DRAFT

March 29, 1961

THE MESSENGER RNA AND THE CONTROL OF THE FORMATION OF SPECIFIC PROTEINS IN BACTERIA

By Leo Szilard

The Enrico Fermi Institute
The University of Chicago
Chicago, Illinois

- - - - - - - - - - - -

This model is based on the assumption that the rate of formation of a given enzyme is controlled by the presence of a small molecule which is specific for that enzyme in the cell. In particular, it is assumed that the repressor, which is composed of a metabolite moity and an R moity, can combine with the enzyme molecule which is in the process of formation and is still attached to the enzyme forming site. Presumably the metabolic moity of the repressor combines with the specific site of the enzyme molecule, the controlling site, and the R moity of the repressor presumably combines with the enzyme forming site itself. It is assumed that while the repressor remains combined with the enzyme molecule sitting on the enzyme forming site, the enzyme molecule does not get detached from the enzyme forming site.

At the time when this model was proposed, it was assumed that the enzyme forming sites are the ribosomes and that each ribosome is specific for a given enzyme. As a result of recent work centering on the Institute of Pasteur in Paris, it appears most likely that the ribosomes do not carry the information which deter-

mines the specificity of the enzyme molecules and that even though the enzyme molecules may be formed inside of ribosomes, the enzyme forming site proper is not the ribosome but an RNA molecule called the messenger RNA molecule. According to this new concept, a messenger RNA molecule which is specific for a given enzyme can locate in any ribosome, and after an enzyme molecule is formed alongside the nessenger RNA molecule and is detached from it, the messenger RNA molecule is hydrolized. After the ribosome is thus emptied, it may house another messenger RNA of a different specificity.

The concept of the messenger RNA and its role in the formation of proteins is described in a paper, "Genetic Regulatory Mechanisms in the Synthesis of Proteins," (Journal of Molecular Biology, in press) by ~~Francis~~ Francois Jacob and Jacques Monod.

A messenger RNA molecule may be assumed to be formed alongside the DNA molecule which determines the specificity of the corresponding enzyme, and Jacob and Monod discuss the possibility that the repressor molecules slow the rate of the formation of the corresponding enzyme, not by combining with the enzyme molecule that is being formed alongside the messenger RNA molecule inside of a ribosome, but rather by directly combining with the DNA molecule, thereby slowing the rate of formation of the messenger RNA. Because we find it difficult to reconcile such a model with a number of observations on enzyme repression, some of them mentioned below, we propose to discuss, as a more promising alternative, the following possibility.

We revert to our model for enzyme repression mentioned

above and take into account the role of a messenger RNA by postulating the following:

If an enzyme molecule is formed alongside the specific messenger RNA molecule inside the ribosome, and if a repressor molecule combines with it while still attached to the messenger RNA, the whole complex, consisting of the messenger RNA, the enzyme molecule and the repressor, leaves -- as a compact unit -- the ribosome. If the concentration of the repressor is high, such units accumulate in the cytoplasm and, as a rule, will slow down the rate of formation of the messenger RNA, because the messenger RNA moity of the complex combines with a DNA molecule which is specific for it, and while that DNA molecule is so combined with a unit, it will be prevented from forming additional messenger RNA molecules.

According to this concept, the enzyme molecule and the slowing of the formation of the messenger RNA molecules by the repressor does not involve any recognition of the site of formation of the messenger RNA by the repressor.

The genes which determine the enzymes that lie on the metabolic pathway leading to an amino acid or a purine or pyrimidine are not, in general, adjacent on the genetic map. There are, however, exceptions. In those cases when the genes are adjacent, we might assume that the DNA which determines the enzymes of the series is contiguous and perhaps forms a single DNA molecule. Assuming that the formation of the messenger RNA starts at one end -- the head of this molecule, which corresponds to the first enzyme of the series --, in this case there would be no need for the repressor molecule to be able to combine with each enzyme of the series and, as a result of mutations, all enzymes of the series except the first one might well have lost their controlling site. According to the concepts here presented, if the repressor concentration is high enough, the formation of all the enzymes of the series would be repressed because a repressor molecule would combine with a molecule of the first enzyme of the series while that molecule is still attached to the messenger RNA on which it is formed. The repressor-enzyme-messenger RNA complex would leave the ribosome and these complexes would accumulate in the cytoplasm. The messenger RNA moiety of the complex can combine with the head of the DNA molecule and thus, with the accumulation of the complex, the formation of all the messenger RNAs which correspond to this particular series of enzymes would be slowed.

Our model accounts for the fact that an enzyme may be

induced by postulating that the inducer is a chemical analoid of the metabolic moiety of the repressor and that it, accordingly competes with the metabolic moiety of the repressor for the controlling site of the enzyme. In the case of the bio chemical pathways which lead to an amino acid, a purine, or a pyrimidine, the amino acid, purine or pyrimidine, or a chemical derivative of them may be assumed to form the metabolic moiety of the repressor. In the case of the enzymes that lie on the bio chemical pathway leading to arginine, we may assume arginine or a chemical derivative of arginine to form the metabolic moiety of the repressor of these enzymes.

We have postulated the existence of coupling enzyme C in the cell, which catalizes the formation of the repressor from the metabolic moiety, arginine, and some specific R moiety which we may assume to be a direct gene product. In the K strain of coli, the enzyme ornithine transcarbamylase can be repressed by growing the strain in the presence of arginine and it can be boosted to a very high value by growing the strain under conditions in which the intercellular concentration of arginine is fairly low. In our previous paper we have postulated that the repressor is formed through the intervention of Coupling enzyme C, which couples arginine or a derivative of arginine to a specific R moiety which is presumed to be a direct gene product. If the Coupling enzyme C contained in the K strain does not circulate at low arginine concentrations, and if the R moiety of the repressor is produced at an adequate rate, then we would expect the repressor

concentration to rise in proportion to the internal concentration of arginine; and therefore we would not expect an enhancement of the enzyme ornithine transcarbamylase and with increasing concentration of arginine. On the other hand, let us now consider another bacteria strain which does not contain the coupling enzyme C, but contains a coupling enzyme C* which saturates it at very low concentration of arginine and has a low turn-over number. In the case of such a bacteria strain, we would not expect to be able to boost the enzyme ornithine transcarbamylase when we reduce to a fairly low level the intercellular concentration of arginine; and we should expect the enzyme to be induced rather than to be repressed when we raise the arginine concentration above the value that prevails in the cell growing in arginine-free minimal medium. According to experiments conducted by Luigi Gorini (oral communication), the B strain of coli appears to exhibit this type of behavior. If we now assume that the coupling enzyme C in the K strain and the coupling enzyme C* in the B strain are located at some distance from each other along the bacteria chromosome, we should expect, if we cross the K strain and the B strain, among the recumbents, the following four types of recombinants:

1) Recumbents in which one cross-over occurred between the loci of C and C* should resemble either the B strain or the K strain with respect to the effect of the arginine concentration on the level of the enzyme ornithine transcarbamylase. Among the recombinants in which two cross-overs occurred between the loci of C and C*,

there should be strains

(a) which lack C as well as C*. These recumbents are not able to couple arginine to the R moiety of the repressor and therefore the level of the enzyme ornithine transcarbamylase should be high and not responsive to the arginine concentration; and

(b) which contain both C and C*. In these strains it should not be possible to boost the enzyme ornithine transcarbamylase by reducing the intercellular concentration of arginine to a moderately low level, but it should be possible to repress the enzyme by raising the arginine concentration.

~~It seems that all these~~ ~~arginine four~~ If K is crossed with R the above mentioned recombinants can be produced

It seems that these four types of recombinants

~~the~~

DRAFT

March 28, 1961

THE MESSENGER RNA AND THE CONTROL OF THE FORMATION OF SPECIFIC PROTEINS IN BACTERIA

By Leo Szilard

The Enrico Fermi Institute, The University of Chicago, Chicago 37

- - - - - - - - -

In a paper which appeared in the proceedings of the National Academy of Sciences (page 277, vol. 46, 1960), I described a model for the control of the formation of the enzymes and other specific proteins. I assumed at the time that different enzyme molecules are formed in different ribosomes and that each ribosome is specific for a given enzyme and only that particular enzyme can be formed in that particular ribosome.

At present there is under discussion the possibility that protein molecules are formed in the cells in a quite different manner. The present state of knowledge in this regard is described in a paper, "Genetic Regulatory Mechanisms in the Synthesis of Proteins", (Journal of Molecular Biology, in press) by Francois Jacob and Jacques Monod. According to the new concept, the sequence of protein basis of DNA determines the amino acid sequence of the corresponding specific protein, and it does so in the following manner:

Alongside the DNA, an RNA molecule is formed, which is called the "messenger RNA". This specific messenger RNA goes to a

ribosome which is suppossed to be void of any specificity. A protein molecule is formed alongside the messenger RNA within the ribosome and the messenger RNA is hydrolized, excepting if, for the sake of argument, this mechanism has a general pattern of protein sequences. I propose to describe a model for enzyme repression and enzyme induction which is applicable to this pattern of protein synthesis. This model is as follows:

From each enzyme a specific protein mechanism which is produced at a variable controlled rate, there is a repressor molecule present in the cell, as described in my above-mentioned paper. If such a repressor molecule combines with the enzyme molecule which is in the process of formation alongisde the messenger RNA in the ribosome, the enzyme molecule remains attached to the messenger RNA. In this case, the messenger RNA is not hydrolized, but the complex system of the RNA, the enzyme molecule which is attached to it and the repressor molecule which is attached to both, leave the ribosome. Accordingly, such complexes accumulate in the cytoplasm. As the concentration of these complexes in the cytoplasm increases, there may be an increasing probability that one of these complexes will recognize, by virtue of its messenger RNA moity, the corresponding DNA and will combine with it. In this manner, the rate of formation of this particular messenger RNA will be kept low if the concentration in the cell of the specific repressor molecule is high. According to this model, the primary control of the rate of enzyme formation occurs at the enzyme forming cite,

in the manner described in my above-mentioned paper. But secondarily, control is also exercised at the level of the DNA molecule through the accumulation of specific messenger RNA molecules which are kept from being hydrolized.

Jacob and Monod discussed in their paper a quite different model, which assumes that the repressor molecule itself controls directly, at the DNA level, the rate of formation of the messenger RNA for which it is specific. It seems that our model makes it possible to explain phenomena for which it would be difficult to find an explanation on the basis of the model described by Jacob and Monod. Take, for instance, an effect of argenine on the rate of synthesis of certain enzymes which lie on the pathway of argenine synthesis. In the B strain of coli, argenine induces the enzyme which transforms into whereas in the K strain of coli, argenine represses the same enzyme (Luigi Gorini, oral communication). If the B strain is classed with the K strain, one obtains four different strains in the progeny. Two of these strains are like the parental strains. In one of the strains, the enzyme can be repressed by raising the intercellular concentration of argenine above that prevailing during growth in minimal medium, but the enzyme level cannot be raised by reducing the argenine concentration below the value which prevails during growth in the minimal medium. The fourth strain

Our model would account for these facts if the B strain of coli contains a Coupling enzyme which forms the repressor from a specific weight and argenine or some argenine derivitive. And if we further assume that this Coupling enzyme saturates at low argenine concentrations and has a low turn-over number, in contrast to this we would have to assume that the K strain of coli contains a Coupling enzyme C which is not saturated at low intercellular concentration of argenine which can be experimentally obtained. If we then assume that the B strain is and that the K strain is , then we would expect to find in the progeny of classes of these two strains, four strains which have the properties observed by Gorini.

controlling site of the enzyme molecule, as I have postulated, or whether the controlling site is located on the chromosome and the repressor, by combining with that controlling site, lowers the rate at which the enzyme forming site is produced by the chromosome.

This new concept of protein synthesis is as follows:

For each enzyme molecule there is a specific RNA molecule -- the messenger RNA -- which is formed alongside the chromosome. The ribosomes are void of any specificity and merely serve temporarily to house a messenger RNA molecule.

Each messenger RNA molecule moves, after it has been formed alongside the chromosome, into a ribosome. A specific protein molecule is formed alongside such a messenger RNA molecule; after the protein molecule separates from the messenger RNA and is discharged into the cytoplasm, the messenger RNA molecule is hydrolized. During the synthesis of a specific enzyme molecule, the corresponding RNA molecules turn over very fast.

At first sight, this model appears to favor the view that the repressor must combine with the controlling site ~~of~~ located on the chromosome because, if the chromosome were to continue to form messenger RNAs for enzymes which are repressed, a very wasteful production of messenger RNAs would ensue. The purpose of this paper is to show that the repressor need not combine with a controlling site on the chromosome and yet there need be no wasteful production of the messenger RNA~~s~~ molecules which are specific for the enzymes that are repressed. The model that is proposed is as follows:

A repressor molecule may combine with the enzyme molecule which is in the process of formation alongside the messenger RNA in the ribosome, and the enzyme molecule remains then attached to the messenger RNA. In this case, the messenger RNA is not hydrolized, but the complex system of the RNA, the enzyme molecule which is attached to it and the repressor molecule which is attached to both, leave the ribosome. Accordingly, such complexes accumulate in the cytoplasm. As the concentration of these complexes in the cytoplasm increases, there will be an increasing probability that one of these complexes will recognize, by virtue of its messenger RNA moiety, the site of formation of the messenger RNA xxdxxxxx on the chromosome and will combine with it. In this manner, the rate of formation of this particular messenger RNA will be kept low if the concentration in the cell of the specific repressor molecule is high. According to this model, the primary control of the rate of enzyme formation occurs at the enzyme forming site, in the manner described in my above-mentioned paper. But secondarily, control is also exercised at the level of the DNA molecule through the accumulation of specific messenger RNA molecules which are kept from being hydrolized.

DRAFT

April 4, 1961

THE MESSENGER RNA AND THE CONTROL OF THE FORMATION OF SPECIFIC PROTEINS IN BACTERIA

by Leo Szilard

The Enrico Fermi Institute

The University of Chicago, Chicago, Illinois

- - - - - - - -

In a paper which appeared in the Proceedings of the National Academy of Sciences (page 277, vol. 46, 1960), I described a model for the control of the formation of the enzymes and other specific proteins in bacteria. This model is based on the assumption that the rate of formation of an enzyme may be controlled by the concentration of a small molecule, the repressor, which is specific for that enzyme. The repressor is composed of a metabolite moiety and an R moiety which might be a direct gene product. It is assumed that the repressor can combine with the enzyme molecule which is in the process of formation and is still attached to the enzyme forming site. The metabolite moiety of the repressor may combine with a specific site of the enzyme molecule -- the controlling site -- and the R moiety of the repressor may combine with the enzyme forming site itself. It is postulated that while the repressor remains combined with the enzyme molecule attached to the enzyme forming site, the enzyme molecule cannot get detached from the enzyme forming site.

~~Our~~ this model accounts for the fact that an enzyme may be induced by postulating that the inducer ~~is~~ may be a chemical analogue of the metabolite moiety of the repressor and, accordingly, ~~it would~~ it may compete with the metabolite moiety of the repressor for the controlling site of the enzyme. In the case of the biochemical pathways which lead to a metabolite such as an amino acid, a purine or a pyrimidine, the metabolite may be assumed to be the metabolite moiety of the repressor or ~~as~~ else a precursor of it.

For instance, in the case of the enzymes that lie on the biochemical pathway leading to arginine, we may assume that arginine or a chemical derivative of arginine may be ~~to form~~ the metabolite moiety of the repressor of these enzymes. We postulated the presence of a coupling enzyme C in the cell, which catalyzes the formation of ~~a specific~~ the repressor for these enzymes from ~~the metabolite moiety~~ arginine, ~~arginine~~, and the specific R moiety.

In the K strain of coli, the enzyme ornithine transcarbamylase can be repressed by growing the strain in the presence of arginine and it can be boosted to a very high value by growing the strain under conditions in which the intracellular concentration of arginine is ~~fairly~~ moderately low. If the coupling enzyme C contained in the K strain does not saturate [illegible] for arginine at the arginine concentrations used and if ~~the~~ R moiety of the repressor is produced at an adequate rate, then we would expect the repressor concentration to rise pro-

portionally with the intracellular concentration of arginine. In this case we would expect, on the basis of formula (4), page 283 of our paper (The National Academy of Sciences, 46, 1960) that the enzyme will be at a very high value when the bacteria grow under conditions in which the intracellular concentration of arginine is fairly low. and that with increasing intracellular arginine concentration, the enzyme level will fall and approach a certain fixed minimal value. This is the behavior that the enzyme exhibits in the K strain. In the strain of coli, however, which does not contain the coupling enzyme C, but contains another coupling enzyme C*, which saturates at very low concentrations of arginine and has a low turn-over number, it should be possible to lower intracellular arginine concentration to fairly low levels without obtaining a rise in the level of the enzyme. Further, we should expect the enzyme to be induced rather than to be repressed when we raise the intracellular arginine concentration above the value which prevails in a cell xxx growing in arginine-free minimal medium. The B strain of coli appears to exhibit this type of behavior. (Luigi Gorini, oral communication)

If we now assume that the coupling enzyme C in the K strain and the coupling enzyme C* in the B strain are located at some distance from each other along the bacterial chromosome, we should expect, if we cross the K strain and the B strain, four types of recombinants:

Recombinants in which one cross-over occurred between the loci of C and C* should resemble either the B Strain or the K strain with respect to the effect of the arginine concentration on the level of the enzyme ornithine transcarbamylase. Among the recombinants in which two cross-overs occurred between the loci of C and C*, there should be strains

(a) which lack C as well as C*. These recombinants are not able to couple arginine to the R moiety of the repressor and therefore the level of the enzyme ornithine transcarbamylase should be high and not responsive to the arginine concentration; and

(b) which contain both C and C*. In these strains it should not be possible to boost the enzyme ornithine transcarbamylase by reducing the intracellular concentration of arginine to a moderately low level, but it should be possible to repress the enzyme by raising the arginine concentration.

It would appear that the experiments of Luigi Gorini mentioned above support the view that the underlying basic phenomenon of the control of the rate of reduction of enzymes is the repression, rather than induction, and that the inducer must act either by reducing the concentration of the repressor or by competing with the repressor for some "controlling site". A new concept of protein synthesis in bacteria which has been recently formulated by Monod and Jacob ("Genetic Regulatory Mechanisms in the Synthesis of Proteins", Journal of Molecular Biology, in press) makes it however necessary to examine the question of whether the controlling site is the

DRAFT

April 4, 1961

THE MESSENGER RNA AND THE CONTROL OF THE FORMATION OF SPECIFIC PROTEINS IN BACTERIA

by Leo Szilard

The Enrico Fermi Institute

The University of Chicago, Chicago, Illinois

- - - - - - - -

In a paper which appeared in the proceedings of the National Academy of Sciences (page 277, vol. 46, 1960), I described a model for the control of the formation of the enzymes and other specific proteins in bacteria. This model is based on the assumption that the rate of formation of a given enzyme is controlled by the presence of a small molecule which is specific for that enzyme in the cell. The repressor is composed of a metabolite moiety and an R moiety which might be a direct gene product. It is assumed that the repressor can combine with the enzyme molecule which is in the process of formation and is still attached to the enzyme forming site. The metabolic moiety of the repressor would combine with a specific site of the enzyme molecule -- the controlling site and the R moiety of the repressor would combine with the enzyme forming site itself. It is postulated that while the repressor remains combined with the enzyme molecule attached to the enzyme forming site, the enzyme molecule cannot get detached from the enzyme forming site.

Our model accounts for the fact that an enzyme may be induced by postulating that the inducer is a chemical analoque of the metabolite moiety of the repressor and, accordingly, it would compete with the metabolite moiety of the repressor for the controlling site of the enzyme. In the case of the biochemical pathways which lead to a metabolite such as an amino acid, a purine or a pyrimidine, the metabolite may be assumed to be the metabolite moiety of the repressor or as a precursor of it.

For instance, in the case of the enzymes that lie on the biochemical pathway leading to arginine, we may assume arginine or a chemical derivative of arginine to form the metabolite moiety of the repressor of these enzymes. We postulated the presence of a coupling enzyme C in the cell, which catalyzes the formation of a specific repressor for these enzymes from the metabolite moiety, arginine, and the specific R moiety.

In the K strain of coli, the enzyme ornithine transcarbamylase can be repreesed by growing the strain in the presence of arginine and it can be boosted to a very high value by growing the strain under conditions in which the intracellular concentration of arginine is fairly low. If the coupling enzyme C contained in the K strain does not saturate [illegible] for arginine at the arginine concentrations used and if the R moiety of the repressor is produced at an adequate rate, then we would expect the repressor concentration to rise pro-

portionally with the intracellular concentration of arginine. In this case we would expect, on the basis of formula (4), page 283 of our paper (The National Academy of Sciences, 46, 1960) that the enzyme will be at a very high value when the bacteria grow under conditions in which the intracellular concentration of arginine is fairly low, and that with increasing intracellular arginine concentration, the enzyme level will fall and approach a certain fixed minimal value. This is the behavior that the enzyme exhibits in the K strain. In the strain of coli, however, which does not contain the coupling enzyme C, but contains another coupling enzyme C*, which saturates at very low concentrations of arginine and has a low turn-over number, it should be possible to lower intracellular arginine concentration to fairly low levels without obtaining a rise in the level of the enzyme. Further, we should expect the enzyme to be induced rather than to be repressed when we raise the intracellular arginine concentration above the value which prevails in a cell growing in arginine-free minimal medium. The B strain of coli appears to exhibit this type of behavior. (Luigi Gorini, oral communication)

If we now assume that the coupling enzyme C in the K strain and the coupling enzyme C* in the B strain are located at some distance from each other along the bacterial chromosome, we should expect, if we cross the K strain and the B strain, four types of recombinants:

Recombinants in which one cross-over occurred between the loci of C and C* should resemble either the B Strain or the K strain with respect to the effect of the arginine concentration on the level of the enzyme ornithine transcarbamylase. Among the recombinants in which two cross-overs occurred between the loci of C and C*, there should be strains

(a) which lack C as well as C*. These recombinants are not able to couple arginine to the R moiety of the repressor and therefore the level of the enzyme ornithine transcarbamylase should be high and not responsive to the arginine concentration; and

(b) which contain both C and C*. In these strains it should not be possible to boost the enzyme ornithine transcarbamylase by reducing the intracellular concentration of arginine to a moderately low level, but it should be possible to repress the enzyme by raising the arginine concentration.

It would appear that the experiments of Luigi Gorini mentioned above support the view that the underlying basic phenomenon of the control of the rate of reduction of enzymes is the repression, rather than induction, and that the inducer must act either by reducing the concentration of the repressor or by competing with the repressor for some controlling site. A new concept of protein synthesis in bacteria which has been recently formulated by Monod and Jacob ("Genetic Regulatory Mechanisms in the Synthesis of Proteins", Journal of Molecular Biology, in press) makes it necessary to examine the question of whether the controlling site is the

controlling site of the enzyme molecule, as I have postulated, or whether the controlling site is located on the chromosome and the repressor, by combining with that controlling site, lowers the rate at which the enzyme forming site is produced by the chromosome.

This new concept of protein synthesis is as follows:

For each enzyme molecule there is a specific RNA molecule -- the messenger RNA -- which is formed alongside the chromosome. The ribosomes are void of any specificity and merely serve temporarily to house a messenger RNA molecule.

Each messenger RNA molecule moves, after it has been formed alongside the chromosome, into a ribosome. A specific protein molecule is formed alongside such a messenger RNA molecule; after the protein molecule separates from the messenger RNA and is discharged into the cytoplasm, the messenger RNA molecule is hydrolized. During the synthesis of a specific enzyme molecule, the corresponding RNA molecules turn over very fast.

At first sight, this model appears to favor the view that the repressor must combine with the controlling site ~~of~~ located on the chromosome because, if the chromosome were to continue to form messenger RNAs for enzymes which are repressed, a very wasteful production of messenger RNAs would ensue. The purpose of this paper is to show that the repressor need not combine with a controlling site on the chromosome and yet there need be no wasteful production of the messenger RNA~~s~~ molecules which are specific for the enzymes that are repressed. The model that is proposed is as follows:

A repressor molecule may combine with the enzyme molecule which is in the process of formation alongside the messenger RNA in the ribosome, and the enzyme molecule remains then attached to the messenger RNA. In this case, the messenger RNA is not hydrolized, but the complex system of the RNA, the enzyme molecule which is attached to it and the repressor molecule which is attached to both, leave the ribosome. Accordingly, such complexes accumulate in the cytoplasm. As the concentration of these complexes in the cytoplasm increases, there will be an increasing probability that one of these complexes will recognize, by virtue of its messenger RNA moiety, the site of formation of the messenger RNA ~~xxxxxxxx~~ on the chromosome and will combine with it. In this manner, the rate of formation of this particular messenger RNA will be kept low if the concentration in the cell of the specific repressor molecule is high. According to this model, the primary control of the rate of enzyme formation occurs at the enzyme forming site, in the manner described in my above-mentioned paper. But secondarily, control is also exercised at the level of the DNA molecule through the accumulation of specific messenger RNA molecules which are kept from being hydrolized.