The Determination of the Minimal Lethal Dose of various Toxic Substances and its Relationship to the Body Weight in Warm-Blooded Animals, together with Considerations bearing on the Dosage of Drugs.

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In the course of investigations on the production, distribution, and rate of disappearance in the body of immune substances, we were occupied in 1908 and previous years with a series of experiments on agglutinins, and we arrived at conclusions pointing to their close relationship to the blood and blood-forming organs (1, 2). In association with these inquiries, one of us (G. D.), together with W. Ray, published a communication on the relationship between the blood volume and the distribution of agglutinins within the circulation (3).

It was there shown that the concentration of this substance (agglutinin) in the blood after inoculation into an animal was proportional to the body surface of the animal concerned, and was thus approximately proportional to the two-thirds power of the weight. Hence was deduced the conclusion that the blood volume of the animals examined was proportional to their body surface.

The recognition of this relationship between surface and blood volume made it clear that the assumptions hitherto made use of in attempting to determine dosage for the administration of therapeutic substances such as antitoxins and drugs required complete revision, at any rate, in so far as the activity of these substances might be supposed to be dependent on their concentration in the circulating blood. Subsequently the surface relation ($W^{\frac{2}{3}}$) was taken up by B. Moore (4) in an interesting communication dealing with the dosage of drugs, and especially with the therapeutic action of atoxyl and various other compounds of the heavy metals in the treatment of trypanosomiasis. Moore came to the conclusion that, in regard to these drugs, tolerance was limited by the surface area of the mucous membrane of

the alimentary canal. This, in his opinion, offered a valid explanation of the fact that it is often difficult or impossible to administer effective doses of these drugs to large animals, since these animals do not tolerate the doses which would be required to produce the same concentration in their blood as is needed for successful therapeutic action in small animals.

The observations on agglutinins had already led us to the conclusion that the concentration of inoculated drugs and other foreign substances distributed in the blood plasma would necessarily be proportional to the surface of the animal, since it was shown that the blood volume was always proportional to the body surface. And this fact would equally apply within any given species to an internal surface such as that of the alimentary canal.

The blood volume formula had, however, immediately and seriously been called in question (5, 6). Accordingly, it was necessary to turn aside from the problems in hand until the criticisms offered had been carefully examined, and the relationship of blood volume to the surface area had been adequately confirmed. This, so far as we are able to judge, has now been done (7).

Accordingly, we now proceed on the assumption that the blood volume of warm-blooded animals is a function of their body surface, and is given by the formula $B = W^n/k$, where n is approximately 0·72, and k is a constant to be ascertained for each particular species of animal.

Using this assumption, we find that the minimal lethal dose of a long series of substances of widely different origin and composition can satisfactorily be expressed as a function of the body surface. The series of substances which have been found to follow this law includes not only organic bodies both of animal and vegetable origin, but also a number of inorganic compounds.

It follows that we are entirely in accord with the main conclusion reached by Moore in his very suggestive discussion of the subject, namely, that dosage must be proportional to body surface (in warm-blooded animals). But, in view of the results which follow from the application of the blood volume formula, we are unfortunately not in a position to agree with the line of argument by which he deduces this conclusion from a consideration of the area of the alimentary tract. Moreover, we are quite unable to admit as satisfactory the explanation which he offers of the fact that drugs which are successful in the treatment of various species of small animals are not successful in the case of species of large size in any dose which can be used with safety. For reasons which will be given below, the explanation of these facts appears to us to be dependent on a specific tolerance or intolerance, as the case may be, in different species of animal, and not upon

the difference in their size or relative area of alimentary surface as suggested by Moore.

In proceeding to discuss our own examination of the subject of the present communication, we begin by endeavouring to show how the dose of a given poison which kills animals of a particular species in a given time is related to the weight of the individual.

For this purpose certain experiments with diphtheria toxin, the full details of which will be found in a subsequent paper ("An Analysis of the Problem of the Minimal Lethal Dose, etc."), are made use of, and some of the results obtained are given below.

In the case of diphtheria toxin, if the death time ($3\frac{1}{2}$ days) which is usually taken in the standardisation of this substance be made use of, it is found that for guinea-pigs which die in about 80 hours the lethal dose expressed as a percentage of the weight works out as follows :—

For animals of between—

200	and	250	grm.	weight,	about	6.0	cu. mm. of Toxin B	per 100 grm.
310	„	370	„	„		5·2	„	„ „
415	„	530	„		$<$	5·0	„	„ „

Again, taking a death time of some 40 hours, it is found that in the lightest group of guinea-pigs the minimal lethal dose per 100 grm. of weight is about 6·5 cu. mm. of the toxin, in the group of medium weights it is about 6·2 cu. mm., while in the heaviest group it is about 6 cu. mm.

Hence it follows that, for individuals of differing weights, the minimal lethal dose cannot be rightly expressed as a percentage of the body weight. This fact is, of course, well known to those familiar with the routine estimation of toxicity.

In Tables I and II are given two groups of animals, the one group consisting of light individuals and the other of heavy ones; where the dosage expressed in per cent. of body weight was approximately the same.

The average weight of the animals in Table I is 234 grm., the average dose per 100 grm. is 6·3 cu. mm., the dose estimated in relation to the surface area, and calculated from the expression $D = d/W^{0.72}$, where d is the actual quantity of the drug introduced, is 29·1 cu. mm., and the average time to death is 46 hours.

The average weight of the animals in Table II is 425 grm., the average dose per 100 grm. is again 6·3 cu. mm., but the dose calculated in relation to the surface area has increased to 34·3 cu. mm. and the average time to death is seen to be reduced to 37 hours. It is, therefore, evident that when the dose per 100 grm. of weight is made the same in light and heavy groups of

Table I.—Experiments with Diphtheria Toxin B in Guinea-pig (subcutaneous injection).

Group of Light Animals.

No.	No. of experiment.	Weight of animal, in grm.	Actual dose d, in c.c.	Dose (D) in relation to surface × 10^7. $D = d/W^{0.72}$.	No. of hours to death.	Dose in per cent. of weight, cu. mm. per 100 grm.
1	44	215	0·01400	2940	42	6·51
2	43	230	0·01375	2745	64	5·99
3	42	255	0·01575	2920	40	6·19
4	45	235	0·01535	3020	38	6·53
Average.....		234	0·01471	2906	46	6·31

Table II.—Experiments with Diphtheria Toxin B in Guinea-pig (subcutaneous injection).

Group of Heavy Animals.

No.	No. of experiment.	Weight of animal, in grm.	Actual dose d, in c.c.	Dose (D) in relation to surface × 10^7 $D = d/W^{0.72}$.	No. of hours to death.	Dose in per cent. of weight, cu. mm. per 100 grm.
1	28	425	0·02780	3560	30	6·55
2	32	415	0·02715	3525	49	6·54
3	31	435	0·02845	3580	30	6·54
4	35	415	0·02480	3220	44	5·98
5	30	435	0·02590	3258	32	5·96
Average.....		425	0·02682	3429	37	6·31

animals of the same species the lighter animals survive for a much longer period than do the heavier. The explanation of this difference in death time is to be sought in a comparison of the doses calculated in relation to the surface. It is then seen that the dose thus calculated is much smaller in the lighter animals than in the heavier group.

That this is a valid method of calculating dosage follows from the fact that, under ordinary conditions, substances administered as drugs, to act after absorption into the body, must become diluted in proportion to the volume of the blood. They are carried to the tissues of the body through the medium of the plasma in a relative concentration which is determined by the volume of the circulating blood. But the volume of the blood is a function of the body surface. Accordingly, it follows that the concentra-

tion in the plasma of any substance administered to animals under like conditions in doses proportional to their body weights will be much less in the lighter animals than in the heavier individuals of the same species.

On the other hand, if the doses be administered in relation to the body surface, their initial and their maximal concentration in the plasma will be the same whatever be the weights of the individual animals concerned.

The results brought forward for diphtheria toxin do not constitute an isolated instance in support of this view, that in any given species of animal dosage must be used in relation to the volume of the blood. Very numerous observations from the literature of toxicology which we have collected and analysed confirm the accuracy of this method of measurement. It appears to hold, so far as we have been able hitherto to ascertain, for a large number of substances of very different constitution and of diverse mode of action in warm-blooded animals. Wherever a sufficient number of accurate data can be found the effect of dosage can be shown to be related to blood volume and surface area in any given species. Numerous results which have been thought to be inexplicable when the dosage was expressed in per cent. of body weight, except on the ground of special individual susceptibility or individual resistance, in reality give precisely the results which would have been expected had the dosage been expressed in terms of body surface.

In the case of arsenic (As_2O_3) in the rabbit the observations of Morishima (8) afford an interesting illustration. The data and the calculations from these observations are given in Table III. Here it is seen that the time of death shows no exact relation to the dose expressed in per cent. of weight, but it follows quite closely the dose in relation to surface, though animal 5 shows an irregularity in living longer than animal 4. It will, however, be seen that the average dose per surface of animals 3 and 5, taken together, and their average time of death are identical with

Table III.—Arsenic (As_2O_3) in Rabbit, Morishima's Experiments (subcutaneous injection).

No.	Weight of animal, in grm.	Actual dose (d), in mgrm.	Dose (D) in relation to surface, in mgrm. $D = d/W^{0.72}$.	No. of hours to death.	Dose in per cent. of weight, mgrm. per 100 grm.
1	1324	8·61	4·86	∞	0·65
2	1103	7·72	4·95	∞	0·70
3	1495	10·47	5·42	84	0·70
4	1112	8·90	5·67	96	0·80
5	1702	11·90	5·91	108	0·70

the surface dose and time of death of animal 4, while the doses in per cent. of weight differ by 14 per cent. Again, if we compare the three animals which received equal doses, if the dose is expressed in per cent. of weight (viz., 2, 3, 5), the lightest one survives while the two heavier ones succumb. The explanation is at once evident on comparing the size of the doses expressed in relation to surface.

In Table IV is given another series of observations by Morishima where the injection was made intravenously. This method is, of course, likely to yield more precise results than subcutaneous inoculation, and it is seen that the effects of the doses, when the latter are expressed in relation to body surface, are remarkably regular and striking. On the other hand, when the dose is given in percentage of body weight, as was done by Morishima himself, the time to death varies very widely in animals which received equal dosage with the drug on his method of calculation. Morishima's results might be taken to indicate great individual differences in susceptibility in different individual animals. But such individual differences do not appear when the dose is calculated in relation to blood volume and body surface.

Table IV.—Arsenic (As_2O_3) in Rabbit, Morishima's Experiments (intravenous injection).

No.	Weight of animal, in grm.	Actual dose (d), in mgrm.	Dose (D) in relation to surface, in mgrm. $D = d/W^{0.72}$.	No. of hours to death.	Dose in per cent. of weight, mgrm. per 100 grm.
1	1135	6·81	4·30	∞	0·60
2	1190	7·73	4·71	432	0·65
3	970	6·79	4·81	48	0·70
4	1155	8·08	5·04	21	0·70
5	1952	13·66	5·82	8	0·70

Similar facts can readily be made out from various other experiments which have been carried out with arsenical compounds by a number of observers.

In the case of another heavy metal, cobalt, the same results hold good when the dosage is expressed in relation to surface instead of in the usual manner as a percentage of the body weight. This fact has been determined by an analysis of Meurice's experiments (9) on pigeons injected into the breast muscles with cobalt nitrate, $Co(NO_3)_2$. This is of special interest in view of the fact that it has already been shown in the experiments which we carried out in association with H. K. Fry, referred to elsewhere (10), that the blood volume of birds (like that of mammals) is proportional to their surface area.

Without further multiplying detailed instances it may be stated that we have obtained the same results on calculation from a variety of published observations on a number of different substances administered by various methods in different animals. Among these substances are *sulphate of methyl brucium* injected subcutaneously in the rabbit, and *codeine hydrochloride* administered by the stomach in the same animal (Crum Brown and Fraser (11)); *sulphate of physostigma* given subcutaneously in rabbits (Fraser (12)); *morphia* and *atropine sulphate* administered subcutaneously in the rat (Bashford (13)); various *snake venoms*—krait, *Enhydrina valakadien*, *Enhydris curtus*, cobra—inoculated in rats, rabbits, guinea-pigs, and cats by different observers (Fraser and Elliott (14), Elliott, Siller, and Carmichael (15), Madsen and Noguchi (16), and others); *adrenalin* both natural and synthetic in the mouse (Schultz (17)); *tetanus toxin* injected subcutaneously in the mouse (Knorr (18)); *potassium chloride* (KCl) introduced intravenously in the rabbit (Hald (19)); and *caffeine* subcutaneously, intraperitoneally, intravenously, or by the mouth in dogs, cats, rabbits, and guinea-pigs (Salant and Rieger (20)).

In view of the conclusions to which the results obtained with all these very diverse toxic agents lead, it seems clear that in animals of different size in any given species the dose required to produce a given effect is related to the surface and blood volume of the animal and not directly to the body weight. That is to say, the smaller individuals require a relatively larger dose than the heavier animals to produce the same effect.

While we are not prepared to maintain that this constitutes a *universal* rule to which there are no exceptions, yet it follows from what has been already stated that it possesses a very wide application, and we have not up to the present met with any exception in the case of mammals and birds.

Accordingly we conclude that if it is desired to administer comparable doses of drugs in warm-blooded animals of different size and weight in any given species, they must be calculated in relation to the body surface.

It follows from this that if one administers any given toxic substance in doses such as will kill each of the animals employed in about the same period of time, one is now in a position to use animals of various size over a wide range of weight within the same species instead of only animals of one particular size in carrying out experimental work upon toxicity and lethal dosage. One is no longer restricted to the use of carefully selected animals of a given and standard weight, as has hitherto been the case, for example, in all determinations of the strength of toxins as well as in the standardisation of antitoxins. This result will naturally prove of value in facilitating toxicological investigation in very many directions.

In case of *cold-blooded animals* we are not at present able to put forward any definite statement; but the problems which they present are under investigation.

As regards the influence of *sex* in warm-blooded animals, we find an indication in our figures that female animals require a somewhat smaller dose to produce a given effect than male individuals of corresponding weight. This agrees with what has frequently been pointed out as the result of clinical experience. The observation seems to find its explanation in the fact that the blood volume of female animals is slightly smaller (7) than that of males. For both the initial and the maximal concentration in the plasma of any drug administered by a given route in a series of animals of different size and weight will naturally be related to the volume of the plasma. Whatever be the rate at which it is selected from the plasma by particular cells, and whatever be the rate of its elimination from the body, the concentration in the blood plasma of any given substance must at every stage be related to the volume of that plasma in the individual animal concerned. Thus a given dose of any substance administered (in one and the same dilution) will reach a higher effective concentration in those individuals whose blood volume is less than in those in which it is greater.

The importance of this question of concentration may be illustrated by a reference to the experiments carried out by Hald (19) with potassium chloride. These showed that in individuals of equal weight the effect of one and the same dose of the active substance was greater, and manifested itself more rapidly, the higher the *concentration* in which it was given.

In view of these considerations it becomes of interest to return to the question of the failure encountered in the treatment of trypanosomiasis in large animals with drugs successfully employed in the smaller species.

If one compares the doses necessary to produce the same concentration of a given drug in the plasma of man and the rat, it can readily be shown that even if a man of 70 kgrm. could be given the same dose per kilogramme as a rat of 140 grm. weight—the figures selected by Moore in his discussion—the concentration of the drug in the man's blood plasma would only be about 75 per cent. of that obtained in the rat. Accordingly, the same therapeutic effect could not be produced. Man, however, cannot tolerate anything approaching this degree of dosage, and hence the treatment which is curative in rats becomes inapplicable in the human subject. But even these facts do not, as it seems to us, afford the whole explanation of the difficulty in question. For it appears that differences in tolerance and intolerance to particular substances in different species of animal are of a specific character and cannot be explained merely by relative differences in blood volume and body surface.

In proof of this, attention must be drawn to the fact that it is not always the larger species which are more susceptible than the smaller species to dosage proportional to their relative body surface, or even to their relative body weight. Sometimes the conditions are reversed. Thus, as is well known, a horse infected with tetanus may be found in apparently excellent condition and as yet exhibiting no symptoms of the disease at a period when its blood already contains enough tetanus toxin to kill a guinea pig injected with only a few cubic centimetres of the horse's serum. Similarly in the case of rats and guinea pigs, rodents of about the same size, the rat can resist several hundred times the dose of diphtheria toxin which will be fatal to the guinea pig within a few days.

In the case of substances other than bacterial toxins similar examples showing a greater resistance in the larger species than in the smaller can readily be found, as for instance in the experiments of Meurice, already referred to (9), in Bock's experiments (21) with cobalt compounds, in Jodlbauer's paper on Tetramethyl ammonium chloride (22), in Fraser and Elliott's experiments on Cobra venom and on Enhydrina venom (14), and in many other pharmacological investigations. It follows that drug susceptibility is by no means necessarily greater in the larger species than in the smaller, but on the contrary it is frequently less. Accordingly, any general explanation of drug action in different species of animals, which is based upon the relative size of their surface, cannot be maintained. Only within one and the same species of animal will the surface relation prove a reliable guide in dosage.

In this connection it is of some interest to consider briefly formulæ for dosage in the human subject such as have been made use of or suggested by various writers. For the sake of ease in calculation these have usually been based on the age of the patient, and most of them appear to aim at giving dosage in relation to the body weight.

But in the case of the formula of Thomas Young, 1813, we meet the earliest example of dosage calculated so as to give younger individuals a relatively greater dose per unit of body weight than is given to adults. Young wrote that "for children under twelve years old, the doses of most medicines must be diminished in the proportion of the age to the age increased by twelve: for example at two years old $1/7 = 2/(2 + 12)$. At twenty-one the full dose may be given. Y." (23).

We owe the exact reference to the kindness of Dr. A. J. Jex Blake; but how Young arrived at his formula, Age/(Age + 12), it has not been possible to discover from his writings. However this may be, his formula actually gives for all ages from about four or five to about 16 a dosage fairly

approximating to dosage by the surface area. But below the age of five years the dosage by Young's formula falls more and more rapidly below the dose calculated in relation to body surface.

We append a table showing the doses which would be given at different ages from 1 year to 21 years in a system of dosage calculated in relation to blood volume and body surface, taking the weights at the different ages as given in Vierodt's tables, 1893.

Table of Dosage.

Age, in years.	Average weight, in grm.	Dose in relation to surface.	Dose as a fraction of dose for adult.
21	61,200	**100·0**	$\frac{1}{1}$
20	59,500	98·8	
19	57,600	95·7	
18	53,900	**92·5**	
17	49,700	86·2	
16	45,400	**81·4**	
15	41,200	75·1	$\frac{3}{4}$
14	37,100	**70·1**	
13	33,100	64·7	
12	29,000	**58·3**	
11	27,000	55·4	
10	25,200	52·8	
9	23,500	**50·6**	$\frac{1}{2}$
8	21,600	47·2	
7	19,700	44·6	
6	17,800	**41·1**	
5	15,900	38·1	
4	14,000	34·3	$\frac{1}{3}$
3	12,500	31·7	
2	11,000	**29·2**	
1	9,000	25·1	$\frac{1}{4}$
0	3,100	**11·8**	$\frac{1}{10}$

In the above table the dose in relation to the surface is given as calculated from the body weight, and points are indicated where the calculated dose approximates to a simple fraction of the adult dose. These work out extremely conveniently for practical application. Thus at 15 years (approximately three-quarters of the adult age of 21) the dose is $\frac{3}{4}$; at 9–10 years (nearly half the adult age) the dose is $\frac{1}{2}$; at 3–4 years it may be given as $\frac{1}{3}$; at 1 year of age it is $\frac{1}{4}$; below that age it sinks to as little as $\frac{1}{10}$ of the adult dose.

In conclusion we would draw attention to the fact that as long ago as 1818 Hufeland (24) gave the dose at fifteen years as $\frac{3}{4}$ and the dose at one year as $\frac{1}{4}$, though he placed the half dose at six years of age instead of at nine or ten as our table makes it. Thus it appears that both he and Young already recognised the necessity of giving relatively larger doses than

would be proportional to body weight in the younger and smaller individuals of the species. On the other hand Dilling (25) in a recent communication proposes a formula which approximates roughly to a dosage per kilogramme of body weight. This is a system of dosage the fallacy of which was emphasised by Moore. In view more especially of the considerations brought forward above, we venture to suggest that it should now be entirely abandoned.

Conclusions.

1. In warm-blooded animals of the same species but of different weights dosage must be calculated in relation to the body surface.

This result agrees with the conclusion already reached by Moore* though on different grounds.

2. This statement is to be explained on the ground that the concentration in the plasma of any given substance administered is dependent on the volume of the circulating blood, which is itself proportional to the body surface in any given species of animal.

3. It follows that in the accurate measurement and standardisation of toxic substances and antitoxins it will now be possible to make use of animals of different weights within a given species instead of using only animals of an arbitrarily selected weight, as has hitherto been necessary.

4. Results in dosage calculated from one species of animal cannot directly be applied to another species merely by taking surface into due consideration, since tolerance and intolerance are specific characters which are shown to be in many cases independent of the size of the species concerned.

5. For the human subject dosage in relation to the surface works out very simply as approximately:—

At 21 years.....	Full dose	At 3–4 years	$\frac{1}{3}$ dose
„ 15 „	$\frac{3}{4}$ „	„ 1 „	$\frac{1}{4}$ „
„ 9–10 „	$\frac{1}{2}$ „	In the early months ...	$\frac{1}{10}$ „

REFERENCES.

1. Dreyer, Georges, and Walker, E. W. Ainley, "Observations on the Production of Immune Substances," 'Journ. Pathol. and Bacteriol.,' 1909, vol. 14, p. 28.
2. Dreyer, Georges, and Walker, E. W. Ainley, "On the Difference in Content of Agglutinins in Blood Serum and Plasma," *ibid.*, 1909, vol. 14, p. 39.
3. Dreyer, Georges, and Ray, W, "Observations on the Relationship between Blood Volume and the Total Amount of Agglutinin recoverable from Actively and Passively Immunised Animals," *ibid.*, 1909, vol. 13, p. 344.

* Moore's conclusions seem to rest in the main on a consideration of "substances which act by stimulation or inflammation of surfaces."

4. Moore, B., "The Relationship of Dosage of a Drug to the Size of the Animal treated, especially in regard to the Cause of the Failures to cure Trypanosomiasis and other Protozoan Diseases in Man and large Animals," 'Biochemical Journal,' 1909, vol. 4, p. 323.
5. Chisolm, R. A., "On the Size and Growth of the Blood in Tame Rats," 'Quart. Journ. Exper. Physiol.,' 1911, vol. 4, p. 207.
6. Boycott, A. E., "The Size and Growth of the Blood in Rabbits," 'Journ. Path. and Bacteriol.,' 1912, vol. 16, p. 485.
7. Dreyer, Georges, Ray, W., and Walker, E. W. Ainley, "On the Blood Volume of Warm-blooded Animals, together with an Inquiry into the Value of some Results obtained by the Carbon Monoxide Method in Health and Disease," 'Skandinav. Archiv f. Physiol.,' 1913, vol. 28, p. 299.
8. Morishima, K., "Giftigkeitsgrad, Absorptionsgeschwindigkeit und Immunisirungsvermögen des Arseniks," 'Archives Internat. de Pharmacodynamie et de Thérapie,' 1900, vol. 7, p. 65.
9. Meurice, J., 'Intoxication et Désintoxication de différents Nitriles par l'Hyposulfite de Soude et les Sels Métalliques," 'Archives Internat. de Pharmacodynamie et de Thérapie,' 1900, vol. 7, p. 11.
10. Dreyer, Georges, and Walker, E. W. Ainley, "The Effect of Altitude on Blood Volume, together with Further Observations on the Blood in Warm-blooded and Cold-blooded Animals," 'Lancet,' 1913, vol. 2, p. 1175.
11. Crum Brown, A., and Fraser, J. R., "On the Connection between Chemical Constitution and Physiological Action," 'Roy. Soc. Edin. Trans.,' 1869, vol. 25, p. 151.
12. Fraser, J. R., "An Experimental Research on the Antagonism between the Actions of Physostigma and Atropia," 'Roy. Soc. Edin. Trans.,' 1872, vol. 26, p. 529.
13. Bashford, E. F., "Ueber Blutimmunität," 'Archives Internat. de Pharmacodynamie et de Thérapie," 1901, vol. 9, p. 451.
14. Fraser, J. R., and Elliott, R. H., "Contributions to the Study of the Actions of Sea-snake Venoms," 'Phil. Trans.,' 1905, B, vol. 197, p. 249.
15. Elliott, R. H., Siller, W. C., and Carmichael, G. S., "On the Action of the Venom of *Bungarus cæruleus* (the Common Krait)," 'Phil. Trans.,' 1905, B, vol. 197, p. 327.
16. Madsen, Th., and Noguchi, H., "Toxines et Antitoxines," 'Oversigt Kgl. Danske Videnskab. Selsk. Forhandl.,' 1906, No. 4, p. 233.
17. Schultz, W. H., "Quantitative Pharmacological Studies: Adrenalin and Adrenalin-like Bodies," U.S. Treasury Department, Hygienic Laboratory, Bulletin No. 55, Washington, 1909.
18. Knorr, A., "Experimentelle Untersuchungen über die Grenzen der Heilungsmöglichkeit des Tetanus durch Tetanusheilserum," 'Habilitationsschrift,' Marburg, 1895.
19. Hald, P. T., 'Kaliums Virkning paa Blodomlöbet,' Dissert., Köbenhavn, 1905.
20. Salant, W., and Rieger, J. B., "The Toxicity of Caffeine," U.S. Department of Agriculture, Bureau of Chemistry, Bulletin No. 148, Washington, 1912.
21. Bock, J., "On Virkningen af Kobolt-, Rhodium-, og Chromammoniakforbindelser paa den dyriske Organisme," 'Oversigt Kgl. Danske Videnskab. Selsk. Forhandl.,' 1904, No. 4, p. 159.
22. Jodlbauer, A., "Ueber die Wirkung von Tetramethylammoniumchlorid," 'Archives Internat. de Pharmacodynamie et de Thérapie,' 1900, vol. 7, p. 183.
23. Young, J., 'Introduction to Medical Literature,' London, 1813, p. 428.
24. Hufeland, 'Lehrbuch der allgemeinen Heilkunde,' 1818, p. 113, referred to in H. Vierodt's 'Daten und Tabellen,' Jena, 1893.
25. Dilling, W. J., "The Calculation of Drug Dosage for Children," 'Brit. Med. Journ.,' 1912, vol. 2, p. 1177.