262. *Alternative Reaction Patterns in Autosynthetic Systems.*

By Sir Cyril N. Hinshelwood.

Systems of components with enzymic character in which each part depends for its increase upon the operation of another part may in the steady state obey the law of exponential growth as though each separate part were autosynthetic in its own right. In continuation of a previous study (*J.*, 1952, 745) it is shown that this result also holds good if there are alternative ways in which the mutual interdependences operate (alternative reaction patterns). In such cases both patterns may operate simultaneously, or one may show a lag in attaining its steady state while the other is fully operative. If there is competition for some intermediate substance by two competing reaction patterns, the lag of one may be indefinitely prolonged, or only terminated by special circumstances. There may then be fluctuations in growth rate before the steady condition is reached.

The analogy between these effects and some characteristic phenomena observed in the growth of unicellular organisms is pointed out, for example, the persistence of less efficient growth mechanisms in conditions where they can be, and ultimately are, superseded by more efficient ones.

Living cells, such as bacteria, capable of independent growth and reproduction contain a considerable number of enzyme systems responsible for very varied reactions of synthesis and degradation. These reactions are co-ordinated and interdependent and can be used in different orders and combinations to give the final duplication of the cell material. A particular combination of the partial reactions associated with definite proportions of the enzymic components and definite velocity constants may be termed a reaction pattern of the cell. In view of the widely different substrates which a bacterial cell can utilise and the great number of individual steps in the synthesis or breakdown of its substance, there must be alternative sequences in which the individual steps of oxidation, reduction, hydrolysis, condensation, deamination, transamination, and so on are arrangeable, and these constitute alternative reaction patterns. Sometimes the alternatives will be in competition, and it is the purpose of this paper to examine some of the consequences.

The basic assumptions are those of a previous paper (*J.*, 1952, 745), namely, that autosynthesis of the whole cell system occurs not by the self-replication of individual units, but by the co-ordinated action of components whose mutual dependence is expressed by equations of the type :

$$dX_1/dt = \alpha X_2,\ dX_2/dt = \beta X_3,\ dX_3/dt = \gamma X_4,\ dX_4/dt = \delta X_1$$

In such a system the proportion of the constituents varies at first irregularly, but in a final steady state so that each conforms to a simple autocatalytic equation $X_n = (X_n)_0 e^{kt}$.

The mode of interdependence represented by the above equations is indeed that thought to be shown by proteins and nucleic acids in cells (Malmgren and Heden, *Acta Path. Microbiol. Scand.*, 1947, **24**, 448; Caldwell and Hinshelwood, *J.*, 1950, 3156), each of which directs the formation of the other.

In the previous paper the model employed was that of a single sequence of changes, and the consequences indicated the possibility of adaptive phenomena, reversible in principle but in appropriate conditions very much delayed. The general correspondence of the predicted phenomena with observations on the growth and training of bacteria was pointed out. The problem now is to schematise in a simple way the existence of the alternative networks just referred to. The following assumption will therefore be made. A given component present in total amount R in the whole system (irrespective of the number of cells) gives rise by interaction with one substrate or intermediate to an enzyme represented in amount by X_1 and with another substrate or intermediate to a different enzyme represented by Y_1. Thus

$$dX_1/dt = \alpha R \quad \text{and} \quad dY_1/dt = aR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

X_1 and Y_1 in their turn condition the formation of X_2 and Y_2 respectively according to the equations :

$$dX_2/dt = \beta X_1 \quad \text{and} \quad dY_2/dt = bY_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In order that the mutual dependences shall form a closed cycle and so typify the essential organisation of a cell, as in the earlier discussion, R must be formed under the influence of X_2 or Y_2 or both :

$$dR/dt = \gamma X_2 + cY_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Thus schematically the system $R \longrightarrow X_1 \longrightarrow X_2$ of the earlier treatment has now been elaborated to $Y_2 \longleftarrow Y_1 \longleftarrow R \longrightarrow X_1 \longrightarrow X_2$. For comparison it is also convenient to consider at the same time the simpler branched system $Y_1 \longleftarrow R \longrightarrow X_1$, which will be represented by the equations :

$$dX_1/dt = \alpha R, \; dY_1/dt = aR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$dR/dt = \beta X_1 + bY_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The meaning of (1) and (4) can be further developed as follows. In certain suitably supplied media there will occur substrates and intermediates such that α and a are both finite. One compound is guided by R (*e.g.*, by a nucleic acid structure) into the building up of an enzyme X_1, while another, probably not differing too much from the first in character, is guided by the same structure R into the building up of a different enzyme Y_1. In some other medium the available materials may be such that either α or a is permanently equal to zero. α and a thus determine alternative and on occasion competing reaction paths. X_1 and Y_1 according to this view would represent structurally related enzymes, or, perhaps better, structural modifications of a given enzyme system arising from modified substrates under the influence of a single formative agency.

Steady Ratios and Exponential Growth.—The solutions of (4) and (5) are found by standard methods and are :

$$R = \tfrac{1}{2}\left\{R_0 + \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}e^{kt} + \tfrac{1}{2}\left\{R_0 - \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}e^{-kt} \quad . \quad . \quad . \quad (6a)$$

$$X_1 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} =$$

$$\tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} + \frac{\alpha}{k}R_0\right\}e^{kt} + \tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} - \frac{\alpha}{k}R_0\right\}e^{-kt} \quad . \quad (6b)$$

$$Y_1 = (a/\alpha)\{X_1 - (X_1)_0\} + (Y_1)_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6c)$$

where $k^2 = \alpha\beta + ab$.

When growth has been long continued under constant conditions, steady ratios of R, X_1, and Y_1 are established, and each of these quantities follows the simple exponential law during its subsequent increase. The steady ratios are $X_1/R = \alpha/k$, and $Y_1/R = a/(\alpha\beta + ab)^{\frac{1}{2}} = a/k$. If a small portion of the system is isolated and transferred to a

fresh supply of medium, as in the subculture of bacteria, R_0, $(X_1)_0$, and $(Y_1)_0$ are now in the ratio $\alpha : a : k$ so that equations (6*a*), (6*b*), and (6*c*) become respectively $R = R_0e^{kt}$, $X_1 = (X_1)_0e^{kt}$, and $Y_1 = (Y_1)_0e^{kt}$.

It has been shown that the length of the chain of interdependent processes does not affect the conformity with the simple law, and it now appears that, in principle, bifurcations in the chain also do not.

The same result holds good for the rather more complex example described by equations (1), (2), and (3). The solutions are as follows

$$\mathrm{R} = A_1e^{kt} + B_1e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_1e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad (7a)$$

$$X_1 + D_2/k^3 = A_2e^{kt} + B_2e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_2e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad . \quad (7b)$$

$$Y_1 + D_3/k^3 = A_3e^{kt} + B_3e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_3e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad . \quad (7c)$$

$$X_2 + E_4/k^3 = A_4e^{kt} + B_4e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_4e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - D_4t/k^3 \quad . \quad . \quad . \quad (7d)$$

$$Y_2 + E_5/k^3 = A_5e^{kt} + B_5e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_5e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - D_5t/k^3 \quad . \quad . \quad . \quad (7e)$$

where $$k^3 = \alpha\beta\gamma + abc.$$

and

$$A_1 = \frac{1}{3}\left\{R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{c}{k}(Y_2)_0 + \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_1 = \frac{1}{\sqrt{3}}\left\{-\frac{bc(Y_1)_0}{k^2} - \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{c}{k}(Y_2)_0 + \frac{\gamma}{k}(X_2)_0\right\}$$

$$C_1 = \frac{1}{3}\left\{2R_0 - \frac{bc}{k^2}(Y_1)_0 - \frac{\beta\gamma}{k^2}(X_1)_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$A_2 = \frac{\alpha}{k}A_1,\ A_3 = \frac{a}{k}A_1,\ A_4 = \frac{\alpha\beta}{k^2}A_1,\ A_5 = \frac{ab}{k^2}A_1$$

$$B_2 = \frac{1}{\sqrt{3}}\frac{\alpha}{k}\left\{R_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_3 = \frac{1}{\sqrt{3}}\frac{a}{k}\left\{R_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_4 = \frac{\alpha\beta}{\sqrt{3}k^2}\left\{-R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0\right\}$$

$$B_5 = \frac{ab}{\sqrt{3}k^2}\left\{-R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0\right\}$$

$$C_2 = \frac{1}{3}\frac{\alpha}{k}\left\{-R_0 + \frac{2bc}{k^2}(Y_1)_0 + \frac{2\beta\gamma}{k^2}(X_1)_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$C_3 = \frac{a}{\alpha}C_2$$

$$C_4 = \frac{1}{3}\frac{\alpha\beta}{k^2}\left\{-R_0 - \frac{bc}{k^2}(Y_1)_0 - \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{2c}{k}(Y_2)_0 + \frac{2\gamma}{k}(X_2)_0\right\}$$

$$C_5 = \frac{ab}{\alpha\beta}C_4$$

$$D_2 = -abc\left\{(X_1)_0 - \frac{\alpha}{a}(Y_1)_0\right\}$$

$$D_3 = -\alpha\beta\gamma\left\{(Y_1)_0 - \frac{a}{\alpha}(X_1)_0\right\}$$

$$D_4 = -\beta abc\left\{(X_1)_0 - \frac{\alpha}{a}(Y_1)_0\right.$$

$$D_5 = -b\alpha\beta\gamma\left\{(Y_1)_0 - \frac{a}{\alpha}(X_1)_0\right\}$$

$$E_4 = -abc\left\{(X_2)_0 - \frac{\alpha\beta}{ab}(Y_2)_0\right\}$$

$$E_5 = -\alpha\beta\gamma\left\{(Y_2)_0 - \frac{ab}{\alpha\beta}(X_2)_0\right\}$$

The subscript zero indicates the value when $t = 0$. The above solutions can be verified by substitution into equations (1), (2), and (3), and they give the correct values for zero time. When t becomes great enough the ratios $R : X_1 : X_2 : Y_1 : Y_2$ are $1 : \alpha/k : \alpha\beta/k^2 : a/k : ab/k^2$, and if in a new system the initial values are in these ratios, all the components again increase according to the simple autocatalytic law. This may be illustrated, for example, by Y_2 :

$$Y_2 = \frac{1}{3}\frac{ab}{k^2}\left\{R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0\right\}e^{kt}$$
$$+ \frac{ab}{\sqrt{3}k^2}\left\{-R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0\right\}e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt$$
$$+ \frac{1}{3}\frac{ab}{k^2}\left\{-R_0 - \frac{abc}{k^3}R_0 - \frac{\alpha\beta\gamma}{k^3}R_0 + \frac{2abc}{k^3}R_0 + \frac{2\alpha\beta\gamma}{k^3}R_0\right\}e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt$$
$$+ b\alpha\beta\gamma\left\{\frac{aR_0}{k} - \frac{a}{\alpha}\frac{\alpha R_0}{k}\right\}t/k^3 + \alpha\beta\gamma\left\{\frac{ab}{k^2} - \frac{ab}{\alpha\beta}\cdot\frac{\alpha\beta}{k^2}\right\}$$

and since $k^3 = \alpha\beta\gamma + abc$

$$Y_2 = \frac{ab}{k^2}R_0\,e^{kt} + 0 + 0 + 0 + 0 = (Y_2)_0e^{kt}$$

Lag Phenomena.—The principal interest is now in the early stages of growth in a new medium. Let us suppose that the cells have been grown for a long time in a medium in which a and b are zero, and that a sample is then transferred to a new medium in which a and b as well as α and β are finite. The initial values of the various quantities will be

$$(X_1)_0 = (\alpha/k_1)R_0,\ (X_2)_0 = (\alpha\beta/k_1^2)R_0,\ (Y_1)_0 = 0,\ (Y_2)_0 = 0,$$

where $\alpha\beta\gamma = k_1^3$, these being the proportions established after a long time in the first medium.

Growth in the new medium now conforms to the equations :

$$X_2 = \frac{1}{3}R_0\frac{\alpha\beta}{k^2}\left(1 + \frac{\alpha\beta\gamma}{k_1k^2} + \frac{\alpha\beta\gamma}{k_1^2k}\right)e^{kt} + \frac{1}{\sqrt{3}}R_0\frac{\alpha\beta}{k^2}\left(-1 + \frac{\alpha\beta\gamma}{k_1k^2}\right)e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt +$$
$$\frac{1}{3}R_0\frac{\alpha\beta}{k^2}\left(-1 - \frac{\alpha\beta\gamma}{k_1k^2} + \frac{2\alpha\beta\gamma}{k_1^2k}\right)e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt + \frac{\beta abc}{k^3}\left(\frac{\alpha}{k_1}R_0\right)t + \frac{abc}{k^3}\left(\frac{\alpha\beta}{k_1^2}\right)R_0 \quad . \quad (8a)$$

$$Y_2 = \frac{1}{3}R_0\frac{ab}{k^2}\left(1 + \frac{\alpha\beta\gamma}{k_1k^2} + \frac{\alpha\beta\gamma}{k_1^2k}\right)e^{kt} + \frac{1}{\sqrt{3}}R_0\frac{ab}{k^2}\left(-1 + \frac{\alpha\beta\gamma}{k_1k^2}\right)e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt +$$
$$\frac{1}{3}\frac{R_0ab}{k^2}\left(-1 - \frac{\alpha\beta\gamma}{k_1k^2} + \frac{2\alpha\beta\gamma}{k_1^2k}\right)e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - \frac{ab}{k^2}\frac{\alpha\beta\gamma}{k_1k^2}R_0kt - \frac{ab}{k^2}\cdot\frac{(\alpha\beta\gamma)}{k_1^2k}R_0 \quad . \quad . \quad (8b)$$

as is found by insertion of the above zero-time values in equations (7*d* and *e*).

The initial rate of growth in the new medium may be found by expansion of the last two expressions to the first power of t, that is by substituting

$$e^{kt} = 1 + kt,\ e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt = (1 - \tfrac{1}{2}kt)\frac{\sqrt{3}}{2}kt = \frac{\sqrt{3}}{2}kt,\ \text{and}\ e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt = (1 - \tfrac{1}{2}kt)\times 1 = (1 - \tfrac{1}{2}kt).$$

From (8*a*) the coefficient of the first power of t is then found to be

$$\frac{\alpha\beta R_0}{k_1} = \frac{\alpha\beta R_0}{k_1^2}k_1 = (X_2)_0k_1.\quad \text{Thus initially } X_2 = (X_2)_0k_1t.$$

From 8(*b*), on the other hand, the coefficient of the first power in t in the expansion is zero, and only the quadratic term has a finite coefficient. Thus, while X_2 begins to increase at a rate similar to that prevailing in the old medium, Y_2 shows an initial rate of increase of zero, that is, its formation is attended with a lag.

This result, although a simple one, is of some importance in principle, in that it clarifies in an elementary case how of two competing processes in a single system one may lag behind the other even when the basic requirements for its operation are present.

The result which follows from equations (8*a* and *b*) may now be contrasted with that given by (6*b* and *c*) for the simpler branched system where the branches only contain one member. Here, although $(Y_1)_0$ would be zero after transfer from a medium where a and b are zero, the formation of Y_1 in the new medium sets in immediately. Thus in the earliest stages the coefficient of the first power of t in any expansion for Y_1 is not zero. The addition of an extra member to the branch makes the first power vanish, and the addition

of yet another member, it is safe to conclude, would make the first finite term in the expansion the cube in t. Thus if there is a rather elaborate network, the final members of the sequence will only be formed after very considerable lags. In the meantime the members of the alternative sequence will be formed, although not at maximum rate, at least in a progressive and continuous manner. Growth of the whole system will thus occur, but at a rate which does not attain its optimum value till the long induction period associated with the development of the extra branch of the complete reaction pattern is over.

In such circumstances the growth rate will continue for a considerable time at a lower value, and then show a rather rapid transition to a higher value.

Experimental Analogies.—The idea of alternative and competing reaction patterns, one of which may be out of use until after the lapse of a lag during which the other operates alone, is of great help in the interpretation of many experimental observations. It has been invoked, with less definite theoretical basis than the foregoing, to explain the supersession of a slower mode of growth by a faster revealed in certain segmented growth curves ("Chemical Kinetics of the Bacterial Cell," Oxford Univ. Press, 1946, pp. 180 *et seq.*). It can also explain some rather surprising phenomena observed when bacteria are transferred from one medium to a second and then later back to the first, *e.g.*, kept for a long time in glucose, then in acetate or succinate, and then taken back to glucose. In the acetate or succinate their growth is much slower, and on retransfer they sometimes grow in the glucose much more slowly than they did originally, but then slowly recover their original capacity. The retraining process may require quite a long time, though continuous growth in the glucose occurs. The more efficient reaction pattern is not established in preference to the less efficient one although it exists throughout as a potentiality.

The glucose in this example provides a large variety of intermediates in the cycle by which it is metabolised, more presumably than substances such as acetic acid can do. We may therefore apply the analogy of the example where α, β, a, and b are all finite (preceding section). In the poorer medium we will suppose a and b to be zero. On the retransfer to the glucose medium there will thus be the kind of lag discussed above.

Sometimes there is another very curious effect, namely, a violent fluctuation in the growth rate from one subculture to the next during the retraining process. These fluctuations finally disappear, and quite steady conditions return. They are characteristic in many cases of the lag in the establishment of the new reaction pattern. Not until this is over will the growth rate in the glucose regain its original value. The reason why this lag may be so long that many generations of growth by the imperfect mechanism have time to occur is a special question which will be dealt with below, together with the question of the instability of the growth rate when it is recovering towards the optimum.

Another example of long-continued growth by a less efficient mechanism eventually succeeded by a more efficient one occurs in the retraining to utilise a simple synthetic medium of cells which have been exposed to ultra-violet light (Dean and Hinshelwood, *J.*, 1951, 1169).

A significant observation is that made on the training of *Bact. lactis aerogenes* to utilise D-arabinose (Jackson and Hinshelwood, *Trans. Faraday Soc.*, 1947, **44**, 568): continuous culture of the cells in another sugar prevents the growth in arabinose which would, in the absence of the second sugar, supervene after a day or so of lag. Here it seems that the growth by the route available in presence of, for example, glucose, actually consumes something required for the establishment of the alternative arabinose route. An analogous inhibition of one mechanism by the consumption of a necessary substance in a competing mechanism probably occurs also in the Pasteur effect.

If one of the competing reaction patterns considered in the previous sections can destroy a metabolite required by the other, then highly unstable conditions can arise. These will be discussed further in the next section.

Metabolic Interference.—We suppose there to be two enzymic components (X and Y) of the cell, in amounts X and Y respectively. Y requires some diffusible intermediate the concentration of which in any cell is c. c may be taken to reach a stationary value by the balance of formation, consumption, and loss by diffusion. Let n be the total number of cells at time t. In a given cell the intermediate is formed at a rate A, lost by diffusion

from the cell at a rate Bc, and uselessly destroyed by X at a rate CcX/n, the last being necessarily proportional not to the total amount of X but to the amount in any one cell. (Destruction of substances by enzymes without cell growth is of course a familiar occurrence.) We have then :

$$dc/dt = A - Bc - CcX/n = 0$$

whence

$$c = \frac{A/B}{1 + \gamma X/n}, \text{ where } \gamma = C/B$$

The rates of increase of X and Y are then given by

$$dX/dt = k_X X, \qquad dY/dt = \frac{k_Y Y}{1 + \gamma X/n}$$

The changes in the ratio $Y : X$ are shown by

$$\frac{d(Y/X)}{dt} = \frac{1}{X}\frac{dY}{dt} - \frac{Y}{X^2}\frac{dX}{dt}$$

whence

$$\frac{1}{(Y/X)}\frac{d(Y/X)}{dt} = \frac{d \ln (Y/X)}{dt} = \frac{k_Y}{1 + \gamma X/n} - k_X \quad \ldots\ldots\ldots \quad (9)$$

If, at $t = 0$, $\frac{k_Y}{1 + \gamma X_0/n_0} < k_X$, then Y decreases relatively to X from the start and never recovers. If, however, $\frac{k_Y}{1 + \gamma X_0/n_0} > k_X$ then Y begins to increase relatively to X, but the rate of increase falls as X itself increases. A limit is set to the change in equation (9) by the fact of cell division. If X is, in the initial state of the cells, the dominant component compared with Y, then division will be governed by X, and X and n will be proportional to one another in the steady state. Suppose then that $X/n = \beta$, then the right-hand side of equation (9) becomes $k_Y/(1 + \beta\gamma) - k_X$. If this is negative, Y loses in the race and there can be no training to Y.

Suppose, however, that X_0 is so small that not only is $k_Y/(1 + \gamma X_0/n) > k_X$, but that Y increases enough to provoke division of the cell before X has increased enough to reverse the sign of equation (9); then we shall have $Y/n = \beta'$ and now

$$\frac{d \ln (Y/X)}{dt} = \frac{k_Y}{1 + \beta'\gamma(X/Y)} - k_X \quad \ldots\ldots\ldots \quad (10)$$

If X_0 is small enough, expression (10) can start positive so that Y gains on X. As this happens, X/Y decreases so that (10) becomes still more positive and thus the race is won by Y. But the condition that expression (10) can come into operation at all is that the initial amount (or activity) of X should be sufficiently reduced.

Now the activities of all enzymes are much modified by ageing (and for this purpose an enzyme reduced in activity may be regarded as equivalent to one reduced in mass at constant activity), so that both X and Y during periods of non-proliferation of the cells will decrease, each at its own rate. We may therefore envisage in special cases short periods of growth with Y gaining on X, followed by periods of rest when the activities change in such a way that X can regain some of its preponderance during the next subculture. There will be at some stage an extremely unstable state where the two alternative reaction patterns are fairly evenly balanced and where fluctuations in growth rate will occur from one subculture to the next.

This is very similar to what is observed in some training experiments. Moreover, training to optimum growth in a medium already supporting growth by a less efficient mechanism occurs more readily if the cells are allowed periods of rest (Dean and Hinshelwood, *loc. cit.*). Examples of wide fluctuations in growth rate (not attributable to any experimental inaccuracy) are also given by Mims and Hinshelwood (*J.*, 1953, 663). Mutation and selection would hardly account for such rapid fluctuations.

It must also be remembered that the cell processes are organised in space as well as in time (cf. *op. cit.*, p. 23; Pontecorvo, Symposia Soc. Exp. Biol., 1952, VI, 218). If the intermediate to be used by Y has previously to diffuse through a region in which X is already established, there will be quite an effective inhibition of the more efficient mechanism by a less efficient but previously established one.

In conclusion it should be emphasised that the properties of autosynthetic systems here discussed are of interest in their own right and that no attempt is made in this place

to deal directly with the question of how far the analogies which they present with real biological systems may be more, or less, satisfactory than theories based upon selection. The kind of investigation attempted here is, however, a necessary preliminary to such a decision.

PHYSICAL CHEMISTRY LABORATORY, UNIVERSITY OF OXFORD. [*Received, November 11th*, 1952.]