THE DISTRIBUTION OF LETHAL SENSITIVITY TO HISTAMINE IN NORMAL AND HISTAMINE PRE-TREATED GUINEA PIGS.

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(With 2 Figures and 4 Tables in the text.)
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In 1934 Rusznyák, Karády, Szabó, and Karády and Bentsáth in 1935 reported that repeated intravenous histamine (H) injections (HT) act as a preventive in postoperative shock in certain sensitive human patients. To denote this kind of histamine treatment these investigators coined the expression: "histamine desensitization."

From this observation, research branched in two directions. One of them was the critial repetition on human patients of the original clinical observation (Bretschger (1936), Rusznyák, et al., 1936; Milkó, 1936), the other a series of animal experiments in order to furnish more decisive evidence (Karády, 1936, MacKay and Clark, 1938, Karády, 1938.)

The underlying hypothesis of "histamine desensitization" was that repeated injections of small doses of histamine enable the organism, through some unknown mechanism, to withstand larger amounts of this substance supposed to be released according to the Bayliss and Cannon shock-hypothesis. By surgical statistics the question of the development of such a histamine desensitization cannot be decided. Even if it were proven that surgical shock is a H poisoning — which it is not — the differences between surgical shock in man and H poisoning in different animals are so great and so numerous that the two should be subjected to separate investigations. In the case of H desensitization in man against traumatic shock, the question can be decided only with very large human material, because a) in this case the "trauma" cannot be

administered as exactly as the H can and there is therefore no fixed scale to which the frequency of mortality may be referred; b) the individual variations of sensitivity in man are very great.

The question whether pre-treatment with small doses of H increases the resistance against larger doses given at a later occasion can be decided only by comparing the resistance of non-treated and treated animals to H. Such attempts have already been made. Thus HORTON, MACLEAN and CRAIG (1929) found that 50% of the desensitized animals survived a H dose killing 87% of the controls. CLARK and MACKAY (1939) found that the survival time after the injection of 0.5—0.6 mg/100 mg b. w. is not greater in the pre-treated animals than in the controls. FARMER (1939, a and b) finds an increased resistance to histamine after both s. c. and peroral H treatment. BARLOW and HOMBURGER (1941), on the other hand, arrived at negative results, as did KOKAS, SARKADY and WENT (1938). These experiments, however, all fall victim to the same criticism: They cannot be subjected to statistical testing, and without this they do not warrant any conclusion.

The correctness of this attitude is easily proved. SCHENK (1922) gives 350 μg/100 g. b. w. as the MLD for s. c. injections in the guinea pig. SCHMIDT and STÄHLIN (1929) report that some guinea pigs succumb only to 1000 μg/100 g b. w. When lethal sensitivities differing as widely as 1 to 3 occur in a population, as in this case, differences of 50—100% in the mortalities, and still less in survival time, found on comparing two groups, generally of small number, are meaningless. So long as the comparison of the HT and control animals is not made on an indefinitely large population and with the knowledge of the standard deviation of the two sets of results, the question whether the occurrence of some apparently more resistant animals in the HT group was not merely a chance effect, cannot be decided. TREVAN (1927) developed a method of comparative measurement of the sensitivity of two groups of animals to the same drug. His method fulfills the requirements of variation statistics. A similar, improved, method was elaborated by GADDUM (1933). The statistical analysis in our work consists in the comparison of the entire "characteristic curves" of the two populations, of normal and histamine pre-treated (HT) animals. The characteristic curve is a frequency curve in which corresponding percentages of mortalities are plotted against several doses, causing mortalities between 0 and 100% (TREVAN l. c.). The shape and slope of such curves are characteristic of the species and the drug applied. Whether the differences in the scale of the doses between two characteristic curves is

merely due to the variation of sampling or is outside the limits of same, can be determined — in the case of normal distribution — by the calculation of the significance of difference between the average lethal doses (ALD) of the two groups. The ALD is that amount of drug which kills 50% of an indefinitely large number of animals. It is usually expressed in mg/kg.

The standard deviation must be kept as low as possible. Variations of the lethal sensitivity are often due to variations in the experimental circumstances, such as: the sex, weight, age of the animal, the site of the injection, the amount, the pH, the temperature of the solvent, the rate of the injection, etc., and not to a variation of the sensitivity. Proper precautions must therefore be taken to standardize in the two groups compared all experimental circumstance of which an influence is known.

Since the earlier experiments quoted were made without due regard for these aspects, neither the affirmative nor the negative results are satisfactory. SMITH-KARÁDY (1940) made an attempt to produce more evidence. Of her results, as will be shown below, only the intra-cardiac (i. c.) injection experiments are statistically conclusive.

In order to decide the alleged question of an H desensitization against H, we therefore determined the "characteristic curve" for H in normal and H pre-treated guinea pigs of both sexes and compared them statistically.

METHODS.

For the comparison of the death-rate in normal and HT animals, young guinea pigs 312 ± 68 g of both sexes, divided into groups according to sex, were used. All the animals lived in the same climatically conditioned room (25° C) and received the same diet for at least 1 month before the experiment. This consisted of oats, carrots (yellow and white), alfalfa, and fresh green stuff, but no milk or water.

Table I shows the groups formed of the animals. As is seen in this Table altogether 321 male and 80 female animals were used. The experimental period extended, with long interruptions, from October 1941 to November 1946.

The HT was carried out on the 5 Groups VI, VII, VIII, IX and X, as shown in Figure I. The HT of all the groups began with a dose of 5, 10, or 40 μg/100 g. b. w. H (crystalline dichlorhydrate dis-

TABLE I.

The groups of guinea-pigs in the death-rate comparison experiments.

Nr.	HT Treatment	Site of injection	Site of testing injection	Total Nr of animals.	Sex	BW g.	Time of experiment
I.	none	—	s. c.	83	male	287	1. VI. 43—28. VIIII. 43.
II.	none	—	s. c.	34	male	225	XII. 1941.
III.	none	—	i. p.	95	male	235	25. III. 43—29. IV. 43.
IV.	none	—	i. p.	12	male	385	XII. 1941.
V.	none	—	i. p.	40	female	302	XI. 1943.
VI.	short	s. c.	s. c.	40	male	251	1. VI. 43—28. VII. 43.
VII.	short	s. c.	s. c.	24	male	385	6. III. 1942.
VIII.	short	s. c.	i. p.	13	male	385	6. III. 1942.
IX.	long	s. c.	s. c.	40	female	302	XI. XII. 1943.
X.	short	s. c.	s. c.	20	male	369	13. X. 46—7. XI. 46.
				401		312.1 ± 68.4	

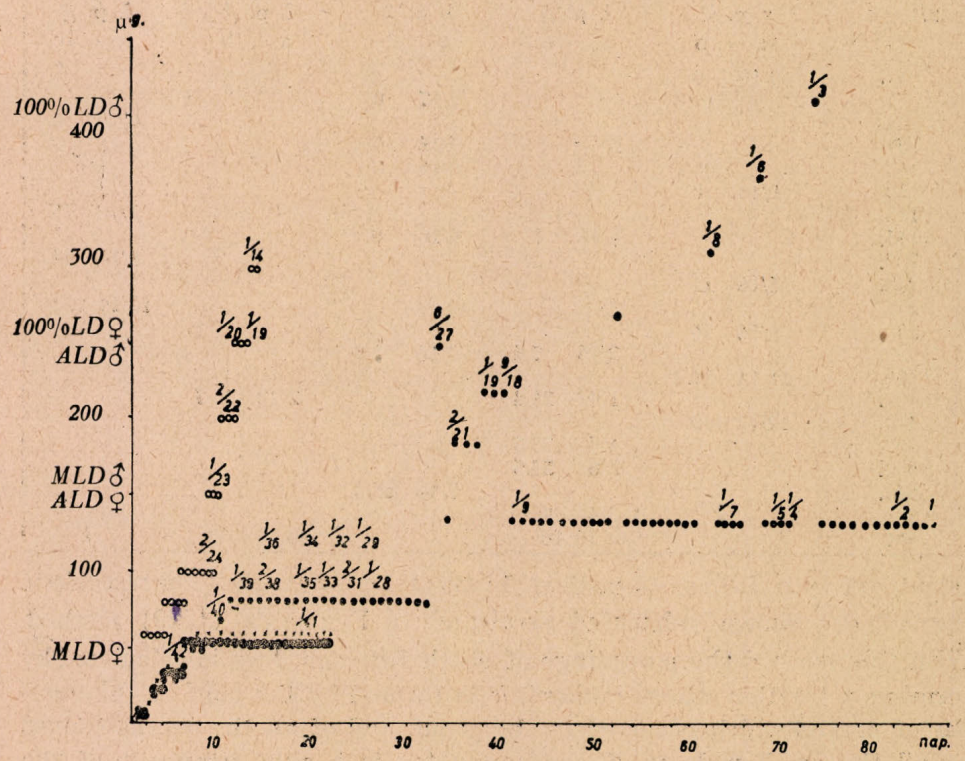

Figure 1. Modes of HT (histamine treatment). x-axis time in days; y-axis dose of H. in μg/100 g. b. w. Each sign (circle, cross or black point) indicates an H injection. In the fractions the denominator is the number of animals injected, the numerator the number of deaths occurred. ooo Group VII.: ••• Group VI.; xxx Group X.; ●●● Group IX.;

solved in dist. water) given subcutaneously (s. c.), and this dose was raised by small additional amounts. (All doses of H are given in μg/100 g. b. w.) Special care was taken to give the s. c. injections only in the upper, the i. p. in the lower abdominal regions. 0.025 ml/100 g. b. w. was the amount of fluid in which the H was injected.

In the Tables we present our results as they were obtained in the different groups and the percentage distribution of mortalities

TABLE II.

The mortalities of normal guinea-pigs characteristic for histamine.

$a = \frac{\text{number of inj. animals}}{\text{number of mortalities}}$ b= Behrens %.

Doses γ/100 g.	Group I. s. c. ♀		Group II. i. p. ♂		Group III. i. p. ♂		Group IV. i. p. ♂		Group V. i. p. ♂	
g.	a	b	a	b	a	b	a	b	a	b
13.	0/10	0								
15.					0/17	0				
25.									0/10	0
39.					0/16	0				
62.					0/16	0				
80.	0/15	0								
115.									3/10	25
143.			0/16	0	0/16	0				
200.									8/10	84.6
220.	6/16	22								
255.									10/10	100
270.	8/16	56								
320.			2/16	7.4	2/16	8 7				
360.	11/14	89.2								
400.			1/4	21.4			2/12	16.7		
410	12/12	100								
500.			1/4	33 3						
600.			2/6	54.5						
640.					7/14	56.2				
700.			3/4	90						
800			16 16	100			12/12	100		

calculated with Behrens's method. In the Figures the "characteristic curves" are shown calculated according to Behrens's (1929) method. With this method the percentage of death for each dose is calculated by forming a fraction whose numerator is formed by the sum of the number of deaths which occurred in the group and of all the deaths caused by all the smaller doses. The denominator is a sum composed of the number of animals in this group and the sum of the differences between the denominator and numerator in the groups of all the higher doses (i. e., the total of the animals which survived larger doses) plus the sum of the deaths which occurred in the groups of lower doses.

EXPERIMENTAL RESULTS.

The "characteristic curve" of guinea pigs for H was determined with the animals of Groups I—V of Table I. The results are shown in Table II. and Figure 2.

From the results of Groups I and V it is clear that the sensitivity or resistance to subcutaneous H amongst the normal guinea pigs is

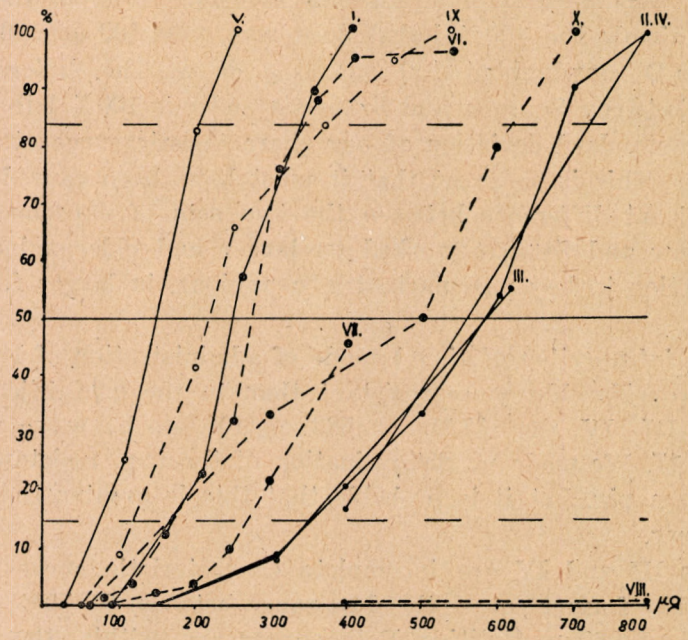

Figure 2. Characteristic curves of different guinea pigs for H. x-axis dose of H in μg/100g b. w., y-axis % of mortality o———o s. c. normal female, Group V; ●———● s. c. normal male, Group I; •———• i. p. normal male, Groups II, III, IV; o·····o HT female, Group IX; ●·····● HT male, Group X; ●·····● HT male, Group VI; ●·····● HT male, Group VII; ●·····● HT male, Group VIII.

distributed normally, the female animals being more sensitive than the male. The ALD for the former found by the integrated curve is 150 μg/100 g. b. w. $\mu = \pm 60$ $\mu_{ALD} = \pm 6$.

The ALD for male animals found by the integrated BEHRENS's curve is 250μ/100 g. b. w., $\mu = \pm 85$, $\mu_{ALD} = 9$. The distance between the ALD male and female is 100, the "k", the significance

of difference = 10. Consequently the difference betwen the male and female ALD cannot be due to sampling but is the consequence of the sex difference.

A comparison of our results with the earlier ones reveals the following relationship: SCHMIDT and STÄHLIN (1929) found that some animals die only after 1000 μg/100 g. b. w., SCHENK (1922) gives 350 μg/100 g. b. w. as the MLD for s. c. H. These are rather high values compared to ours, though the 350 μg 100 g dose falls within our male characteristic curve, not however as MLD. Even in the case of our male animals the 100% lethal dose was only 400 μg/100 g. b. w. and the MLD round about 100 μg/100 g. b. w. The difference (600 μg/100 g.) between SCHMIDT and STÄHLIN's and our 100% lethal dose is 6 times the standard deviation of our characteristic curve at the point of the ALD. This is so great that it must have been caused by some very significant difference between the two sets of experiments. Possibly SCHMIDT and STÄHLIN worked on larger and older animals, gave the H injection to less vascularized s. c. regions, in larger fluid quantities.

To the *intraperitoneal* (i. p.) mode of administration of H the male animal is considerably more resistant than to the s. c. injection. For Group II—III—IV the ALD = 583 μg/100 g. b. w., $\mu = \pm 175$ $\mu_{ALD} = \pm 17$. We made no determination of the i. p. resistance of the female guinea pig, but it is probable that this is greater than that of the s. c. ones.

Groups III and IV are incomplete characteristic curves for i. p. injections. The former covers the dose-range between 0—50%, the latter between 20—100% mortalities. Both curves are within the value of $1\,\mu_{ALD.}$ Indeed the agreement between the results of the three groups at most points of the curve is almost complete. This is the more remarkable because not only the groups differed from one another, but the time intervals between the three experiments was two years.

The distribution of the resistance to intracardiac (i. c.) injection of H amongst the female guinea pigs taken from the paper of Mrs. SMITH-KARÁDY is: ALD = 25 μg/100 g. b. w. $\mu = \pm 9.5, \mu_{ALD} = \pm 1.0$. This value is only about 17% of the s. c. resistance of female guinea pigs.

In describing *the characteristic curves for H of the HT animals,* the peculiarities in obtaining these curves are first to be explained. The experimental results are tabulated in Table III, and Fig. 2.

In groups IX and X the guinea pigs were treated with H as shown in Figure 1. For three weeks the animals in both groups received

an s. c. injection of H twice a day, early in the morning and late in the evening. On the first day the dose was 5 μg/100 g, and by raising the dose by 10 μg/100 g daily, on the 5th day a dose of 55 μg/100 g was arrived at. This dose was maintained for the rest of the three weeks.

At the end of this period the 40 female HT guinea pigs in Group IX were divided into four equal subdivisions. These were given the

TABLE III.

The mortalities of HT guinea-pigs characteristic for histamine.

$a = \frac{\text{number of mortalities}}{\text{number of inj. animals}}$ b= Behrens %

Doses /100 g.	Group VI. s. c. ♂		Group VII. s. c. ♂		Group VIII. s. c. ♂		Group IX. s. c ♀		Group X. s. c. ♂	
	a	b	a	b	a	b	a	b	a	b
55							0 10	0	0 20	0
60			0/24	0						
70	2/80	0.2								
80	13/711	1.1								
100			2 48	0.8						
105							2 10	9		
130	17/281	4.1								
150			1/64	1.4						
170	19/77	12·8								
200			3/61	3.9			5/10	41.1		
250	34/94	32 3	4/54	10						
265							7/10	66.6		
300			1/28	21.5					3/5	33·3
310	35/41	76								
360	37/40	88								
370							8/10	84.5		
400			0/13	45.8	0/13	0				
410	38/39	95								
465							11/3	94 2		
500									2/5	50
540	36/39	97.4								
570							2/2	100		
600									3/4	80
700									5/5	100
800					0/12	0				

doses of 105, 200, 265 and 370 μg/100 g respectively. H injection causes two kinds of death, one within two hours of the injection with the animal showing symptoms of acute H poisoning, the other some time the next day, after the animal had recovered from the effects of acute H poisoning. In the Table only the "acute death" cases are reported. In the four subdivision of group IX altogether 22 animals died an acute, and 5 more a delayed H death. The remaining 13 animals were 3 days later given 465 μg/100 g H s. c. Two guinea pigs survived.

These died after 3 days at the injection of 570 μg/100 g H. During the 3 day intervals the animals received two daily injections of 55 μg/100 g H.

Group X, consisting of 20 HT male guinea-pigs was divided into four equal sub-divisions, receiving 300, 500, 600, 700 μg/100 g H respectively.

The comparison of the characteristic curve of the normal animals (Groups V and I) with that of the HT ones (Groups IX and X) reveals in the case of both sexes the same changes. The most obvious of these is the change in the shape of the curve. In the HT animals the characteristic curve loses its normality and assumes a very marked positive skewness. At the lower doses between 0—40% normal and HT curves run close together.

The MLD is, of course, uncertain in all the groups. It lies probably nearer the higher doses than to the 0 value on the X-axis. Thus the probable MLD for the female HT guinea pig is about 70 μg/100 g. b. w., for the males about the same. As is seen in Fig. 2, these values are about the same in the corresponding normal controls. But the 50% LD is already greater in the HT than in the normal guinea pigs. The 50% LD for HT female animals is 222 μg/100 g. b. w., $\mu = \pm 132$, $\mu_{ALD} = 13$, for the males 500 μg/100 g. b. w., $\mu \pm 215$, $\mu_{ALD} = 22$. The shift towards the larger doses is greatest at the 100% LD this for the HT females being 530 μg/100 g. b. w., for the HT males 700 μg/100 g. b. w.

Owing to this alteration of the frequency of greatly varying sensibility the standard deviation of the ALD of the HT animals is increased. These changes in the characteristic curve mean that HT leaves the lethal sensitivity of a number of animals to H unaltered, whereas in certain other animals considerably decreases it. If HT had caused in each animal a certain increase of resistance the characteristic curve of the HT animals would have retained its normal shape but the entire curve would have been shifted towards the larger doses compared to the normal untreated animals. As is, e. g., the case between the normal female and normal male animals.

In Group VII we compared the effect of a change in the HT on the H resistance of animals. In this Group (see Fig. 1) the animals were given during the first 8 days 3 injections of H. The first day's dose was 4 μg, that of the second day 60 μg/100 g, and so on: 60, 80, 100, 100 μg/100 g on the consecutive days. From the 9th day on the following doses were given: 150 μg,- 200-, 200-, 250-, 300-, 400-, μg/100 g. The difference between this H treatment and the one applied in Groups

IX and X is that here the H doses are being raised rapidly during a short period towards and beyond the lethal values, whereas in Groups IX and X a dose certainly less than the minimum lethal dose was given for three weeks. In Table III column "a" the fractions of the sub-divisions for Group VII are formed as follows: The numerator indicates the number of acute H deaths in this sub-division. The denominator is formed by multiplying the number of the animals with the number of the injections of the dose given to this sub-division. E. g., out of the 24 animals with which we started, 2 died before the dose of 150 μg/100 g was begun. This dose was given once to 22 animals, 1 died, the remaining 21 animals received twice the dose of 150 μg/100 g, and this results in $22 + 42 = 64$ for the denominator.

Comparing the curve of Group VII with that of Groups I and X respectively we see that this curve is incomplete, yet as far as the curve goes it does not agree with curve X. It runs at the small doses parallel to the normal curve but shifted to the higher doses as it approaches the 50% LD it begins to skew away towards the larger doses. We may assume that had the increase of the s. c. injections been continued to the 100% LD the same shaped curve would have been observed as was found in Group X. With reservation therefore we conclude that the repetition during a short period of larger, even lethal, H doses has the same effect on the H resistance of the guinea pig as has a slow HT with less than lethal doses.

Group VIII is formed by those 13 animals which out of the 24 guinea pigs in Group VII survived after HT even the largest (the 100% normal s. c. LD) H dose. These animals were given the normal 20% and the normal 100% i. p. dose, 72 hours being allowed between the two injections. All the animals survived both doses. This is an indication that the animals which have acquired an increased resistance to H given s. c. would probably show an increase against i. p. H injections as well.

In Groups IX and X we saw the effect of a medium long HT with doses well below the MLD, in Group VII that of a short HT with rapidly increasing H doses up to the MLD on the sensitivity to large H doses. In Group VI 40 male guinea pigs were treated somewhat similarly to Groups IX and X, with the difference that after the 10th day when the 55 μg/100 g was attained the dose was slowly increased to 80 μg/100 g and this dose was continued till the 30th day. Then in 3 steps the dose was raised to 250 μg/100 g; i. e., almost the normal 50% LD, each rise having been given for 3 days. This was followed by daily injections of

130 μg/100 g of H until the 86th day. At intervals the surviving animals were tested with large doses of H as indicated in Fig. 1. In column "a" of Table III the fractions of the different doses are formed as in Group VII. On comparing, in Fig. 2, the curve of Groups VI to the normal curve and to the curve of Group X, we see that this curve assumes the same shape as that of Group X. Both curves while running

TABLE IV.

The maximum tolerance of histamine in HT animals succumbing to a smaller dose.

Nr.	Lethal dose μg/100 g.	LD given on how many days?	Survived doses μg/100 g. larger than lethal.
9.	220.	2	250;
71.	130.	22	170×3; 220×3; 250; 270×2; 310;
78.	170	3	170×2; 250;
46.	130	3	170×3; 220×3; 250;
90.	130	27	170×3; 220×3; 250; 310; 360; 250;
29.	220	1	170×3; 220×3; 250; 270; 310;
51.	130	36	360; 410; 450;

fairly close to the normal at the lower doses, show a positive skewness at the higher ones.

The following additional conclusions may be drawn. 1.) The daily repetition of a fairly strong H shock for a long period does not appear to alter (neither diminish nor increase) the resistance once developed. 2.) During the first third of the H treatment the daily dose of 80 μg/100 g was given 21 times, killing on each of the first 14 days some of the remaining animals, thus killing 11 out of 38 animals. Seven of the 40 animals in this group died at a later date of a smaller H dose than had previously been resisted. This is shown in Table IV. These two latter circumstances clearly show that the H resistance of the HT guinea pigs is not a fixed value, but has a periodical oscillation between a minimum and maximum.

From the data of Mrs. Smith-Karády we calculated the characteristic curve of H for intracardiac injection in both normal and HT animals. Here we found that both curves show a normal distribution.

The ALD of the normal females for i. c. given H was found to be 25 μg/100 g, $\mu = \pm 7.5$, $\mu_{ALD} = \pm 0.8$. The same values for the HT animals are: ALD 55 μg/100 g, $\mu = \pm 7.5$, $\mu_{ALD} = \pm 0.8$. The significance of difference for the difference between the normal and the HT ALD is, $k = 26$.

DISCUSSION.

The experiments described answer as follows the question whether histamine desensitization exists or not: It appears certain that after HT the resistance of each and all of the pre-treated animals does not increase with an individually varying but definite value. This clearly follows from the circumstance that the mortality curve loses its normal shape and is not shifted towards the larger doses with a distance at least twice that of the standard deviation. The most obvious effect of the HT in both sexes is the positive skewness of the curve. This means that after HT a certain number of the treated animals acquires a resistance considerably greater than that of the normal 100% mortality value, and that the value of the lethal doses from 60% upwards is also increased. Is this caused by the HT, or is it merely a sampling effect? The distance between the ALD for normal males (G. I. 250 μg) and the 100% LD for HT males (G. X = 700 μg) = 450. The μ for the normal males is $\pm$ 85. By dividing the 450 by 85, we find that the 100% LD of the HT animals lies 5.3 μ distant from the normal ALD. This means that amongst 10,000.000 normal male guinea pigs one will occur which is able to resist the 100% lethal dose (700 μ) of the HT animals. Whereas after HT 5 out of 100 treated animals will be enabled to resist this or perhaps even higher doses.

In the case of the female animals the normal ALD (G. V.) is 150, the 100% LD of the HT females (G. IX.) is 530. The μ for the normal female cases is $\pm$ 60. The difference between the 100% LD of the HT females and the ALD of the normal females divided by the normal $\mu = \frac{530 - 150}{60} = 6.3$ normal μ. This means that it will take well over 10,000.000 normal females to find one with the resistance of the 100% HT lethal dose.

Unlike our results, Mrs. SMITH-KARÁDY's point to a general and even increase both in the s. c. and i. c. testing of the resistance after HT. Her normal subcutaneous results also differ from ours. This difference is possibly caused — as she kindly informed us personally — by the fact that her guinea pig population was not definitely homogen-

eous as regards virginity. Since ours was from this point of view strictly homogeneous — and showed a smaller standard deviation — we feel entitled to attribute the difference to this inhomogeneity and not to that between the time or place (her experiments were carried out some 6 years before ours; she worked in North Dakota, and we in Hungary).

As regards the effect of the time-interval between two series of experiments, it is instructive that we have several series of experiments differing from one another in one to two years (Groups I and VII, Groups II and III, yet their curves fell well within one μ of the ALD. Besides being inhomogeneous Mrs. SMITH-KARÁDY's data are also incomplete. We are therefore inclined to attribute the differences between her own normal and HT results and ours to the circumstance that her inhomogeneous population had a great standard deviation. This means that in the lower doses there is no difference between her normal and her own normal and HT results and ours to the circumstance that her observed the same agreement. She failed to observe in the course of her work the possible positive skewness of her curve because these high doses had not been tested.

Though in the case of the s. c. results the differences between Mrs. SMITH-KARÁDY's and our own may in this way be understood, her i. c. results definitely support the conclusion of an even increase of resistance. There are two possible explanations for this difference. One is that the mode of action of a s. c. given H is different from that of an i. c., and that the HT alters just this differing link in the chain of physiological processes. The other is that the HT i. c. curve is in the large dose range actually based only on two groups.

A few words must be said about the observations proving that the sensitivity of one and the same animal to one and the same drug is not a fixed value, but varies from time to time. It has long been claimed by several pharmacologists that the variability of the lethal doses is due to the characteristic coincidence of the variations of the sensitivity of one and the same animal (GADDUM l. c. 1933; MORELL and CHAPMAN, 1933). Our experiments furnish additional evidence in favour of this theory. It must be pointed out that in no cases out of the 7 deaths from a smaller dose did death take place on a day following the day of a large dose. It is therefore impossible that this relatively decreased resistance was caused by this preceding larger dose. The recurrence of the same sensitivity on a later date as described above is, of course, the consequence of this same oscillation of the resistance.

From this it is clear that when the characteristic curve of a population of animals is tested, the observed frequencies are not due to the sampling of animals of different sensitivity with a fixed value, but to the coincidence of certain sensitivities oscillating within limits. How great can this oscillation of the sensitivity in the same animal be?

From Table IV it was seen that it is possible that one and the same animal may have a sensitivity of 130 μg/100 g or less, and may exhibit on a previous day a sensitivity enabling it to withstand 450 μg/100 g. That is to say, it is possible that in one and the same animal the sensitivity from day to day may vary between the lower and higher asymptote of the drug. The standard deviation of a sensitivity means therefore the range within which $\frac{2}{3}$ of the variations of the periodical oscillation of the sensitivities of one and the same animal will fall.

Accordingly, the distance of any given sensitivity from the ALD expressed in standard deviation would mean the frequency with which this sensitivity will occur in any animal out of the total of its sensitivity's variations. E. g., a sensitivity 3.09 distant from the μ_{ALD} does not mean that amongst 500 animals one will occur with this sensitivity, but that any of the animals have periodical oscillations of sensitivity round the ALD and that out of 500 oscillations, one will occur with this sensitivity.

The other possibility is a combination of the standard individual value of resistance with smaller oscillations around this value. Which of these two possibilities is the one actually existing, and whether there are drugs towards which one, and others towards which the other, is manifested are questions awaiting further experiments for their elucidation.

The relationship between experiments and the observations on the alleged H desensitization against surgical shock in man remains to be discussed. The two sets of observations differ: in the mode of the HT in the physiological properties of the two observed organisms (man versus guinea pigs), and finally in the mode of testing (lethal dose of H versus surgical shock) the change brought about by the HT.

The mode of the HT in the case of man consists in giving for 8—10 days 0.5—1 mgm-g H twice a day, whereas to guinea pigs 7—13 times larger doses are given. Further, man with his 70 years' average life-span is treated for about a week, the guinea pig with its life-span 1/10th as short is treated for 2—3 weeks. Significant as these differences are, the differences between the mode of action of a lethal dose of H on the guinea pig and that of surgical shock in man are still

greater. The most important of these differences is that the accumulating experimental evidence, though favouring the humoral origin of the *Bayliss-Cannon* shock hypothesis, appears to disprove the idea of the shock being essentially a histamine poisoning. This circumstance naturally excludes the possibility of using directly the results of the HT in guinea pigs as an argument in favour of the existence of a histamine desensitization against surgical shock in man. It must, however, be emphasized that though our experiments cannot be used to support this hypothesis, they do not argue against it either. The question of the existence of histamine desensitization in man against surgical shock, difficult as it is, can be decided only on well controlled and statistically sound human material.

SUMMARY.

1. In normal guinea pigs of both sexes and in those which underwent a pretreatment of repeated injections with small doses of histamine (HT animals), the "characteristic curve" for s. c. histamine injections was determined.

2. The ALD for H in normal female guinea pigs is 150 μg/100 g. b. w. $\mu_{ALD} = \pm 6$, same for normal males 250 μg/100 g. b. w. $\mu_{ALD} = \pm 9$. The female guinea pig is 66% more sensitive to this drug than the male.

3. The „characteristic curve" of HT guinea pigs loses its normal shape and assumes a very pronounced positive skewness. Part of the animals therefore develop an increased resistance in consequence of the HT while the sensitivity of another part of the animals remains unaltered.

4. Experimental evidence is presented proving, in the HT animals, the oscillatory nature of the resistance of one and the same guinea pig towards H. It is suggested that the characteristic curve is formed rather by the regular coincidence of certain sensitivities oscillating within limits than by distribution of animals with standard but individually varying sensitivity.

5. Whether HT is carried out with doses considerably below the MLD for a medium time (3 weeks) or with doses rapidly (in one week) reaching the lethal dose range does not seem to alter the result of the HT. The maintenance of H shocks with 40% LD for a long time neither increases nor diminishes the acquired resistance of the animals.

6. The authors emphasize that the results of their experiments are

not to be used as arguments in favour of the existence of histamine desensitization in man against surgical shock.

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