25

A-15e

POSTMASTER: IF NOT DELIVERED IN TEN DAYS RETURN TO

THE UNIVERSITY OF CHICAGO
RESEARCH INSTITUTES

5640 ELLIS AVENUE · CHICAGO 37 · ILLINOIS

Dr. L. SZILARD

Sept. II. book

L. SZILARD

CONTENTS—MERCHANDISE—FOURTH-CLASS MAIL. THIS PACKAGE MAY BE OPENED FOR POSTAL INSPECTION. RETURN POSTAGE GUARANTEED

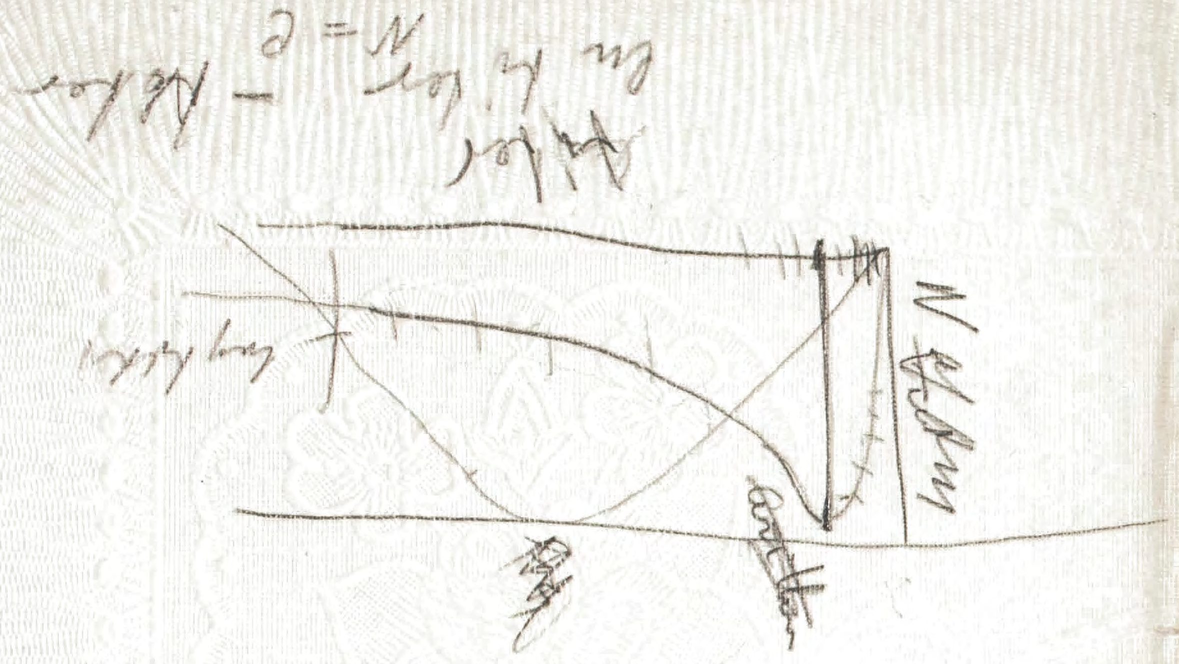
THEME AND NOTE BOOK

No. 2583 N
No. 2583 NM
No. 2583 WM

NARROW RULED
25c NARROW & MARGIN
WIDE & MARGIN

P80 antibody/ml Protein/ml Protein/Body 200

Primary 20 120ug N <1mg/ml 200mg



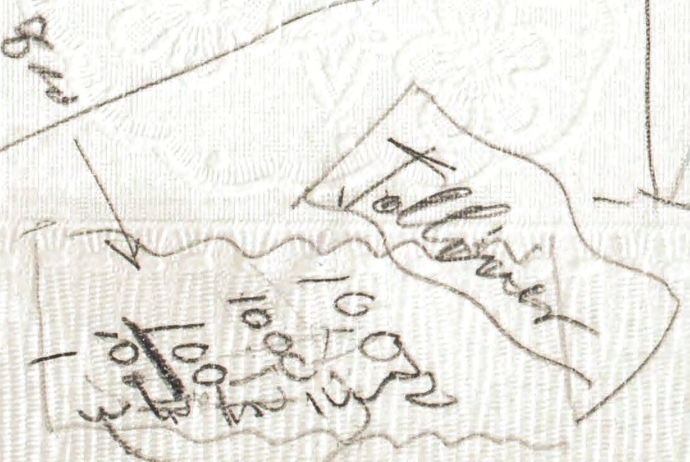
15 days

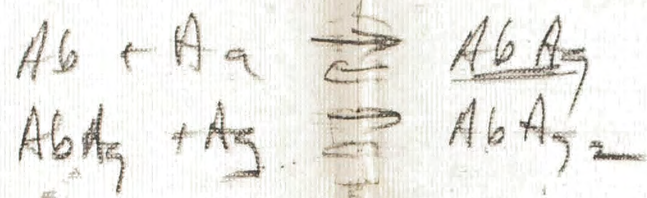
10mg protein

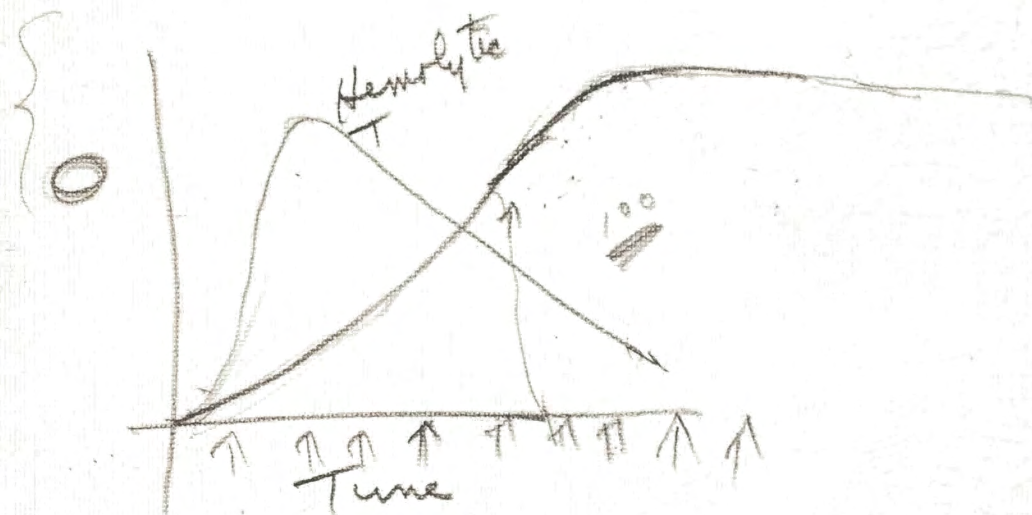
with BSA

60mg protein

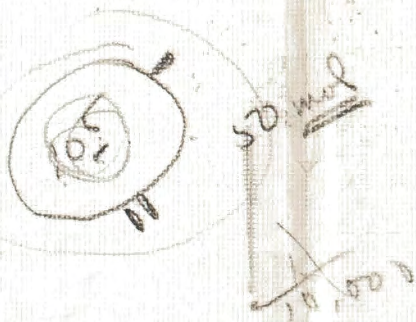
30







S-RBC



In a biosynthetic pathway leading to an AA

Such a nonsynthetic analog of AA would slow or inhibit the production of an AA and thereby slow or inhibit the rate of protein synthesis but no such side-effect would occur along a strong branch pathway.

Specificity of repressor for proline and arginine analogues on page 10 XXX

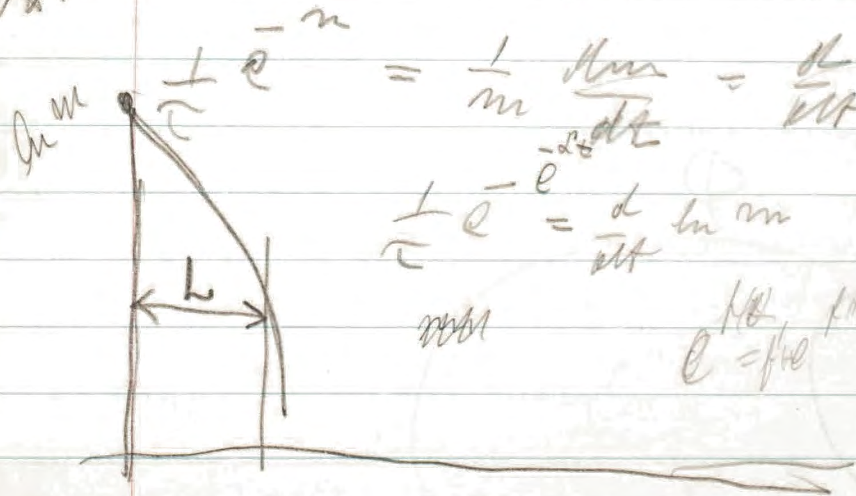
More proper / Applying Gompertz law

$n = e^{-\alpha t}$ / for number of cells alone

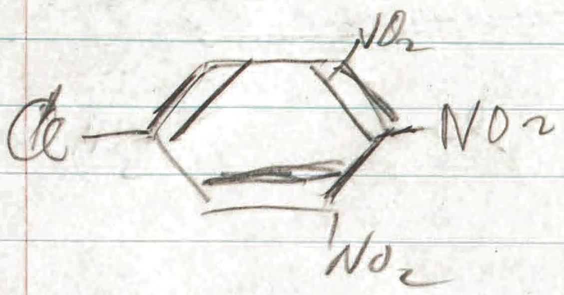
$\frac{1}{\tau} n e^{-n} = \frac{dn}{dt}$

$\frac{1}{\tau} e^{-n} = \frac{1}{n}\frac{dn}{dt} = \frac{d}{dt}\ln n$

$\frac{1}{\tau} e^{-e^{-\alpha t}} = \frac{d}{dt}\ln n$



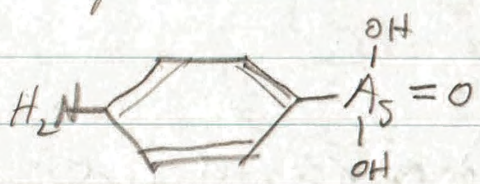
P



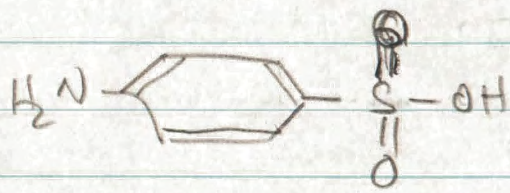
Picryl Chloride

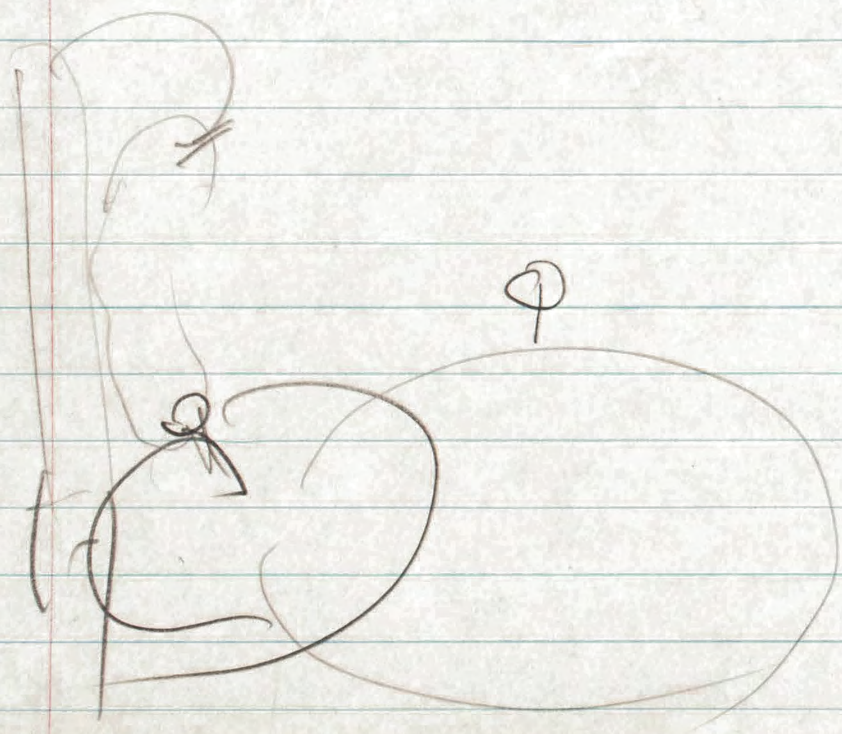
Arsanilic acid

p-amino benz



sulfanilic acid





Combining antibody in lower animals where no precipitating antibody is formed! —

Talmadge says:
Into Anablast 1st day 10 mgm
B.S.A. after 30 days 60 μ grms
1/2 maximum amount[illegible] response
but ties down only 50% of
circulating antibody. Think!

fire of response

Rate of antibody production

primary

maximum content produced in 3 days
(antibody / gm of antigen) 200 mg total. most of it first day

1 mgm antibody per cc serum.

~~[illegible] half life~~ produced in

200 mg/day 10 gm total lymphatic

secondary 2 gm 10 gm total lymphatic.

Burnet's first book Staph. toxoid
Talliver Gatlinburg paper

B.G.G. (4)

First sign: Antibody prod. starts:
5th day after Ist inj;
2nd day " IInd inj;
3 rd day IIIrd inj.

BSA.
Antibody prod starts
7th day after 1st inj;
2nd day after IInd "
3 day after IIIrd inj

Exp. Talmadge proposes to try ascorbic acid inject into rabbit, does it ~~protect~~ repress formation of antibody response to Protein coupled Hapten.

Dixon 1956 or 57
no antibody produced in newborn rabbit by mature lymph fluid

Theory:

assume RNA produced with
each prot. molecule.

$$\frac{dg}{dt} = -kg + ag\, f(S) - \frac{g}{\tau} + A\frac{g_0}{g}$$

$$g = \frac{\frac{A}{\tau} + \ldots}{\frac{1}{\tau} + k - a f(S) + b f(S)}$$

(put back) repressor

Experiment:
lag as function of
how long "tryptophane"
is stopped in
Chemostat?

Antibodies Exp. (important)

make Protein-Hapten
Immunize! as antibody gets
more avid to ~~protein~~ antigen
does it also get more avid
to Hapten.?

(5)

Exp: How fast does newborn rabbit excrete arsanilic acid? —

Experiment:

Intravenous, first injection of B.S.A. into Rabbit. (Wait 4 weeks. — Inject antigen locally will it cause anamnestic response elsewhere?

Experiment: important

How is ~~antibo~~ good or bad antibody formation for one antigen inherited, dominant or recessive? —

$$\frac{N_1}{\tau_{gen}} = \frac{g_1}{f(1) + \tau(AA) + \tau(E)}$$

$$\frac{\tau^*}{\tau_{gen}} + \frac{g_1 \tau^*}{f(1) + \tau(AA) + \tau(E)} = \frac{g_1}{\tau^*}$$

$$\frac{\tau^*}{\tau_{gen}} = g_1\left(1 - \frac{\tau^*}{f(1) + \tau(AA) + \tau(E)}\right)$$

$$= g_1 \left(\frac{f(1) + \tau(AA) + \tau(E) - \tau^*}{}\right)$$

$$g_1 = \frac{\tau^*}{\tau_{gen}} (f(1) + \dots) \frac{1}{(\quad) - \tau^*}$$

$$\left(\frac{N_1}{\tau_{gen}}\right)_{max} = \frac{\tau^*}{\tau_{gen}} \frac{1}{f(1) + \tau(AA) + \tau(E) - \tau^*} = N_1$$

$$N_1 = \tau^* \frac{1}{\quad}$$

~~limitation would be diffusion~~

$$\frac{\tau^*}{\tau_{gen}} \frac{1}{f(1) + \tau(AA) + \tau(E) - \tau^*} = N_1$$

Experiment for Anker
incubate liver slices with
[illegible] taken 6 hours
after II [illegible] injection
of antigen [illegible] rabbit. —

Maximal Protein synthesis
animal cell = 100 bacterium
division time = 10^5 sec = 100. 1000 sec
bacteria $10^4 \times 60$ — 1200 sec = 20 min
2% of total prot in 20 min
10^4 enzymes = 1000 sec
10 ~~[illegible]~~ molekules per sec. — 10^4 enz. per 2000 sec
5 molekules per sec. —

~~$a f(S) = \frac{1}{\tau} a f(S) \quad \frac{1}{\tau} + K + b f(S) - a f(S)$~~

probability parazene free = p
g number of parazenes

~~$\frac{dg}{dt} = \frac{g p}{\tau(AA)(\ldots)} - K g + \frac{1}{\tau}$~~

$$\frac{g}{AR \cdot \frac{1}{p} + \tau(AA) + \tau(\ldots)} = K g$$

$f(N)$

$$0 = \frac{1}{\tau_{gen}} + g\left(\frac{\tau^* \tau_{gen} - \tau_{gen}(\sim) - \tau^*(\sim)}{(\sim)\tau_{gen}\tau^*} \right)$$

$$\frac{1}{\tau_{gen}} \cong g \frac{(\sim - \tau^*)\tau_{gen}}{(\sim)\tau_{gen}\tau^*}$$

$$g = \frac{\frac{1}{\tau_{gen}} \tau_{gen} \tau^* (\quad)}{(\sim - \tau^*)\tau_{gen}}$$

$$g = \frac{\tau^*}{\tau_{gen}} \frac{(\sim)}{(\sim - \tau^*)}$$

$$\frac{N}{\tau_{gen}} = \frac{g \sim}{(\sim)} = \frac{\tau^*}{\tau_{gen}} \frac{1}{\Delta + \tau(AA) + \tau(E) - \tau^*}$$

assume $\tau^* >> \tau(AA)$ O.K.

$$g \cong \frac{\tau^*}{\tau_{gen}} \frac{\Delta + \tau(AA) + \tau(E)}{\Delta + \tau(AA) + \tau(E) - \tau^*}$$

$$\approx \frac{\tau^*}{\tau_{gen}} \frac{1}{1 - \frac{\tau^*}{\Delta + \tau(AA) + \tau(E)}}$$

between $\frac{N}{N_{tot}} = \frac{1}{1000}$ and $\frac{1}{100}$

$$\frac{N}{\tau_{gen}} = \frac{\tau^*}{\tau_{gen}} \cong \frac{\tau^*}{\tau_{gen}} \frac{1}{\Delta} \frac{1}{1 - \frac{\tau^*}{\Delta}}$$

~~any between $\frac{\tau^*}{\Delta}$~~

Enzymes

H.

Paragene multiplication!
Per protein molecule one paragene produced which lives τ^* sec. —

$$\frac{N}{\tau_{gen}} = \frac{g}{\Delta + \tau(AA) + \tau(E)} - \frac{g}{\tau^*} - \frac{g}{\tau_{gen}}$$

$$\frac{1}{\tau_{gen}} + \frac{g}{\Delta + \tau(AA) + \tau(E)} - \frac{g}{\tau^*} - \frac{g}{\tau_{gen}} = 0$$

$$N = \frac{g\,\tau_{gen}}{\Delta + \tau(AA) + \tau(E)}$$

$$g\left(\frac{-1}{\sim\sim} + \frac{1}{\tau^*} + \frac{1}{\tau_{gen}}\right) = \frac{1}{\tau_{gen}}$$

$$\frac{1}{\tau_{gen}} = g\,\frac{(\sim\sim) - \tau^*\tau_{gen}}{(\sim\sim)\,\tau^*\tau_{gen}}$$

$$(\Delta + \tau(AA) + \tau(E)) = (\sim\sim)$$

$$g = \frac{(\sim\sim)\,\tau^*}{(\sim) - \tau^*\tau_{gen}}$$

$$N = (\sim\sim)\,\tau^*\tau_{gen}$$

$$\frac{1}{a} + \frac{1}{b} + \frac{1}{c}$$

emuy with bacteria
$10^4 60 = 6 \, 10^5$ emy.
$\approx 10^4$ specific emy.

| $60 \frac{?}{?}$ mol / sec |

1000 sec

(20) more/sec. in animall

1 billion cells transferred
antigen injected ~~too~~ 10^8 molecules
$3 \, 10^8$ and [illegible] molecules
removed by antigen
1 billion cells

20 to 40 billion "cells" in Rabbit

~~[illegible]~~ Talmadge
X-rayed animal give
30 mgm/Kg ~~BSA~~, BGG gives good secondary (non-X-rayed needs less)
BSA non X rayed [illegible] /kg
X rayed 50 mg/mm/Kg

Yeast extract might not work with BGG ??

Talmage; [illegible] Paper : B.S.A.

— Protein synthesis. — 11

Rabbit I 1 to 10 mμm

10^{-8} molar

$K = \frac{3}{10} \mu N/cc$ | ~~20~~ 2 μ Protein/cc
~~to~~ 2 mg Protein/liter

20 min 24 hours 1,500
B.S.A.

Dixon 2/3 of wet weight of transferred cell in 8 days.

Recipient X-rayed, cells transferred, antigen inject.

350 molecules anti B.S.A. per cell transferred

more than $\frac{1}{3}$ of wet weight

RNA / protein production

ratio $\frac{\text{RNA Phosphorus}}{\text{Protein N}}$ (to get RNA multiply by 10) (to get protein multiply by 6)

chick heart muscle tissue culture	$\frac{30}{1000} \times \frac{10}{6} = \frac{300}{6000} = \frac{1}{20}$	
normal liver	$\frac{25}{1000} \times \frac{10}{6} \cong \frac{1}{25}$	
liver tumor	$\frac{36}{1000} \times \frac{10}{6}$	40/1000
Rat liver regenerating	$\frac{25}{1000}$	← 4 days →

Paragene multiplication:

assume you make 1 protein in $\frac{4\,\text{[illegible]}}{100} = 40$ sec will maintain ~~less~~ 100 long molecule

If we ~~wanted~~ want to maintain 10^4 we must go up factor 100 paragenes

$1000 = A\int t = 310^{10} \times 10^{-8} t$

$300\,t$

$Q = 10^5/$

$t_0 = 3\,\text{sec}$ for prot. prod. [illegible]

$g =$

10^4 enzymes $\sim \frac{10^4\,P_g}{4000}$

Palumadge [illegible]

H

1 μ N/cc $6\ 10^{-6}$ gm Pr/cc

$6\ 10^{-3}$ gm/l.

B.S.A.* $6\ 10^{-8}$ mol/l

2 animal

5 days

$$\frac{1}{1+\frac{S}{K}}$$

N

(N)

K = 0.01 μN/cc = 0.06 μPr/cc

60×10^{-6} gm Pr/l

$6\ 10^{-5}$ gm Pr/l.

[illegible] $6\ 10^{-10}$ M/l

average

20×10^{-10} M/l

$2\ 10^{-9}$ M/l

$10^{-\infty}$

[illegible]

$$N = \frac{\frac{\tau_{gen}}{\Delta}}{1 - \frac{\tau^*}{\Delta}} = \frac{\tau_{gen}}{\Delta}\,\frac{1}{1-\frac{\tau^*}{\Delta}}$$

$$N = \frac{\tau_{gen}}{\Delta}\,\varphi$$

Experiment crucial for ...
~~Transfer~~ from first injection to
Rabbit A (mature) most of one
month transfer lymph gland
into newborn Rabbit B for 3 days.
transfer into mature X rayed
rabbit C and try to elicit
immunestic response!

Control transfer from
A → C

Sept 19/57

Paragen multiplication De Novo : changed assumption

$$\frac{1}{\tau_{gen}} + \frac{g}{(\sim)} - \frac{(g-1)}{\tau^*} - \frac{g}{\tau_{gen}} = 0$$

$$\frac{\left(\frac{1}{\tau_{gen}} + \frac{1}{\tau^*}\right)(\sim)\,\tau^*\tau_{gen} + g\,\tau^*\tau_{gen} - g(\sim)\tau_{gen} - g(\sim)\tau^*}{(\sim)\,\tau^*\tau_{gen}} = 0$$

$$(\tau_{gen} + \tau^*)(\sim) = g\left[(\tau_{gen} + \tau^*)(\sim) - \tau_{gen}\tau^*\right]$$

$$= g\,\tau_{gen}\left[\left(1 + \frac{\tau^*}{\tau_{gen}}\right)(\sim) - \tau^*\right]$$

$$g = \frac{\left(1 + \frac{\tau^*}{\tau_{gen}}\right)(\sim)}{\left(1 + \frac{\tau^*}{\tau_{gen}}\right)(\ ) - \tau^*}$$

$$\frac{N}{\tau(gen)} = \left(1 + \frac{\tau^*}{\tau_{gen}}\right)\frac{1}{\left(1 + \frac{\tau^*}{\tau_{gen}}\right)(\Delta + \tau(AA) + \tau(E)) - \tau^*}$$

$$\simeq \frac{1}{1 + \frac{\tau^*}{\tau_{gen}} \quad \Delta - \tau^*}$$

$$g \simeq \frac{1}{1 - \frac{\tau^*}{\Delta}}$$

More accurately!

$$g - 1 = \frac{1}{\frac{(\quad)}{\tau^*} + \frac{(\quad)}{\tau_{gen}}}$$

$$g = \frac{1}{\frac{(\quad)}{\tau^*} + \frac{(\quad)}{\tau_{gen}}} + 1$$

$$\frac{N}{\tau_{gen}} = \frac{\tau^*}{(\quad)^2} \frac{\tau_{gen}}{\tau^* + \tau_{gen}} + \frac{1}{(\quad)}$$

$$(\quad) = \Delta + \tau(AA) + \tau(E)$$

Orders of magn

assume 5% of Prot = RNA

$$\frac{\text{~~Prot~~ molecules}}{\text{RNA molecules}} = \frac{200}{1}$$

---

for $N = 10^5 \simeq \frac{\tau^* \tau_{gen}}{(\Delta + \tau(AA) + \tau(E))^2} = \frac{\quad}{3^2}$

$\Delta = 0$

$$10^6 = \tau^* \tau_{gen}$$

$$\frac{10^6}{4\,10^3} = \frac{1}{4} 10^3 = \boxed{250 \text{ sec}}$$

1 RNA makes ~ 100 prot mol

H.

Modified Prograde increase

$$\frac{dg}{dt} = \frac{1}{\Delta+\tau(AA)+\tau(E)} - \frac{(g-1)}{\tau^*} - (g-1)\frac{1}{\tau_0} + \frac{1}{\tau_{gen}} - \frac{g}{\tau_{gen}}$$

$$\frac{dN}{dt} = \frac{g}{\Delta+\tau(AA)+\tau(E)} - \frac{N}{\tau_{gen}}$$

$$0 = \tau^*\tau_{gen} - (\Delta+\tau(AA)+\tau E)\tau_0(g-1) - (\sim)\tau^*(g-1)$$

$$g = 1 - \frac{(\sim)}{\tau^*}(g-1) - \frac{(\sim)}{\tau_{gen}}(g-1)$$

or if $\tau^* \ll \tau_{gen}$

$$(g-1) \sim \frac{\tau^*}{(\sim)}$$

$$g \sim \frac{\tau^*}{\sim} + 1$$

$$\frac{N}{\tau_{gen}} \cong \frac{\tau^*}{(\sim)^2} + \frac{1}{(\sim)}$$

Now look at correct solution of non stationary states in early drafts ($\tau^* = 0$)

$$\frac{dN}{dt} = \frac{1}{\Delta} - \frac{N}{\tau_0} \quad \Big| \quad N = \frac{\tau_0}{\Delta}$$

$$\frac{dN}{dt} = \frac{1}{\Delta+\Delta(1-e^{-\frac{t}{2\tau_0}})} - \frac{N}{2\tau_0}$$

$N = N_0$ at $t=0$

$$\frac{\tau^*}{\tau(AA)} = 200$$

$$10^5 = \frac{\tau^* \frac{\tau_0}{\tau^* + \tau_0} \, O\gamma_{en}}{[\tau(AA)]^2}$$

$$10^5 = 200 \, \frac{\tau_0}{\tau^* + \tau_0} \, \frac{\Phi\gamma_{en}}{\tau(AA)}$$

$$\tau(AA) = \frac{200 \times 4000}{10^5} = \frac{800000}{10^5} = 8\,\text{sec}$$

$$\tau^* = 2000\,\text{sec}$$

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Once more:

$$\frac{dg}{dt} = k(\Delta) - \frac{g-1}{\tau^*} + \frac{1}{\tau_{gen}} - \frac{g}{\tau_{gen}}$$

$$- \frac{(g-1)}{\tau_{gen}}$$

~~$k(\Delta)$~~ $$(g-1)\left(\frac{1}{\tau^*} + \frac{1}{\tau_{gen}}\right) = k(\Delta)$$

$$g-1 = \frac{k(\Delta)}{\frac{1}{\tau^*}+\frac{1}{\tau_{gen}}} = k(\Delta)\tau^* \frac{\tau_{gen}}{\tau^*+\tau_{gen}}$$

$$k(\Delta) = \frac{1}{\Delta + \tau(AA) + \tau(G)}$$

large may be

$$g = k(\Delta)\tau^* \frac{\tau_{gen}}{\tau^*+\tau_{gen}} + 1$$

$$\frac{N}{\tau_{gen}} = \frac{k(\Delta)\tau^* \frac{\tau_{gen}}{\tau^*+\tau_{gen}}}{\Delta + \tau(AA) + \tau(E)} + \frac{1}{\Delta + \tau(AA) + \tau(E)}$$

for $\Delta = 0$ $$\frac{N}{\tau_{gen}} \approx \frac{1}{\tau(g)} \frac{\tau^*}{\tau(AA)}$$

$$N = \frac{\tau^*}{\tau(g)} \frac{\tau_{gen}}{\tau(AA)} + \frac{\tau_{gen}}{\tau(AA)}$$

10^5

$m, \tau(AA) = 3$ sec $\quad \frac{\tau^*}{\tau(g)} = 100 \quad$ $\#$ 10^3

10^3

Ag [illegible]

10^{10} 10 k^1

$\tau^* = 600$ sec
$\tau(g) = 6$ sec

$$\frac{dN}{dt} = \frac{g}{(\Delta + \tau(AA) + \tau(E))} - \frac{N}{\tau_{gen}}$$

$$0 =$$

60 10^{-4}

600000

---

again

$$\frac{dg}{dt} = \frac{1}{\Delta + \tau(AA) + \tau(E)} + \frac{1}{\tau_{gen}} - \frac{g}{\tau_{gen}}$$

$$g = \frac{\tau_{gen}}{\Delta + \tau(AA) + \tau(E)} + 1$$

$$\frac{dN}{dt} = \frac{g}{(\quad)} - \frac{N}{\tau_{gen}}$$

$$N = \frac{g\,\tau_{gen}}{(\quad)} = \frac{(\tau_{gen})^2}{(\Delta + \tau(AA) + \tau(E))^2} + \frac{\tau_{gen}}{(\quad)}$$

De Nurp but different

$$\frac{dg}{dA} = \frac{1}{\Delta + \tau(AA) + \tau(E)} = \frac{g}{\tau_{gen}}$$

H

4000 33

$$g = \frac{\tau_{gen}}{(\sim\sim)}$$

$$N = \frac{\tau_{gen}\, g}{(\sim\sim)}$$

$$N = \frac{(\tau_{gen})^2}{(\Delta + \tau(AA) + \tau(E))^2}$$

manual

$$\left(\frac{10^5}{\tau(AA)}\right)^2$$

for $\Delta = 0$

$$10^5 = \left(\frac{\tau_{gen}}{\tau(AA) + \tau(E)}\right)^2$$

$$\frac{(4000)^2}{10^5} = \left(\tau(AA) + \tau(E)\right)^2$$

$$16\,\frac{10^6}{10^5} =$$

$$\tau(AA) + \tau(E) = \sqrt{160} = 12 \tfrac{1}{2}\ \text{sec}$$

$$g = \frac{4000}{12}$$

$$\frac{N}{g} = \frac{4000}{(\sim\sim)} = 330$$

weight ratio 33

$\Delta = 0$

N.O.K.

3%.

2×10^{-13} gm

~~600~~ $6\ 10^{5}$

$0.6\ 10^{-14}$ gm

$$= \frac{6 \times 0.6\ 10^{-14}\ 10^{23}}{6\ 10^{5}}$$

$$\frac{6}{10}\ 10^{4}$$

Number of genes: H

Enzymes mol weight 10^5
DNA to Prot 1:30 in weight
1:300 [~~double~~ single helix] molecule for molecule
(AA) = 100 gm

Proteins 10^{-13} gm $\quad 6 \times 10^{23} \frac{10^{-13}}{10^5} = 6\ 10^5$ molecules enzyme

~~#~~ Number of genes $\frac{6\ 10^5}{300} = 2\ 10^3$

or if enzyme <u>30000</u> Number of genes <u>6000</u>

Molarity for 3000 molecules/cell

10^{-12} cc $\quad 3.10^{15}$/cc $= 3\ 10^{18}$/l

$\frac{6\ 10^{23}}{3\ 10^{18}} = 2\ 10^{-5}$ mol/l

may be 10% of enzymes at 3000/cell

$$\frac{N}{\text{gen}} = \frac{1}{(\sim\sim)} \quad \frac{1}{1-\frac{c^{*}}{(\sim\sim)}}$$

O.K.
but no good

Exp. if temp lowered
by 10°C is then cell size
unchanged? (per nucleus)

Exp. Mass prod
Arginineless Uracil-less
Production of Arginine is
added no mutants appear
(spontaneous) but if we
add arginine and provide
for slow supply of Uracil
they should appear

---

what about Bromouracil
induced mutations. — these do not have
to restitute and should come up
even in presence of Arg. and Uracil, both.

Exponential DNA · H

De Novo

$$\frac{1}{\tau_{gen}} - \frac{g''}{\tau^*} - \frac{g'}{\tau_{gen}} - \frac{1}{\tau_{gen}}$$

$$+ \frac{g'}{(\sim)} + \frac{1}{(\sim)} = 0$$

$$(\sim)\, g''\left(\frac{1}{\tau^*} + \frac{1}{\tau_{gen}}\right) = g' + 1$$

$$\left[(\sim)\left(\frac{1}{\tau^*} + \frac{1}{\tau_{gen}}\right) - 1\right] g = 1$$

$$g' = \frac{1}{(\sim)\left(\frac{1}{\tau^*} + \frac{1}{\tau_{gen}}\right) - 1} = \frac{\frac{\tau^*}{(\sim)}}{1 - \frac{\tau^*}{(\sim)}}$$

$$g' \cong \frac{\tau^*}{\Delta + \tau(AA) + \tau(E) - \tau^*}$$

$$\frac{N}{\tau_{gen}} = \frac{g' + 1}{(\sim)}$$

$$\frac{N}{\tau_{gen}} = \left(\frac{\tau^*}{(\sim) - \tau^*} + 1\right) \frac{1}{(\sim)}$$

$$\frac{N}{\tau_{gen}} = \frac{1}{(\sim) - \tau^*} \qquad \frac{(\sim)}{(\sim) - \tau^*} \quad \frac{1}{(\sim)}$$

cf Monod–Jacob Theory

If an enzyme $E \rightarrow$ RA shoots up amount ... of gene may be governed by interference with prot. synthesis by tying up [sketch labelled RA] – s. — !

diffusion equation?

Modified formula for $\tau(R)$ in new new theory (full τ independence of enzyme ratio's)

1) assume enzyme shows up connection even during the time when enzyme is covered by repressor:

$$\bar{\tau}(R) = \tau(E)\, e^{-ARp} + \tau(R)(1 - e^{-ARp})$$

probability that enz is not combined with inducer

$$\bar{\tau}(R) = \tau_0(R)(1 - e^{-AR(1-q)})$$

[crossed out] $p =$

$$\frac{1}{\tau_0(R)(1 - e^{-ARp})} = \frac{e^{ARp}}{\tau_0 (e^{ARp} - 1)}$$

H

Antibody "important experiments":

BSA into Rabbit (first inj.); and immunize antigen at time t!
One month later inject antigen and look at antibody response
Two month later inject antigen and look at antibody response.

Vary t!

Theory of Enzymes — $\tau(E) = C\tau(gen)$
what happens if we lower Temp. ~~$\tau(E)$~~ goes up. prop to $\tau(AA)$
Special enzyme which denatures lives longer, by say factor 3, ~~so $\tau(E)$ goes down~~ but is also produced more slowly by say the same factor. This would mean $\tau(E)$ remains same but $\tau(R)$ may increase with same same way as $\tau(gen)$ so that ratio of enzymes constant.

What determines gen. time?
Another spec. enzyme perhaps which decomposes and saturates?

With best wishes.

THE EFFECTS OF RIBONUCLEASE AND DEOXYRIBONUCLEASE ON BACTERIOPHAGE FORMATION IN PROTOPLASTS OF *BACILLUS MEGATERIUM*

by

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LESTER[1] and BELJANSKI[2] have shown that cells of *Micrococcus lysodeikticus* after digestion with lysozyme in the presence of sucrose retain the ability to incorporate amino acids into proteins. The same type of treatment converts the cells of *B. megaterium* into spherical protoplasts[3], in which amino acid incorporation has recently been demonstrated by MC QUILLEN[4]. It seems reasonable to assume that the lysozyme-sucrose lysates of *M. lysodeikticus* also contained protoplasts and that these structures were responsible for the observed incorporation of amino acids. Both LESTER[1] and BELJANSKI[2] observed distinctive effects with ribonuclease (RNase) and deoxyribonuclease (DNase); the addition of RNase suppressed amino acid incorporation completely while DNase exerted a marked stimulatory effect. From these results it appeared possible that protoplasts were permeable to high molecular weight enzymes and that ribonucleic acid was essential for protein synthesis.

Protoplasts of *B. megaterium* preserve sufficient structural and functional integrity to support the growth of bacteriophages provided that the cells are infected prior to lysozyme treatment[5,6]. The present experiments were originally undertaken to investigate the effects of DNase and RNase on bacteriophage growth in protoplasts with the object of establishing the respective roles of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in virus replication. This expectation was not in fact realised, but since the experiments throw light on the reactions of protoplasts with enzymes they are reported in the present communication.

MATERIALS AND METHODS

Strain KM of *Bacillus megaterium* and the *megaterium* bacteriophage, strain C, were obtained from the Department of Bacteriology, University of California, Berkeley. The method of assay of bacteriophage is described in the previous paper[5].

Asparagine-phosphate medium: 1 g L-asparagine, 0.54 g NaCl, 0.3 g KCl, 0.1 mM Na_2SO_4, 0.01 mM $CaCl_2$ and 0.1 mM $MgCl_2$ in 100 ml 0.03 M phosphate buffer, pH 7.0.

Sucrose-buffer: 0.2 M sucrose in 0.03 M phosphate buffer, pH 7.0.

Enzymes: Crystalline DNase (Worthington) and crystalline RNase (Armour) were gifts from Dr. H. K. Schachman.

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EXPERIMENTS AND RESULTS

1. Effects of DNase and RNase on bacteriophage formation in cells and protoplasts

Cultures of *B. megaterium* KM were grown at 35° C with aeration in asparagine-phosphate medium. The cells were harvested when they had reached a density of 5–$7 \cdot 10^7$ per ml, infected with C phage at a multiplicity of 0.01, and a portion treated with lysozyme using procedures described previously[5]. At time $t = 0$, the suspensions of infected cells and infected protoplasts were diluted tenfold into 2.5 ml of asparagine-phosphate medium made 0.2 M with respect to sucrose in 6″ × 1″ tubes. RNase and DNase were added, and the growth tubes shaken at 60 oscillations per minute in a waterbath maintained at 25° C. Samples were removed at $t = 0$ and after four hours incubation. Appropriate dilutions were assayed for their phage content and the protoplasts counted in a haemocytometer chamber.

The results of this experiment are given in Table I, from which it can be seen that the addition of either DNase or RNase to intact infected cells does not affect the growth of bacteriophage. These results may be compared with those of BELJANSKI[2] who found that incorporation of aminoacids by intact cells was not influenced by these enzymes. After treatment with lysozyme, the input infective centres decrease because the protoplasts at this stage do not contain mature phage, the original particles having entered the eclipse period of intracellular development[5]. At the end of the growth period there is a marked increase in phage concentration, the average burst size being smaller than that obtained with the intact cells. The addition of DNase decreases the burst size in the protoplasts, but this is probably not significant because of the known variability of phage production by protoplasts. On the other hand, RNase produces a thousandfold decrease in the average burst size. This effect of RNase is correlated with the low survival of the protoplasts and it appeared probable that the suppression of phage formation was due to lysis of the protoplasts induced by RNase.

TABLE I

EFFECTS OF DNASE AND RNASE ON BACTERIOPHAGE FORMATION IN CELLS AND PROTOPLASTS

Culture	*Enzyme*	*Phage per ml of growth tube*		*Average burst size**	*Protoplasts per ml of growth tube*	
		$t = 0$ hour	*$t = 4$ hours*		*$t = 0$ hour*	*$t = 4$ hours*
Cells	None	$1.4 \cdot 10^5$	$6.4 \cdot 10^6$	46		
	DNase 10 μg/ml	$1.4 \cdot 10^5$	$6.0 \cdot 10^6$	43		
	RNase 50 μg/ml	$1.4 \cdot 10^5$	$5.8 \cdot 10^6$	42		
Protoplasts	None	$3.2 \cdot 10^2$	$4.2 \cdot 10^6$	30	$1.8 \cdot 10^7$	$1.6 \cdot 10^7$
	DNase 10 μg/ml	$3.2 \cdot 10^2$	$3.4 \cdot 10^6$	24	$1.8 \cdot 10^7$	$1.5 \cdot 10^7$
	RNase 50 μg/ml	$3.2 \cdot 10^2$	$4.9 \cdot 10^3$	0.035	$1.8 \cdot 10^7$	$< 10^4$

* Average burst size is calculated in all cases on the basis of input infective centres, *i.e.* $1.4 \cdot 10^5$/ml.

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2. Lysis of protoplasts by RNase

A culture of *B. megaterium* KM was grown in asparagine-phosphate medium to a density of $8 \cdot 10^7$ per ml, centrifuged, and the cells resuspended in sucrose-buffer. 20 µg/ml lysozyme was added and the changes in turbidity followed at 23° C in a photoelectric colorimeter. After 30 minutes, the suspension was divided into two portions, 50 µg/ml RNase added to one portion, and the changes in turbidity recorded. The results are presented in Fig. 1. The addition of lysozyme produces a rapid drop in the optical density of the suspension as the cells are transformed into protoplasts. When this process is completed, the optical density remains constant. Subsequent addition of RNase induces a further decrease of the turbidity of the suspension resulting eventually in a viscous suspension of ghosts.

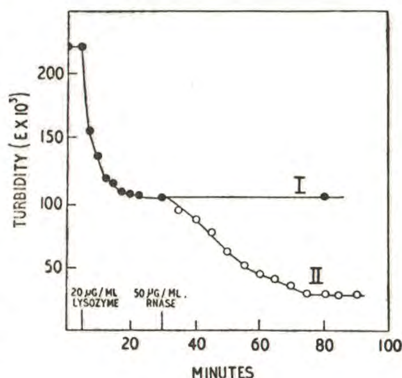

Fig. 1. Turbidity changes in a suspension of *B. megaterium* cells treated with lysozyme (I) and then with RNase (II).

DISCUSSION

When a bacteriophage infects the cell, the viral DNA enters the host carrying all the genetic information for the synthesis of new progeny phages[7]. Even if this information is transferred to another structure, replication of DNA is necessary for the formation of mature phage. The absence of any marked effect of DNase on phage development in protoplasts suggests that the phage DNA is not accessible to the enzyme; the simplest hypothesis that can be put forward is that the protoplasts are impermeable to DNase. Although BELJANSKI[2] found evidence for the degradation of DNA by DNase in protoplast suspensions, it is probable that the DNA had been released into the medium by spontaneous lysis of the protoplasts. Protoplasts are extremely fragile and unless precautions are taken spontaneous lysis commonly occurs. GALE AND FOLKES[8] have shown that purines and pyrimidines stimulate protein synthesis, and it is likely that the stimulatory effects observed with DNase are due to the enhancement of amino acid incorporation in intact protoplasts by low molecular degradation products of DNA released into the medium by spontaneous lysis.

The lysis of the protoplasts induced by RNase with consequent dispersion and dilution of the contents of the structure provides sufficient reason for the suppression by this enzyme of both phage formation and amino acid incorporation. In the light of the experiments with DNase, it is unlikely that RNase penetrates into the protoplasts. It is possible that RNA forms an integral part of the structure of the protoplast membrane and that its depolymerisation by the enzyme destroys the permeability barrier to sucrose producing osmotic lysis. This possibility is supported by WEIBULL's finding[9] that 15% of the RNA of lysed protoplasts sediments with the ghost membranes.

The present experiments indicate that protoplasts are not, in general, permeable to macromolecular substances. This is not surprising in view of the existence of a permeability barrier which prevents both the leakage of low molecular weight intra-

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ecllular substances[3] and the entry of sucrose. The main conclusion to be drawn is that the experiments of LESTER[1] and BELJANSKI[2] do not afford any evidence as to the possible role of RNA in protein synthesis. To what extent inhibition of amino acid incorporation by RNase in microsomes[10, 11] and other systems[8] is due to a similar disintegration of aggregated structures containing RNA cannot at the moment be decided. However, it is evident that this effect of RNase must be excluded in all experiments in which this enzyme is used to demonstrate the role of RNA in protein synthesis.

SUMMARY

DNase has no significant effect on bacteriophage formation by protoplasts of *Bacillus megaterium*, while RNase suppresses bacteriophage growth almost completely. This action of RNase is due to lysis of the protoplasts induced by the enzyme with consequent dispersion of the protoplast contents. It is concluded that protoplasts are not generally permeable to macromolecular substances such as enzymes.

RÉSUMÉ

La DNase n'a pas d'action significative sur la formation du bactériophage par les protoplastes de *Bacillus megaterium*, tandis que la RNase supprime presque complètement la croissance du bactériophage. Cette action de la RNase est due à une lyse des protoplastes provoquée par l'enzyme et suivie de la dispersion de leur contenu. Les auteurs concluent que les protoplastes ne sont pas, en général, perméables aux substances macromoléculaires telles que les enzymes.

ZUSAMMENFASSUNG

DNase übt keine bedeutsame Wirkung auf die Bakteriophagenbildung durch Protoplaste von *Bacillus megatherium* aus, während RNase das Wachstum der Bakteriophagen fast vollständig unterbindet. Diese Wirkung von RNase ist der Lyse der Protoplasten zuzuschreiben, welche durch das Enzym verursacht und von der Dispersion des Protoplasteninhaltes gefolgt wird. Daraus wird die Folgerung gezogen, dass Protoplaste makromolekularen Substanzen wie z.B. Enzymen gegenüber nicht immer durchlässig sind.

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BACTERIOPHAGE GROWTH IN PROTOPLASTS OF *BACILLUS MEGATERIUM**

by

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Treatment with lysozyme of suspensions of *Bacillus megaterium* in 0.2 *M* sucrose solution converts the bacterial cells into spherical protoplasts. These protoplasts are bounded by a membrane which, no longer supported by the rigid cell wall, is readily disrupted by any reduction in the osmotic pressure of the suspending medium. The protoplasts constitute 80% of the cell mass and preserve some of the physiological properties of intact bacteria, but they are incapable of colony formation[1]. It is the purpose of this report to show that such protoplasts are capable of supporting bacteriophage growth. SALTON AND MCQUILLEN have independently also demonstrated bacteriophage formation in protoplasts and, by mutual agreement, the results of the two investigations have been submitted simultaneously.

MATERIALS AND METHODS

Bacterium and phage. Strain KM of *Bacillus megaterium* and the *megaterium* bacteriophage, strain C, active on KM were obtained from the Department of Bacteriology, University of California, Berkeley.

Asparagine-tris buffer medium. 1 g L-asparagine; 10 ml 1.0 *M* tris (tris-hydroxymethylaminomethane) buffer, pH 7.2; 10 ml salts (a solution of 54 g NaCl, 30 g KCl, 0.1 m*M* $CaCl_2$, 1.0 m*M* $MgCl_2$ in 1000 ml of distilled water); 2.2 mg KH_2PO_4; 2.3 mg Na_2SO_4; 80 ml distilled water.

Sucrose-buffer. 0.2 *M* sucrose in 0.03 *M* phosphate buffer, pH 7.0.

Sucrose-buffer-peptone. 2 g bacto-peptone DIFCO in 100 ml sucrose-buffer.

Bacteriophage assay. The double layer plating method[2] was used; 2.5 ml of 5% peptone, 0.7% agar containing the phage and bacteria was poured on the surface of plates containing 5% peptone, 2% agar.

EXPERIMENTS AND RESULTS

It was reported by WEIBULL[1] that protoplasts of *B. megaterium* do not adsorb a bacteriophage active on the intact cells, indicating that the lysozyme-sensitive cell wall is necessary for phage fixation. This is complemented by the observation that such bacteriophage *is* readily adsorbed to isolated *B. megaterium* cell walls[3]. In order to examine the possibility of bacteriophage growth in protoplasts, therefore, it is necessary first to infect the intact bacteria and then convert the infected cells into protoplasts by lysozyme treatment in sucrose. Phage development can then be followed in a one-step growth experiment, such as described below.

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A culture of *B. megaterium*, strain KM, was grown in asparagine-tris buffer medium to a density of $5 \cdot 10^7$ cells per ml, centrifuged and resuspended in half of its original volume of 5% peptone water. The culture was then infected with about $2 \cdot 10^6$ phages of strain C per ml. After incubation for 5 minutes at 37° C, more than 90% of the phages were adsorbed. The culture was centrifuged, washed and resuspended in sucrose-buffer. One aliquot of this suspension was digested at room temperature with 10 μg per ml lysozyme. Microscopic examination indicated protoplast formation to be complete after 30 minutes. A second aliquot of the suspension of infected cells remained untreated. At time $t = 0$, both aliquots were diluted one-thousand fold into sucrose-buffer-peptone maintained at 25° C, and sampled and assayed periodically for infective centres.

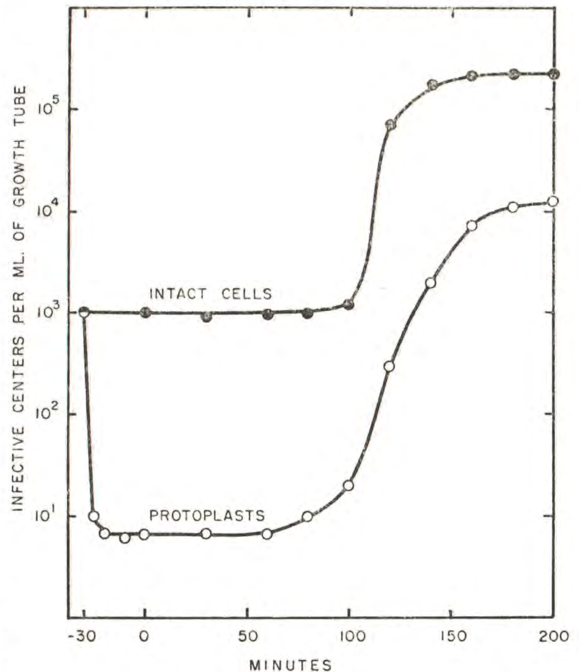

Fig. 1. One-step growth curves of intact cells of *B. megaterium* and of protoplasts infected with phage C at 25° C. Lysozyme treatment for protoplast formation commenced at $t = -30$ min. Phage development was initiated at $t = 0$ min.

The results of this experiment are presented in Fig. 1. It is seen, first of all, that the untreated infected bacteria exhibit a normal one-step growth curve, with latent period of 90 minutes and final burst size of 230. Lysozyme treatment of the infected cells, on the other hand, rapidly reduces the number of infective centres to less than 1% of its intitial level. (The surviving infective centres appear to be free phage, which had been either liberated by lysozyme treatment or carried over in the washings.) Sixty minutes after dilution of the infected protoplasts into the sucrose-buffer-peptone, however, a rapid rise in the number of infective centres commences until a level is reached fourteen times greater than the original number of infected cells. The initial decrease of the number of infective centres in the lysozyme-treated suspension must be due to the fact that the phage had entered the eclipse period[4] of intracellular virus development and that the instantaneous lysis of the protoplasts upon plating prevented any further maturation of the vegetative phage. The subsequent increase in infective centres is a reflection of the intracellular growth and maturation of the vegetative phage in the protoplasts maintained in sucrose-buffer-peptone.

A single burst experiment[5] was carried out in order to examine whether the phage ultimately produced in the lysozyme-treated suspension represented a small burst issuing from the majority or a very large burst issuing from a small minority of the infected protoplasts. In this experiment, an average of one infected protoplast suspended in sucrose-buffer-peptone was distributed into each of forty tubes and phage growth was allowed to take place for 4 hours at 25° C. The total contents of each tube were then

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assayed for infective centres. The result of this experiment is presented in Table I, where it may be seen that at least half of the infected protoplasts do produce phage and that the individual bursts are small.

The small burst size of the phage-infected protoplasts is probably due to an aggravation of the well-known fragility of *intact* bacteria at the conclusion of the eclipse period[4,6], thus terminating phage synthesis prematurely by spontaneous lysis shortly after the intracellular appearance of the first mature progeny phages. Microscopic examination reveals that *uninfected* protoplasts remain intact for up to six hours under the same experimental conditions.

TABLE I

SINGLE BURST EXPERIMENT ON INFECTED PROTOPLASTS

Number of plaques	*Number of tubes*
0	24
1	5
2	2
3	4
5	1
12	2
23	1
25	1

Fraction of tubes without burst: 24/40 = 0.60; Multiplicity of bursts per tube: —ln 0.60 = 0.51; Multiplicity of infected protoplasts per tube: 1.0; Fraction of protoplasts yielding burst: 0.51/1.0 = 0.51.

B. megaterium protoplasts, therefore, preserve sufficient structural and functional integrity to be capable of carrying out all those reactions subsequent to invasion by the parental phage which are necessary for growth and maturation of infective progeny. There is presumptive evidence[7,8] that high molecular weight substances like enzymes, to which intact bacterial cells are impermeable, may be able to penetrate into protoplasts. The possibilities of influencing intracellular bacteriophage development through addition of specific macromolecular substances to protoplast suspensions are being explored.

SUMMARY

One-step growth experiments show that bacteriophage C can grow in protoplasts of *B. megaterium* KM if the cells are infected prior to treatment with lysozyme. The phage yield of infected protoplasts is smaller that that of intact cells, and a single burst experiment establishes that the burst size of individual protoplasts is small.

RÉSUMÉ

Des expériences de multiplication à cycle unique montrent que le bactériophage C peut croître dans les protoplastes de *B. megaterium* KM si les cellules sont infectées avant le traitement par le lysozyme. Le rendement en phage des protoplastes infectés est plus petit que celui des cellules intactes et une expérience de production individuelle établit que le rendement moyen des protoplastes individuels est faible.

ZUSAMMENFASSUNG

Fortpflanzungsversuche in einem einzigen Zyklus beweisen, dass sich der Bakteriophage C in Protoplasten von *B. megaterium* KM entwickeln kann, falls die Zellen vor der Lysozymbehandlung infiziert werden. Die Phagenausbeute aus infizierten Protoplasten ist geringer, als aus unversehrten Zellen, und ein individueller Produktionsversuch ergibt, dass die Durchschnittsausbeute der einzelnen Protoplasten gering ist.

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THEME AND NOTE BOOK

No. 2583 N
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NARROW RULED
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Paper

The end:

Nach dem Ersten Weltkrieg veröffentlichte ein Am. Physiker ein gewisser Miller (an dessen Namen sich kaum jemand mehr erinnert) Versuche die zeigen das die Einsteinsche Relativitätstheory falsch is. Als jemand Einstein fragte was er hätte wenn es sich herausstellen sollte das die Theory falsch ist, sagte er "Ich würde mich wundern."

Die Theory die ich Ihnen hier vorgesetzt habe regt eine Anzahl von Versuchen an und innerhalb von zwei Jahren sollten wir wissen ob das alles was diese Theory jetzt vorausgesagt wirklich genau zutrifft.

Wenn Sie mich aber fragen

check: For paper De Novo

~~$\tau(\text{cov}) = \tau(\text{gen}) - \tau_{free} - N\tau(AA)$~~

~~$\tau_{free} = \tau_{gen} - N\tau(AA) - \tau(\text{cov})$~~

~~$N = \dfrac{\tau_{gen} - \tau(E)\frac{R}{k}(1-\pi) - N\tau(E)}{\tau(E) + \tau(AA)}$~~

~~τ_{gen}~~

~~$\tau(\text{cov}) \quad \tau(E\ \text{total})$~~

$\tau(\text{covd}) = \tau(\text{gen}) - N\tau(AA)$

$\tau(\text{free}) = (\tau_{gen}) - N\tau(AA) - \tau(\text{covd})$

$\tau(\text{free } E)$

$[\tau(\text{gen}) - N\tau(AA) - \tau(\text{cov})]\frac{R}{k_1}(1-\pi) = \tau\ \text{cov}$

$\tau_{gen} - N\tau(AA) = \tau(\text{cov})\left(1 + \frac{R}{k}(1-\pi)\right)$

$\tau(\text{cov}) = \dfrac{\tau_{gen} - N\tau(AA)}{1 + \frac{R}{k}(1-\pi)}$

$\dfrac{\tau_{gen} - \tau_{cov}}{\tau_{gen}} = \dfrac{\tau(\text{gen})}{\tau_{gen}} - \dfrac{\tau_{gen} - N\tau(AA)}{\left(1 + \frac{R}{k}(1-\pi)\right)\tau_{gen}}$

$\frac{R}{k}(1-\pi)\tau(E) = \tau E$

↑ is fraction of time gene can make enzyme

$= \dfrac{\tau_{gen}\left(1 + \frac{R}{k}(1-\pi)\right) - \tau_{gen} - N\tau(AA)}{\left(1 + \frac{R}{k}(\ )\right)\tau_{gen}}$

was ich tun würde wenn sich
hier alles 100% bestätigt. So
muss ich Ihnen ehrlich
antworten; Ich würde
mich wundern & In diese
Beziehung ist moderne
Biologie etwas anders als
moderne Physik. ~~[illegible]~~
Die Schwierigkeit ist in
der Biologie – das kann man selbst
man sich hin und beginnt
Versuche zu machen die
die die Richtigkeit einer
Theorie prüfen sollen,
macht man eine /
gänzlich unerwartete
Entdeckung. Aus diesem
Grunde dürfen Sie nicht
annehmen, dass das was
ich Ihnen hier vorgesetzt
habe die ~~[illegible]~~ endgültige
Wahrheit ist in einer
thermodynamisch
stabilen kristallinen
Form. Vielmehr ist es
wahrscheinlich ~~die~~ Wahrheit
in Status nascendi.—

$N\tau(E) + N\tau(AA) = \tau\, 4\pi n - N\tau(E)\frac{R}{K}$

O.K.

To paper

Formula holds:

$$W = \frac{\tau\, 4\pi n - N\tau(E)\frac{R}{K(R)}(1-\bar{\pi})}{\tau(E) + \tau(AA)}$$

To paper

$A \rightarrow \frac{1}{\tau}$

$A = 3 \cdot 10^{10} \times 3$

$A = 10^{11}$ reasonable

$M = 100$

K does not depend on mass; better use

Mol weight 100

and for Mol weight 1000

use $\tau_{ov} = \frac{1}{3}\, 10^{13}\, e^{-\frac{\Delta H}{RT}}$

also for Mass to 10^{12}

$\frac{R}{K}$ moves $\frac{R}{K}(1-\bar{a})$ H

~~Fraction of time since cut-in make unequal:~~

$$\frac{\tau(\text{Active})}{\tau_{gen}} = \frac{\tau_{gen} R/K(\ ) - N\tau(AA)}{(1+R/K)\,\bar{\tau}_{gen}}$$

$$\frac{\tau(\text{Active})}{\bar{\tau}_{gen}} = \frac{R/K(\ )}{1+R/K} - \frac{N\tau(AA)}{\tau_{gen}} \frac{1}{1+R/K(1-\bar{a})}$$

for $R/K >> 1$

$$\sim 1 - \frac{\tau(AA)}{\tau(gen)} \frac{N}{1+R/K}$$

$$\sim 1 - \frac{\tau(AA)}{\tau(gen)} N$$

$$\tau_{gen}\frac{R}{K} - N\tau(AA)\frac{R}{K} = (1+\frac{R}{K})\,\tau(cov)$$

$$\tau(cov) = \frac{R/K}{1+R/K}\left(\tau_{gen} - N\,\tau(AA)\right)$$

$\tau(Act)$ check!

$$N = \frac{\tau_{gen} - \tau(cov)}{\tau(E) + \tau(AA)} = \frac{\tau(gen) - \frac{R/K}{1+R/K}\left(\tau(gen) - N\tau(AA)\right)}{\tau(E) + \tau(AA)}$$

~~$\tau(Act) = $~~

$$N = \frac{\tau_{gen} - N\tau(E)\frac{R}{K}}{(\tau(E) + \tau(AA))}$$

$$\frac{\tau(gen)}{\tau(E)(1+\frac{R}{K}) + \tau(AA)} = \frac{\tau_{gen} - \tau(E)}{\tau(E) + \tau(AA)}$$

solve for N

If R goes up prop to generation time then the fraction of the time during which gene free to synthesize protein does not change with generation time.
Therefore when $\tau(AA)$ is lengthened τ_{gen} goes with it.

2/19 Measure dependence of AA concentration for τ_{gen} with permease less mutant

---

Back induction.

Automatic in my theory.

use for protein synthesis — H

$A = 3\,10^{10}$

$$\text{for } \frac{1}{\tau_{er}} = \frac{1}{3}\,10^{12}\,e^{-\frac{\Delta H}{RT}} = AK$$

---

use for $M = 100$.

$$\frac{1}{\tau_{er}} = 4\,10^{12}\,e^{-\frac{\Delta H}{RT}}$$

Growth rate indep. of enzymatic comp in flavor group of enzymes.—

We assume N the same (indep of M-metabolites flow through τ_{gen}) and the conc of each remains unchanged.

Q N+d-s flow through and their conc remains the same.

R-N+d do not flow through and are just diluted out by growth.

~~explanation~~ ~~time available for Prot. synth.~~

$$N = \tau_{gen} - N(\Delta E)\,[\text{illegible}]\,R(1-R) \,/\, (\tau(X) + \tau(XA))$$

Temperature coeff.

$$Q_{10} \quad e^{-\frac{\Delta H}{RT} + \frac{\Delta H}{R(T+10)}}$$

$$e^{+\frac{\Delta H}{R(T)^2} 10} = e^{\frac{16~~0000~~}{6~~00~~ \times 3~~00~~}}$$

about $e^{0.9} = 10^{0.4}$

$$Q_{10} = \boxed{\text{about } e}$$

In ~~[illegible]~~ minimal of temp drops 10 degrees spawnbrate should drop on account of this effect

from 1 to $\frac{1}{2} + \frac{1}{2 \times 2.7}$

$= 0.5 + 0.18 = 0.68$

ratio ~ 1.5 2

What about first term?

$$I \approx \frac{1}{AS} \frac{m}{1+\frac{S}{K}} = \frac{1}{AK\frac{S}{K}} \frac{m}{1+\frac{S}{K}} = \frac{\text{[illegible]}}{A}$$

Good Ross paper

Protein synthesis

correction. —

$A = 3\,10^{10}$ $\frac{1}{\tau_{ev}} = \frac{1}{3} 10^{12} e^{-\frac{\Delta H}{RT}}$

2nd term page 11 * of old paper *

τ_0 (II nd term) Fully induced

$\frac{10000}{\tau_0 \ldots} = \frac{1}{2.5}$

$= 70 \times 60$

$\frac{1}{A} \frac{\rho}{K} \ln m = \frac{1}{5}$ sec

$m = 1000$

$7\,\tau_{ev} = \frac{1}{5}$ sec

$\tau_{ev} = \frac{1}{35}$ sec $\sim \frac{1}{35}$ sec

$\frac{1}{\tau_{ev}} = 35$

$\frac{5}{A} \ln m = K =$ or $35 = \frac{1}{3} 10^{12} e^{-\frac{\Delta H}{RT}}$

$\frac{35}{3 \times 10^{10}} = K$ mol/cc $= 10^{-9}$

K mol/l $= 10^{-6}$

$100 \sim 10^{12} e^{-\frac{\Delta H}{RT}}$

$1 \sim 10^{10} e^{-\frac{\Delta H}{RT}}$

$\Delta H = 15{,}000$ Cal

$23 = \frac{\Delta H}{600}$

$\frac{1}{A\rho} \frac{m}{1 + \frac{\rho}{K}} = \frac{1}{5}$

$\frac{1}{A\rho} = \frac{1 + \frac{\rho}{K}}{5000} \approx$

$A\rho \cong 500$

ρ (mol/cc) $= \frac{500}{3\,10^{10}} \cong 2\,10^{-8}$ mol/cc $= 2\,10^{-5}$ mol/l

ΔH for mid weight $\frac{100}{6}$

$K = 10$

gives of course same ΔH

$$I_{st}^{term} = \frac{\tau_{ev}}{A^2} \frac{KA}{\rho} \frac{\cancel{A}}{\cancel{A} + \frac{\rho}{K}} \rho \tau_{ev}$$

4

$$I_{st\,term}(\text{better}) = \frac{\tau_{ev}}{A^2} \frac{KA}{\rho} \frac{m/A}{\frac{1}{A} + \frac{\rho}{KA}} = \frac{1}{A} \frac{m}{\frac{1}{A} + \rho\tau(ev)}$$

$$= \frac{m}{1 + A\rho\tau_{ev}}$$

first term: ? → $\frac{m}{1 + 500\rho \frac{1}{2}\tau_e}$

$$\frac{m}{1 + 500 \frac{1}{35} \rho_1}$$

ratio: $\frac{\rho_1}{\tau_1 ev} \Big/ \frac{\rho_2}{\tau_2(ev)}$

if τ_{ρ} does not ~~increase~~ change with temp — ~~falls~~ first term would increase ~~decrease~~ by perhaps e

$\frac{1}{2} e$ + 0.18

I II

no Good because τ changes

gene, which is a desoxyribose nucleic acid molecule may be a sequence [illegible] actually forms the enzyme. But the enzyme must ~~simply refer to structure along~~ ~~that plays an active~~ be formed by a structure which must contain the same information as the gene ~~that a sequence of amino acids that actually line up along the gene are joined by some chemical reaction chain into a polypeptide which then in turn folds up into the enzyme.~~

Leaving this question open we shall simply speak ~~as the paragene~~ of structure that does form the enzyme as the "paragene."

~~It has been suggest~~

The amino acids must somehow be able to read the code of the paragene, perhaps ~~they are each amino acid is~~ carried ~~on~~ on ~~a trinucleotide~~ a specific molecule which can read the code and permits each amino acid to find its "proper" position alongside of the paragene. No satisfactory model has so far been described even though there was a suggestion by Crick that each amino acid might be carried by one

On the rates of Protein synthesis in bacteria.—

~~It is believed Generally that a specific strand of Nucleic acid~~

It is ~~believed~~ believed that the sequence of amino acids in a given ~~enzyme~~ enzyme ~~is~~ may be determined by the sequence of the purine and pyrimidine bases along the gene which is specific for the production of this enzyme. This does not necessarily mean that the ~~amino acids~~ ~~enzyme is actually formed on the gene which is a [illegible] base nucleic acid polymer. Therefore we shall designate here the polymer that actually [illegible] actually forms the enzyme, this task might be performed by another entity which might conceivably be a ribose nucleic acid but which must contain the same information as the gene. Leaving this question open we shall~~

now stripped from the amino
acid complex from the
[illegible] thus making ~~[illegible]~~
~~[illegible]~~ the space free for ~~[illegible]~~
carriers which are loaded
with amino acid to attach
to the [illegible]. ~~[illegible]~~
~~This picture~~ assumes again ~~that~~
the concentration of the stripped
carriers in the ~~[illegible]~~ cell is
small compared to the amount
of the carriers that are loaded
with AA (—

If the amino acid ~~is~~ were carried
as an acid anhydride ~~when~~
~~[illegible]~~ on a phosphate group
then about 12 000 calories
will be freed when the AA
is split off ~~which [illegible]~~ thus you [illegible]
~~be plenty for~~ and ~~the the~~
~~AA might carry~~ the
~~free energy~~ that each AA
might carry the energy
need for the formation
of peptide bonds between
the adjacent amino acids.

specific trinucleotide and ~~the~~ each ~~trinucleo~~ trinucleotide may find its proper place along the paragene (because ~~by attaching through hydrogen bonds to the complementary~~ the nucleotides of the trinucleotides may attach through the hydrogen bonds (6 in toto) to the complementary nucleotides on the paragene. The coding problem involved is discussed in a recent paper.*

We shall for the purposes of our arguments merely assume that ~~alongside of the paragene~~ the amino acids — which might be complexed with some carriers and diffuse freely around in the cell may attach to the proper places alongside of a paragene, ~~and~~ that a chemical reaction then joins the ~~amin~~ amino acids into a polypeptide.

That this polypeptide folds up into the enzyme, which evaporates at a fast rate $\frac{1}{\tau(E)}$; and the carriers which are

small K is longer and vice versa. We shall assume that K has the same value whether the carrier is loaded ~~or is~~ with ~~or~~ the AA or stripped. ~~We shall also assume that all carrier which are loaded with any one of the 20 different AA~~ Since there are 20 different AA there are 20 different loaded carriers and for the sake of argument we shall assume that they all have the same concentration ξ within the cell. —

We may now ask ~~the~~ what determines the rate at which ~~the~~ such a paragene can synthesise its enzyme.

~~We shall assume for all purposes of our computations that the~~ This ~~[illegible]~~ depends of course on the number of amino acid residues, m, contained in the enzyme and for the purposes of our computations we shall

Prior the onset of the chemical reaction chain that splits off the amino acids from the carriers which are attached to the paragene may attain an equilibrium distribution which ~~is~~ may be symbolically represented as follows:

In the equilibrium there is ~~constant~~ evaporation of the carriers and condensation of the carriers ~~and~~ ~~with a certain number~~ and the number of gaps present is determined by the concentration of the amino acids and the equilibrium constant of the carrier for combining with the proper spots on the paragene. ~~For our case~~ ~~We shall assume that the equilibrium~~ If the binding energy ΔH ~~of the~~ ~~for this carrier is small~~ of the carrier to the paragene is

the polypeptide ~~leaves to me shall assume~~ (evaporates) fold into an enzyme molecule and evaporates within a time interval $\tau(E)$ which we assume is so small that it can be neglected for our present purposes. But it will now take a time τ_2 for the ~~carri~~ carriers which are now stripped to evaporate and for carriers that are loaded to take their place so that a condition close to equilibrium is again established and the next chemical reaction chain can sweep along the sequence.—

For τ_2

$\tau_0 =$

We may now see that ~~the~~ if (at a fixed value of ξ—) we may take ΔH ~~very~~ large so that K is small the ~~term because~~ term in τ_0 becomes large ~~f~~ so that enzyme synthesis is small and if we make ΔH small and K lower so that K is large the first

assume that the enzyme has a mol weight of about 100000 and accordingly contains about 1000 AA residues ($m = 1000$). —
~~the time it takes~~
~~If we~~ Let us assume that the chemical reaction chain which joins the assembled amino acids into a polypeptide starts from one end, the head of the polygene. ~~Then the time that it takes~~ and proceeds very fast until it reaches the first gap, then there is a delay lasting ~~the~~ the time ~~$\frac{1}{A\rho}$ (where A is the~~ $\frac{1}{A\rho}$

where A is a constant that we can estimate from kinetic theory. Since the number of gaps which cause such delay in equilibrium is given by

$$\text{number of gaps} = \frac{m}{1 + \frac{\rho}{K}}$$

The total time ~~T~~ for the reaction chain to be completed is

$$T_1 = \frac{1}{A\rho} \frac{m}{1 + \rho/K}$$

medium — ~~like~~ something trouble — forms same
which contains all AA, and then
a short time the bacterial
pop becomes so large that
the AA's are exhausted and then
the bacteria ~~[illegible]~~ have to turn to grow
on inorganic nitrogen. —
In these conditions the bacteria
have a generation time of 70
min.
The bacteria may contain about
10 000 genes and may make
1000 different enzymes.
~~Some are present in large~~
~~quantities some in~~
(approx.) There may be 10000 molecules
(in the steady growing state of the culture)
of ~~one~~ enzyme present. If the
production of the enzyme is ~~[illegible]~~
enhanced by adding an "inducer"
to the medium but on the
average ~~[illegible]~~ there may be
only 60 molecules of any given
enzyme present. According
to the notion here represented
the different ~~enzyme~~ ~~[illegible]~~ which ~~[illegible]~~ are
present in vastly different quantities
differ not in the number of

term gets large and again the
enzyme synthesis is small.

There is an optimum value
for $\frac{S}{K}$ at

which the enzyme synthesis is fastest
and for $n = 1000$ this optimum
is at $\frac{S}{K} =$ and at this

value we just have
$\tau_1 \sim \tau_2$

We shall now boldly assume
that when bacteria grow at
their favorite temperature in
a nutrient medium which
contains no AAs but just inorganic
constituents and a carbon
source like for instance
sugar
they are growing under
optimal conditions
where $\tau_1 = \tau_2$
In nature if even a bacterium
should at one time find neither

growing the bacteria rates in minimal medium with only inorganic Nitrogen present but in broth where the conc of all amino acid is high then we can reason as follows:
~~the growth rate in broth is~~ The generation time in broth is $\frac{1}{2}$ of that in minimal medium
In minimal med the bacteria make 1000 in ~~600~~ 4000 sec in broth they make it in 2000 sec.
This we may now say means that in broth because ρ is high the first term becomes very small the second term however is unchanged $\left[\frac{1}{AK} \ln n\right] = \frac{7}{AK} = \frac{1}{5}$

$AK = 35$

~~$AK = 5$~~ sec

hence we have

$$\frac{2000}{10000} \cdot \frac{~~14000~~}{2000} = \frac{7}{AK}$$ ~~[illegible]~~

~~$AK = 3 \cdot 10^{10}$~~ for

$$\left.\begin{array}{l} M = 1000 \\ \sigma = 10^{-15} \\ p = \frac{1}{100} \end{array}\right\}$$

$$v = \sqrt{\frac{2RM}{\pi M}}$$

$$v = 5 \times 10^{3}$$

$$A = 6\,10^{23}\, v\, p\, \sigma$$

$$\boxed{A = 3\,10^{10}}$$

$$3 \cdot 10^{26} \cdot 10^{-17} = c$$

for $p = \frac{1}{100}$

$\sigma = 10^{-15}$ (~~10~~ square $\AA$)

$$\sigma p = 10^{-17}$$

genes which manufacture
the particular enzyme but rather
the fraction of the time during
which a gene is permitted
to make enzyme is different
for the different enzymes. If an
enzyme is fully induced ~~it~~
~~is~~ that is if the ~~gene~~ gene
forms the enzyme all the time
there are about 10,000 molecules
present in the cell and this
holds whether the ~~enzyme~~
bacterium is allowed to grow
fast or is forced to grow slowly
by changing ~~the concentration~~
controlling the rate of its
growth through controlling
the concentration of any
one amino acid. ~~This can~~
~~be done~~ Such control of ~~[illegible]~~
the growth rate is possible
in [illegible] [illegible] —
— chemostat — [illegible] If we
now ~~perhaps somewhat~~ readily
say that the same number of enzymes
(10,000) will be present in the growing cell also
when we speed up the growth by

[illegible] [illegible] [illegible]

(2) $\tau_2 = \frac{1}{A\rho} \frac{m}{1+\frac{\rho}{K}}$ | $\frac{\rho}{K} = x$ — $\frac{1}{A\rho}\frac{m}{1+x}$ | $\frac{m}{A\rho}\frac{1}{(1+x)^2}$

(1) $\tau_1 = \frac{\rho}{\rho A K} \ln m$ | $\frac{x}{A} \ln m$ | $\frac{1}{A} \ln m$

swap!

$$\frac{m}{A\rho}\frac{1}{(1+x)^2} = \frac{1}{A\rho} \ln m \; (1+x)^2$$

$$\sqrt{\frac{m}{\ln m}} = 1 + x$$

$$\frac{\rho}{K} = \sqrt{\frac{m}{\ln m}} - 1 \simeq 12 - 1 = 11$$

~~check from (1) $K = \frac{\ln m}{A\tau_1}$~~

$$\tau_2 = \frac{m}{\sqrt{\frac{m}{\ln m}}} = \underbrace{\sqrt{m \ln m}}_{84} \frac{1}{A\rho} =$$

$$\tau_1 = \frac{1}{A\rho} \frac{\rho}{K} \ln m = \frac{1}{A\rho} \ln m \left(\sqrt{\frac{m}{\ln m}} - 1\right)$$

$$\tau_1 = \frac{1}{A\rho}\left(\underbrace{\sqrt{m \ln m}}_{84} - \underbrace{\ln m}_{7}\right)$$

both within 10% of the same

H

This gives $K \cong 10^{-9}$ mol/cc
$K = 10^{-6}$ mol/l

~~[illegible]~~

$AK = 35$ gives rate of evap = Tev

---

rate of evap $= 10^{12} e^{-\frac{\Delta H}{RT}}$ for molecular weight 100

for $M = 1000$. rate of ev $= \frac{1}{3} 10^{12} e^{-\frac{\Delta H}{RT}}$

ΔH = 15000 Cal

from $AK = \frac{1}{3} 10^{12} e^{-\frac{\Delta H}{RT}} \cong 35$/sec

Q_{10} for ~~[illegible]~~ $AK \sim Q_{10}$ for $K = e^{0.9}$

Exp. Temp. ~~cutoff~~ of V. fully ~~induced~~ and say half fully induced!

~~Now when growing in minimal medium we saw optimum at $\frac{\rho}{K} \sim 10$~~

~~since $K = 10^{-6}$ mol/liter $\rho \cong 10^{-5}$ mol/l~~

ΔH from $\frac{10^{12}}{43} e^{-\frac{\Delta H}{RT}} = AK$

$= 3\,10^{10} \times 5\,10^{-4}$

$e^{-\frac{\Delta H}{RT}} = 9 \times 5\ 10^{-13} = 4.5\ 10^{-12}$

$-\frac{\Delta H}{RT} = \ln 4.5 - 12 \times 2.3$

[illegible] 23 $\quad 25.15 = -24$

1.15

$\Delta H = 14500$ Cal

Ingelfinger O.K.!

ΔH to be calculated straight as before from Taslum

If metaxime more than 1 presque say 10 then AK is ten times ~~lower~~ ~~the~~ and ~~K is 10 times~~ being the same as calculated but A ten times higher and K " times lower

For a factor 10 drop in K the binding energy increases by 1400 Cal and ρ goes down with K

Dont use breath argument except as follows:

(H)

~~$\tau_1 = AK \ln m$ (totally term of the breath)~~

~~$AK \ln m = \frac{1}{2000} = 5/\text{sec}$~~

~~$A = 3\,10^{10}$~~

~~$K = \frac{5}{A \ln m} = \frac{5}{21} 10^{-10} =$~~

only term in breath ↓

$\tau_1 = \frac{1}{AK} \ln m = \frac{12000}{10000}$ ~~$= 1/5/\text{sec}$~~ ~~$\frac{50}{21} 10^{-11} = 2\,10^{-11}$ mol/cc~~

$K = \frac{7}{5 \times 3 \times 10^{10}} \cong$ ~~$\frac{7}{5} 10^{-10}$ mol/cc~~ ~~A~~ $2\,10^{-7}$ mol/l

$\frac{\rho}{K} = 11 \quad \rho \cong 2\,10^{-6}$ mol/l

Check!

from $\tau_2 = \frac{1}{5}$ sec we would get

~~$\frac{K}{5} \times 84$~~ ~~$\frac{\rho}{A} = \frac{84}{A}$~~

$\rho \quad \frac{\rho}{5} = \frac{84}{5A} = \frac{84}{15\,10^{+10}} = 5.5 \cdot 10^{-10}$ mol/cc $= 5\,10^{-7}$ mol/l

$\frac{7}{15} 10^{-10} = \frac{1}{2} 10^{-10} = 5\,10^{-11}$ mol/cc $= 5\,10^{-8}$ mol/l

$\frac{35}{AK} = 1 \quad K = \frac{35}{3} 10^{-10} \quad \frac{\rho}{K} = 11$

$\rho \cong 5\,10^{-7}$ mol/l

But why can thermophiles not grow faster they "evaporate" faster and in broth they condense as fast as one could wish! Is there a limit to ρ_x on basis of solubility for one amino acid?
Work this out!

Remarks for paper
call: $\tau_1 = \tau$(~~assembling~~ & gap filling)
$\tau_2 = \tau$(~~[illegible]~~ assembling)

$\tau(AA) = 2 + \tau_2$

write $\tau(\text{carrier}) = \frac{1}{AK} = \frac{1}{35}$ sec

Metabolite M and M'
$\tau(M) \sim \tau(M')$ may have a $K > 10^{-6}$ — 20 times larger
$5 \cdot 10^{-8}$ — A may be 3 times larger
or AK is 60 times larger or
$\tau(M), \tau(M) \approx \frac{1}{35 \times 60}$ sec $= \frac{1}{2000}$ sec

Compute $\tau(R)$
~~of repre~~ suppression either 1000 fold
or 10000 fold

4

In broth first term being zero second term is only left and one should be able to make 10000 molekules of the enzyme in half the time If all enzymes retain their proportions — the law of which I am very tentatively postulating the growthrate should double: It does.—

Temp coeff of K should be temp coeff of growthrate in broth

Not so in minimal medium there the growthrate should go down more slowly

Do experiment!

Presentation: Would it at 37°C not be better to assume K = 15,000 cal and then deduce fastest rate at which bacteria can grow in Broth? —

a.)

~~$$\tau(R) = \frac{1}{A\,k(R)} = \frac{1}{R}\,\frac{1}{3\,10^{10}}\;10^{3}\,\frac{\tau(AA)}{\tau(E)}$$~~

b.) $$\frac{1000}{} = \tau(E)\,\frac{RA}{A\,k(R)}\,\frac{1}{\tau(AA)}$$

$$1000 = \frac{\tau(E)}{\tau(AA)}\;\frac{\tau(R)}{\tau_{AA}}\;RA\,\tau(AA)$$

$$\frac{\tau(R)}{\tau(AA)} = 1000\,\frac{\tau(AA)}{\tau(E)}\;\frac{1}{RA\,\tau(AA)}$$

$$\frac{\tau(R)}{\tau(AA)} \times \frac{\tau(AA)}{\tau(E)} = 1000\,\frac{1}{RA\,\tau(AA)}$$

a.) $$\frac{\tau(R)}{\tau(E)} = 1000\,\frac{1}{RA\,\tau(AA)}$$

b.) $$\frac{\tau(R)}{\tau(E)} = 10^{4}\,\frac{1}{RA\,\tau(AA)}$$

a) ~~$\frac{\tau(R)}{\tau(E)} = 10^{3}$~~ $\boxed{\tau_{max} = 5\,sec}$

$$\frac{\tau(R)}{\tau(E)} > \quad R = \frac{10^{3}}{\frac{\tau(R)}{\tau(E)}\,A\,\tau(AA)}$$

$$\frac{1}{3}\,10^{-7}\,\frac{1}{5} >> 1$$

means

this means a) $1000 \frac{\tau(E)}{\tau(A)} \frac{R}{K(R)} (1-\pi)$ H

or b.) $10{,}000 =$

a.) $\frac{R}{K(R)} \frac{(1-\pi)}{1000} = \frac{\tau(AA)}{\tau(E)}$

$\frac{R}{K(R)} = \frac{1000}{\tau(E)} \tau(AA)$

assume $\frac{1}{\tau(E)} > 25$ ~~$\frac{\tau(AA)}{\tau(E)}$~~

$\tau(AA) = \frac{1}{2.5}$

$\tau(E) = \frac{1}{25}$

~~a.) $\frac{R}{K(R)} > 25{,}000$ 10^4~~

~~b.) $\frac{R}{K(R)} > 250{,}000$ 10^5~~

~~a) $\frac{K(R)}{R} < 10^{-4}$~~ ~~$K(R) < R\, 10^{-4}$~~

~~b.) $\frac{K(R)}{R} < 10^{-5}$~~ ~~$K(R) < R\, 10^{-5}$~~

~~[illegible] is 10^{-10} as is~~

~~b.) $K(R) < R\, 10^{-5}$~~

~~$K(R) <$~~

~~a.) $\frac{R}{K(R)} = 1000 \frac{\tau(AA)}{\tau(E)}$~~

~~b.) $\frac{R}{K(R)} = 10^4 \frac{\tau(AA)}{\tau(E)}$~~

$$\rho^{mol/cc} \; \frac{1.5\ 10^{-7}}{1 + \frac{\rho}{K}}$$

$$\rho^{mol/l} = \frac{1.5\ 10^{-4}}{1 + \frac{\rho}{K}}$$

$$\rho \cong 1.5\ 10^{-4}\ \frac{K}{\rho}$$

$$\rho^2 \cong 1.5\ 10^{-4} \times 5\ 10^{-8}$$

$$= 1.5\ 10^{-12}$$

$\rho =$ [crossed out]

$$T_{1/2} = \frac{1}{5}\ \text{sec} = \frac{100}{A\rho}$$

$$A\rho = 500$$

$$\rho = \frac{500}{A} = \frac{500}{3\ 10^{10}} = 2\ 10^{-8}\ \text{mol/cc}$$

$$\rho = 2\ 10^{-5}\ \text{mol/l}$$

H

letter many classical and non classical formulas side by side! Two formula are identical!

Case of AA limitation: (permease-less organism for experiment) Select permeaseless with chemostat: Take ~~[illegible]~~ wild type and grow it slowly with chemical analog of AA present ~~[illegible]~~ Permeaseless will appear in growth tube after a while. —

Let ~~[illegible]~~ the fraction of ~~[illegible] which~~ is say tryptophane. ~~[illegible]~~ ~~[illegible]~~ there all AA high except tryptophan which has conc. X [assumption now made ~~[illegible]~~ the same for all enzymes]
for low tryptophane ~~first term~~

$$\tau(\text{to fill gaps}) = 0 + \frac{19m}{A\rho_{tryp}\left(1+\frac{S_{tryp}}{K}\right)}$$

for $m = 1000$

$y = 10\%$

growth rate drops to half when $\tau \simeq \frac{1}{5}$

$$\frac{1}{A\rho}\,\frac{100}{1+\frac{S_{tryp}}{K}} = \frac{1}{5}\text{ sec} \qquad \frac{3\times 500\;10^{-10}}{\frac{1}{5}\times10^{10}\left(1+\frac{S}{K}\right)} = S$$

$$x = \frac{-10^{-9} \pm \sqrt{10^{-18} + 8\,10^{-17}}}{2} = \frac{+9\,10^{-8}}{2}$$

$$\rho = 4.5 \times 10^{-8} \text{ mol/l}$$

$$\boxed{4.5 \times 10^{-5} \text{ mol/liter}}$$

ρ_0 = [illegible] conc.

$$\frac{1}{KA\frac{\rho_0}{K}} \frac{q_m}{1+\frac{\rho_0}{K}} = \frac{1}{5}$$

[illegible] AK

$Ak = 35$

$$\frac{1}{x} \cdot \frac{1}{1+x} = \frac{35}{5 q_m} = \frac{7}{q_m} = \frac{1}{\alpha}$$

$$\alpha = x + x^2 \qquad \alpha = \frac{q_m}{7}$$

$$x^2 + x - \alpha = 0 \qquad 4\alpha = \frac{4 q_m}{7}$$

$$x = \frac{-1 \pm \sqrt{1+4\alpha}}{2} = \frac{-1 + \sqrt{4\alpha}}{2} \qquad 4 \cdot \frac{1}{100}$$

$$\frac{\rho_0}{K} = \frac{\sqrt{\frac{4 q_m}{7}} - 1}{2}$$

for $q = \frac{1}{10}$

$$\frac{\rho_0}{K} = \frac{\sqrt{\frac{400}{7}} - 1}{2} = 3.3$$

$$\rho_0 = 3.3 K$$

H

4

Check proper

$$\tau_2 = \frac{1}{A\rho}\frac{m}{1+\frac{\rho}{K}} = \frac{10^4}{A\rho} = \frac{1}{5}\ \text{sec}$$

$$\frac{5\ 10^{2}}{A} = \rho = \frac{5}{3}\ 10^{-8}\ \text{Mol/cc}$$

$$= 2\ 10^{-5}\ \text{Mol/liter}$$

$$\tau_1 = \frac{1}{5\ \text{sec}} = \frac{\ln m}{\ } \frac{1}{AK}$$

$$K = \frac{35}{A} = 10^{-9}\ \text{mol/cc}$$

$$\rho = 10^{-8}\ \text{mol/cc}$$

$$\rho = 10^{-6}\ \text{mol/l}$$

control

$$\frac{1}{5}\ \text{sec} = \frac{1}{A\rho_{hyp}}\frac{100}{1+\frac{\rho_{hypot}}{K}}$$

$$\rho = \frac{500}{A}\frac{1}{1+\frac{\rho_{hypot}}{K}}$$

$$\rho_{hy} + \frac{\rho_{hy}^2}{K} = \frac{500}{A} = 2\ 10^{-8}$$

$$K\rho + \rho^2 = 2\ 10^{-8} K$$

$$AK = 35/\text{sec}$$

$$K = 10^{-9}$$

$$10^{-9}\rho + \rho^2 = 2 \cdot 10^{-17}$$

$$\frac{-b \pm \sqrt{4b^2 - 4ac}}{2a}$$

~~$\rho = 10^{-}$~~

$20\ 10^{-16}$

$5\ 10^{-8}$

What binding energy say

$K = 10^{-12}$ mol/liter $|| 1400 \times 7 \; 10^{10} = 10$ Kcal

What is $\frac{\tau(R)}{\tau(E)}$

$$\tau(R) = \frac{1}{AK} = \frac{1}{3\,10^{10} \times 10^{-15} \text{ mol/cc}} = \frac{10^{5}}{3} \text{ sec}$$

Rise of ? line in Novick's experiments after many generations shows suppression of permease may be by factor 10^{5}

If we make K very ~~large~~ small we get a non poisson distribution of enzyme; some bacteria will be ~~locked up~~ covered "forever"; others make more than one enzyme! In the case of permease this gives a non linear rise of Novick R when repressor goes down. (inducer goes up)

Therefore induction of a permease may permit measurement of K(R)!

↓ slower than linear!

4

Concentration of "hypophosphane" in test tube probably 25 10 γ/l = 250γ/l

---

~~Assume~~ ~~$\frac{\bar{c}(R)}{\bar{c}(E)}$~~

What is value of R for max fold suppression

$$1000 = \frac{\bar{c}(E)}{\bar{c}(HA)} \frac{R}{K(R)} \quad R = 1000 \text{ or } 10^4 \; \frac{\bar{c}(HA)}{\bar{c}(E)} K(R)$$

assume: $\frac{K(R)}{K(\text{carrier})} = 10^{-4}$

$K(\text{carrier}) = 10^{-6}$ mol/liter
$K(R) = 10^{-10}$ mol/l

$$R = \underbrace{1000}_{10^4} \times 10 \times 10^{-10}$$
$$\text{or } 10000 \times 100 \times 10^{-12}$$
$$10000 \times 100 \times 10$$

$\frac{R}{K(R)}$; 10^{-6}; 10^{-4}; 10^{-6}; 10

$\frac{\bar{c}(HA)}{\bar{c}(E)}$

Example ~~K(R)~~

~~Binding en of~~

~~Bind~~ ΔH for M assume $K = 10^{-5}$ mol/l

$$A_0 \sqrt{\frac{M_0}{M}} K \qquad \frac{1}{AK_{-5}} = 10^{12} e^{-\Delta H}$$

$$\sqrt{\frac{M_0}{M}} 10^{12} \cdot e^{-\frac{\Delta H}{RT}}$$

relationship between ΔH and K is independent of mass.

Non permease exps
to determine "something"
could one measure number
of bact which have enzyme
by looking at colony size
distribution under
non gratuitous conditions
~~in roughly repressed case?~~
Hey! If lactose does
not get into cell without
permease how does it
induce permease? ?
Maybe at low lactose ~~as~~
(as only carbon source we
could see how many
cells have enzymes for only
these will grow into
colonies. —)

H

As enzyme is worked for paraspine or gene how can gene reproduce?? Will this force us back to "trigger theory."?

When does deviation from Poisson distribution become marked?
When $\tau(R) \times 10^{-4} \gg \tau(AA)$

suppression factor

when $\tau(AA) = \frac{1}{2.5}$ sec

$\tau(R) > \frac{10^4}{2.5} = 2000$ sec

~~R $\frac{1}{1+\frac{M^*}{K(M)}}$~~ M^* rises linearly

~~when R~~ In the non poisson ~~Re~~ region where R falls linearly & there is no apparent change in permease because of bunching! (assuming $\left(\frac{M^*}{K(M^*)} \gg 1\right.$ region$\Big)$

ΔH for conversion
from enaptidine of wo...

$$35\frac{\not{1/2}}{\not{35}} = \frac{10^{12}}{3} e^{-\frac{\Delta H}{RT}}$$

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

~~2.3 × 13 = ΔH/RT~~

~~30 × RT = 18,000 cal~~

Check!

$$\frac{1}{AK} = \frac{10^{12}}{3} e^{-\frac{\Delta H}{RT}}$$

$$AK = \frac{10^{12}}{3} e^{-\frac{\Delta H}{RT}}$$

100 = ..

OK For paper

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

$$23 = \frac{\Delta H}{RT}$$

15,000 cal

less 5,500 less

gives 9500

Sept 2 /57 H

New theory!

$AR\,\tau(E)$ = probability of chem

$N = \frac{1}{AR\,\tau(E)}$ ~~HC~~

$N = \frac{1}{3\,10^{10}\,\frac{1}{100}\,R}$ up to $N = 10^4$

~~$N = \frac{1}{3\,10^{10}}$~~

$1 = \frac{1}{3\,10^{10}\,\frac{1}{100}\,R}$

$R = \frac{1}{3\,10^8} = \frac{1}{3}\,10^{-8}$ mol/cc

$\frac{1}{3}\,10^{-5}$ mol/l

if $\tau(E)$ longer than $\frac{1}{100}\,\frac{3}{\text{sec}}$ R can be correspondingly smaller

$R = 3\,10^{-6}$ mol/l

overlap time if ionized $\frac{1}{35}$ sec to stretch this to 10×4000 sec $= 40{,}000$

added to ΔH about $5 \times 1400 = 9000$ cal

ΔH for Arginine would be for $K = 10^{-2}$ $4 \times 1400 = 5500$ cal less than ΔH for carrier

10^{-20} mol Arg/sec

$6\ 10^{23}$ — $6\ 10^{3}$ molecules of Arg made

If made by 100 enzyme molecules

$$\frac{6000}{100} = 60$$

τ(turnover) $= \frac{1}{60}$ sec

~~$X = 10^{-6}$ moles~~

fraction of ~~protection~~ / sec

$\frac{A[M]}{60}$ ~~sec~~ $= \frac{3\,10^{10}[M]}{60}$ — mol/cc protected

If $M = 10^{-7}$ mol/cc $= \frac{3\ 10^{6}}{60}$ sec

10^{-4} mol/l

energy to $\frac{1}{2} 10^{-6}$ ~~M~~ 10^{-4}

two fold increase $M = 10^{-4}$ mol/cc

$K = \frac{1}{2} 10^{-6}$

$$N = \frac{1}{AR\left(\frac{1+\frac{1}{K}}{1+\frac{M^*}{K(M^*)}}\right)\tau(E)}$$

prob to be free

$$= 1 - \frac{\frac{M^*}{K(M^*)}}{1+\frac{M^*}{K(M^*)}} =$$

Average ~~time to~~ number of trajects which it will go with no ~~split~~

$$\int^{m} n \frac{p}{(1-p)^n}$$

p is prob for hit $\frac{AR\,\tau(E)}{1+\frac{M^*}{K(M^*)}}$

$$\int_0^\infty n\, e^{-np} \cdot p\, dn = \frac{1}{p}\int_0^\infty x e^{-x} dx$$

turnover number

e^{np}

pe^{n}

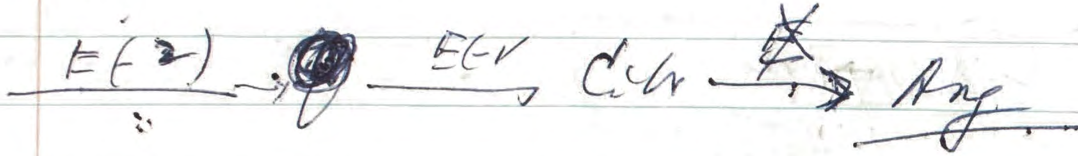
~~[illegible]~~ 10^{-13} gm Protein

$\frac{1}{20}\, 10^{-13} = \frac{1}{2}\, 10^{-14}$ gm Any

made in 4000 sec

$\frac{1}{8}\, 10^{-17}$ gm Any/sec $= 10^{-18}$ gm

Chamber

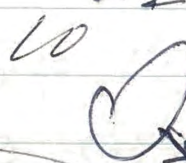


M*

W

B

40000. 60000 ΔE



$\rho =$

10^{-2}

$N = \frac{1}{\rho}$

$\rho = B(E) A[R] \frac{1}{1+\frac{[M:]}{K[M]}}$

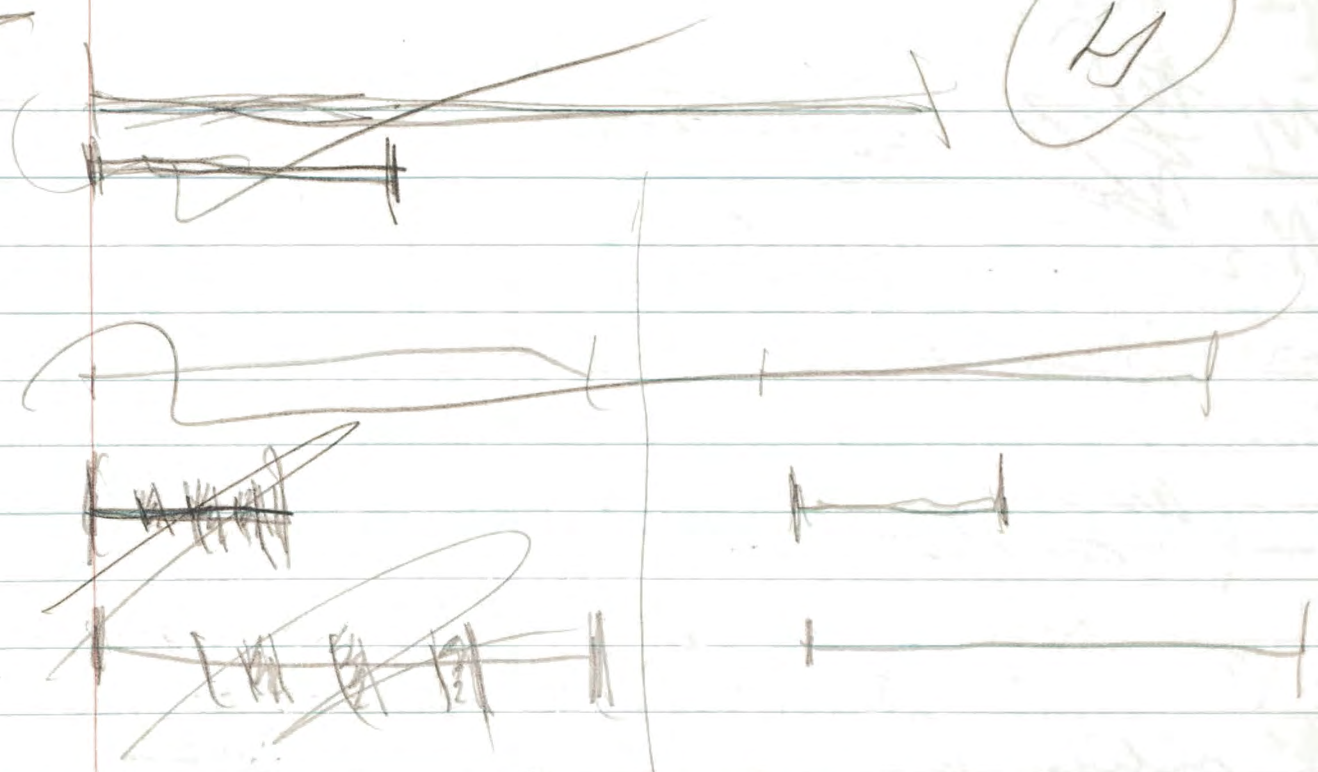
10^{-4} 10^{-6} m/l

M* nal

M*, E M

cytoplasmic

[illegible]



$$\frac{N_1}{N_2} = \frac{\dfrac{1}{\tau(E)(1) + \tau(AA)}\ (1)}{\dfrac{1}{\tau(E)(2) + \tau(AA)}\ (2)}$$

~~if $\tau(E)(1) = 100\ \tau AA$~~
and
$\tau(E)(2) = \tau(AA)$ ~~+ τAA~~

~~now if we drop denominator (1) to~~
~~we drop τ~~ half

Assume now (1) highly induced
so that $\tau(E)(\ \ ) \sim \tau(AA)$
and (2) highly repressed
$\tau(E)(2) = 100\ \tau AA$

when we raise $\tau(AA)$ ~~to 100 $\tau(E)$~~
hundred fold expr. (2) will go
to half but expression (1) to
one hundreds of its value. —

old formula
analyses:

$$N = \frac{\tau(gen) - N\,\tau(E)\frac{R}{K(R)}(1-\pi)}{\tau(E) + \tau(AA)}$$

to get $\tau(gen)$:

N_1 small $\quad N_1[\tau(E) + \tau(AA)] + \tau(E)\frac{R}{K(R)}(1-\pi)N_1 = \tau gen$

N_2 large $\quad$ ~~$N_2 \neq N_1(\tau(AA) + \tau(E))(1 + \frac{R}{K(R)}(1-\pi))$~~ —

$$N_2 = \frac{N_1[\tau(AA) + \tau(E)(1 + \frac{R_1}{K(R)}(1-\pi)] - N_2\,\tau(E)\frac{R_2}{K(R)}(1-\pi)}{\tau(AA) + \tau(E)}$$

$$N = \frac{\tau(gen)}{\tau(E)\left(1 + \frac{R}{K(R)}(1-\pi)\right) + \tau(AA)}$$

if τgen is doubled in order
to maintain N $\tau(AA)$ which is small to R
$\tau(AA)$ has to become = R term

$$N_1 = \frac{\tau(gen)/\tau(AA)}{\frac{\tau(E)}{\tau(AA)} + 1}$$

$\frac{1}{B}$

$B = 100$

$$N_1 = \frac{\tau gen}{\tau(E)(1) + \tau(AA)}$$

$N_2 =$

$2N_1$ old

100 $\quad$ large compared to τAA

to 100 $\quad$ 1

$$\frac{N_1}{N_2} = \frac{\tau(E)(2) + \tau(AA)}{\tau(E)(1) + \tau(AA)}$$

1 $\quad$ 1

$$\frac{\int_0^{N_0} n e^{-nh}(1-e^{-h})\,dn + N_0 e^{-N_0 h}}{\int e^{-nh}(1-e^{-h}) \quad + e^{-N_0 h}}$$

$N_0 h \ldots (1-e^{-})$

First term $e^{-h}/(1$

for large h — num: $e^{-h}(1-e^{-h})$

denom $\frac{(e^{-h})}{1-e^{-h}}$ $\qquad e^{-h}$

New theory

to be completed if $(Np \gg 1)$

$h \ll 1$

~~$p \ll 1$~~

$\int$ is replaced by sum

$$N = \frac{\sum_{0}^{N_{max}} n e^{-nh/p} + N e^{-N_{max}h/p}}{\sum_{0}^{N_{max}} e^{-nh/p}}$$

p is probable that ~~energy is not~~ energy is completely

$$N = (1e^{-1h} + 2e^{-2h} + 3e^{-3h} + \ldots)\Gamma$$

$$+ he^{-1h} + he^{-2h} + he^{-3h} + \ldots$$

~~$N = pe^{-h}$~~

~~$p \, p$~~ sum

$$\frac{e^{-1/p}}{1-e^{-1/p}}$$

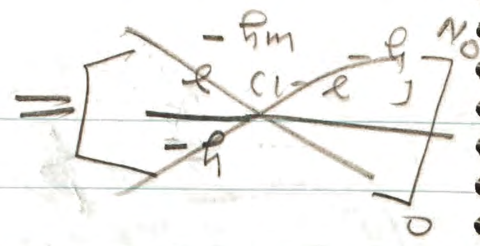
for $p \gg 1$

$$\frac{\sum}{1-e^{-1/h}}$$

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

$$N = e^{-h}$$

$$\int_0^{N_0} m e^{-hm}(1-e^{-h})\,dm =$$



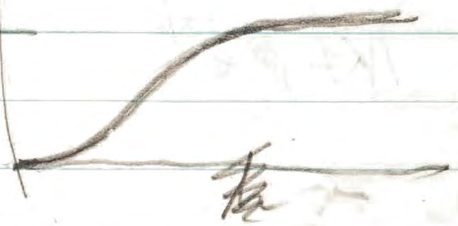
$$= \frac{1-e^{-h}}{-h}\left(e^{-hN_0} - 1\right)$$

$h \ll 1$

Nonlinear ... linear $h = \frac{1}{1000}$ ... $N_0 h = \frac{1}{10}$

$$1 - e^{-(N+1)h} + e^{-Nh}$$

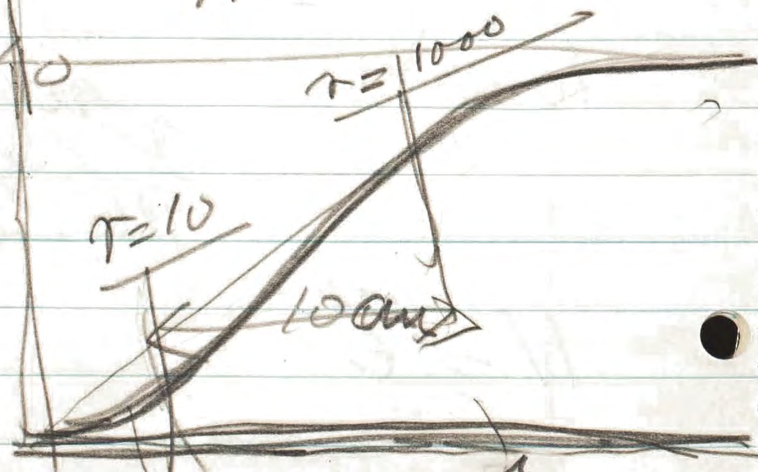
$N = f(h)$ $\quad f(h)$



$$h = \tau(E)\,A[R] \Big/ \left(1 + \frac{M}{K}\right)$$

A is two times smaller ... R is ... more is small

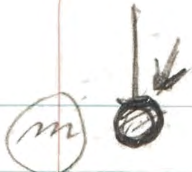
$$\frac{1}{h} = r$$



$$N = F(r)$$

$$r = \frac{1}{h} \qquad r = \frac{1 + M/K}{\tau(E)\,AR}$$

N_0



m

$$n = \frac{\sum_0^{N_0} m e^{-hm}(1-e^{-h}) + N_0 e^{-hN_0}}{e^{-hm}(1-e^{-h}) + e^{-hN_0}}$$

$h \gg 1$

$$\frac{1\, e^{-h}(1-e^{-h})}{e^{-h} \quad e^{-2h} + e^{-2h}}$$

$h \ll 1$

e^{-h}

$$\mu = \frac{}{\frac{1-e^{-h}}{1-e^{-h}}}$$

$= 1 + q + q^n$

$$\frac{1-q^{n+1}}{1-q}$$

$\int$

$$\frac{}{(1-e^{-h})\, 1 + e^{-(N+1)h} + e^{-hN}} \quad ?$$

$e^{-(N+1)h} - e^{-N}$

>>

2f $\tau(M)$ more longer than $\tau(E)$

$h = \frac{1}{1 + \frac{AM}{AR}}$

$h = \frac{AR}{AR + AM + \frac{1}{\tau(E)}}$

$r = \frac{1}{AR}\left(1 + \frac{AM}{AR} + \frac{1}{\tau(E) AR}\right)$

3a $h = AR \frac{1}{AM}$

No

$AK = \frac{1}{\tau(M)}$

for M $\tau(M) = \frac{1}{AK} < \tau(E)$

for M $AK > 100$ $\frac{1}{100}$ sec

K molec $> 10^{-9}$

$A \geq 10^{11}$ ok if $\tau(E) = \frac{1}{10}$ sec

36

$\tau(E) > \tau(M)$

~~for $\tau = \frac{1}{A[R]}(1+\frac{M}{K})$ $AK = 10^{12}$~~

M evap. rate $\frac{1}{35}$ sec for carrier at $K = 10^{-6}$
3 x longer than for carrier
for M < M at $K = 10^{-6}$ $\frac{1}{100}$ sec

$\frac{1}{100}$ sec $\ll \tau(E)$; for $K > 10^{-6}$ (first bullfrog somewhere $\tau(E) > \tau(M)$ if A ≤ ? ≥ ?)

sec

$\tau(E) = \frac{1}{10}$ sec

$A M \tau(E) = 10^4$

$[M]$ mol/cc $\Rightarrow \frac{10^4}{[M] A \tau(E)} = \frac{10^4 \times 10}{10^9}$

$A = 10^9$ for repressor

$= \frac{1}{10} 10^{-4}$ mol/cc

$\rho = \frac{1}{3000}$ (instead of $\frac{1}{100}$) M = or 10^{-7} Mol/liter

but such an enzyme ~~as we shall show~~ it must ~~be expe[illegible] according to the conclusion~~ ~~that we shall se~~ ~~be indisputable~~ ~~according to the no~~ but the formation of such an enzyme can also be enhanced — ~~–~~ we shall be forced to conclude — by a suitably chosen chemical analogue of the precursor.

How can ~~an~~ a chemical compound enhance the rate at which an enzyme is formed in the growing bacterial culture?

~~It is generally held~~

I assume — as is now generally believed — that

Alternatives of 3rd formula with respect to M

$\tau(E) < \tau(M)$

case a

life time $= \dfrac{1}{\frac{1}{\tau(E)} + A M}$

$$h = A_R \frac{1}{\frac{1}{\tau(E)} + A M} = \frac{A_R R\,\tau(E)}{1 + A_M M\,\tau(E)}$$

$$r = \frac{1}{A_R}\left(\frac{1}{\tau_E} + A M\right) = \frac{1(1 + A M \tau(E))}{A_R R\,\tau(E)}$$

limit for large R $= \dfrac{A_M M}{A_R R} = 90\dfrac{M}{R} = r$ where by [illegible]

case b

when [illegible] $A_M \dfrac{\tau(E)}{\tau(M)}$ ... $R\,k(M)\,\tau(E)\,\tau(M)$

$\dfrac{A_M M}{A_R R}\,\dfrac{\tau(M)}{\tau(E)} = r\,N$ ... unimportant

$R\,\tau(E)$

during which an enzyme molecule that has been formed hangs on to the passage.
~~We shall postulate~~
In our search for a ~~model~~ mechanism that can account for the phenomenon of enzyme induction we shall ~~to~~ allow ~~for~~ ourselves to be guided ~~by the law of growthrate independence~~ by a postulate which says: ~~the~~ ~~If the~~ at will as argument. If we ~~slow~~ set the growthrate of bacteria in the chemostat by ~~controlling the rate of protein synthesis~~ using one amino acid as the controlling growth factor ~~the~~ enzymatic composition of the bacteria will be independent of the growthrate. ~~There are exceptions~~ There ~~may~~ be certain obvious exceptions to this rule which will become apparent further below. ~~This means that if~~ I shall keep refer to this postulate in brief as of the law of growthrate independence!

molecules of this enzyme per cell maintained in the steady state in the growing culture is given by

$$N = \frac{\tau_{gen}}{\tau_{syn}(M) + \tau(E\text{-}M)_{E\text{-}M} + \tau(AA)_{AA}}$$

where [M] is the conc. of the metabolite M, ~~and~~ φ[M] is a ~~of~~ function of this concentration ~~which is zero for M = 0 and~~ ~~of which goes to infinity when~~ rises ~~goes~~ to infinity if [M] falls ~~goes~~ to zero and which falls ~~goes~~ to zero if [M] ~~goes~~ rises to infinity.

Preface

There ~~is at~~ exists ~~present~~ no (acceptable) accepted theory of enzyme induction. Through what mechanism may a compound which can combine with an enzyme and which does not necessarily have ~~to react or~~ to react otherwise with that enzyme enhance the formation of that enzyme in a growing

{when T.W.

II Case

$$N = \frac{\tau\, gen}{R\varphi(M) + \tau(E) + \tau AA}$$

$R\varphi$ is the time

continued from previous page

$\tau\, gen \to 10000\, sec$

$$\frac{N_1}{N_2} = \frac{\dfrac{\tau\, gen}{\tau_1(E-M) + \tau(AA)_1\, sec}}{\dfrac{\tau\, gen}{\varphi(M_2) + \tau_2(E-M) + \tau(AA)}} = \frac{\varphi(M_2) + \tau_2 AA}{\tau_1 + \tau(AA)}$$

100

first: 100 : 1 100 Ratio 100

about 100: $\frac{10000}{200}$ = 100 : 50 Ratio = 2

$N_2 \quad \frac{\tau\, gen}{}$

202

1 to 100

~~Having thus postulated for obtaining satisfactory mechanism for enzyme induction we~~

~~Having reached this point we may well consider that enzyme induction is just this~~

Having ~~thus postulated~~ encountered difficulties to ~~obtain a~~ interpret in a ~~satisfactory~~ mechanism that would explain ~~enzyme~~ induction in this most straight forward manner ~~we~~ we may now try if ~~we~~ we can ~~at least~~ perhaps ~~on enzyme repression~~ do better with the phenomenon of enzyme repression. This phenomenon ~~[illegible]~~ which was discussed by Vogel and [illegible] may be described as follows:

Vogel stressed the fact that there is no induction ~~that an~~ [illegible] in the biosynthesis of the level of the enzyme acetylornithinase that an inducer operates in this system at that

$R > \frac{1}{4} 10^{-9}$

$$K \geqq [N+R] = [R] > \frac{1}{4} 10^{-9}$$

$$K \geqq \frac{1}{4} 10^{-6}$$

perhaps even ten times [illegible] higher!

this gives binding energy 15000 cal just about right.

(for N + R we have an A of 3×10^{10})

then growth is assuming [illegible]

$[N+R] = [R]$

George Sacher

$\underline{k}$ (1)

$$\frac{d \ln N}{dt} = -k e^{\alpha t + 2kD}$$

~~$t = A$~~

$$\boxed{\frac{d \ln N}{dt} = -\varkappa e^{\alpha t + \underbrace{2kD}_{B}}}$$

~~$t = A$~~

$$\ln N = -\frac{\varkappa}{\alpha} e^{2kD} e^{\alpha t}$$

$$N = e^{-\frac{\varkappa}{\alpha} e^{2kD} \cdot e^{\alpha t}}$$

mice [2 years]

rats [2 years]

rabbits ~~9 10^-5~~ [5 years]

guinea pig 0 5 years

(2)

dogs

10 years

man

t_0 = mean survival time of control

t = " " " " irradiated

$$\frac{1}{t} - \frac{1}{t_0} = k I$$

k =

rabbit 9×10^{-5}

mouse-rat 17

dog 35

guinea pig 35

$$1 - \frac{t}{t_0} = k D$$

$k = 10$

$h = 10^{100}\ 10^{-5}$

10^{-2}

Mouse ③

Dir Rösky

Single

$B(D) = 300 \times 10^{-6} D + 1 \times 10^{-6} D^2$

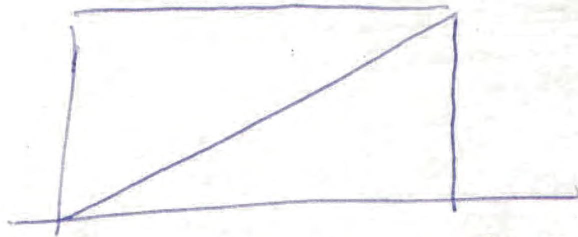
Fractionation

~~B(D, R, θ)~~ $= 300 \times 10^{-6} D + 1 \times 10^{-6} D R \theta (1 - e^{-\tau/\theta})$

$B(D, R, \tau) =$

$\theta = 5$ days

(doses per day (in simple irrad.)



$\Delta t = d$

$t_0 \quad A$

$x \geq x_0$ death

$y > y_0$

$(\bar{x}, \bar{y}, \bar{z})$

$+ \quad y \quad /$

$\bar{X} = t$

speed
constant
with t

which we may call the head of the paragene. If the -Ntd were only more a nucleotide - composed perhaps of three nucleotides - these three ~~two~~ nucleotides could attach with 6 hydrogen bonds to complementary purine or pyrimidine bases on the paragene: If we ~~take 50~~ assume 3000 cal per hydrogen bond we may have a binding energy of

~~the~~ [~~At~~ $Z(R)$ = 4000 sec / ~~AH~~

There must be ~~necessarily~~ for some enzymes a hit ~~Oyen~~ = 4000 sec a hit ~~within~~ by the repressor ~~of~~ within 4 sec (repression by factor 1000)

therefore ~~AR~~ $A_R > \frac{1}{4}$

$[R] > \frac{1}{4 A_R}$ $\quad A_R = \frac{1}{30} 3 \cdot 10^{10} = 10^9$

If conc. of Ntd = [R] Ntd must not attach too much [illegible] to paragene.

$$\frac{1}{1 + \frac{[Ntd]}{K}} \geq 1/2$$

$$\frac{Ntd}{K} \leq 1$$

theory is not obviously wrong. One of the attractive aspects of this theory is that it might [the mechanism which it postulates for adapt enz form] [another] account for the formation of antibodies in mammals including

the mechanism operating in these two phenomena may be similar has been somewhat frequently surmised but it is difficult to compare mechanisms as long as one was not able to describe either.

improbable

that the mechanism of antibody formation might be similar to the mech of adaptive enzyme formation

Fraction ~~of the~~ of time enzyme E ~~[illegible]~~ spends on Parogene combined with M!

free $X = 1$ combined $y = 0$

$$\frac{dx}{dt} = -\alpha X - AMX + \beta y$$

$$\frac{dy}{dt} = AMX - \beta y - \alpha y$$

$$y = \int_0^\infty x \, dt$$

~~words, has been frequently~~ studied in the past ten years but it is ~~often~~ [illegible] difficult to compare the mechanisms ~~of~~ as long as one can~~not~~ describe methods. —

and M^+ can enhance itself

What power does this

mean?

and is sitting on the precipice.
But it is difficult to see why
the un-tiny complex should not
evaporate off the precipice
just as fast as would the
free enzyme ~~itself~~ itself.
Therefore it any. is to
lengthen the time which
such an enz. spends
on the p.q.

I am greatly indebted to Mrs
Mildred Mikes for carrying
out ~~many of the~~ and interpretations
~~and~~ summations upon which
~~the~~ some of the formulae
given in this paper
are based +

Multiple action of Inducer

Inducer can inhibit
enzyme E that makes M
(it also can inhibit E_0)
by inhibiting ME in case
increase [illegible] of M' which induces

$\tau(E)$ ~~R~~ ... $\tau(R)$

~~$\tau(E)$~~

$N_1 >>> N_2$

$\Delta_1 << \Delta_2$

$\Delta_2 >> \tau(AA)_{min}$

Grammatical independence

$$\frac{N_{1a}/\tau_{gen}}{N_{2a}/\tau_{gen}} = \frac{\dfrac{1}{\Delta_1 + \tau(E) + \tau(AA)}}{\dfrac{1}{\Delta_2 + \tau(E) + \tau(AA)}} = \frac{\dfrac{1}{\Delta_1 + \tau(E) + \tau(AA)}}{\dfrac{1}{\Delta_2}}$$

$\Delta_2 >> \tau(AA)$ $\quad$ $\Delta_1 << \Delta_2$

slower ... 2 ... rate of N_2 $= N_2/\tau_{gen}$

$\Delta_2 = \tau(E) + \tau(AA)_{2nm}$

$$\frac{N_{1a}/\tau_{gen}}{N_{2a}/\tau_{gen}} = \frac{\dfrac{1}{\Delta_1 + \Delta_2}}{\dfrac{1}{2\Delta_2}}$$

$$\frac{N_1}{N_2} = 2$$