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DROPLET INFECTION. SOME THEORETICAL CONSIDERATIONS.

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IT is generally accepted that the infection of many diseases is conveyed by the discharge of droplets containing the biological *materies morbi* in the acts of coughing, speaking, etc. In some cases, for instance that of measles, it is believed that if a person harbouring the *materies morbi* has the opportunity of projecting it upon the upper respiratory tracts of non-immunes, a considerable proportion of the latter will develop the clinical disease. In other cases, for instance cerebro-spinal fever or acute poliomyelitis, it is believed that although, in consequence of the activity of the primary source of infection, many other persons will acquire and harbour the *materies morbi*, only a small proportion of them will develop the disease.

Clearly this distinction might arise in more than one way. It might be that effective resistance to the disease arises in biologically different ways in the two cases. It is possible that the proportion of non-immunes with respect to measles as a clinical illness in any population of children is so large and resistance to it so little developed that the size of dose of infective material received by each is of little importance. It is possible that in the same population very few are so sensitive to the virus of poliomyelitis that on receiving even a small dose they will fall sick, and that many would never fall ill, however great the dosage received. The work of Stocks has made it probable that the case of measles is by no means so simple as here suggested. He has shown not only that 100 per cent. of children who had not previously had measles do not go down with the disease when exposed (a fact suspected before), but also that the subsequent history of such children points to an immunity acquired during the exposure and thereafter gradually lost, so that after a time these children again exposed to measles may suffer a clinical attack of the disease.

With respect to poliomyelitis there is fairly satisfactory evidence that in the currency of a clinical epidemic "cases," "abortive cases," persons whose serological equilibrium has been modified by exposure, and "sub-clinical cases" form a series of increasing percentages of the exposed population. But we are not very well informed, and it may be worth while to examine some of the consequences flowing from the hypothesis that the difference between the carrier state and the sickness state in these diseases is a function of dosage in the following sense. A number of persons is imagined to pass across the field of fire of a battery of pop-guns discharging pellets at a constant rate. Some of these persons will not be hit at all, some will be hit once, some twice and so on. Upon the frequency of and interval between hits depend the fates of the

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passers-by, whether they are unaffected, become carriers, become patients or become immune.

It is easy to give algebraical expression to such a hypothesis. If we suppose a target under gun fire and the average number of hits scored on the target in the unit of time to be λ, then it may easily be shown that the proportional distribution of 0, 1, 2, 3, etc. hits scored will be given by the successive terms of the expansion

$$e^{-\lambda}\left(1+\lambda+\frac{\lambda^2}{2!}+\ldots\right),$$

the bracketed terms being merely the expansion of $e^{+\lambda}$. This expression, Poisson's limit to the binomial, possesses a number of convenient properties. Thus, if we desire the distribution after not one but n rounds of fire, we have merely to substitute $n\lambda$ for λ.

If again the rate of fire of the gun varies from round to round, being measured by λ_1 in the first round, λ_2 in the second, and so on, the form remains unchanged, and we have simply to replace $n\lambda$ by the sum of $\lambda_1, \lambda_2, \ldots, \lambda_n$. These properties render the Poisson expression a less fantastic representation of conceivable biological happenings than would *a priori* appear. The analogy of targets under gun fire with children in a school or household mixing with a carrier of some disease must seem faint. A gun remains always a gun and a target a target; but a child carrying and distributing organisms one day may cease to do so the next and be replaced by a previously harmless child who has become a carrier. But that, if we are only concerned with the final state of affairs at the end of some discrete interval, does not preclude the Poisson representation. With this preamble, I come to the application of the method not to the solution —the solution requires at present unattainable data—but to the statement of a problem which has been much discussed, viz. under what circumstances is the closure of a boarding school or other residential institution, in which cases of a disease known to assume epidemic form have occurred, the proper course to follow?

Suppose then that in some such institution containing N inmates it is known that some of them, say n of them, are carrying a particular *materies morbi*. Ought we to keep the pupils together or to send them home?

To bring the discussion at least within hailing distance of reality, we must assume that we cannot identify, and therefore individually segregate, the n carriers, and only know that n is not greater than N.

If the school is kept together t weeks, then by hypothesis the total number of boys receiving 0, 1, 2, etc. doses will be given by

$$(N-n)\,e^{-L}\,(1+L+L^2/2!+L^3/3!\ldots) \qquad \ldots\ldots(1),$$

where $L=t\lambda$, λ being an unknown parameter. If the school had been dismissed, then its N members would have been distributed among a number of families; if the average size of such families is a, then we are concerned with aN instead of N individuals and of these n are carriers. These aN individuals are distributed into N groups each of a, and if we suppose that there is no bias in the

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allocation of carriers, the proportional distribution of groups having 0, 1, ..., a carriers apiece will be given by the terms of the binomial

$$\{(aN-n)/aN+n/aN\}^a,$$

and if n is small in comparison with aN, the result will be substantially that n of the groups receive one carrier apiece.

We may for the present purposes neglect the refinements that as brothers might go to the same school N individuals would not return to N different families and that some families might have more than one carrier. The hypothesis that each carrier returned from school goes to a different family brings the largest possible number of previously unexposed persons under some risk. This is so because, on the assumption of n different families, there will be $n(a-1)$ *persons* subject to risk of illness.

Now our formulation is

$$n(a-1)\,e^{-kL}\left(1+kL+\frac{k^2L^2}{2!}+\ldots\right) \qquad \ldots\ldots(2),$$

where k like λ is unknown.

The advantage or disadvantage of the second method turns on a comparison of the two expressions.

Both L and kL are in Lewis Carroll's terminology portmanteau expressions (that is of course an advantage of the Poisson formulation, that it permits such compression). Each expresses the resultant of the gun fire, dependent on the efficiency of the guns, the distance of the targets from the guns and the number of rounds the guns fire*.

To the disadvantage of the school, we have the fact that *all* the guns are firing on *all* the targets; in its favour we have the fact that the ratio of guns to targets is smaller than in the families unless the carrier proportion at the school exceeds one in a, where a is the average size of family. Further the contact of members of the family with the carrier is likely to be more intimate than between members of the school. That likelihood, however, is subject to the objection that if the school carriers happened to be concentrated in a particular dormitory or class-room, then the contact of the carriers, not with the whole herd but with a portion of it, would be *more* intimate than in the domestic life of the middle classes.

It is seen then that we cannot confidently assert that k is greater or less than unity, but, perhaps, on balance, we should incline to rank it as greater than unity.

We will, however, examine every possible case. The ratio of the $(r+1)$th term of (2) to the $(r+1)$th term of (1) is (writing $(N-n)\,m$ for $n(a-1)$)

$$\frac{me^{-kL}.k^rL^r}{e^{-L}.L^r}=me^{-L(k-1)}.k^r \qquad \ldots\ldots(3).$$

If k is less than 1 this diminishes with r, and we can always find a value of r such that the families will have the advantage, if m is less than 1. If k is equal

* We are *assuming*, of course, that other members of the family are neither more nor less resistant than the schoolboys.

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to 1 the ratio is equal to m for all values of r and the families have the advantage, if m is less than 1. If k is greater than 1 then we can always find a value of r such that (3) is greater than 1. Hence if the disease is such that only those individuals who have received more doses than the value of r fulfilling the above condition go sick, the families will be at a disadvantage.

Let us take as an example a school of 550 boys of whom 50 are carriers, and suppose the division into families of 6 produces 50 groups of 5 to each of which a carrier has been returned, *i.e.* $m=0{\cdot}5$.

Now put $\lambda=0{\cdot}1$, $t=10$ and so $L=1{\cdot}0$ and $k=1{\cdot}5$,

$$0{\cdot}5\times e^{-0{\cdot}5}\times(1{\cdot}5)^r=0{\cdot}3032653\,(1{\cdot}5)^r$$

is the value of (3), *i.e.* it is greater than 1 if r is 3 or more. Hence if 3 or more doses are necessary to produce a case of illness, the families will have a greater number of cases than the school.

Thus the distribution in the school would be

$$500\times e^{-1}\,(1+1+\tfrac{1}{2}+\tfrac{1}{6}\ldots)=500\times 0{\cdot}3678794\,(1+1+\tfrac{1}{2}+\tfrac{1}{6}\ldots),$$

i.e. 183·94 would be unaffected,
183·94 would receive 1 dose,
91·97 would receive 2 doses,
30·66 would receive 3 doses,
9·49 would receive 4 or more doses.

In the members of affected families it would be

$$250\times e^{-1{\cdot}5}\left(1+1{\cdot}5+\frac{2{\cdot}25}{2}+\frac{3{\cdot}375}{6}+\ldots\right)$$
$$=250\times 0{\cdot}2231302\,(1+1{\cdot}5+1{\cdot}125+0{\cdot}5625+\ldots),$$

i.e. 55·78 would be unaffected,
83·67 would receive 1 dose,
62·76 would receive 2 doses,
31·38 would receive 3 doses,
16·41 would receive 4 or more doses.

If then the limiting dosage were 4, the families would provide 73 per cent. more cases than the school. Had the limit been 3, the former would give 47·79, the latter 40·15, an excess of 19 per cent. Had the limit been 2, the figures would be 110·55 and 132·12, a defect of 16 per cent.

The point is that the smaller multiplier, *i.e.* the smaller number of persons involved, a consequence of the fact that a number of the schoolboys will henceforth be exposed to no risk at all, is compensated by the relatively increasing weight of the later terms of the expansion of e^{Lk} in comparison with those of e^{L}.

But this schema is so remote from practicality that it has little value. One can get to a little closer quarters with reality by discussing a hypothesis sug-

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gested by the controversy between Drs J. S. Collier and F. M. R. Walshe on the method of spread of acute poliomyelitis; I say *suggested by*, because I have simplified Dr Collier's conception. Let us suppose that there is a simple dichotomy between "carriers," and "non-carriers," all persons who have received in the time unit one or more doses of infection pass into the former category. Of these carriers a fixed proportion become "cases," the remainder become permanently immune and a proportion of them ceases to be "carriers." What in these circumstances will be the history of the group? It will be sufficient to give an arithmetical illustration, anybody who prefers a symbolic statement can provide it for himself, anybody who cannot would not be interested in symbols.

Suppose then that the unit of time is a week and the conditions such that, beginning with a single "carrier," 10 per cent. of a school of 500 are "carriers" at the end of the week. We must first find the Poisson parameter, which we do from the equation

$$450 = 499e^{-L},$$

giving $L = 0{\cdot}1033$. Of the 50 "carriers" 2 per cent., say (*i.e.* one boy), become "cases," 24 are immune and also cease to carry, 25 also immune continue to carry through the next time interval. For this interval since L was approximately 0·1, when there was but a single carrier at the beginning, it might be proper to take $L = 2{\cdot}5$ as we have 25 times the previous gun power; this, however, is a very arbitrary assumption. As $e^{-2{\cdot}5} = 0{\cdot}082085$, at the end of the week only 37 (approximately) will remain un-hit out of the 450 exposed to risk, *i.e.* 413 new "carriers" will have been created. Of these 2 per cent., say 8, become "cases," 199 are immunes ceasing to carry and 206 immunes continuing to carry and available to bombard the 37 surviving non-carriers. Since for the next week our gun power, L, has reached 20·6, we may say that for all practical purposes at the end of that week the whole 37 will be "carriers," among whom approximately one "case" will occur, and 18 will continue to carry the following week. As, however, there are no more targets to fire at, no more carriers or "cases" will be produced, and at the end of the week these carriers will cease to carry and we shall be left with an immune and also harmless population which has suffered 10 clinical attacks, 1, 8, 1, in successive weeks.

But suppose the school had been broken up at the end of the first week, *i.e.* after one clinical case had occurred and when 25 active carriers were available? These 25 are each returned let us suppose to be in-contacts of 4 susceptibles. Then in each of these groups the play will proceed just as in the large group, viz. each of the set of 4 exposed will ultimately be carriers to the extent of 100 per cent., and so of the $4 \times 25 = 100$, 2 per cent. $= 2$ will become "cases" and our total score will be 3 instead of 10. But if the dispersal had been delayed until the following week, *i.e.* to the time when 206 carriers were available, then the dispersal would produce 2 per cent. of $206 \times 4 = 16$ cases, and the total score would be 25 instead of 10. On this hypothesis, whether dividing the herd

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will reduce or increase the total damage depends upon whether at the time of dispersal the proportion of carriers reached is large or small. In Dr Collier's view of the poliomyelitis problem there is a time lag, cases do not eventuate until some process of ripening has taken place, *e.g.* through passage through "carriers." If we met this in our example by postponing the cases, *i.e.* dating the 1, 8, and 1, not in the first, second and third, but in the second, third and fourth weeks, then by the time a case came to light, the proportion of carriers would be so great that the favourable moment for splitting up would have been passed. Even this schema, however, is still remote from biological probability. Indeed the whole discussion which raged in the lay and medical press regarding the proper measures to be taken when poliomyelitis appeared in a school 7 years ago suffered from too free a use of faint analogies and gratuitous assumptions to be practically valuable. I can say this with less offence in that I also then attached importance to analogies which now seem to me too faint to be really helpful. As our positive knowledge is not much—it is a little—less incomplete than in 1927, we must still use analogies and make unproven assumptions, but we can at least work out their consequences. The first criticism to be passed on the hypothesis then proposed is that it is not probable that a carrier rate of approximately 100 per cent. is a condition necessarily precedent to the generation of even a single case. In infectious diseases of which we really do know a good deal, say smallpox and diphtheria, both dosage of infective material and natural susceptibility are important variables. We can hardly doubt that, given a sufficiently massive dosage, even naturally highly resistant persons will succumb and that for one and the same dose the range of resistance is wide. It may, however, be said that in some instances, and possibly poliomyelitis is such an instance, extremely susceptible individuals are so rare that the presence of one or more in any group of order 100 to 500 is an extremely unlikely event. It would then follow that, although the occurrence of a clinical case before the group carrier rate had reached a high figure was a theoretical possibility, it would be so rare an event as to be reasonably neglected in practice. The same argument applies to the dosage consideration. If the dosage capable of breaking down *any* natural resistance be so high that its arithmetical representation is given by a late term in the Poisson expansion, then, again, in the finite groups of our ordinary experience, we shall not meet with cases until, by multiplication of carriers, the Poisson parameter has become very much greater than its value at the beginning of the exposure.

Other and, as I think, much more formidable criticisms of the proceeding are that (1) carriers do not cease to carry with the slickness postulated, (2) the rather mechanical treatment of the intra-group evolution of carrying is biologically unnatural.

With regard to (1) such work as that of Hartley and Martin on a group of post-clinical diphtheria carriers suggests that carriers cease to carry in a geometrical progression, and that the rate of decrement is not very rapid. Their results (which have been substantially confirmed by others) were to the effect

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that the decrement of carriers was of the order of 5 per cent. per diem or, say, 30 per cent. per week. This would mean, when we have reached the position that 100 per cent. of the institutional group are carriers, that at the end of 7 weeks there would *still* be 8 per cent. carrying. Take the case of a school in which a first case of disease appears at the beginning of October and that by the middle of October 100 of the exposed have become carriers; in 9 weeks at most they must be dispersed and then some 4 per cent. of carriers will be distributed to homes. This, in a school of 500, would mean from 18 to 20 released carriers to be brought into contact with, say, 70 to 80 previously unexposed, leading on the old hypothesis to one or two more clinical cases. It does not appear, then, that such a modification as this of the hypothesis would greatly affect the results. Of course, if the first cases appeared later in term, the results would be more serious.

The problem suggested by (2) is a very much more important one. So far we have treated the matter as one of simple dichotomy; individuals pass from the exposed to risk into the "carrying" class; of these a fixed percentage become "cases," and the remainder are taken to be permanently immune, they cease to be carriers discontinuously or continuously but, blow high, blow low, whether kept together or taken away from contact one with another, *they* are never to become cases.

In the course of the poliomyelitis controversy an argument by analogy stressed by the believers in segregation was the result so frequently obtained by Topley and his co-workers in England and by the American investigators, that the addition of susceptibles to a group which had passed through an epidemic and settled down into a steady state was followed by a recrudescence in which not only the added susceptibles but the survivors of past epidemics perished. In parenthesis it should be remarked that the mortality experienced within the closed community was often exceedingly heavy. Take as an illustration an earlier experiment by Topley. On August 23rd, 1920, there were surviving of mice in 12 cages 124 animals; 42 of these mice had lived in 4 cages in each of which deaths had occurred (the infections were *Bact. suipestifer* and *Bact. gaertner*), the remainder came from 8 cages which had shown no such evidence but were exposed to risk of infection. These mice were all brought together in a single large cage and there segregated. By October 14th there were only 11 survivors; from 68 of the dead *Bact. suipestifer* was isolated. No more died in the next month and, on November 20th, 44 normal mice were added; the epidemic revived and, by March 10th, 39 of the newcomers and 7 of the veterans were dead. In infections of this kind the proportion of survivors of segregation is extremely small. The epidemic does come to an end—which, ordinarily, it will not do, so long as healthy immigrants are admitted to the herd—but only a tiny remnant of the original population is left alive. But why is there an end at all? The obvious answer is that the survivors have acquired an immunity or represent the natural immunes left after weeding out of the group by mortuary selection. But we know that when these "immunes" are again

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exposed to unsalted stock, both the latter *and* the former go down with the disease. In the particular example chosen nearly two-thirds of the veterans who had survived were themselves victims of the new experience and more than 88 per cent. of the newcomers. If such experiences as these are to be used as analogies to, say, the course of events in schools, and if we are to permit ourselves to change the ratio of survivors, *i.e.* to postulate that, instead of 11 out of 124, 113 out of 124 reach the "immune" stage, we are still not entitled to say that the mixing of these 113 with non-immunes must be free from risk for themselves and their new associates. The answer that an epidemic in a closed community comes to an end because the survivors are immune and permanently immune is obscure in so far as it is not a truism (it is a *truism* if our definition of "immune" is the condition of survivors of an epidemic who during a period of observation do not contract the disease). Suppose we are dealing with a droplet infection; the nearest experimental analogy is with *pasteurella* outbreaks. The revival of the disease when unsalted stock are brought in shows that the veterans or some of them are still emitting infective doses. Perhaps we may suppose that, among the survivors of the closed community, the position is such that, whether through elimination of susceptibles by death or by improvement of powers to destroy infective material through active immunisation, the proportional mortalities of those who in the unit of time receive 0, 1, ..., r doses of infection will be $q_0, q_1, \ldots, q_r$, where the q's increase from 0 to unity. Suppose that for newly introduced animals these coefficients are $Q_0, Q_1, \ldots, Q_r$, the Q's also increasing from 0 to unity but except for $r=0$ or r tending to infinity, Q_r greater than q_r. If then the rapidity of discharge, the Poisson parameter, remained constant it would follow that the introduction of new stock would be followed by increased mortality. Suppose that the system of q coefficients is such that for values less than r all are zero; then at the time of introduction, if r is large and the Poisson parameter not too large, deaths will have ceased to occur but may or must begin again when the new stock is introduced. They will, however, be confined to the new stock. But if the production of new cases itself alters the value of the Poisson parameter, then deaths may or must begin again to occur among the old stock.

For instance, suppose that in the old stock the Poisson parameter is 0·1 and the resistance of the stock such that in order to produce a "case" at least four unit doses must be received *in the time unit*. The chance of this happening is 0·000004, so that on the average 250,000 time units of exposure would be needed to produce a single case, or, in a herd 100 strong, 2500 days' exposure. Suppose that new stock introduced has a much lower resistance, that only 2 or more doses received in the time unit are needed to produce a case, then, if 100 were added, on the average a case would be generated within 3 days and, if the generation of a new case doubled the Poisson parameter, the risk of the old stock would be increased 14 times.

Of course in biological reality the situation would be much more complex than this, but the point I am trying to make is that the cessation of "cases,"

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an intermission of overt pathological acts lasting a long time, would be wholly consistent with the view that recrudescence might occur. It does not seem to me that we have in the data of experimental epidemiology a very satisfactory basis for practical decision in this matter of school closure. So far as practical experience goes it is known that, in the particular season when the English controversy arose, both methods, that of keeping the school together and that of breaking up, were tried and in neither case were the consequences serious. The experience was, however, too scanty to be a reliable basis for any induction.

Indeed, from the point of view of practice, it is clear that we are still without adequate means of reaching a sound decision. If, as in the case of diphtheria, we had a satisfactory test of individual resistance, much of the difficulty would be removed. We should no longer have to guess whether the occurrence of a clinical "case" means (*a*) that a large proportion of the exposed to risk is already infected, or (*b*) that in the community there happened to be one or two highly susceptible persons.

For these reasons, it seemed to me worth while to set out a few of the arithmetical possibilities.

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