cake of ice, or an icicle held between two in a circle, likewise prevents the shock, which one would not expect, as water conducts it so perfectly well . – – – Gilding on a new book, though at first it conducts the shock extremely well, yet fails after ten or a dozen experiments, though it appears otherwise in all respects the same, which we cannot account for (*8*).

28. There is one experiment more which surprises us, and is not hitherto satisfactorily accounted for; it is this: Place an iron shot on a glass stand, and let a ball of damp cork, suspended by a silk thread, hang in contact with the shot. Take a bottle in each hand, one that is electrified through the hook, the other through the coating: Apply the giving wire to the shot, which will electrify it *positively,* and the cork shall be repelled: then apply the requiring wire, which will take out the spark given by the other; when the cork will return to the shot: Apply the same again, and take out another spark, so will the shot be electrified *negatively,* and the cork in that case shall be repelled equally as before. Then apply the giving wire to the shot, and give the spark it wanted, so will the cork return: Give it another, which will be an addition to its natural quantity, so will the cork be repelled again: And so may the experiment be repeated as long as there is any charge in the bottles. Which shews that bodies having less than the common quantity of electricity, repel each other, as well as those that have more.

Chagrined a little that we have been hitherto able to produce nothing in this way of use to mankind; and the hot weather coming on, when electrical experiments are not so agreeable, it is proposed to put an end to them for this season, somewhat humorously, in a party of pleasure, on the banks of *Skuylkil* (*9*). Spirits, at the same time, are to be fired by a spark sent from side to side through the river, without any other conductor than the water; an experiment which we some time since performed, to the amazement of many (*10*). A turkey is to be killed for our dinner by the *electrical shock,* and roasted by the *electrical jack,* before a fire kindled by the *electrified bottle*: when the healths of all the famous electricians in *England, Holland, France,* and *Germany* are to be drank in (*11*) *electrified bumpers,* under the discharge of guns from the *electrical battery.*

Notes

1. This was a Discovery of the very ingenious Mr. *Kinnersley,* and by him communicated to me.
2. To charge a bottle commodiously through the coating, place it on a glass stand; form a communication from the prime conductor to the coating, and another from the hook to the wall or floor. When it is charged, remove the latter communication before you take hold of the bottle, otherwise great part of the fire will escape by it.
3. I have since heard that Mr. *Smeaton* was the first who made use of panes of glass for that purpose.
4. Contrived by Mr. *Kinnersley*..
5. We have since found it fatal to small animals, though not to large ones. The biggest we have yet killed is a hen. 1750.
6. This was afterwards done with success by Mr. *Kinnersley.*
7. Probably the ground is never so dry.
8. We afterwards found that it failed after one stroke with a large bottle; and the continuity of the gold appearing broken, and many of its parts dissipated, the electricity could not pass the remaining parts without leaping from part to part through the air, which always resists the motion of this fluid, and was probably the cause of the gold's not conducting so well as before; the number of interruptions in the line of gold, making, when added together, a space larger perhaps than the striking distance.
9. The river that washes one side of *Philadelphia,* as the *Delaware* does the other; both are ornamented with the summer habitations of the citizens, and the agreeable mansions of the principal people of this colony.
10. As the possibility of this experiment has not been easily conceived, I shall here describe it.—Two iron rods, about three feet long, were planted just within the margin of the river, on the opposite sides. A thick piece of wire, with a small round knob at its end, was fixed on the top of one of the rods, bending downwards, so as to deliver commodiously the spark upon the surface of the spirit. A small wire fastened by one end to the handle of the spoon, containing the spirit, was carried a-cross the river, and supported in the air by the rope commonly used to hold by, in drawing the ferry-boats over. The other end of this wire was tied round the coating of the bottle; which being charged, the spark was delivered from the hook to the top of the rod standing in the water on that side. At the same instant the rod on the other side delivered a spark into the spoon, and fired the spirit. The electric fire returning to the coating of the bottle, through the handle of the spoon and the supported wire connected with them.

    That the electric fire thus actually passes through the water, has since been satisfactorily demonstrated to many by an experiment of Mr. *Kinnersley*'s, performed in a trough of water about ten feet long. The hand being placed under water in the direction of the spark (which always takes the strait or shortest course, if sufficient, and other circumstances are equal) is struck and penetrated by it as it passes.
11. *An electrified bumper* is a small thin glass tumbler, nearly filled with wine, and electrified as the bottle. This when brought to the lips gives a shock, if the party be close shaved, and does not breath on the liquor.

April 29, 1749.

Significance of "Heat-Activated" Enzymes

Morton N. Swartz, Nathan O. Kaplan, Mary E. Frech

The mechanism of regulation of metabolic routes in the intact cell has been a subject of much interest. It has, of necessity, assumed an even greater significance recently as studies with cell fractions have revealed alternative pathways of metabolism for a given normal metabolite. Mutation, suppressor genes, and new enzyme formation as in the phenomenon of adaptation have recently been explored intensively (*1*) and certainly could provide potent agencies of metabolic control. Another possible mechanism of cellular regulation, the synthesis by the cell of specific enzyme inhibitors, has also been suggested by many workers (*1*). It is this latter concept that we propose to emphasize in this paper (*2*).

Dr. Swartz is a research fellow, U.S. Public Health Service–National Cancer Institute. Dr. Kaplan is a staff member, and Miss Frech is a research assistant at the McCollum-Pratt Institute, Johns Hopkins University.

"Heat-Activated" Enzymes

In the course of assays on the pyridine nucleotide content of various microorganisms, it was noted that whereas trichloracetic acid extracts of *Proteus vulgaris* X-19 (strain No. 6380) contained considerable amounts of these nucleotides, extracts prepared from boiled cells showed predominantly nicotinamide riboside and very little diphosphopyridine nucleotide (DPN) or nicotinamide mononucleotide (NMN). Subsequent investigation revealed the presence, in sonic extracts of this organism, of two enzymes (a DPN pyrophosphatase and a 5′-nucleotidase) that were ordinarily present in an inhibited state. Only after these extracts were placed in a boiling water bath for several minutes could any significant activity be shown. The strik-

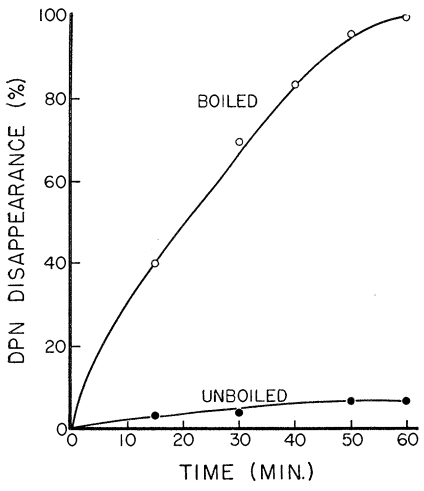

Fig. 1. Effect of heating to 100°C on the activation of an otherwise inactive DPN pyrophosphatase from *Proteus vulgaris*. The reaction mixture contained 0.5 ml of crude enzyme preparation (1 to 6 sonicate in H_2O), 4.3 μmoles of DPN, and 0.08*M* tris buffer (final concentration) at *p*H 7.5 in a final total volume of 3.0 ml. DPN remaining at given times was assayed by the use of the alcohol dehydrogenase method and the reduced DPN was read at 340 mμ. Unboiled enzyme, ●—●; enzyme boiled for 2 minutes, ○—○.

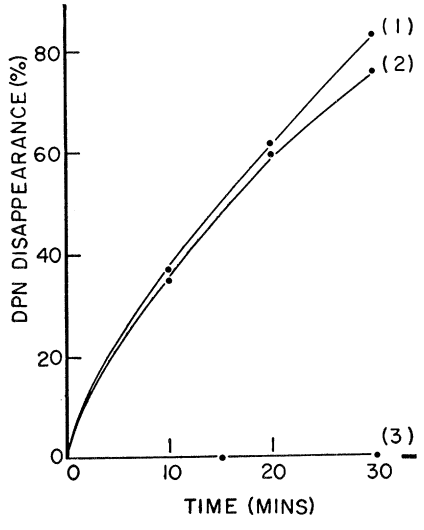

Fig. 2. Requirement for inorganic pyrophosphate to protect enzyme during boiling. The reaction mixture contained 0.5 ml of crude enzyme preparation (1 to 6 sonicate in H_2O) that was boiled for 2 minutes, 2 μmoles of DPN, 0.08*M* tris buffer (final concentration) at *p*H 7.5, and 1 μmole of $CoCl_2$ in a final volume of 1.5 ml. Curve *1*, undialyzed enzyme; curve *2*, enzyme dialyzed for 18 hours against distilled H_2O, then 2 μmoles of inorganic pyrophosphate added to 0.5 ml of enzyme and boiled for 2 minutes; curve *3*, same as curve *2* except that the pyrophosphate was added to the reaction after the enzyme had been boiled. DPN assayed by alcohol dehydrogenase method.

ing heat stability of these enzymes is shown by the fact that even after 15 minutes of boiling 50 percent of the maximum activity (that obtained after 2 minutes of boiling) remains. These enzymes, in the inhibited form, have been purified 20 to 40 fold by some of the common methods of protein fractionation (protamine, acetone, calcium phosphate, and alumina C γ gels), and they still exhibit the phenomenon of "heat-activation." Parenthetically, it might be noted that most of the enzymes in these extracts are not heat stable—for example, alcohol dehydrogenase and nucleoside phosphorylase are markedly heat-labile proteins.

As can be seen in Fig. 1, there is evidence of only slight DPN pyrophosphatase activity in unboiled extracts, whereas after boiling there is a marked capacity to cleave DPN. The explanation of this apparent heat-activation lies in the fortuitous coincidence of a heat-stable enzyme and a heat-labile inhibitor. The ability of the enzyme to withstand boiling appears to require a dialyzable component such as inorganic pyrophosphate. As can be seen in Fig. 2, dialyzed preparations are inactive after boiling, even when inorganic pyrophosphate is subsequently added to the test system. However, when inorganic pyrophosphate (6 μmoles/ml) is added to the enzyme prior to boiling, there is retention of essentially full activity. Neither DPN, NMN, 5′-adenylic acid (5′-AMP), nor metaphosphate will replace pyrophosphate in this protective role. An as yet unidentified organic phosphate compound, which is normally present in extracts of *Proteus vulgaris*, will also afford protection against high temperatures. This compound is in the barium-soluble, alcohol-insoluble fraction of trichloracetic extracts of fresh *Proteus* cells.

Proteus vulgaris sonicates contain roughly a 50-percent excess of free inhibitor—that is, inhibitor not bound to the enzyme. The inhibition of active enzyme by the free inhibitor can be seen in Fig. 3. There is an approximately linear relationship between the amount of inhibitor and the degree of inhibition at the end of 30 minutes. A period of preincubation of the enzyme and inhibitor prior to the addition of substrate would probably have made such a relationship evident earlier in the course of incubation. This inhibitor is nondialyzable, and is, as previously stated, heat labile. Acid treatment (*p*H 1 to 2) for 10 minutes at room temperature destroys the free inhibitor. Bound inhibitor is inactivated by similar treatment, and the enzyme then becomes fully active without boiling. The unbound inhibitor has been purified several fold by alkaline ammonium sulfate and ethanol fractionation. These points of evidence strongly

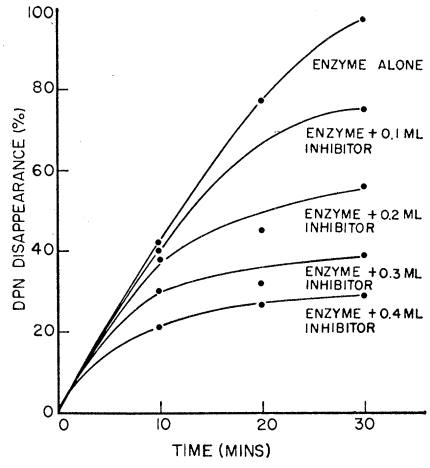

Fig. 3. Effect of free inhibitor on active DPN pyrophosphatase of *Proteus vulgaris*. The reaction mixture contained 0.3 ml of an 18-fold purified enzyme preparation, 2 μmoles of DPN, 0.08*M* tris buffer (final concentration) at *p*H 7.5, and 1 μmole of $CoCl_2$ in a final volume of 1.5 ml. Enzyme boiled with 2 μmoles of inorganic pyrophosphate. Inhibitor fraction dialyzed for 18 hours against distilled H_2O. DPN assayed by alcohol dehydrogenase method.

suggest that the inhibitor is a protein. Furthermore, the purified inhibitor-enzyme complex contains no detectable ribonucleic acid (RNA), and ribonuclease (RNase) does not activate the inhibited enzyme.

In this laboratory, similar enzyme-inhibitor relationships have been found in several other widely divergent types of bacteria: *Mycobacterium butyricum* (*3*), *Bacillus subtilis, Proteus morganii,* and *Proteus rettgeri.* These protein inhibitors appear to be quite species-specific, and no cross reactions have as yet been noted (*3*). The heat-activated enzymes from *Mycobacterium* and *Bacillus subtilis* split DPN at the nicotinamide-ribose linkage, yielding adenosine diphosphate ribose and free nicotinamide as products. Milton Kern of this laboratory has found free inhibitor in *Mycobacterium butyricum* in approximately a 10-fold excess over that amount closely bound to the enzyme, and he has achieved some purification of this inhibitor by utilizing ammonium sulfate procedures (*3*). Thus far, heat-activated DPNases have not been found in any higher plant or animal tissues.

The facts that the inhibitor from *Proteus vulgaris* can be split from the enzyme at *p*H 1 to 2 in 10 minutes at room temperature and that it can be inactivated by boiling strongly suggest that these two components are bound by a salt type of linkage rather than through a peptide bond.

The heat-activated pyrophosphatase and the 5′-nucleotidase from *Proteus* are relatively nonspecific in regard to sub-

Table 1. Relative nonspecificity in regard to substrates of heat-activated pyrophosphatase and the 5′-nucleotidase from *Proteus*.

Pyrophosphatase		5′-Nucleotidase	
Split	Not split	Split	Not split
DPN	Thiamine pyrophosphate	5′-AMP	Flavin mononucleotide
DPNH	Metaphosphate	NMN	Glucose-6-phosphate
TPN (slowly)		Ribose-5-phosphate	β-Glycerophosphate
ADP			2′-AMP
ATP			3′-AMP
Deamino DPN			
Adenosine diphosphate ribose			
3-Acetyl pyridine analog DPN			
Inorganic pyrophosphate (slowly)			

strates (Table 1). A purification of the pyrophosphatase completely free of 5′-nucleotidase activity has not thus far been achieved. That these are, nonetheless, two discrete enzymes is evident from the fact that the former has an absolute requirement for cobalt or manganese, whereas the latter has no metal requirement.

A less marked example of the phenomenon of heat activation has been noted previously in the case of the protyrosinase-tyrosinase relationship. Bodine *et al.* (*4–6*) demonstrated that tyrosinase occurs in certain of the lower animals (grasshopper eggs and mealworm larvae) as an inactive material that has been called protyrosinase. The protyrosinase obtained from grasshopper eggs and purified by ammonium sulfate fractionation can be converted into active tyrosinase by treatment with various detergents (sodium oleate, sodium dodecyl sulfate, and others), acetone, or urea. Activation can also be accomplished by the addition of extracts from grasshopper embryos or by heating the protyrosinase fraction to 60° to 70°C. However, the mechanism of the heat activation in this case is thought to be an autocatalytic process rather than the destruction of a heat-labile inhibitor.

A similar phenomenon, activation of an inactive tyrosinase, has been studied in detail recently by Horowitz and Fling (*7*) in *Drosophila melanogaster*. Whereas fresh extracts obtained from adult *Drosophila* exhibit no tyrosinase activity, extracts that have been allowed to stand at 0°C become active. On the basis of a study of the kinetics of activation, it was suggested that tyrosinase formation was most likely an autocatalytic process similar to that in the trypsin-trypsinogen relationship, with the notable exception that the reaction product (tyrosinase), unlike trypsin, takes no part in the autocatalytic reaction. These workers did, however, find a definite tyrosinase inhibitor in fresh extracts of their *Drosophila* system. Although they concluded, from kinetic considerations, that this inhibitor was not responsible for the absence of tyrosinase activity in fresh extracts, they did feel that they had not ruled out some less evident role for it in the activating system.

Enzyme Inhibitors in Mutants

The enzyme-inhibitor mechanism that is suggested by the finding of heat-activated enzymes is also indicated in the studies of Wagner and Guirard (*8*) and Wagner (*9*), who noted that pantothenic acid could be synthesized from beta-alanine and pantoyl-lactone by intact, nongrowing mycelial pads of the wild type of *Neurospora crassa*. However, no synthesis was detectable using pads from a pantothenic acid-requiring mutant that was incapable of utilizing a mixture of these two moieties for growth. It was subsequently shown that pantothenic acid synthesis could be performed by acetone-dried, washed residues from the mutant strain as well as from the wild type. The enzyme isolated from the mutants showed the same chemical and physical properties as that isolated from the wild type with the single exception of a different temperature coefficient of enzymatic activity. Although no mention was made of the isolation of an inhibitor, it is readily conceivable that in the mutant strain the synthetic enzyme, which is definitely present, is kept in an inhibited or inactive state in the whole cell by a specific inhibitor. On fractionation of the cell, this inhibitor is separated from the enzyme or perhaps destroyed. Thus, what at first appeared to be a simple genetic block leading to the loss of a single enzyme may be actually due to an enzyme-inhibitor relationship.

A similar, although less clear, suggestion of a naturally occurring inhibited enzyme has been reported by Gordon and Mitchell (*10*). Cell-free extracts of certain tryptophan-requiring mutants of *Neurospora* contained no demonstrable tryptophan desmolase activity, but similar extracts from the wild type could synthesize tryptophan from indole and serine. After dialysis or ammonium sulfate fractionation, the mutant extracts exhibited considerable tryptophan desmolase activity, although on a dry weight basis this activity never exceeded more than one-half that of the wild type extracts.

Ribonucleic Acids as Enzyme Inhibitors

One type of enzyme in particular has been associated with a natural inhibitor, namely desoxyribonuclease (DNase). DNase inhibitors have been found in yeast (*11*), in streptococci (*12*), and in various animal tissues (*13, 14*). The inhibitor in the case of the streptococcus is a specific RNA, whereas the others are proteins. A very striking example of this enzyme-inhibitor relationship in *Escherichia coli* has been described by Kozloff (*15*). When freshly prepared and assayed, sonic extracts of this organism show essentially no DNase activity. T6r+ phage infected *Escherichia coli* cell sonicates, on the contrary, readily depolymerize DNA. It has been shown that the uninfected cells contain quantitatively as much DNase as the infected cells, but that the enzyme is completely inhibited by a specific RNA of the bacteria. Destruction of the inhibitor by aging the extracts or by treatment with RNase leads to full activation of the enzyme.

A further possible role of RNA as a specific enzyme inhibitor has been tentatively advanced by Rotman (*16*) during the course of studies on the beta-galactosidase of *Escherichia coli* cells. The activity of this enzyme in bacterial extracts has been noted to be about 20 to 100 times what it is in the intact cell. When *Escherichia coli* cells were treated with small amounts of benzene or lysozyme, agents that usually destroy the cell membrane, beta-galactosidase activities of the same magnitude as that in bacterial extracts were observed. A striking parallelism was noted between the increase in enzyme activity and the appearance of RNA break-down products in the suspending medium. The degree of polymerization of the released products ranged from highly polymerized nucleotides to free bases. The material lost appeared to be rather specific, for other cell components such as amino acids were not found among the products. In an attempt to explain the diminished activity in whole cells as compared with the activity in extracts, Rotman has suggested the presence in the intact cell of an RNA-enzyme com-

plex that dissociates on disruption of the cell. Direct demonstration of this RNA-enzyme complex has not as yet been accomplished. This demonstration would seem to be necessary in order to rule out permeability factors as the explanation for the difference between the activities of whole cells and extracts.

Specific Protein Inhibitors

That extracts of adrenal cortex were inhibitory to hexokinase activity in muscle extracts of alloxan diabetic rats has been demonstrated by Colowick *et al.* (*17*). However, the hexokinase activity of normal rat muscle or beef brain extracts was not inhibited on the addition of adrenal cortical extract alone, but it was significantly inhibited by the further addition of a second inhibitory factor, a labile protein fraction from the anterior pituitary. These inhibitions could then be completely removed by insulin. It was suggested that the inhibitory effect of adrenal extracts on diabetic muscle extracts was dependent on the presence in the latter of an inhibitory factor, probably identical with the inhibitory factor in pituitary extracts. A perhaps similar inhibitor for brain hexokinase has been found by Weil-Malherbe (*18*) in the blood of untreated human diabetics. This inhibitor diminished markedly following treatment of the patients with insulin.

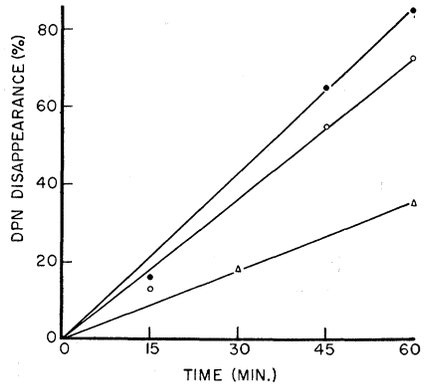

Fig. 4. Effect of nutritional factors on presence of inhibited enzyme. Reaction mixture consisted of 0.1 ml of crude sonicate, 4.3 μmoles of DPN, and 0.08*M* tris buffer (final concentration) at *p*H 7.5. Boiled enzyme from cells grown on minimal medium, ●—●; unboiled enzyme from cells grown on medium containing yeast extract, ○—○; active unboiled enzyme plus 0.1 ml of inhibitor △—△. DPN determined by alcohol dehydrogenase method.

If the role of the natural inhibitor of hexokinase were important and if one could isolate the inhibited enzyme along with the free enzyme without loss of inhibitor, one might expect to find significantly less hexokinase in diabetic tissues than in normal tissues, and perhaps more of the uninhibited enzyme in hypophysectomized animals. Very few comparisons of this sort have been made. Christensen *et al.* (*19*) carefully examined the hexokinase content of hemolyzates of rat red blood cells and were unable to find any significant difference between the activity of normal and of diabetic or hypophysectomized animals. Reiss and Rees (*20*), however, did find that the hexokinase activity extractable from rat brain is higher after hypophysectomy or adrenalectomy than it is before.

The enzyme-inhibitor protein relationship (*21, 22*) has been described in great detail for trypsin inhibitor (various legumes, ovomucoid, pancreas, plasma, colostrum, and *Ascaris*); the relationship is distinct from the autocatalytic conversion of trypsinogen to trypsin. One might teleologically assign a role to the inhibitor from *Ascaris* in inhibiting the action of the pepsin and trypsin that are found in the intestinal tract of the host; but the role of trypsin inhibitor in the other cases is not very evident. The trypsin inhibitor-trypsin complex has been isolated as such from pancreas. This relationship appears to be similar to that of the heat-activated pyrophosphatase in that the two components apparently are held together by secondary rather than by direct chemical bonds. Dissociation occurs outside the *p*H range of complex stability, but within the range, they behave ostensibly as a single protein.

An unusual feature has been noted (*23*) in the conversion of pepsinogen to pepsin. The initial change in the pepsinogen at *p*H 5.4 yields an inactive pepsin-inhibitor compound; and thus it is not, in the strictest sense, an autocatalytic reaction. When the *p*H is reduced below 5, the enzyme-inhibitor compound dissociates into free enzyme and free inhibitor (a large basic polypeptide). Prolonged incubation with pepsin can then cause destruction of the inhibitor.

Nutritional Control of Inhibitors

The existence of certain enzymes in a normally inhibited state could conceivably be a mechanism of cellular control of enzyme action. It would be possible to control enzymatic patterns, then, not only through the limitation of synthesis of an enzyme, but also through the synthesis or lack of synthesis of a specific inhibitory protein or RNA. Indeed, it has been possible to obtain cultures of *Proteus vulgaris* that are essentially free of the inhibitor of the pyrophosphatase by growing the organisms on a medium containing yeast extract rather than on the usual minimal medium (Fig. 4). Crude sonicates of the organism grown on yeast extract showed essentially the same pyrophosphatase activity whether boiled or unboiled. That the enzyme obtained from the organism grown in this way is the same as that obtained from cultures grown on the usual minimal medium is suggested by the remarkable heat stability of both enzymes and by the inhibition of the former by the protein inhibitor obtained from the latter (Fig. 4). The fact that the inhibitor in *Proteus* is subject to nutritional control indicates that protein inhibitors may play a significant role in regulating the metabolic activities of bacteria.

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The ancients tell us what is best; but we must learn from the moderns what is fittest.—BENJAMIN FRANKLIN.