of urinary excretion or of blood constituents can be performed without recourse to nutritional controls. My experience is that it may take 3 months (or the equivalent of 3 days of a rat's life) to achieve a nutritional steady state after a change in the dietary regimen.

3) *Liver dysfunction or suboptimal liver function.* It has been frequently claimed that some schizophrenic patients have decreased rates of clearance of bromsulfalein or hippuric acid. The study of liver function in such patients is well worth more attention, but only additional work can clarify whether such changes are related to diet, inactivity, training, slower circulation time, physiological hibernation, infection, or other factors. Although the pattern of urinary excretion is not expected to vary in a 24-hour sample from subjects with mild liver dysfunction, tolerance tests that can evaluate the *rate* at which a substance is absorbed or removed, or both, from the blood stream may show sluggish activity in some schizophrenic patients.

In one controlled study, which was designed to estimate the effects of a diet that provided borderline levels of protein, signs of liver dysfunction became apparent and were not repaired until after the protein intake was raised (*4*). Whether a schizophrenic patient is more susceptible to liver disorder during protein deficiency or whether the slower removal of injected compounds is a consequence of long-term inactivity cannot be determined with the data at hand, but whatever the cause of mild liver dysfunction in the mental patient, the possible presence of such defects should be evaluated more frequently.

4) *Training.* One does not have to be oriented in athletics to recognize that the cardiovascular efficiency of an individual can be markedly influenced by repetitive exercise or work, or conversely, by extreme inactivity. The activity of mental patients may vary widely, from prolonged states of fierce agitation that are acted out by considerable physical movement, to conditions of relative hibernation. Such differences make for important variations in studies of oxygen consumption, circulatory rates, and all related concomitants of biological efficiency. When one considers that the maximum oxygen uptake of a trained individual may be double that of the untrained subject (*5*, *6*), it is not surprising to note that data from most biological studies on mental patients have greater variations from the mean than are obtained from nonpsychotic subjects. In addition, in most mental institutions there are patients who do productive work and others who remain sedentary for years, and the differences in functional muscle mass between these subjects are considerable.

5) *Diurnal variations.* Those acquainted with mental hospitals are aware of the great differences in night restlessness that may exist in various wards. Many mental patients have a high level of nocturnal activity. (It is assumed that sedated or tranquilized patients are not used for basal studies.) The all-too-frequent practice of comparing overnight urine samples from mental patients with similar samples from normal individuals can lead to unwarranted conclusions that might not be made if full 24-hour samples were collected instead. In this connection, one should also be aware of the prolonged fasting period of more than 14 hours between supper and breakfast that is a characteristic of many of our institutions and of the possible effect of such a schedule on diurnal variations.

Conclusion

It is earnestly hoped that investigators who are impelled to study the biology of schizophrenia or of other mental disorders will attempt to control the variables mentioned so that we may better distinguish between the causes of schizophrenia and its effects. Admittedly such controls are expensive and difficult to administer, but they are worthy of incorporation into any research program where man is the experimental subject. Much has been said about the faults of psychiatrists who do not make sufficient use of the laboratory concepts of cause and effect in evaluating mental disease. Conversely, the biologist should not be so naive in the interpretation of his data that he loses cognizance of the fact that schizophrenia is not a simple entity, and that he, too, must beware of the trap of confusing cause and effect.

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Physical Mechanism of Bacteriophage Injection

Aadne Ore and Ernest Pollard

It is currently accepted by many that a bacteriophage attaches itself to its host at the tip of its tail (*1*). It has also been found that the outer part of the phage particle, the protein coat, is left outside, while the inner part, which is predominantly desoxyribose nucleic acid (DNA), enters the bacterium and there undergoes multiplication (*2*). Very little is known about the mechanism of the penetration process. It is the purpose of this article (*3*) to show that quite ordinary physical processes offer the possibility of explaining the phenomenon of entry, and that, although no one clear explanation is presented here, there is certainly no reason to feel that this process offers anything extraordinary.

The processes we call attention to are, first, the linear Brownian movement of a long thin object through a tube containing a viscous medium and, second, the centrifugal pull exerted by oscillatory thermal movement of the part of the genetic thread that has already entered. The analysis we give of the two processes indicates that they can offer a plausible explanation for the entry of the viral DNA into the host, but that, under some circumstances, entry by these methods may be severely restricted. It is also suggested that hydration changes in the viral DNA might play a certain role.

The dimensions of the nucleic acid thread that enters the host are not accurately known. If we take the figures for phosphorus atoms per virus particle as given by, for example, Stent and Fuerst

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Table 1. Dimensions of virus tails.

Virus	l, assuming a single Watson-Crick structure B (in A)	l, from radiation data (in A)	Assumed r	Virus tail	
				length L	radius R
T1	2.4×10^5	1.1×10^4	10	1500	50
T2	7.7×10^5	1.25×10^5	10	1000	125
T5	6.0×10^5	Not available	10	1700	50

(*4*) and assume a single long unit of Watson-Crick structure B (*5*) we find DNA-lengths (l) for three bacterial viruses as given in the second column of Table 1. It would appear that these values of the lengths are overestimates, owing to the fact that plating efficiency enters into the calculations. Radiation data (*6*) for T1 and T2 indicate, for the same radius (r) of 10 A, smaller values for the lengths than would be calculated from the figures of Stent and Fuerst. The same is true of some unpublished work by one of us (E. P.) and Jane Setlow on T2. It is likely that these lower figures are due to the DNA's being coiled in some way, thus giving a low figure for the sensitive area. Whether such a coiled object is completely uncoiled as it enters the bacterium or whether a set of two or more molecules make up the physical unit is not, at present, known.

The dimensions given in Table 1 for the virus tails are those of frozen-dried phages as determined with the electron microscope by Williams and Fraser (*7*).

The processes we envisage are as follows. Subsequent to irreversible attachment (*8*) and production of the necessary opening in the bacterial wall and possibly also of liquefaction of some material in the phage, the "genetic thread" is expected to perform kinetic fluctuations in a viscous fluid. The resulting Brownian motion will be confined to a volume consisting of the interior of the phage-host complex. It is conceivable that the initially coiled structure will have to orient itself for one end of the thread to get into the tail. Estimates for the time taken, on the average, for fluctuations to lead to the desired result can be made in terms of rotational Brownian movement, and they indicate that such a process may be quite rapid compared with the actual passage through the tail, which is discussed in following paragraphs. It is presumed that the coil is not prevented by chemical forces from rotating and uncoiling.

As a first consideration we can suppose that the tube formed by the tail of the bacteriophage represents the "bottleneck." In our model then, the motion leading to entry into the bacterium will be approximated by a linear Brownian motion, with a mobility (*9*) corresponding to the conditions assumed to prevail in the tail. In computing this mobility, no attempt is made to take into account a possible non-Newtonian character of the fluid in question. Its viscosity coefficient is designated by η. The inner wall of the tube and the structure moving through it are considered as coaxial cylinders of radii R and r, respectively. Their respective lengths we denote by L and l.

As in the Einstein theory of ordinary Brownian motion, we need the mobility (velocity/resistance), which refers to uniform motion. In our case, the resistance per unit area equals η times the velocity gradient in the liquid, at the surface of the inner cylinder. The latter quantity is derivable from the hydrodynamic equations (*10*) for stationary viscous flow parallel to the axis. If we assume that the mass transport represented by the moving thread is always compensated by a net flow of liquid in the opposite direction, the resulting mobility B can be expressed as

$$B = \{2\pi\eta L f(x)\}^{-1}$$

where $x = R/r$ and

$$f(x) = \frac{x^2 - 1}{(x^2 + 1)\, ln\, x - (x^2 - 1)}$$

For values of $l \gg L$, it suffices for our purpose to let the total length of the tube enter the expression for B. The type of flow just postulated is, however, by no means the only conceivable one. More favorable to rapid entry would be one that would give transport of fluid into the bacterium. According to the findings of Puck and Lee (*11*) of an increase in cellular permeability subsequent to the irreversible attachment of phages to their host cell, a flow of the latter type would not seem unreasonable. Rather than derive an alternative form of $f(x)$, we take it to be the following simple one,

$$f'(x) = \frac{1}{x - 1}$$

which would result if the fluid velocity could be approximated by a linearly decreasing function of the distance from the inner cylinder.

On our model, the time, t, required on the average for the genetic structure to enter the bacterium is approximately that taken for the root-mean-square displacement to equal the length l of the structure. Accordingly, we put (*9*)

$$t = \frac{l^2}{2kTB}$$

where k is Boltzmann's constant and T is the absolute temperature.

It will be seen that t is proportional to η. The value of the latter is unknown, but a value of 0.1 poise—that is, a value 10 times that of water at room temperature—is assumed. We take for the effective inner radius of the tail in the transient state the external values (Table 1) as determined (with some 10-percent accuracy) in the frozen-dried state. Alternative lengths and radii are considered for the entering substance. The values of these radii are such as to allow space for sufficient fluid to render the hydrodynamic approach not unreasonable. The results are summarized in Table 2. Both forms of the function $f(x)$ have been considered. T was placed equal to 310°K (37°C).

It will be seen from Table 2 that, on the basis of radiation data, our model leads to reasonable durations of the penetration process for T1 and T2. [Similar results were presented in a preliminary report (*12*).] Time values derived on the basis of determinations of total DNA content, however, are definitely too great when a radius of 10 A is assumed, although the results are more satisfactory for larger values of the radius, which would correspond to a folded Watson-

Table 2. Injection times taken for $\eta = 0.1$ poise and $T = 310°K$.

Virus	l (in cm)	r (in cm)	$x = R/r$	$f(x)$	t (in sec)	$f'(x)$	t' (in sec)
T1	2.4×10^{-3}	10^{-7}	5	1.35	860	0.25	160
	0.6×10^{-3}	2×10^{-7}	2.5	3.76	150	0.67	27
	1.1×10^{-4}	10^{-7}	5	1.35	2	0.25	0.3
	0.27×10^{-4}	2×10^{-7}	2.5	3.76	0.3	0.67	0.06
T2	7.7×10^{-3}	10^{-7}	12.5	0.642	2800	0.087	380
	0.31×10^{-3}	5×10^{-7}	2.5	3.76	26	0.67	5
	1.25×10^{-3}	10^{-7}	12.5	0.642	74	0.087	10
	0.06×10^{-3}	5×10^{-7}	2.5	3.76	0.7	0.67	0.1
T5	6×10^{-3}	5×10^{-7}	5	1.35	6100	0.25	1100
	1.5×10^{-3}	2×10^{-7}	2.5	3.76	1050	0.67	190
	10^{-3}	10^{-7}	5	1.35	170	0.25	31
	0.25×10^{-3}	2×10^{-7}	2.5	3.76	29	0.67	5

Crick structure, in particular, if the net flow of liquid is inward. It is interesting to note the value obtained for T5 in this case; it is of the order of a few minutes. Luria and Steiner (*13*) found the injection time for T5 to be several minutes. They suggested that the narrowness of the tail might be responsible for the rather slow penetration of the phage DNA. In our model, the length of this structure would appear to be equally important.

In proceeding, we wish to mention that one should perhaps not exclude the possibility of a stretching of the DNA subsequent to irreversible attachment and possibly enzymic liquefaction of part of the interior of the phage. It is well known that the length of Watson-Crick structure B, which represents purified DNA at high relative humidity, exceeds by 30 percent that of structure A obtained at a lower humidity (*5*). If a similar stretching does take place, it may cause part of the structure to be pushed into and partly through the tail. This would mean that our mechanism would need to be active for a shorter period of time, thus reducing the values presented in Table 2.

It remains to be considered whether partial entry into the bacterium changes the conditions radically enough for the foregoing model to become meaningless. In point of fact, it is conceivable that the process will be speeded after partial entry. Qualitatively, we may say that uncoiling and entry amount to an increase in entropy. Again, if biochemical reactions involving a reduction in free energy are initiated already by partial entry, the effect will amount to a pulling force. Similarly, the greater freedom of sidewise motion of the part of the thread pointing into the bacterium permits oscillations that give rise to a net centrifugal force. To get an idea of the size of this effect we can consider that a fraction λ of the thread is capable of such oscillation in a plane. Giving it a mean oscillatory kinetic energy of $\frac{1}{2}\ kT$ (thermal energy) we shall take this to be the instantaneous energy $E = \frac{1}{2}I\omega^2$, where I is the moment of inertia about the point of entry and ω is the angular velocity. In terms of mass (μ) and length, we have $I = 1/3\mu\lambda^2$, while the centrifugal force is $F = \frac{1}{2}\mu\lambda\omega^2$. Thus,

$$F = \frac{3E}{\lambda} = \frac{3KT}{2\lambda}$$

We conclude that, to the extent that these considerations apply, the force may accelerate the entry appreciably. Thus, if we insert in this formula a value for λ of, say, 100 A, the corresponding value of F is of the order of 10^{-7} dyne. The corresponding velocity (v) would be B times this quantity—that is, of the order of 10^{-2} cm/sec. If, more generally, the expression for F were valid during entry, the time taken for it to effectuate the process would be given by

$$t = \int dt = \int \frac{d\lambda}{v} = \int \frac{d\lambda}{FB} = \frac{l^2}{3kTB}$$

(assuming a constant B, compare preceding discussion). Hence, such an approach to the problem of entry would lead, essentially by itself, to durations of the process that would roughly equal those found by the preceding treatment based on the assumption of Brownian motion. To some extent, a centrifugal pull will occur which will stimulate entry; it would appear to be somewhat unrealistic, however, to neglect completely any freedom of transverse motion in the tail and also to employ the afore-stated expression for F throughout a large range of values of λ.

Although we definitely do not wish to claim that we have presented *the* mechanism for the entry of nucleic acid through the tail of a virus into the host bacterium, we do feel that the main mechanism proposed, which should take place in any case, together with the supplementary ones, offers a good possibility of explaining the method of entry. It should be noted that, since B depends on $1/\eta$ and t on $1/BT$, the time of entry should be temperature-dependent according to the factor, viscosity/temperature. If a method of measurement of the time of injection should become more practicable, this relationship could perhaps be verified to some extent. Likewise, observations with partial replacement of cellular water by a more viscous solvent (*14*) deserve consideration.

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Science and Freedom

Freeman Dyson

I spent 2 weeks in May of this year going to scientific meetings in Moscow, talking with Russian physicists and sitting in Russian laboratories. A dozen Americans and many other foreigners were there. All of us reported, after we came home, that we were astonished at the enthusiasm, the competence, and the solid achievements of the Russian scientists.

Now, the editor of the *Sun* asks me a question. He says, "It is commonly stated by men of science that freedom is essential to a healthy scientific climate. And yet we learn from members of your group that Russian science, which has surely had to put up with security arrangements more stringent than ours, is in a flourishing condition, and that Russian scientists show evidence of the highest morale in their personal and scientific life. How can this be so?" He invites me to set down my thoughts about this question. And I am happy to do so, because

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