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Blockade of Morphine Abstinence by Δ^9-Tetrahydrocannabinol

Hine *et al.* (*1*) reported that Δ^9-*trans*-tetrahydrocannabinol (THC) suppresses certain symptoms of naloxone-precipitated morphine abstinence in rats. However, the title of their report, "Morphine-dependent rats: Blockade of precipitated abstinence by tetrahydrocannabinol," is quite misleading since three important abstinence signs, including ear blanching, ptosis, and vocalization, were not significantly reduced even by the highest dose of THC (two were induced by THC alone). Thus, the most that can be claimed is that THC reduced two of the symptoms of precipitated abstinence, wet shakes and defecation.

At the doses of THC that were effective in suppressing abstinence symptoms in the study, THC has a substantial sedative effect (*2*) (although the authors state that doses of 5 mg/kg or less did not produce sedation in their rats). It is not surprising that THC might suppress a variety of behavioral symptoms of precipitated abstinence because of its general sedative properties. Unfortunately, the study failed to include controls that were treated with other sedative drugs such as benzodiazepines or barbiturates, which do not exhibit cross dependence with narcotics. It is possible that these drugs would be as effective as THC in suppressing certain signs of precipitated abstinence.

Finally, the authors propose that their data suggest that further exploration of the therapeutic utility of THC in narcotic detoxification is warranted. They argue that THC, if it were effective in suppressing abstinence signs, would be preferred to drugs such as methadone since the latter produces physical dependence, while the former does not. However, the doses of THC required for effective suppression of abstinence symptoms in their study, 5 to 10 mg/kg, were far beyond the range of doses required to produce intoxication in human subjects (about 0.02 mg/kg) (*3*). I am not familiar with any other reports of doses in this range administered to human subjects. If such extremely high doses of THC are required to suppress abstinence signs in humans, there is no strong reason to believe that THC would be desirable as an agent for detoxification.

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The only agents capable of specifically suppressing all components of a narcotic abstinence syndrome are opiates or their derivatives (*1*). At sedative doses, barbiturates may not block or even attenuate narcotic abstinence signs in humans (*2*) or rodents (*3*). Benzodiazepines, clinically effective in controlling seizure activity (*4*), also do not suppress all abstinence signs when used to treat neonatal or adolescent narcotic withdrawal (*5*), notwithstanding evidence of effective suppression by low doses of benzodiazepines of naloxone-induced jumping in morphine-pelleted mice (*6*). Thus, the question of which abstinence signs in animals dependent on narcotics are most "important" is a complex one which cannot be easily answered.

The purpose of our report was to determine the effect of pharmacologically active doses of Δ^9-*trans*-tetrahydrocannabinol (THC) in the rat on nine (by no means exhaustive) components of a precipitated abstinence syndrome in this species. When abstinence scores for each animal were determined from the total number of the nine signs present, the data clearly indicated a THC dose-dependent decrease in number of signs displayed, statistically significant at doses of 2 mg per kilogram of body weight and at higher doses. Moreover, wet shakes, one abstinence sign in the rat elicited at moderate (*7*) to high (*8*) degrees of dependence only with high naloxone doses (*8*), was the sign most affected by THC. Our conservative statistical presentation did not emphasize the fact that, even at 1 mg/kg (the lowest dose used), prior treatment with THC resulted in significantly ($P = .048$, one-tailed Fisher test) fewer rats exhibiting wet shakes compared to control animals. Frequencies of occurrence of two other signs (not one, as Carder suggests), presence of diarrhea at 30 minutes and an elevated fecal bolus count at 15 minutes, were also significantly reduced—to zero in some cases.

Finally, there are two problems with Carder's extrapolation of appropriate THC doses for humans and rodents on a milligram per kilogram basis. There is at least a tenfold difference in doses required for psychopharmacological effects in these species, attributable, in part, to differences in absorption and distribution with different routes of administration. This difference is illustrated in acute toxicity studies in the rat and mouse by a median lethal dose (MLD) after intraperitoneal administration that is 10 to 13 times higher than the MLD after intravenous administration (*9*), since most of the drug remains at the injection site after intraperitoneal injection and relatively little enters the brain or is converted to active metabolites (*10*). Second, 0.02 mg/kg was the approximate average intravenous dose at which autonomic and subjective effects of THC were first perceived by the subjects of the study cited in Carder's reference 3, whereas "intoxicating" human doses generally range from 100 to 250 μg/kg for the inhalation route (*11*). This route is at least as effective as the intravenous one for producing psychoactive and toxic effects (*12*), although impaired performance on some cognitive tasks may not occur even at these doses (*13*). Thus, doses of THC found effective in our study are within a reasonable range for extrapolation to clinical use.

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Quantum Organic Chemistry: An Alternative View

In "Quantum organic chemistry" Dewar (*1*) rightly emphasizes the use of quantum chemical calculations as cost-effective alternatives to experiment, but errs in suggesting this as being the ultimate goal of quantum chemistry. Calculations also serve to illuminate experiment. By rigorously treating particular physical models, ab initio methods enable us to evaluate critically and, if necessary, ultimately improve the models themselves. In contrast, parameterization schemes employed in semiempirical methods, such as Dewar's MINDO/3, inevitably obscure the physical bases for success (however striking) and failure alike, thereby limiting the prospects for learning why the results are as they are. No simple cost accounting of the type Dewar proposes can be meaningful for ab initio studies which are intended not so much to predict a given experimental result as to examine what that result can tell us. By way of illustration, Parr's elegant recent account (*2*) which we recommend highly, includes several examples of computational tasks to which semiempirical techniques could not meaningfully have been applied.

Moreover, Dewar misstates the relative costs of MINDO/3 and ab initio calculations when he cites \$1 billion versus \$5000 as estimates for ab initio 4-31G and MINDO/3 studies of the barriers to interconversion of the benzene valence isomers, $(CH)_6$. In particular, the relative costs for individual 4-31G and comparable INDO calculations are ~400 : 1 for our computers. Although large, this figure falls considerably short of the factor of ~200,000 : 1 Dewar advances. Moreover, we estimate that we could conclude 4-31G studies for these processes for approximately the lower figure of \$5000 by coupling an efficient new technique for potential surface investigations (*3*) with a rapid approximate ab initio procedure (*4*) for the initial calculations. Key structures obtained in this way would then be reassessed by 4-31G calculations. Such a dual usage of minimum and extended basis set calculations greatly reduces the overall costs and is by now an accepted practice.

In summary, the difference in the motivations for doing ab initio and semiempirical calculations needs to be considered alongside the question of relative costs when judging the merits of these approaches for a given problem. At bottom, neither approach can be the method of choice for all computational problems, and surely each will have a vital role to play in the continuing development of quantum chemistry.

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I am all in favor of rigorous quantum mechanical calculations—that is, ones leading to results that are accurate in an absolute sense—and entirely agree that these provide information of a different order of value to that given by empirical procedures such as ours. If such calculations could be carried out for complex chemical systems, I would be their most ardent champion. However, the only reasonably accurate methods currently available are limited to atoms and small molecules, systems of interest more to astronomers and physicists than to chemists. As I pointed out in my article, the best ab initio methods that can be applied to complex chemical systems are inaccurate. If they lead to results that agree with experiment, this can be due only to errors canceling with quite unexpected precision, so such treatments can be used only empirically. My criticisms were directed at those who try to attribute to these essentially empirical procedures the same aura of illumination and meaningfulness that applies to the rigorous ones.

As regards cost, the cost of a single 4-31G calculation for C_6H_6 is indeed about 400 times that for MINDO/3 (3/4 hour versus 7 seconds on our computer). However a full geometry optimization requires the equivalent of far more such calculations in the case of 4-31G than MINDO/3 and the location of a transition state far more again. No one has attempted such a calculation for a system as large as C_6H_6; indeed, no one until recently had even optimized the (4-31G) geometry of benzene, although this is trivial if D_{6h} symmetry is assumed. Needing this value we calculated it ourselves; the calculation took 4 hours, which at \$500 per hour (the rate I assumed) would have cost \$2000. A single optimization for an unsymmetrical C_6H_6 species would have cost many times more than this, so it seems clear that the figure of \$5000 quoted by Lipscomb *et al.* is somewhat unrealistic.

My objection is not to ab initio calculations but to their misuse. What is needed in chemistry in the ab initio area is some better approach than those currently available, not vast and very expensive calculations for problems that can be treated at least equally effectively in other ways at far less cost.

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Model for Differentiation Based on DNA Modifying Enzymes

The theory by Holliday and Pugh (*1*) of differentiation controlled by modifying enzymes of DNA relies on several assumptions, some of which can be readily refuted by existing biochemical data.

If DNA adenine deaminase, which deaminates adenine at the polymer level, were operative, then its product whether deoxyribohypoxanthine (not inosine!) or hypoxanthine, should be detectable in DNA hydrolyzates. Neither was ever found. Inosine is found in hydrolyzates of transfer RNA (tRNA).

The deamination of 5-methylcytosine in the polynucleotide to yield thymine in situ proposed by Scarano had some evidence in its favor, but a new interpretation of the data may cast doubt on the mechanism of that phenomenon as well. The methylation of DNA in eukaryotes is achieved by the transfer of an intact methyl group from *S*-adenosylmethionine (SAM) to cytosine