ON THE ORIGIN AND EVOLUTION OF THE GENETIC CODE. III. TRANSITION FOM A BINARY TO A QUATERNARY ALPHABET SYSTEM. THE INTRODUCTION OF HEREDITARY DNA.

Nils Aall Barricelli
Department of Mathematica
University of Oslo
Blindern, Norway

Received October 10, 1980; June 22, 1981

ABSTRACT: The aim of this paper is to attempt a reconstruction of the events which led to the transition from an original binary (Pu, Py) alphabet to a quaternary (U,C,G,A) alphabet (Barricelli 1977 and 1979).

According to our interpretation, Cytosine was the last nucleotide whose synthesis was brought under biologic control, and its introduction was the event which triggered the transition. In most organisms the transition was also characterized by the substitution of DNA genomes for the original RNA genomes, and a transition from a primordial 6 codon system (Barricelli 1979) to the more elaborate genetic codes reconstructed in the first (Barricelli 1977) paper. Some implications:
1. The original crossbreeding mechanism between RNA molecules, based on copying processes involving a binary (Pu,Py) alphabet, has been dropped. The mysterious absence of a direct RNA-recombination mechanism for RNA viruses can be understood on this assumption (see section 4).
2. The recombinations necessary for an adequate speed of evolution (see section 3) are in many RNA-viruses obtained by transscribing their RNA into DNA. The effect these processes may have for the host organisms and their possible role in malignancy phenomena are discussed.

* * *

1. Introduction

In two preceeding papers of this series (Barricelli 1977 and Barricelli 1979) several earlier genetic codes have been reconstructed by the wobbling reintroduction procedure. This procedure is based on the (Pu-Py) hypothesis, supported by various lines of evidende (Barricelli 1977, 1979 and 1980), holding that wobbling was originally a common phenomenon in all of the three bases of each codon, and that in the ancestors of present RNA molecules purines capable of pairing with more than one pyrimidine, as well as pyrimidines capable of pairing with more than one purine were a common feature in all processes involving pairing, including RNA copying processes. As a result the genetic alphabet of the early RNA was assumed to be a binary (Pu, Py) alphabet (rather than a quaternary (U,A,C,G) alphabet) where the two purines (or pyrimidines) could replace one another. Pairing of U and G bases (U-G pairing) is still commonly found in the secondary structures of RNA molecules (Barrell and Clark 1974, Barricelli 1980), where frequencies of U-G pairs greater than 25% of the frequancy of U-A pairs are not uncommon.

The earliest genetic code-structures (codon and anticodon tables) reconstructed by this procedure are the six amino acid stage (Barricelli 1977, table 11), which is presented in table 2, and the six codon stage (Barricelli 1979, table 1) which is presented in the following table 1. In both cases only the structure of the code, without attempting to identify the amino acids designated by the respective codons is represented.

Table 1 is assumed to represent a very early stage in which only RNA (or precursor RNA) genomes were used, and the communities of cooperating RNA molecules were able to produce (or secure a regular supply of) Uracil, and at least one purine, but were unable to secure a regular supply of Cytosine. The idea that the biologic control of nucleotide production and supply may have evolved gradually and at dif-

* * * * * * *

Evolutionary Theory 5: 233-241 (September 1981)
The editors thank two referees for help in evaluating this paper.

Table 1: Hypothetic code (A) and anti-codon table (B) for the 6 codon stage preceding the 6 amino acid stage, presented in the following table 2. Pu-Py pairing (wobbling) was supposedly generally used at this stage also for RNA copying. One of the codons indicated in parenthesis (UPuPu) may have been a non-sence triplet, and the corresponding anti-codon may have been missing. The only pyrimidine available is U. Base 3 is ignored when anti-codon Base 2 is not U. X designates an unspecified base.

(A) Codons		(B) Anticodons	
U U X	U PuU (U PuPu)	PuPuX	PuU Pu
PuU X	PuPuU PuPuPu	U PuX	U U Pu U U U

* * * * * * * * * * * * * *

ferent times for different nucleotides is proposed among others by Crick (1968) and Orgel (1968). In the preceeding papers (Barricelli 1977, 1979 and 1980), we have presened evidence suggesting that Cytosine may have been the last nucleotide whose production was brought under biologic control, and that Cytosine may have been missing in the central nucleotide of the early anticodons for a long time even after its introduction in other places. Table 2 presents one of these stages (the six amino acid stage) in which Cytosine was already available and DNA genomes had been introduced, but an earlier specialization depending on the use of Uracil in the central anticodon base (Barricelli 1977) had prevented the introduction of Cytosine in this place.

Both table 1 and table 2 represent stages in which wobbling in general and U-G pairing in particular were common to all of the three codon bases, and moreover the third codon base was ignored except in those triplets in which the central anticodon base was U. This function of U explains why even after C had been introduced (table 2) anticodons with a central C could not be used without creating ambiguities between the two amino acids AA2 and AA3 or between the two amino acids AA5 and AA6 or both.

The aim of this paper is to give an orientation on the problems which arise if one attempts to understand the evolutionary processes involved in the transition from a binary (Pu,U) or (Pu,Py) genetic alphabet, supposedly characterized by a genetic code like the one presented in table 1, to a quaternary (U,A,C,G) alphabet supposedly associated with a genetic code like the one presented in table 2, and other more advanced genetic codes.

This paper like the preceeding ones deals with the biotheoretical and evolutionary aspects of the problems, not with the chemical aspects.

2. Transition from a binary to a quaternary alphabet system. The introduction of hereditary DNA.

The transition from a binary (Pu,Py) to a quaternary (U,C,G,A) alphabet may have been a gradual process in which, however, two events may have played a decisive role, namely:

1. The introduction of cytosine.
2. The introduction of hereditary DNA.

As soon as organisms arose which were capable of securing a regular supply of cytosine, a series of drastic changes and new evolutionary adaptations were rendered necessary in the RNA-collector commutities. In order to illustrate this point we shall assume that at the time when cytosine was introduced only two purines (A and G) and one pyrimidine (U) were being used by the primordial collector societies of RNA molecules (the argument would however not be seriously affected if

Table 2: Example of hypothetic six amino acids code (a) and anticodon table (b) during Pu-Py pairing (general wobbling) stage. AA1, AA2, etc., designate unspecified amino acids. In parentheses are indicated those triplets which may have been missing (anticodons) or replaced by nonsense triplets (codons).

(a) Codons				(b) Anticodons				
	Base 2				Base 2			
Base 1	Py	Pu	Base 3	Base 1	Pu	U	C	Base 3
U	AA1	AA2	Py	A	AA1	AA2		Pu
		AA3	Pu			AA3		Py
C	(AA1)	(AA2)	Py	G	(AA1)	(AA2)		Pu
		(AA3)	Pu			(AA3)		Py
A	(AA4)	(AA5)	Py	U	(AA4)	(AA5)		Pu
		(AA6)	Pu			(AA6)		Py
G	AA4	AA5	Py	C	AA4	AA5		Pu
		AA6	Pu			AA6		Py

* * * * * * * * * * * * * * *

there were other bases in addition to these, provided they also could be easily removed by the very introduction of cytosine; see below).

Because of the well known triple hydrogen bonding between C and G, during the RNA copying process C would have a strong tendency to replace U in every place where the strand to be copied contained a G. On the other hand in those places in which the strand to be copied contained a U, either an A or a G could be placed in front of it with comparable probabilities. As a result, since C does not pair with A, U's and A's would often be replaced by C's and G's respectively. If there were other bases in a similar competitive disadvantage with respect to C and G, they could also have been removed, or at least subject to frequent replacement.

Also removal of C bases and restoration of U bases could later on take place by U-G pairing. But if there were places where U had acquired a specific function essential for survival (for example the central anticodon base, see Barricelli 1977) its replacement by C could be lethal. The introduction of C could probably have been used as a powerful and destructive antibiotic weapon against organisms depending on other bases.

In many cases organisms capable of producing cytasine, or even cytosine itself, may have operated as parasytes for organisms without adequate defenses. There are, however, at least two ways in which a protection against cytosine invasion could have been achieved:

(1) One way, which is applied by all cells and many viruses today, is to use a DNA genome instead of an RNA genome (the DNA way).

(2) An other way still aplied by modern RNA viruses is to develop polymerases capable of avoiding U-G pairing during the copying process of RNA into RNA. This would also avoid a replacement of U's by C's (the RNA way).

According to Barricelli (1979), DNA and possibly other polynucleotides might have been used together with RNA in the earliest collector societies of polynucleotide molecules. The appearance of C-producing organisms may have rendered the use of DNA as keeper of hereditary information an important protection against the destructive replacement of U's by C's in many organisms. Since tymine (T), which replaces U in the DNA molecule, does not pair with G as easily as U does, collector societies capable of copying both their hereditary information and their tRNA molecules from DNA templates were relatively well protected against the replacement of U by C in their RNA molecules. Even better protection could be obtained by improving their polymerases thus increasing their precision of transcription.

The adoption of either one of these solutions (the DNA way or the RNA way) would have created cytosine-resistant organisms capable of surviving after the introduction of cytosine. Symbiotic associations between cytosine producers and cytosine resistant organisms may gradually have opened the way for the utilisation of cytosine in the genetic code as well as in the hereditary material. By the introduction of cytosine and the following stabilisation of the genetic information in response to this event, the transition from a binary (Pu,Py) alphabet to a quaternary (U,C,A,G) alphabet was already a fact. The subsequent evolution of the genetic code opening the possibility of introducing new codon triplets capable of representing an increasing number of amino acids (see Barricelli 1977) was made possible by this transition.

Before discussing other consequences of the introduction of cytosine it may, however, be helpful to give a brief orientation about the role of crossbreeding in early evolution.

3. The role of crossbreeding

An all important role in the evolution of polynucleotide collectors and in the processes leading to the joining of the hereditary information of the members of a collector society into a single genome, was the role plaid by the crossbreeding process.

Crossbreeding is well known to be a most important attribute of living organisms as a means to enhance the speed of evolutionary adaptation*. Without interbreeding, the maximum speed of adaptation a species would be able to achive could be thousands of times slower than that of crossbreeding species, with which it may have to compete; the very possibility of adapting to a changing environment would be seriously in question.

The RNA collectors both as individual RNA molecules and as collector societies may have had different ways of interchanging hereditary characteristics (i.e. interbreeding) at different times. A simple mechanism for exchanging hereditary characteristics may have been available to the very first selfreproducing polynucleotides if we assume that the copying process of a molecule could be carried out not only by successively adding individual nucleotides, but also complementary segments (by annealing) if available (Barricelli 1963, section 10). This copying process, designated as "complementary association" of polynucleotides as well as individual nucleotides is illustrated in fig.1, using a single kind of unspecified purine Pu and a single kind of unspecified pyrimidine Py. The process may, for eksample, start with complementary association (fig. 1A). If the two single stranded polynucleotide chains are complementary only in a border segment (overlap) shorter than either of the two chains (fig. 1A) the result can be a longer double stranded polynucleotide (fig 1C).

* * * * * * * * * * * * * * *

* According to Fisher's law (R. A. Fisher 1930, Reed, Tombs and Barricelli 1967):

The maximum speed of evolution a species is capable of (or potential speed of evolution) is proportional to the number of genes. A species unable to interbreed is to be considered in this connection as a specied with only one gene. For example, if a breeding species has 10.000 genes it could evolve roughly 10.000 times faster than a non-breeding species, other conditions being equal.

In the application of Fisher's law the "speed of evolution" can roughly be measured by the number of positively selected mutations able to spread to a fixed large portion of the population (for example, 50% of the population) in a fixed period of time (which must be large compared with the spreading time of each individual mutation).

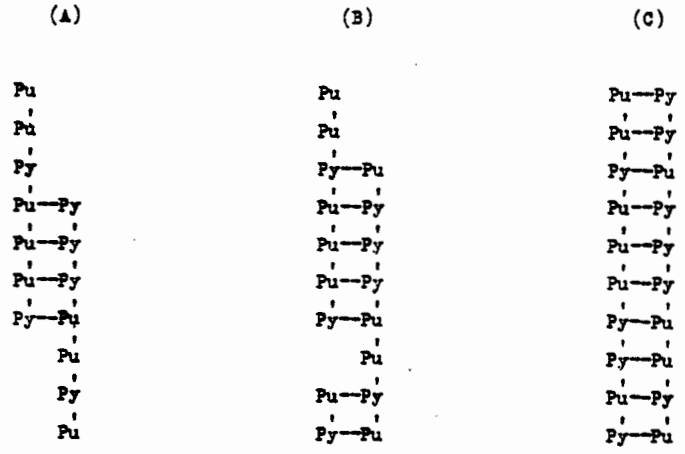

Fig. 1

Fig. 1. (A) Association of two single stranded polynucleotides with a complementary segment. (B) Complementary association and insertion of single nucleotides. (C) Formation of a double-stranded polynucleotide longer than both original chains (permitting evolutionary growth in size and complexity).

Phosphat bonding between contiguous nucleotides and polynucleotide segments associated to a complementary polynucleotide may have been promoted by primordial catalysts or enzymes.

* * * * * * * * * * * * * *

This complementary association mechanism provides a possible interpretation of evolutionary growth and increase of complexity in polynucleotides. A fact of considerable interest is, however, that it also provides a primitive crossing mechanism for polynucleotides. In fact the two single-stranded polynucleotides in Fig. 1A could be the result of incomplete duplication (partial replicas) of larger polynucleotides identical or homologous to the double-stranded polynucleotide in fig. 1C. Such incomplete replicas or partial replicas could for instance be the result of possible damages or too early separation of the two strands after duplication (separation before all nucleotides are filled in): In this case, the processes represented in fig. 1 will only restore the original information and can be considered a repairing mechanisn (like multiplicity reactivation Luria 1947). On the other hand if the two single-stranded polynucleotides in fig. 1A contained genetic markers (as a result of mutations or copying mistakes), the double-stranded polynucleotide of fig. 1C may be recombinant (containing copying mistakes inherited from both parents). Evidently the process described in fig. 1 can operate as a crossing mechanism. Partial replica models for virus crossing and reproduction (Doermann,1953; Doermann & Boehner, 1963; Barricelli, 1952, 1955, 1956, 1960,1971; Barricelli & Doermann, 1961) might be based on some mechanism of this or similar nature.

The complementary association mechanism described in fig. 1 is an example of a process which might have opened various possibilities not only for repairing of damages and formation of crossing products, but also for the formation of extended hybrid molecules including the hereditary information of two or more RNA species. The evolutionary development of collector societies whose hereditary information is contained in a single genome (Barricelli 1979, section 3) would have been pos-

sible by this process - as well as by other hybridization processes which are known in modern organisms - provided enzymes had been made available, as they are available today, for the various copying operations which would be needed after the creation of a single genome.

Other interbreeding mechanisms may have developed later by the exchange of RNA segments (including not only tRNA, mRNA and rRNA segments, but also whole genetic RNA molecules as well as parasites, symbionts and other precursors of modern episomes) between the various collector societies. These exchanges of polynucleotide segments carrying genetic information from one collector community to an other, even before each community had been separated from its surroundings by a cellular membrane, may be considered the precursors of modern cellular interbreeding mechanisms, including transduction, transformation and regular crossing (Barricelli 1947, 1952 and 1955).

The acquisition of a crossbreeding mechanism is the major step that marked the transition from a slow chemical evolution of macromolecules to a much faster biological evolution process characteristic of complex and well adapted species.

There are, however, some kinds of population in which crossbreeding is not wanted and would inevitably lead to disastrous consequences. Examples of such populations are: (1) A collector society of RNA molecules. (2) A society of collector insects (bees, ants, thermites, etc.) (3) A society of somatic cells in the body of a multicellular organism. In all of these cases crossbreeding is restricted to specialized individuals, notably the genome in a society of RNA collectors, queens and drones in a society of collector insects, gamets in a society of cells forming a multicellular organism. The reason is obvious. A subpopulation of freely interbreeding and reproducing individuals could rapidly evolve into a predator or parasitic species capable of destroying the society in which it develops (see Barricelli 1979, section 3). The extraordinary rapidity with which malignant cells can adapt and overcome all sorts of therapies and all sorts of defences by the organism could be understood if they are the result of a newly acquired (or enhanced) crossbreeding capability (see next two sections).

4. Recombination in RNA viruses

We are now in a position to discuss one of the most conspicuous implications of the transition from a binary to a quaternary alphabet. One of the major mysteries of virus genetics is that the formation of recombinant RNA-sequences is absent or unfrequent in RNA viruses which do not transcribe their RNA into DNA. One would expect that the lack of recombination would give these viruses a much too low speed of evolutionary adaptation compared with that of DNA viruses and other possible competitors. Recombinants can be found in those RNA viruses (such as influenza viruses) whose genome is subdivided into several segments which (like chromosomes) are randomly distributed among the progeny. Recombinant RNA viruses may moreover be formed when RNA is transcribed into DNA by inverse transcriptases and integrated into a cellular genome (see Coffin 1979, retroviruses). Recombinations may arise both during the transcription process and subsequently when the cellular genome is subject to occasional crossovers, before the provirus is transcribed again into RNA. Still the reason why RNA segments do not directly recombine deserves an explanation.

We may recall the two ways described in section 2 (the DNA way and the RNA way) for solving the cytosine introduction problems. The question we will ask now is: whether any one of the two ways was independently succsessful in the creation of organisms resistant to cytosime damage.

Let us look at the implications of the two alternatives.

Alternative 1: If the RNA way was independently successful, the collector societies would have needed not only polymerases capable of avoiding U-G pairing during the RNA copying process. They would also have needed at the same time some enzimes or

some other devise capable of preventing U-G pairing during the crossbreeding processes, including the complementary association process described in the preceeding section. Otherwise the replacement of U's and A's by C's and G's would have continued during the crossbreeding operations.

Alternative 2: If the DNA way was independently successful, polymerases capable of transcribing RNA into DNA (inverse transcriptases), DNA into RNA (RNA polymerases) and DNA into DNA (DNA polymerases) must either have been introduced as a response to and a defense against the introduction of cytosine, or (more likely) may have existed beforehand in some collector societies (see Barricelli 1979). Organisms capable of transcribing their hereditary information into DNA and keeping it in the form of DNA by using DNA polymerases for reproduction would have been practically immune to cytosine damage. If crossbreeding could be restricted to the DNA structures, the only operations vulnerable to cytosine would be RNA to RNA transcription and RNA to DNA transcription*. Neither of these operations would be strictly necessary for DNA organisms, since all transcriptions and copying operations needed could take place from DNA templates. Many of the organisms, notably the ancestors of modern cells and modern DNA viruses, may have dropped transcriptions from RNA, which were both unnecessary and vulnerable to cytosine. Other organisms, namely the ancestors of modern RNA viruses may gradually have developed polymerases capable of avoiding U-G pairing during the processes of transcribing RNA into RNA or into DNA, thus insuring transcription fidelity in the four letter alphabet. Also these organisms would be able to convert their hereditary information into DNA and could therefore restrict their crossbreeding operation to the transcription process or the DNA structures created by their improved inverse transcriptases. There was no compelling need for recombination between RNA molecules, and no need for developing enzymes capable of preventing U-G pairing during RNA recombination. The whole RNA crossbreeding operation could be dropped and replaced by DNA crossbreeding.

According to this interpretation the fact that most RNA viruses do not yield recombinant RNA is evidence that the DNA way was the only adopted independent solution to the cytosine introduction problems. The RNA way was only subsequently adopted in some of the organisms which had stubbornly maintained their capability of transcribing information from RNA templates. A common characteristic of these organisms is that they do not have a capability of their own for transcribing infirmation from DNA templates, and are largely dependent on host enzimes for such transcription.

However, the same interpretation imply that RNA viruses are not deprived of the possibility of generating recombinant RNA. Such recombination products can still be obtained when RNA is copied into DNA by using inverse transcriptases produced either by the virus itself or by other coinfecting viruses. The transcription of viral RNA into DNA and its integration into the cellular genome may be the primary source of recombinations for RNA viruses. As mentioned above, both transcription and the integration process and possible crossovers in the cellular genome can contribute recombinations in the transcribed virus (provirus).

5. The cellular crossbreeding interpretation of malignancy. Experimental predictions.

An important consequence of the need for RNA viruses to transcribe their RNA into DNA for crossbreeding purposes is that cells containing such transcriptions will be subject to genetic recombination at least in the transcribed segments. The very insertion, removal or replacement of proviruses possibly with occasionally

* * *

* Later on, after cytosine became established as an essential ingredient in all RNA molecules, the need would arise to avoid U-G pairing in the transcription of DNA into RNA. This need was, however, not compelling at the beginning, and there was plenty of time to develop gradually the necessary RNA polynerases as the need arose.

attached host DNA is a form of cellular crossbreeding, that might even develop into some other forms of crossbreeding between somatic cells. Crossbreeding phenomena based for example on transduction, or transformation or exchange of episomes can be involved.

Crossbreeding between somatic cells may, however, have farreaching consequences. As pointed out in section 3 (see also Barricelli 1979, section 3), somatic cells, as well as worker ants or bees, and tRNA molecules are not supposed to crossbreed, if the formation of parasitic colonies is to be avoided in this kind of societies. We have pointed out above that, according to Fisher's law crossbreeding can lead to a more than thousandfold enhancement of the speed of evolutionary adaptation. What would be the consequence of a growing, rapidly adapting and evolving cell colony in a higher organism is easy to imagine. The extraordinary capability of malignant cells to adapt and overcome all sorts of therapy and all sorts of defences by the organism clearly suggests this kind of explanation. A crossbreeding capability may well be the main difference between malignant and not-malignant cells. If so, drugs preventing exchange of hereditary material by transduction or transformation phenomena (interferon) can be expected to have a crucial therapeutic effect in some cancers.

RNA viruses are not the only ones which may promote crossbreeding between somatic cells. Also DNA viruses can only do their crossbreeding inside cells. But while DNA viruses have the option of specializing into doing their crossbreeding either in a lytic or a lysogenic process, RNA viruses have no choice, and can only do their crossbreeding in a lysogenic process. Either type of virus when they crossbreed in a lysogenic process may lead to the development of cellular crossbreeding and cancer.

This does not mean that all cancers are produced by proviruses. Any form of crossbreeding between somatic cells, no matter how originated, could start a malignant process. But in order to make their own crossbreeding method work, RNA viruses and lysogenic DNA virus crossbreeders may have to produce cancers in their host organisms. Only by transcribing their RNA information into DNA can RNA viruses obtain crossover products. An investigation of these problems could have important application in cancer therapy, for example, by improving the method for the use of interferon (applied by Merigan et al. 1978 in USA, Jon Cresser in France, Hans Strander in Sweden and others). Interferon can be used as a means to prevent the formation of (often more adapted and resistant) recombinants by transduction and/or transformation phenomena involving cancer cells. The anti-virus capability of interferon may interfere with transduction and transformation, and that may be one of its therapeutic effects against cancer. This suggests an important application of interferon in association with other therapies as a means to prevent the development of cancers resistant to an applied therapy. (For experimental observations concerning the combination of interferon therapy with other therapies, see Horoszewicz, Leong and Carter 1979).

We may suggest a couple of in vitro experiments with somatic cells in order to test this theory. As well known in vitro crossbreeding experiments are often done with malignant or fast growing mammalian cells in order to allow selection of unfrequent recombinants.

Proposed experiments type 1. Verify by adequate tests and controls whether the application of interferon prevents the formation of recombination products in this kind of experiments.

Proposed experiments type 2. Try the application of interferon with cells exposure to drugs usable in cancer therapy, in order to verify whether the onset of resistance to such drugs is delayed in the presence of interferon.

Our theory predicts that if genetic recombination is needed in order to develop resistance to cancer drugs, the use of interferon will substantially delay the onset of resistance. (See also L. Hayflick 1980 suggesting the possibility that exchange of genetic information, even if mediated by viruses, may trigger uncontrolled cell duplications.)

It should, however, be noted that, according to our interpretation, interferon by itself does not kill cancer cells. Its main therapeutic effect is to temporarely prevent the formation of recombination products in those cancers in which recombination is dependent on the exchange of viruses and/or nucleic acids between cells. The killing must be done by other therapies or by the body's own defense. If the killing is not compleated by other means, the malignant process will restart as soon as the interferon therapy is suspended.

We hope this information will lead to a better use of interferon in cancer therapy.

ACKNOWLEDGEMENT

The author is indebted to Howard Temin for advises and information concerning recombination in retroviruses.

* * *

REFERANCES

Barrell, B.G. and Clark, B.F.C. (1974). Handbook of nucleic acid sequences. Joynson-Buvvers Ltd., Oxford, England.
Barricelli, N. Aall (1947). The hypothesis of the genesymbiosis and its importance in the explanation of the origin of the gamic reprodiction. Oslo, Cammermayers Boghandel, 9 p.
Barricelli, N. Aall (1952). Naturen, 6, 162.
Barricelli, N. Aall (1955). Acta Biotheor, 11, 75.
Barricelli, N. Aall (1956). Acta Biotheor, 11, III/IV, 107.
Barricelli, N. Aall (1960). Virology, 11, 99.
Barricelli, N. Aall & Doerman, A.H. (1961). Virology, 13, 460.
Barricelli, N. Aall (1963). Acta Biotheor. 16, III/IV, 99.
Barricelli, N. Aall (1971). J. Theor. Biol. 32, 559-623.
Barricelli, N. Aall (1977). J. Theor. Biol. 67, 85-109.
Barricelli, N. Aall (1979). Biosystems 11, 19-28.
Barricelli. N. Aall (1980). Evolutionary Theory, 5, 29-33.
Coffin, J.M. (1979). J. Gen. Virol., 42, 1-26.
Crick, F.H.C. (1968). J. Mol. Biol., 38, 367-379.
Doerman, A.H. (1953). Cold Spring Harbor Symp. Quant. Biol., 18, 3.
Doerman, A.H. & Boehner, L. (1963). Virology, 21, 551.
Fisher, R.A. (1930). The genetical theory of natural selection. Oxford, 122-123.
Hayflick, L. (1980). The Cell Biology of Human Ageing. Scientific American (Jan.1980)
Horszewicz, J.S., Leong, S.S. and Carter, W.A. (1979). Noncycling Tumor Cells are sensitive Targets for the Antiproliferative Activity of Human Interferon: Science, Vol. 206.
Luria, S.E. (1947). Proc. nat. Acas. Sci. Wash. XXXIII, 253-264.
Marx, J.L. (1978). Science, 199, 161.
Merigan, T.C. et al. (1978). New England Journal of Medicine, 26, Vol. 229, p. 1449-1453.
Orgel, L.E. (1968). J. Mol. Biol., 38, 381-397.
Reed, J., Toombs, R. and Barricelli, N. Aall (1967). J. Theor. Biol., 17, 319-342.
Rae, P.M.M. (1976). Science, 194, 1062.
Silberklans, M., Prochiantz, A., Haenni, A.L. and Rajbhandary (1976). In animal Virologi ICN-UCLA Symposia IV. Edited by D. Baltimore & al Acad. Press (N.Y.), 583-594.