

still exists, and in the quiescent state the external genitalia are still retained within the cloaca.

In *Echidna* the intracloacal genital tubercle of the male presents a completed penile channel in distal portion, but at its proximal end the seminal guides have not completely united over the seminal groove and a state of normal hypospadias exists at the root of the penis, this deficiency being obliterated with erection of the organ. In the cloacal Insectivora, such as *Blarina* and *Crocidura*, the closure of the seminal canal is completed in the male, and the hypospadiac condition of *Echidna* is lost. (Fig. 7.)

We have therefore in some of the mammalian orders a retention of a cloacal condition, and in these an advance has been made on the chelonian condition mainly by the closing in of the seminal groove. In the cloacal Insectivora the penis has reached a high degree of development and is usually remarkable for its great length, so much so that it is retained, more or less coiled, in a diverticulum of the ventral part of the cloaca. It is very important to recognise that the cloacal condition *does* exist among the Insectivora, and I have come to think that the appreciation of the differences to be detected in the methods of formation of the external genitalia within the limits of this group forms a basis for a better understanding of the inter-relations of the other mammalian groups. To this point it will be necessary to revert later on. It is equally important to recognise that the chelonian condition is not only practically identical with the lowest mammalian type of external genitalia, but it is also represented as an early stage in the embryonic development of the external genitalia of all mammals. From a simple stage in which an intracloacal genital tubercle, bearing a seminal groove marked laterally by seminal guides, is present, the adult external genitalia of all mammalian orders are derived; but the method of derivation and the final condition produced present very striking differences, first, within the limits of the group Insectivora, and second, within the whole compass of the mammalia. It is necessary to describe the stages of the development from this simple condition as they are displayed in various mammalian embryos.

I have come to believe that there are two main types of development and two main types of resulting external genitalia; that all mammals may be placed in the one group or the other; and that an examination of the adult genitalia will generally, and an examination of the embryonic stages will always, reveal definitely into which group a particular species falls.

A POST-GRADUATE COURSE IN VENEREAL DISEASES.—A special course of lectures and demonstrations for post-graduate and advanced students will be given at St. Mary's Hospital on Mondays and Thursdays at 4 P.M., beginning April 27th and ending July 2nd. Dr. Sidney P. Phillips will deal with syphilis of the abdominal viscera, Mr. J. Ernest Lane with the treatment of venereal diseases and syphilis of the tongue, Dr. Wilfred Harris with syphilis of the nervous system and parasyphilis, Dr. W. J. Gow with syphilis in relation to obstetrics and gynaecology, Dr. E. G. Graham Little with syphilis and the skin, Mr. A. Fleming with the biological and laboratory aspects of syphilis, and Mr. Leslie J. Paton with the ophthalmology of syphilis. Applications for admission to the course, for which the fee is 4 guineas, should be made to the school secretary, a reduction being made in the case of former St. Mary's men.

AN ANALYSIS OF THE PROBLEM OF THE MINIMAL LETHAL DOSE AND ITS RELATIONSHIP TO THE TIME FACTOR.*

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AND

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IN a previous paper¹ evidence has been brought forward to show that over a wide range of weight in any given species animals of different size can readily be employed for the standardisation of toxic substances and antitoxins, instead of animals of an arbitrarily selected weight as has hitherto been necessary. All that is required is that the doses given shall be calculated in relation to the body surface and blood volume of the individual animals employed. For this purpose we have suggested the use of the formula $D = \frac{d}{W^{0.72}}$, where D represents the dose in relation to the surface of the individual, W is the weight of the animal, and d is the actual quantity of drug administered. From this formula one calculates with equal readiness the "surface dose" † (D) for any actual quantity of drug (d) administered, or the quantity (d) of drug which must be given in order to produce a dosage (D) in relation to the surface of the individual animal concerned. But in the standardisation of toxins, antitoxins, and drugs by means of animal experiment another factor of the greatest importance comes into play—namely, the time to death. Accordingly, it has hitherto been the accepted custom not only to employ animals of an arbitrarily selected weight, but also to fix upon an arbitrary time to death as a means of rendering such experiments comparable *inter se*. This method, the only accurate one hitherto available, we owe to the pioneer work of Ehrlich, which has been fundamental for the study of the problems involved in the phenomena of protection and the action of toxins. But how far this method of comparison actually falls short of affording a true measure of relative toxicity will appear from the following considerations, which in our opinion have long demanded a detailed investigation.

First, if one takes two samples of diphtheria toxin and determines the dose of each toxin which will kill a guinea-pig of standard weight in standard time (and would therefore be considered equivalent doses), it is found that equal multiples or submultiples of these doses are no longer equivalent in their action in the animal body. Accordingly, the equivalence thus determined is merely a coincidence, and not in any sense a real equivalence, since if any other lethal times be chosen the equivalent doses experimentally determined will be found to have an entirely different ratio to each other.

Thus, taking two samples of diphtheria toxin, we

* A more detailed account of this work is published in the *Biochemische Zeitschrift*, 1914, vol. ix., p. 112.

† Dose calculated in relation to body surface (and blood volume).

arrive at the following results for the equivalent doses at different times.

TABLE I.—Showing Comparative Strengths of Diphtheria Toxins (B) and (C).

To kill a guinea-pig of 250 grm. in hours.	Toxin B. Dose in relation to surface $\times 10^7$ in c.cm.	Toxin C. Dose in relation to surface $\times 10^7$ in c.cm.	Ratio between equivalent doses = $\frac{\text{Dose of B.}}{\text{Dose of C.}}$
36	3519	3233	1.09
48	2860	2241	1.28
60	2632	1867	1.41
72	2522	1672	1.51
96	2413	1472	1.64
120	2359	1366	1.73
144	2327	1303	1.79

It will at once be seen that the ratio of the equivalent doses of the two toxins increases steadily as the time to death is increased. Thus, when the standard time for death—namely, 96 hours—is taken, the equivalent dose of toxin B is about 65 per cent. greater than that of toxin C. But if 36 hours is selected as the lethal time the equivalent dose of toxin B is only about 9 per cent. greater than that of toxin C, while if 6 days is taken as the death time, the dose of toxin B is approximately 80 per cent. larger than that of toxin C.

Again, if instead of comparing the effect of two different samples of toxin on a given species we take the observations of Wolfgang Ostwald and Dernoscheck² on the small crustacean Gammarus poisoned by immersion in sea-water of varying concentration, and thus compare the effect of one and the same toxic substance on the male and female animal respectively, we find the following results:—

TABLE II.—From Wo. Ostwald's Observations on Gammarus.

Concentration of sea-water in ‰.	Time to death in the male animal in minutes.	Time to death in the female animal in minutes.	Ratio between death times $\frac{\delta}{\varphi}$
58.7	36	36	1.00
47.2	48	46	1.04
40.1	79	53	1.49
35.4	120	77	1.56
33.0	147	86	1.71
28.3	326	185	1.76
25.9	lives.	328	∞

Table II. thus shows that for the same concentration of the toxic fluid the ratio between the lethal times for the two sexes steadily increases as the concentration of the toxin is diminished. Thus, with a concentration of 58.7 the time to death is the same in the two sexes, while with a concentration of 40.1 it takes about 50 per cent. longer to kill the male than the female, and with a concentration of 28.3 over 75 per cent. longer.

Accordingly, whether we take times to death in a given species of animal, and compare the equivalent doses of two toxins which will kill in these times; or take different concentrations of one and the same toxin and compare the times to death in male and female animals of the same species, we find that the standard method hitherto employed cannot afford a true measure of relative toxicity. This

conclusion necessarily follows from the fact that with different death times the ratio between the equivalent doses of the toxins is found to vary; and with different concentrations of the toxic fluid the ratio between death times is also found to vary. As these respective variations are extremely marked it is evident that the point requires no further elaboration.

It follows that a method of calculation must be sought by means of which toxicity can be estimated quite independently of any arbitrarily selected death time or any particular dosage chosen from comparison. After a prolonged consideration of a large mass of material one of us (G. D.) arrived at the following formula for the relationship between concentration and quantity of dose and the time required to cause death (or to produce any other desired effect in animals of

any given species)—namely, $\frac{1}{D_0 - a} - \frac{1}{D_1 - a} = k(T_0 - T_1)$, where D_0 and D_1 are "surface doses" (doses expressed in relation to body surface corresponding to the times T_0 and T_1 , in which the death of the animal (or other desired effect) is produced, a is a figure the value of which is dependent both on the particular species of animal employed and the particular toxin, and k is a constant to be determined for the particular toxin and the particular species of animal employed. Expressed in words, the formula simply states that to every equal increment in time there corresponds a definite decrease in the active dose ($D - a$).

This formula we have tested over a very extensive series of observations of the most diverse character, and find that it affords an extremely satisfactory method of calculation. As will be shown below, it allows equal significance to be placed on each individual observation in a long series of animals of different weights, entirely independent of the dose and death time.

Before proceeding further it is now desirable to consider briefly the quantity a . In determining the minimal lethal dose of any toxic substance (or the dose required to produce any given effect) one arrives, by gradually diminishing the dosage, at a quantity less than the critical dose in question, which appears to be inactive. The animal does not die, or the other desired effect, whatever it may be, is not obtained. How closely the size of a , as determined by our method, approaches the size of the minimal effective dose (M.L.D. or other) depends not only on the character of the particular substance under investigation, but also on the character of the effect desired—whether this be death or any other manifestation of toxic action. But to the precise meaning of a we shall return.

The importance of discovering the relation between the concentration or quantity of dosage and the corresponding time to death has been fully realised by several of previous workers, and especially by Arrhenius,³ Warren,⁴ Wolfgang Ostwald,⁵ and Ostwald and Dernoscheck.² Of these, Warren, Ostwald, and Ostwald and Dernoscheck suggest definite formulæ for the case of small crustaceans poisoned by immersion in solutions of various salts.

Warren's formula is $\frac{1}{T} = k(c - n)$, where T is the time to death, c the concentration of the salt solution, n a number constantly subtracted from c , and k a constant. This formula states that the

time to death is inversely proportional to the concentration diminished by *n*. But this is not the case.

Ostwald and Dernoscheck's formula is $\frac{1}{T} = k(c-n)^m$, and it is clearly a generalisation of Warren's formula (which they criticise), obtained by the introduction of a varying power *m* instead of the power 1. This formula they substitute for Ostwald's original formula $\frac{1}{T} = k.c^m$, in recalculating his observation on Gammarus. They show how much more satisfactory is the agreement between observed and calculated figures when this formula is used instead of Warren's formula or even Ostwald's own earlier formula.

As regards the significance of *n* Warren appears to consider it to represent the concentration of salt *normal* to the animal observed (*Daphnia*), while Ostwald and Dernoscheck arrive at its value by a process of calculation. It does not, however, appear that the latter observers attach any rational significance to the meaning of *n* in their formula.

One of us (E. W. A. W.) in 1901,^{6,7} in attempting to clear up the difficulty which obtained regarding the relation between the amount of antitoxin or antibody required to neutralise one M.L.D. in the body of an animal, and the amounts required to neutralise multiples of the M.L.D. showed that a certain non-effective dose (*a*) must always be subtracted in calculating the amount of antitoxin required. As, however, no attention was then given to the time factor, the results obtained by administering doses on this system only held good over a quite short range of multiples of the M.L.D. But in the formula devised by the other of us (G. D.) the value of (*a*) is made to be dependent on the *rate of killing*, and not merely on the fact that death does or does not occur.

We now proceed to show how successfully this formula may be applied, not only to our own experimental results, but also to a mass of diverse published observations. In all the cases which we have examined where a sufficient range and number of observations is provided to afford a material suitable for calculation the formula holds good, and represents the experimental findings in an extremely satisfactory manner.

In Table III. is given a series of our own experiments with a diphtheria toxin (B). The doses (D) are given as calculated in relation to surface by the formula $D = \frac{d}{W^{0.72}}$ where W is the weight of the animal in grammes, and *d* is the *actual dose* administered.

The results in Table III. show clearly that the formula proposed represents the experimental data for the grouped experiments in a very satisfactory manner. Although the animals employed cover a range of weight from 200 grm. to 530 grm., the difference between the death times calculated by the formula and those actually observed averages only 0.38 per cent. Similar results were obtained for two other samples of diphtheria toxin (A) and (C). In the case of toxin (A) it was found that $k \times 10^7 = 330$, and *a* = 1140, while for toxin (C) $k \times 10^7 = 316$ and *a* = 1045. For toxin (A) the average death times ranged from 85 to 220 hours, and for toxin (C) from 67 to 148 hours.

But, as has already been pointed out above, it is impossible to draw any reliable conclusion regarding the actual strengths of the three samples of

TABLE III.—*Diphtheria Toxin (B) in Guinea-pig: Subcutaneous Injection (Own Experiments).*
 $\frac{1}{D_0 - a} - \frac{1}{D_1 - a} = k(T_0 - T_1), \quad k \times 10^7 = 665, \quad a = 2200$
(*T*₀ = 36.3, *D*₀ = 3555).

No.	Weight of animal in group.	Actual dose (<i>d</i>) in c.cm.	Dose (D) in relation to surface $D = \frac{d}{W^{0.72}} \times 10^7$	Hours to death.	Dose (D) in relation to surface grouped animals.	Hours to death grouped animals = T observed.	Hours to death calculated for grouped animals = T calculated.	Percentage differ- ence between T calculated and T observed.	
1	440	0.01900	2370	30	2496	76.0	76.0	0.00	
2	355	0.01750	2552	118					
3	310	0.01600	2565	80					
4	200	0.01200	2640	100	2659	57.8	58.0	0.34	
5	470	0.02215	2640	38					
6	400	0.01990	2661	55					
7	330	0.01750	2696	38	2788	51.0	50.8	0.39	
8	230	0.01375	2745	64					
9	530	0.02560	2800	38					
10	435	0.02240	2820	51	2953	45.0	45.2	0.44	
11	255	0.01575	2920	40					
12	215	0.01400	2940	42					
13	460	0.02480	3000	53	3039	43.3	43.1	0.46	
14	430	0.02375	3015	44					
15	235	0.01535	3020	38					
16	400	0.02270	3040	44	3283	39.0	39.1	0.26	
17	360	0.02135	3080	47					
18	415	0.02480	3220	44					
19	425	0.02520	3230	49	3555	36.3	36.3	0.00	
20	435	0.02590	3258	32					
21	370	0.02415	3424	31					
22	415	0.02715	3525	49	3555	36.3	36.3	0.00	
23	425	0.02780	3560	30					
24	435	0.02845	3580	30					
Average									0.38

diphtheria toxin A, B, and C from a comparison of the doses required to cause death in any given fixed time; for, as already stated, their ratios to one another vary for each particular time. A measure of relative strength can, however, be obtained by comparing the size of the three different constants *k*, which are dependent on the size of the effective doses of the toxins. These constants vary in this sense, that in toxic substances of the same quality the weaker toxin has a larger *k* in the formula while the stronger toxin has a smaller value for *k*. This comparison is the only one that can be obtained, which is independent, not only of the weight of the animal (in any given species), and of the dosage, but also of the time factor. It gives an expression for the relative strengths of the three samples of toxin. These are related to each other as *k*_A : *k*_B : *k*_C. Expressing the facts in words, one is able to say that if we have two samples of toxin—for example, two diphtheria toxins P and Q where the value of *k* for P is the *double* of that for Q—then for each given increment of time the *increase* in the reciprocal of the effective dose in the case of P will be the double of the *increase* in the reciprocal of the effective dose in the case of Q. The effective dose is given in each case by the expression (*D* - *a*).

In regard to the significance of *a* in the formula, this quantity represents the "non-effective" portion of the dose—that is to say, the dose which in itself

is insufficient to cause death (or other desired effect). Accordingly, its size varies with the resistance of the sex and species, being larger for the more resistant type and smaller for the more susceptible. Further, with one and the same toxic substance, α is greater the less the toxicity of the particular sample which is employed. Thus, in the case of the three samples of diphtheria toxin dealt with above it was found that for C, the most active toxin, α had a value of 1045, while for A, which was somewhat less active, it was 1140, and for B, much the weakest sample, it was 2200.

TABLE IV.—*Synthetic Adrenalin in the Mouse: Subcutaneous Injection (Schultz's Experiments).*

$$\frac{1}{D_0 - \alpha} - \frac{1}{D_1 - \alpha} = k(T_0 - T_1). \quad k \times 10^3 = 48, \alpha = 900$$
$$(T_0 = 30.7, D_0 = 1677).$$

Group.	Number of animals in group.	Dose (D) in relation to surface grouped animals $D = \frac{d}{W^{0.72}} \times 10^3$.	Minutes to death. Grouped animals. = T observed.	Minutes to death calculated for grouped animals. = T calculated.	Percentage difference between T calculated and T observed.
1	6	1677	30.7	30.7	0.00
2	5	1886	25.0	25.0	0.00
3	5	2051	22.0	22.0	0.00
4	6	2357	18.8	18.2	3.30
5	3	2634	14.3	15.9	10.10
Average					2.68

In Table IV. is given an analysis of experiments by W. H. Schultz⁹ with a synthetic adrenalin (ethyl-amino-aceto-catechol) in the mouse. Twenty-five experiments done about the same time (Jan. 5th and 16th, 1909) on animals not previously injected with the drug are taken from his series (his Table XIV.). The observations were made on mice varying in weight from about 12 grm. to 25 grm. After they had been arranged in order according to "surface dosage" they were collected into five groups by averaging the "surface doses" and lethal times. From these data the constant k was determined, and by its use the theoretical time to death was calculated for each group. It was found that the average difference between the calculated and the observed lethal times was only 2.68 per cent. From this it follows that the formula proposed also applies very satisfactorily to the case of synthetic adrenalin, where the death times are extremely short (minutes), as contrasted with the long death times (up to several days) with diphtheria toxins.

The value of employing the method of calculation here brought forward is well illustrated by comparing the observations of Madsen and Noguchi¹⁰ on filtered and unfiltered samples of cobra venom. As already pointed out, it takes account not only of the size and surface area of the animal concerned, but also of the time required to produce the desired effect (e.g., death), while at the same time it gives results which can be applied (within a given species) quite independently both of lethal time and of the size of the individual animal employed.

Madsen and Noguchi came to the conclusion from their experiments with cobra venom that the toxicity of the venom was not sensibly diminished by filtration through a Chamberland filter. This result contrasted strongly with their further observation, that after similar filtration *crotalus venom* was diminished in toxicity by as much as

50 per cent. The data for cobra venom (from their Tables XIX. and XXIX.) were, therefore, calculated by our formula. For the unfiltered venom k was found to be 110 and α 185, while for the filtered venom k was 130 and α 270. These results show that the toxicity of the cobra venom was in reality *greatly reduced* by the process of filtration, since the "surface dose" of filtered venom which is needed to kill a guinea-pig with certainty is much greater than the surface dose required for unfiltered venom.

In view of the evidence which has now been given it is unnecessary to adduce further detailed calculations of experiments in support of the method and formula here proposed for dealing with questions of dosage and toxicity. But it should be mentioned that the formula is in excellent accord with all the published observations which we have analysed where an adequate series of data is available. Among the observations which we have examined from this point of view and which we find to fit the formula are the following: Knorr's experiments with tetanus toxin injected subcutaneously in the mouse¹¹; Elliott, Sillar, and Carmichael's experiments with krait venom injected subcutaneously in rabbits¹²; Fraser and Elliott's experiments with the venom of *Enhydrina valakadien* injected subcutaneously in rabbits¹³; natural adrenalin in the mouse, Schultz⁹; sulphate of physostigmia subcutaneously in rabbits, Fraser¹⁴; caffeine subcutaneously in guinea-pigs and cats, Salant and Rieger¹⁵; cobalt nitrate subcutaneously in guinea-pigs, Bock¹⁶; and potassium chloride injected intravenously in rabbits, Hald.¹⁷

From these facts we conclude that so far as evidence at present goes the formula is one of general application in regard to dosage and death time in warm-blooded animals. That it holds not only in regard to lethal effects but also in the case of ordinary pharmacological and toxic action in general is seen from the experiments of Schultz⁹ on the mydriatic action of synthetic adrenalin in the excised frog's eye. These experiments are analysed and calculated below in Table V., where it is seen that the percentage differences between Schultz's observed times and the times calculated by our formula are in every case but one very small indeed, and even taking in the one obviously divergent figure give an average error of only 2.73 per cent.

TABLE V.—*Mydriatic Action of Synthetic Adrenalin on the Excised Frog's Eye (Schultz's Experiments).*

$$\frac{1}{D_0 - \alpha} - \frac{1}{D_1 - \alpha} = k(T_0 - T_1). \quad k \times 10^5 = 805, \alpha = 2.2,$$
$$(T_0 = 20, D_0 = 500).$$

Group (Schultz).	D = relative dose—i.e. concentration of the solution employed.	Time to maximum mydriatic effect = T observed minutes.	Time to maximum mydriatic effect calculated = T calculated minutes.	Percentage difference between T calculated and T observed.
1	1000	21	18.8	11.70
2	500	20	20.0	0.00
3	200	24	23.8	0.84
4	40	50	50.4	0.99
5	8	232	231.7	0.13
Average				2.73

One further example of the application of the formula may be given in a case where the animal

concerned (a crustacean, Gammarus) was immersed in the toxic fluid the action of which was to be tested. The observations are taken from the experiments of Wo. Ostwald and Dernoscheck.² These authors deduced from their observations the formula to which reference has already been made: $\frac{1}{T} = k(c - n)^m$. The formula in question is based on a consideration of the phenomena of adsorption. Their data can, however, be expressed even more satisfactorily by the formula here proposed than by their own.

Our calculations give for male Gammarus $k \times 10^6 = 841$, $a = 24.6$, and for female Gammarus $k \times 10^6 = 1055$, $a = 23$. Using these constants we find that the average difference (disregarding signs) between death time observed and death time calculated for male Gammarus is 4.48 in the case of Ostwald and Dernoscheck's calculation and 4.50 in our own. But in the case of the females Ostwald and Dernoscheck's calculation gives an average difference of 5.94, while ours gives an average difference of only 4.42. Moreover, if one examines in detail the operation by which they arrive at their results, one finds that the n in their formula is actually chosen of a smaller size for the more resistant male than for the less resistant female animal, being in the two cases 23.88 and 24.557 respectively.

Now, in our opinion n (a in our formula) can only have a rational significance if it represents the "non-effective" fraction of the dose, and this must obviously be greater for the more resistant sex. In our operation, on the other hand, a possesses, as it should, a higher value for the males than for the females—namely, 24.6 for male Gammarus against 23.0 for the female.

Furthermore, it is a matter of no little importance that the new formula applies equally well to the results obtained by the inoculation of warm-blooded animals with a long series of toxic substances as to the observations now under consideration. It offers a ready explanation of the facts observed in each case, and possesses a simple and obvious interpretation.

Conclusions.

1. In warm-blooded animals dosage (D) must, as shown in a previous paper,¹ be calculated in relation to the body surface according to the expression

$D = \frac{d}{W^{0.75}}$ where D is the "surface dose" of the drug, toxin, or antitoxic substance used, d represents the actual quantity administered, and W is the weight of the animal in grammes.

2. No method, however, at present exists by which a true comparison of the relative toxicity of different substances (or of different samples of the same substance) can be instituted. The methods hitherto employed depend on the selection of an arbitrarily fixed weight of animal and lethal time, and do not afford a rational basis for the accurate measurement and standardisation of drugs, toxins, and antitoxins.

3. The formula here proposed

$$\frac{1}{D_0 - a} - \frac{1}{D_1 - a} = k(T_0 - T_1),$$

offers a simple means of making such measurements. In this formula D_0 and D_1 are the concentrations of the drug or "surface doses," corresponding to the times T_0 and T_1 in which the death of the animal (or other desired effect) occurs; a is a figure representing the "non-effective" dose of the substance employed, and k is a constant to be

determined for the particular substance and species of animal under investigation.

4. The formula states that to every equal increment in time there corresponds a definite decrease in the "active dose" ($D - a$).

5. This formula is here shown to afford a satisfactory expression for all the varied and diverse experimental data to which it has been applied.

6. The use of the formula renders it possible not only to carry out the comparison desired, but also to make use of animals of every size over a wide range of weight within a species, and all observed death times, in the standardisation of toxic substances, antitoxins, and the like.

7. By this means a great saving both of time and animal material is introduced, since an equal value, independent of the actual lethal time and weight of individual animal, can now be attached to all the experimental data.

8. The results obtained will also possess a greater validity and a wider application than it has hitherto been possible to attain by the use of an arbitrary death time and a fixed standard weight of experimental animal.

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THE special annual service for members of the University of London will be held in Westminster Abbey, at 6 P.M., on Wednesday, May 13th, when the sermon will be preached by the Bishop of London. Admission will be by ticket only, which can be obtained by graduate or undergraduate members of the University on application to the Secretary of the Westminster Abbey Service Committee, 88, Gower-street, W.C. A stamped addressed envelope should be enclosed.

THE PRICE OF RADIUM.—The possibility of cheapening radium in the interests of suffering humanity is foreshadowed by a scheme for acquiring mining properties, covering an area of 42,000 acres, in the centre of what is acknowledged to be the greatest radium deposits known in the world—St. Joachimsthal, in Bohemia. They surround the great radium mines of the Austrian Government, and investigations have proved conclusively that the deposits of the Government are continued into the properties at many points. For over 200 years silver, bismuth, cobalt, tin, nickel, and iron have been extracted from this rich mining district, of which only a small portion has been worked at present. Mr. Karl Stegl and Professor Dr. Krusch have examined the properties, which include 30 opened-up mines and 687 mining claims situated in 34 different districts. Portions of the properties have been worked for many years for various minerals, and a large number of shafts and galleries are already in existence. For the last two years all the development work has been concentrated on the discovery of the pitchblende deposits, from which the pure radium is obtained, and it is claimed that one ton of ore yields over 200 milligrammes of radium bromide. Works and laboratories fully equipped with modern appliances are to be installed without delay.