In a single-mutant strain, mutations may occur in other genes for resistance; and when two mutant genes are together in one individual (double mutants) their effect is cumulative. Moreover, it happens that the resistance of a double mutant is higher than the sum of resistances of two single mutants. If a third gene for resistance, a fourth, etc., mutate in the same line, the combined effect of all these mutations is a high degree of resistance or complete resistance.

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Summary.—In experiments with *Staphylococcus aureus*, strains resistant to penicillin were developed, which retained the property of resistance during the period covered by the experiments. Evidence is presented indicating that resistance is not induced by the action of penicillin on bacteria, but originates through mutation, and that penicillin acts as a selective agent to eliminate nonresistant individuals. Degree of resistance can be increased by exposure to higher concentrations of penicillin, and this increase is interpreted as due to summation of the effects of several independent genetic factors for resistance which undergo consecutive mutation.

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THE LAW OF MASS ACTION IN EPIDEMIOLOGY

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Almost all workers in the analytical theory of epidemics assume that the rate at which an infection passes in a population is proportional jointly to the product of the number of persons I who are infectious and the number of persons S who are susceptible to the infection.[1–6] This is called the law of mass action. Thus if the rate of new infections be C the law is written as

$$C = r I S, \tag{1}$$

where r is a constant. The *a priori* rationalization of the law generally is based upon the assumption, explicit or implicit, that the infectious I are mixing uniformly with the susceptibles S throughout the population. According to the law, if we had a population with twice as many susceptibles and infectious and with the same rate r of mixing, the rate C at which the infection passed would be not twice but four times as great. As a matter of fact, it is unlikely that any such condition exists in detail. For example, it is known that for the childhood infectious diseases such as measles the liability to infection within the family is greater than within the schoolroom and this is in turn greater than that within the community at large. The mixing of the susceptibles and infectious is not uniform throughout the population. Thus the real utility of the assumption for the explanation of the course of an epidemic must be found from the *a posteriori* observation that with the proper choice of a constant r the equation (1) yields a theoretical curve of new cases which is in satisfactory agreement with the observed curve of new cases. Such a value of r is presumably some complicated sort of average value of the different values of r under different degrees of intimacy of contact between different groups of infectious and susceptibles within the population.

In the application of (1) the analytical developments vary according to the special assumptions made with respect to the particular disease under consideration. For example, if one is considering malaria and assumes that those once infectious remain so indefinitely and if one neglects accessions to or losses from the population and further neglects the incubation period whether in man or in mosquito, one writes

$$C = \frac{dI}{dt} = r\,I\,S, \qquad S = S_B - I, \tag{2}$$

where S_B is the number of susceptibles at the beginning; then (1) leads to

$$\frac{dI}{dt} = r\,I(S_B - I), \tag{3}$$

which on integration gives

$$I = {}^1/_2 S_B[1 + \tanh {}^1/_2 r S_B(t - t_0)], \tag{4}$$

$$C = {}^1/_4 r S_B{}^2 \operatorname{sech}^2 {}^1/_2 r S_B(t - t_0). \tag{5}$$

This means that the curve of total cases I is the logistic or growth curve, and the curve of new cases is symmetrical with respect to $t = t_0$. The rate of new cases when $t = t_0$ is $rS_B{}^2/4$ and the number of susceptibles remaining at that time is $S_B/2$, half of those at the beginning. In due time all the susceptibles are exhausted.

On the other hand, if the disease is one like measles in which it is generally assumed that there is an incubation period τ and a short period of infectiousness one may write

$$C = rSC(t - \tau) \text{ or } C = (S/m)C(t - \tau), \tag{6}$$

where $m = 1/r$ is the number of susceptibles just sufficient for one infectious case at $t - \tau$ to generate a new infectious case at t. Then, following Soper, and using $C = -dS/dt$ with $u = \log C$, one may obtain, to the order of approximation he uses,

$$\frac{d^2u}{dt^2} = -\frac{r}{\tau} e^u. \tag{7}$$

The integral is

$$u = 2 \log \operatorname{sech} \sqrt{\frac{rC_0}{2\tau}} (t - t_0) + \log C_0 \tag{8}$$

where C_0 is the rate of new cases when $t = t_0$, and then

$$C = C_0 \operatorname{sech}^2 \sqrt{\frac{rC_0}{2\tau}} (t - t_0). \tag{9}$$

It should be noted that the curve of new cases (or, more precisely, the curve of the rate of new cases) is under these assumptions and approximations of the same type as (5) which arose under very different assumptions.

In the third place if one modifies the law of mass action by assuming that the rate of new cases is proportional jointly to some power p of the number of susceptibles[7] and to the case rate lagged by τ, i.e.,

$$C = (S/m)^p C(t - \tau) \tag{10}$$

and eliminates S by $C = -dS/dt$ with $u = \log C$ one finds

$$\frac{d^2u}{dt^2} = -\frac{p}{m\tau} e^{u+(1/p-1/2)u'} \tag{11}$$

where the first correction term $(1/p - 1/2)(du/dt)$ has been kept in the exponent on the right. This term is neglected by Soper and was neglected, in the analysis above, for $p = 1$; it would appear to be equally negligible for other small values of p, and will be neglected. The integral is then

$$C = C_0 \operatorname{sech}^2 \sqrt{\frac{pC_0}{2m\tau}} (t - t_0), \tag{12}$$

and is still of the same type as (9) and (5). It is therefore clear that the form of the curve of new cases, apart from an interpretation of the constants which are involved and the assumptions which have been made in its derivation, cannot discriminate between a number of different laws of epidemic spread.[8] One could apparently get Soper's equation (7) and an epidemic curve of new cases as the derivative of the growth curve with better approximation from (11) if $p = 2$ than if $p = 1$.

As a matter of fact, one may show directly that when $p = 2$ equation (10) with $C = -dS/dt$ is exactly satisfied by a solution of type (12). For, given

$$\frac{dS}{dt} = \left(\frac{S}{m}\right)^2 \frac{dS}{dt}\bigg|_{t-\tau} \tag{10'}$$

we may substitute therein

$$S = m\left[\cosh \alpha - \sinh \alpha \tanh \alpha \frac{t - t_0}{\tau}\right] \tag{13}$$

and find that the equation is satisfied identically. Then

$$C - \frac{dS}{dt} = \frac{m\alpha}{\tau} \sinh \alpha \operatorname{sech}^2 \alpha \frac{t - t_0}{\tau} \tag{14}$$

and the value of α is connected with the case rate when maximum by

$$C_0 = \frac{m}{\tau} \alpha \sinh \alpha = \frac{m}{\tau}\left[\alpha^2 + \frac{\alpha^4}{6} + \frac{\alpha^6}{120} + \ldots\right] \tag{15}$$

or

$$\alpha = \sqrt{\frac{C_0\tau}{m}}\left[1 - \frac{C_0\tau}{12m} + \frac{29}{1440}\left(\frac{C_0\tau}{m}\right)^2 - \ldots.\right] \tag{15'}$$

For this case the initial and final values of S are

$$S_B = m(\cosh \alpha + \sinh \alpha), \qquad S_E = m(\cosh \alpha - \sinh \alpha)$$

and the value of S at the peak of the epidemic is $S_0 = m \cosh \alpha$ which is halfway between the initial and final values; moreover, $S_B S_E = m^2$ so that the "equilibrium value" m is the geometric mean of the initial and final values of S.

If we return to the general case where $p \neq 2$ and approximations are made in deriving (12) we obtain on integrating (12)

$$S = \text{const} - \sqrt{\frac{2m\tau C_0}{p}} \tanh \sqrt{\frac{pC_0}{2m\tau}} (t - t_0). \qquad (13')$$

The total number of cases from beginning to end of the epidemic is

$$\text{Total cases} = S_B - S_E = 2\sqrt{\frac{2m\tau C_0}{p}} \qquad (16)$$

and to the order of approximation used we find

$$\frac{m}{p} = \frac{(\text{total cases})^2}{8(\text{peak cases})}, \qquad (17)$$

provided we agree to call $C_0\tau$, which is the case rate at the peak of the epidemic multiplied by the incubation interval τ, the "peak cases." Thus what could be determined from an observed epidemic would not be either m or p severally but their ratio. In any such determination it would, of course, be necessary to use the estimated real numbers of total cases and of peak cases and not the total cases or peak cases reported unless the reporting were complete. It should further be observed that actually an epidemic may last over a considerable time and that recruits are coming into the population of susceptibles, which might well make necessary some modification in (17).

Instead of pursuing these considerations at this time we shall turn to the matter of the exact stepwise integration of (10). For notational simplification we introduce as in earlier papers,[6] $x = S/m$, and $T = t/\tau$ so that (10) becomes

$$\frac{dx}{dT} = x^p \left.\frac{dx}{dT}\right|_{-1} \text{ or } \frac{1}{x^p}\frac{dx}{dT} = \left.\frac{dx}{dT}\right|_{-1}. \qquad (10'')$$

The equation may be integrated exactly as[9]

$$\frac{1}{qx_T^q} + x_{T-1} = k = \frac{1}{qx_0^q} + x_{-1}, \qquad (18)$$

where $q = p - 1$ and x_0, x_{-1} are any two values of x which are one incubation period apart. At the beginning and end of the epidemic there are no cases and $x_T = x_{T-1}$. Hence the equation

$$\frac{1}{qx^q} + x - k = 0 \text{ or } \frac{1}{q}e^{-qv} + e^v - k = 0 \qquad (19)$$

with $v = \log x$ will have as solutions the initial and final values x_B, x_E of x or their logarithms. We have

$$f(v) = \frac{1}{q} e^{-qv} + e^{v} - k, \qquad f'(v) = -e^{-qv} + e^{v},$$

$$f'(v) + f'(-v) = 2(\cosh v - \cosh qv).$$

Hence the plot of $f(v)$ has a minimum at $v = 0$, and the (positive) slope for a positive value of v is numerically greater than the (negative) slope for the same numerical but negative value of v, provided $q < 1$, but for $q > 1$ it is less. This means that $v_B + v_E < 0$ or $x_B x_E < 1$ when $q < 1$, i.e., when $0 < p = 2$, but that $x_B x_E > 1$ when $q > 1$, i.e., when $p > 2$.

At the end of the epidemic where the case rates are very small and the values of x are not changing appreciably, C/C_{-1} being x^p is essentially constant and hence the curve of case rates in portions remote from the mode is essentially an exponential curve with a constant difference $p \log x_B$ for the ascending tail and with a constant (negative) difference $p \log x_E$ for the descending tail. The rise will be faster than the fall if $x_B x_E > 1$, i.e., if $p > 2$, but will be slower than the fall if $x_B x_E < 1$, i.e., if $p < 2$. We have seen that for $p = 2$ the curve of case rates is strictly symmetrical. It appears, however, that for $p > 2$ the longer tail would be on the right whereas for $p < 2$ it would be on the left.[10]

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[6] Wilson, E. B., and Burke, M. H., these PROCEEDINGS, **28**, 361–367 (1942); **29**, 43–48 (1943); and Wilson, E. B., and Worcester, J., *Ibid.*, **30**, 37–44 and 264–269 (1944).

[7] A word should be said about the assumption that we might use some power p of S in (10). The assumption may be difficult to justify on *a priori* grounds, but the justification for the case $p = 1$ is none too satisfactory. It would, in fact, be remarkable in a situation so complex as that of the passage of an epidemic over a community if any simple law adequately represented the phenomenon in detail—even to assume that the new case rate should be set equal to any function $f(S)$ of the susceptibles multiplied by the case rate one incubation period earlier might be questioned. We propose to discuss the assumption (10) merely as a possible empirical variant of the case $p = 1$ to see what its

consequences may be. Although mathematics is used to develop the logical inferences from known laws, it may also be used to investigate the consequences of various assumptions when the laws are not known, i.e., one of the functions of mathematical and philosophical reasoning is to keep us alive to what may be only possibilities when the actualities are not yet known.

[8] Ross (Part I, p. 226) develops under the case of "proportional happening" considerations of circumstances which he says "are probably just the conditions which hold in many of the short and sharp epidemics of zymotic diseases, such as measles, scarlatina and dengue." It is perfectly true that the curve of new cases has the form found in epidemics of those diseases, but we have seen that this sort of curve may arise under a variety of different hypotheses. It seems tolerably clear that Ross's theory of happenings, despite its generality, does not include the hypotheses appropriate to the discussion of epidemics of such diseases as measles, for he assumes that his population P has only two divisions, namely, the affected population Z and the susceptible population A and that immunity and the affected condition disappear together. In the case of measles and similar diseases there is a third population, namely, the immunes, let us say Y, so that $P = Z + A + Y$ and his fundamental equations would be replaced by something like:

$$dP = (n - m + i - e)Adt + (N - M + I - E)Zdt + (N' - M' + I' - E')Ydt,$$
$$dA = (n - m + i - e - h)Adt + (N + r)Zdt + (N' + r')Ydt,$$
$$dZ = hAdt + (-M + I - E - r - s)Zdt,$$
$$dY = (-M' + I' - E' - r')Ydt + sZdt.$$

Here n, m, i, e and their correlatives in capitals are natality, mortality, immigration and emigration rates, r is the rate at which the affected return to the susceptibles directly according to Ross's assumption of simultaneous cure and loss of immunity, r' is the rate at which the immunes lose their immunity, s is the rate at which the affected become cured and immune, and h is a factor which under the assumption of proportional happening has the form cZ. These equations do not allow for lag; they assume that births to the affected and to the immunes are susceptible rather than either affected or immune, though for measles children born to the immune mothers are generally themselves immune for a time.

We have tried to reconcile Ross's formulation (which is abstracted by C. O. Stallybrass in his *Principles of Epidemiology*, 1931, pp. 515 ff) and in particular the statement that in infectious diseases the reversion element $rZdt$ implies loss of both immunity and infectiousness, not recovery from disease, by considering the population of affected persons Z to remain affected whether infectious or not as long as they remain immune, but this construction appears impossible. We therefore seem to be forced to the conclusions that Ross's *a priori* pathometry does not cover those zymotic diseases in which immunity with non-infectiousness is a prime phenomenon; it might well cover those in which immunes were permanent carriers, especially if the rates of transfer of infection from the ill and from carriers to susceptibles were not materially different.

[9] If in equation (18) we take $x = 1$ when $T = 0$ and assume $x = 1 + aT + bT^2 + cT^3 + dT^4 + eT^5$, we find, on equating coefficients of powers of T, the following values of b, c, d, e, k in terms of a, good to the power a^5, inclusive.

$$b = pa^2\left[\frac{1}{4} + \frac{p-2}{48}a + \frac{p^2-2p}{192}a^2 + \frac{p^3-2p^2}{768}a^3\right]$$

$$c = pa^2\left[\frac{1}{6} + \frac{7p-6}{72}a + \frac{11p^2-21p+12}{432}a^2 + \frac{97p^3-222p^2+168p}{10368}a^3\right]$$

$$d = pa^3\left[\frac{5p-2}{48} + \frac{8p^2-15p+12}{288}a + \frac{79p^3-186p^2+168p}{6912}a^2\right]$$

$$e = pa^3\left[\frac{p}{30} + \frac{13p^2-24p+24}{1440}a + \frac{35p^3-84p^2+84p}{8640}a^2\right]$$

$$k = \frac{p}{p-1} - a + \frac{p}{12}a^2 - \frac{p^2}{180}a^3 - \frac{13p^3-24p^2+24p}{8640}a^4 - \frac{35p^4-84p^3+84p^2}{51840}a^5.$$

For any assumed slope of the x-curve at $x = 1$ one could plot a short range of that curve, say from $T = -1/2$ to $T = +1/2$. With the value of k one could then proceed stepwise from (18) to any other value of x removed an integral number of units of time for any value assumed within that range.

Particularly interesting, however, is to derive expressions in terms of the maximum case rate $z_0 = C_0r/m$. This requires the value of T when $d^2x/dT^2 = 0$, which is

$$T_0 = -\frac{1}{2} + \frac{p-2}{48}a + \frac{5p^2-10p}{576} + \frac{11p^3-26p^2+12p-8}{3072}a^3,$$

and is valid only to the term in a^3 whereas x was valid to the term in a^5. For this value of T, $z = -dx/dT$ takes the value z_0, viz.,

$$z_0 = -a + \frac{p}{8}a^2 - \frac{p^2}{96}a^3 \quad \text{or} \quad a = -z_0 + \frac{p}{8}z_0^2 - \frac{p^2}{48}z_0^3.$$

Hence a may be found in terms of z_0, good to the term in z_0^3, inclusive. With this value of a one may derive expressions in z_0 for k and for the value of x_0 of x at the peak of the epidemic, as follows:

$$k = \frac{p}{p-1} + z_0 - \frac{p}{24}z_0^2 + \frac{p^2}{180}z_0^3, \tag{A}$$

$$x_0 = 1 + \frac{1}{2}z_0 - \frac{1}{24}z_0^2 - \frac{113p^2-290p}{11520}z_0^3. \tag{B}$$

With these values one may compute stepwise from (18) the values of x for successive values of x removed from the mode by integral numbers of units of time under any assumed value of the ratio C_0r/m and for any value of p.

For the approximation that leads to the symmetrical curve, we may write (13′) nearly enough as

$$S = m + \frac{1}{2}C_0r - \sqrt{\frac{2rmC_0}{p}}\tanh\sqrt{\frac{pC_0}{2rm}}(t - t_0). \tag{C}$$

Therefore for the beginning and end of the epidemic we should have

$$S_B = m + \frac{1}{2} C_0\tau + \sqrt{\frac{2\tau m C_0}{p}}, \qquad S_E = m + \frac{1}{2} C_0\tau - \sqrt{\frac{2\tau m C_0}{p}}.$$

In general for x at the beginning and end, equation (19) for x may be solved in series. If we set

$$Y = \frac{2}{p}\left(k - \frac{p}{p-1}\right) = \frac{2}{p} z_0 - \frac{1}{12} z_0^2 + \frac{p}{90} z_0^3,$$

$$x = 1 \pm Y^{1/2} + \frac{p+1}{6} Y \pm \frac{(p+1)(2p-1)}{72} Y^{3/2} + \frac{(p+1)(2p-1)(p-2)}{540} Y^2 \pm \frac{(p+1)(2p-1)(2p^2-23p+23)}{17280} Y^{5/2}$$

and x_B will be the value with the positive sign, x_E that with the negative, and

$$\text{Total cases} = 2Y^{1/2} + \frac{(p+1)(2p-1)}{36} Y^{3/2} + \frac{(p+1)(2p-1)(2p^2-23p+23)}{8640} Y^{5/2}$$

provided we measure cases relative to m. Transformed to actual numbers

$$\text{Total cases} = m\left[2Y^{1/2} + \frac{(p+1)(2p-1)}{36} Y^{3/2} + \frac{(p+1)(2p-1)(2p^2-23p+23)}{8640} Y^{5/2}\right], \quad \text{(D)}$$

$$Y = \frac{2}{p}\frac{C_0\tau}{m} - \frac{1}{12}\left(\frac{C_0\tau}{m}\right)^2 + \frac{p}{90}\left(\frac{C_0\tau}{m}\right)^3. \quad \text{(E)}$$

Equation (D) with Y defined as in (E) gives a relationship between total cases, peak cases $C_0\tau$ and m and p which may be solved for any one of those four quantities in terms of the other three to give a more exact expression than (17) which was based on an approximation. If we solve for m and retain only the first approximation beyond (17) we find

$$m = p\frac{(\text{total cases})^2}{8(\text{peak cases})}\left[1 - \frac{5p^2+4p-4}{9p^2}\left(\frac{\text{peak cases}}{\text{total cases}}\right)^2\right]. \quad \text{(F)}$$

For $p \geqq 1$ the correction term in (F) is at most two-thirds of the square of the ratio of peak cases to total cases. This ratio in sharp epidemics of measles (after allowance for under-reporting) is rarely as much as $1/6$ so that the correction rarely amounts to more than two percent, and, therefore, considering the difficulty of accurate estimation of actual total cases or peak cases, we may consider (17) a sufficiently good approximation.

[10] The actual calculation of the course of $S = mx$ from (18) for three comparative special cases, with $z = -dx/dT = C/m$, is as follows:

$p = 1, m = 1, z_0 = 0.3$		$p = 2, m = 2, z_0 = 15$		$p = 3, m = 3, z_0 = 10$	
S	Cases	S	Cases	S	Cases
1.9789					
	0.0001				
1.9788		2.9326			
	0.0002		0.0002		
1.9786		2.9324			
	0.0004		0.0002		
1.9782		2.9322		3.9165	
	0.0008		0.0004		0.0003
1.9774		2.9318		3.9162	
	0.0016		0.0008		0.0006
1.9758		2.9310		3.9156	
	0.0032		0.0018		0.0015
1.9726		2.9292		3.9141	
	0.0063		0.0038		0.0033
1.9663		2.9254		3.9108	
	0.0123		0.0084		0.0072
1.9540		2.9170		3.9036	
	0.0238		0.0178		0.0156
1.9302		2.8992		3.8880	
	0.0455		0.0368		0.0336
1.8847		2.8624		3.8544	
	0.0837		0.0732		0.0694
1.8010		2.7892		3.7848	
	0.1446		0.1356		0.1320
1.6564		2.6536		3.6528	
	0.2231		0.2190		0.2175
1.4333		2.4346		3.4353	
	0.2866		0.2864		0.2865
1.1467		2.1482		3.1488	
	0.2857		0.2864		0.2865
0.8610		1.8618		2.8623	
	0.2140		0.2190		0.2205
0.6470		1.6428		2.6418	
	0.1246		0.1356		0.1389
0.5224		1.5072		2.5029	
	0.0612		0.0732		0.0768
0.4612		1.4340		2.4261	
	0.0274		0.0366		0.0396
0.4338		1.3974		2.3865	
	0.0117		0.0178		0.0198
0.4221		1.3796		2.3667	
	0.0049		0.0084		0.0096
0.4172		1.3712		2.3571	
	0.0021		0.0038		0.0048
0.4151		1.3674		2.3523	
	0.0009		0.0018		0.0024
0.4142		1.3656		2.3499	
	0.0003		0.0008		0.0009
0.4139		1.3648		2.3490	
	0.0002		0.0004		0.0006
0.4137		1.3644		2.3484	
			0.0002		0.0003
		1.3642		2.3481	
			0.0002		
		1.3640			

The left-hand skewness for $p = 1$ and right-hand skewness for $p = 3$ show in the figures. The different values of z_0 were chosen so that the case rates at maximum $C_{0r} = z_0 m$ and total cases should be the same provided the approximate formula (16) were used and the value of x_0 were taken from (B) in footnote 9. Slight irregularities in the numbers must be expected due to the limited number of places carried, and slight discrepancies in verifying (16) from the calculations because of the approximative nature of (16) and (B).

J. Brownlee stated, *Proc. Roy. Soc. Med., Epid. Sect.*, 2, Part 2, 243–258 (1909): ... the symmetry of the course of the epidemic is an obvious and marked feature. The deduction from this phenomenon is direct and complete, namely, that the want of persons liable to infection is not the cause of the decay of the epidemic. On no law of infection which I have been able to devise would such a cause permit epidemic symmetry. The fall must in all cases be much more rapid than the rise, though, on the contrary, when asymmetry is markedly present the opposite holds. Ross[1] comments on this statement. We may point out that if we accept the generalization of the law of mass action suggested in (10) there is symmetry for $p = 2$, negative skewness for $p < 2$ and positive skewness for $p > 2$. Thus a rather simple law has been devised which may explain symmetry or skewness of either sign. Furthermore, in the examples above which correspond to rather severe epidemics of measles the rise is at the (logarithmic) rate $p \log x_B$ or 0.68, 0.77, 0.81, respectively, for $p = 1, 2, 3$; and the rate of the fall is $-p \log x_B$ or 0.89, 0.77, 0.74, respectively. In the first case the rate of fall is considerably greater than the rate of rise, in the second case they are equal, and in the third case the rate of fall is but slightly less than the rate of rise. With higher values of p the rate of fall would become considerably less than the rate of rise, but even with very high values of p and with the same values of peak cases and of total cases as in the illustrations above the rate of rise could probably not exceed 0.89 and the rate of fall not be lower than 0.69.

A LETTER FROM LORD RAYLEIGH TO J. WILLARD GIBBS AND HIS REPLY

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Communicated December 4, 1944

In the small collection of letters left by J. W. Gibbs and now in the possession of Ralph G. Van Name is one from Lord Rayleigh the answer to which I presumed still existed because the present Lord Rayleigh quoted three sentences from it in his biography of his father.[1] When I sent a copy of his father's letter to Lord Rayleigh, he kindly sent me a transcript of Gibbs's reply. As this exchange of letters between a foreign associate and a member of this Academy seems to me likely to be of sufficient interest to our members and of sufficient importance to the history of science to justify publication in full even at this late date, I have secured the permission of Lord Rayleigh and of Professor Van Name to print them here.