Thus, ER phenomena resulting from the ability to attain large values of λ will have no analogs in ferrofluids. Furthermore, the image forces that play a large role in the macroscopic behavior of ER fluids do not exist for ferrofluids, which are generally studied in solenoidal fields. One can impose pseudosolenoidal fields on ER fluids by operating at high frequencies and inserting a nonconducting dielectric between the electrodes and the fluid; however, no significant experiments have been conducted in this geometry.

From both an engineering and a scientific point of view, a better understanding of the microscopic mechanisms of interaction between particles and between particles and electrode surfaces is needed. Such an understanding would be very helpful in synthesizing fluids with superior properties. I have hardly touched on this subject in this review; many topics, such as the role of polydispersity, or the nature of solid structures beyond the idealized Tao and Sun model, have not been addressed here.

I have also not discussed the nature of the early phases of aggregation. Aside from the time scale and some preliminary analyses of the scaling (*34*), very little work has been done on the early phases of aggregation, which is perhaps the area that can most easily be studied by the techniques of molecular dynamics. More detailed theories of late-stage aggregation and rheological response, which go beyond the rather simple arguments above, are also needed.

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What If Minkowski Had Been Ageusic? An Alternative Angle on Diabetes

J. Denis McGarry

Despite decades of intensive investigation, the basic pathophysiological mechanisms responsible for the metabolic derangements associated with diabetes mellitus have remained elusive. Explored here is the possibility that traditional concepts in this area might have carried the wrong emphasis. It is suggested that the phenomena of insulin resistance and hyperglycemia might be more readily understood if viewed in the context of underlying abnormalities of lipid metabolism.

Recognized since the time of Aristotle, diabetes mellitus is now known to encompass a variety of syndromes with distinct etiologies that collectively afflict 1 to 6% of the population in the United States. Of these, 10 to 25% fall into the category of insulin-dependent diabetes mellitus (IDDM), which generally appears before age 40, frequently in adolescence, and results from autoimmune destruction of insulin-producing cells within the pancreas. Far more common is non–insulin-dependent diabetes mellitus (NIDDM) which, at least in its early stages, is characterized not by insulin deficiency but by the failure of the hormone to act efficiently in target tissues such as muscle, liver, and fat. Unlike IDDM, NIDDM is often associated with obesity (*1*). In this article, I will examine fuel metabolism in diabetes, with a view to advancing a key role for the lipid component.

Regardless of type, uncontrolled diabetes represents a serious disruption of fuel homeostasis with ravaging consequences throughout the body. Although much has been learned, current knowledge remains largely descriptive, consisting mainly of an ever expanding list of the metabolic, vascular, and neurological abnormalities that accompany the active disease process. What has not yet emerged, despite immense investment of resources, is a clear understanding of the basic pathophysiological mechanisms of diabetes and their temporal relations to each other.

Why has this problem remained so intractable? A major contributing factor has been that, compared with other hormones, insulin elicits a bewildering array of metabolic responses in target cells. Deciding

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which of these are dependent or independent events continues to pose a major challenge. One wonders if there might also have existed for decades a less well recognized stumbling block of a more philosophical nature. Is it possible that our historical perception of the primary metabolic derangement in diabetes has carried the wrong emphasis?

It is of interest to reflect back on two of the generally accepted landmark discoveries in diabetes research and to consider how they have influenced our thinking. Legend has it that on a momentous day in 1889 Oskar Minkowski noticed that urine collected from his pancreatectomized dogs attracted an inordinate number of flies. He is then said (by some) to have tasted the urine and to have been struck by its sweetness. From this simple but astute observation, he established for the first time that the pancreas produced some entity essential for control of the blood sugar concentration, which, when absent, resulted in diabetes mellitus. A second milestone was reached some 30 years later when Frederick Banting and his colleagues identified the active pancreatic principle as insulin. Thus, in 1921 the concept of an insulin-glucose axis as a central component of fuel homeostasis came into being. In keeping with its etymological derivation, diabetes mellitus has been viewed ever since as a disorder primarily associated with abnormal glucose metabolism.

Now let us suppose that Minkowski had lacked a sense of taste but had a good nose. Presumably, instead of detecting sugar in the diabetic urine he would have smelled the acetone. Although this might have left him even more bemused as to the swarm of flies, he would surely have concluded that removal of the pancreas causes fatty acid metabolism to go awry. Extending this hypothetical scenario, the major conclusion of Banting's work might then have been that the preeminent role of insulin is in the control of fat metabolism. No doubt, soon thereafter hyperglycemia (high blood sugar concentration) and glycosuria (spillage of glucose in the urine) would have been recognized as additional untoward effects of insulin deficiency and would likely have been considered secondary to disordered fat metabolism. It might well be asked whether such a viewpoint deserves more consideration than it has received hitherto.

Studies in IDDM

The complete absence of circulating insulin, as occurs in untreated IDDM, gives rise in a very short period of time to life-threatening diabetic ketoacidosis. The hallmarks of this condition are severe hyperglycemia coupled with marked elevation in the circulating concentrations of acetoacetic and β-hydroxybutyric acids. It is now clear that both disturbances, although triggered by insulin deficiency, require for their development the simultaneous presence of glucagon (*2*).

The first prerequisite for accelerated ketogenesis is mobilization of free fatty acids (FFA) from adipose tissue to the liver, an invariable response to falling insulin levels. Concomitant elevation of the glucagon-insulin ratio leads to an increased concentration of adenosine 3′,5′-monophosphate in liver. This has the effect of suppressing the synthesis of malonyl–coenzyme A (CoA), thus relieving inhibition of carnitine palmitoyltransferase I such that the capacity of the liver to oxidize incoming FFA to ketone bodies is greatly enhanced (*3*). What distinguishes the physiological ketosis of starvation from the pathological ketosis of uncontrolled IDDM is the difference in plasma FFA concentrations. In prolonged starvation, these seldom exceed 0.8 mM because of the ability of FFA and ketone bodies to stimulate insulin secretion, thereby limiting the lipolytic stimulus (*3*). In IDDM, this feedback loop is lost, and plasma FFA concentrations may rise to about 3 mM such that hepatic ketone production is driven maximally. The key point is that even the much reduced concentration of circulating insulin in starvation is highly protective, and this effect is exerted primarily on the process of adipose tissue lipolysis.

The hyperglycemia that accompanies loss of pancreatic β-cell function stems from accelerated hepatic glucose production coupled with inefficient peripheral glucose uptake. Here again, what is a crucially important physiological role of FFA in starvation (that is, the sparing of glucose for use by the central nervous system) turns into a harmful effect in the uncontrolled diabetic state. Thus, excessive oxidation of FFA in liver, in addition to causing ketoacidosis, stimulates gluconeogenesis by providing the acetyl-CoA necessary to activate pyruvate carboxylase as well as the adenosine triphosphate and reduced nicotinamide adenine dinucleotide (NAD^+; reduced form NADH) needed for conversion of pyruvate into glucose at high rates. In muscle, via the operation of the Randle glucose–fatty acid cycle (*4*), the oxidation of FFA and ketone bodies will cause elevation of the intramitochondrial acetyl-CoA/CoA and NADH/NAD^+ ratios with subsequent inactivation of pyruvate dehydrogenase. The resultant increase in citrate concentration is thought to inhibit phosphofructokinase, causing accumulation of glucose-6-phosphate, which in turn acts to inhibit hexokinase and thus glucose uptake. Many of the individual components of the Randle cycle have been verified in in vitro experiments with animal tissues (*4*). Its relevance in vivo is also amply supported. For example, the predicted result of pharmacological blockade of fatty acid oxidation in a setting of diabetic ketoacidosis would be to reverse both the hyperketonemia and hyperglycemia more efficiently than could be accomplished with insulin alone. Such was found to be the case when (+)-decanoylcarnitine, a carnitine palmitoyltransferase I inhibitor, was infused into severely ketotic diabetic rats (*5*). Similar effects have since been obtained with more potent and selective inhibitors of carnitine palmitoyltransferase I such as tetradecylglycidate and etomoxir (*6*). From studies in humans, it is also clear that fat loading interferes with glucose disposal, whereas the use of antilipolytic agents to reduce plasma FFA concentrations promotes an increase in whole body glucose oxidation (*7*).

Studies in NIDDM

Compared with the situation in IDDM, understanding of the metabolic derangements in NIDDM is far less clear. A confounding problem here has been the lack of consensus on what is meant by the term "insulin resistance" and its importance relative to altered β cell function in the progression from a normal state to one of impaired glucose tolerance and finally to NIDDM. However, there now seems to be general agreement on the following issues (*8*). In patients with impaired glucose tolerance, the fasting plasma glucose and fasting plasma insulin levels rise in parallel until the former reaches 7 to 8 mM. Beyond this point, there is a progressive fall in the fasting insulin concentration. A similar inverted U-shaped curve is seen when the plasma insulin response during an oral glucose tolerance test is plotted as a function of the fasting plasma glucose concentration. The combined effects of these aberrations on the handling of a glucose load are generally interpreted as follows. In obese, nondiabetic subjects, tissue sensitivity to insulin is markedly reduced, yet oral glucose tolerance is little affected because of the ability of the β cells to augment insulin secretion, offsetting the defect in insulin action. Even with progression to impaired glucose tolerance and further reduction in insulin-mediated glucose disposal, postprandial glucose levels might be only modestly elevated because of the capacity of the β cells to meet the extra demand for insulin. However, the transition from simple glucose intolerance to overt diabetes mellitus is characterized not by a worsening of the insulin

resistance but by failure of the β cells to maintain adequate insulin secretion. At this point, profound glucose intolerance is seen, the magnitude of which is dictated by the residual β cell function.

Another factor contributing to the development of fasting hyperglycemia is excessive hepatic glucose production, but this defect becomes particularly noticeable only when individuals shift from impaired glucose tolerance to frank diabetes mellitus. Presumably, in the former case the elevated basal insulin concentration is sufficient to restrain hepatic glucose production to near normal rates. Because in the fasted state the rate of glucose utilization equals that of hepatic glucose output, it follows that individuals with NIDDM actually dispose of glucose at a higher than normal rate. However, this is achieved at the expense of an expanded glucose pool size; that is, there is diminished glucose clearance. In patients with impaired glucose tolerance, the elevated fasting plasma insulin, though sufficient to keep hepatic glucose production in the normal range, cannot normalize glucose clearance. The above considerations are summarized by De Fronzo and co-workers (*8*, p. 336):

> In the earliest detectable stage of NIDDM, that is, normal glucose-tolerant offspring of two diabetic parents and normal glucose-tolerant relatives of NIDDM individuals, insulin resistance is already well established and is offset by the presence of compensatory hyperinsulinemia. Overt diabetes mellitus develops only in individuals whose β cells are unable to meet the increased and sustained demand for insulin secretion.

What then are the cellular mechanisms of insulin resistance? Leaving aside those rare cases that are a result of mutations in the insulin receptor, it is now broadly accepted that most forms of insulin resistance are manifestations of disturbances in target cell metabolism that lie distal to the insulin-insulin receptor interaction. Several candidate sites have been proposed, including defects in the receptor tyrosine kinase, glucose transport, pyruvate dehydrogenase, and glycogen synthesis. During a euglycemic-hyperinsulinemic clamp (*9*), the bulk of glucose metabolism takes place in skeletal muscle. Of the glucose taken up in this compartment, approximately two-thirds is used for glycogen synthesis, the remainder traversing the glycolytic sequence for oxidation or lactate production. The major defect in NIDDM (and impaired glucose tolerance) is thought to reside in the storage component (*8*). Although the underlying mechanisms remain obscure, evidence is beginning to accumulate that deranged fat metabolism might once again play a key role. In keeping with this notion are the results of a detailed around-the-clock study by Reaven and co-workers (*10*) in nonobese normal, mildly diabetic, and severely diabetic individuals. In the diabetic patients, blood glucose concentrations were elevated, as expected, but it was shown that both plasma FFA and lactate levels were also chronically increased and in rough proportion to the degree of hyperglycemia. Patients with mild NIDDM displayed marked hyperinsulinemia. In the severely diabetic group, insulin concentrations were decreased only modestly during the day and were no different from normal between midnight and 8:00 a.m.—yet at all times, and particularly at night, FFA levels were strikingly elevated. In a second study (*11*), the same laboratory examined the suppressibility of FFA concentrations during a hyperglycemic clamp at low- and high-insulin infusion rates. Patients with NIDDM again exhibited a marked increase in FFA levels at basal insulin concentrations, and these failed to suppress to normal with insulin infusion. Moreover, the higher the FFA concentration at basal insulin levels, the lower was the insulin-stimulated rate of glucose disposal.

The implication from these studies is that patients with NIDDM are resistant to insulin action not only in terms of suppression of hepatic glucose output and stimulation of peripheral glucose uptake but also at the level of the fat cell. The inappropriate elevation in plasma FFA concentration can be expected to contribute to hyperglycemia by enhancing the rate of Cori cycling according to the principles of the Randle hypothesis. It follows that blockade of adipose tissue lipolysis or interference with fatty acid oxidation in liver or muscle (or both) should reduce the level of glycemia in such conditions. Evidence of this effect has now been obtained both in experimental animals and in humans. Reaven and co-workers (*12*) induced nonketotic hyperglycemia in rats by administration of streptozotocin. Subsequent treatment of the animals with nicotinic acid (an antilipolytic agent) or etomoxir (an inhibitor of fatty acid oxidation) caused a rapid lowering of circulating glucose levels. The antilipolytic agent Acipimox was tested by Saloranta and co-workers (*13*) in nonobese patients with NIDDM who underwent a hyperinsulinemic clamp at their basal glucose concentration. The drug was effective in lowering plasma FFA levels and significantly improved the suppression of hepatic glucose production and stimulation of peripheral glucose uptake induced by insulin infusion. A salutary effect of etomoxir on blood sugar concentrations in obese patients with NIDDM has also been documented (*14*).

Studies in First-Degree Relatives of Patients with NIDDM

From the reports cited, it is evident that abnormally high concentrations of plasma FFA are detrimental to glucose homeostasis both in IDDM and NIDDM. It is equally clear, however, that an increased plasma FFA concentration is not a sine qua non for the appearance of insulin resistance. This point is illustrated in a study by Vaag and co-workers (*15*) in first-degree relatives of patients with NIDDM (such individuals are known to be at greatly increased risk for development of the disease). The test subjects were not obese and had basal glucose concentrations identical with those of an age-, weight-, and sex-matched control group with no family history of NIDDM. During a euglycemic-hyperinsulinemic clamp study, the relatives displayed a normal basal plasma FFA level that was suppressed appropriately by insulin. Nevertheless, their insulin-stimulated rate of glucose disposal was clearly subnormal, the defect relating exclusively to nonoxidative glucose metabolism. The authors went on to show that the underlying cause of the problem was diminished muscle glycogen deposition and that this in turn stemmed from a lower than normal insulin activation of glycogen synthase. They suggested that the latter might be a primary, possibly genetically determined, defect that contributes to the ultimate emergence of NIDDM in many of these individuals.

Certainly, this idea deserves further exploration. At first glance, it would seem to indicate that before NIDDM develops, insulin resistance is unrelated to the status of lipid metabolism. However, such a conclusion might be premature in light of other findings reported by Vaag and co-workers (*15*). Specifically, it was observed that in response to an oral glucose tolerance test, the relatives of patients with NIDDM and the controls exhibited essentially superimposable blood glucose profiles; yet, the insulin response in the relatives was twice that seen in the controls (the same was true in terms of basal insulin and C-peptide concentrations). It was supposed that the compensatory hyperinsulinemia in the relatives enabled them to overcome their insulin resistance. But herein lies a crucial question. If the rise in blood glucose concentration was not different in the two groups, what was the extra stimulus to the β cells in the relatives (*16*)? Also unanswered from this or any other such study is whether in relatives of patients with NIDDM muscle insulin resistance precedes the postprandial hyperinsulinemia, as is generally assumed, or vice versa. If, in fact, hyperinsulinemia (regardless of cause) is the earlier event, this might be expected to place the liver

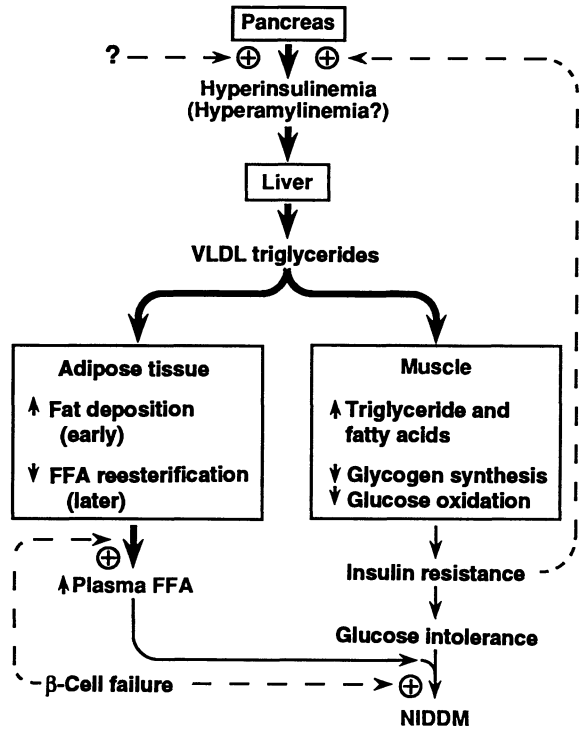

Fig. 1. Hypothetical steps in the development of NIDDM. An unidentified (inherited) factor stimulates the pancreas to overproduce insulin (and amylin), which in turn drives lipogenesis in the liver. Excessive delivery of VLDL to muscle and adipose tissue causes deposition of triglycerides in both compartments. Fat accumulation in muscle interferes with glucose storage and oxidation, which results in insulin resistance at this site. Mild episodes of postprandial hyperglycemia further stimulate β cell function, which sets up a vicious cycle and progression to glucose intolerance. Subsequently, the fat cell becomes refractory to insulin action (mechanism unknown) such that plasma FFA levels rise inappropriately. This has the effect of enhancing hepatic glucose output (not shown) and aggravating the defect in muscle glucose uptake. Eventually, β cell failure occurs (mechanism unknown), which causes exaggeration of existing abnormalities and the emergence of NIDDM.

under an extra anabolic drive, thus promoting the synthesis of very low density lipoproteins (VLDL) and the excessive delivery of triglycerides to adipose tissue and muscle. A key issue, therefore, would be whether the relatives of patients with NIDDM studied by Vaag and co-workers (*15*) had elevated muscle triglyceride levels. If so, it is possible that this abnormality, in the absence of increased circulating FFA concentrations, might have contributed to their defective uptake and storage of glucose in muscle. Other observations would be consistent with this line of thinking. First, a major gene effect for hyperinsulinemia occurs in familial NIDDM pedigrees (*17*). Second, patients with insulinoma displayed degrees of insulin resistance that were directly related to the extent of their hyperinsulinemia (*18*). Third, it has been suggested that muscle insulin resistance may not be a primary etiological factor in the genetically obese Zucker rat (*19*). Fourth, transgenic mice that overexpress the human insulin gene developed insulin resistance subsequent to hyperinsulinemia (*20*). Fifth, in a group of individuals with NIDDM, muscle triglyceride levels were shown to be elevated sixfold when compared with age- and sex-matched controls (*21*). Finally, in studies with normal rats, manipulation of their dietary fat constituents produced varying degrees of insulin resistance that correlated positively with the increment in muscle triglyceride content (*22*).

Overview

There can be no doubt that the acute metabolic complications of uncontrolled IDDM (that is, life-threatening diabetic ketoacidosis) stem in large measure from excessive rates of delivery of FFA from adipose depots to liver and muscle. This abnormality, a direct result of insulinopenia, greatly exacerbates whatever hyperglycemia would develop in response to isolated insulin deficiency (that is, in the hypothetical situation of simultaneously small amounts of insulin and FFA). Clearly, disordered fat metabolism plays a central, if not primary, role in the metabolic sequelae of β cell destruction.

As to the etiology of NIDDM, a working hypothesis that attempts to accommodate findings from numerous laboratories over the past 5 years or so is presented in Fig. 1. According to this formulation, hyperinsulinemia is an early event and serves to drive hepatic lipogenesis and VLDL synthesis. Should the hyperinsulinemia result from hyperactivity of the β cell (as opposed to defective insulin clearance), then concomitant oversecretion of amylin, a newly discovered polypeptide cosecreted with insulin from β cells, would be expected. If, as has been suggested (*23*), amylin promotes Cori cycling of lactate from muscle to liver it might further enhance the production of VLDL (lactate is a better substrate than glucose for hepatic fatty acid synthesis). The net effect would be increased flux of triglycerides from liver to muscle (and adipose tissue). As fat accumulates in muscle, insulin-stimulated glucose metabolism at this site becomes compromised. Operative factors could include acyl-CoA–induced suppression of glycogen synthesis (*24*) as well as of glucose oxidation (Randle mechanism). The progress of these events leads from simple insulin resistance to glucose intolerance with elevated glucose levels causing even greater postprandial hyperinsulinemia, which sets up a vicious cycle. At some point, the fat cell also becomes insulin resistant and fails to reesterify fatty acids efficiently. This leads to a gradual elevation of plasma FFA, which compounds the insulin resistance in muscle and drives hepatic glucose production, thus placing even greater demands on β cells. Eventually, β cell failure occurs, and glucose intolerance gives way to frank diabetes mellitus (*25*).

Obviously, this speculative proposal leaves many questions unanswered. (i) If hyperinsulinemia does indeed precede insulin resistance, what is its cause? (ii) How can hyperinsulinemia in the absence of overt insulin resistance be reconciled with a normal fasting plasma glucose level? Is this because in the basal state most glucose utilization occurs in insulin-insensitive tissues? Might concomitant hyperamylinemia afford protection from hypoglycemia by promoting Cori cycling of glucose carbon? (iii) Does persistent hyperamylinemia in a setting of hyperinsulinemia provide a further stimulus to hepatic VLDL synthesis (by enhancing lactate flux from muscle to liver), thus contributing to the accumulation of triglycerides in muscle? (iv) What is the precise defect in muscle glycogen synthesis in individuals with simple insulin resistance? Does it in fact stem from triglyceride (or fatty acyl-CoA) accumulation within the muscle cell? (v) How does insulin stimulate glucose uptake into muscle and fat tissue? (vi) What causes adipocyte insulin resistance in NIDDM? (vii) Why do some individuals with impaired glucose tolerance never progress to NIDDM? Is this because insulin resistance and the propensity for β cell failure are distinct inherited characteristics? (viii) What is the basis of β cell failure in NIDDM?

Despite these questions, the case for an underlying role of abnormal fat metabolism in the pathogenesis of NIDDM is becoming stronger. Even if the mechanisms postulated here turn out to be only partially correct, we could well ask why these developments occurred so late in the history of diabetes research. We might in turn come to lament the fact that Minkowski never emphasized the acetone!

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RESEARCH ARTICLE

Femtosecond Resolution of Soft Mode Dynamics in Structural Phase Transitions

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The microscopic pathway along which ions or molecules in a crystal move during a structural phase transition can often be described in terms of a collective vibrational mode of the lattice. In many cases, this mode, called a "soft" phonon mode because of its characteristically low frequency near the phase transition temperature, is difficult to characterize through conventional frequency-domain spectroscopies such as light or neutron scattering. A femtosecond time-domain analog of light-scattering spectroscopy called impulsive stimulated Raman scattering (ISRS) has been used to examine the soft modes of two perovskite ferroelectric crystals. The low-frequency lattice dynamics of $KNbO_3$ and $BaTiO_3$ are clarified in a manner that permits critical evaluation of microscopic models for their ferroelectric transitions. The results illustrate the advantages of ISRS over conventional Raman spectroscopy of low-frequency, heavily damped soft modes.

The manner in which cooperative structural change occurs in condensed matter has been examined extensively. Structural phase transitions between different crystalline forms are particularly amenable to study because the microscopic pathway along which ions or molecules in the lattice move from their positions in one phase to their positions in the other may be inferred from x-ray and other spectroscopic analysis of the two phases. This microscopic pathway may be considered a cooperative "reaction coordinate" for the phase transition, which in some respects may be thought of as a cooperative chemical reaction. Unimolecular chemical reaction coordinates are described in terms of molecular vibrational modes, or tunneling (or thermally assisted hopping) between different local potential energy minima, or both; cooperative motions in structural phase transitions are described in terms of lattice vibrational modes or hopping degrees of freedom. In both cases, a microscopic understanding requires information about the potential energy surface along which "reaction" occurs and about the dynamics of motion along this surface. In the molecular case, both time-domain and frequency-domain experimental methods have been used extensively (*1*). Time-resolved spectroscopy has been possible because optical absorption provides a mechanism with which to initiate motion along excited-state photochemical reaction coordinates. In the collective case, frequency-domain spectroscopic methods have been used almost exclusively (*2*), mainly because phase transitions occur in ground electronic states and a mechanism for controlled optical initiation of the microscopic motions involved in phase transitions has not been available.

Structural phase transitions can be described in two limiting cases as either displacive or order-disorder, and are characterized, respectively, by a single potential energy minimum whose position shifts at the transition temperature T_c or by several minima among which a "choice" is made at T_c (*3*) (Fig. 1). For displacive transitions, motion between the two phases involves lattice vibrations that are termed "soft" modes because of their reduced frequencies near T_c (*4*, *5*). Order-disorder transitions occur through collective tunneling or thermally assisted hopping modes. Lattice vibrational and hopping modes are usually examined through Raman spectroscopy (*2*), in which their signatures may be very different. Most lattice vibrations show distinct Stokes and anti-Stokes Raman features whose frequency shifts and widths yield quantitative values of the vibrational frequency and dephasing rate, whereas hopping modes give rise to central peaks whose widths yield the hopping rates. Unfortunately, soft vibrational modes generally show low frequencies and very strong damping near T_c so that the Stokes and anti-Stokes lines merge into a broad central peak that closely resembles

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