the diet of one group was further supplemented with 0.5 mg. iron (as $FeCl_3$) and that of the other group with 0.5 mg. iron plus 0.05 mg. copper (as $CuSO_4$). Fifteen of the rats were thyroidectomized at the age of 3 weeks and continued on the milk diet. At the end of 7 weeks, the diet of 5 animals was supplemented with iron, and that of 5 others with iron and copper, the remaining 5 serving as thyroidectomized controls. Water distilled from glass was used throughout and rigid precautions observed to prevent metallic contamination. Hemoglobin was determined weekly in tail blood with a Newcomer hemoglobinometer, calibrated by oxygen capacity determinations in the Van Slyke and Neill manometric apparatus.

The curves given in the chart are the average values of at least 4 animals in each group. They indicate that various functional levels of the thyroid as induced by the addition of iodine in organic or inorganic combination, and even the complete absence of the thyroid, in no way modify the development or severity of the anemia produced by milk feeding or the hematopoietic response to iron and copper. The results with iron and iodine alone and in combination with copper further substantiate the specific stimulating effect of copper demonstrated by Hart and his co-workers.[6]

Sections of the thyroid glands made at the conclusion of the experiments failed to show any significant abnormalities. Slight hyperplasia was present in several of the negative controls, which, however, in no case exceeded that commonly found in supposedly "normal" animals.

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Relation Between Toxicity, Resistance, and Time of Survival.*

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With collective phenomena it has been often observed that the curve describing the frequency of the occurrence of an event is asymmetrical and not symmetrical as should be expected if the occurrence of the event depended merely on chance. (Gauss's proba-

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[6] Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A., *J. Biol. Chem.*, 1928, **77**, 797.

* Thanks are due to Professor E. B. Wilson for reading critically the manuscript.

bility curve.) This has been generally ascribed to the asymmetrical variation of the parameter on which the occurrence of the event depends. A different explanation is given below. It is shown that asymmetry is to be expected whenever the time which registers the event is a non-linear function of the parameter on which the occurrence of the event depends even though the variation of the same follows the probability rule.

The parameter ξ will be a non-linear function of the time if the event is the consequence of the upset of an equilibrium, *i. e.*, the equilibrium between an existing noxious power (for example, the toxic action of a chemical) and resistance, which upset may result in destruction (for example, death of an organism) which is the registered event. If x and y are the parameters which determine the equilibrium, then the latter will be characterized by

$$\xi = \phi(x) - \psi(y) = 0; \quad t = \infty.$$

Hence

$$t = f\left(\frac{1}{\xi}\right) = f\left[\frac{1}{\phi(x) - \psi(y)}\right].$$

The simplest assumption about f is that any small increase of t will be proportional to the relative decrease of ξ. Thus

$$dt = -a\frac{d\xi}{\xi} = -a\frac{d[\phi(x) - \psi(y)]}{\phi(x) - \psi(y)} \qquad 1$$

and by integration

$$t = -a \ln \xi + K = -a \ln [\phi(x) - \psi(y)] + K. \qquad 2$$

The validity of this equation was tested on the mortality curves of bacteria exposed to a disinfecting agent (disinfection rate curves). These curves very often show a remarkable asymmetry, which is so great that the curves were considered by some to be of the type characteristic of the course of a monomolecular chemical reaction (Madsen and Nyman,[1] Chick,[2] Arrhenius,[3] and others). Eijkman,[4] Hewlett,[5] Reichenbach,[6] Brooks,[7] and others have attributed the asymmetry to a peculiar distribution of resistance among bacteria. From the experiments of Smith[8] and of Loeb and Nor-

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[1] Madsen and Nyman, *Z. f. Hyg.*, 1907, **57**, 388.

[2] Chick, *J. Hygiene*, 1908, **8**, 92; 1910, **10**, 237.

[3] Arrhenius, "Quantitative Laws in Biology," 1915.

[4] Eijkman, *Biochem. Z.*, 1908, **11**, 12.

[5] Hewlett, *Lancet*, 1909, March 13, 20, 27.

[6] Reichenbach, *Z. f. Hyg.*, 1911, **69**, 171.

[7] Brooks, *J. Gen. Physiol.*, 1918, **1**, 61.

[8] Smith, *Ann. Appl. Biol.*, 1921, **8**, 27.

throp[9] among others, one notices, however, that the asymmetrical frequency curve changes into a practically symmetrical one for the same culture of organisms if the disinfecting power is increased. Thus it is obvious that the asymmetry cannot be due to a peculiar distribution of resistance in such a case.

It was found that if in equation (1) one puts $\phi(x) = h$ for the constant disinfecting power and $\psi(y) = r$ for the resistance and allows the latter to vary according to the probability rule, symmetrical curves are obtained if $h \gg r$ and asymmetrical curves if h and r are of the same order. Furthermore, if equation (2) was solved for r[†] and experimental values plotted against $r/(h - r_{med}) = r'$, symmetrical curves were obtained. Applying the Gauss law on the variation of the resistance the experimental curves were recalculated with satisfactory agreement.

It is obvious that the validity of this theory cannot depend on the object of observation, hence it must be applicable to toxicity determinations and to epidemiological phenomena as well as to some analogous processes of non-biological nature. The common feature of these processes is that if the noxious power is sufficiently low a part of the group will escape the occurrence of the event. According to the theory this will occur in spite of the fact that the distribution of the resistance obeys the law of probability. Further consequences of the theory along with details of its proof will be published elsewhere.

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[9] Loeb and Northrop, *J. Biol. Chem.*, 1917, **32**, 103.

[†] This was done as follows: Integrating between t_{med} and t_n one obtains $t_{med} - t_n = a \ln \xi_n/\xi_{med}$; a was calculated from values for the median at which point $\xi_o/\xi_{med} = 2$ if the curve is symmetrical. Hence, $a = t_{med}/\ln 2$. Finally resistance intervals were obtained in the usual way:

$$\frac{\xi_n + \xi_{n+1}}{2\,\xi_{med}} = \frac{e^{\frac{t_{med} - t_n}{a}} + e^{\frac{t_{med} - t_{n+1}}{a}}}{2} = \frac{2h - (r_n + r_{n+1})}{2(h - r_{med})} = \text{const.} - \frac{r'_n + r'_{n+1}}{2}$$

From experiments by Smith[8] the average resistance (r_{med}) of *botrytis* spores against phenol was calculated and found to be proportional to the concentration throughout the range for which experimental data were available (0.4—0.7%). Further calculations made since on the action of phenol on anthrax spores (2) showed that in case of a wider range of concentration, the disinfecting power is proportional to the amount of disinfectant adsorbed.