LEO SZILARD Room 381
The Enrico Fermi Inst. for Nuclear
Studies, 5630 Ellis Avenue, Chicago.
Midway 3-0800; Ex. 3789

old

Enrico Fermi

Return to

L. SZILARD

1155 E 57 St

Chicago 37, Ill.

Thymine

Decay rates DNA
Release RNA Ad, Guanine, Uracil, Cytosine

ABC
ABA
RNA

TNR⊕ $P = 10^{-4}$ 10^{-4}

RNA+

PO-AA

P-O-AA

$3\,10^{3}$ cm/sec 1000 = M

1000

Engines

1457

Suppose now #1 makes T of E^* mutates back to E_R. Now there is not enough repressor ($T_r - R$) produced and balance is upset. But now another foreign template #2 can mutate to T_2 producing E_2

$(T_r(1) - R)$ — E_2 → $(T_r(2) - R)$

$T - E_2 - (T_r(2) - R)$

and controls self represses E_1

$T - E_1 - (T_r(2) - R)$

If now T mutates again to yield E_0^* instead of E

again a foreign gene arise producing E_2 which leads from $(T_r(2) - R)$ to $(T_r(3) - R)$ which represses production of E_2 etc. etc. and in limitum

Yanofsky ① 4

Prior to mutation

Ind + Serine $\xrightarrow{E(Tr)}$ Tryptophane $T_r + R \xrightarrow{E_r} (T_r - R)$

[$T - E(T) - (T_r - R)$]   [$T - E_R - (T_r - R)$]

$E(T_r)$

Mutation occurs in template of E_r as a result in place of enzyme E_r we have E_R^* and weak binding

This leads to production of too much repressor $(T_r - R)$. As a result of too much $(T_r - R)$ enzyme E is repressed.

[$T - E_R^* \sim (T_r - R)$] weak

~~Now a supp~~

Now ~~first~~ suppressor mutation occurs in a foreign gene ① the new enzyme produced called E_1 catalyzis reaction:

$$(T_r - R) \xrightarrow{E_1} (T_r^{①} - R)$$

Controll over E_1:

[$T_1 - E_1 - (T_r - R)$]

[$T_1 - E_1 - (T_r^{①} - R)$]

~~$(T_r Z R)$~~

$(T_r(1) - R)$ represses production of E

[$T - E_R - (T_r(1) - R)$]

write AA (1)
AA (2)
write:
E_0
E_0 for E_R
Write
for $(T_r(1) - R)$
Rep(1)

(3)

overall | T − E(2) − Rep(2) |

but also

| T − E(1) − Rep(2) |

AA level may now be restored to normal but now again E(0) mutates to E*(0) Now again bottle AA is made but level can be restored by a third suppressor mutation in which an enzyme E_3 makes its appearance

$$(AA(2) - R) \xrightarrow{E_3} (AA(3) - R) \quad repr(3)$$

overall

| T − E(3) − repr(3) |

| T − E(2) − repr(3) |

now AA level may be just right until ~~E*~~ ~~again~~ a mutation in T(0) again changes E*(0) into E(0)

Thus there will be an accumulation of Enzymes which catalyze a biochemical step of the type — rep (n+1)

$$(AA(n) - R) \xrightarrow{E_{n+1}} (AA(n+1) - R)$$

~~Explains Shantee~~ | Remark first about

adapt. Enz formation

Class I Enzymes lying directly in met pathways involved | in regulating level of

Class II Enzymes more or less remotely involved

E(0) — E*(0) — E(0)

Class II of enzymes

Transcription rewrite 4

(2)

~~Precursor of AA~~ $\xrightarrow{E(AA)}$ ~~Template~~ AA

$AA + R \xrightarrow{E(0)} (AA - R) = Rep(0)$

Rec AA $\xrightarrow{E(AA)}$ AA(0) || $AA + R \xrightarrow{E_0} (AA(0) - R)$ ~ Rep(0)

$T - E(AA) - Rep(0)$ | $T - E_0 - Rep(0)$

Template making E_0 mistakes and making E^*_0 bind weakly to Rep 0 in the series that

$T - E^*_0 \sim Rep(0)$

high diss. rate

(then E^*_0 to bake $E(AA)$ will be made and we have a slow grower or aster cell requiring AA as a growth factor)

Therefore too much Rep(0) will be made

This is now remedied by a suppressor mutation.

A Foreign template

~~protein~~ now mistakes and make an enzyme E_1 which does this

$(AA - R) \xrightarrow{E(1)} (AA(1) - R)$ ~ Rep(1)

Where AA(1) is one step removed from the original AA.

template

control $T - E(1) - Rep(1)$

but also strong binding

$T - E^*(0) - Rep(1)$

Therefore now $E^*(0)$ being represed less ~~too little~~ Rep(0) is made ~~and too much~~ ~~AA is made~~ and everything is fine until E_0 & E^*_0 mut

Then ~~now too much~~ AA is made

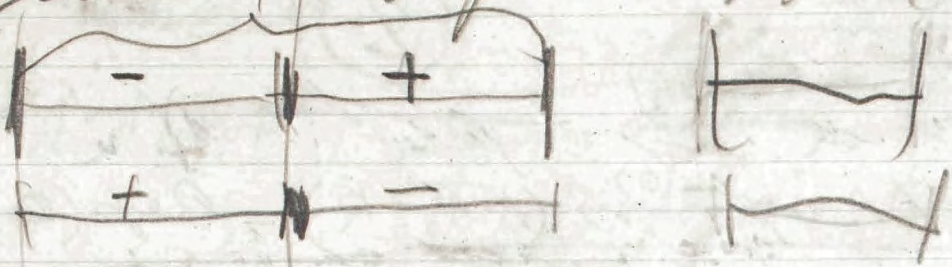
This is ~~also~~ remedied by a second suppressor mutation in another gene

E(0)

Some template mistakes to produce an Enzyme E_2

$(AA(1) - R) \xrightarrow{E_2} (AA(2) - R)$ ~ Rep (2)

5) Gene cooperation (short after Autr and forward)



AA(0) + R $\xrightarrow{E_0}$ (AA(0) - R)

AA(0) $\xrightarrow{E_{AA(1)}}$ AA(1)

Differentiation at end

Is in this growth system a situation where a substrate is not produced (except perhaps at a very low level) but if once level is raised new stable equilibrium is reached. Is it stable or do fluctuations throw it back down to low level. Is this reset of origin?

When only few enzymes are

However a substrate S_n which resembles $(AA)_n$ there is in the host ~~cell~~ an E_{n+1} rep(n+1)

$(AA(n)-R) \xrightarrow{E_{n+1}} (AA(n+1)-R)$

T-E(n+1)- rep(n+1)

T-E(n+1)- rep(n)

T-E(n+1)- rep(n+2)

~~rep(n+1)~~

We assume now

AA(n) $S_n \xrightarrow{E_{n+1}} S_{n+1}$ ~~$\rightarrow$~~ AA(n+1)

~~AA~~ Because of the chemical analogy of S_n or S_{n+1} ~~to AA(n)~~ may combine the enzymes E(n-1); E(n+1) or E(n+2) which make rep(n), rep(n+1) or rep(n+2) and thus we may expect that the enzyme E_{n+1} will arise when the host grows in the presence of S_n which resembles AA(n)

① Antikörper

~~(R-H)~~ $\overset{E_n}{\underset{n-1}{\rightarrow}}$ ~~(H$_n$-R)~~

(R-H(n-1)) $\xrightarrow{E_n}$ (H$_n$-R)

~~Enzym~~ ~~Protein~~ Antigen

~~Antikörper~~

~~A~~ ~~H$_n$~~

T ~ R

rep(n)

Genese of rep(n)

~~VLA~~ ~~Rep(n)~~

more Metab-

made, since evaporation is a ~~1st~~ first order process sometimes more is made and cell falls back in low equilibrium.

Drug tolerance:

$E_{(M)}$ Metab. | Metab + R E_0 (Metabolite - R)

Drug $\xrightarrow{E(M)}$ drug (1)

of drug which is chemical analog of M inhibits E_0 which produces repressor.

$$T - E(M) - rep(M)$$

Symbols

$\frac{E - A(O)}{T - R}$ or $\frac{E}{T}$ > rep, AA $\frac{E - Hm}{T - R}$

Let us set $\alpha = \beta$ $a = b$ $A = B$

$$\begin{cases} 0 = \dfrac{k}{k + E_2} - \lambda E_1 \\ 0 = \dfrac{k}{k + E_1} - \lambda E_2 \end{cases}$$

$\alpha E_2 = E_2$

$\beta E_1 = E_1$

$\dfrac{A}{a} = \lambda$

$k_1 = k_2 = k$

maximum value possible for $E_1 = \dfrac{a}{A} = \left(\dfrac{1}{\lambda}\right)$

for $E_2 = \dfrac{b}{B} = \left(\dfrac{1}{\lambda}\right)$

$$\begin{cases} K = \lambda E_1 (K + E_2) \\ K = \lambda E_2 (K + E_1) \end{cases}$$

$K = \lambda K E_1 + \lambda E_1 E_2$ $\quad \dfrac{K}{\lambda} = K E_1 + E_1 E_2$

$K = \lambda K E_2 + \lambda E_1 E_2$ $\quad \dfrac{K}{\lambda} = K E_2 + E_1 E_2$

clearly not possible except for $E_1 = E_2$ for if we subtract the two from each other

$$0 = K(E_2 - E_1)$$

or $E_2 = E_1$

Now what is rate of dissociation?

All this assumes no contact by own substrate so far

(4)

Differentiation

Enzyme kinetics

S substrate

e tot. enzyme

e^* free enzyme $= e - p$

p complex [ES]

equilibrium rate of disieve of [ES]

$$K_1 e^* S = K_2 p$$

$$e^* = e \frac{k}{k + s} \qquad k = \frac{K_2}{K_1}$$

when rate of evaporation of enzyme is high (weak binding) k is large

Differentiation:

T_1 makes E_1 at rate aX conc of free template

$$\frac{dE_1}{dt} = a \frac{k_1}{k_1 + \alpha E_2} - AE_1$$

αE_2 is conc. of product of E_2

$$\frac{dE_2}{dt} = b \frac{k_2}{k_2 + \beta E_1} - BE_2$$

Is there a stationary state

$$0 = a \frac{k_1}{k_1 + \alpha E_2} - AE_1$$

$$0 = b \frac{k_2}{k_2 + \alpha E_1} - BE_2$$

$E_1 = 10$

$$1 = \frac{\lambda}{10} + \frac{\lambda}{k}\frac{1}{10}E_2 + \frac{k}{\ell}\frac{1}{100}$$

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$$\frac{1}{10} = x$$

$$E_2 = \frac{1}{\lambda} - \left[\frac{k}{k}\frac{1}{x} + \frac{1}{\ell}\frac{1}{x^2}\right]$$

$$1 = \frac{k}{x} + \frac{1}{x}\frac{k}{k}$$

$$\frac{k}{\lambda} = kE_1 + E_1E_2 + \frac{k}{\ell}E_1^2 \qquad \frac{k}{k}\frac{1}{E_1} = k + E_2 + \frac{k}{\ell}E_1$$

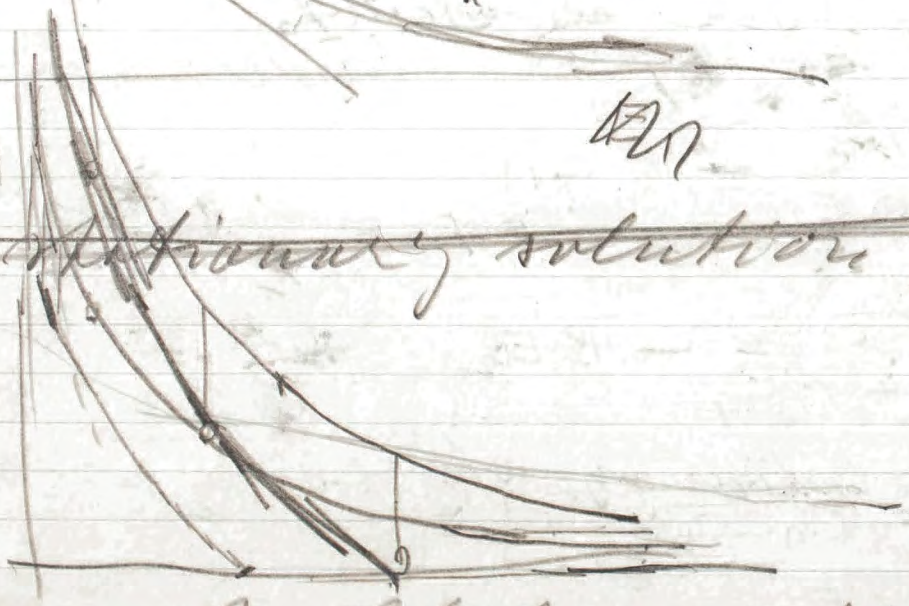
$$\frac{k}{\lambda} = kE_2 + E_1E_2 + \frac{k}{\ell}E_2^2$$

$$E_2 = \frac{1}{E_1}\frac{k}{\lambda} - \left[k + \frac{k}{\ell}E_1\right]$$

$$E_2 \frac{1}{E_1}\frac{k}{\lambda}$$

$$E_1 = \frac{1}{E_2}\frac{k}{\lambda} - \left[k + \frac{k}{\ell}E_2\right]$$

Now express from here E_1 as function of E_2



No satisfactory solution!!

No satisfactory solution it seems.

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Differentiation (double interaction) 4
(control by own substrate also)

$$\begin{cases} K_1 * e^* \times S_1 = K_3 p_1 \\ K_2 \times e^* \times S_2 = K_3 p_2 \end{cases} \qquad p_1 + p_2 + e^* = e$$

guess $e^* = e \dfrac{1}{1 + \frac{S_1}{K_1} + \frac{S_2}{K_2}}$ check!! $\quad k_1 = \dfrac{K_3}{K_1}$

$\frac{1}{K_1} = l_1$

$\frac{1}{K_2} = l_2$

$$\begin{cases} e^* S_1 = k_1 p_1 \\ e^* S_2 = k_2 p_2 \end{cases}$$

condition for stationary state now because if ~~binding~~ constant for own template is not k but l

$\boxed{l >> k}$

$$\begin{cases} 0 = \dfrac{1}{1 + \frac{E_2}{k} + \frac{E_1}{l}} - \lambda E_1 \\ 0 = \dfrac{1}{1 + \frac{E_1}{k} + \frac{E_1}{l}} - K E_2 \end{cases}$$

$$\begin{cases} 1 = \lambda E_1 + \frac{\lambda}{k} E_1 E_2 + \frac{\lambda}{l} E_1^2 \\ 1 = \lambda E_2 + \frac{\lambda}{k} E_1 E_2 + \frac{\lambda}{l} E_2^2 \end{cases}$$

$$1 = \lambda (E_2 - E_1) + \frac{\lambda}{l} (E_2 - E_1)(E_2 + E_1)$$

RNA turnover in Brain
Hyden

(1)

Antibodies (part 4)

$[R - H_n] \xrightarrow{E} [H_{n+1} - R]$ rep(H)

antigen = (Prot − H)

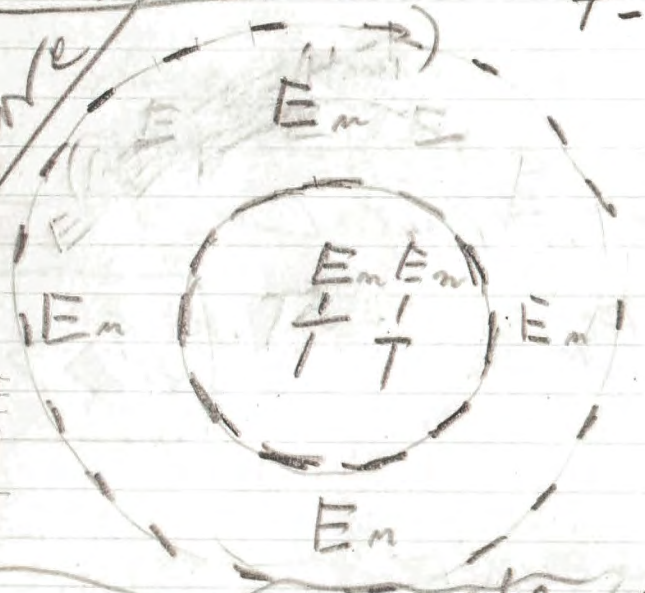
Rem: $E \sim (H_{n+1} R)$; $A_i \sim H(n)$, $T \sim R$

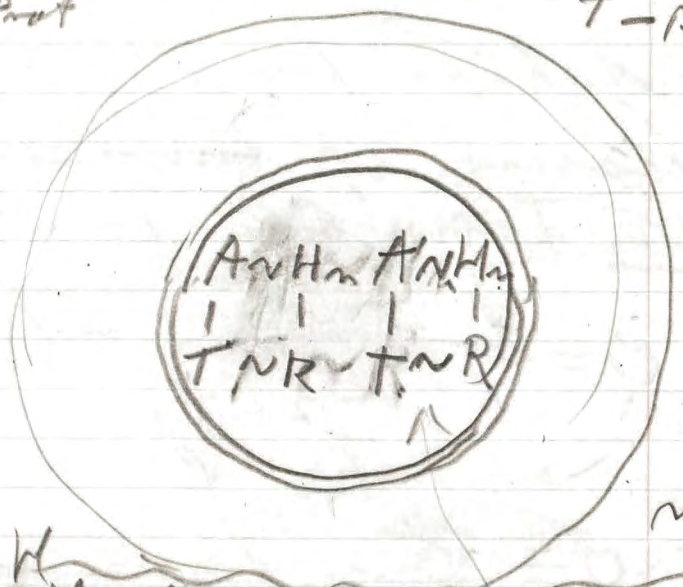
Rem: $(Prot - H) + E = (Prot - H) - E$

If it gets back: $E - H$, $T - Prot$

If it gets to it: $H - H$, $T - Prot$

(2) before





3 after 6 H-days

insert

put in her

mouth

comport

even

value of typing: Test of theory

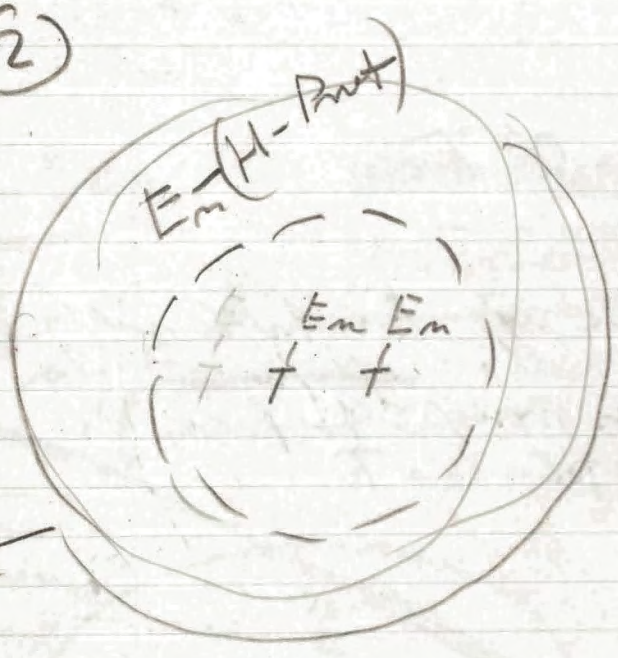
Quantitative distribution of R might give four per cent dissociation

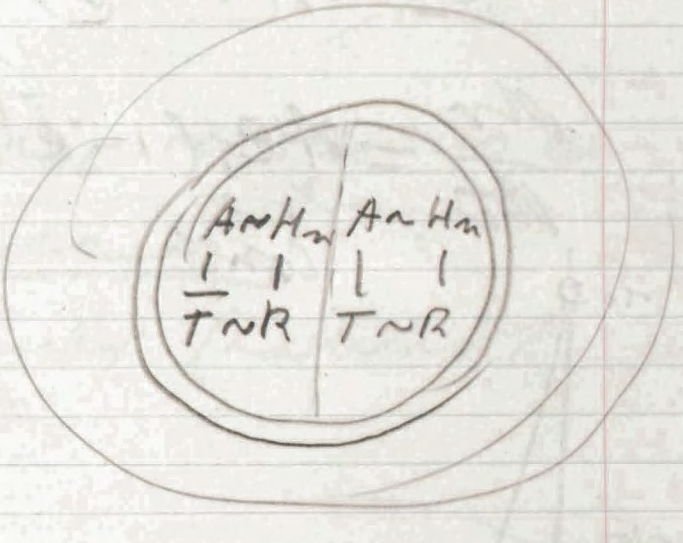
$R\text{-}G \xrightarrow{E_1} R\text{-}G_1$

$R\text{-}G \xrightarrow{E_2} R\text{-}G_2$

immediately after antigen is added

(2)





$A_n H_m$ / $T_n R$ $\quad$ $E\text{-}(H\text{-}Prot)$

Rhose,

(Ft-flow)

Conc. resp (Hm R) ~~tolerance~~ τ e concentration of ζ_E

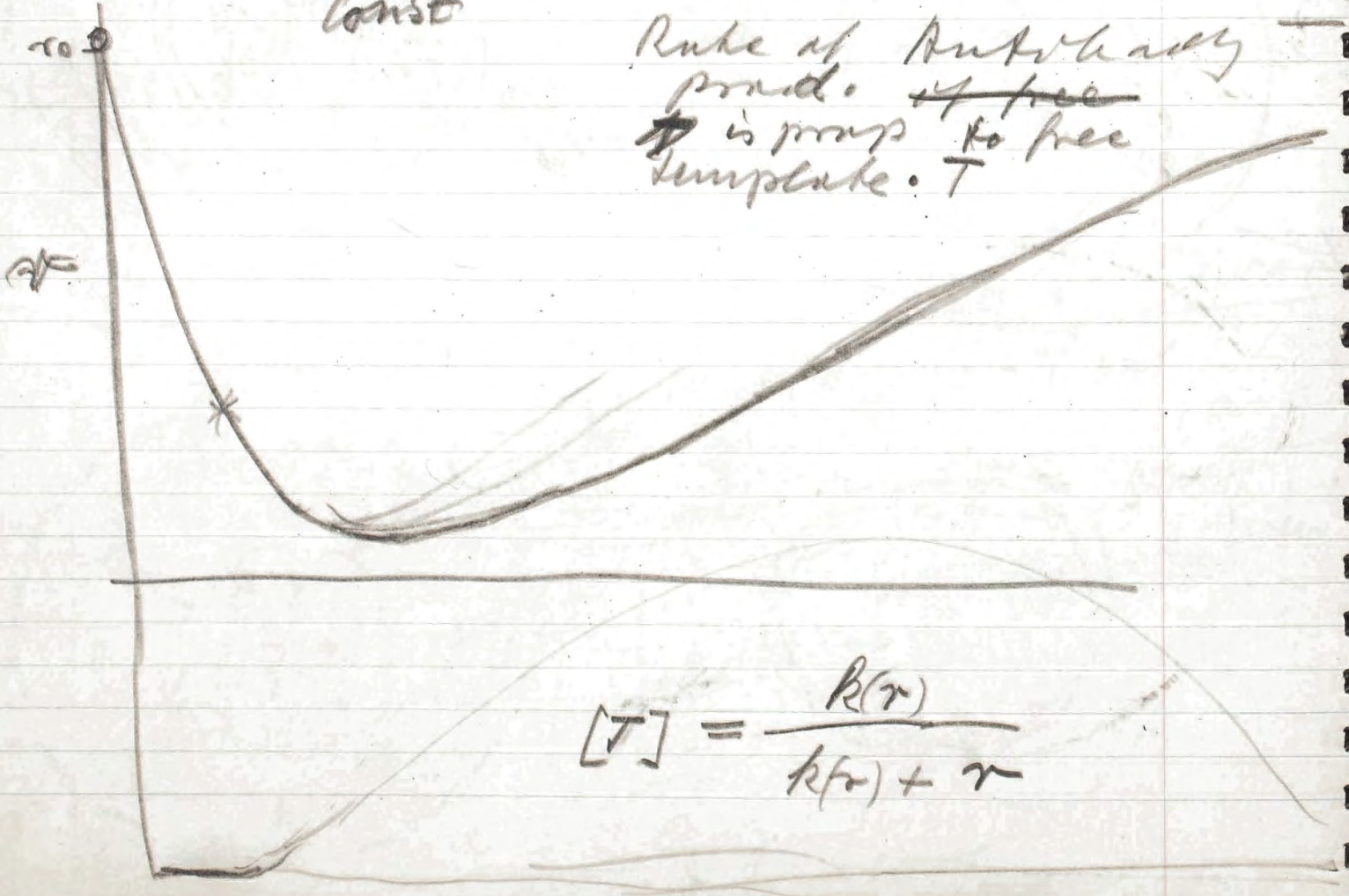
$$\frac{dr}{dt} = Ae - \frac{r}{\tau(r)} \qquad \text{Exp day} = \frac{1}{\alpha}$$

$$\frac{de}{dt} = B - \frac{e}{\tau(E)} \qquad \frac{1}{\beta} = \tau(E) \sim \text{month}$$

$$B = e_1$$

$$e = e_1(1 - e^{-\beta t})$$

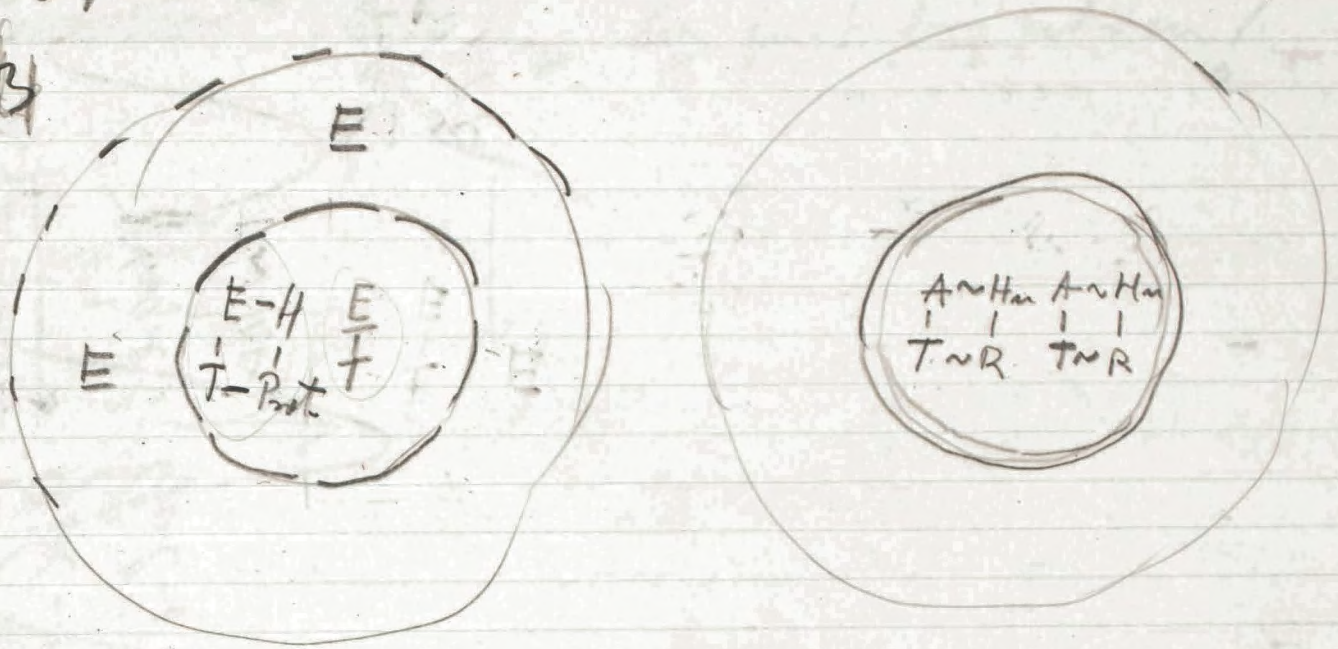
$$\frac{dr}{dt} = \underbrace{Ae_1}_{\text{const}}(1 - e^{-\beta t}) - \alpha r$$



$$[T] = \frac{k(r)}{k(r) + r}$$

~~Single antigen~~ Single Intersection

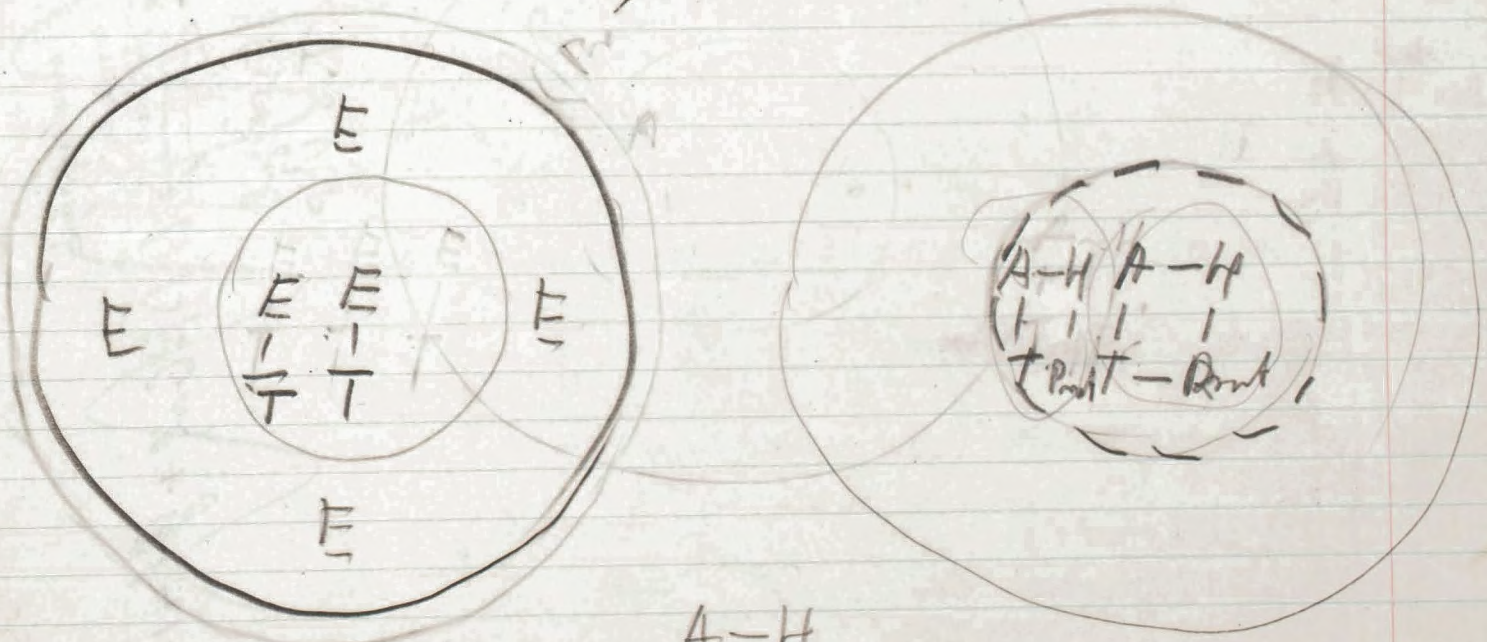
after several weeks



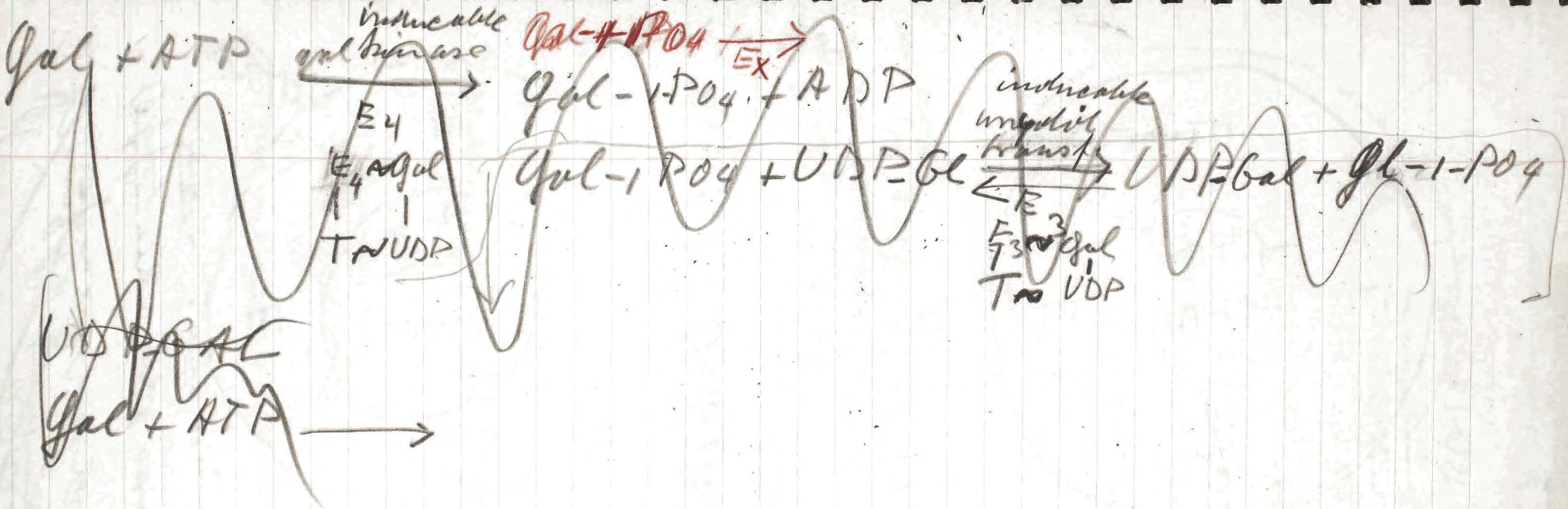
Explain anamnestic response

Presence

in Ambivo or Tony Rabbit if antigen is given



A-H
T-Prot


Gal + ATP
inducible galactokinase
Gal-1-PO4 + ADP
Ex
E4
E4 ~ Gal
T ~ UDP
Gal-1-PO4 + UDP-Glc
inducible interconvertible transferase
E3
E3 ~ Gal
T ~ UDP
UDP-Gal + Glc-1-PO4
UDP-Gal
Gal + ATP

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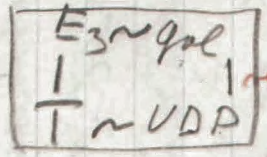
Then ~~consistent as~~ compute i_E in anamnestic response as assumption r_0 is 1/2 log first injection!

When bug grows on gal and no glucose present
UDP-GAL low and E_3 as well as E_4 must be induced
When grown on glucose UDPGal high (because of
only escape cell wall) and E_3/E_4 synthesis repressed

β-galactoside story

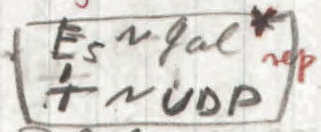
Gal + ATP $\xrightarrow[E_3]{\text{gal-kinase}}$ Gal-1-PO4 + ADP

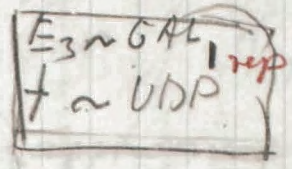


Gal-1-PO4 $\xrightarrow[E_6]{}$ cell wall

Gal-1-PO4 + UDP-Gl $\underset{E_3}{\overset{\text{uridyl transferase}}{\rightleftharpoons}}$ UDP-GAL + Gl-1-PO4

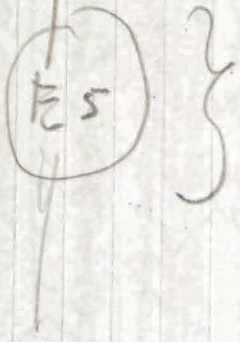
UDPGAL $\xrightarrow[E_5]{\text{β-galactosidase}}$ UDP-GAL*





UDP-GAL $\underset{E_2 \text{ (slow diss} \leftarrow)}{\overset{\text{epimerase}}{\rightleftharpoons}}$ UDP-Gl

UDP-Gl + PP $\underset{E_1}{\overset{\text{pyrophosphatase}}{\rightleftharpoons}}$ UTP + gl-1-PO4



Handman with Spiegelman: Enzyme β-galactosidase

10

may play an important

Vandrechian ~~stays~~ a role in regulating the ~~two~~ level of enzymes ~~which~~ ~~catalyse the formation of~~ ~~which lie~~ in the pathway of the synthesis of crabbit proteins such as for instance amino acids and that perhaps each ~~predetermined~~ ~~step~~ metabolites ~~directing~~ the enzyme

The next biochemical ~~step~~ ~~that catalyzes~~ ~~its~~ ~~begins~~ ~~formation~~ ~~incomplete~~ ~~step along the set~~ ~~biochemical~~ ~~to the next biochemical step~~ ~~in the~~ ~~via the~~ ~~one of the~~ biochemical pathway ~~the terminal~~

Thus one may have thought that in the synthesis ~~of arginine along the pathway~~ leading from ornithine to arginine

~~acetylornithine~~ E_3 ~~ornithine~~ E_2 ~~this~~ E_1, arginine

acetylornithine induces ~~E_3~~ the formation of E_3, ornithine induces the formation of E_2 ~~the~~ in the core of E_3

Vogel has shown ~~that~~ this is not ~~what~~ the case; ~~but rather~~ the ~~he~~ found that arginine represses the formation of E_3 ~~and~~ and ~~the~~ has studied

8

Chemical analogy theory of enzyme ~~Repressor Metabolites~~ ~~repressor~~ induction
~~Repressor metabolites and adaptive enzymes~~ & adaptation.
~~Enzyme Adaptation.~~ in bacteria of ~~ferm~~ enzymes

~~Bacteria~~ ~~In modern microbiology~~
one ~~finds~~ (enzyme) enzyme ~~which~~ which are
usually present in small amounts
in growing bacteria but which may
~~just after~~ ~~when~~ ~~which appear~~
greatly increase ~~in~~ amount of the
bacteria grow in the presence of
certain ~~bacteria~~ chemical ~~enzymes~~ or ~~synthetic~~
~~analogs~~ compounds which the bacteria
can metabolize ~~or this chemical~~
~~analogs~~ are called inducible enzymes
~~and~~ the ~~same~~ chemical compounds which
make their ~~by~~ increased synthesis are
called inducers. ~~It was generally~~
~~believed~~ Recently largely due to the
work of J. Monod and ~~his~~ ~~later~~ at his
(others
laboratory much attention was focused
on the phenomenon of enz. ind
in general and the enzyme β-galacto-
sidase (which splits lactose) in part-
icular. ~~It has been~~ up until recently
~~It was~~ ~~assumed~~ it has been generally
recognized
~~It was generally believed~~ that
the phenomenon of enzyme

paper

~~to be ~~specially~~ ~~brought~~~~

I find it indeed difficult to think of a mechanism by which any of the ~~above~~ known "inducer" could throw intermittently with a template inducer that template for an enzyme production of the precursor enzyme it is making, therefore I set out to see if bias is possible can be substantiated in face of the apparently overwhelming evidence to the contrary.

The present paper is a summary of my conclusions.— In order to distinguish the concepts with which I must operate I must mention and to arrive at a correct formulation of the problem I must start out with some of the conclusions reached and the assumptions which

1) ~~There are as I believe no~~ ~~inherent~~ ~~difficulties~~ (apparently) ~~insurmountable~~ ~~as~~ ~~intermediates~~ as well as certain intermediate metabolites of enzymes

2) Growth factors ~~&c~~ can repress the formation as illustrated in the

[~~and accordingly organisms which~~ they do not represent]
that there is no indication that
~~an~~ induction operates in this system

Werner Braun ~~and M~~ ~~about and~~
~~pin his investigations~~ and [illegible]
an extensive investigation / ~~at the appearance~~
~~to the~~ ~~cause~~ came
investigated / the dependency of the enzyme
~~to the space of the amount of~~ present
~~in the growing bacteria as a~~ in the
bacteria on the presence ~~of~~ or absence
of organisms, a million and million
and could find no indication for
any "induction". ~~By induction~~
~~we mean that~~

Werner Braun reviewing several ~~the~~ other
~~several~~ pieces of work biochemical
path ways and finding ~~that~~ a similar
situation ~~personally~~ in every case
~~concluded~~ reached the
~~concluded~~ that induction in the
sense of compounds which enhance
the synthetic rate of an enzyme
by interacting ~~with~~ with the Template
which synthesizes ~~the~~ the enzyme
~~may~~ not exist * ~~It is not~~ ~~to this theory~~
~~not~~ If this be true we must find
some explanation for the apparent
existence of induction.

Return

* ~~Indeed~~ Azel Lwin
Brookhaven Nov 27 '57 paper

while the suppressor is attached no enzyme is made. ~~In general such suppressors usually~~ Usually suppressors - so we assume - must be specific and ~~it~~ occurs only if the compound complexed to R (~~or~~ the universal carriers as one of several possible universal carriers) has specific affinity

Having thus defined what a suppressor ~~is~~ compound is we may now ~~try~~ define what an (reul-) inducer is as opposed to the rather loosely defined term of inducer ~~for example~~ which is used whenever a substrate evokes the appearance of an enzyme ~~As an illustrative example for such an inducer which~~ We shall speak of a real inducer strictly if we deal with a compound that ~~inhibits~~ an enzyme that produces a suppressor ~~because it is a chemical analog of the substrate~~ ~~As example for an inducer~~ of that enzyme. In general the real inducer ~~is~~ is therefore a chemical analog

case of arginine the repressor need however not be the growth product, arginine itself, but more likely it is a derivative produced by an enzyme which is ER which need not lie in the biochemical pathway leading to the end product (known example the end product as the end-product). This enzyme employs a non-specific radical R to arginine and the repressor is R-arginine In the case of lysine and tube arginine the repressor may well be the (allergic) Amino acid. Suppression at the enzyme level that lies in the biosynthetic pathway of the mutants according to this view by the reversible union of the enzyme template complex with the repressor which may be modulated by the original

enzyme-template complex $\sum \begin{matrix} E \sim AA \\ + \\ \sim R \end{matrix}$ } repressor binds and gives the $E \sim AA$ + ~ Adenyl

While the E-Template complex is free the template makes enzyme at the maximal rate.

proper

25

But when the cell grows on glucose the UDPGall ~~becomes high~~ may reach a high level for ~~the~~ its only ~~purpose~~ ~~is~~ is probably to supply galactose for the ~~synthesis of~~ cell wall. — ~~Therefore~~ Thus galactose may one might say ~~of~~ we wishes that it "induces" the formation of E3 is not ~~an~~ real inducer in the sense of our definition. ~~One would~~ In a more consistent terminology one would say that all certain sugars ~~as~~ except galactose are substitutors of enzyme E3 × A real inducer of E3 would be an activator of E3 and the β-gal ~~that would~~ from our point of view it is useful to dissociate the real inducer ~~which activates the enzyme that makes~~ a suppressor into two classes

1.) inducers which ~~activate an enzyme that~~ ~~lie on the normal metabolic~~ are chemical analogues ~~and~~ of a substrate of an enzyme that makes a suppressor compound and ~~are~~ therefore activators of that Enzyme

↳ where MG+ types (which are known ~~which induce~~ to ~~activate~~ ~~the~~ ~~enzyme which~~ to induce the beg β-gal

of the substrate ~~that~~ the

4

enzyme that produces the suppressor.
An example for an inducer, i,
that is not a real inducer, is
galactose + the metabolic pathway
~~in this case~~ as elucidated by K and -
is as follows:

E_3 and E_4 are "inducible" enzymes
in the sense that when the cell
grows on galactose they are
present at a high level while
when the cell grows on glucose
there level is very low. We assume
that UDPGAL is the suppressor for
E_3 as indicated by the symbol

E_3 ~ Gal
|
⊣ — UDP

When the cell grows on Galactose
UDPGAL ~~does~~ need not accumulate to a high level
for the end product UTP ~~and~~ source
Gl-1-P04 are needed as an energy source as
a ~~if for the~~ carbon source ~~of~~ ~~and~~
~~the~~ by the pairing mechanism.

proper

Mutants ~~of~~ (B negative mutants and their co-workers have shown

An example for this ~~fast~~ class are the

~~is probably the most the best~~

~~studied system~~ the inducers.

of β-galactosidase. ~~the inducers substrate~~

~~E2~~ When grown on ~~the~~ the bacteria are

~~the inducer~~ β-galactosidase can be

induced by β-galactosi a number

of β-galactosides ~~which~~ which presumably

inhibit E2

and this co-workers

I presume - the

In this class fall ~~presumably the~~

~~mutants~~ ~~As found by mutants~~ ~~of~~

~~β-galactosides~~ which ~~induce~~

on bacteria plant grow an succ or lactose

β-galactosidase. They presumably

~~inhibit~~ inhibit E2 ~~which~~ and

thereby ~~reduce~~ the ~~some~~ of ~~flat~~ UDPGal

which ~~is the key~~ may be the suppressor

(or a precursor thereof) of β-galacto

sidase.

~~More in this paper soon~~

+ M.G ~~of~~ of mutants which lack E2 as I

suspect it does - would fall into this class

Enzyme two classes

1.) Those which interact an enzyme that lies ~~along the pathway~~ one of the normal metabolic pathways of the ~~bacterium~~ cell and produces a repressor (or a precursor of a repressor) (because they are chemically like)

2.) Those which interact an enzyme that produces a repressor, ~~for another enzyme the repressor might not~~ ~~repress the formation of an enzyme that lies along one of the metabolic pathways but in general~~ in general ~~that represses in general~~ ~~just an enzyme that acts as an inducer~~ ~~not but on but below~~ does not lie along the metabolic pathways. ~~or any part~~ normal ~~or may be any~~ The general case is illustrated in Table I ~~the reaction~~ For the sake of argument ~~one~~ we may postulate that S_0 denotes an amino acid but it can ~~in fact~~ denote any growth factor that the bacterium can make ~~use of~~. S_1, S_2, S_3 etc ~~are precursors but one~~ S_1 is one biochemical step removed from S_0 ~~naturally~~. S_2 is one biochemical step removed from S_1, etc

~~P~~ This paper deals exclusively with this second class of inducers.

P. T. O.

paper

is coupled to R. Only then can we understand why there are so many enzymes Y which can find an Y_n to which they resemble sufficiently to be able to substrate the enzyme E_n

$$(R - Y_n) \xrightarrow{E_n} (Y_{n+1} - R)$$

$\uparrow$
Y

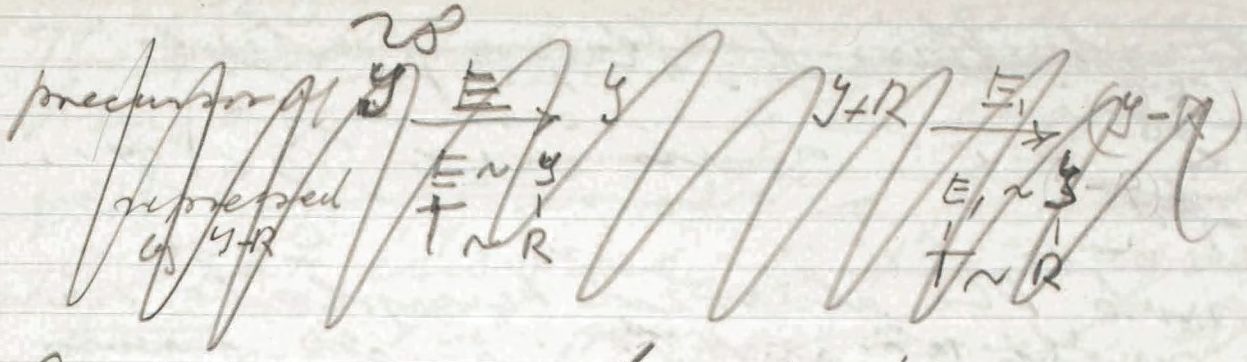
What can be the origin of such a large variety of enzymes and the repressor R which

It is our contention

In the following I shall describe one way in which they may arise

Let us focus our attention on one template which forms an enzyme E_0 that couples a few pieces Y_0 for instance an amino acid such as tryptophane to a carrier R to yield $Y_0 - R$ the repressor $(Y_0 - R)$

paper



We propose do deal in this paper mainly with this second class of real inducers there ~~are~~ is a great number compound which bacteria can ~~oxidise~~ and metabolize. ~~The~~ ~~These~~ these compounds do not resemble closely any of the ~~known~~ ~~metabolites~~ ~~products of~~ ~~no~~ intermediate which be on the lowest path of breaking ~~down~~. Yet ~~the bacteria assimilate this~~ these compounds ~~by them~~ ~~make~~ induce enzymes which can carry them through one or more biochemical steps. If they are are real inducers in the ~~first~~ ~~then~~ that the ~~molecules~~ sense of our definition ~~are there~~ ~~does the bacterium~~ the bacterium must contain a ~~very small~~ a very great variety of enzyme produce ~~repressors~~ ~~all bringing the~~ so many of them having the same answer R but differing in the compound Y_n which

paper

~~We investigate this by the equilibrium~~

~~E_0^*~~
~~$\downarrow$~~
~~T^*~~

(3.)

We investigate the altered template and enzyme with E_0^* and T^* and express ~~the fact of~~ the weakening of the bond by working up:

$$\frac{E_0^* \times T_0}{T^* \times R}$$

~~Because~~ Because of the weakened bond the enzyme-template complex will now be free a greater proportion of the time and will thus produce more E_0. ~~and~~ The level of $(E_0 - R)$ will then be raised less ~~enzyme~~ enzyme will be produced and less T_0. If the change is large enough the ~~backening~~ weakening will be ~~unable to grow unless T_0 is supplied~~ unable to grow unless T_0 is supplied

This can be remedied by a suppressor mutation occurring in some other gene which provides a template that ~~synthesis~~ forms an enzyme E_1 for which we have

paper

The growth factor Y ~~is produced~~ (reduces) from a precursor by an enzyme. And the ~~add~~ $(Y - R_0)$ ~~keeps supplies~~ the formation of that enzyme ~~to the required level~~ to the proper level. We may write!

Precursor of $Y_0 \xrightarrow{E} Y_0$ $\quad R + Y_0 \xrightarrow{E_0} (Y_0 - R)$

$E = Y_0$ + $-R$; E or Y_0 + R

Y also ~~keeps~~ ~~shuts down the rate of~~ shuts down the rate of its own synthesis to the proper rate

We shall now consider what happens ~~if repeated mutations~~ a mutation if a certain type occurs in the template that makes the ~~repressor~~ enzyme E_0 that produces the repressor ~~it~~ and if this mutation later on reverts ~~and subsequently~~ and then keeps on occurring and reverting.

~~We~~ We have in mind a mutation in the template that may or may not ~~affect~~ affect the enzyme itself that makes the ~~bond~~ between the enzyme template complex and the repressor compound

proper

3

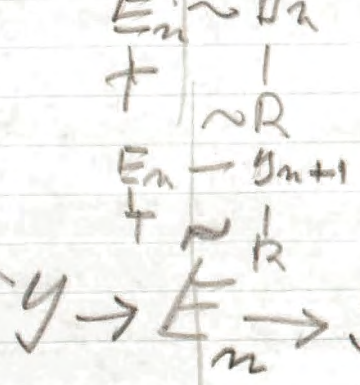
Later mean another mutation from T to T+ occurs a further suppressor mutation of the same general types may correct it so that we obtain a series of enzymes where

~~and E_n~~

~~and~~ $(R - y_{n-1}) \xrightarrow{E_n} (y_n - R)$ ~~+ $(R - y_n)$~~

y_n is a ~~steps~~ number steps away from the original amino acid (or other ~~substance~~ essential substance) and may bear little chemical resemblance to it.

~~But in this general~~



~~This may be very much~~

Because of the abundance of

paper

$$y + R_0 \xrightarrow{E_0^*} (y_0 - R) \qquad (R - y_0) \xrightarrow{E_1} (y_1 - R)$$

$E_0^* \not\sim y_0$
$T^* \sim R$

$E_1 \sim y_2$
$T \sim R$

and $E_0^* \sim y_2$
$T \sim R$

This suppressor mutation now by producing the interbacter $y_1 - R$ that is sufficiently strongly bound to the enzyme template complex $E_0^* - T$ corrects the defect of T^*

If there is now a back mutation from T^* to T, then there is again an imbalance which needs correction and there may occur a second suppressor mutation producing an enzyme E_2 so that we now have

$$(R - y_0) \xrightarrow{E_1} (y_1 - R) \qquad (R - y_1) \xrightarrow{E_2} (y_2 - R)$$

$E_1 \sim y_1$
$T \sim R$

$E_1 \sim y_2$
$T \sim R$

$E_2 \sim y_2$
$T \sim R$

Bayer

(4)

for purpose.
Plaster & remove pens
Authorized

~~but the repressor is dissociated off from~~
or that the template is free then the
the template mates enzyme at the
full rate.

$(R-G_{n-1})\frac{E_n}{}$ $(G_n - R)$ ~~$(R-G_n)\frac{E_{n+1}}{}(G_{n+1}-R)$~~

E_n ~~&~~ G_n
| |
T ~ R

E_{n+1} G_{n+1}
| |
T ~ R

~~A inducer~~
~~to be added~~
~~ratio~~

When a compound G is presented to the bacterium which is a chemical analog of G_n the enzyme E_n may catalyse a similar biochemical step:

G E_n G ~~produced~~ E_{n+1}

~~Each~~
Such a compound will act as an inducer by competing for the enzyme with the repressor ~~and also by substituting the enzyme E_{n+1} which also produces the repressor~~ and the decreasing the output of the repressor $G_n - R$. Thus there will be an increased ~~an increase in the synthetic rate of~~ E_7. ~~G~~ has an effect ~~different~~ of repressors to ~~do~~ and
There may be many series ~~of~~ or perhaps
10 to 100 members each, ~~and~~ and each
series may originate with a repressor composed of an essential metabolite complex to a carrier. In the case of AA for instance the first member could be an AA enzyme and/or acid in each series.
As we proceed ~~down~~ to higher number of
or along one series ~~with~~ in each higher
mixed step (which leave the carrier R

In a paper dealing with the formation of ~~adaptive~~ inducible enzymes in bacteria and other organisms I have endeavoured to show that it is possible to understand ~~the~~ ~~appearance of~~ only bacteria respond to a great variety of inducers. ~~This~~ ~~was~~ My explanation was based on ~~the~~ Hypothesis the presence in bacteria of a great variety of enzymes a E_n each ~~which~~ ~~catalyzes~~ ~~catalytic~~ acts as a repressor ~~R_n~~ ~~that can reversibly combine the enzyme template complex that synthesizes the enzyme. These repressors are small~~ ~~compounds of small molecular~~ weight that it transforms. The repressors are compounds of small molecular weight of the form $(Y_n - R)$ where R is ~~a~~ one of several universal carriers ~~probably~~ [in the case of A A the carrier is presumably an adenyl amino acid] ~~the~~ the repressor Y_n can reversibly combine with the template - Enzyme complex ~~of~~ which produces the ~~template~~ enzyme E_n and probably also with the enzyme E_{n+1}. ~~So long as~~ the repressor is attached to the enzyme template ~~complex~~ complex the template does not make enzyme

enhances the rate of production
of the antibody. ~~This theory does~~
~~not prove~~ ~~There is nothing in~~ ~~the~~
~~the~~ theory ~~does not~~ prove a model
of how this enhancement is accom-
plished by the antigen. Nor are the
basic phenomena - such as the greatly
shortened lag period - ~~that follows~~
~~the second injection~~ of an antigen
~~the~~ and the ~~greater~~ rate of
antibody production ~~of the~~
~~second~~ that follow the second
injection ~~if (provided several weeks~~
~~are interposed between~~ there is an inter-
~~val~~ val of several weeks between
the two injections) ~~the phenomena of~~
~~the basic phenomena~~
~~of secondary~~
response and ~~to~~ ~~be captured~~ ~~and~~
~~explained~~ ~~explainable in the~~ ~~other~~
~~words~~ necessarily explainable on the
basis of the theory. ~~In the meanwhile~~
~~response [of] upon the second injection~~
~~the response~~
the anamnestic response is obtained
if subsequent to a first inj. of an antigen
one allows several weeks to
pass and then injects the same
antigen a second time. Antibody
then appears after a latent period
which is ~~+ to~~ ½ of the latent
period after the first injection
and the rate of antibody produc-
tion may be more than 10 times greater
than after the first inj.
~~In addition that~~

probably adenyl-) nucleotide ~~complex~~ ~~the repressor~~ ~~further and further away from~~ the origin changes the chemical structure more and more until there is no resemblance left to the original amino acid moiety. ~~I have tried to make it plausible in what manner this great variety of repressors~~ This variety of repressors arose - according to my thesis - through mistakes which compensate for mistakes ~~of the other of~~ which affect the amount of the amino acid or the corresponding adenyl amino acid. ~~I should like to mention that I have~~ ~~Two specialized~~ ~~by this~~ ~~amino~~ ~~acids~~ I have singled out amino-acids over other essential metabolite ~~only~~ have only for the sake of convenience of argument.

Introduction III

A chemical analogy theory of antibody formation -

~~The~~ ~~It is apparent that the~~ ~~Clonal~~ ~~Selection~~ theory of antibody formation assumes that all antibodies that ~~are~~ Rabbit 4 are formed in response to the injection of an antigen are formed in ~~the example~~ small ~~about~~ amounts by the rabbit ~~of cells~~ prior to ~~the~~ first injection of the antigen and that somehow the antigen

(4) found that when the embryo reaches the antitoxin tempstake complex it combines irreversibly with it and thus causes tolerance.

The theory here presented is based on the assumption that some cells of the lymphatic system produce a great variety of enzymes E_n which produce such a specific compound of small molecular weight. Many of these compound have one part in common the carrier R while the other part designated by H_n is. The compound which may thus be described by the symbol $(H_n - R)$. ~~is a repressor~~ the enzyme E_n catalyzes ~~as a repressor~~ ~~It is reversibly combine first of all with the enzyme template complex and the receptor~~ the reaction

$$(R - H_{n-1}) \xrightarrow{E_n} (H_n - R)$$

$(H_n - R)$ is a repressor of the production of the enzyme E_n. It acts as a repressor by reversibly combining with the template that synthesizes the enzyme E_n or to be more precise

The Ehrlich Perne theory seems to have some elements of truth in it but it contains only half of the truth; This paper ~~to suggest~~ to suggest the missing half of the theory. It should therefore enable us to understand the basic phenomena of antibody formation and predict the outcome of certain hitherto not performed experiments. In principle

I assume that the Ehrlich-Perne theory that the cells ~~that~~ the ~~are~~ begin the antibody forming cells of the hypothetic tissues of the rabbit ~~that are~~ capable of forming an antibody, have a template which is specific but that only by the injection of the antigen the formation of the specific protein is repressed and that upon injection of an antigen that has a hapten that can specifically combine with the antibody this repressor is temporarily lifted. But here the similarity ends. I do not assume that the antigen reaches the template in the adult Rabbit which can form antibody. On the contrary I assume that it can reach it only in the newborn Rabbit which can not form antibody

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While the antibody template complex is thus covered by a repressor no antibody is formed by it. When the repressor is dissociated off antibody is formed at the full rate ~~as should these with the antigen injected~~ ~~the antigen~~ ~~the antibody~~

In contradistinction to the antibody-template complex ~~which is the antigen~~ which the adult rabbit the antigen ~~can not react~~ reacts the enzyme-template complex can be reacted gradually ~~but it can be reacted only~~ ~~clearly and with difficulty~~ When an antigen appropriately reaches the enzyme template complex ~~with~~ which is specific for ~~the~~ ~~R~~ and H is a chemical analogue of the there is an immediate combination formed

$$\frac{E_n - H}{\quad} \\ | \quad | \\ T. - Prot$$

Further upon dissociation of the antigen all the enzyme E_n which is present in the cytoplasm of the cell that makes this enzyme is reacted by the antigen Prot-H and the irreversible complex

$$E_n - (H - Prot)$$

is formed.

with the enzyme-template complex as indicated below

enzyme template complex
$$\left\{\begin{array}{ccc} E & \sim & Hn \\ | & & | \\ T & \sim & R \end{array}\right\} \text{repressor}$$

While the enzyme template complex is thus covered the template can not form enzyme. When the repressor is dissociated off the template ~~makes~~ ~~enzyme~~ enzyme at full rate. ~~For the subject of~~ For the sake of argument we shall regard the antigen as composed of a non antigenic Protein and a hapten H. Thus antigen = (Prot - H)

If the hapten H is a chemical analog ~~to~~ of some group Hn of a repressor ~~contained in the~~ represented in the rabbit then that repressor will also reversibly combine with with that protective antibody template complex that forms an antibody that is specific for hapten H

R. Roger

45

If we assume that the repressor (Hm-R) are manufactured in the rabbit with a half life of the order of a day and that the enzymes in ~~one~~ have a half lives of a few weeks or months. ~~we can now~~ ~~predict the sequence of events in~~ ~~this~~ this mistake!

We ~~shall~~ can now describe the ~~what is~~ ~~supposed~~ response of the rabbit to the injection of an antigen on the basis of some plausible assumptions if the numbers is ~~reduced~~

We shall assume that in a man primed animal the titer of the repressor has to drop 100 fold before there is enough antibody-template complex present to give an appreciable antibody production. — The ~~cause~~ reason for the ~~of the~~ (the) ~~checking~~ for the moment and the fact that ~~too~~ ~~perhaps~~ ~~a trace of~~ ~~some~~ ~~of the enzyme template complex is~~ ~~the cause~~ ~~in fact~~ ~~although~~ ~~errors~~ ~~may~~ ~~will be due to~~ ~~by the antigen~~ gradually & inversely - break up of the antigen. We can then compute

46

Gas repressors - Nitrogen breakdown and the process of aging in humans

III Paper

49

Small number of templates for $\pm$ some cells will produce much antibody titers

cells divide until templates are produced again.—

If anyone knows lawyer in area law firm that finds and produce evidence in favor wins Rabbit

Secondary response
Matters from primary because T-E does not fall much!

Can you protect with tapden or that first inj of antigen does not cause anamnestic response
Can you cause tolerance by injecting Hapten with small protein?

Remarks

Explain whole and minimum basal conditions.

Antibody

If $T-E$ is destroyed in first injection but little destruction in second observed things may be explained

Write rate of antibody ~~per template~~

$N(m)\, a_m \frac{1}{1+\frac{x_m}{k_m}}$ is rate of Antibody prod

x_m conc. of inhibitor, k equilibrium constant

Virus

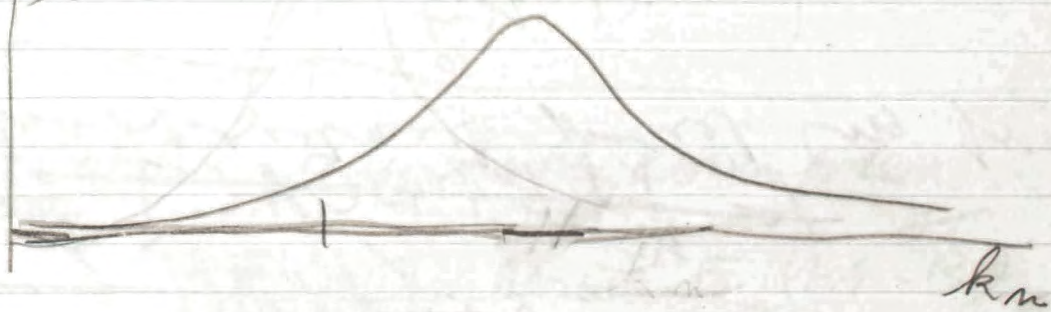
assume $t=0$ & $x_m^{(0)} = 10000\ k_m$

$x_m^{(1)} = 100\ k_m$

$x_m^{(2)} = 50\ k_m$

Effect of virus

$a(m) N(m)$



5 Enzyme equilibrium

E / I	E ~ Gal I T	E ~ Gal I T ~ UDP

What is true inducers and pseudo inducers in enzyme induction?

$$x\,e^* = K_1[xe] \qquad y\,e^* = K_2[ye]$$

$$1 = e^* + K_1[xe] + K_2[ye]$$

$$e^* = \frac{1}{1 + \frac{x}{K_1} + \frac{y}{K_2}}$$

$$e^* + [xe] = \frac{1 + x/K_1}{\left(1 + \frac{x}{K_1} + \frac{y}{K_2}\right)}$$

$$[ye] = \frac{y/K_2}{1 + \frac{x}{K_1} + \frac{y}{K_2}}$$

rate of any prod proportional

~~$\frac{1 + [UDPGAL]/K_2}{1 + GAL}$~~

$$\frac{1 + [GAL]/K_1}{1 + \frac{[GAL]}{K_1} + \frac{[UDPGAL]}{K_2}}$$

rate of Prod

"dopamine" control — Enzyme

better for galactose

assume precursor X, enzyme Y, product synthesis of E

$$\frac{C}{C_T} = \frac{1}{1 + \frac{y}{k_R}}$$

$\sigma = 1$

~~X enzyme~~

$$\frac{dy}{dt} = xe - b - y$$

Adj.

$$b + y = xe$$

$$y + b = x \frac{1}{1 + \frac{y}{k_R}} - b$$

precursor

$$y + \frac{y^2}{k} + b\left(1 + \frac{y}{k}\right) = {}^{k_R} xe$$

In this with enzyme interaction at template level! Enzyme complex with (AA - R)

~~(C) Template~~ template complex

~~AA + R~~ $AA + R \xrightarrow{E} (AA - R)$

T. Wolff: What about growing cells on galactose and study THG and other inducers?

53

Aug 4/57

Jacus: repressor ~ repressor 52 /4

→ antagonist

this kind of adaptation always less steep than tumor. –

K_2 for UDPGAL might be

assuming 1 mgm/cc (10^{-5} molar)

$\Delta H = RT \log K$ and $\frac{\text{UDPGal}}{K_2} = 1000$

$K = 10^{-8}$ mol

8.2.3 = 16/24 [cal/rad] 18.4

Kalckar purposes Kiyoshi Kurahashi

Science Vol 125 pp 114 116 1957

Mahler Sandstein (the last two enzymes E_4 and E_3 are not present when cell (cells) is grown on glycerol in absence of Gal part present when grown in presence of Gal

Cocus: J.E. Med. 104 (1958)

Stanier R.Y. Simultaneous adapt

J. Bact 54 339-348 /47

55 Antibodies

Lavies. — collaborators | all complete to
added not have much | antibodies

Dixon Frank J. et al Maurer, Paul H. Wolfle
and Deichmiller Lucia P. p425 Vol 103 1956

Rabbit + bovine γ globulin
cross persistent | antibodies

Cannon & Exp. Med. 102 p49. 1955 Prod
Cannon Albert H, Deane, Elizabeth 61 rabbit Hemag
73 Ehrlich receptor
rabbit (83.

For Miranda:

$$\frac{dr}{dt} = P E_0 - \frac{r}{\tau_r}$$

$\tau_r = 1$ day

$r = P E_0 \tau_r$ for $t = 0$

$$E_1 = \frac{E_0}{f_1}\left(1 - e^{-\frac{t}{\tau_e}}\right)$$

$\tau_e = 10$ days
$f_1 = 100$

1.) $$\frac{dr}{dt} = \frac{P E_0}{f_1}\left(1 - e^{-\frac{t}{\tau_e}}\right) - \frac{r}{\tau_r}$$

$r = A E_0 \tau_r$ for $t = 0$

2.) anamnestic response no change rate

$$\frac{dr}{dt} = \frac{P E_0}{f_2}\left(1 - e^{-\frac{t}{\tau_e}}\right) - \frac{r}{\tau_r}$$

$f_2 = 100$
$f_1 = 100$

$$r = \frac{A E_0 \tau_r}{f_1 \tau_r} \text{ for } t = 0$$

write X_m for r

write P for A above!

$$\frac{dA}{dt} = N(m)\,a(m)\,\frac{1}{1 + \frac{X_m}{k_m}} - \frac{A}{\tau_A}$$

$A = 0$ for $t = 0$

$$A E_0 \tau_r = 10^4 k_m$$

$\tau_A = 10$ days

put $A E_0 \tau_r = 1$

$N(m)\,a(m) = 1$

$\Delta F = -RT \ln K$ $\Delta H = -RT \ln K$ ☆

Multistep

cellubiuronic acid as Hapten
makes antibody reacting with type III and VIII pneumococci
III and VIII contain this hapten
cellubiuronic acid inhibits (some how) an enzyme which depolimerizes III and VIII

→ assume molecule of inhibitor

$$\frac{1\ \mu g\ /\ liter}{10^{-8}\ mol\ /\ liter}$$

K • Eng

$^{\circ}N^{-}$ 10^{-16}

10^{-16} G x 10^{12} molecules 10^{5} cm

58

phenomena ~~on the lines~~ on the
basis of ~~a~~ ~~common~~ ~~for~~ ~~to~~
the ~~natural~~ mechanisms ~~to~~ ~~exist~~
that appear to control the level
or enzymes in cells.
Those ~~are~~ seemingly unrelated
phenomena are as follows
1) ~~adaptation~~ to ~~galactose~~ of Bacteria
when adapt to galactose
grown ~~on~~ ~~glycerol~~ in minimal medium
~~on~~ (glycerol) ~~to~~ in the presence of galactose
~~the fact that a~~ ~~the fact that~~
2) ~~there are a number of suppressor~~
~~mutations in neurospora which~~
~~restore~~ when
there are a number of different
mutations in neurospora all lying
within the same functional gene
which lead to ~~loss (or reduction~~
absence [or reduced level] of the
enzyme tryptophane synthetase
(a gene)
(b an enzyme that condenses indol
and serine to give tryptophane.
[wrote fascinatingly] ~~the ability to synthesize~~
grown in pyst
~~this group~~ ~~mutations~~
according in molecule different ways (suppressors) can
3) The fact that there is
a great variety of compounds of
small molecular weight which
do not appear to be normal
metabolites of bacteria. Yet
bacteria can metabolize them
and respond to them in many cases

restore to the wild type the ability to synthesize tryptophane (2)

Enzyme Return here

~~Using a method and I advise~~ made up/our
~~to~~ preliminary examination
~~of~~ of the known facts of the
induction of the enzyme by
~~prolonged dose~~ ~~which we~~
~~at once and which we jointly~~
~~conducted~~ ~~which from this point~~
~~of view formulated by Henri~~ which
~~Author~~ Henri ~~Fact Does~~ not
~~at once~~ broke in the face of it
encouraging.

~~In the following I shall attempt~~
~~to interpret a number of apparently~~
~~puzzling phenomena~~ ~~which are~~
~~not afterwards~~
~~In the following I shall attempt~~
~~to~~

We have

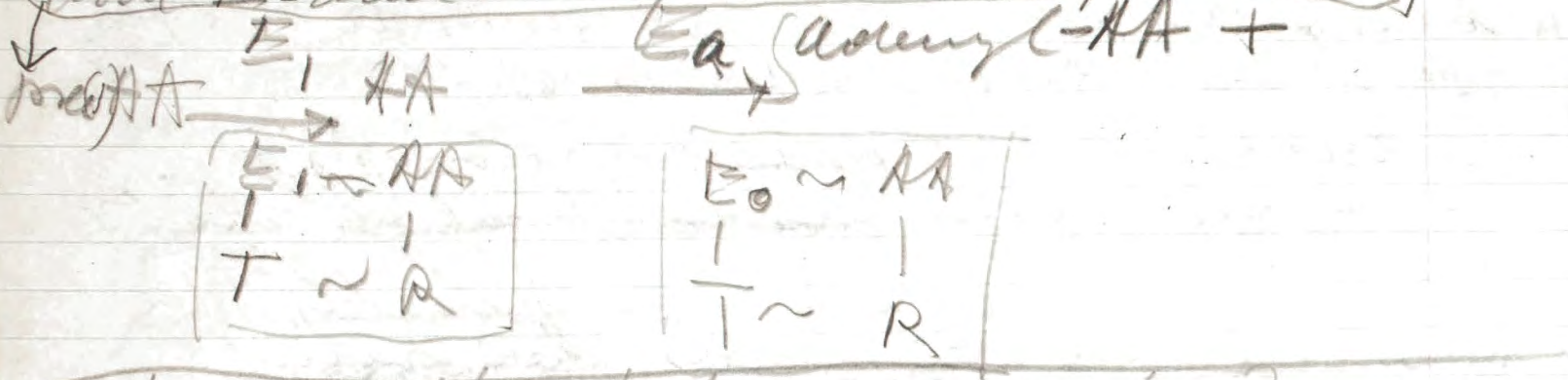
- Maas ~~HHHH~~ expressed the hope that
whenever ~~there is~~ a case ~~of~~ an ~~appears~~
enhancement of the production of an
enzyme ~~a case of~~ ~~brought to~~
~~to~~ in the end be interpretable as the
~~an indirect~~ an indirect ~~issue~~ of the
~~production~~ ~~impression~~ of the production
~~of an induction~~.

I shall now attempt ~~to develop~~ set forth
in the following a set of assumptions
which ~~of which~~ ~~would~~ may
permit us ~~to~~ ~~understand~~ to
interpret a number of [illegible] enzyme
- and seemingly unrelated Paper

I Paper follows Paper; return

an adenyl amino acid.

~~could E₂ and Prec 2 AA or also prec 3 AA~~



~~Need would be structure upon~~
No point of having an inducer
~~of the~~ Principle
stop direct

H. T. Vogel ~~140 (23) 145~~ Proc. Nat'l Acad. Sc. US 39 5 700/53
Charles Yanofsky p. 147 in Enzymes
units of Intergenic ~~structure~~ and
Function: The formation of the Amino acid

~~the enzyme~~ E, that ~~catalyzes~~ ~~each~~ are synthesized always
~~the~~ ~~AAA~~ their specific repressible T
We assume that E and ~~R~~ assume that
~~the enzyme~~ there will be an equilibrium
~~or at any rate a stationary state~~ between the
in which the enzyme template complex
T-E is reversibly combined with
the AA, a precursor of AA ~~and~~ or adenyl AA
~~We need not to form~~

E_1 E_1 - Prec 3 AA E_1 - AA E_1 - AA
T or $\frac{1}{1}$ or $K_{Prec\,AA}$ or $\frac{1}{T}$ K_{AA} or $\frac{1}{T - Adenyl}$ K_r

We shall now further assume that
~~note~~ with the template can not form
the enzyme unless "covered" with
adenyl AA but can

3 the fact that ~~was~~ noticed — and ~~was~~ many other animals of course can form ambiguities

5.) ~~For two~~ ~~paragraphs the~~ I Paper a certain ~~phenomenon called~~ gene expression

~~For the sake~~ ~~In order to make communication easier~~ I shall ~~make~~ For the sake of ~~the order~~ making communications easier ~~clarity of my presentation~~ I shall ~~propose~~ make my assumptions more ~~precise~~ detailed and therefore less likely to be true) ~~in all of this~~ then ~~emphasis~~ is demanded by the ~~red engine~~ thoughts that lies behind the argument. I believe however that the mistakes I may thereby introduce can be easily corrected later on. —

~~How for instance~~ First of all I shall make a ~~precise~~ ~~assumption~~ ~~from~~ concerning ~~the~~ my an ~~an~~ ~~and~~ and such as ~~inside~~ represses the formation of ~~an~~ an enzyme that lying along the ~~right~~ left hand pathway leading from some precursor ~~to the~~ through several enzymatic steps to the AA stuff.

I assume that the AA stuff is not the repressor of ~~the~~ any such enzyme and that there is beyond the AA stuff another step that also

It is not clear why the operators of an ~~producers~~ would offer any advantage to the ~~bacteria~~ in the biosynthesis

~~It Whether a process by bacteria the the synthesis of a gene~~

We assume that

For the E whole the enzyme complex is combined with AA or free AA ~~This model~~ ~~assumes~~ ~~assumed~~ ~~assume~~ assumes that the concentrations of free AA and KAA are very large ~~and~~ ~~how~~ ~~quickly~~ enzyme and KR is small then this model demands that ~~raising~~ the conc. of AA must repress the formation of the enzyme E ~~protein already~~ and if ~~that~~ the level of ER is not already saturated with the AA ~~so that the~~ (which may occur is the KR content of the cell is low.)

If on the other hand the ~~whole~~ complex ~~KAA~~ ~~free AA~~ is very low ~~compared to KR~~ ~~the~~ ~~to KR~~ ~~has a free AA~~ ~~of~~ has a high association constant for the precursor of the amino acid ~~free AA~~ and a low const KR for the repressor ~~ER~~ than the model demands that raising the level of ~~the~~ the precursor ~~would~~ must enhance the production of the enzyme. The precursor would then act as an inducer of the enzyme.

~~In amino acid synthesis these~~ ~~repressors~~ furnish an advantage ~~in~~ ~~regulation~~ and the synthesis of the amino acid and ~~to advantage~~ the operon ~~of~~ ~~other~~ would yield an ~~select~~ favorable

It is not clear why the operation of an inducer should offer any advantage to the bacteria and in the biosynthetic pathway of ~~the synthesis of~~ AA synthesis

~~It is therefore not likely~~ Therefore in general - precursors of ~~AA~~ an AA ~~will~~ should not be inducers.

We may however look for inducers in a different system!

Oval story

~~The~~ term protector

Beta galactosidase

Inducer Kinase

The Lac Galactosidase story

Paper

The model further demands that ~~is necessary~~ when ~~the~~ a bacterium that lacks an enzyme in the biosynthetic pathway leading to the AA ~~is~~ and is grown in the presence ~~of the AA~~ in a chemostat ~~with the AA as the limiting~~ in a medium supplemented with the AA ~~which serves as~~ (with the AA as the controlling growth factor) ~~at~~ the E_i must be formed ~~at~~ at least twice ~~the rate that is~~ at the normal ~~rate~~ (relative to the other enzymes) ~~and~~ and ~~if~~ this is likely to occur ~~in the event~~ if the gene ~~for~~ ~~AA-R~~ is ~~kept~~ ~~under~~ ~~the template must make enzyme~~ ~~at the first a~~ ~~very high rate~~

~~Think if AA-R is half~~ growth rate is half AA-R must be less than 1/2 its normal value; thus enzyme must shut

$$\frac{1}{1000} = \frac{1}{\left(1 + \frac{[AA]}{k}\right)^n} \sim 1000$$

fast

And that ~~it~~ formation of the enzyme is repressed by the reversible formation of

E~T-Gal
|
T ~ UDP

On the presence of an chemical analog of UDPGal or UDPGalactose we have the Enzyme-template complex in these forms

E/T ; E~Gal (K1) ; E/T ~ Gal (K2) ; E/T (K3) ; E-G* (K4) ; E~Gal / T (K5) ; E~Gal / T~UDP (K6)

(1) ~~The last two~~ (2) (3) ~~In the last two forms~~ (4) (5) (6)

While the enzyme-template complex is covered as shown in 3 or 6 there is no enzyme formation. A chemical analog of ~~Gal~~ UDP gal for which K4 is small is an inducer because it covers the E-T complex. UDPGAL is both a substrate and a repressor of the enzyme. ~~Glucose which~~ If cells are grown in glucose the UDPGal ~~level rises and the enzyme is repressed~~ (and the UDPGal) also levels rise and the enzyme is repressed. ~~However the inducer may not be~~ ~~TMG may not~~ is ~~not as good as~~ ~~the~~ In this unfortunate system an inducer like TMG might

~~The introduction of the enzyme~~
~~β galactosidase~~

Round

~~The~~ ~~lactose~~ ~~The (Rous~~ ~~to the~~ ~~cell~~
~~recognition of the operation of~~
~~this system was opened by that~~
~~Rous~~ ~~which we had to pass~~
~~before we could begin to~~ ~~test~~ ~~and~~
~~two tape~~ ~~+~~ Recently Kurlan
Weiner ~~opened the door to~~
showed the way to the unraveling
of this system by characterizing
the inducer that ~~is not~~ ~~does in~~ is (correctly described as) contains ~~of~~ ~~or~~ of
lactose [which contains of] not
~~in~~ because it is useful in enabling
them to split lactose but because
rather that this enzyme ~~is~~ does is
the named by which synthesize path
way needed to transport galactose
residues to the cell wall. He suggested
in particular that the enzyme acts
on ~~UDP Gal~~ Gal-1-P or more likely UDPGal
I shall ~~have~~ here assume ~~for the~~
~~sake of argument~~ rightly or wrongly
merely for the sake of argument that
β-galactosidase does catalyze ~~UDP~~ a reaction
which leads from UDP ~~E~~ Gal to a ~~galactose acceptor~~ coupled
UDPGal → (Gal UDP with UDP)

Paper

(57) ~~The From~~ It follows from
Newton Werner's concept that
β-Galactosidase is a normal enzyme
acting on a normally present
metabolite that in the wild
type there is always present
a basal level of enzyme below
which the enzyme can not be pushed
as long as the bacteria grow at
the normal rate, that is of course
the level at which the enzyme ~~is fully saturated~~ even when fully saturated
can make only as much UDP Gal as
~~it~~ the cell needs for synthesis
of the cell wall? ~~so that almost escapes~~
this enzyme
~~I~~ am inclined to believe that
is inducible only if cell wall synthesis
rate but-UDP is not too important.

TPG which inhibits the synthesis
of the enzyme may act by interfering
Es and thereby slowing the ~~flow~~
~~of~~ UDP Gal to Gal-1-PO4 ~~by~~
interconversion

~~Possibly~~ The fastest way of
checking these minutes would
be to study the effect of TPG and
TPG ~~of~~ on the ~~in~~ of cell
growing on Galactose.—

act in three different ~~ways~~ ways. ~~For one thing~~ for one it can ~~undoubtedly~~ combine with the enzyme itself and thus reduce the production of UDPGal from UDPGal which is a repressor. But it can also combine with E_2 and thus stop the production of UDPGal since it appears that cells (Lac$^-$ mutants) that can not make β-galactosidase grow quite well on succinate or lactate and therefore must be able to build their cell wall from Gal-1-P, UDPGal can escape, and a E_3 which makes the introduction of E_2 by PM6 more effective in lowering the UDPGal level than it would otherwise be. It is inherent in this theory that the rate of enzyme production can not increase with increasing inducer. Perhaps then ~~the~~ only one of the inducer molecules acts only on one spot. If it acts on two or three spots it may ~~be~~ with the second or third power of the ~~rate~~ concentration ~~At least~~ in a limited region at concentrations only. Thus the ~~A~~ notions stated above permits us to explain the ~~fact that PM6~~ that the enzyme curve rises with the second or third power of the ~~PM6~~ conc in the cell

Jumping

AA+R — E_0 — AA—R

E_0~AA | E_0~AA(1) | E_0~AA(2)
T₀~R | T | T~R

E_0~AA
T₀~R

E_0—AA(2)
T₀~R

(R+AA) $\xrightarrow{E_1}$ (AA(1)—R) E_1

R+AA(1) $\xrightarrow{E_2}$ AA(2)—R

R—AA(2) $\xrightarrow{E_3}$ AA(3)—R

R—AA(n-1) $\xrightarrow{E_n}$ AA(n)—R

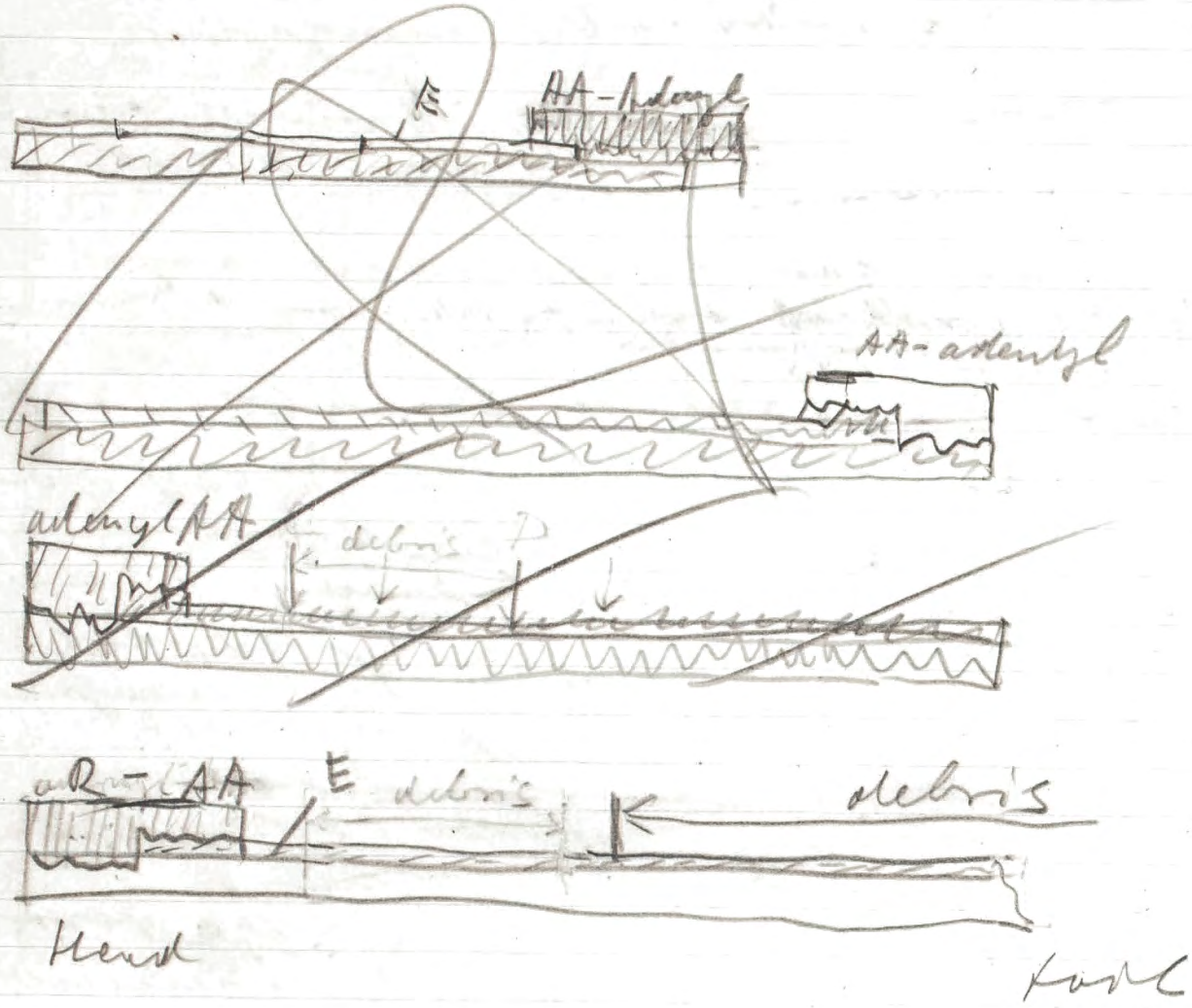
similar for T, E, where temperature-enzyme can combine with
AA(1)—R, AA(1), (AA-2—R), (AA(2) AA(3)—R
and AA(3) etc.
and in general for the T_n—E_n complex
The further we go away

$\frac{E \sim AA}{T \sim R}$ → $\frac{E^* \simeq AA}{T^* \simeq R}$ ←

reAA $\xrightarrow{E}$ AA AA+R $\xrightarrow{E_0}$ etc

Cells which are unable to
display level of the enzyme
& even when the gene is lost
or mutated in the
absence of ~~it~~ inducer are
called "constitutive". ~~This~~
~~is a misnomer~~ from the
point of view of the mutations
here presented. This is a
misnomer. — In the wild
type the production of this enzyme
is repressed to ~~perhaps~~ about 1/1000 of its
full value, as the
~~result of this~~ the wild type resembles
"debris" which crossreacts immunologically
~~with the~~ antibody is
prepared against the enzyme. Just
as the ~~repress~~ mutants described
by Jacob whose level of
transacetylase synthetase is repressed
~~only by a~~ (and not fully restored
by the suppressor mutation)
(explain in Jacob's case
that reversal ~~of~~ F'-s are involved
and because a chemical analog
restores only 4
wrote up
Jacob

Paper


AA-adenyl
AA-adenyl
adenyl-AA
debris
debris
R-AA
E
debris
debris
Hand
Kante


E
E-Ha
T-R

Explain here about 4 TP 4
and specificity ×

I Paper ~~Bi-functional~~ Structure

continued:

~~Mutation in one~~

The so called constitutive strain
~~one finds~~ contains about four times the wild type
transferase T. In the mutant
the "equilibrium constant" K_1^* and K_2^*
the for the formation of the
enzyme complex between the enzyme
~~transferase~~ complex ~~is smaller~~ and
UDPGal ~~is high~~ as well as UDPGal
might be much higher than the
constant K for wild type

wild type

E ~ Gal + UDP ⇌ E + Gal-1-P

E ~ Gal ⇌ E + Gal (K1)

E + UDP ⇌ E ~ UDP (K2)

mutant

E* ~ Gal + UDP ⇌ E* + Gal-1-P

E* ~ Gal ⇌ E* + Gal (K1*)

E* + UDP ⇌ E* ~ UDP (K2*)

K_1 and $K_2 << K_1^*$ and K_2^*

As the result a large amount of
enzyme is formed and UDPGal-T
~~and~~ reaches a high level ×
~~Another assessment~~

End of galactokinase
story

I Paper

Transposition

~~mutants~~ mutants requiring tryptophane because they lack tryptophan synthetase produce CRM (KK1A1) (wild type Pz) antigenic; cross reacting

Outline

Title: A theory of enzyme induction, enzyme repression and ~~feedback inhibition~~ repressor mutations.

Pages 18, 19, 20 ↔

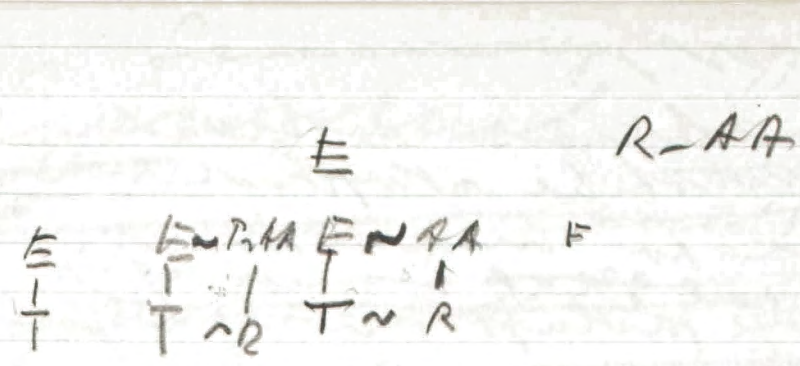
Challenged by this postulate

I have another look at a number of disconnected facts relating to enzyme induction to see if it were possible to bring some order in to chaos that is in general- as we shall see taken it is quite understandable ~~why~~ inducers do not operate in the biosynthetic pathway ~~to~~ that leads to the formation of an amino acid and also that they do operate in other biosynthetic pass ways; ~~and~~ moreover ~~above all we~~ it is possible to make it at least plausible why bacteria are able to metabolize ~~enzyme not~~ ~~biosynthetic steps~~ - ~~as~~ but ~~for~~ instance in the adaptive degradation of a large number of assimilable compounds ~~and why the enzymes involved are~~ ~~adapt~~ ~~made~~ which resemble only very remotely the essential metabolites, and why they produce the enzymes which are involved in the process.

pages 57, 58, 59, 60, 61, 62, 63, 64

Galactose story p.

Model: (page 71)



Summary

~~Until~~ ~~gene~~ the nervous network in my opinion must be adapted in order to be able to understand the formation like ~~adaptive~~ enzyme in ~~my~~ the ~~fragment~~ ~~and~~ recurrence ~~of~~ and behaviour

of suppressor mutations ~~and~~ in microorganisms and the formation of antibodies in animals.

There might be ~~in~~ microorganisms perhaps 10 and different templates ~~each producing a~~ and also of each there is synthesized ~~one~~ an "enzyme" (may be) of different specificity

We shall single out one of these Templates T which forms an enzyme $\overline{E}$, this enzyme forms a metabolite M from a precursor one step removed which we shall designate M(-1)

$$M(-1) \xrightarrow{\overline{E}} M$$

~~which~~ The metabolic pathway which leads to M may be written as follows

$$M(-3) \xrightarrow{\overline{E}(-2)} M(-2) \xrightarrow{\overline{E}(-1)} M(-1) \xrightarrow{\overline{E}1} M$$

~~M might be an~~ M might be any metabolite which is ~~essential for~~ an essential building block such as an amino acid or a coenzyme or a

Summary

Conceptual Enzymes

Enzymes are produced by a gene which is self-reproducing or a paragen which contains the same information as the gene and but is not self-rep as for the moment not relevant

We assume that

Enzymes are produced by bacteria by an enzyme forming locus which might be the gene itself which is self reproducing or something we might call a paragen - a structure which is not self rep — but contains the same information content as the gene but is not self reproducing the paragen is made by the gene and would thus have to wait by the gene - presumably at the site at cell division. We shall designate the enzyme forming structure with the letter T and refer to it for the sake of brevity as the template according to the following rules

Enzyme development in an attempt to put order into chaos.

for the metabolite. Summary former

$$R + M \xrightarrow{E_0} \{M\text{-}R\}$$

~~We shall designate~~ The enzyme-synthetase complex can reversibly combine with the metabolite M or certain chemical analogues M* ~~(compounds which may be present in the Zedekeria or products of M i.e. M(1) or M(2) etc.)~~ ~~and there will be an equilibrium constant for each different chemical analog~~ ~~of the metabolite~~ ~~M that will be treated as the same chemical and~~ added by the experimenter to the ~~system~~ suspension

Likewise the enzyme hemoglobin complex can reversibly with the corresponding metabolite or ~~the~~ a corresponding chemical analog of the metabolite

Explain M* (M^*-R)

~~Thus the~~ ~~we have is opposite~~ ~~to~~ In equilibrium we should have

E $E \sim M$ $E \sim M(1)$ | $E \sim M^*$ $E \sim M(1)$

$+$ $+$ $\frac{}{K_M}$ $+$ $K_{M(1)}$ | $\frac{}{K_{M^*}}$ $\frac{}{K_{M^*}}$

$+$ $\sim R$ $1 \sim R$

forms E at maximal rate

$\sim M^{**}$ does not form enzyme

$\frac{1}{T}$

virtually free

owned

~~Summary~~

a carbohydrate residue

In case of the amino acids as ~~a~~ tyrosine or tryptophan for instance the precursors are known and the enzymes the enzymes have been isolated

In the case of arginine for instance we have M(-1) = citrulline; M(-2) = ornithine; M(-3) = acetyl ornithine.

Accordingly to the notations here prescribed the enzyme - Template complex for which we shall write

$$\left.\begin{matrix} E \\ \| \\ T \end{matrix}\right) \quad \begin{matrix} E \sim M \\ | \\ T \sim R \end{matrix}$$

if ~~it~~ were not ~~not~~ restricted in the manner ~~~~ that will be presently explained would ~~have~~ (in bacteria) ~~to build~~ and other nitrogen at a rate of about 10000 higher than ~~does the~~ ~~do the templates~~ ~~partial~~ ~~accepts~~ would than the templates in growing bacteria actually do.

~~There is however for~~ ~~not~~ ~~will be~~ ~~partial~~ ~~an~~ ~~Normally however~~ This comes about in the following manner The molecule M is coupled to a radical R [conceivably ~~with~~ when M = Galactose and conceivably ~~always~~ when M is an amino Acid] by a coupling enzyme which is specific

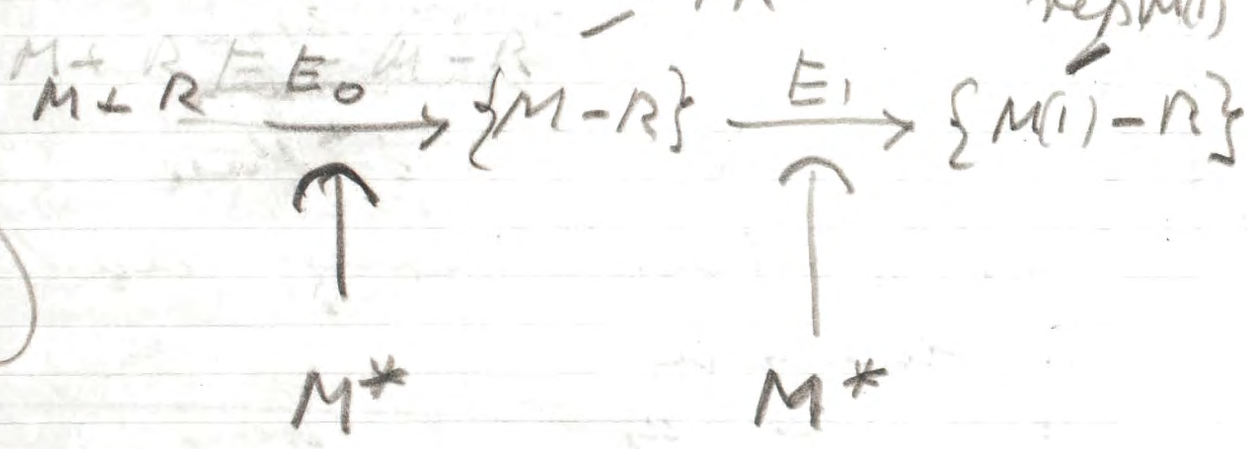
E_0

~~for~~ as well as in other interconversions

Summary

~~Is by a factor~~ of about 10^4.

However if this ~~the~~ is the only effect that an inducer M** has then ~~as it may be shown through enzyme formation~~ as it may be shown the rate of enzyme prod is a function of the inducer concentration can not rise faster than linearly. ~~Inducer~~ a chemical analog M** of the metabolite can however raise the enzyme level not only by protecting the enzyme-template complex but also by inhibiting ~~an~~ enzymes which makes an inducer



1

It is likely that during evolution mutations that occured in template T which sometime ~~increased~~ increased ~~sometime decreased~~

We shall designate the repressor {R-M} with rep. and (R-M**) with rep(M**) and accordingly designate the equilibrium constants for binding with the E-T complex with K_M, K_{M*}, K_{M**}, K_{rep}, K_{rep*} (6)

By from these equilibrium constants abundance of computing the amount of aporepressin concentrations for the E-T virtually free and the covered forms of the E-T complex one can see that if K_{M**} is small compared to both K_{rep} and K_{rep*} then at appropriately small concentration of M** almost all the E-T complex might be present in the virtually free form and enzyme production will be greatly enhanced. Since M** may be called an inducer of the enzyme. Since in many cases enzyme production is repressed to about $\frac{1}{104}$ of the enzyme production of the free enzyme template complex an inducer may enhance enzyme production

Summary

What are suppressor mutations

to day Triphosphate [illegible]

P_2 Stamieri case

[illegible] must

Autolumdog. (II)

E E~g E~galdor
| | | |
T + T R

Ed galdor
| | [illegible]
T R

E E~g
| |
T [illegible]

$$(H_m - R) \xrightarrow{E_m} (H_{m+1} R)$$

$[H_m - R] = r_m$ $[E_m] = e_m$

$$\frac{dr_m}{dt} = Const_1 e_m - \frac{r_m}{\tau_m}$$

$$\frac{de}{dt} = Const_2 N_m$$

$e = [E_m]$

TDP
must needed
Enzyme Template
complex

{H-Prot} = antigen

E ≅ H-Prot E ≅ H
T ≅ Prot

A A~H
| |
T T

in embryo and
newborn only

A ≅ H
| |
T ≅ Prot

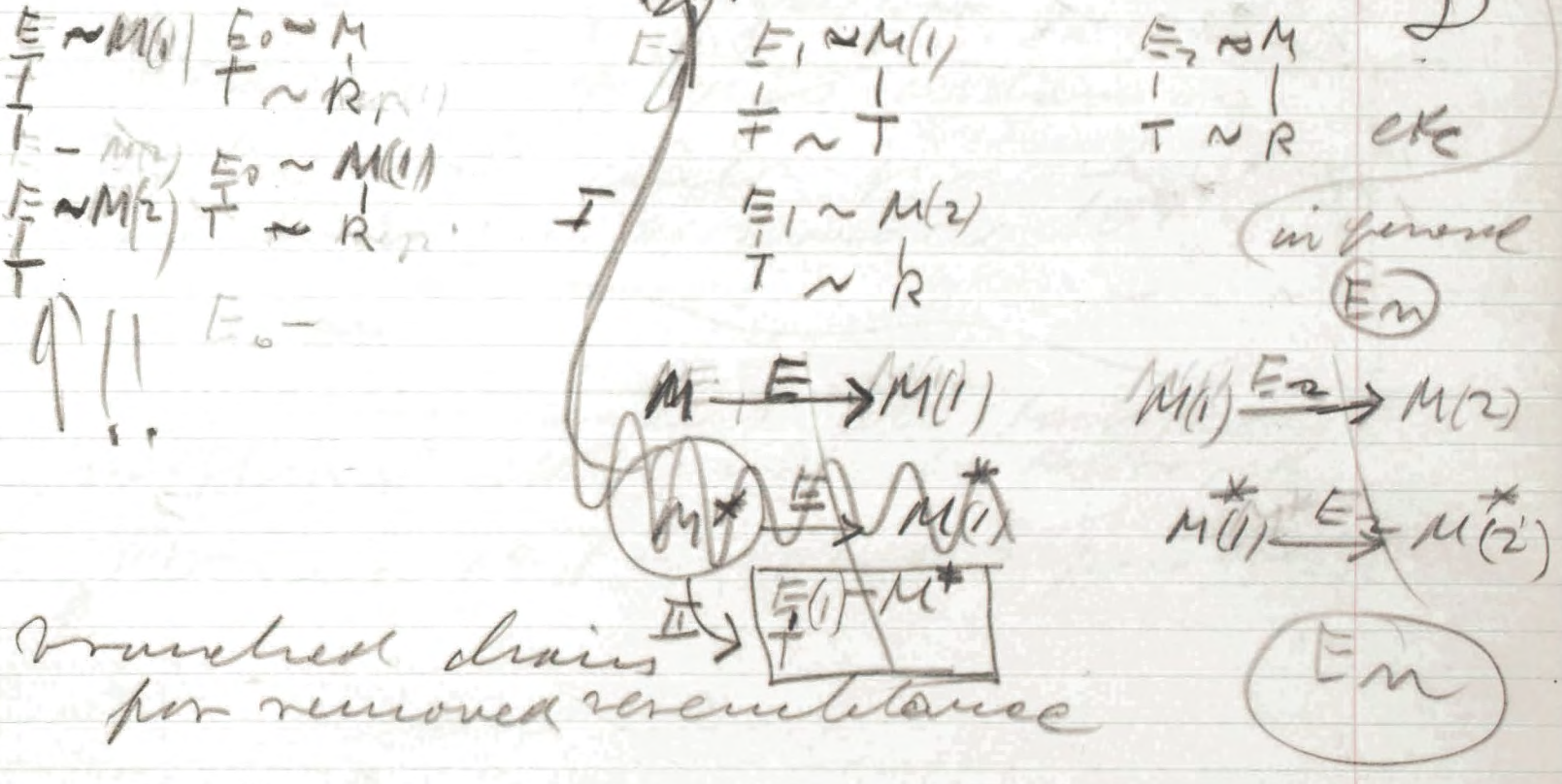
Secondary response
~~chase~~

Chase

Curious phenomenon

the nature of the equilibrium
constant K_{rep} ~~was such that~~
it were suppressed by mutations
occurring in other loci and
that this had led to a series of
enzymes and new chemical analogs
of the metabolite so that
by this one line in bacteria
~~data~~ metabolic chains of
this sort $M \xrightarrow{E} M(1) \xrightarrow{E_1} M(2)$

$M + R \xrightarrow{E_0} \{M-R\} \xrightarrow{E(1)} \{M(1)-R\} \xrightarrow{E_2} (M_2-R)$



Mutated chains
per removed repressor

~~Equipartition~~ Energie Kinetics

for Turbulences

Saturation $\frac{1}{1+\frac{\tau}{\tau_0}}$

if energie is saturated ! $\tau \gg \tau_0$ sup E_0

(1) $\frac{dE}{dt} = A \frac{1}{1+\frac{\tau}{\tau_0}} - \frac{E}{\tau}$

$\tau = \text{const} E$

$\frac{E}{\tau} = \frac{A}{1+\frac{\tau}{\tau_0}} \quad \left(1+\frac{\tau}{\tau_0}\right)\frac{E}{\tau} = A$

$1 + \frac{\text{const} E}{\tau_0} \frac{E}{\tau} = A \qquad E = \sqrt{A}$

$\Delta F = RT \log k$ 4

Arguments for antibody formation

N/cc 10^{-16} $m^3 \times v$

10^{-6} gm/cc -16 10^{16}

10^{-4} 10^{-8} mole/cc 10^{6} 2 ~ $10^{13} e^{-\frac{\Delta H}{RT}}$ $\frac{10^{-8}}{R}$ mole/cc

10^{-8}

$\approx 10^{4}$

10^{-12}

$-12 \times 7.3 \approx 24$

e

Concentrations about micrograms/cc

0.1 gm/liter gm/cc

Concentrations as low as 1 μ/cc still could give $\frac{1}{10^4}$ free at binding equilibrium

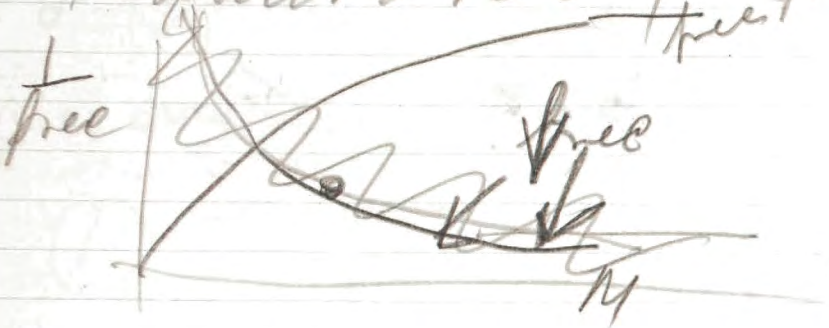
Experiments means all templates F-5
nothing cell must be destroyed

Assume 10 templates per cell

~~Orders of magnitude~~

When we start with very low M, free decreases & and takes ~~6 x M~~ saturates 1/free transfer

$$\frac{1}{f_{free}} = \frac{1 + \frac{[M]}{K_M} + \frac{[P]}{K_{rep}}}{1 + \frac{[M]}{K([M]_0)}}$$

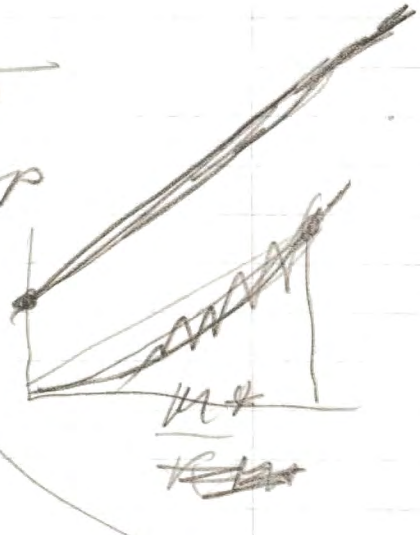


half saturation for $[M] = \frac{[M]}{K([M])}$

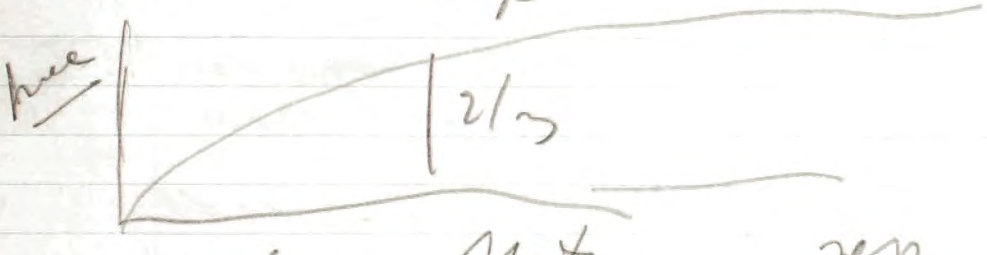
orders of magnitude that takes to reduce

type of enzyme found elsewhere where [M] is returned from very high conc to

$$V = \frac{1 + \frac{[M]_0}{K([M]_0)}}{1 + \frac{[M]_0}{K([M]_0)} + \frac{[rep]}{K_{rep}}}$$



$\frac{[M]_0}{K([M]_0)} \frac{[rep]}{K_{rep}}$



when $\frac{[M]_0}{K([M]_0)} = \frac{[rep]}{K_{rep}}$

Kinetic for phenylethyl goal

10^{-5} Molar

for $[M] = 100$ gm 10^{-10} Molar or more 10^{-8} gm/liter

Depolymerization

free $e^* = \frac{1}{1 + \frac{M^*}{K_1} + \frac{rep}{K_{rep}}}$

virtually free

(1) $e^* + [M^* e] = \frac{1 + \frac{M^*}{K_{M^*}}}{1 + \frac{M^*}{K_{M^*}} + \frac{rep}{K_{rep}}} = V \cdot f$

(2) $\frac{M^*}{K_{(M^*)}} \ll \frac{rep}{K_{rep}}$ and $1 \ll \frac{rep}{K_{rep}}$

$M = M^*$

3) $\frac{M^*}{K_{(M^*)}} = 1$

~~If we raise M and to for transkat.~~

~~If we split M~~ (and to for trans

1) ~~M is reduced~~ and $\frac{M^*}{K_{M^*}} \ll \frac{rep}{K_{rep}}$

so that rep rises more in $\frac{M^*}{K_{M^*}}$ than $M = M^*$

4) $rep = Const\, M(n)$

We assume E is not never saturated

then $rep = Const\, M^*$ and $\frac{M}{K_{(M)}} \ll \frac{rep}{K_{rep}}$

1.) $1 \ll \frac{M^*}{K_{(M^*)}}$ then "free" indep of M^*

2.) $1 \gg \frac{M}{K_{(M)}}$

5) $\frac{[M]}{K_{(M)}} = 1$

6) $\frac{M}{K_{(M)}} \gg 1$

~~free falls with increasing M~~

~~rises with more~~

~~In other~~

7.) $\frac{M}{K_M} \ll 1$

free must thus always become very large if we make M low enough

$V = \frac{1 + \frac{M}{K_M}}{1 + 11 + \frac{rep}{K_{rep}}}$

20% of dry weight
20% enzyme in beef
which has 15 and enzyme
1000 orth. dens. 700 dry weight

15,000 unit enzyme in 700 g
1 mg N 1.6 105 units of dry weight

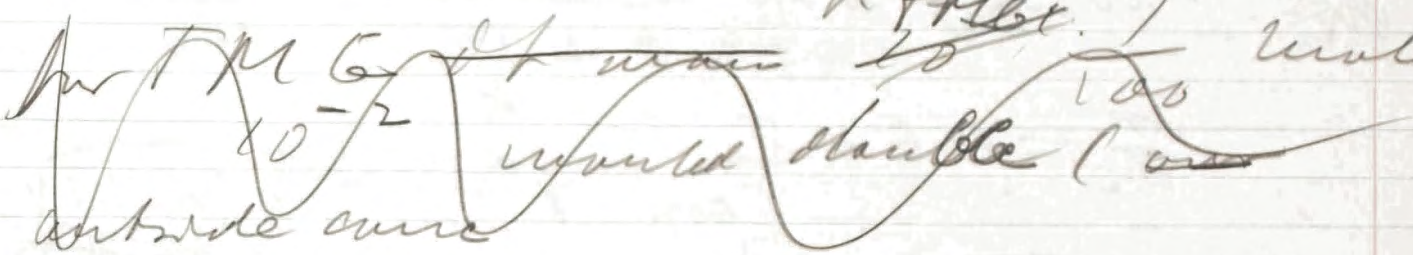
40% of total protein. —

~~$K_{inh} = 10^{-5}$ M~~ 61

$\frac{n_{ep}}{K_{inh}} = 10^4$

~~$n_{ep} = 10^{-4}$ mole~~

This means that 10^{-5} Molar inducer may double level



outside cure

and 10^{-2} molar would raise by a factor 1000

(What is rep conc.?)

Amino acids & those with can not ~~be~~ ~~rep~~ represed by raising "precursor" conc

$M \sim K_M$ or $K_M = 10^{-5}$

$M = 10^{-5}$ or Molecular 100

10^{-3} gm per liter

may be 10^{-6} or 10^{-4} gm.

outside ~~1000~~ 100×10^{-6} inside

where M is lower inversely as well depress enzyme

Antibody neu Assay 8/15

~~Tumor take rate~~ ~~inversely~~ ~~proportional~~ (# of Templates)

$$\beta \propto \frac{1}{\#\text{ of templates}}$$

number of templates ↓

$$\frac{dE}{dt} = \beta k \frac{q}{1 + \frac{r_0}{k}} - \frac{E}{\tau_E}$$

$$\frac{dr}{dt} = \beta E - \frac{r}{\tau_{rep}} \qquad q \frac{\alpha k}{r} = \frac{E}{\tau_E} \qquad (0 < q < 1)$$

$$r = \beta E \tau_{rep} \qquad \frac{\alpha k}{r}$$

$$q \alpha k \tau(E) = \beta E^2 \tau_{rep} \qquad \frac{q \alpha k \tau(E)}{E} = r$$

50 fold increase

$$10^{13}\left(e^{-\frac{Q}{RT}}\right) = 10^{-5}$$

$$e^{-\frac{Q}{RT}} \qquad 10^{-18}$$

$$\frac{Q}{RT} = \qquad 18 \times 2$$

40 600

4 000

Rep E →

10^{-5} M/liter

Bulars

$N = \frac{n}{u}$

$1u = 10^{-3}\ell$

$N = \frac{n}{10^3}$

$\Phi - TS$

$e^{-7_1}\ e^{-10}$

e^{-3}

RT×7

1000 x

1A°

10A°

$N/_{cc} \quad x\ 10^{+4}\ cm \quad 10^{-15} = 10^{12} e^{-10} (1-f)^{\frac{1}{2}}$

$= 10^{19} 5\,10^{-5}$

$N = 5\,10^{19} f^{\frac{1}{2}}$

$f = \frac{1}{1 + \frac{N/u}{K}}$

$N = \frac{5\,10^{22}}{2}$

$f = \frac{1}{1 + \frac{A(1-f)}{K}}$

$f \sim \frac{1}{1 + \frac{A}{K}}$

$x\,10^{23}\ 10^{-5}\ 10^{-3}\ 10^{4}\ 10^{-15} = \frac{1}{12} 10^{12} e^{-\frac{\Delta H}{RT}}$

$10^{27}\ 10^{-23}\ 10^{-11} = e^{-\frac{\Delta H}{RT}\,10^{12}}$

$10^{\vec{7}}$

$K_D = 10^{-6}$

$K_{(12)} = 10^{-5}$

$\frac{K_{(12)}}{K_1}$

$K_{(12)} = 10^{-11}$

---

transpeptidase $\frac{1}{10}$ per hour $M = 100$

10^{-4} gram $K = 10^{-6}$ $\Delta H_1 = \Delta H_2 =$ 12 kcal/mol

$\frac{K_{rep}}{K_M} = 10^{-5}$

$\frac{1 + \frac{M}{K_M}}{1 + \frac{[rep]}{K_{rep}}}$

$\frac{[rep]}{K_{rep}} \sim 10^4$

10^{-6} mol = 0.1 mgm
100 gm organism 100 g

$M = K_M$ $[K_D] = [K_M]$ K_D

$\frac{[rep]}{10^{-5} K_M} = 10^4$ $[rep] = 10^{-1} K_M$

Bulanos A B A-B

$N_1\ \nu\ 10^{-16} \rightarrow \frac{1}{2}\,10^{13}\,e^{-\frac{\Delta H_1}{RT}}$

$N_{(2)}\ \nu\ 10^{-16} \rightarrow \frac{1}{2}\,10^{13}\,e^{-\frac{(\Delta H_1+\Delta H_2)}{RT}}$

$\frac{1}{4} = 10000$

$\frac{K_{12}}{K_1} = \frac{1}{q}\,e^{-\frac{\Delta H_2}{RT}}$

$\frac{K_{12}}{K_1} = 10000\,e^{-\frac{\Delta H_2}{RT}} = 10^4\,e^{-20} = \boxed{10^{-5}}$

10^4

$K_1 = 10^{-6}$ mol

$N_1\ \nu\ 10^{-16} = \frac{1}{2}\,10^{13}\,e^{-20}$

$N_1 = \frac{1}{2}\,10^{-4}\,10^{16}\,10^{13}\,e^{-20}$

$= \frac{1}{2}\,10^{25}\,e^{-20}$

Per mol/Liter

$K = \frac{10^3}{6\,10^{23}}\,\frac{1}{2}\,10^{25}\,e^{-20}$

$\boxed{10^{-6}} = K_1$

$1 = 10^9\,e^{-23}\,e^{x}$

$10 = e^{x}$

$x = 9.23$

with (12 decimals)

Antithresholds / graded theory

$\frac{dE}{dt} = bq \frac{1 + \frac{r}{K(M)}}{1 + \frac{r}{K_{rep}}} - \frac{E}{\tau}$

$\frac{dr}{dt} = a - \frac{1}{1 + \frac{r}{K(M)}} E - \frac{r}{\tau}$

$\frac{E_0}{q} = bq \frac{\varepsilon}{10^4 (m+1)}$

10 drugs

drug

m

$r = r_0$

$1 + \frac{r_0}{K(M)}$ N

$r_0 = K(M)$

at $t=0$ $\quad \frac{2K}{1 + \frac{r_{rep}}{K_{rep}}} = \frac{E_0}{\varepsilon}$

$q/\varepsilon 10^4 = E_0$ $\quad (\varepsilon = 10$ drugs$)$

$t=0 \quad a = \frac{bq\varepsilon 10^4}{2} + \frac{K(M)}{\tau}$

$0 = a - \frac{E_0}{m} - \frac{r_0}{\rho}$

$0 = a - bq\varepsilon \frac{1}{10^4} - \frac{r_0}{\rho}$

$K(M) = 10^{-6}$

$a = bq\varepsilon$

$\frac{r}{r_0} = \frac{a\rho}{(m-1)K(M)} = \frac{r_0 + bq\varepsilon \frac{1}{10^4}}{(m-1)K(M)}$

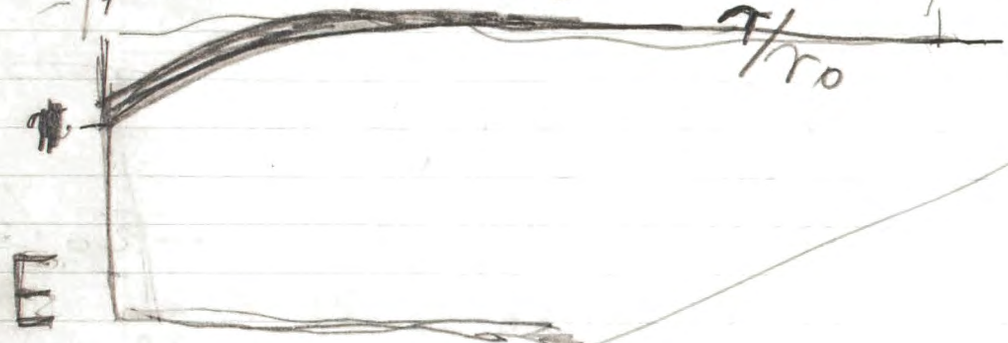
$= 1 + \frac{bq\varepsilon 10^4}{(m-1)K(M)}$ $(m \neq 1)$

Antithresholds / Quad theory

$\frac{dE}{dt} = bq \frac{1 + \frac{r}{k(M)}}{1 + \frac{r}{k_{rep}}} - \frac{E}{\tau}$

$\frac{dr}{dt} = a - \frac{1}{1 + \frac{r}{k(M)}} E - \frac{r}{\rho}$

for $t = 0$ $E = E_0$ $r = r_0$



at $t = 0$ $\frac{2}{1 + \frac{r_{rep}}{k_{rep}}} = \frac{E_0}{\varepsilon}$

$q/\varepsilon 10^4 = E_0$ ($\varepsilon = 10$ drugs)

$t = 0$ $a = \frac{bq\varepsilon 10^4}{2} + \frac{k(M)}{\rho}$

$0 = a - \frac{E_0}{m} - \frac{r_0}{\rho}$

$0 = a - bq\varepsilon \frac{1}{10^4} - \frac{r_0}{\rho}$ $k(M) = 10^{-6}$

$a = bq\varepsilon$

$\frac{r}{r_0} = \frac{a\rho}{(m-1)k(M)} = \frac{r_0 + bq\varepsilon \frac{1}{10^4}}{(m-1)k(M)}$

$= 1 + \frac{bq\varepsilon 10^4}{(m-1)r_0}$ $(m \neq 1)$

10 drugs

$\frac{E_0}{q} = bq \frac{\varepsilon}{10^4 (m+1)}$

1 drug

$r_0 = k(M)$

$m = 2$ or 6

m

$1 + \frac{r_0}{k(M)}$ N

Fair 10 days Tolerodge

$$10^{12} e^{-\frac{\Delta H^0}{RT}} = 10^{-5}$$

$$e^{-x} = 10^{-17}$$

34

$$e^{-\frac{40}{RT}}$$

Does it matter a bit difference when too much?

Experiment:

Antibody response when antigen removed at a time

"t" Rabbit makes radioactive antibody.

Experiment

Will the adoptive animal get sick and die?? 2, 2, 1, 1

Both already produced after
Dimj: only little by spots into
molecules; [illegible] combines proteins
in a few days and others continue.

Hp inside

The Repressor

Repressor:
Sites occupied with rep

$$\frac{\frac{[rep]_{up}}{K_{gene}}}{1 + \frac{[Rep]_{up}}{K_{gene}}} = [Rep]_p$$

$$\frac{[rep]_{low}}{K} \Big/ 1 + \frac{[rep]_{low}}{K} = 1/2$$

$$\frac{[rep]_{low}}{K} = \frac{1}{2} + \frac{1}{2}\frac{[rep]_{low}}{K}$$

$$\frac{[rep]_{low}}{K} = 1 \quad \left\| \quad \frac{[rep]}{K} = s + s\frac{[rep]}{K} \right.$$

$$(1-s)\frac{[rep]}{K} = s$$

$$[rep] = \frac{s}{1-s} \qquad s \approx 1$$

$$= \frac{1}{1-s}$$

$\Delta = \beta^{n} g$ fold

Antibody formation check

$$\frac{d\Sigma}{dt} = bq \frac{\left(1+\frac{r}{K(M)}\right)^{m+1}}{1+\frac{r_{sp}}{K_{sp}}} - \frac{\Sigma}{\varepsilon} \quad 1.)$$

$$\frac{dr}{dt} = a - \frac{c}{1+\frac{r}{K(M)}}\Sigma - \frac{r}{\rho}$$

$$\frac{r_0}{K(M)} = M \qquad \cancel{\Sigma_0 \left(a - \frac{r_0}{\rho}\right)(m+1)}$$

r

1.) $\frac{\Sigma_0}{q} = bq\varepsilon 10^{-4}(m+1)$

$r_\infty = a\rho \qquad r_0 \;||\; \cancel{a}\left(a - \frac{1}{1+m}\Sigma_0\right)\rho = r_0$

$r_\infty = a\rho = (m+1)K_m + \frac{dq}{1+bq}\varepsilon 10^{-4}\rho$

$$\boxed{\frac{r_\infty}{r_0} = 1 + bcq\varepsilon\rho}$$

if $\rho_{sp} \ll \rho_M$ then we are all right!! ρ and ε are dimensionless constants.

100 micrograms

1000 10 molecules or

2×10^{-13} gm Protein 10,000 mol wt

$2\ 10^{-18}$ moles

$6\ 10^{23}\ 10^{-18} = 6\ 10^{5}$ 10^6

1000 mg 100 molecules

100 mg 10 molecules

Why is there a minimum growth rate ? ? ? Great!

10,000 micrograms/τ 100 $\frac{\text{micrograms}}{\text{min}}$

100 micrograms per min

1/per sec 100 000 Mol weight 1,000 residues

n=100 Avg. #. $\frac{\tau}{n} =$ [illegible]

n 10 ppm/sec

$\tau =$ [illegible] 10 sec

$10^{-13} e^{-X} = \frac{1}{n10^{-13}}$

$e^{-X} = \frac{10^{-13}}{n10}$

10^{-14} or 10^{-15}

Wilson rep curve. & in "acquaintance" experiments, & should be really 10^4 under assumptions.

Shape of curve important!

~~E(Cooperation)~~

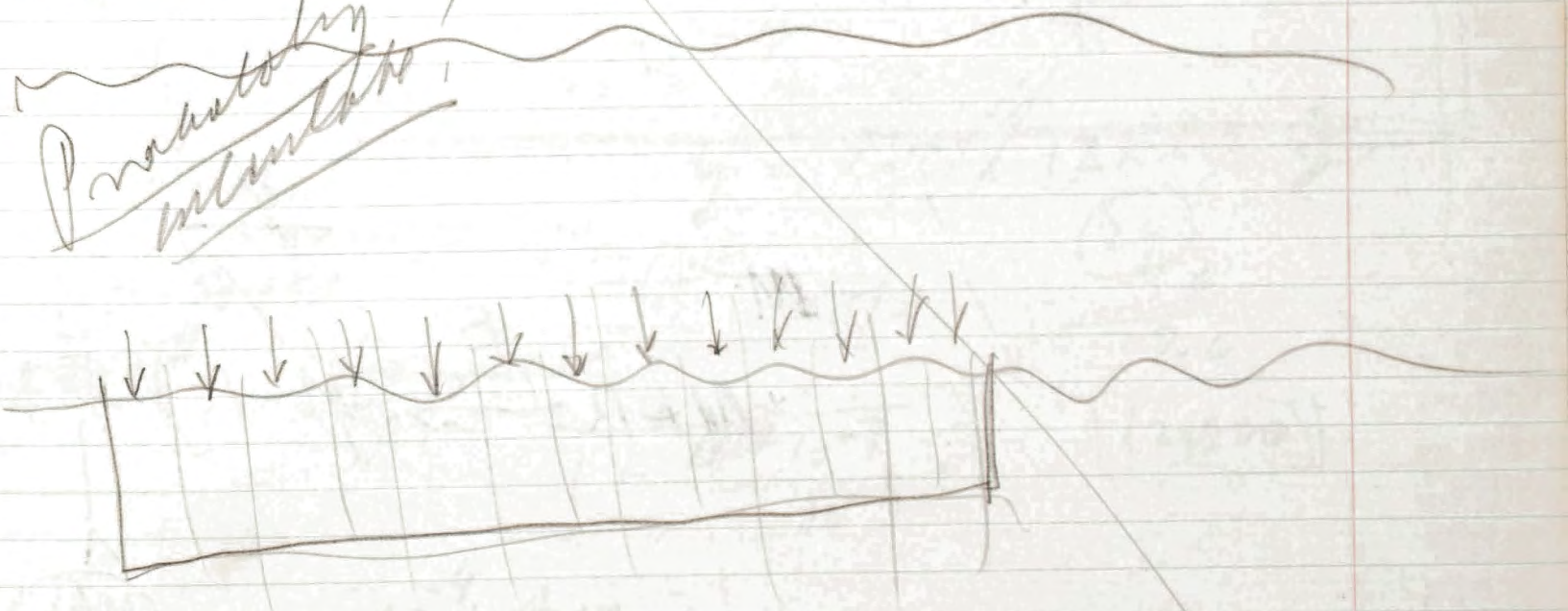
E(C) very important

$$\frac{\text{Vector}}{K} = \text{rep}$$

$$K_{\text{rep}}$$

If means AA one to one put on. If we get large increase rep when granite is other. No!

Probability?



M $\xrightarrow{E_1}$ M(1)

(M+1) E_n

(M-1) E_{n-1} → M(n)

will be transient

E_{n+1} will not be

$M^+(n)$

rep(n+1) low

rep(n) low

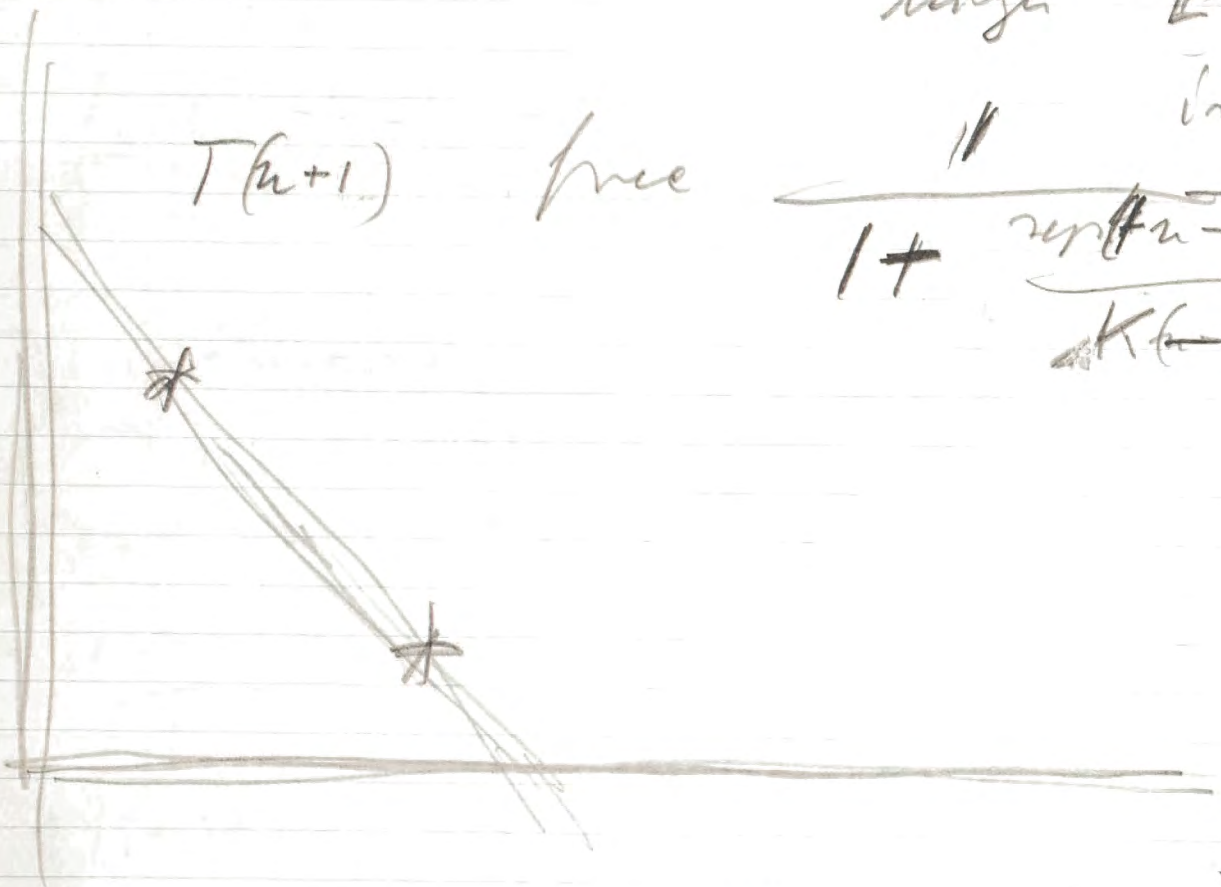
rep(n-1) high

low

rep(n-1) high

E_{n+1} must be induced

$T(n+1)$ free $\dfrac{\text{rep}(n-1)}{1 + \dfrac{\text{rep}(n-1)}{K(n-1)}}$



into polymers

M

$M+R \xrightarrow{E_0} \{M-R\} \xrightarrow{E_1}$

M(1)

is induced by E_2

How hot is an enzyme molecule

10^{14} molecules/cc

100 J/L

$10^{14} \times 10^{5}$ 10^{-16} 10^{1}

1/1000 sec

n boxes after x sec probab $\frac{1}{1000}$

10^{-12}

$\left(\frac{2}{1000}\right)$ α = Probab to evaporate $\times \frac{1}{2}$

prob of evap e^{-x}

prob of not evap $1 - e^{-x} = 1 - e^{\frac{-t}{1000}}$

$\left(1 - e^{\frac{-t}{1000}}\right)^{100} = \frac{1}{e}$

10 sec

1 sec better 1000 J/L

of 1 out of 100 evaporates then trouble

life time $10^{12} e^{-y} = \tau$

$y = \log \tau \times 12 \times 2.3$

24

3.6

27.6

10^{-6} molar

100 gm wt/lit 10^{-4} amp/cm 100 J/L

100 boxes

$K = 10^{-11}$

$\frac{1}{1 + \frac{10^{-7}}{10^{-11}}}$

12,000

10^{-4} is sec

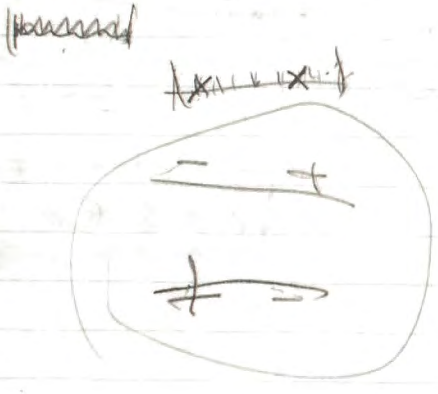
Bence Jones Proteins (Milk)

10% of serum / γ fraction / multiple myelomatosis
in stead of 1/2 to 2% in normal urine

Type + 10 gm Bence Jones excreted in 1/2 hour the urine / total excreted 10 to 15 gms)

2 5% excrete both + - Glob and Bence Jones.

1/2 excrete Bence Jones and 1/2 Gamma Glob.

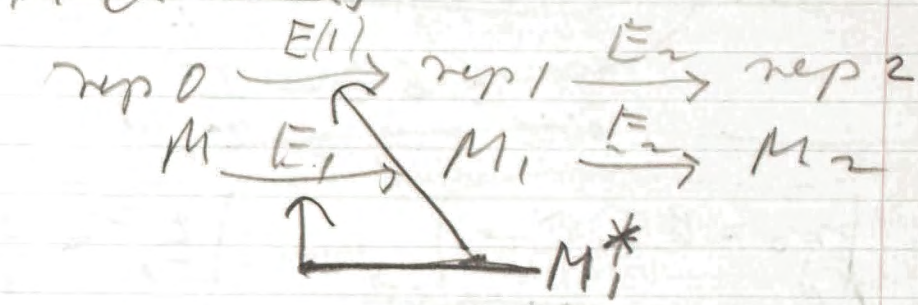


M(-3) → M-2 M-1 M

M + R —E→ {M-R} = rep(0)

~~rep(0) E(1) E(2)~~

rep(0)



M1 or M1* intimacy of E2

---

enhances rep(0) decreases rep(1)
gradually induces E1 also

Drug tolerance

~~tolerance~~ ~~pre metabolites~~
~~post metabolites~~

$$\frac{dE}{dt} = aT(1-p_1-q_1)\frac{1}{K+\frac{r}{K_1}} - \frac{E}{\tau_E}$$

t_0 :

$$E_0 = aT\tau_E\frac{K_1}{\tau_0}(1-p_1-q_1)$$

$$\frac{dr}{dt} = bE - \frac{r}{\tau_r}$$

$p_1 = 0.2 \quad q_1 = 0.1$

$$r_0 = bE_0\tau_r$$

$$E_1^2 = \frac{a}{b}\frac{\tau_E}{\tau_r}TK_1(1-p_1-q_1)$$

$$r_1^2 = ab\,T\tau_E\tau_r K_1(1-p_1-q_1)$$

$$\frac{r^2}{K^2} = \frac{abT}{K}$$

dt 毎に $E=0$, $\frac{dE}{dt}=0$

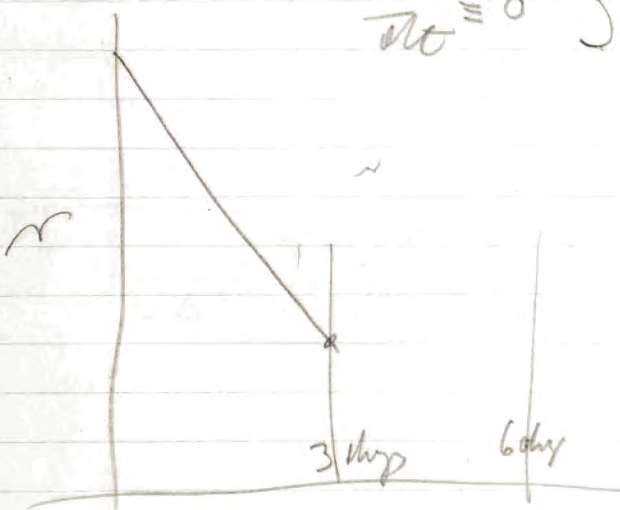
$\frac{r}{K}$

$\tau_E = 2$ day

$t_n = 1$ day

$\frac{r_1}{K_1} = 10^4$

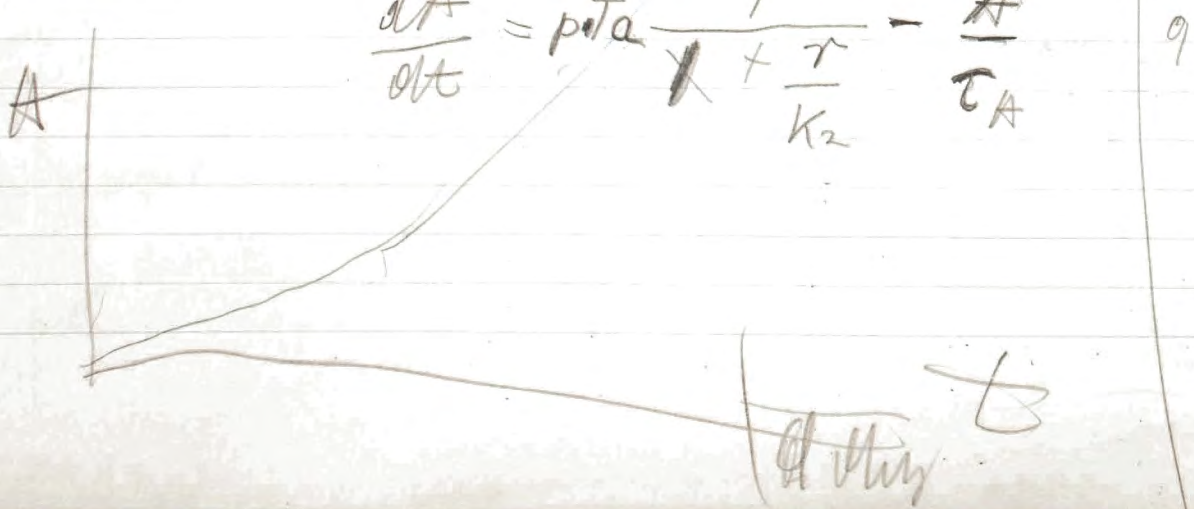
$\frac{r_1}{K_2} = 10^2$

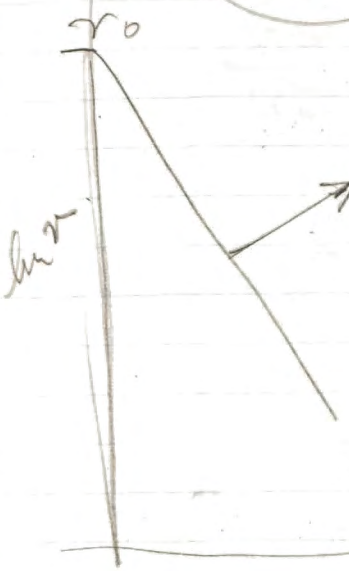


$$\frac{dA}{dt} = p_2Ta\frac{1}{K+\frac{r}{K_2}} - \frac{A}{\tau_A}$$

$p_2 = 0.2 + 0.7\times 0.2$

$q_2 = 0.1 + 0.7\times 0.1$





$$\frac{dE_m}{dt} = a \frac{T}{1 + \frac{r}{\kappa_{E_m}}} - \frac{E_m}{\tau_E}$$

$\frac{r_0}{\kappa_{E_m}} = 10^3$

loading

E_m

$rep(n-1) \xrightarrow{E(n-1)} rep(n) \xrightarrow{E_m} rep(n+1)$

$M(n)$

$$\frac{dr}{dt} = b E - \frac{r}{\tau} \quad \text{loading}$$

$$r_0 = b E_0 \tau_r$$

$$E_0 = \frac{a \sqrt{k_e \tau_E}}{r_0}$$

$$1 + \frac{r}{\kappa_E} \approx \frac{r}{\kappa_E}$$

T is crucial temperature!

$$E_0^2 = \frac{a}{b} \frac{\tau_E}{\tau_r} k_e T$$

$$r_0^2 = a b \tau_r \tau_E k_e T$$

$E \to E_0$ when

E_0, r_0 at $t = 0$ || at $t = 0 + \Delta t$, $E \equiv 0$ now + falls

$$e_1 = \frac{E_1}{\beta \tau_E} \qquad e_2 = \frac{E_2}{\beta \tau_E}$$

~~$\alpha \times \beta \times E_1(0)$~~

$$E_1(0) = \beta \tau_E$$

$$x(0) = \alpha \beta \tau_E \tau_x$$

$$\frac{x(0)}{K} = 10^4$$

$$\left.\begin{aligned} \frac{de_1}{dt} &= \frac{1}{\tau_e} \frac{1}{1 + 10^4 e_2} - \frac{e_1}{\tau_e} \\ \frac{de_2}{dt} &= \frac{1}{\tau_e} \frac{1}{1 + 10^4 e_1} - \frac{e_2}{\tau_e} \end{aligned}\right\}$$

$t = 0 \quad e_1 = 1$
$\quad\quad e_2 = 0$

$\tau_e = 1$

$N \; e_2 = 1$

$N = 10^4$
$N = 10^6$

$$\frac{k_\infty}{\tau_4} = \beta_1 T \frac{1}{\frac{r_2}{r_0}\frac{r_0}{k_2}}$$

$$\frac{dx_1}{dt} = \alpha E_1 - \frac{x}{\tau_x} \qquad \tau \text{ small}$$

$$\frac{dy}{dt} = \alpha E_2 - \frac{x}{\tau_y} \qquad \tau_x = \tau_y$$

$$x = \alpha E_1 \tau_x$$

$$y = \alpha E_2 \tau_x$$

$$\frac{dE_2}{dt} = \frac{\beta}{1 + \frac{x}{k_x}} - \frac{E_2}{\tau_E} \qquad \tau_E >>> \tau_x$$

$$\frac{dE_1}{dt} = \frac{\beta}{1 + \frac{y}{k_y}} - \frac{E_1}{\tau_E} \qquad k_x = k_y$$

$$\frac{dE_1}{dt} = \frac{\beta}{1 + \frac{\alpha \tau_x E_2}{k}} - \frac{E_1}{\tau_E}$$

$$\frac{dE_2}{dt} = \frac{\beta}{1 + \frac{\alpha \tau_x E_1}{k}} - \frac{E_2}{\tau_E}$$

$E_2 = 0$ $\quad E_1 = \beta \tau_E$ $\quad \frac{\alpha \tau_x E_1(0)}{k} = 10^4$

$t = 0$

$$Ne_2 = \frac{1}{e_1} - \frac{e}{e_1} = 1$$

$$\boxed{1 - e^{-t} = e_1}$$

$$\frac{de_1}{dt} = \frac{1}{1 + \frac{1}{e_1}\{1 - e^{-t}\}} - e_1$$

$$\frac{e_1}{e_1 + 1 - e^{-t}} - e_1$$

$$\boxed{e_1 = 1 - \frac{1}{N} - \frac{1}{N}}$$

$$\frac{1}{N} - e_2 e$$

$$e_1 = 1 - \frac{1}{N}$$

$$\frac{1}{1 + N - 1}$$

$$-\dot{y} = -\frac{1}{Ne_1} e^{-t}$$

$$-\dot{y} = +y = \frac{1}{Ne_1}$$

$$\frac{1}{N} - e_2 e_1 = \frac{1}{N} e^{-t}$$

$$1 - (Ne_2) e_1 - e^{-t}$$

$$\frac{1}{1} \quad \frac{1 - \frac{1}{N}}{}$$

$$\boxed{\frac{1}{N} = e^{-\tau}}$$

$$\frac{1}{N} - e_1 = \frac{1}{N} e^{-\tau}$$

$$\frac{1}{N} - N + \frac{1}{N} = \frac{1}{N} e^{-\tau}$$

$$-y + \frac{1}{Ne}$$

$$\frac{1}{e_1} - Ne_2 = \frac{1}{e_1} e^{-t}$$

$$1 - (Ne_2)\left(1 - \frac{1}{N}\right) = \frac{N}{N-1} e^{-\tau}$$

$$1 - 1 + \frac{1}{N} = \frac{N}{N-1} e^{-\tau}$$

$$\frac{1}{N}$$

$$\frac{1}{1+10^4 e_2} = -\alpha e^{-\alpha t} + e^{-\alpha t}$$

$$(1-\alpha)\, e^{-\alpha t}$$

$$e_1 \sim e^{\alpha t}$$

$$\frac{1}{1-\alpha} e^{\alpha t} = 1 + 10^4 e_2$$

$$10^{-4}\left(\frac{1}{1-\alpha} e^{\alpha t} - 1\right) = e_2$$

analyses
ring theory
of networks

e_2

$$\frac{de_1}{dt} = \frac{1}{1+Pe_2} - e_1$$

$$\frac{de_2}{dt} = \frac{1}{1+Ne_1} - e_2 \approx \frac{1}{Ne_1} - e_2$$

$$\frac{dy}{dt} = \text{Const} - y$$

$$\frac{N-P}{N}$$

$$e^{-t}\left\{\frac{1}{Ne_1} - \left\{\frac{1}{Ne_1} + \frac{1}{Ne_1} e^{-t}\right\}\right.$$

$$-e^{-t} = -e^{-t}$$

$$e_2 \to \frac{1}{Ne_1}$$

$$c - y = \eta$$

$$\eta = c - y$$

$$-\frac{d\eta}{dt} = \eta$$

$$\eta = \eta_0 e^{-t}$$

$$\frac{c}{Ne_1} - y = \text{Const}\, e^{-t}$$

$$e_2 = \frac{1}{Ne_1} - \frac{1}{Ne_1} e^{-t}$$

$$\frac{1}{Ne_1} - y = \frac{1}{Ne_1} e^{-t}$$

$1 - \frac{N}{P} e_1 = e^{-t}$

$P \gg N$

$\tau = \log \frac{1}{1 - N/P}$

$\tau = \log\left(1 + \frac{N}{P}\right) \approx \frac{N}{P}$

$t_{1/2} = \frac{N}{2P}$

$1 - \frac{N}{P} e_1 = e^{-t}$ $\qquad e_1 = (1 - e^{-t})$

$1 - \frac{N}{P} = e^{-t}$

Solution for $P \ll N$

$\left(1 \ll P \ll N\right)$

$\frac{de_2}{dt}_{t=0} \approx \frac{1}{1+Ne_1} - e_2$ $\qquad \boxed{e_2 = \frac{1}{1+Ne_1}}$

$\frac{1}{1+Pe_2} = e_1$

$\frac{1}{1 + \frac{P}{1+Ne_1}} = e_1$

$\frac{1+Ne_1}{1+Ne_1+P} = e_1 \cancel{(1+Ne_1)}$

$1 + Ne_1 = Ne_1^2 + Pe_1$

$\boxed{1 + (N-P)e_1 = Ne_1^2}$

Balance $\frac{N}{P} \gg 1$ $\quad P \gg 1$

$e_1 = \frac{N-P}{N}$

$e_2 = \frac{1}{N-P}$ $\quad n_T$

$$\frac{1}{Ne_1} - e_2 = \frac{1}{Ne_1} e^{-t}$$

$$1 - (Ne_2)\, e_1 = e^{-t}$$

4

$e_1 = 1 - \frac{1}{N} - \delta$

$Ne_2 = 1$ at $t =$

$\frac{1}{N} - e_2 e_1 = \frac{1}{N} e^{-t}$

$\frac{1}{N} - e_2\left(1 - \frac{1}{N} - \delta\right) = \frac{1}{N} e^{-t}$

$1 - Ne_2\left(1 - \frac{1}{N} - \delta\right) = e^{-t}$

if $Ne_2 = 1$

$$\frac{1}{N} + \delta = e^{-t}$$

$e^{-\tau}$ $\qquad$ $e^{-(t-\tau)}$

$\delta = e^{-(t-\tau)}$

$\ln \frac{1}{\delta} = \Delta t$

$\ln 10$

$\ln N = \tau_0$

$\ln \frac{1}{N}$

$-\log \frac{1}{N}$

$$e_1 = \frac{1}{2}$$

$1 - \frac{1}{2} = e^{-\tau_{1/2}}$

$\frac{1}{2}$

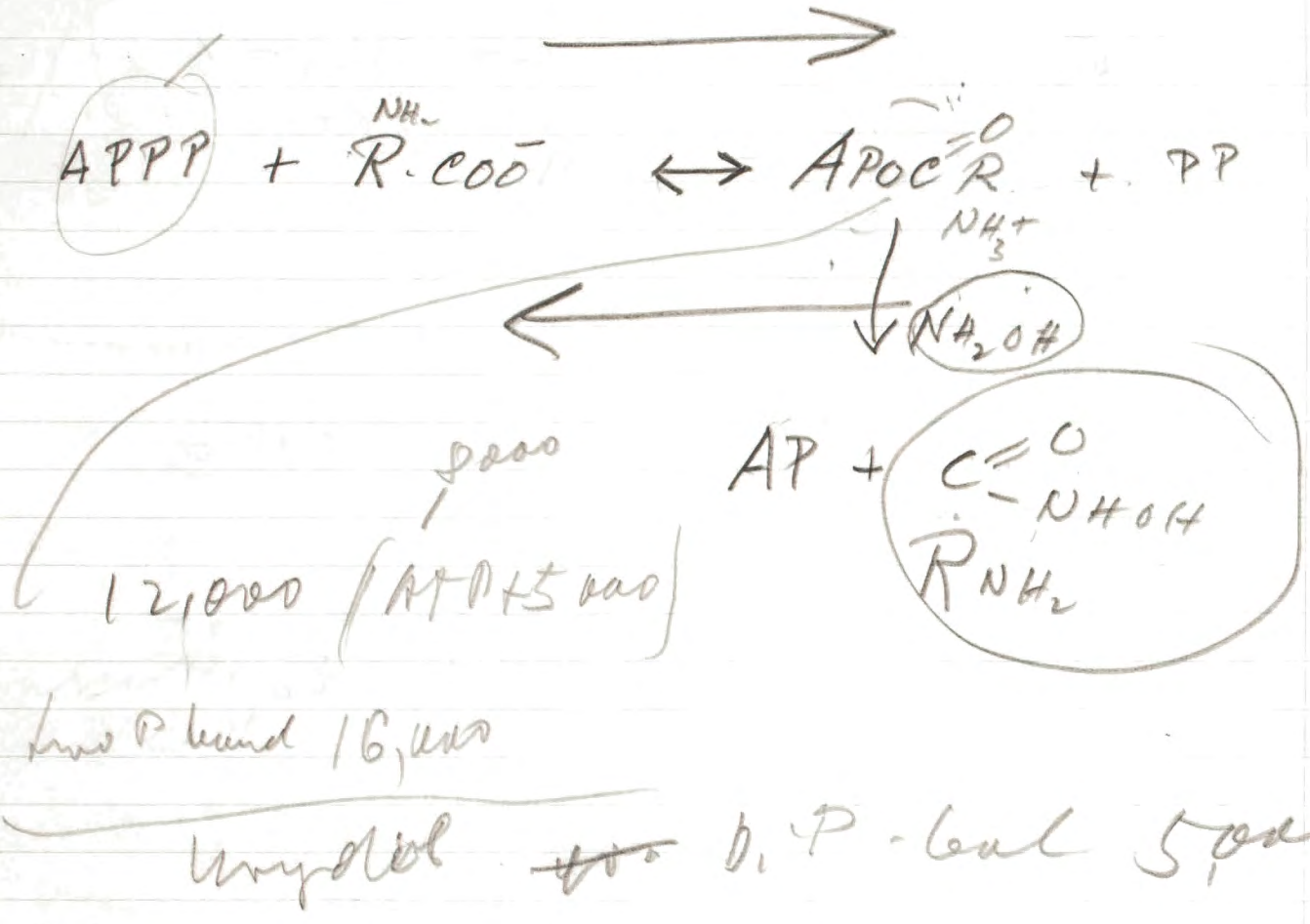
$$e_2 = \frac{1}{N_{1/2}} - \frac{1}{N_{1/2}} e^{-t}$$

$1 = 2 - 2e^{-t} = 2(1 - e^{-t})$

$\frac{1}{2} = 1 - e^{-t}$

Lipmann

13 Amino acids are activated



two P bond 16,000

Amyl Alc ~~to~~ D. P. bal 5,000

Novelli [~~extract~~ enzymes out of bacteria with simple adenine will AA support bacteria to grow them with AA administration. ——]

$1 - (N e_2) e_1 = e^{-t}$

$e_2 = \frac{1}{I}$

$e_1 = \varepsilon$

$1 - \frac{N}{I}\varepsilon = e^{-\tau}$

$\frac{N}{I}\varepsilon < 1$

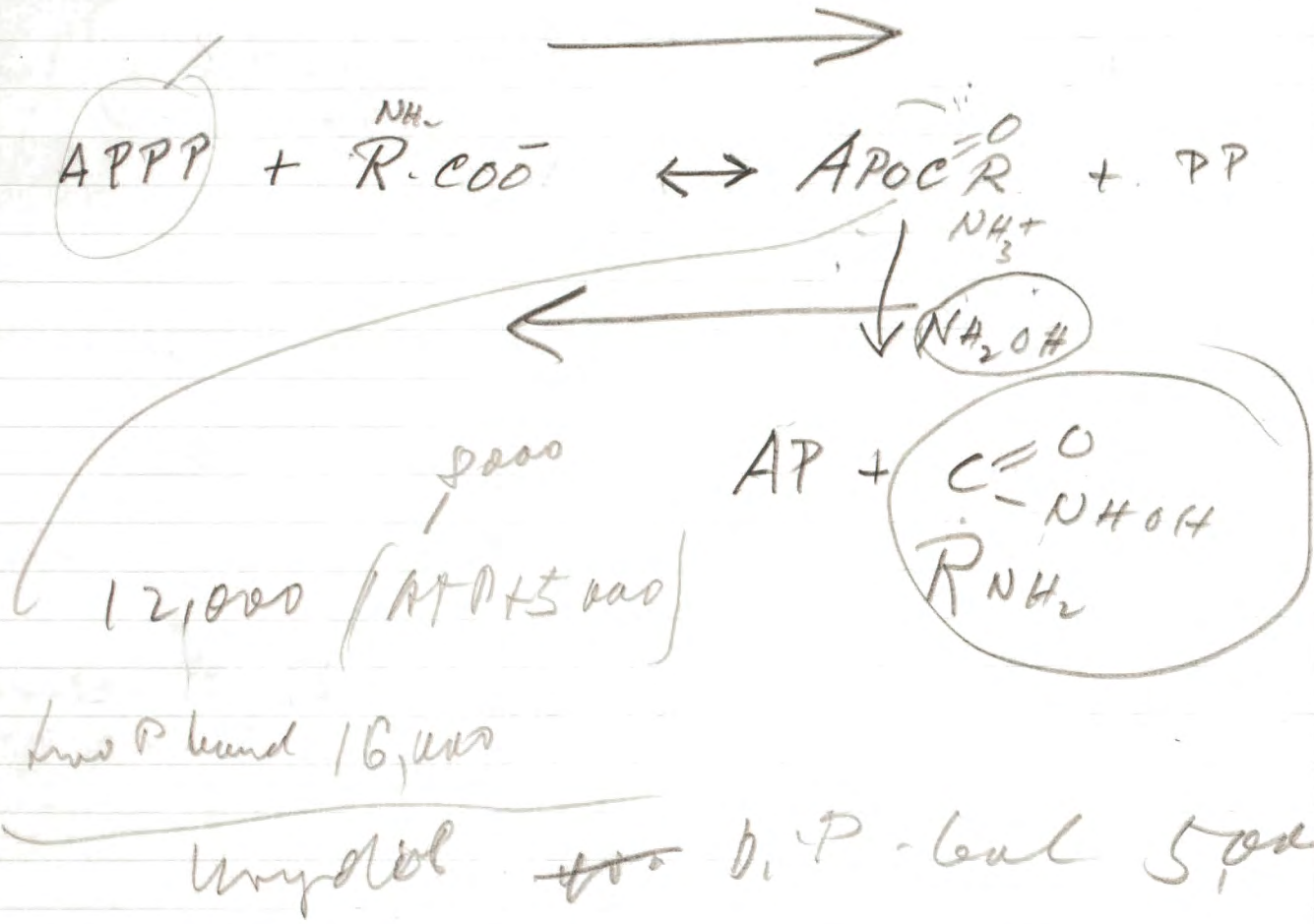
$\tau = \ln\left(\frac{1}{1 - \frac{N}{I}\varepsilon}\right)$

$\varepsilon = \frac{1}{10}$

$\frac{N}{I} = 2$

$\tau \sim \frac{N}{I}\varepsilon$ lifetime

Lipmann
13 Amino acids are activated



Novelli [~~activate~~ enzymes out of bacteria with enzyme adenine with AA support bacteria to grow them with AA administration. ——]

$1 - (N e_2) e_1 = e^{-t}$

$e_2 = \frac{1}{I}$

$e_1 = \varepsilon$

$1 - \frac{N}{I}\varepsilon = e^{-\tau}$

$\frac{N}{I}\varepsilon < 1$

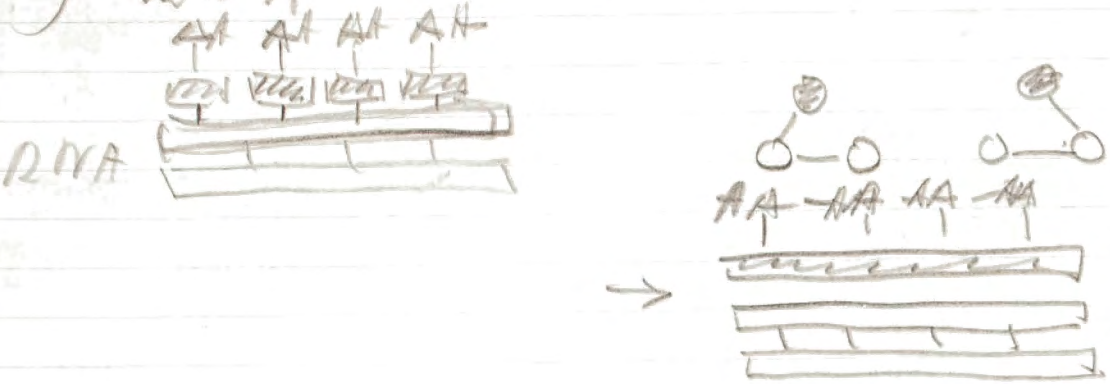
$\tau = \ln\left(\frac{1}{1 - \frac{N}{I}\varepsilon}\right)$

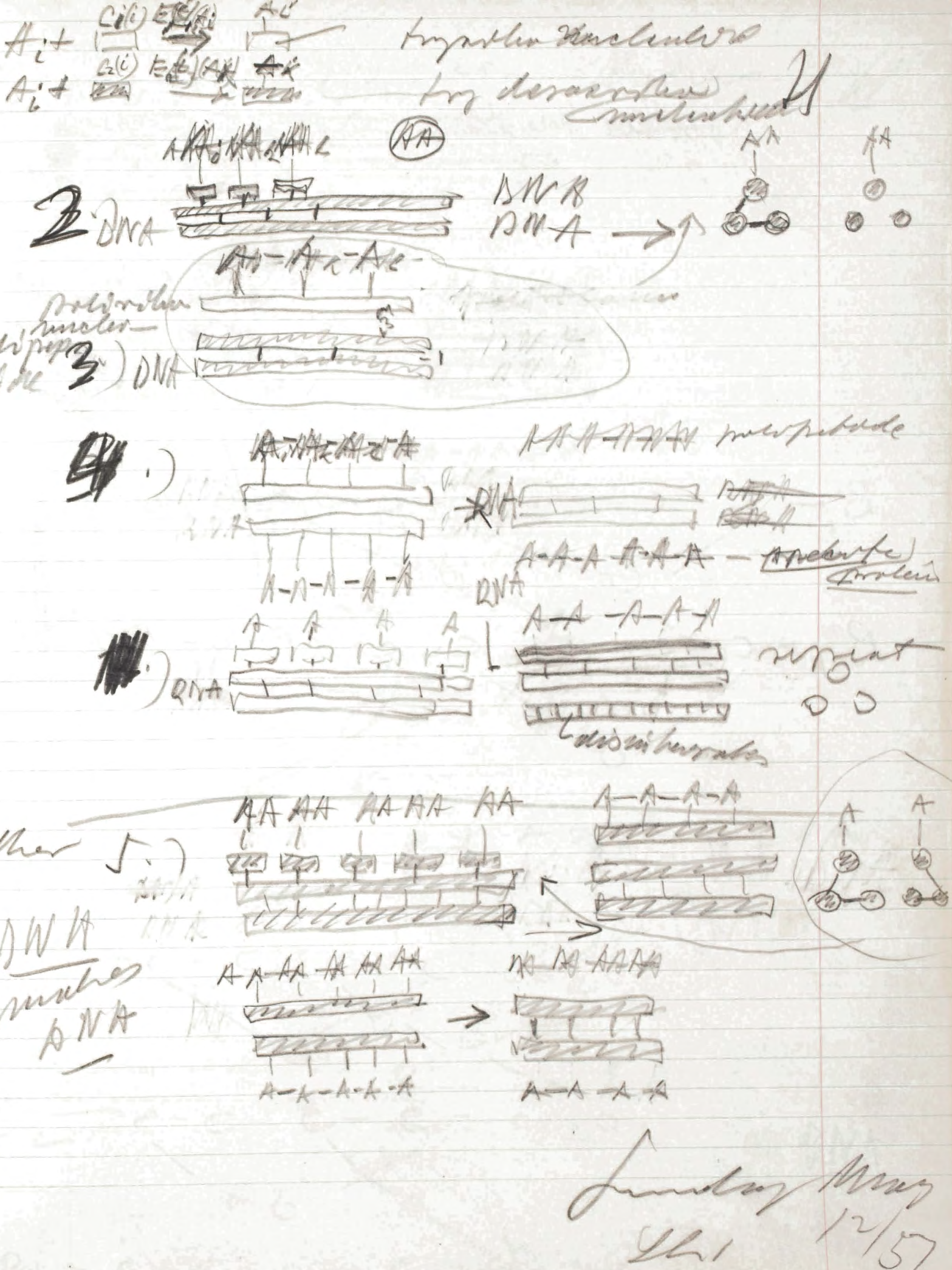
$\varepsilon = \frac{1}{10}$

$\frac{N}{I} = 2$

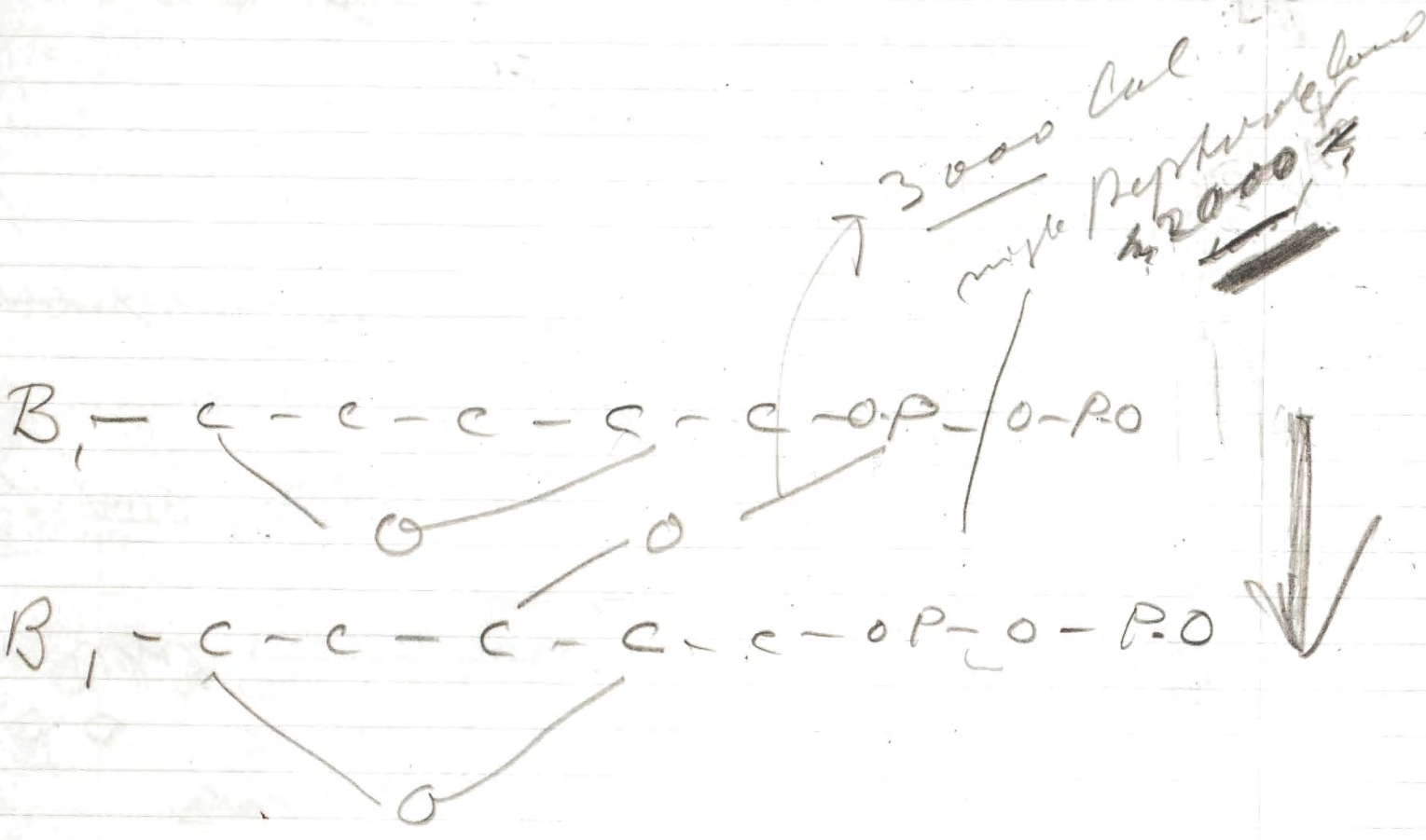
$\tau \sim \frac{N}{I}\varepsilon$ life time

or 6.) RNA makes DNA




DNA
DNA
DNA
DNA
DNA
DNA
DNA
DNA

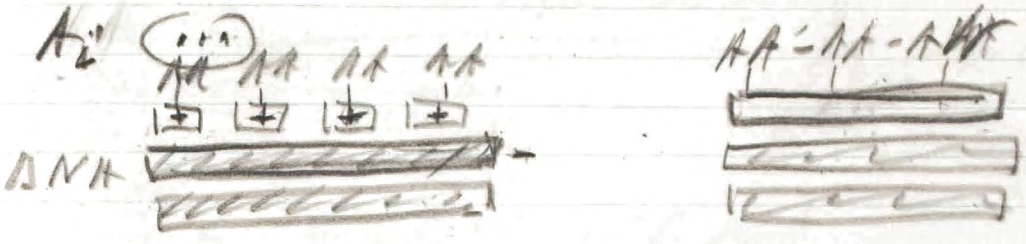
Ester bonds

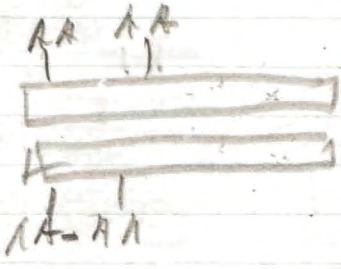


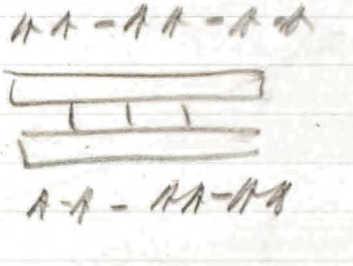
DNA ↑↑

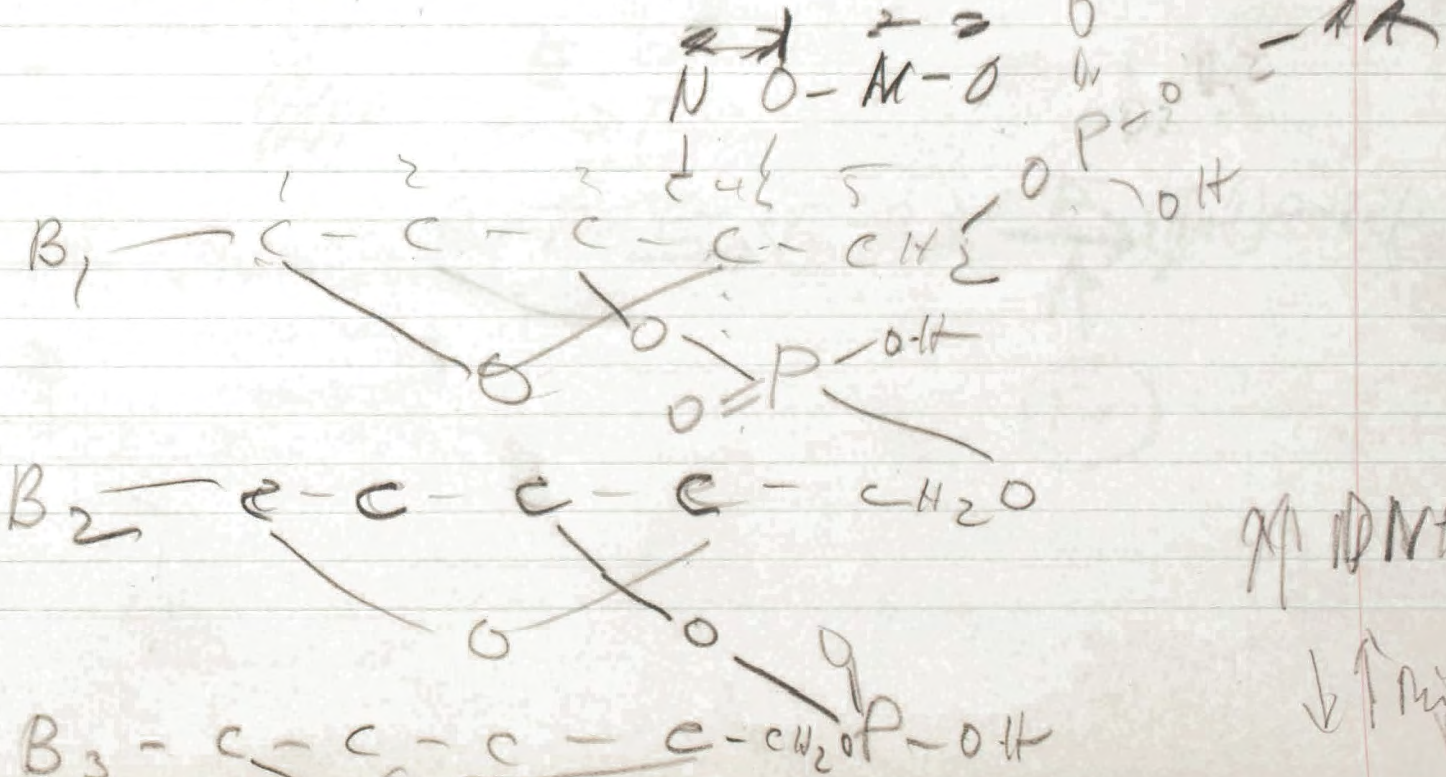
RNA ↓↑

I









Demand at least 1 A or 1 U

AUC

AUG

ACU

AGU

UAC

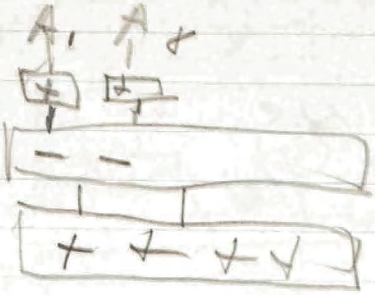
UAG

UCA

UGA

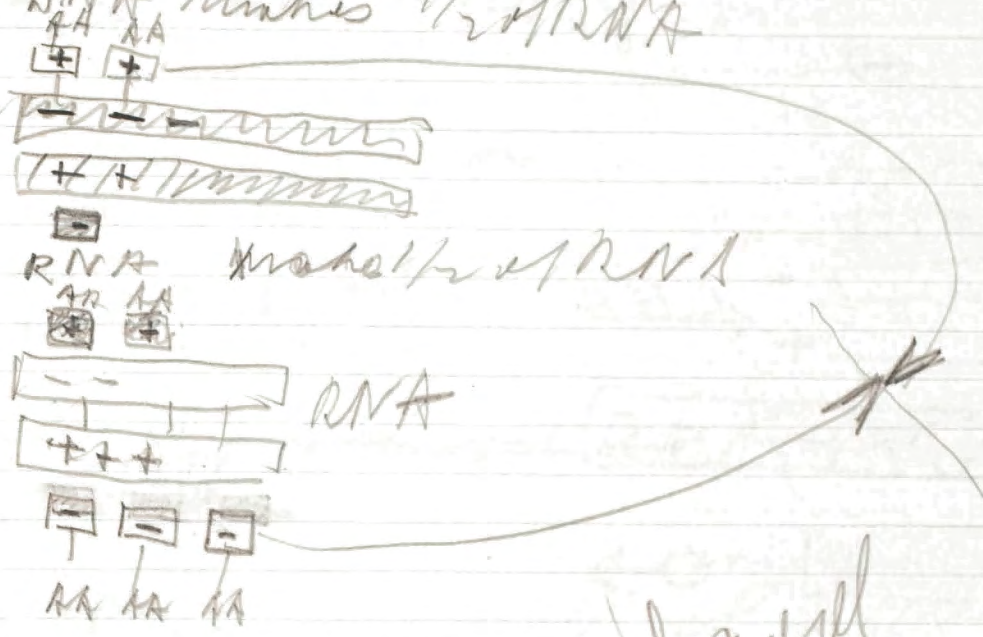
UUG

UAA



Protein and

DNA makes m-RNA



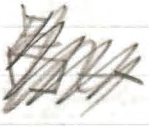
RNA makes RNA

RNA

C

Good

Starch



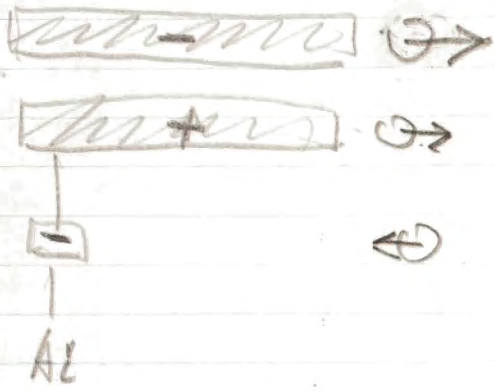
$\xrightarrow{E}$ T_n

$R + T_n \underline{E_0} \{T_n - R\} \xrightarrow{E_1} \{T_n(1)A - R\}$

T_n

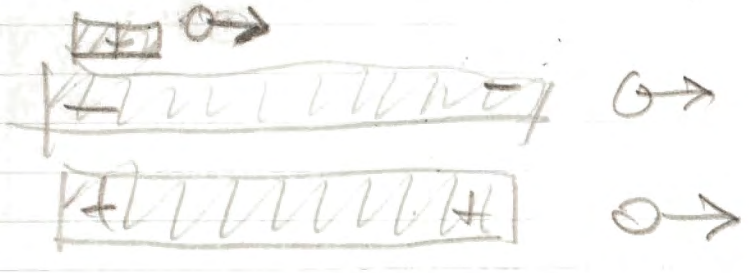
5) RNA makes ½ RNA

E_i^{**} (Ai, ribose −)



gives ½ RNA [−] ←

6.) DNA makes ½ DNA

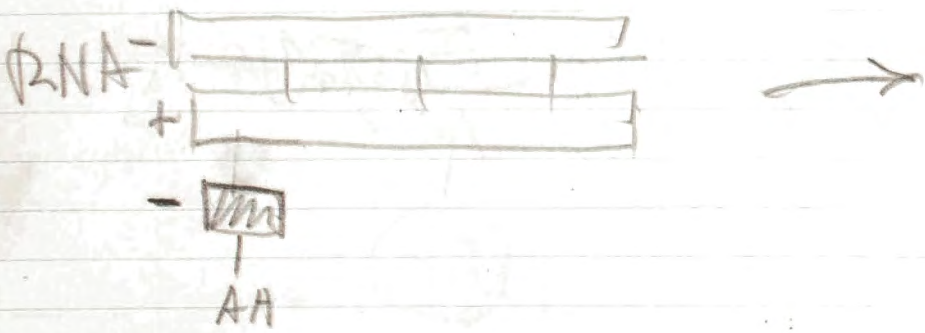


E_{AA}^{*} (AA, deoxyribose +)

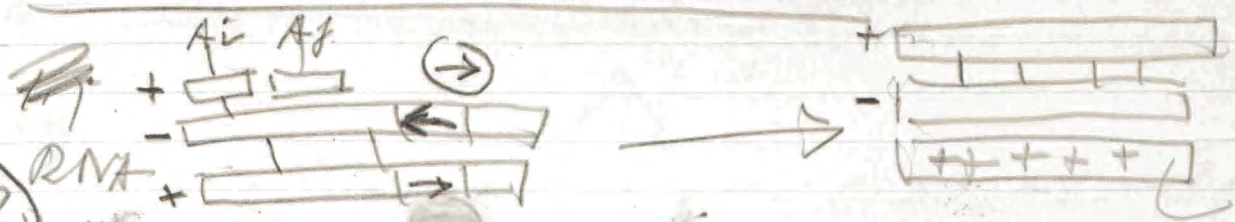
---

4 RNA makes ½ DNA

E_{AA}^{*} (AA, deoxiribose −)

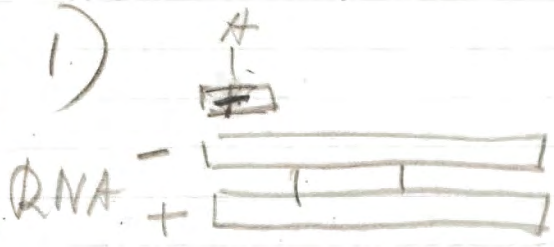


RNA makes Proteins A-A-A Prot

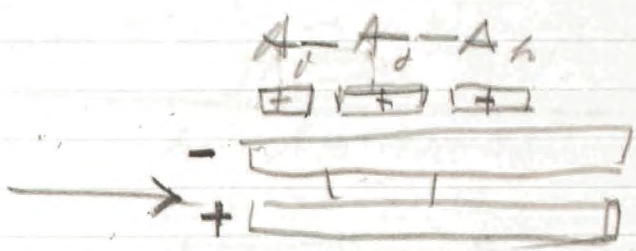


2.) E_i^*(Ai; + ; release +) E_j^*(Aj; + ; release +)

1.)

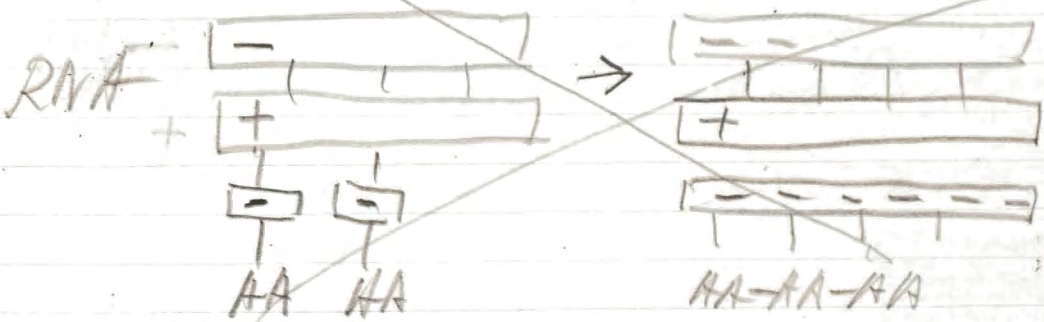


or



or 3.) ~~1/2 positions~~ RNA the positions

3.) RNA makes 1/2 of RNA



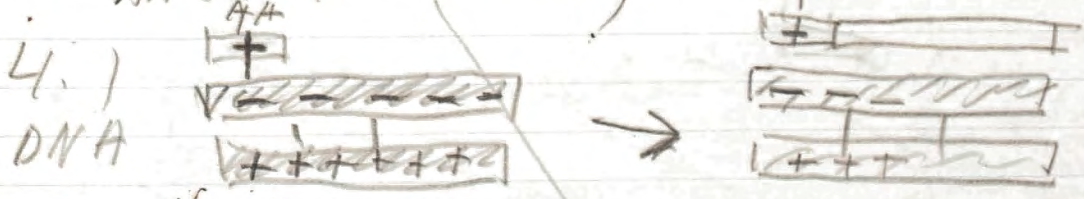
nucleoprot (RN release −)

~~E_{AA}^{**}(AA; release −)~~

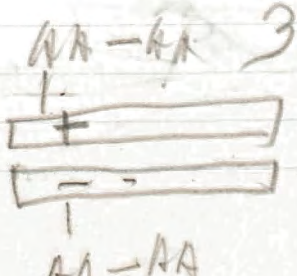
DNA makes 1/2 RNA

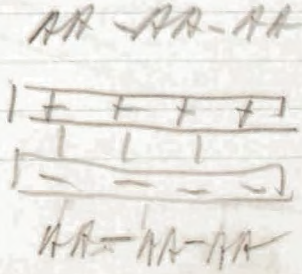
nucleoprot (release +)

4.)



3 and 4





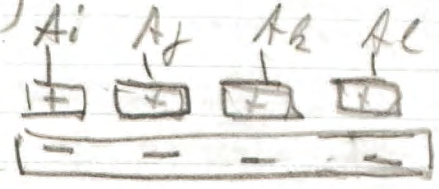
polypeptide

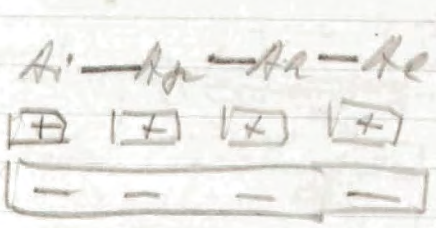
polypeptide

P.TO

~~5.) RNA makes ½ of D.N.A~~

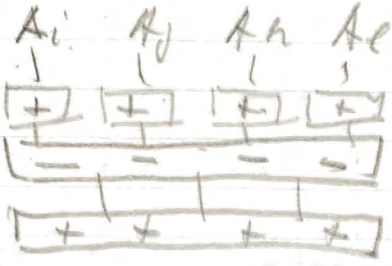
6.)

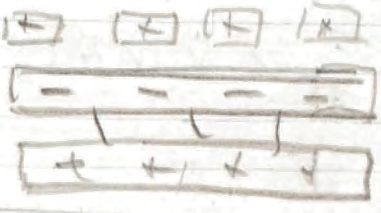




$E^*(A_i, \text{reverse} +)$ 20 amynes

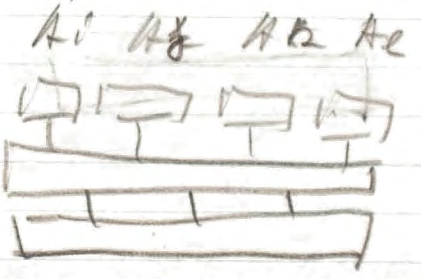
7.) or.)

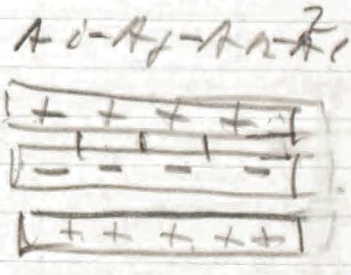




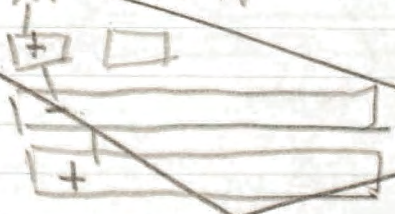
$E^*(A_i, \text{reverse} +)$.
RNA makes Proteins

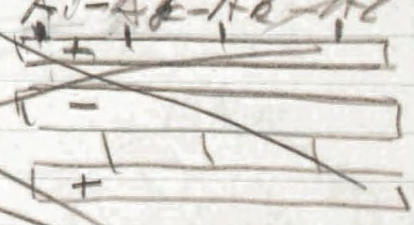
b.) RNA makes Protein turns over ½ RNA





c.) RNA makes ½ RNA (undesirable)





$\frac{1}{2}$ RNA(+) → $\frac{1}{2}$ RNA(−) → $\frac{1}{2}$ DNA(+)

$\frac{1}{2}$ DNA(+) → $\frac{1}{2}$ DNA(−) → $\frac{1}{2}$ RNA +

chemy enzymatic levels by mutation

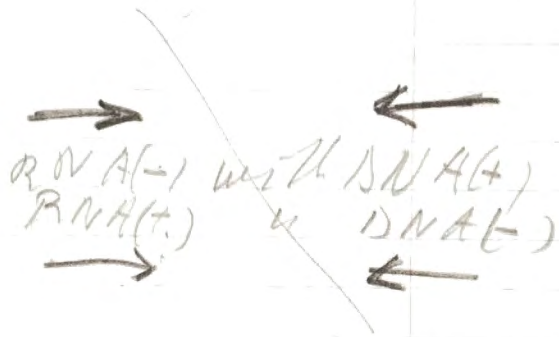
↑ Prepenetic

RNA(+) → RNA(−)

RNA(−) → DNA(+)

DNA(+) → DNA(−)

DNA(−) → RNA(+)

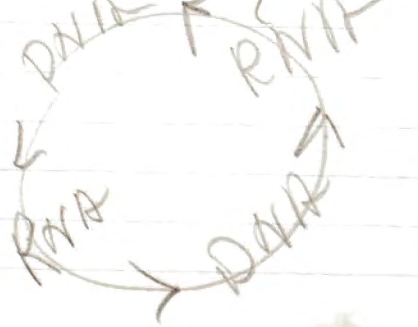


2 Alternatives:

$\frac{1}{2}$ RNA(−) → $\frac{1}{2}$ RNA(+) → $\frac{1}{2}$ RNA(−)

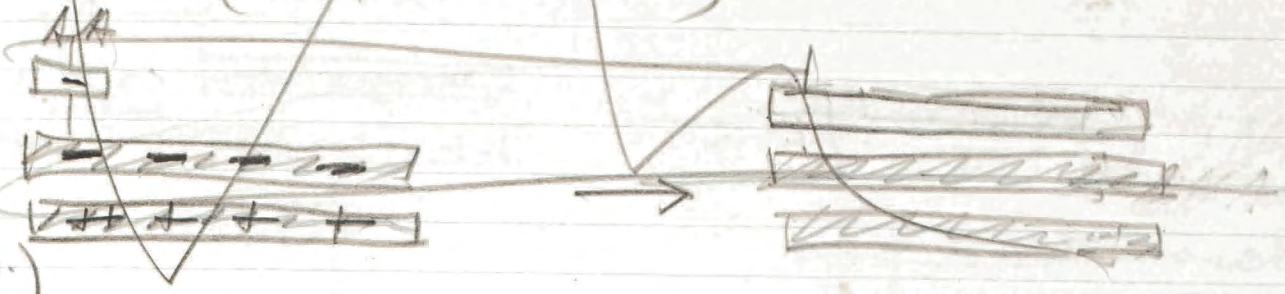
$\frac{1}{2}$ DNA(−) → $\frac{1}{2}$ DNA+ → $\frac{1}{2}$ RNA(−) → RNA Prot.

Chromosomes per RNA



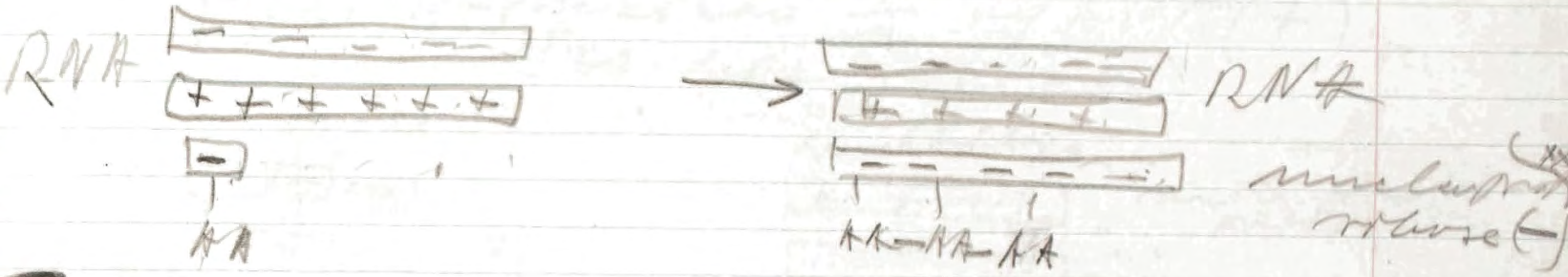
2) DNA makes ½ RNA (nucleoprot)

E(AA, ribose −)



½ RNA(+) makes ½ RNA(−) nucleoprot**

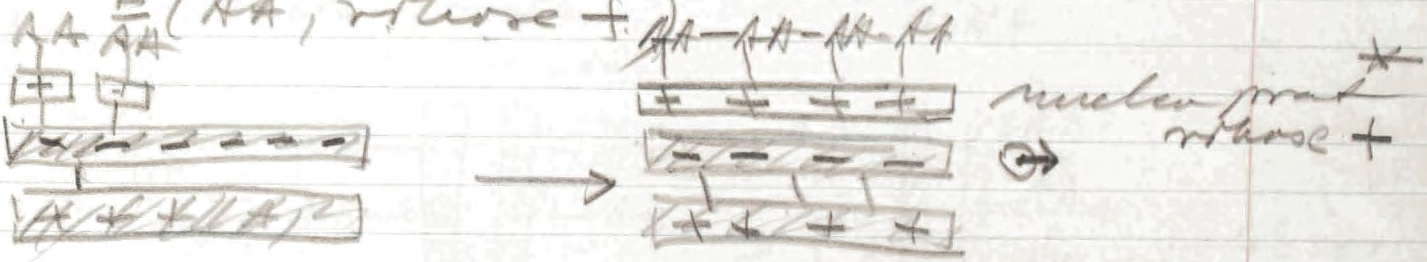
E**(AA ribose −)



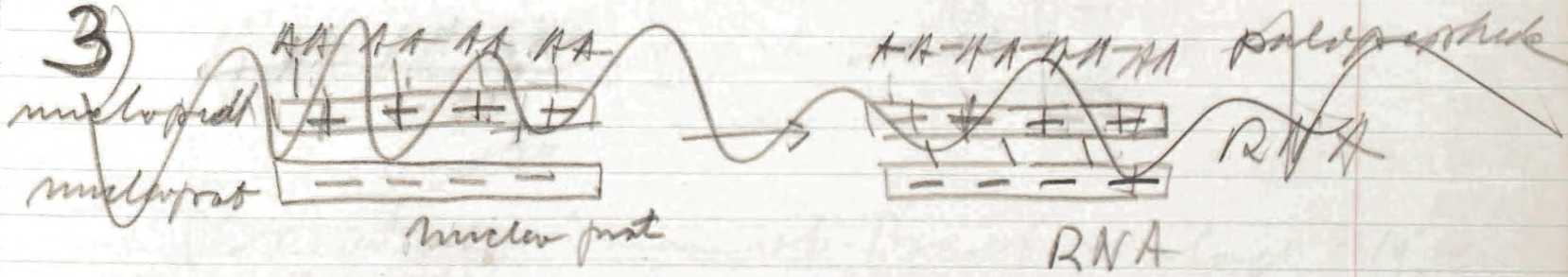
2

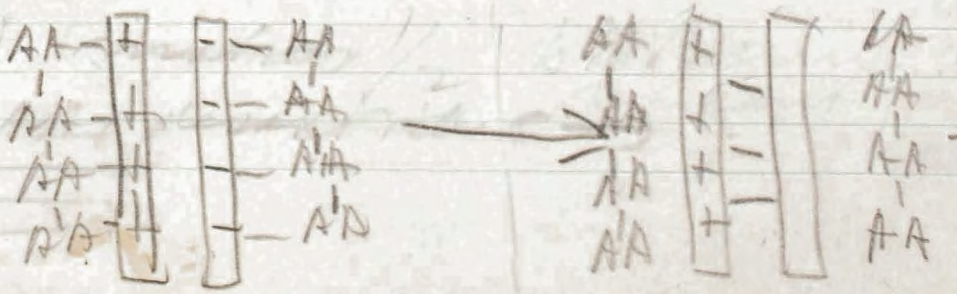
½ DNA(+) makes ½ RNA(+)

E*(AA, ribose +)

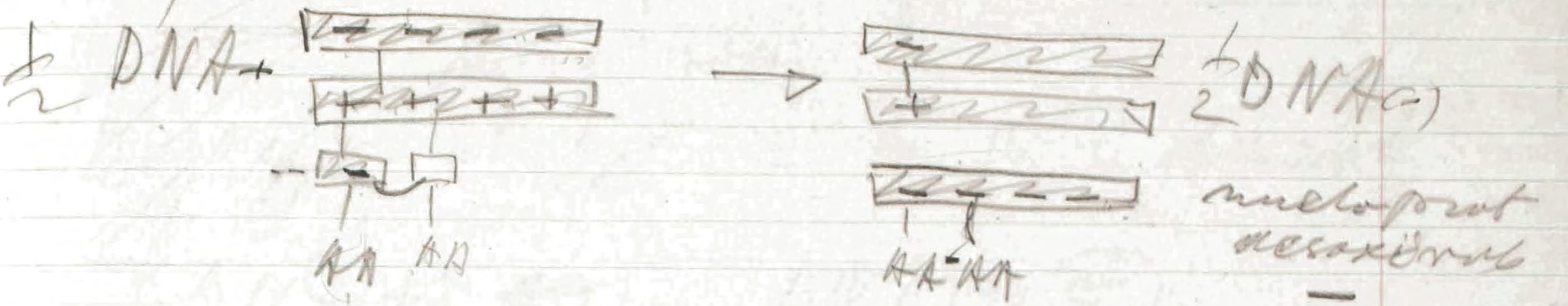


3)

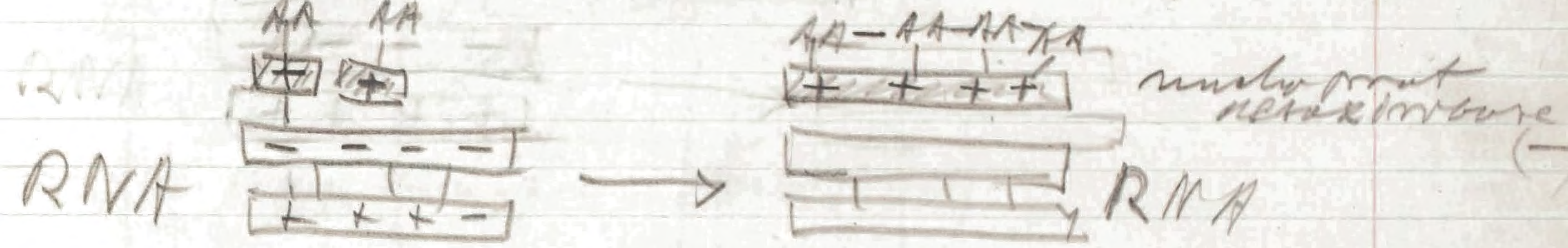




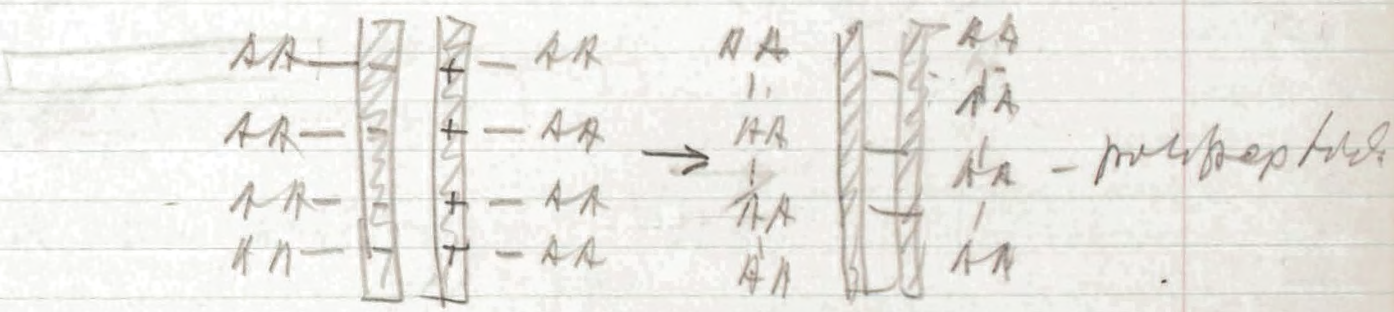
4.) ½ DNA(+) makes ½ of DNA (–)
E (AA, deoxyribose (–)) H



5.) ½ RNA(–) makes ½ of DNA(+)
E (AA deoxyribose +)

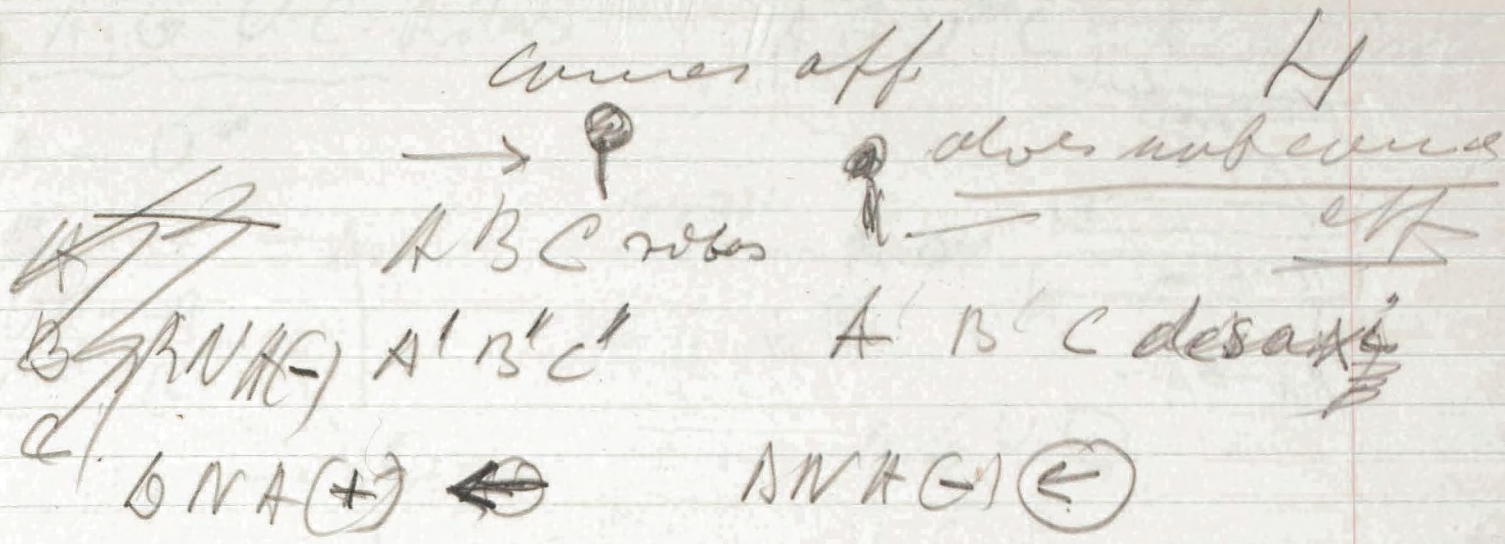


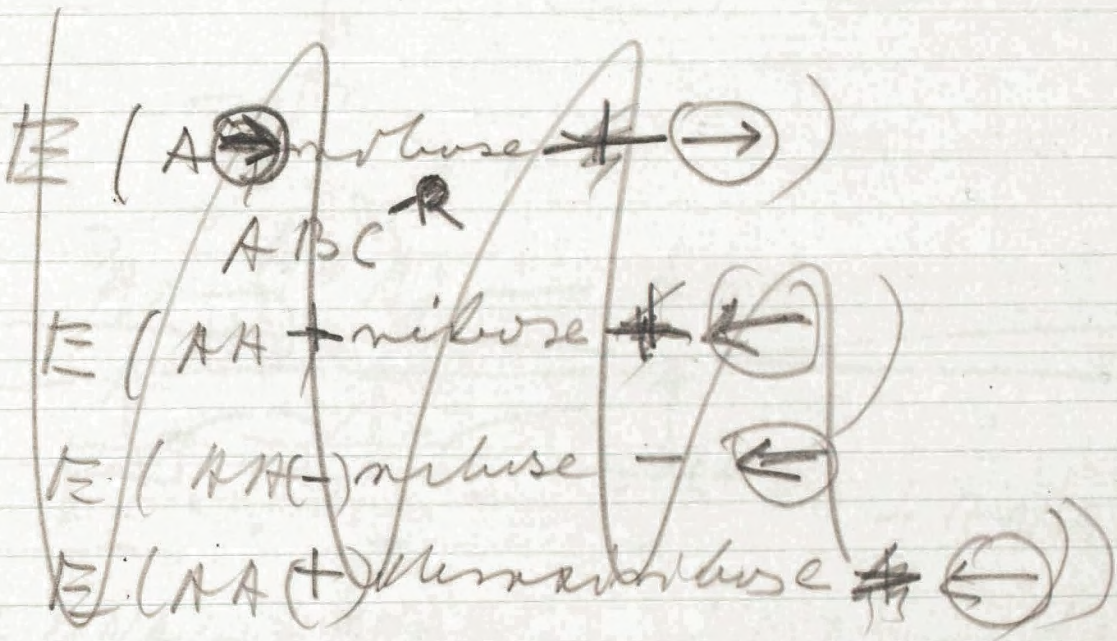
6.) nucleoproteins DNA



Brock: Journal of Bacteriology 1956
Salmonella (methionine requiring mutant)

1)





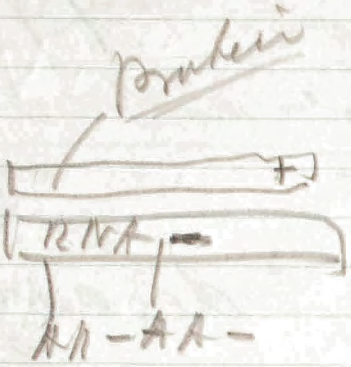
E(A nrhose+)

E(AA(←) nrhose+)

E(AA ← nrhose−)

E(AA ← desnrhose+)

E(AA ← desnrhose−)


Proteín
+
RNA
-
AA-AA-

A G U C Ribos A G U* C basoxinlase

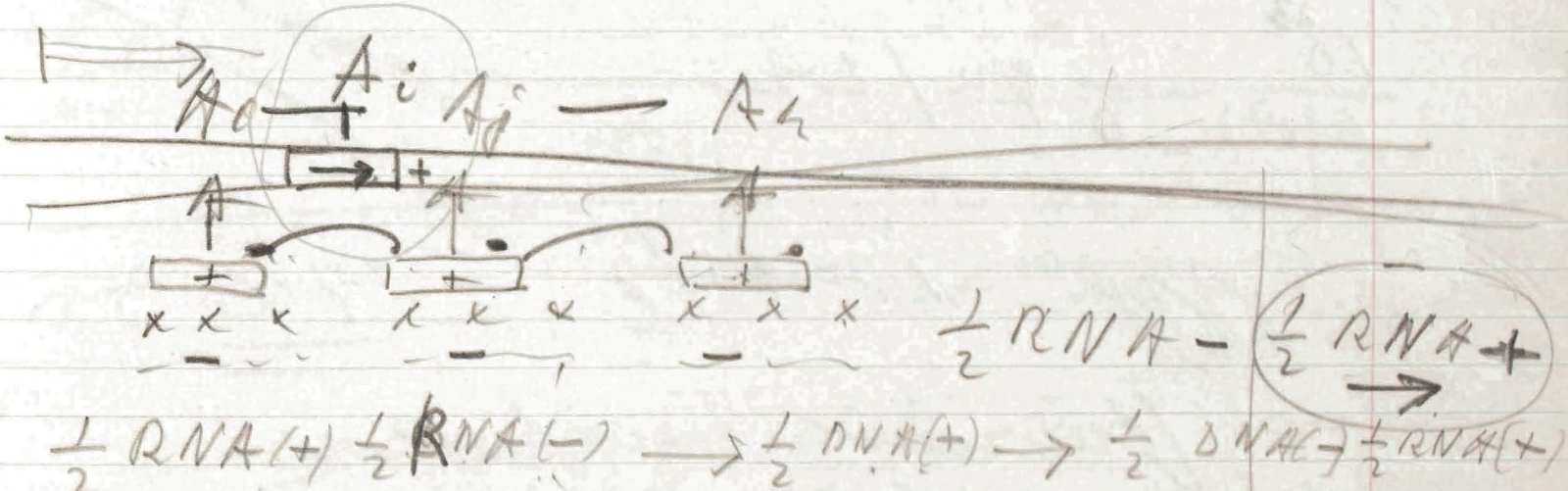
A – U*
C G – A
U* – A
C G

→ Hn

– Hn

AGG ⊕

A G U ⊖
U C A



½ RNA(+) ½ RNA(–) → ½ DNA(+) → ½ DNA(–) ½ RNA(+)

Encytoplasme

Here arrows
On DNA are
On opposite direction

$v = 10^4$ cm/sec

$N\ 10^4\ 10^{-16}\ 10^{-3} = \rho$

$N\ 10^{-15} = 1000$

$N = 10^{18}$ molecules

$\bar{t} = \frac{1}{10^{18}} \frac{1}{10}$

$r = \frac{m}{\epsilon}$

$r = 1000$

in terms of Avogadro's

10^{18} molecules/cc

10^{21} molecules (liter)

for 100 gm (Hg) molecular weight

$\frac{10^{23}}{6 10^{23}} = \frac{1}{6}$ gm/liter

~~$\frac{1}{600}$~~ ~~1~~ mgm/l 1%/l

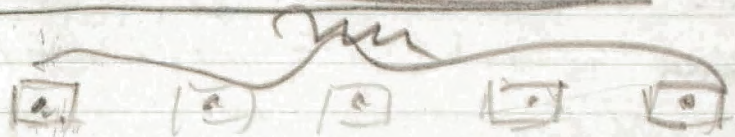
However molecular concentration can be much higher than AA conc.

Orders of magnitudes

10^4 molecules in 20 min | 1200 | (4)

enzymes

10 ~~molecules~~ /sec | 100 Amprindre



$\frac{1}{n}$ $e^{-\frac{1}{n}}$

$$\sum_{k=0}^{n} \frac{x^k}{k!} = e^x$$

$$P(k) = \frac{n^k}{k!} e^{-n}$$

$$\sum_{k=0}^{\infty} P(k) = 1 =$$

$r t = n$

$m e^{-rt}$ | $1 - m e^{-rt}$

$$W(t) = \frac{d}{dt}\left[1 - m e^{-rt}\right] = r m e^{-rt}$$

$$\bar{t} = \int_0^\infty r m t e^{-rt} dt = r m \frac{1}{r^2}$$

$$\int_0^\infty t e^{-rt} dt = -\frac{d}{dr} \int_0^\infty e^{-rt} dt =$$

$$= -\frac{d}{dr} \frac{1}{r} = \frac{1}{r^2}$$

$$\bar{t} = \frac{m}{r}$$

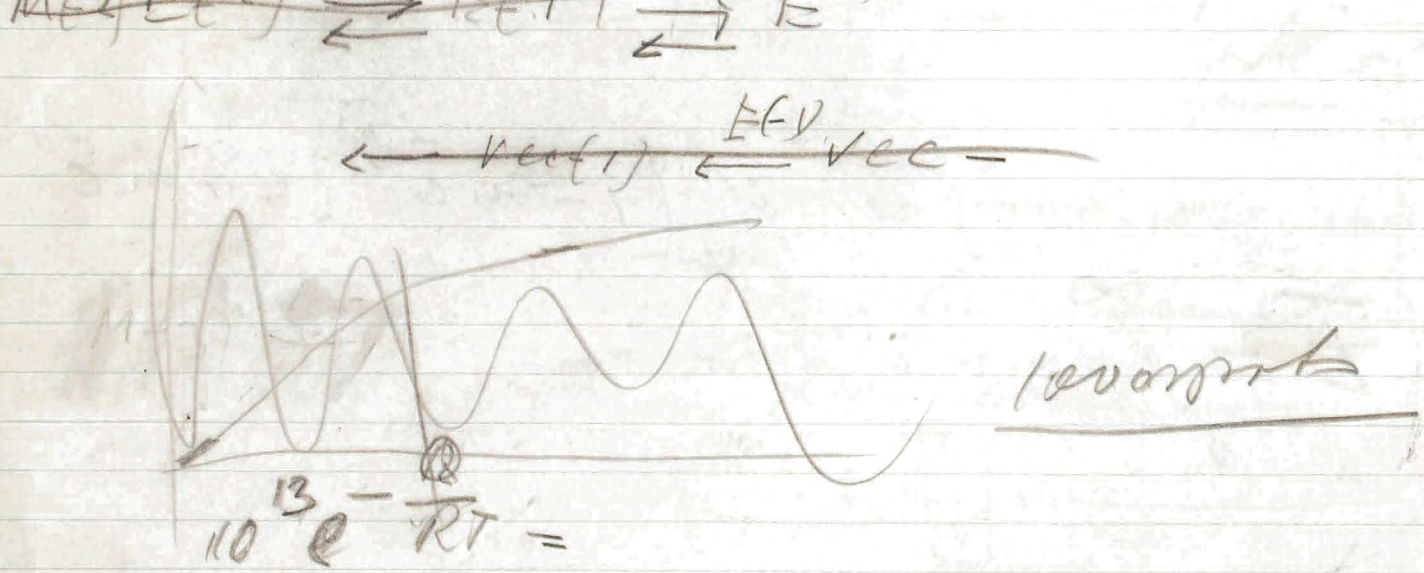
$\frac{1}{2}$ RNA(-) makes $\frac{1}{2}$ DNA+

$\frac{1}{2}$ DNA(+) makes and links with $\frac{1}{2}$ DNA− = DNA

DNA makes $\frac{1}{2}$ RNA(−)

Demand complementary code must not be identical with code

[A B a b] 1 2 3 4 = 24 give 12



RNA(+) →

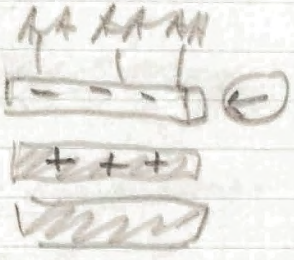
RNA(−)

RNA(−) → DNA(+) →

DNA(+) = DNA(−) DNA(+) =

RNA(−)-AA

RNA(−)-AA



DNA nuclei RNA(−)-AA

RNA-AA nuclei RNA(+) naked

+Protein

In the nucleus (in nucleus)

RNA(+) RNA(−)

AA-DNA(+) = DNA(−)-AA DNA(+) =

In the nucleus

DNA

In the cytoplasm

T dependence of Z production in collisions :—

N molecules
t_1 time it takes to assemble
t_2 " " " to evaporate if free
(1-f) fraction of those formed ~~that~~ survived

$$\frac{1}{\text{rate}} = t_1 + \frac{N}{\text{Const} f}$$

$$\text{rate} = \frac{\text{Const} f}{\text{Const} f t_1 + N}$$

dimensionless
$$[\text{Const}] = \left[\frac{1}{t}\right]$$

OK

Const $f t \gg N$

~~$t = A$ Const t~~

1000 places = m

$n = \frac{t^*}{\rho}$ average marking time for one place

$$e^{-\frac{t^*}{\rho}} = e^{-t}$$

probab that $m-1$ are holed ;
probab that 1 is empty not holed

$$m e^{-t} (1 - m e^{-t})^{m-1}$$

$$\int t \, m e^{-t} (m-1) m e^{-2t} \, dt \quad \frac{1}{2} \int t e^{-2t} \, dt$$

$$-m e^{-t} + 2(m-1) e^{-t} \qquad m -$$

$$\int 2t(m-1) e^{-2t} - t e^{-t} \, dt$$

$$m$$

Orders of magnitude

$\frac{1}{2} 10^{-12}$ cm Protein

Number of enzymes at 10000 a piece!

~~$\frac{1}{3} 10^{-12} \times 10^{-5} \times 6\,10^{23} = 2\,10^{6}$~~ enzymes molecules

or 10^4 genes = 200 molecules of enzyme

say 100

If 1000 genes have 1000 enzymes that leaves nothing or say 10 for the other 9000 genes

[1 gene could produce 10^5 molecules of enzyme per 30 min ≈ 2000 sec ~ $5\,10^2$ molecules/sec ~~10.~~]

~~Reading say $5\,10^3$ molecules of arginase/sec~~

~~In general however assuming 100 molecules of enzyme 5 Arginine per sec needed~~

~~or at most 50~~

In general assuming at most 1000 enzyme level

5 molecules of enz/sec

Assume lamps on $\frac{1}{10}$ sec

$$10^{13} e^{-\frac{Q}{RT}} = 10$$

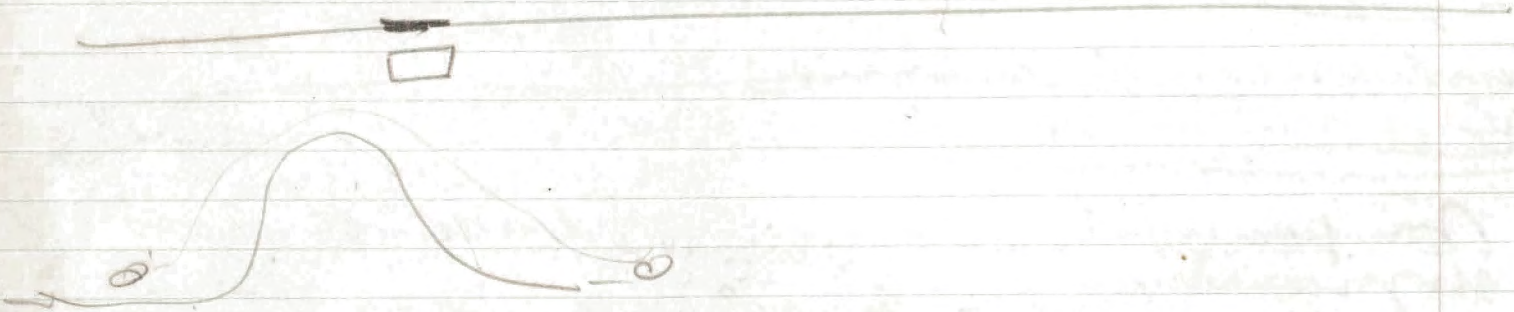
$$e^{-\frac{Q}{RT}} = 10^{-12}$$

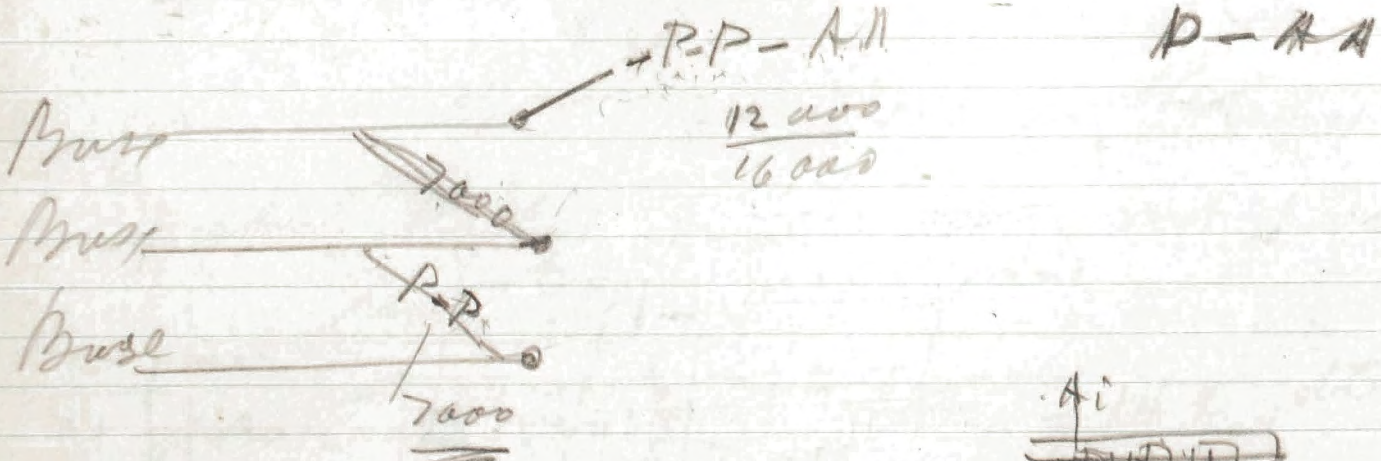
$$\frac{23}{46}$$

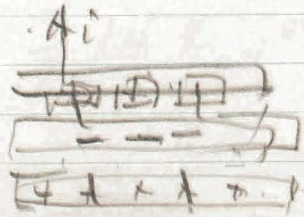
$$27.6 \times 600 \cong 12$$

$$\frac{48}{16,000}$$

7+7+9







$(1-e^{-t})^m = e^{-t}$ $\quad m = 1 - \frac{1}{m}$ (4)

$1 - e^{-\frac{1}{m}} = e^{-t}$

$1 + \frac{1}{m} = e^{t}$ $\quad 1 + t$

$t = \log m$ OK.

---

per unit/l mol weight 100

average time if they want — If they want

10^{-5} mol/or ~~6×10^{-10}~~ 10^{-8}/cc or 610^{-15} N/cc

$6\,10^{-15} \times 10^{-15} \times 10^{6} \left(10^{-3}\right) 1.37 \times 10^{4}$ cm/sec $= 100$ or $\frac{1}{100}$ sec

$\frac{m}{10}$ sec $\sim \frac{1}{10}$ sec $\quad$ 30 min $= 1800$

~~$\frac{1}{10}$~~ second letter

Problem If each hangs on for Δt. more than

if $m\, e^{-\frac{t}{\Delta t}}$ probab of 1 missing

probab of

Hangs on, assume $\frac{1}{10}$ sec

~~10^{-13}~~ $e^{-\frac{Q}{RT}} = 10^{-13}\, 10^{12}$

$2 \times 7 + 16$ $\quad \frac{23}{30000}$

$DNA^+ \rightarrow RNA(-) \rightarrow DNA+$

DNA^- makes RNA+ which makes DNA

2

30# 60 x 10 = 18,000

AA = 1000

Purine C

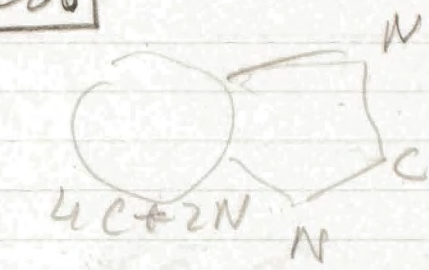
C_5N_5

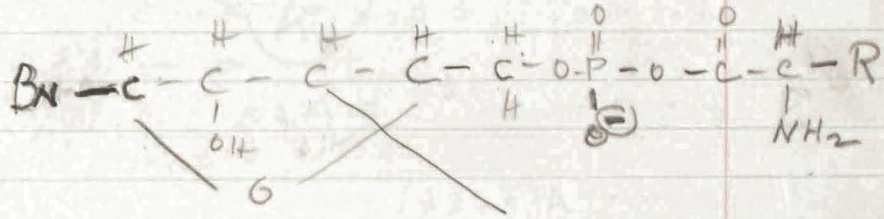
140

Pyrimidine

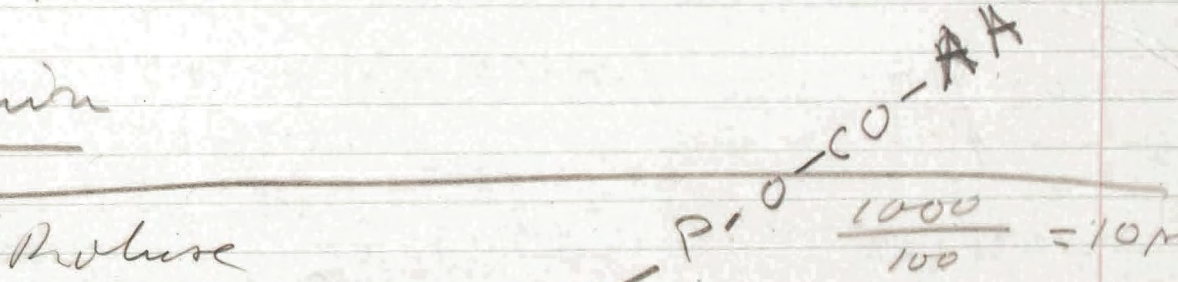
4C+3N

Polar 5C 50



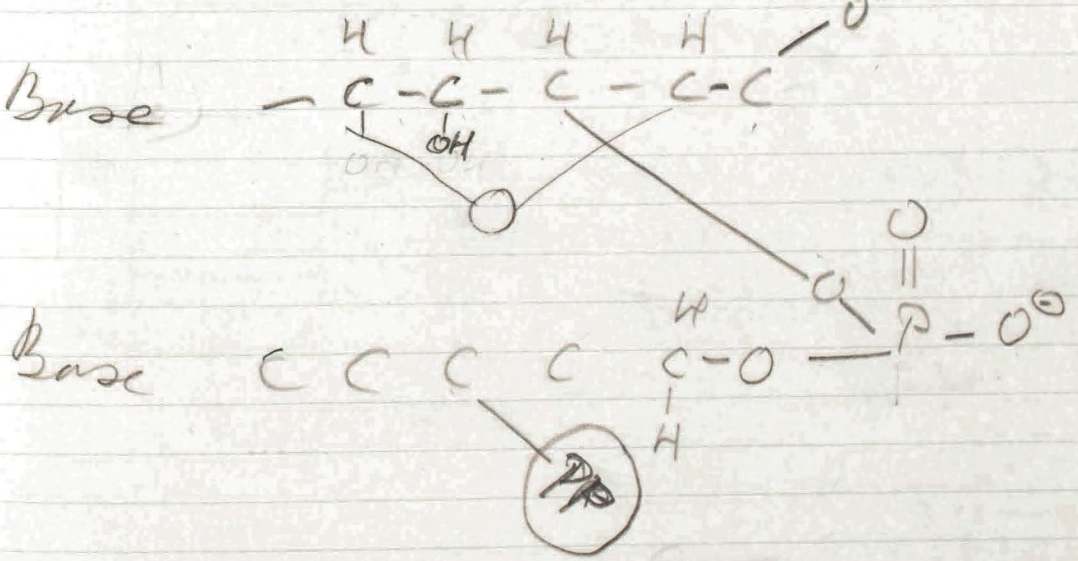


$\frac{1000}{10}$ | 2min



$\frac{1000}{100}$ = 10 pmole/min

Pentose



Tumbe

$$-a2Ake^{-2Akt} = Ap - 2Akae^{-2Akt} - 2Akb$$

$$b =$$

$\dot{m}$: $Ap(m - f(t))$

m: $2Akf$

$$\dot{f} = Apm - Apf - 2Akf$$

$$= Apm - Af(p - 2k)$$

$$f = ae^{-\lambda t} + b \qquad a = -b$$

$$\dot{f} = -\lambda a e^{-\lambda t} = Apm - A(p-2k)ae^{-\lambda t} - A(p-2k)b$$

$$\lambda = A(p-2k)$$

$$b = \frac{Apm}{A(p-2k)}$$

$$f = b\left(1 - e^{-A(p-2k)}\right) = \frac{pm}{\underbrace{p-2k}_{\sigma}}\left(1 - e^{-A(p-2k)t}\right)$$

$$m - 1 = \frac{pm}{p-2k}\left[1 - e^{-A(p-2k)t}\right]$$

$$\frac{2k}{p} \to 1$$

$$k = \frac{p}{2}$$

$$1 - \frac{1}{m} = \frac{1}{1 - \frac{2k}{p}}\left[1 - e^{-Ap\left(1-\frac{2k}{p}\right)T}\right]$$

$$1 - \frac{1}{m} - \frac{1}{1-\frac{2k}{p}} = -\frac{1}{1-\frac{2k}{p}} e^{-Ap\left(1-\frac{2k}{p}\right)T}$$

$$\left(1 - \frac{2k}{p}\right)\left(1 - \frac{1}{m}\right) - 1 = -e^{-Ap\left(1-\frac{2k}{p}\right)T}$$

$$\frac{1}{2} m\left(\overline{v_x^2} + \overline{v_y^2} + \overline{v_z^2}\right) = \frac{3}{2} kT$$

$$\frac{3}{2} m \overline{v_x^2} = \frac{3}{2} kT$$

$$\sqrt{\overline{v_x^2}} = \sqrt{\frac{kT}{m}}$$

$e^* = \frac{1}{2} e$

$q + s \rightleftharpoons qs \; a$

$n_a = \frac{1}{2} n_q$

$$\frac{n_q \cdot n_s}{n_a} = K$$

e

$$\frac{2 n_q}{n_q} = K$$

$$c\, e^* \rightleftharpoons [ec]\left(\frac{K_2}{K_1}\right) = k$$

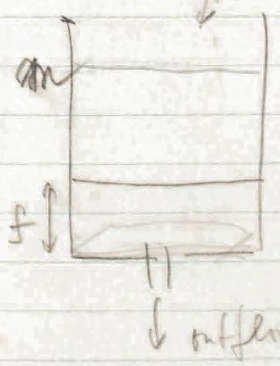
$$e^* + [ec] = e$$

$$(ec) = e - e^*$$

$$c e^* = (e - e^*) K$$

$$e^*(c + K) = e \qquad K = c$$

$$e^* = \frac{e}{c + K}$$



A_p = rate of flux

$\downarrow$ outflux $2AKf$

$$\int_0^T [A_p - 2AKf(t)]\,dt = f(t+dt) = f(t) + [A_p - 2AKf(t)]\,dt$$

$$f(t) + f'(t)\,dt$$

$$\frac{df(t)}{dt} = A_p - 2AKf$$

$$f = a e^{-2AKt} + b = a e^{-2AKt} - 1$$

$$0 = a + b \qquad b = a$$

$$f = a\left(e^{-2AKt} - 1\right)$$

$$\frac{df}{dt} = -2AKt\, a e^{-2AKt} - 2AK(f - 1)$$

$\frac{2k}{\rho} = \mu$ $\quad\therefore\quad \Delta T = \frac{\delta}{A\rho}$

$$1 - \frac{1}{m} = (1+\mu)\left(1 - e^{-A\rho(1-\mu)\left[\frac{1}{A\rho}\ln m + \frac{\delta}{A\rho}\right]}\right)$$

$$= (1+\mu)\left(1 - e^{-(1-\mu)\ln m - \delta}\right)$$

(a)

$$\varepsilon\left(1-\frac{1}{m}\right)-1=-e^{-A\rho\varepsilon T} \qquad 1-\varepsilon\left(1-\frac{1}{m}\right)>1$$

$$\ln\left[1-\varepsilon\left(1-\frac{1}{m}\right)\right]=A\rho\varepsilon T \qquad \varepsilon\left(1-\frac{1}{m}\right)<1$$

$$T=\frac{1}{A\rho\varepsilon}\ln\left[1-\varepsilon\left(1-\frac{1}{m}\right)\right] \qquad \left(1-\frac{2k}{\rho}\right)\left(1-\frac{1}{m}\right)<1$$

$$0<\left(1-\frac{2k}{\rho}\right)<1$$

$$\frac{\partial T}{\partial k}=\frac{\partial T}{\partial \varepsilon}\cdot\frac{\partial \varepsilon}{\partial k} \qquad \frac{2k}{\rho}<1$$

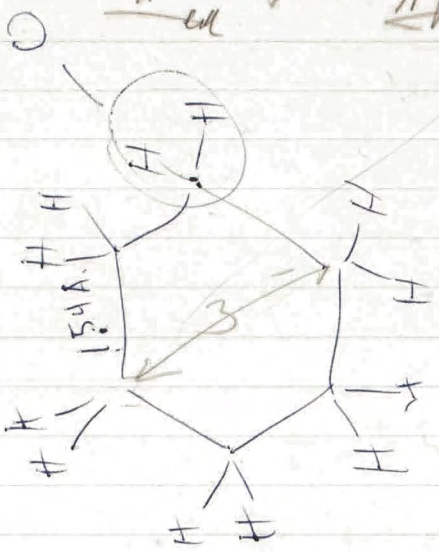
$$\frac{\partial \varepsilon}{\partial k}=-\frac{2}{\rho}$$

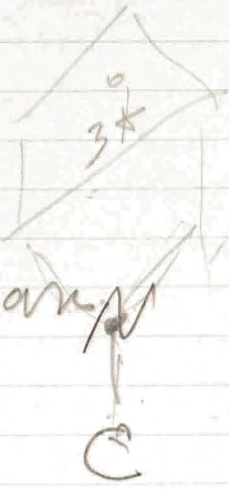
$$-\frac{2}{\rho}\left[-\frac{1}{A\rho\varepsilon^2}\ln[\ ]+\frac{1}{A\rho\varepsilon}\cdot\frac{1}{1-\varepsilon\left(1-\frac{1}{m}\right)}\cdot-\left(1-\frac{1}{m}\right)\right]<0$$

$$-\frac{1}{\varepsilon}\ln(1-\varepsilon)+\frac{1}{1-\varepsilon}=0$$

George W.
~~W.~~ Wheland

Resonance in
Organic Chemistry
1955 Appendix





Martin
Gantzermann
Platt
(12 June)

Enzyme Antigens of Virus

F. Macfarlane Burnet

(London Lancet Press 1956

Burnet (Ken) Biochemical Journal (Engel

lost to Jens.

Brach June 1956

Journal of Bact.

ERP.

Trypsin/C

10^{-6} gm/cc

6×10^{10} ~~number~~ 1.5^{10} 10^{-15} 10^{-3} = 100

$10^{24} \times 10$

$\frac{1}{100}$ x log 1000 = $\frac{1}{10}$

~~10~~ xt

C = 40

$1.5^{-} \times 23 = \frac{3}{}$

xt = 3.5

x = 3.5

~~40~~ 20 ½

~~10~~ $\frac{1}{5}$ $\frac{5}{1.44}$ =

10 (5)

J. B. C. Kornberg (1956)

Liver (Immunity) ~~CRT~~

Mr Lwoff with David Nil, Bonner

Dr Siegmund R. Furkind

5) Furkinse [illegible] Bonner

Proc. Nat. Ac Sc US. 41, 577, 1955

P2 Mc[illegible]n and Anne Myers Trypan Biochimica et Biophysica Acta

Vol 10 p. 280 1953

Stanier R.Y. Aspects of Synthesis and growth-Princeton University Press 1955 — two adaptive enzymes

← Lipmann 130 (Rockefeller) TNA

University Press | miss Mary Alexander

Rollin Hemens

3321

John Westley (Vanderbilt)

Instructor Assistant Professor

Enzymes are they found [illegible]

in nature 6,000

12,000

Pharmacologists hardening tolerance

— Roth or Fitzhugh. — Tachyphylaxis (Pendennum & Goldman)

NIH to acetylcholine by acetylcholinesterase

~~Pharmacologist~~

DHH Glendower Proc Nat. Acad Vol 40 in 41/1955

to circle Mrs Cathcart Pratt