</sub> W and followed by 10' D <sub>5</sub> W	Double-blind, (blind?) staff attending, no information about instructions									
	Freedman et al. (41)	All preceded instructions									
*Abbreviations:											
20' 1/2 sl:	Half molar racemic (D/L) sodium lactate is given at a rate of 10 ml/kg body weight for 20 min or until a panic attacks occurred. Pitts and McClure (25) and Fink et al. (44) always continued for 20 min. It is unclear when Lapiere et al. (38) stopped.										
20' 1/1 sl:	Same as above, but 1 molar sodium lactate given at rate of 5 ml/kg body weight [Bonn et al. (45, 46)] or 6 ml/kg body weight [Rainey et al. (39, 40), Freedman et al. (41)].										
CaCl <sub>2</sub> :	Calcium chloride.										
D <sub>5</sub> W:	Five percent dextrose in water.										
NaCl:	Sodium chloride.										
AG:	Patients fulfill the DSM-III criteria for agoraphobia with panic attacks.										
GAD:	Patients fulfill the DSM-III criteria for generalized anxiety disorder.										
PD:	Patients fulfill the DSM-III criteria for panic disorder.										
AEP:	Auditory evoked potential.										
API:	Acute Panic Inventory [cf. Liebowitz et al. (29, 31)]										
Methodologic Criticisms:											
A: Generally insufficient information about relevant parameters of the study.											
B: No continuous monitoring of subjective anxiety.											
C: No data on subjective anxiety (no standard measure of anxiety).											

TABLE 2. Overview of Studies Without Comparison Groups<sup>a</sup>

Study	Infusions	Control of Demand Characteristics and Expectancy Biases	Patients	Criteria for Panic Attacks	Dependent Measures	Other Criticisms
<i>Design A: Different Infusions on Separate Days</i> Haslam (47)	a) 20' 1/2 sl b) 20' glucose in NaCl *	Double-blind, patients were "aware of nature and purpose of trial"	N = 16, presumably GAD and agoraphobia	?	Anxiety self-rating scale	A, B, D, heterogeneous patient group
<i>Design B: Sequential Infusions on the Same Day</i> Knott et al. (37)	a) D <sub>3</sub> W (time ?) b) 20' 1/2 sl	Single-blind, patients alone during infusion, different drip rates, sufficient instructions	N = 6, PD and AG	?	Unstandardized patient reports lever pressing, EEG and AEP (unspecified time samples), vEOG, HR, SCL, NSF, EMG ratings, API (3 x), EEG, BP (unspecified)	A, C
Gorman et al. (34)	a) 30' D <sub>3</sub> W (slow) b) 20' 1/2 sl	Single-blind, nonblind observers present, different drip rates, no information about instructions	N = 6, PD and AG	?	Unspecified observer ratings, API (3 x), EEG, BP (unspecified)	A, C
Gorman et al. (35)	Same as Gorman et al. (34)	Same as Gorman et al. (34)	N = 10, PD and AG	?	Apparently only unspecified patient statements and blood glucose levels (3 x)	A, B, D, only valid as study of lactate effects on blood glucose levels
<sup>a</sup> Abbreviations: 20' 1/2 sl: Half molar racemic (D/L) sodium lactate is given at rate of 10 ml/kg body weight for 20 min or until a panic attack occurs. Haslam (47) always continued for 20 min. It is unclear when Knott et al. (37) stopped. NaCl: Sodium chloride. D <sub>3</sub> W: Five percent dextrose in water. AG: Patients fulfill the DSM-III criteria for agoraphobia with panic attacks. GAD: Patients fulfill the DSM-III criteria for generalized anxiety disorder. PD: Patients fulfill the DSM-III criteria for panic disorder. AEP: Auditory evoked potential. API: Acute Panic inventory [cf. Liebowitz et al., (29, 31)]. BP: Blood pressure.						
				EEG: EMG: HR: NSF: RR: SCL: EOG:	Electroencephalogram. Electromyogram. Heart rate Nonspecific skin conductance fluctuations. Respiration rate Skin conductance level Vertical electrooculogram (for blinks and eye movements).	
				<i>Methodologic Criticisms:</i> A: Generally insufficient information about relevant parameters of the study. B: No continuous monitoring of subjective anxiety. C: No data on subjective anxiety (no standard measure of anxiety). D: Measures restricted to self-reports of symptoms.		

important, although not definitive information, since the convergence may also be due to shared methodologic inadequacies.

#### **INCIDENCE OF LACTATE- AND PLACEBO-INDUCED PANIC IN PATIENTS AND CONTROLS**

The results of the eight comparisons of patients and controls are shown in Table 3. There were clear differences in the responses of patients and controls to both lactate and placebo. Across all studies, 56% of the patients (110 of 197) panicked after roughly 12 min of lactate infusion whereas only 9% of the nonclinical control subjects (7 of 76) panicked, usually after a longer period of time [15–18 min—Kelly et al. (48, 49) and Rainey et al. (39–41)]. Similarly, up to 36% of the patients (39–41) as compared to 0% of the controls panicked on placebo. The greater responsiveness to placebo in patients is an important finding. Nonspecific factors are likely to be involved in their response to the lactate infusions as well. Thus the basic finding of patients responding differently from controls may be more true of the response to placebo than the response to lactate. However, the difference in response to lactate and to placebo clearly indicates an active effect of lactate both on patients and, to a lesser degree, on controls. In interpreting these results, we have to take into consideration the methodologic shortcomings discussed above. Especially relevant in the context of possible placebo effects is the issue of insufficient control of expectancy bias and demand characteristics.

A panic rate in controls of up to 30% (39–41) and no significant difference between the panic rates of panic patients and patients with generalized anxiety disorder

[Lapierre et al. (38)—26.1% vs. 12.5%] indicate a lack of specificity of the lactate procedure that invalidates its clinical usefulness for discriminating between diagnostic groups.

The four studies without comparison groups are not included in the above analysis since they do not give data on control subjects and were generally less methodologically adequate. They may, however, provide useful information on specific questions, such as a possible contribution of hypoglycemia or the blocking effects of propranolol. [Their percentages of panic attacks in patients under lactate range from 65% (ref. 47—a total of 16 patients) to 100% (refs. 34, 35, and 37—a total of 22 patients).]

Interestingly, all studies yielding 100% panic rates in patients used samples of 10 or fewer patients. There is a strong negative correlation of  $-0.83$  [Spearman rank correlation, Siegel (50)] between sample size and percentage of patients panicking under lactate, meaning that bigger samples yield fewer panicking patients. This correlation could indicate a publication bias in that small samples are only published when rates are high, or that the experimenters give more personal attention to subjects in small studies and select them for more severe illness or create stronger implicit demands on them to panic during infusion. The only double-blind study relying entirely on automatized (noninteractive) self-report of panic symptoms as criterion for panic attacks found a clearly lower proportion of attacks in patients than all other studies, namely 26% (38). Although this lower proportion could also be due to the 500-ml limit that Lapierre et al. imposed on their infusion (0.5 molar sodium lactate, 10 ml/kg/20 min), the average panic attack is reported to occur at doses well below 500 ml of 0.5 molar so-



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TABLE 3. Proportion of Panic Attacks in Nine Studies with Comparison Groups

Study	Number of Patients/ Controls	Percent Panic Attacks Under Placebo (P) and Lactate (L)						Mean Time to Panic
		Panic Patients		Controls		GAD Patients		
		P	L	P	L	P	L	
Pitts and McClure (25)	14/10	0	93	0	20	—	—	1'–2'
Fink et al. (44)	5/4	0	100	0	25	—	—	8'–12'
Kelly et al. (48) <sup>a,b</sup>	20/10	5	80 <sup>a,b</sup>	0	10	—	—	12'
posttreatment	8	13	25, “less severe”: 50	—	—	—	—	?
Bonn et al (45, 46) <sup>c</sup>	20/9	0	“overt panic”: 20 “would have”: 60 <sup>d</sup>	?	? <sup>c</sup>	—	—	14'
Rifkin et al (27)	9/7	0	100	0	0	—	—	?
posttreatment	6	0	0	—	—	—	—	—
Appleby et al. (26) <sup>e</sup>	25/15	16	64 <sup>a</sup>	0	0	—	—	15'
Liebowitz et al. (28, 31)	43/20	7	72	0	0	—	—	12'
posttreatment	27	0	15	—	—	—	—	?
Lapierre et al. (38) <sup>e</sup>	23/16 <sup>c</sup>	0	26	—	—	0	13	?
Rainey et al. (39, 40), Freedman et al. (41) <sup>f</sup>	11/10 <sup>f</sup>	36	91	0	30	—	—	11'

<sup>a</sup>Some patients panicked after the end of the lactate infusion [Kelly et al. (48)—5%, Appleby et al (26)—4%].

<sup>b</sup>An unspecified number of patients reported only the "physiological concomitants of anxiety without the usual degree of mental fear" (48, p. 133).

<sup>c</sup>Although the total number of patients was 24, results are reported for 20 patients only. Results for controls are not reported.

<sup>d</sup>Twelve patients "would have panicked but for your presence, doctor" [Bonn et al. (45), p. 469].

<sup>e</sup>Lapierre et al. (38) compared 23 panic patients with 16 generalized anxiety disorder patients.

<sup>f</sup>Lapierre et al. (38) compared 23 panic patients with 16 generalized anxiety disorder patients.

<sup>f</sup>Results are based on the larger sample of the Rainey et al. papers (39, 40), not on the smaller *N* of Freedman et al. (41).

dium lactate (average onset time is about 12 min; cf. Table 3).

A general problem in all attempts to establish the incidence of panic attacks is that they show considerable variation across and within individuals and that there are no generally accepted objective criteria for panic attacks. In our opinion, the best approach is to record in detail the symptoms experienced and concomitant physiologic changes. This comprehensive approach is the only one that permits comparisons across studies and minimizes the influence of experimenter bias.

#### **SPECIFIC EFFECTS OF LACTATE INFUSIONS**

##### **Self-Reported Symptoms and Subjective Anxiety**

Table 4 shows the occurrence of self-reported symptoms of lactate infusions in patients and controls in the five studies that provide this information. Significant numbers of symptoms related to anxiety and distress were described as accompanying lactate infusions. The symptoms were significantly more frequent and intense under lactate than under placebo in all of these studies. Similarly, the average effects were stronger in patients than in controls in those studies that reported values for both groups. However, the controls still reported a significant number of symptoms under lactate, which were qualitatively comparable to those reported by the patients. Unfortunately, the symptom lists used were not comparable across all studies and did not contain control scales for response styles. Moreover, symptoms were established only by self-report, no behavioral measures were taken, and concurrent

validation from psychophysiologic measures was largely missing.

Three studies employed standard anxiety measures that have been widely used in other settings: subjective units-of-discomfort scales, the Hamilton Anxiety Scale, and the State-Trait Anxiety Inventory (STAI). The results on a 10-point subjective units-of-discomfort scale were 7.9 for patients and 6 for controls (48, 49). Rainey et al. (39-41) found Hamilton Anxiety Scale scores of 30 and 7 as well as STAI scores of 54 and 38 (state form) for patients and controls, respectively (numbers derived from graphs in these reports). Thus, overall only moderate levels of anxiety were reached. The scores on the psychometric STAI are within one standard deviation of the mean of Spielberger et al.'s (51) general sample of neuropsychiatric patients (T-scores of 55 and 43, compared to an undergraduate sample 66 and 55). Lapierre et al. (38) reported scores of about 5 on the 10-point numeric transformation of their visual analog anxiety scale for the subgroup of patients who panicked (nonpanickers averaged 0). Thus, although lactate induces a considerable number of self-reported symptoms in patients and (to a lesser degree) in controls, much lower levels of subjective anxiety were reached than one would expect for "panic attacks."

Since the definition of panic attacks clearly specifies sudden onset and limited duration as criteria (14, pp. 230-231), the time course of the effects of lactate should be closely monitored. Only Kelly et al., (48, 49) attempted this. All of the other studies we have discussed could be doubted by a radical critic as ignoring the distinguishing "attack" property of the anxiety experience, and instead concentrating on nonspecific sustained components of anxiety. From a practical point of view, there is a trade-off between the comprehensive-

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Table 4. Self-Reported Symptoms

Symptom	Pitts and McClure (25)		Kelly et al (48)		Bonn et al. (45)		Rifkin et al. (27)		Liebowitz et al. (28, 31) <sup>a</sup>	
	P <sup>b</sup>	C <sup>b</sup>	P	C	P	C	P	C	P	C
<i>Symptom List by Pitts and McClure (25)</i>										
Paresthesias <sup>c</sup>	100	100	75	60	58	<sup>d</sup>	100	100		<sup>d</sup>
Tremor <sup>c</sup>	100	50	90	100	75		100	100		
Shakiness <sup>c</sup>	100	80	100	60						
Dizziness <sup>c</sup>	93	40	45	10					58 <sup>a</sup>	
Palpitations <sup>c</sup>	93	50	75	60	50				66	
Giddiness	93	50	70	10						
Cold <sup>c</sup>	79	30	65	10						
Nervousness	79	60	95	40						
Dyspnea <sup>c</sup>	71	30	65	50					67	
Chest pain or constriction <sup>c</sup>	64	0	50	40					50	
Blurred vision	64	30	30	20						
Nervous chill <sup>c</sup>	64	10	45	10						
Weakness	57	50	80	40						
Lump in throat	50	10	35	10						
Headache	50	50	60	30						
Smothering <sup>c</sup>	43	10	35	0						
Sighing	43	10	70	60	33					
Faintness <sup>c</sup>	36	20	40	10					29	
Irritability	36	10	80	20						
Nausea	29	30	45	30					26	
Choking <sup>c</sup>	14	0	30	0						
<i>Symptoms not Included in Pitts' and McClure's Original List</i>										
Dysphoria					92					
Vibration					74					
Dry mouth					71					
Twitching					33				76	
Difficulty doing job									90	
Fearfulness									79	
Difficulty concentrating									58	
Difficulty speaking									53	
Confusion					38				45	
Fear of dying <sup>c</sup>									41	
Sweating <sup>c</sup>									36	
Urgency to urinate									36	
Detachment from body <sup>c</sup>									20	
Sense of unreality <sup>c</sup>									14	
Urgency to defecate									3	

<sup>a</sup>Liebowitz et al (28, 31) do not give the proportion of subjects experiencing these symptoms. Instead, the average intensity of symptoms (scale from 0 to 3) is reported. We transformed the results to percent of the maximal intensity. Thus, the percentages listed for Liebowitz et al. are not directly comparable to the other studies.

<sup>b</sup>The percentage of patients (P) and controls (C) experiencing symptoms.

<sup>c</sup>DSM-III symptom.

<sup>d</sup>No information about controls is given by Bonn et al. (45) and Liebowitz et al. (28, 31)

ness of self-reports and how frequently they can be given. One advantage of most psychophysiological measures is that they can be monitored continuously.

#### Psychophysiological Measures

In panic attack research, psychophysiological measures can be chosen to assess the activity of the different parts of the nervous system or to provide objective reflections of different symptom groups. In the first case, one could choose measures representing central (CNS), autonomic and somatic nervous system events. In the second case, one could choose measures of cardiac, pulmonary, sweat gland, and muscle activities. Both strategies have been followed in practice [e.g. Lapierre et al. (38), strategy 1; Freedman et al. (41), strategy 2]. Table 5 gives the results on psychologic measures reported in eight studies.

In summary, the data show clear and consistent increases in autonomic (heart rate, blood pressure, skin conductance level, forearm blood flow) activity, whereas nonautonomic indicators of somatic activity (electromyogram, respiration rate) fail to show consistent changes. Interestingly, the commonly reported pulmonary and muscular symptoms are not reflected in objective respiration rate and EMG measures. The CNS changes reported are typical for anxiety patients in general (52) and can be interpreted as indicators of overarousal (38, 53).

#### Biochemical Measures

Table 6 shows changes in biochemical measures during lactate infusions. Many of the effects may be direct reflections of the infused lactate, such as hypocalcemia and mild metabolic alkalosis. Hypogly-

cemia was not observed. In contrast to the results from psychophysiological and self-report measures, the biochemical findings do not consistently indicate heightened arousal or stress-related changes in hormones. The lack of consistent changes in peripheral catecholamines might be the biochemical expression of the rather moderate levels of subjective anxiety discussed above. Similarly, the decreases in cortisol levels argue against a powerful stressor-effect of lactate infusions. Although effects for bicarbonate and  $pCO_2$  were more marked in panicking subjects than in nonpanicking subjects (33), the changes were generally in the same direction in all subjects. At baseline, subsequent lactate panickers had greater sympathetic arousal (33).

Psychophysiological and biochemical changes occurred in most subjects regardless of diagnostic category and of observer determination of panic attacks. There was no psychophysiological, biochemical, or self-report measure that reliably and consistently differentiated panic attacks from nonattack periods, or lactate-induced from isoproterenol or placebo-induced attacks. No single variable has been shown to be a necessary or sufficient condition for panic attacks. Thus, the psychophysiological and biochemical findings fail to provide objective and reliable criteria for panic attacks and to distinguish reliably between patients and controls.

#### Quantitative or Qualitative Differences Between Patients and Controls?

In the preceding sections, we have described differences between patients and controls in response to lactate. Are these differences qualitative or quantitative? Significant qualitative differences would exist if core symptoms occurred exclu-

TABLE 5. Psychophysiological Measures<sup>a</sup>

Measure	Fink et al. (44)	Kelly et al. (48)	Bonn et al. (45, 46)	Knott et al. (37)	Corman et al. 1983 (34)	Rainey et al. (39, 40) Freedman et al. (41)	Liebowitz et al. (28, 31, 33)	Lapierre et al. (38) <sup>b</sup>
Heart rate	increased	increased	increased	increased	increased	increased	increased <sup>c</sup>	increased <sup>b</sup>
Blood pressure					increased systolic		increased systolic <sup>c</sup>	
Forearm blood flow		increased						
Forearm electromyogram			increased	increased		no change		increased <sup>b</sup>
Respiration rate			no change			no change		
Electroencephalogram	increased beta, decreased alpha for patients			increased beta, decreased alpha in delta				increased delta <sup>b</sup>
Auditory evoked potentials				decreased P2 and N2 amplitudes				no change
Contingent negative variation								no change
Vertical electro-oculogram				increased blink rate				increased blink rate <sup>b</sup>
Skin conductance level				increased <sup>f</sup>		increased <sup>d</sup>		no change
Nonspecific fluctuations				increased <sup>e</sup>				no change
Skin temperature		increased over neck, decreased over hand						
Finger temperature						no change		

<sup>a</sup>Marked increases/decreases occurred in all subjects unless otherwise specified. No change means that no significant specific changes due to lactate were reported.

<sup>b</sup>Lapierre et al. (38) report significant changes only in panicking patients, not in the other subjects. Thus these changes refer only to the panickers.

<sup>c</sup>Greater increases in panickers than in nonpanickers.

<sup>d</sup>Systolic blood pressure increased in most subjects, diastolic only in 50% of the panickers.

<sup>e</sup>Skin conductance level and nonspecific fluctuations increased constantly over the sessions, regardless of whether lactate or placebo was given.

<sup>f</sup>Nonspecific fluctuations in this study increased more under the placebo condition than under the lactate condition.

**Table 6. Biochemical Measures During Lactate Infusion<sup>a</sup>**

Measure	Bonn et al. (45, 46)	Appleby et al. (26)	Gorman et al. (35)	Liebowitz et al. (28, 29, 31, 33)
Lactate	increased			increased
Pyruvate				increased
Blood glucose			no change	
Venous pH				increased
pCO <sub>2</sub>				decreased <sup>b</sup>
Ionized calcium	decreased			decreased
Phosphate	decreased			decreased
Prolactin		increased		increased
Cortisol		no change		decreased <sup>c</sup>
Testosterone		decreased in males		
Epinephrine		increased with panic		no change
Norepinephrine		no change		no change <sup>d</sup>
Bicarbonate	increased			increased

<sup>a</sup>Increases/decreases occurred in patients and controls unless specified otherwise. "No change" means that no significant changes were observed.

<sup>b</sup>Significantly greater changes for panickers than for nonpanickers.

<sup>c</sup>Smaller decreases in panickers than in nonpanickers at 10 min of lactate only (not at 20 min)

<sup>d</sup>At 5 min of lactate (not at 10, 15, or 20 min) panickers had higher levels than nonpanickers.

sively in patients, or if clearly different patterns of symptoms were observed. Table 4 shows that all symptoms with the exception of choking and smothering have been found in both patients and controls. We concluded above that no psychophysiologic or biochemical measure reliably and consistently discriminated between groups. The response profiles in both groups are characterized by paresthesias, tremor and shakiness, dizziness, palpitations, giddiness, dyspnea, and nervousness as well as increased autonomic arousal, hypocalcemia, and mild alkalosis. The lack of qualitative differences between patients and controls in anxiety research in general has led Lader to the conclusion that "pathological anxiety seems to differ only in degree and not in quality from normal anxiety" (54, p. 559; cf. 52, 55-57). Moreover, there appears to be no qualitative difference between the responsiveness of the av-

erage patient and the average control for measures of anxiety and heart rate. Although patients reach higher levels of subjective anxiety and heart rate during lactate infusions, the actual increase from baseline to lactate levels is consistently similar for controls and patients (28-31, 33, 39-41, 48, 49). Together, these findings suggest that lactate has no specific action on panic patients.

#### **SIMILARITY OF LACTATE-INDUCED AND NATURALLY OCCURRING PANIC**

One approach to the question of similarity is to compare the symptoms of both phenomena. Though comprehensive research on the phenomenology of natural panic attacks is largely missing, we can compare lactate-induced symptoms with

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the symptoms of panic attacks listed in DSM-III. A look at Table 4 shows that there is considerable overlap. All 12 symptom groups listed in DSM-III were registered in at least one study, 9 in at least two studies, and 7 in three or more studies of lactate infusions. The percentages of patients experiencing these symptoms varied from 14% to 100% (controls: 0%–100%). However, this approach does not tell us whether individuals experience their personal configuration of symptoms for natural and lactate-inducing panic to be similar.

A second approach is to compare standardized similarity ratings of natural and lactate-induced attacks. So far, only two studies report direct evaluations of similarity. Rainey et al. (40) directly asked their subjects for a similarity rating. Of the 12 panic attacks recorded under lactate, 3 were rated as somewhat or moderately similar, 7 as very much so, and 2 as identical. The ratings for isoproterenol were similar. Of the six placebo-induced panic attacks, one was rated not at all identical and five as somewhat or moderately similar to naturally occurring panic. Liebowitz et al. (31) compared psychologist ratings of patient reports of natural attacks with ratings of lactate-induced panic using a 17-item "acute panic inventory." They found significant differences for the items fear of dying, confusion, sense of unreality, difficulty with concentration, and sweating, which were higher in usual panic. Lactate panics were accompanied by greater urinary urgency and twitching, which were considered direct effects of the infused volume and lactate-induced hypocalcemia.

Further information about similarity can be inferred from two other studies. Kelly et al. report that an unspecified number of patients experienced only "the physiological concomitants of anxiety without the

usual degree of mental fear" (48, p. 133) when infused with lactate. Bonn et al. (45, 46) reported that of 20 patients only 4 (20%) experienced overt panic, whereas 12 (60%) "would have panicked but for your presence, doctor," 3 (15%) experienced "prelude" to panic, and 1 (5%) experienced no "mood change." No patients thought that lactate resulted in an "exact reproduction" of their natural attacks. These results strikingly resemble Maranon's (58) finding that epinephrine injections resulted in so-called cold or as if emotions. Five other studies did not report data on subjective anxiety during their "panic attacks" (criticism "C" in Tables 1 and 2), making it impossible to judge whether the "intense apprehension, fear, or terror" required as part of panic attacks by DSM-III (14, p. 230) was present.

A third approach is comparison of physiologic data. However, for natural panic attacks these data are still sparse. Lader and Mathews (59) recorded heart rate increases of 40–51 bpm in three spontaneous attacks occurring in their laboratory. Taylor et al. (60, 61) measured ambulatory heart rate and observed increases disproportionate to physical activity levels in up to 58% of all self-reported panic attacks. Mean increases were 38.6 bpm. Although heart rate increases with lactate, the increases are considerably lower [average 21 bpm, calculated from seven studies (33–35, 37, 38, 41, 45, 46)]. They are in the range of the 19 bpm recorded in normal students before examinations (62), but much less than the 145 bpm reached by inexperienced parachutists before jumping (63).

It is important to note that lactate researchers have restricted their assessments to a single emotion—anxiety. Thus it is impossible to judge whether lactate specifically increases anxiety or whether

a more general discomfort is induced, of which anxiety may be only a part. Although anxiety may be similar in natural panic attacks, other feelings may be quite different. The only study to evaluate depressed mood did not give information about changes over time or baselines but did find significantly greater peak values for patients than for controls (48).

Thus, the question of similarity is still open. Although there are unquestionable similarities in symptoms and physiologic changes, there are not enough direct and comprehensive investigations of this issue. Both subjective anxiety and heart rates accompanying lactate infusions are relatively moderate, and comparable data on natural panic attacks are lacking.

#### **INFLUENCE OF BASELINE LEVELS OF ANXIETY AND AROUSAL**

In the preceding section we have shown that diagnostic category predicts the level of anxiety and autonomic arousal that subjects reach under lactate. In addition, the baseline (prelactate) values of anxiety and autonomic arousal seem to be a strong predictor of panic response to lactate. The evidence for this is twofold. First, patients as a group are more likely to panic, and as a group they have higher baseline values than do controls for anxiety (28–31, 33, 39–41, 48, 49), heart rate, systolic blood pressure, and forearm blood flow (31, 34, 48). Bicarbonate and  $\text{pCO}_2$  levels were lower (33, 45, 46). Second, among patients, those with higher fearfulness, diastolic blood pressure, and heart rates at baseline are more likely to go on to panic (28–31, 33).

That baseline state can influence the effects of arousing drugs had been reported as early as 1924. Maranon (58) found that whether a subject responded to an epi-

nephine injection with more pronounced and genuine emotions or with weak and "as if" emotions depended on whether the subject was excited or calm before the injection.

The baseline differences between groups may reflect acute anticipatory anxiety rather than chronic differences in level. For example, Liebowitz et al. (33) report that heart rate differences between groups were less marked on a prior testing day on which subjects knew they would not receive lactate. Lactate may simply add to the elevated baseline arousal associated with anticipatory anxiety, and push more highly aroused subjects across a tolerance threshold.

In our own laboratory we recently completed a study that suggests the reactivity of patients and controls to lactate infusions may be the same (64). Subjects with the diagnosis of Panic Disorder or Agoraphobia with Panic Attacks had higher preinfusion subjective anxiety and heart rates than a control group, whereas both groups had equal increases in these measures during infusion. In other words, the groups differed in level but not in reactivity.

#### **POSSIBLE MEDIATORS OF LACTATE EFFECTS**

There are several ways by which a causal chain between lactate infusion and panic might be investigated. The studies reported above looked for psychologic, biochemical, or physiologic correlates of lactate infusions and attempted to establish which ones were most consistently associated with panic. Another approach is to directly manipulate components of the lactate response to discover which are most essential for its panicogenic effect. A third



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approach is to find other agents that induce panic and to look for effects they have in common with lactate that might explain their panic-inducing property.

### Blocking of Response to Lactate

Panic rates of panic patients to lactate infusions are much lower after medium-term treatment (4–17 weeks) with tricyclic antidepressants, MAO inhibitors, and in some cases clonidine and mianserin, than before treatment (27–31, 33, 48, 49). Propranolol, naloxone, and calcium chloride have been tested as acute blockers of lactate effects. Although propranolol lowered tonic levels of heart rate and systolic blood pressure, it failed to alter phasic response to lactate in panic patients (34) and normal subjects (65, 66). Similarly, naloxone did not alter response to lactate in panic patients (32). However, the addition of 20 mM calcium chloride significantly attenuated the effects of lactate infusions (25, 44), although in both studies “the response to lactate-calcium was similar to that of lactate alone, but clearly less intense and of shorter duration . . .” (44, p. 1429). Blockers are not restricted to active pharmacologic agents. The presence of medical personnel during the infusions has been noted to have panic-blocking effects (45, 48, 49).

Unfortunately, except for the calcium chloride studies, blocking studies have not been double blind and have confounded treatment effects with sequence effects, in that the blocker was always given after previous infusions. The importance of sequence effects is underlined by a study of Bonn et al. (45, 46), who gave lactate infusions to 33 patients for 3 weeks twice weekly as a “flooding” procedure. Scores on an anxiety self-rating scale significantly

and greatly decreased over time, and these decreases persisted at a 6-week follow-up.

### Alternative Challenge Techniques

Direct comparisons with lactate have been undertaken for isoproterenol (39–41; cf. 67), bicarbonate (21), CO<sub>2</sub>-inhalation and hyperventilation (36; cf. 68), and placebo. Other reported agents for inducing panic attacks in the laboratory are yohimbine (69–72) and caffeine (72, 73).

While an infusion of 1 µg/min of isoproterenol, a beta agonist, in 6 ml/kg dextrose in water over 20 min (39–41) and the inhalation of a mixture of 5% CO<sub>2</sub> with 95% room air over 20 min produced almost the same rate of panic attacks as lactate, hyperventilation was far less effective (36). In addition, Grosz and Farmer (21) were able to produce symptoms similar to those of lactate by giving 500 mM of sodium bicarbonate (8 ml/kg, 30 min) to ten normal subjects. Placebo infusion can also produce effects similar to lactate in some patients: panic response rates from 0% to 36% have been reported (cf. Tables 3 and 7).

Although not directly compared with lactate, yohimbine, an alpha-2 antagonist, and caffeine have been shown to induce subjective anxiety and autonomic arousal in panic patients and controls (69–72), and even to induce panic attacks in patients (yohimbine, 71, 72) and controls (caffeine, 72, 73). The effects of yohimbine were completely blocked in normals by 10 mg diazepam or 5 µg/kg clonidine.

Surprisingly, psychologic manipulations for inducing or blocking panic have not been explicitly investigated in the context of lactate infusions, although there is evidence that such manipulations could be effective. Van den Hout and Griez (74) were able to manipulate normal subjects’

TABLE 7. Direct Comparisons of Lactate with other Agents<sup>a</sup>

Study	Lactate	Isoproterenol	CO <sub>2</sub>	Hyperventilation	Placebo
Rainey et al. (40)	91	73	—	—	36
Freedman et al. (41) (N = 11)					
Gorman et al. (36) (N = 12)	67	—	58	25	—

<sup>a</sup>The percentage of patients that reported to have had panic attacks is presented. A dash indicates that this condition was not part of the study concerned.

responses to short inhalations of a 35:65 CO<sub>2</sub>-air mixture in the direction of either tension/unpleasant or relaxation/pleasant by different instructions.

#### Proposed Biologic Mechanisms

Pitts and McClure (25, 42, 75) originally proposed a causal link between elevated serum lactate and pathologic anxiety. However, several methodologic criticisms of the evidence and conflicting empirical findings made it clear that elevated serum lactate was neither a necessary nor a sufficient condition for pathologic anxiety (18–24). Similarly Pitts's (76, 77) recent proposal of a beta-adrenergic mechanism has been refuted by the failure of propranolol to block the effects of lactate infusions (34, 65, 66).

A number of biologic mechanisms are currently being discussed as explanations for the effects of lactate infusions (20, 21, 33, 35, 36, 43, 78, 79). Some of these are based on peripheral physiologic changes like the James-Lange theory of emotion and, as such, are subject to its criticisms (cf. 52, 80–82), whereas others are more central. In either case, it has been impossible to show that single mechanisms are necessary or suffi-

cient for panic. Lactate-induced panic can occur without peripheral catecholamine surges, hyperventilation, or hypoglycemia; thus, these mechanisms are not necessary causes. Hypocalcemia and alkalosis may occur in people who do not panic; thus, these mechanisms are not sufficient causes (cf. Tables 5 and 6). For one recent theory that postulates a shift in the ratio of NAD<sup>+</sup> to NADH, crucial data are still missing; the effects of D- and L-lactate need to be compared since the former does not lead to a redox shift (33, 43, 79).

Carr and Sheehan (43) hypothesize that panic patients have central chemoreceptor hypersensitivity. They assume that "pH or CO<sub>2</sub> changes that would have little or no effect on normals would produce significant excitatory effects on brain stem chemoreceptors in panic patients, with secondary excitation of central sympathetic neurons." (33) This implies that lactate should have little or no effect on normals but significant effects on patients. Carr and Sheehan (43) explicitly claim that normals do not complain about "noxious effects of lactate" and that patients do not panic under placebo. However, the studies reviewed above do not support this claim.

Finally, the similarity of common phys-

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biologic changes during lactate infusions to the results of central sympathetic activation, such as heart rate and blood pressure increases, has led several authors to explain lactate-induced panic as a dysfunction of the structures and neurotransmitters subserving this activation (33, 36, 79). This would be consistent with the anxiety-inducing effects of other noradrenergic and adrenergic agents presented above. The specific brain structure advanced most often in this context is the locus ceruleus in the dorsolateral tegmentum of the pons (33, 36, 71, 79, 83, 84). This nucleus contains more than half of the cerebral noradrenergic neurons. The locus ceruleus model of noradrenergic discharge is in keeping with the panic suppressing effects of clonidine, an  $\alpha$ -2 agonist (31, 69, 85, 86), the tricyclics (2), and diazepam (87), since all inhibit locus ceruleus firing (88–90). Increased firing of the noradrenergic neurons of the locus ceruleus also offers a possible common pathway for the panicogenic effects of lactate and  $\text{CO}_2$  (36). Elevated cerebral  $\text{CO}_2$  has been shown in animals to increase the firing rate of its noradrenergic neurons (91).  $\text{CO}_2$ , a metabolic product of L-lactate, is able to cross the brain–blood barrier freely and thus might transiently build up cerebrally in spite of a peripheral decrease in  $\text{pCO}_2$  (33). Thus, there is considerable reason to argue for an involvement of noradrenergic discharge in the locus ceruleus in the effects of lactate infusions.

However, there are many problems with this model. Not even the most frequent sympathomimetic concomitants of lactate-induced panic are present in all attacks, and the same changes appear in a substantial group of subjects that do not panic. Similarly, the evidence from the studies with propranolol and clonidine is

equivocal. Propranolol neither blocks lactate-induced panic (34, 65) nor is significantly better than placebo in the treatment of natural panic (87). The anxiolytic effect of clonidine wears off within weeks and it may even worsen anxiety (85, 92). Furthermore, clonidine may act on nonadrenergic systems (93–96). With regard to the locus ceruleus, animal studies show that it responds to a variety of nonanxiety stimuli (97), and other brain areas respond to anxiety stimuli as well. Pharmacologically specific lesions of noradrenergic systems of the locus ceruleus in rats do not have anxiolytic effects (94). The locus ceruleus seems to be involved in a more global noradrenergic “alarm” system, whereas “anxiety” may be more specifically related to benzodiazepine/GABA-systems (91, 94, 98–101).

More generally, purely biologic theories of lactate effects make the assumption of “identity” (102): they imply a one-to-one relationship between a pattern of physiologic or biochemical processes and specific behaviors or psychological states. However, significant proportions of subjects show no or very little response to lactate in both patient and control groups, and repeated lactate infusions have been effectively used as a treatment. The response to lactate is modulated by cognitive variables as expressed in Bonn’s and Kelly’s findings of physiologic symptoms without subjective anxiety, the placebo responsiveness of patients, and the relevance of anticipation shown in the predictive power of infusion day baseline values. No central or peripheral physiologic change investigated to date is a sufficient or necessary condition for lactate-induced panic. In general, research on emotions has long rejected the assumption of identity (52, 55, 82, 103–106).

# A Cognitive Psychophysiological Formulation

Panic is extreme anxiety and, as such, an emotional state (52, 57, 107, 108). Emotions are generally regarded as complex organized states with several components (103, 106, 109–115). Although different views about the classification of different emotions and the theoretical formulation of cognitive variables exist, modern research has established an unequivocal experimental basis for the role of cognitive and physiologic variables in emotions in general and in anxiety in particular (52, 55, 82, 103, 105, 106, 111–114, 116–123). However, both experimental research on lactate infusions and the theoretical explanations of its effects have neglected cognitive variables.

Experimentally identified cognitive parameters of great relevance for anxiety induction studies include past experience (133, 134), expectancy and anticipation (109, 124, 125), appraisal of external and internal cues (109, 114, 126), helplessness (126), uncertainty and unpredictability (109, 124, 128, 129), and the perception of threat/harm (109, 124, 130, 131), response unavailability (124), control (129–131), situational cues (102, 132, 134), and bodily feelings (correct or incorrect; 117, 118, 121, 135–138). The preceding excitatory state of the organism also has been shown to influence emotional responses (124). Furthermore, the concept that organisms are genetically prepared to learn phobic responses to certain specific stimuli (139) must be taken into consideration.

The importance of cognitive variables has been demonstrated in the body of literature on epinephrine challenges and anxiety, a topic with striking parallels to that of lactate infusion and panic. Some of these parallels are exemplified by Basow-

itz et al. (133). They infused epinephrine in normal volunteers, using a design almost identical to that of Rainey et al. (39–41). The pattern of epinephrine- or placebo-induced symptoms was best predicted by the individual's own prior anxiety experiences. In addition, subjects determined to be more emotion-prone in a preceding interview responded with more genuine anxiety. Basowitz et al. also noted that the "anxiety" often had a "cold" quality and was generally milder than natural anxiety. Breggin (134) concluded on the basis of an extensive review of the literature on epinephrine challenges that apparent inconsistencies in those results could be eliminated by taking into account the presence of two variables:

1. Previously learned association of sympathomimetic symptoms and acute anxiety
2. Anxiety-related cues in the experimental environment

When these two variables are not present to high degrees, the emotions produced have a cold or "as if" quality, as in the previously quoted experiments of Maranon (58), Basowitz et al. (133), Bonn et al. (45, 46), and Kelly et al. (48, 49). This finding was noted both in the pioneering studies of Tompkins et al. (140), Wearn and Sturgis (141), Maranon (58), and Basowitz et al. (133), and in recent studies (52, 77, 81, 135).

Only one of the theories put forward to explain the effects of lactate takes into account biologic and cognitive variables. Ackerman and Sachar (24) proposed a conditioned phobic response to single symptoms or patterns of symptoms of anxiety as the panic-inducing mechanisms in lactate infusions. This hypothesis can explain the differences between patients and controls as being due to a learned phobic response to bodily sensations that can be

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mimicked by lactate. It also can explain the apparent therapeutic success of repeated lactate administrations (and CO<sub>2</sub> inhalations, 47, 68) as extinction. It is congruent with the anxiety-provoking effect of falsely elevated heart rate feedback (117, 118, 137), and the greater treatment success of beta-blocking agents in somatic rather than psychic anxiety (101, 135, 142).

Although Ackerman and Sachar stress the relevance of cognitive factors in modulating the phobic response to somatic symptoms, they are vague on how this modulation takes place. For this reason Ackerman and Sachar have been misunderstood as advancing a nonspecific stress hypothesis (e.g., 33, 79). Their hypothesis is nonspecific in the sense that they do not assume a single specific biologic "stressor," but specific in the sense that it postulates individual-specific learned associations of bodily symptoms with mental states. Thus, the fact that other stress tests such as cold-pressor or mental arithmetic do not provoke panic attacks in panic patients (79) is not a valid argument against Ackerman and Sachar's hypothesis, since the pattern of symptoms produced by these tests might not have been previously associated with panic. The symptoms of hypoglycemia may be more like panic symptoms, but the one study inducing hypoglycemia in panic patients (143) induced it gradually over 3–5 hr and thus failed to mimic the abrupt and rapid onset of symptoms typical for panic attacks. This might explain why no panic attacks were precipitated.

However, the explanatory power of Ackerman and Sachar's original formulation can be considerably enhanced by explicitly taking into account cognitive variables and their interactions with physiologic variables. The data from lactate studies may be best explained by a

cognitive psychophysiologic approach focusing on the association of perceived bodily symptoms with past panic attacks in the following way:

The subject has learned to associate certain bodily sensations with acute anxiety by a process of repeated interoceptive conditioning and subsequent cognitive elaboration. Phobic (anxiety-relevant) stimuli and especially interoceptive stimuli are learned faster and are more resistant to extinction than other stimuli (144–146). The pattern of sensations may differ between people or within an individual at different times, depending on new learning experiences and changes in the internal physiologic "environment." However, the pattern of sensations constitutes a complex anxiety stimulus specific to each individual and derived from past experience. Not all symptoms will be associated equally easily with anxiety, since genetic preparedness makes some more easily learned (139). The fact that panic patients develop individually highly characteristic and stable descriptions of the symptoms associated with their panic attacks points to the role of individual response stereotypy in these attacks. The existence of individually specific physiologic response patterns is well documented (147–149).

Lactate infusions induce anxiety-relevant sensation patterns in a significant proportion of subjects. The response to this stimulus pattern depends on the perception of the bodily changes and on the appraisal of environmental and internal cues in terms of perceived uncertainty, threat/potential harm, and availability of responses or coping strategies. Therefore, instructions and other cues in the experimental environment are crucial variables in anxiety-induction studies. The appraisal process is influenced by both trait variables (individual differences due to

learning history and genetic endowment of the individuals) and state variables (e.g., the preceding excitatory state of the organism or situational determinants). This process is dynamic in the sense that its outcome may lead to changes in emotional state, physiology, general behavior, and environment, which in turn constitute new stimuli and trigger a new cycle of appraisal, etc. This dynamic process can produce a positive feedback loop where the appraisal of the lactate anxiety as being genuine results in an ascending spiral of anxiety and arousal.

This formulation explains 1) the higher panic rate during lactate in patients with panic attacks or Generalized Anxiety Disorder in terms of more numerous or stronger learned associations and higher prior arousal, 2) the higher response to placebo infusions in patients in terms of higher prior arousal and negative expectancies partially related to past anxiety experiences, 3) the higher rate of anxiety responses to lactate than to other agents in terms of closer resemblance of lactate's effects to learned concomitants of anxiety, 4) the effects of baseline levels in terms of prior arousal, anxious cognitions, and negative expectancy, and 5) the anxiety/panic attenuating effect of the presence of medical personnel in terms of reduced perceived threat and increased available coping strategies. In this framework, the efficacy of methods for blocking lactate-induced anxiety depends on changing prior arousal or changing the anxiety-related symptoms or cognitions elicited by lactate. The failure of propranolol to block lactate effects can be related to its failure to block the rise in heart rate produced by lactate and to block the symptoms associated with hypocalcemia.

Our model closely follows Arnold's (126) and Lazarus's (114) theories of emotion and

is compatible with other major theories of emotion and anxiety (e.g., 52, 82, 103, 104, 107). Although we derive it from lactate infusion data, it may be applicable to the effects of CO<sub>2</sub> inhalation, hyperventilation, caffeine ingestion, and so on. In fact, a version of it may apply to naturally occurring panic attacks in that positive feedback loops between physiologic changes and appraisal processes (52) may operate here as well. An "exacerbation circle" (130) or a "spiral" (134) of anxious cognitions and physiologic arousal could produce the intense, sudden peaks typical for panic. Each new occurrence of such a spiral would lead to further enhancement of the association of subjective anxiety and the individually specific patterns of bodily symptoms.

## CONCLUSIONS AND SUMMARY

The response to sodium lactate infusion has been proposed as an experimental model for panic attacks and as a possible biologic marker of the panic attacks typical for Panic Disorder and Agoraphobia with Panic Attacks. We have reviewed the results of 13 published studies that supposedly support a specific panicogenic effect of lactate on patients but not on controls. As we have discussed, however, any interpretations drawn from this literature must be regarded as tentative since significant methodologic problems are present in most of these studies, including the recent ones. Already in 1972, Levitt, commenting on "psychiatric breakthrough" research, criticized lactate research for its "primitive" psychologic and behavioral measurements and lack of "routine precautions against the encroachment of experimenter bias" (23, p. 233). In addition, Levitt emphasized that placebo effects are

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ubiquitous, and warned that "the experiment which fails to turn up a single placebo reaction might be suspect" (23, p. 233). Nine of our thirteen studies reported no placebo-induced panic in patients. In general, studies rarely considered cognitive variables and ignored relevant psychologic and physiologic literature. Given these methodologic shortcomings, what can we conclude from these studies?

First, lactate infusions are an effective laboratory anxiety induction technique, producing anxiety that resembles naturally occurring panic. Thus, the results of lactate studies may bear implications for the theory of Panic Disorder and anxiety disorders in general. However, one cannot regard lactate-induced anxiety as *identical* to natural panic, and we do not know how valid a laboratory model for panic it provides. Among other problems, there are no data to demonstrate that lactate produces the explosive onset of anxiety regarded as characteristic for panic attacks rather than a gradual dose-related increase. The anxiety is generally of only moderate intensity, and for that reason perhaps does not deserve to be called "panic." Therefore, it is premature to use lactate infusion as a substitute for standard clinical methods for evaluating treatments for panic attacks.

Second, response to lactate infusion cannot be regarded as a biologic marker or diagnostic test for Panic Disorder or Agoraphobia with Panic Attacks. A biologic marker should be sensitive, specific, and independent of cognitive and emotional states. However, results summarized above indicate a lack of sensitivity of the procedure in that among studies with comparison groups only 56% of panic patients react to lactate with panic (see Table 3). As for specificity, the one study comparing panic patients to another clinical group found no significant differences (38). Fi-

nally, there is a strong influence of cognitive and emotional states on the likelihood that lactate will induce panic (28–31, 33, 39–41, 45, 46, 48, 49, 64). Baseline differences expressing anticipatory anxiety clearly predict the results of infusion. Therefore, lactate infusion data do not confirm the biologic distinctness of panic disorder claimed by several authors (1, 2, 9, 10–13). The responses of panic patients, controls, and patients with Generalized Anxiety Disorder differ quantitatively rather than qualitatively, which is consistent with findings of anxiety research in general (52, 54–57).

It is interesting to note that a second line of argument for the biologic distinctness of panic, the drug-specificity argument, has also been somewhat shaken by recent evidence. Klein (1, 2, 9) claimed that tricyclic antidepressants and MAO inhibitors suppress panic but not anticipatory anxiety, whereas benzodiazepines suppress anticipatory anxiety but not panic. However, a new benzodiazepine, alprazolam, has been shown to be effective for Agoraphobia with Panic Attacks and Panic Disorder (10, 17). And Noyes et al. (87) only recently showed in a double-blind placebo-controlled design that diazepam, the standard benzodiazepine anxiolytic, effectively and specifically treats panic attacks. On the other hand, controlled studies comparing the effects of tricyclic antidepressants and standard benzodiazepines on anticipatory anxiety are still lacking.

The results of the lactate infusion studies together with the recent drug treatment findings suggest that the interaction of biologic and psychologic mechanisms in anxiety disorders may well be quite different from Klein's model or the simple metabolic disease model of Carr and Sheehan (43). At least for lactate infusions, it is more reasonable to conceptualize the

results in terms of an extension of the learned phobic response theory of Ackerman and Sachar (24). Known lactate effects could be entirely explained by the interaction of perceived physiologic changes, past experience, environmental cues, and their appraisal as threatening or dangerous.

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