[4] Wootton, J. C., Chambers, G. K., Taylor, J. G., and Fincham, J. R. S., *Nature new Biol.*, **241**, 42–43 (1973).
[5] Rossman, M. G., *et al.*, *Cold Spring Harb. Symp. quant. Biol.*, **36**, 179–191 (1971).
[6] Hill, E., Tsernoglou, D., Webb, L., and Banaszak, L. J., *J. molec. Biol.*, **72**, 577–589 (1972).
[7] Brändén, C. I., Eklund, H., Nordström, B., Boiwe, T., Söderlund, G., Zeppezauer, E., Ohlsson, I., and Akeson, A., *Proc. natn. Acad. Sci. U.S.A.*, **70**, 2439–2442 (1973).
[8] Buehner, M., Ford, G. C., Moras, D., Olsen, K. W., and Rossman, M. G., *Proc. natn. Acad. Sci. U.S.A.*, **70**, 3052–3054 (1973).
[9] Blake, C. C. F., and Evans, P. R., *J. molec. Biol.*, **84**, 585–601 (1974).
[10] Bryant, T. N., Watson, H. C., and Wendell, P. L., *Nature*, **247**, 14–17 (1974).
[11] Rossman, M. G., Moras, D., and Olsen, K. W., *Nature*, **250**, 194–199 (1974).
[12] Chou, P. Y., and Fasman, G. D., *Biochemistry*, **13**, 211–222 (1974).
[13] Chou, P. Y., and Fasman, G. D., *Biochemistry*, **13**, 222–245 (1974).
[14] Nagano, K., *J. molec. Biol.*, **75**, 401–420 (1973).
[15] Nagano, K., *J. molec. Biol.*, **84**, 337–372 (1974).
[16] Finkelstein, A. V., and Ptitsyn, O. B., *J. molec. Biol.*, **62**, 613–624 (1971).
[17] Schulz, G. E., *et al.*, *Nature*, **250**, 140–142 (1974).
[18] Dayhoff, M. O., Eck, R. V., and Park, C. M., *Atlas of Protein Sequence and Structure*, **5**, 89 (1972).
[19] Taylor, S. S., Oxley, S. S., Allison, W. S., and Kaplan, N. O., *Proc. natn. Acad. Sci. U.S.A.*, **70**, 1790–1794 (1973).
[20] Melzi D'Eril, G., and Dalziel, K., *Biochem. J.*, **130**, 3P (1972).
[21] Krause, J., Buhner, M., and Sund, H., *Eur. J. Biochem.*, **41**, 593–602 (1974).
[22] Gore, M. G., *thesis*, Univ. East Anglia (1972).
[23] West, D. J., Tuveson, R. W., Barratt, R. W., and Fincham, J. R. S., *J. biol. Chem.*, **242**, 2134–2138 (1967).
[24] Piszkiewicz, D., Landon, M., and Smith, E. L., *J. biol. Chem.*, **245**, 2622–2626 (1970).
[25] Blumenthal, K. M., and Smith, E. L., *J. biol. Chem.*, **248**, 6002–6008 (1973).
[26] Gore, M. G., Wootton, J. C., and Fincham, J. R. S., *Biochem. Soc. Trans.*, **1**, 1278 (1973).
[27] Jörnvall, H., *Eur. J. Biochem.*, **16**, 25–40 (1970).
[28] Davidson, B. E., Sajgò, M., Noller, H. F., and Harris, J. I., *Nature*, **216**, 1181–1185 (1967).
[29] Harris, J. I., and Perham, R. N., *Nature*, **219**, 1025–1028 (1968).
[30] Jones, G. M. T., and Harris, J. I., *FEBS Lett.*, **22**, 185–188 (1972).
[31] Schulz, G. E., Elzinga, M., Marx, F., and Schirmer, R. H., *Nature*, **250**, 120–123 (1974).
[32] Tanaka, M., Haniu, M., Yasunobu, K. T., Mayhew, S., and Massey, V., *Biochem. biophys. res. Commun.*, **44**, 886–892 (1971).
[33] Drenth, J., Hol, W. G. J., Jansonius, J. N., and Koekoek, R., *Cold Spring Harb. Symp. quant. Biol.*, **36**, 107–116 (1971).

Comparison of classical and autogenous systems of regulation in inducible operons

Michael A. Savageau

Department of Microbiology, University of Michigan, Ann Arbor, Michigan 48104

The mechanism of autogenous regulation, whereby a protein directly controls the expression of its own structural gene, is compared on the basis of function with the classical mechanism, in which the structural gene of the regulator is itself unregulated. The autogenous mechanism is superior to the classical one in inducible catabolic systems governed by a repressor; the opposite is true if the regulator is an activator.

CONTROL of transcription by a constitutively synthesised repressor protein is central to Jacob and Monod's model for the regulation of gene expression[1]. Inducible operons were the first to be understood at this level of molecular detail in bacteria, and in several of the best studied examples, such as the lactose[2], galactose[3] and glycerol[4] operons, the classical Jacob–Monod mechanism is believed to be operative. Alternatives, however, have been discovered: the regulator protein in some cases—such as the arabinose[5], maltose[6] and D-serine deaminase[7] operons—is an activator, or positive element, in the control system. In other cases, for example, the histidine utilisation system[8], there is a repressor mechanism but the regulator protein is directly involved in modulating the expression of its own structural gene. This latter feature of the *hut* system provides an example of a more general class of phenomena that has been called autogenous regulation[9].

What are the functional implications of these differences? The relative merits of genetic control by repressors and activators have been explored elsewhere[10]. Here I shall examine the functional implications of control by a constitutively synthesised regulator and by an autogenously regulated one. To answer questions of this type one cannot compare directly two representative systems (for example, *lac* and *hut*) because they have numerous differences that are irrelevant to the comparison of classical and autogenous regulation *per se*. A controlled comparison in which the two systems are identical in every respect except for the difference in regulatory mechanism is desirable but difficult to achieve experimentally. Nevertheless, such comparisons can be simulated by mathematical analysis. I have performed such an analysis comparing models of classical and autogenous regulation in inducible operons[11]. Before discussing the results I shall point out the criteria for functional effectiveness that I have used in comparing these systems.

Criteria for functional effectiveness

To be specific, I will consider inducible catabolic systems in bacteria that allow the cell to utilise nutrients found in its environment. Several criteria can be formulated for functional effectiveness. (1) A sharp threshold in the concentration of the substrate necessary for induction protects the organism from wasteful synthesis of the catabolic enzymes when the substrate level is so low that insufficient benefit would be gained from induction. (2) The ability to make the most product available to the organism from a given supra-threshold increment in substrate is clearly advantageous to the organism whenever that substrate is the only nutrient available for growth. (3) Stability is obviously essential for a system to function properly. (4) A temporally responsive system can be induced rapidly, which is an advantage when substrate levels change abruptly. (5) Insensitivity to perturbations in the system's component parts ensures that the system will continue to function in spite of the continual perturbations it experiences in any real environment. These perturbations result from non-lethal mutations as well as physical changes in temperature and so on. None of these criteria assumes anything about the type of regulatory mechanism involved.

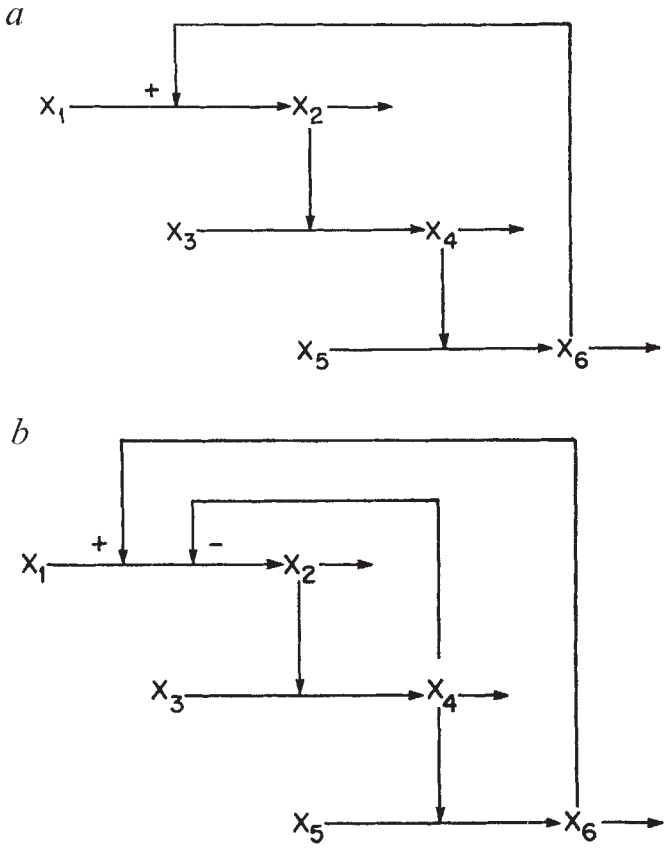

Fig. 1 Schematic models of inducible catabolic systems. *a*, Classically regulated operon in which the structural gene of the regulator protein lies outside the operon and is regulated independently of the operon. *b*, Autogenously regulated operon in which the structural gene of the regulator is located within the transcriptional unit that the regulator controls. X_1, Nucleotide precursors; X_2, specific mRNA; X_3, amino acid precursors; X_4, enzymes of the catabolic pathway (plus regulator in the case of autogenous regulation); X_5, substrate; X_6, product-inducer. Although it is not critical for the comparisons reported here, the product has been chosen as inducer because in most cases the inducer is known to be a metabolic product rather than the substrate of the pathway[12]. The horizontal arrows indicate chemical transformations at the mRNA, enzyme and metabolite levels. The vertical arrows represent modifier or catalytic influences (the sense of the influence is positive unless otherwise indicated). Except for the differences in regulation these models are assumed to be identical.

Comparison of repressor-controlled systems

First, I will compare inducible systems involving repressors that are regulated in the classical manner with those that are regulated autogenously. The two possibilities are represented schematically in Fig. 1. Except for the differences in regulation these models are assumed to be identical.

These two models can be compared under various conditions, and because there are several criteria to consider, a meaningful tabulation of all the results can present a problem. Figure 2, however, is a simple diagram summarising many of the results of these comparisons. This is a two-dimensional plot with the vertical axis representing the strength of the inducer's contribution to the control of transcription and the horizontal axis representing the strength of the autogenous contribution. Each point in this space can be thought of as representing a different system with distinct properties. This space, however, can be divided into subclasses of systems that have similar properties. Since I am comparing inducible systems that utilise a repressor mechanism, the inducer has a positive effect on transcription ($g_{26}>0$) while the autogenous effect is negative ($g_{24}<0$). Thus, I can restrict my attention to the upper left-hand quadrant of this figure. The vertical axis in this quadrant is the locus of points representing classical systems, since the autogenous contribution is zero. Line (*a*) represents another classification. The position of this line is determined by analysing the stability of these models. All systems represented by points below line (*a*) are stable (if perturbed momentarily they will return to their predisturbance condition) whereas all those above this line are unstable (they will not return to their predisturbance condition).

Lines, such as (*b*), radiating from the point where line (*a*) intersects the horizontal axis, are lines of equivalence with respect to the first two criteria. All systems whose regulatory parameters have values that determine points on a given line, such as (*b*), have in common: (1) the same sharpness of threshold in substrate concentration for induction and (2) the same product formation for a given increment in substrate. The slope of the line is a quantitative measure of these properties. The steeper the slope is, the sharper will be the threshold and the greater the product formation.

Systems of the two types now can be compared. As noted before, all of the systems represented on a given line such as (*b*) behave identically according to the first two criteria. They differ, however, according to the third criterion. The position of the classical system is closer to the boundary of instability than are those of the corresponding autogenous systems represented in Fig. 2. In other words, line (*b*) and the boundary of instability, line (*a*), diverge to the left and the autogenous systems lying further from this boundary are more stable.

The fourth criterion, that of temporal responsiveness, is examined in Fig. 3. Curve (*a*) represents the response of the classical system. The system is in a steady state before $t=0$. At time zero the substrate concentration is suddenly increased to a new value that is maintained throughout the experiment. The concentration of the product is plotted as a function of time. Similar responses are plotted for a series

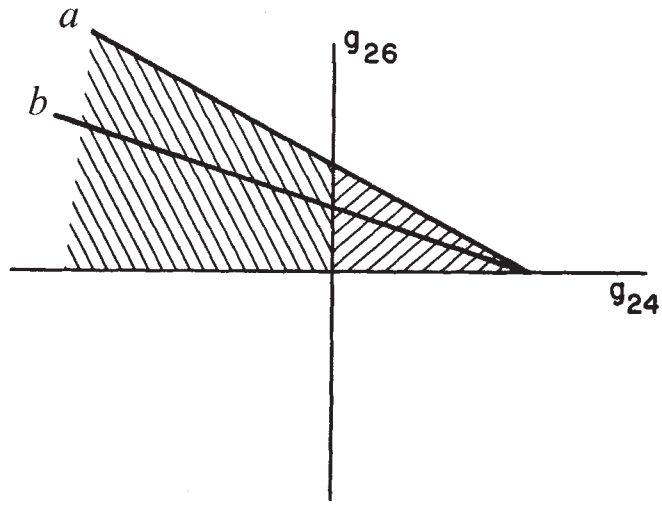

Fig. 2 Graphical comparison of systems with alternative types of regulation. The vertical axis represents the strength of the product's contribution to the regulation of transcription and the horizontal axis represents the strength of the autogenous contribution to this regulation. Line (*a*) represents the boundary of instability. Line (*b*) is a representative line of equivalence with respect to the first two criteria for functional effectiveness. The vertical axis is the locus of points representing the classically regulated systems with either activator or repressor control. The shaded area to the left of this axis is the location of points representing stable systems with autogenously regulated repressors. Similarly, the shaded area to the right of the vertical axis represents stable systems with autogenously regulated activators. See text for further discussion.

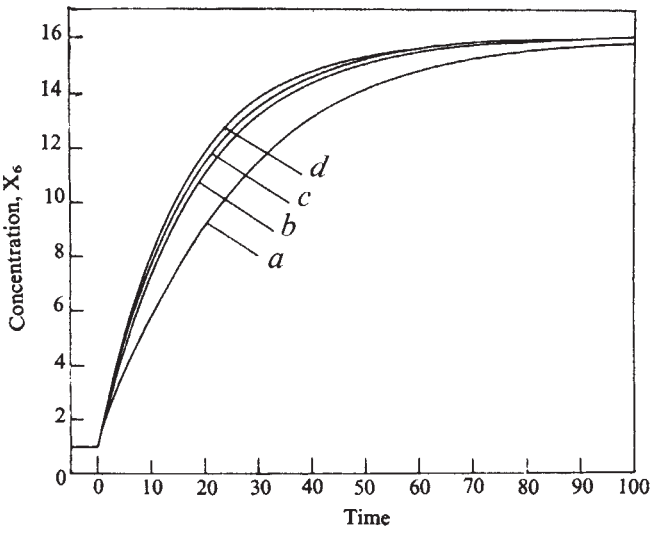

Fig. 3 Temporal responsiveness of equivalent systems with different strengths of autogenous regulation of repressor. The strength is represented by the parameter g_{24}, which has values: *a*, 0.0; *b*, −0.5; *c*, −1.0; *d*, −2.0. The corresponding values for the parameter g_{26} are chosen so that the points representing the different systems all lie on the same line of equivalence. Curve (*a*) represents the classical system with constitutively synthesised repressor. See text for further discussion.

of systems with increasing strengths of autogenous regulation and represented by points on the same line of equivalence (see Fig. 2). Systems with a high degree of stability tend to have more sluggish temporal responses to change. Figure 3 shows that the opposite relationship is true of systems with autogenous regulation of repressor.

Finally, a comparison on the basis of the fifth criterion shows that the sensitivities of the system with autogenous regulation of repressor to various perturbations in the structure of the system itself are always less than or equal to the coresponding sensitivities of the classical system.

These comparisons show that the autogenously regulated systems are equivalent or superior to the corresponding classical system according to all five criteria for functional effectiveness of an inducible catabolic pathway.

Comparison of activator-controlled systems

Quite different results are obtained when classical and autogenous regulation are compared in systems governed by an activator protein. Schematic models representing these two types of systems are identical to those in Fig. 1, except that the negative sign is now positive, to indicate that the regulatory protein X_4 has a positive effect on the transcription process. Again, except for the differences in regulation these models are assumed to be identical. The functions of these two models can be compared as in the previous section. Since the autogenous effect on transcription is now positive, I will restrict my attention to the upper right-hand quadrant in Fig. 2. The classical systems are represented along the vertical axis with zero autogenous contribution. Line (*a*) is the boundary of instability, so the stable systems of physiological interest here are represented by points within the shaded triangular area.

All systems represented on a line of equivalence such as (*b*) are equivalent with respect to the first two criteria. Since lines of equivalence, such as (*b*), and the boundary of instability, line (*a*), converge to the right, systems with increasing strength of autogenous regulation are represented nearer the boundary of instability than the corresponding classical system. Systems with autogenous regulation also show a more sluggish temporal response to change, as Fig. 4 shows. Curve (*a*) represents the response of the classical system to an increase in substrate. The temporal responses are slower for the corresponding systems with increasing strengths of autogenous regulation (curves *b* and *c*). Finally, a comparison on the basis of the fifth criterion shows that the sensitivities of the system with autogenous regulation of activator are always greater than or equal to those of the corresponding classical system.

Thus, the results in this section are the opposite of those previously obtained for systems governed by a repressor protein. According to all five criteria for functional effectiveness, the classical system is equivalent or superior to the corresponding autogenously regulated systems.

Predictions and observations

The functional differences I have discussed have obvious implications for the natural selection of classical and autogenous mechanisms of regulation in simple, inducible catabolic systems of the type represented in Fig. 1. Systems governed by an activator protein are not expected to utilise autogenous regulation. Activator-controlled systems without such regulation are superior to autogenously regulated but otherwise equivalent systems by all the criteria given for functional effectiveness. On the other hand, systems governed by a repressor protein can be predicted to involve autogenous regulation as well. Systems with autogenously regulated repressor are superior to classical but otherwise equivalent systems by all of these same criteria. How well do these predictions agree with experimental observations?

The first prediction agrees with what is known about activator-controlled systems in enteric bacteria. There is no known instance of autogenous regulation in such systems. In the best studied cases, the arabinose[5] and maltose[6] operons, the structural gene for the activator is located outside the transcriptional unit(s) known to be under its control. [The regulator protein of the *ara* operon is both an activator and a repressor. However, the predominant functional properties are those of an activator, and for our purposes the *ara* operon can be considered a (modified) activator-controlled system.] Thus, a simple, autogenously regulated operon is excluded. One could, of course, postulate more complex models of autogenous regulation in

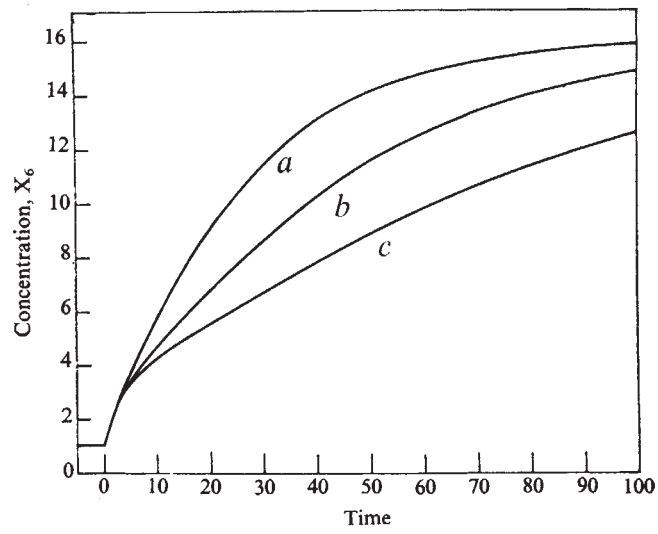

Fig. 4 Temporal responsiveness of equivalent systems with different strengths of autogenous regulation of activator. The strength is represented by the parameter g_{24}, which has values: *a*, 0.00; *b*, 0.15; *c*, 0.20. The corresponding values for the parameter g_{26} are chosen so that the points representing the different systems all lie on the same line of equivalence. Curve (a) represents the system with constitutively synthesised activator. See text for further discussion.

which the activator itself is autogenously regulated and its level varies with the expression of the structural genes in another transcriptional unit under its control. Functionally, this type of regulon model would be indistinguishable in most respects from the simple model in Fig. 1*b*. There is no evidence, however, to support or reject such a model.

The second prediction, concerning repressor-controlled systems, agrees only partially with available evidence. For the histidine utilisation system in *Salmonella typhimurium*, the evidence clearly agrees with the prediction of autogenous regulation. The structural gene for its repressor is located within one of the transcriptional units controlled by the repressor[8]. The expression of the second unit also varies with the level of the repressor[13], which is functionally equivalent to autogenous regulation for most purposes, as previously indicated. There is no evidence for autogenous regulation in the other two well-studied repressor-controlled systems, the lactose[2] and galactose[3] operons. In each case, the structural gene for the repressor lies outside the only transcriptional unit known to be under its control, so that simple autogenous regulation appears to be excluded. This discrepancy might be explained in one of two ways. The systems might be regulated in a way that is functionally equivalent to autogenous regulation (one possibility has already been mentioned). Alternatively, the systems might have additional, as yet unknown, functions that are not reflected in the criteria for functional effectiveness and that require that the repressor not be autogenously regulated. The first explanation indicates that information about the molecular mechanisms is incomplete, while the second implies a lack of information about the physiological functions of these operons.

With regard to this last possibility, it is already clear that the *gal* operon is also a component of a much more complex system involved in the biosynthesis of capsular polysaccharide[14]. Recent evidence indicates that this operon is under the control of two repressors, specified by the *galR* and *capR* genes, respectively[15]. Thus, it would seem that the *gal* operon cannot be considered functionally as a simple, inducible catabolic system. Similarly, the *lac* operon might yet be implicated in additional (dispensible) functions, possibly through the expression of the gene for the transacetylase enzyme, the function of which is presently unknown[16].

It has been shown that autogenous regulation has certain advantages and disadvantages and that these have obvious implications for the natural selection of control mechanisms in inducible operons. There is reasonably good agreement of these predictions based on simple models of inducible catabolic systems with current observations of such operons in enteric bacteria. In those cases where the systems appear to be more complex, additional information about molecular mechanisms and physiological functions will be necessary before definitive comparisons can be made.

This research was supported by a grant from the United States National Science Foundation.

Received August 28; revised October 18, 1974.

1 Jacob, F., and Monod, J., *J. molec. Biol.*, **3**, 318–356 (1961).
2 Reznikoff, W. S., *Ann. Rev. Genetics*, **6**, 133–156 (1972).
3 Nakanishi, S., Adhya, S., Gottesman, M. E., and Pastan, I., *Proc. natn. Acad. Sci. U.S.A.*, **70**, 334–338 (1973).
4 Cozzarelli, N. R., Freedberg, W. B., and Lin, E. C. C., *J. molec. Biol.*, **31**, 371–387 (1968).
5 Cleary, P. P., and Englesberg, E., *J. Bact.*, **118**, 121–128 (1974).
6 Hofnung, M., Schwartz, M., and Hatfield, D., *J. molec. Biol.*, **61**, 681–694 (1971).
7 McFall, E., Bloom, F. R., Young, M., and Crothers, A. M., *J. Bact.* (in the press).
8 Smith, G. R., and Magasanik, B., *Proc. natn. Acad. Sci. U.S.A.*, **68**, 1493–1497 (1971).
9 Goldberger, R. F., *Science*, **183**, 810–816 (1974).
10 Savageau, M. A., *Proc. natn. Acad. Sci. U.S.A.*, **71**, 2453–2455 (1974).
11 Savageau, M. A., *Biochemical systems analysis: a study of function and design in molecular biology* (Benjamin, Reading, Massachusetts, in press).
12 Schlesinger, S., Scotto, P., and Magasanik, B., *J. biol. Chem.*, **240**, 4331–4337 (1965).
13 Hagen, D. C., and Magasanik, B., *Proc. natn. Acad. Sci. U.S.A.*, **70**, 808–812 (1973).
14 Hua, S.-S., and Markovitz, A., *J. Bact.*, **110**, 1089–1099 (1972).
15 Hua, S.-S., and Markovitz, A., *Proc. natn. Acad. Sci. U.S.A.*, **71**, 507–511 (1974).
16 Bourgeois, S., *Current topics in cellular regulation*, **4**, 39–75 (1971).

Seismic precursors before rock failures in mines

B. T. Brady

United States Department of Interior, Bureau of Mines, Denver Mining Research Center, Denver, Colorado*

Seismic precursors (such as anomalous V_p values and/or seismic activity) whose behaviour is qualitatively similar to those reported to precede earthquakes are observed before rock failures in dry underground mines. Similar processes may be involved during failure of rock in the mine and the earthquake, and diffusion of fluids into the focal region of a potential earthquake may not be a necessary condition to produce most of the precursors reported.

EVIDENCE is presented here that seismic precursor effects, such as anomalous V_p values and/or seismic activity, are observed before rock failures in underground mines. Seismic precursor information for rock bursts in a deep (5,000 feet) silver mine in northern Idaho and a roof fall in a Pennsylvania coal mine is discussed. These mines are dry and the effects of fluids on the seismic precursors are precluded.

* Present address.

Rock bursts at Galena

The Galena mine is located in the Coeur d'Alene mining district in northern Idaho. Silver, lead and zinc are the predominant metals mined from steeply dipping veins in the Belt formation series of Precambrian quartzites and argillites. A horizontal cut-and-fill mining system is used, with the mill tailings being pumped back into the mine to become the floor for the succeeding cut as mining proceeds from a lower level to a level 300 feet above. Detailed information relating to this type of mining system is available elsewhere[1].

Rock bursts in the Galena have occurred in dry pillars at depths of 2,000 to 4,900 feet. In this article, rock bursts are qualitatively identified as small bursts (no damage to adjacent mine structures), bursts (no major damage to adjacent mine structures) and major bursts (substantial damage incurred to the adjacent mine structures). Past experience at the Galena has shown that the number of damaging rock bursts increases dramatically once the pillar thickness has been reduced to