On Intravascular Coagulation in Albinoes and Pigmented Animals, and on the Behaviour of the Nucleo-proteids of Testes in Solution in the Production of Intravascular Coagulation.

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CONTENTS.

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Part I.—Introduction.

The work described in this paper was undertaken in order to ascertain the differences in relation to intravascular coagulation which distinguish the albino and pigmented races of a species.

There exists a considerable body of evidence tending to show that in certain qualities albinoes are less constitutionally vigorous than pigmented individuals (Darwin, 1899; Heusinger, 1846; Mudge, 1907; Twining, 1845; Prichard, 1855). Not a few cases of the converse kind are known, however, and are cited by Darwin (1899). Farabee (Farabee and Castle, 1903) has stated that albino negroes are taller and broader than their pigmented fellows, and we may interpret this difference as meaning some sort of physical superiority.

Quite recently we have had the experiments of Halliburton, Brodie, and Pickering (1896, 1897), which show that while the albinoes intravascularly injected by them with nucleo-proteids do not clot, their pigmented fellows do. Halliburton and Pickering (1897) further proved that the three synthesised colloids, A, B, and C of Grimaux, similarly clotted pigmented animals, but failed to do so with the albinoes used by them. Their experiments, while thus showing that albinoes may be more resistant than pigmented individuals, also apparently demonstrate the existence of a fundamental distinction between albinoes and pigmented individuals in their reaction towards injected nucleo-proteids.

But the results of the experiments described in this paper lead to a modification of such a conclusion, and show that two different sub-races of albinoes exist; one resembling pigmented animals, since its individuals clot upon the intravascular injection of nucleo-proteids, while the individuals of the other sub-race fail to clot.

Pickering (1897, 1899) further stated that the Norway hare in its winter coat reacts like an albino, but in its summer coat like a pigmented individual. The Norway hare, however, is not a complete albino when in its winter coat, for it has a patch of colour on its nose, at the tips of the ear pinnæ and the extremity of the tail, as well as possessing black eyes. The Himalayan domestic breed of rabbits, with which I have experimented, are similar to the Norway hare while in its winter coat, but they have pink and not black eyes. They are, therefore, not wholly comparable to the Norway hare. I find the Himalayan rabbits react like true albinoes.

Part II.—The Relation of Albinism and Pigmentation to Injected Nucleo-proteids.

(A) *Albinoes Injected with Nucleo-proteid derived from Pigmented Animals. Table II.*

The first question I investigated was whether albinoes invariably failed to clot when injected with a nucleo-proteid derived—like that used by Halliburton and Brodie—from pigmented animals. I injected (Table II) 43 albinoes, of which five were rats and the rest rabbits, with such a nucleo-proteid. I also injected eight of the partial albinoes known as Himalayan rabbits (p. 107 and Table V). Nine different solutions,* *i.e.*, B, H, D, I, J, K, N, O, and T, were used, most of them while freshly made (on day of preparation), but some both when freshly prepared and at stated intervals of two, five, seven, or more days after preparation, exclusive of the day on which they were made. The solutions were kept in an ice safe during these periods, and their physical characters, such as colour, odour, alkalinity, and viscosity were normal on each occasion of using. The results are shown in a tabulated form in Table II for the pure albinoes, and in Table V for the Himalayan rabbits.

The majority of pure albinoes manifested more or less extensive intravascular coagulation, the general intensity of which is shown in the sixth column of the table. In four albino rabbits, the blood absolutely failed to clot (experiments 26, 53, 71, and 173); while three gave a qualified failure of such a kind that we may, I think, regard it as of the same nature as the absolute failures (experiments 29, 30, and 72). In the case of the four absolute failures, as in all others, the solution was injected by one of the two methods described on p. 110 until death resulted, and an immediate *post-mortem* examination failed to reveal any clots anywhere, though I very carefully examined all the smallest pulmonary vessels that could be seen with the unaided eye, in addition to the main systemic and portal veins. In the three qualified cases, no clots comparable to those produced in a typical intravascular coagulation were found; for these latter clots in a typical case are strands of the form of the containing vessels and are red in colour. The clots which were found in these qualified cases were not red, but colourless, and they were not of the form of the containing vessel, but mere flocculi or flecks. Moreover, they never occurred in the veins, but always in the cavity of the right ventricle, and in two instances attached to the chordæ tendineæ, and in the other lying in the apex.

Three other qualified cases (experiments 6, 65, and 70) also occurred, but

* As to mode of preparation of these solutions, see p. 122.

these, I think, must be regarded rather as very limited coagulations than as failures, because the clots were red. In experiment 70, the clot was red and very small, and it was attached to a few of the chordæ tendineæ where they joined the tricuspid valve. In experiments 6 and 65 no clots occurred anywhere, except that in the former case a very small red one was found in the postcaval vein just before it entered the heart; while in the latter case, in addition to a few colourless fibrin specks in the right ventricle, there was a semi-liquid red clot about 2 inches long formed in the postcaval vein just posterior to the liver.

(B) *Albinoes Injected with Nucleo-proteid derived from Albinoes. Tables I and V.*

I next ascertained whether any failures of coagulation occurred when albinoes are injected with a nucleo-proteid derived from albino animals. As is shown in Table I, 24 albinoes were injected with albino nucleo-proteid, and of this number four were rats and the remainder rabbits. Two Himalayan rabbits were also similarly injected (Table V), but these are considered later (p. 107). Seven different solutions were used, *i.e.*, A, C, F, L, M, P, and S (p. 122). In most of these experiments the solution was freshly made, but in a few of them it was two or seven days old. In no case was there any condition which may be termed an absolute failure of coagulation. In experiment 140 there is the nearest approach to a qualified failure, for the only definite clotting which occurred was in the right ventricle, where a small, colourless, fibrin flocculus was formed. Careful examination of the smallest pulmonary vessels, *i.e.*, those just visible to the naked eye, showed, however, that the blood appeared to be viscous and forming a kind of liquid clot. It was impossible to decide definitely, owing to the smallness of the vessels. Certainly, in the vessels large enough to allow of a definite observation, the blood was neither clotted nor viscous. Experiment 165 helps us in a measure to interpret the results of the experiment just described. In this rabbit a few colourless fibrin clots were found in the right ventricle, as in rabbit 140, but, in addition, there were also a few red clots in the smaller branches of the pulmonary vessels, though the main vessels contained none. In experiment 80, the pulmonary vessels contained no clots, neither did any of the systemic or portal veins, but in the right ventricle there was a mixture, not intermingled, of colourless fibrin clots with the ordinary red clots.

These experiments justify the conclusion that when albinoes are injected with nucleo-proteid derived from albino animals, no absolute failure of coagulation occurs, such as happens in a certain percentage of cases when they are injected with nucleo-proteids derived from pigmented animals.

Doubtless, in the case of experiments 80 and 165, a much more extensive coagulation would have resulted had larger doses been injected; and the fact that coagulation occurred at all, with the formation of the ordinary red clots, with the minute doses used, is evidence that the animals were susceptible to the coagulative properties of the nucleo-proteid, and possibly the same consideration holds for experiment 140; the doubtfully viscous nature of the blood may have become a definite coagulation had a larger dose been injected. But even if we assume that in this rabbit the pulmonary blood in the smallest vessels was not viscous, the case still remains one of qualified and not of absolute failure; for the right ventricle contained colourless fibrin clots.

Thus, when albino rabbits are injected with "pigmented" nucleo-proteid, about 9 per cent. of absolute failures occur, and also about 7 per cent. of qualified failures. But when they are injected with "albino" nucleo-proteid no absolute failures occur, and it is very doubtful if any qualified ones do.

Partial Albinism (Himalayan Rabbits). Table V.

The characters of Himalayan rabbits are described on p. 104. The only feature concerning them which it is necessary to note is that, with the exception of the pink eyes, they externally resemble the winter condition of the Norway hare, in which Pickering failed to obtain intravascular coagulation. I injected 10 of these rabbits, eight with "pigmented" nucleo-proteid and two with "albino" nucleo-proteid (Table V). With respect to the eight rabbits, in experiment 28 there was an absolute failure of coagulation, and in experiment 8 a qualified failure, only a few colourless fibrin specks being detected in the right ventricle. In the remaining six cases, coagulation, though limited, was produced. Thus about 12 per cent. each of absolute and qualified failures occur.

The two which were injected with "albino" nucleo-proteid both clotted in a pronounced fashion, though the dose injected in one case (Table V, experiment 79) was very small. The number of experiments is too few to enable one to positively state that none of them when thus injected fail to clot. But if this should subsequently prove to be the case, and remembering that a certain percentage of them fail to clot when injected with "pigmented" nucleo-proteid, it is evident that Himalayan rabbits behave like pure albinoes.

The Cause of Failure to Coagulate is not due to the Solutions.

In those cases, both with the complete and partial albinoes, where coagulation failed to occur, the cause of failure is due to inherent qualities of

the individuals and not to the solution or to environmental changes. The failures have occurred with both fresh (experiments 26 and 173) and kept (experiments 53 and 71) solutions. Moreover, fresh solutions may cause coagulation in some rabbits (experiments 24, 25, 27, 171, 172, and 174) and the same solution may yet fail in others (experiments 26 and 173). Smaller doses may suffice to clot in some cases (experiments 37, 57, 68), and larger, or sometimes very large doses of even the same solution fail in others (experiments 30 and 71). In all cases the solution is injected until death results. It is obvious that the failure to coagulate is an inherent quality of the organism and is independent of any possible changing conditions of the solution.

(C) *Pigmented Animals Injected with Nucleo-proteid derived from Albinoes. Table III.*

I next ascertained if when pigmented animals are injected with "albino" nucleo-proteid any failure of coagulation would occur, such as is the case when albinoes are injected with "pigmented" nucleo-proteid. Twenty-nine experiments under these conditions were performed and no failures of any kind occurred. There are, however, three instances, *i.e.*, experiments 136, 137, and 163, where the coagulation is very limited. In the first of these only one small clot in one of the smallest pulmonary vessels was found, though the shed blood clotted in 25 seconds. In the other two cases only a few clots could be found in the smallest pulmonary vessels. In experiment 92 the smallest pulmonary vessels contained thin axillary threads of clot, and there was a red clot in the apex of the right ventricle, but none elsewhere. In experiment 89, the coagulation, though very limited in extent, was more pronounced, for the right auricle and ventricle were full of red clot and the left ventricle contained some colourless fibrin clots, but none of the veins contained any. In case of the limited coagulation occurring in the rabbits (136 and 137) just described, it is to be noted that death occurred when a very minute dose only was injected. It is, therefore, probable that had not death occurred when it did, a larger injection would have caused more extensive coagulation.

In experiments 145, 151, 162, and 169, the chief object was to ascertain the degree of variation in the activity of the solution with increased age, and as my solution was limited in quantity, I could not with these particular individuals carry the injection far enough to produce either coagulation or death, owing to a marked reduction in the strength of the solution or to idiosyncrasy of the individuals. In experiments 145 and 162 the animals were idiosyncratic to a marked degree. In the four experiments mentioned, the

animals were not therefore killed by the injections, but doubtless had it been possible to carry them far enough, coagulation would have occurred. In experiment 170, the animal died as the result of the injection, and with the typical symptoms of intravascular coagulation, but owing to the lateness of the hour, a *post-mortem* examination could not be made. These experiments do not, therefore, invalidate the conclusion that failure to clot does not occur when pigmented animals are injected with albino nucleo-proteids.

(D) *Pigmented Animals Injected with Nucleo-proteids derived from Pigmented Animals. Table IV.*

Table IV shows the result of injecting 63 pigmented rabbits with "pigmented" nucleo-proteid. No failure, absolute or qualified, occurred. One or two explanations are necessary. In experiment 34, the blood in the vessels escaped coagulation, but a large red clot was present in the right ventricle; the clotting was therefore of the typical nature, though very limited in extent. In experiment 157, the solution was used on the second day after its preparation, and a comparison of experiments 158, 159, and 160, where the solution was of the same age, with experiments 152 and 153, where it was used fresh, showed that a small fall in activity had occurred. But in experiment 157, a very large dose was injected without death resulting. I did not carry the injection further, because my solution was running low. Doubtless, had the injection been carried far enough, coagulation could have been induced; for it was not an infrequent phenomenon of these experiments that animals possessing an idiosyncratic resistance to injected nucleo-proteids now and then appeared and required abnormally large doses before coagulation could be brought about. Experiments 168 (Table IV), 54, 71, 73, and 74 (Table II) were with rabbits of this kind. In some instances, as in experiments 169, 170 (Table III), 75, and 76 (Table II), the large dose required was due to a falling-off in the activity of the solution through age; but such cases can be distinguished from the idiosyncratic ones by the fact that large doses were uniformly required in all the experiments in which the particular solution of a certain age was used. And in the experiment now under consideration, *i.e.*, 157 (Table IV), there is no doubt that the failure to kill is due to idiosyncrasy and that a sufficiently large dose would have produced coagulation. For larger doses than 16 c.c. per kilogramme of body weight have been necessary to produce such a result, as in experiments 1, 74, and 170, where 21 c.c., 23 c.c., and 20 c.c. respectively were required to clot. It may, therefore, be assumed that experiment 157 does not invalidate the conclusion that pigmented animals are always clotted upon the injection of a nucleo-proteid derived from pigmented animals.

With respect to experiments 166, 167, and 168 (Table IV), the injection resulted in death, with the usual symptoms accompanying death from intravascular coagulation, but I had not time to make a *post-mortem* examination in these cases. These experiments, in fact, were made for another purpose, *i.e.*, to ascertain the variation in strength of the solution with age.

Part III.

(A) *Relative Resistance of Albinoes and Pigmented Animals, as Measured by the Mean Quantity Injected Required to Produce Intravascular Coagulation. Tables I to V.*

In all my experiments the quantity of nucleo-proteid injected was measured and the body weight of the animal determined before the experiment commenced; with but few exceptions the animals were obtained some days before the experiments were made and were kept under uniform conditions with regard to time of feeding; so that differences in body weight were not due to relative differences of time between feeding and weighing. All the animals injected with Solution I, *i.e.*, 14 albinoes and 11 pigmented rabbits, were kept under the same conditions for an interval of six weeks.

The experiments were divided into two series. In the first, the injections were continuous though slow, and were continued until death resulted, the dose required and the time occupied being noted; the mean time is approximately 1 minute 6 seconds for every cubic centimetre injected. This method of injection I shall speak of as Method A. In the second series, very small doses, usually 0·1 c.c., were injected every two minutes until death resulted, and the total quantity injected then noted. As a rule death occurred at from 50 to 60 seconds after the lethal quantity had been injected. This method I shall name Method B, and it is sometimes alluded to as the method of incremental doses. In all cases the injection was made through one of the marginal ear veins, by a syringe capable of containing 11 c.c. of solution. The results of these experiments and the experimental data are given in a tabulated form in Tables I to V, pp. 125—129.

In making the comparisons between the mean dose required to kill pigmented and albino animals, in either of the two series (*i.e.*, in the series of injections of albino and pigmented animals with "albino" nucleo-proteid and in those with "pigmented" nucleo-proteid), we can either take the results derived from each separate solution (group comparisons), or they can be compared in the aggregate (final comparison). Neither one of these two modes of comparison is preferable to the other; since while in the former the factors in each group are homogeneous, it follows that in the latter each

pair of groups (that for the albinoes and pigmented individuals) are also homogeneous. The sequel will show that the conclusion is the same by either method. All group comparisons must be made not only with animals injected with the same solution, but with the same solution of the same age, because the strength of the solution varies with its age (*infra*, p. 119). Below, in Table VI, I give the result in a tabulated form, of obtaining the mean dose required to kill albinoes and pigmented animals respectively with each of the solutions used (group mean doses). The means are calculated from the data given in Tables I to V, pp. 125—129.

Table VI.

Solution.	Age of solution.*	Pigmented animals.		Albinoes.	
		Mean dose per kilogramme of body weight.	Experiments.	Mean dose per kilogramme of body weight.	Experiments.
Series 1.—Continuous but slow injections until death results (Method A).					
I	0	3·68	19—23	4·4	24—27
	5	1·18	32, 34, 36	1·41	29, 30, 31, 33, 35, 37
	7	0·76	43	4·28	40—42
J	2	0·52	57	3·21 or 7·37†	53, *54*, 56
Series 2.—Incremental doses, usually of 0·1 c c. at 2′ intervals until death results (Method B).					
K	0	0·484 or 0·92†	59—64, *63*	0·705 or 1·83†	65—*67*
L	0	0·345	83, 84	0·458	77, 78, 80—82
M	0	0·26	86, 89, 90, 92, 94, 96, 98	0·38	85, 87, 88, 91, 93, 95, 97, 99, 100
N	0	0·206	102, 104, 106	0·33	101, 103, 105, 107
O	0	0·22	108, 110, 113, 114	0·286	109, 111, 115
	2	0·38	116—120, 122	0·58	121
P	0	0·138	136—139	0·235 or 0·437†	140—*141*
S	2	0·45 or 2·40†	161, *162*, 163	1·0	164, 165
T	0	0·41 or 1·75†	171, *172*	0·42 or 2·1†	173, *174*

* The figures under column "Age of solution" have the following meaning:—0 = solution used on day of preparation; 2, 5, 7, etc. = solution used on the 2nd, 5th or 7th, etc., day after that of preparation and exclusive of it.

† The alternative figures are rendered necessary by the appearance in certain experiments (indicated by their reference number being in italics) of individuals of marked idiosyncrasy. The lower figure is the result of excluding these experiments from the calculation.

In arriving at the results tabulated above (Table VI, †) I have, in the case of certain experiments where the influence of idiosyncrasy manifested itself, given two alternative mean results, in one of which the idiosyncratic animals have been excluded and in the other included. But whichever of

the two means is accepted, as the alternative ratios given show, the general result is the same, *i.e.*, the albino is markedly more resistant than the pigmented animal.

An inspection of the figures in Table VI shows at once that in each group of experiments, and with each solution used, whatever its age, the albinoes require a larger mean dose per kilogramme of body weight in order to produce death by intravascular coagulation. If the mean of all the means in the above table is ascertained, it is found that for the pigmented animals it is 0·69 c.c. or 0·98 c.c. per kilogramme of body weight, and for the albinoes it is 1·36 c.c. or 1·91 c.c. The alternative figures depend upon whether the lower or higher mean under Solutions J, K, P, and T for the albinoes, and K, S, and T for the pigmented animals is included in the calculations.

The albinoes thus appear to be about twice as resistant to the coagulating influence of nucleo-proteids than do the pigmented animals, if the idiosyncratic individuals are excluded, or rather less if they are included in the calculations. And, in whichever way we deal with the figures, the same result comes out. For if, instead of taking the mean of the means included in both Series 1 and 2, we ascertain the mean of the means in each series separately, we reach the following figures:—The mean of all the means in Series 1 is for pigmented animals 1·53 c.c. and for albinoes 3·32 or 4·36 c.c. per kilogramme of body weight. The mean of the means in Series 2 is for pigmented rabbits 0·320 or 0·735 c.c., and for albinoes 0·488 or 0·822 c.c. per kilogramme of body weight.

Thus by the Method A of injecting, the relative resisting power of albinoes is about double that of the pigmented animals, the ratio being 2·16 or 2·8, and by the Method B it is less than double, the ratio being 1·52 in favour of the albino. But in the alternative results, under Method B, *i.e.*, those in which the idiosyncratic individuals are included, the pigmented and albino individuals are about equally resistant, the ratio being 1·1 in favour of the albino individuals. This result is apparent and not real, and is due to the markedly idiosyncratic pigmented individual, 162, under Solution S and, as it has been pointed out on p. 115, Part III (B), there can be no doubt that it should be rejected. If the result of the S solution be rejected altogether on both sides—for both the pigmented and albino series—the result is a mean dose for the pigmented animals of 0·527 instead of 0·868, and for the albinoes of 0·80 instead of 0·822; the ratio thus becomes 1·5 in favour of the albinoes. This ratio is the same as that for the whole series under Method B, when all the idiosyncratic animals are excluded.

The difference in the ratios of Series 1 and 2, *i.e.*, 2·16 for the former and 1·52 for the latter, is partly due to the fact that Method A of injection

(Series 1) is not so refined as Method B (Series 2), and partly to the fact that in Series 1 a certain number of experiments in which the solution was used on the second, fifth, and seventh days after preparation are included in the mean results, while fewer of such experiments are included in the second series; the reason for the operation of this latter influence is given *infra*, p. 113. That the ratio of the two series should be in the same direction is corroborative proof of the truth of each.

One possible source of error, arising from a want of complete homogeneity, remains to be considered. It will be seen from an inspection of Tables II and IV, or of Table VI, that the I solution, when of seven days' standing after its preparation, was injected into only one pigmented rabbit (43) but into three albinoes (40 to 42), and that the dose for the pigmented animal is very small. It is possible that had another two pigmented rabbits been used, the mean dose of the solution of this age would have been raised for the pigmented animals. The same consideration holds for the J solution on the second day after its preparation; for only one experiment was performed on a pigmented individual (57), and two on albinoes (53 and 56). But it is obvious from a review of the means of these two solutions at other ages and of the other solutions, that had the number of pigmented and albino individuals been more nearly equal in these particular experiments, the mean result would still have been higher for the albino and the ratio would have been near that arrived at. That it would have been so is rendered all the more certain by the fact that the ratio of resistance of albino and pigmented animals is increased as the age of the solution increases; this fact alone explains the large difference between the albino and pigmented races in these two experiments, *i.e.*, those of the I and J solutions of seven and of two days' standing.

The greater resistance of the albinoes is graphically shown in fig. 1, where the upper line, *i.e.*, line of larger dose is the albino line. *Cp.* p. 117.

(B) *The Relative Resistance of Albinoes and Pigmented Animals to Nucleo-Proteids derived from the Two Alternative Sources. Tables VI and VII.*

The results arrived at above show that albinoes are more resistant to injections of nucleo-proteids than are pigmented individuals, and that this is the case when the nucleo-proteid is derived from either pigmented or albino individuals. The experiments, however, enable us to ascertain whether albinoes and pigmented animals are more resistant or less resistant to nucleo-proteids derived from their own source, or from the alternative source. For, by comparing the mean results (p. 115) of injecting albinoes with "albino" nucleo-proteid with those obtained by using "pigmented"

nucleo-proteid, any difference which may exist in the reaction of albinoes towards nucleo-proteids derived from these two sources, can be ascertained. And the same fact can be similarly ascertained for the pigmented animals.

The mean doses required to kill albino and pigmented animals when both kinds of nucleo-proteids are used in each instance may be obtained by calculation from Tables I to IV, or more quickly from the mean results of Table VI, p. 111. Those experiments only in which the injections were made by the incremental or B method, can be utilised for this purpose, because no albinoes were injected by the A method with nucleo-proteids derived from albinoes. And also, with but one exception, only those experiments have been included in the calculations in which the solutions were used on the day of their preparation; the number of experiments in which older solutions were used are not sufficient to enable more comparisons to be made. Owing to the existence of a few individuals which manifested more or less marked idiosyncratic resistance, it is necessary to obtain, both for the albinoes and the pigmented animals, two mean results instead of one. One of these two results in each case will include the idiosyncratic animals and the other will not. The animals which are regarded as idiosyncratic are those in experiments 63 and 67, Sol. K; 141, Sol. P; 172 and 174, Sol. T; and 162, Sol. S; Tables I to IV and VI.

If we now ascertain the mean dose of the "albino" nucleo-proteid (Solutions L, M, P, and S) required to kill albino animals, it is 0·518 c.c. per kilogramme of body weight, if the idiosyncratic animal 63 is excluded, and 0·575 if included (Table VII). If we similarly determine the mean dose of nucleo-proteid derived from pigmented animals (Solutions K, N, O, T) necessary to kill albinoes, it is found to be 0·435 c.c. (excluding experiment 67), or 1·136 c.c. including it. Thus, by rejecting the idiosyncratic individuals, the mean dose of "pigmented" nucleo-proteid necessary to kill albinoes appears to be smaller than that obtained from albinoes. The albino, therefore, is more resistant to its own nucleo-proteids than to those obtained from pigmented animals.

The mean dose required to kill pigmented rabbits by the injection of "albino" nucleo-proteid is 0·298 c.c., or 1·08 c.c. per kilogramme of body weight; the great increase due to idiosyncrasy occurs under the S solution in relation to one animal only (162), and it must obviously be rejected. The mean dose of "pigmented" nucleo-proteid required to kill them is 0·330 c.c. if we reject the idiosyncrasies (experiments 63 and 172), and 0·777 c.c. if we include them. Thus, disregarding the idiosyncrasies, the pigmented animals appear to require a larger mean dose of their own nucleo-proteid to clot their blood than they do of that obtained from albinoes. They are thus more

resistant to "pigmented" nucleo-proteid than they are to "albino" nucleo-proteid.

If the idiosyncratic animals are included, however, the results are in both cases reversed. The rejected experiments are 63 and 172 (Table IV), 162 (Table III), and 141 (Table I). An inspection of the figures given in the tables will show that these individuals were markedly idiosyncratic, for rabbits Nos. 141, 63, 172, and 162 were respectively three, six, eight, and twelve times more resistant than the average of their fellows injected with the same solution at the same time. They clearly stand above their fellows as marked mutations, and must therefore be excluded in any statement of a mean result.

Stating the results described above in a generalised form, they may be expressed as follows: that both albino and pigmented individuals are more resistant to nucleo-proteids obtained from individuals of their own race than they are to those obtained from the alternative source.

In the following table (VII) the group mean doses extracted from Table VI are arranged to illustrate the results just stated; and, in addition, for the purposes of a later discussion, there is also included the weight of the testes employed in the preparation of the different solutions used. The idiosyncratic animals are not included.

Table VII.—To Illustrate, in the Case of both Albino and Pigmented Animals, the Relative Resistance to "Albino" and "Pigmented" Nucleo-proteids.

Solution used.	Weight of testis.	Mean dose when injected with "albino" nucleo-proteid.	Solution used.	Weight of testis.	Mean dose when injected with "pigmented" nucleo-proteid.
Albinoes.					
	grammes.	c.c.		grammes.	c.c.
P	1·0	0·235	N	0·6	0·330
L	3·2	0·458	O	2·9	0·286
M	4·2	0·380	T	5·2	0·420
S	5·0	1·000	K	5·5	0·705
Mean weight of gland	3·35	Mean of the means	0·518	Mean weight of gland	3·7	Mean of the means	0·435
Pigmented Individuals.					
P	1·0	0·138	N	0·6	0·206
L	3·2	0·345	O	2·9	0·220
M	4·2	0·260	T	5·2	0·410
S	5·0	0·450	K	5·5	0·484
Mean of the means 0·298			Mean of the means 0·330		

An inspection of the table will show that the conditions of the experiments were nearly, but not quite, equal. A comparison of the relative resistance of albinoes and pigmented animals towards nucleo-proteids derived from both albino and pigmented individuals has been made. It is obvious that the nucleo-proteid solutions must be equal in every respect, except in their origin, if the comparison is to be fair. But the mean weight of the glands used in the preparation of the "pigmented" nucleo-proteid is 3·7 grammes, while that for the glands used in the preparation of the "albino" nucleo-proteid is 3·35 grammes. If there should exist any difference in the activity of solutions made from spermatic glands at different stages of maturity, it is obvious that, under the conditions of the experiments, the conclusions stated above would possibly require slight modification. This possibility is discussed (Part IV, A, p. 118). It may be stated, however, that such a modification is probably not needed.

Part IV.

(A) *Variation in the Activity or Quantity of Nucleo-proteids derived from Testes in different Stages of Maturity.*

I was led to investigate, through the suggestion of other facts which I had previously ascertained, and which are described in Section B, what influence weight of gland (and presumably, therefore, degree of maturity) had upon the activity of the solutions made from them. In Table VII are given the weights of the testes (p. 115) from which the solutions used were made, and it will be seen that the mean weight of all the glands used in the preparation of the "albino" solutions was 3·35 grammes, and that of glands used in the preparation of the "pigmented" solutions was 3·7 grammes. If, then, the heavier glands should be either more or less active in the production of nucleo-proteids than the lighter ones of the younger individuals, it is obvious that this slight difference in the mean weight of the glands used from the albino and pigmented animals respectively, might introduce a disturbing factor, and the arrangement of the experimental data available (as in Table VII) in a form to show the relative resisting powers of albinoes and pigmented individuals towards the two classes of nucleo-proteids, might give apparent and not real results.

Accordingly, the experimental data were arranged in a way to show what was the influence of the weight of gland upon the activity of the solutions of nucleo-proteids. I had no data as to the age of the rabbits from which the glands were extracted, but as every gland used had been carefully weighed, and the colour of the individuals from which they were obtained had been recorded, I knew the weight, origin, and number of glands used in the pre-

paration of each of the solutions (p. 122). To an approximate degree of accuracy, it may be assumed that weight of gland will coincide with the proportional age of the animal from which it was extracted.

If the results (only those obtained from the Method B of injection are used) are plotted out, as in fig. 1, in such a way that the abscissæ indicate the weight of the glands, and the ordinates express the measure of the mean dose of the solutions prepared from glands of different weights required to clot the blood of either albinoes or pigmented individuals, one fact stands out prominently. An examination of the figure shows that on the whole there is a fall in strength of the solution as the gland increases in weight (age), since a solution made from a heavy gland requires to be used in a larger mean dose per kilogramme of body weight to produce intravascular clotting than does one made from a lighter (younger) gland. The curves, while on the whole gradually trending upwards, show, however, that the fall in strength is not one without any fluctuations, and the nature of these will be considered later.

The two curves in fig. 1 very clearly show the greater resisting power of the albinoes towards injected nucleo-proteids than that of the pigmented individuals, for the upper curve represents the former, and the lower the latter, and practically through the whole of its range, the "albino line" is

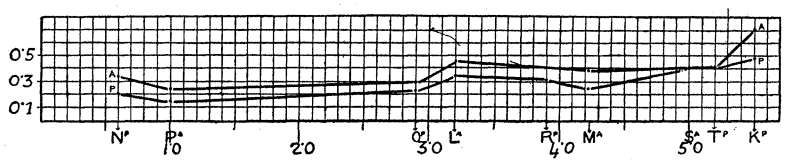

FIG. 1.—Showing the progressive fall in activity of solutions of nucleo-proteids derived from testes of increasing weight (age). The upper line is for albino animals, and the lower line for pigmented individuals. The nature of the solution used (p. 122) is indicated by the large letters, and its origin, *i.e.*, whether from glands of pigmented or albino individuals, is shown by the small index letters P and A respectively. The abscissæ show the weight of the glands in grammes, and the ordinates the amount of injection in cubic centimetres per kilogramme of body weight necessary to kill by intravascular coagulation.

higher than the "pigmented line." The solutions are the same for both varieties of rabbits throughout. The two curves are constructed from all the results; that is, the mean doses of the solutions of both "pigmented" and "albino" nucleo-proteids are used together. In the figure, the solutions are indicated by their reference letters, and the small letter to the upper and right side of them, shows whether it is a solution of a "pigmented" or "albino" nucleo-proteid.

In fig. 2, however, the series of solutions are separated, so that four curves are shown, two each for the "albino" and "pigmented" solutions. The existence of two curves for each solution is due to the fact that the two kinds of solution were injected into both albinoes and pigmented individuals. The higher resisting power of the albino is again well shown

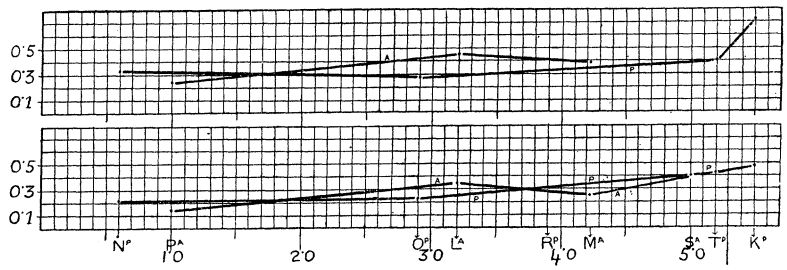

FIG. 2.—The combined results shown in fig. 1 are here separated. In the upper figure the albino individuals only are considered, and in the lower one the pigmented individuals only. The existence of two curves for both albinoes and pigmented animals is due to the fact that both races were each injected with "albino" and "pigmented" nucleo-proteid. The "albino and pigmented solution" lines are indicated by A and P respectively. The other reference letters and numbers have the same significance as those in fig. 1.

and towards both kinds of nucleo-proteids, for the upper line in the two pairs of curves is the "albino" one. And it is obvious that in the general trend, *i.e.*, increasing loss of activity with increasing maturity of gland, the testes of both the albino and the pigmented animal behave much in the same way.

But there is a difference of behaviour at different stages of maturity, and fig. 2 shows that the somewhat abrupt fall in strength at 3·2 grammes weight of testis in fig. 1 is due to the albino gland; but, on the other hand, the increase of strength at 1 gramme and at 4·2 grammes is mainly due also to the albino gland. At the 5 gramme weight stage of maturity the testes of albinoes and pigmented animals appear to be equal in this respect.

The same general trend of variation in activity is shown by solutions on the second day after their preparation, for, as far as the observations go, the maturer glands give less active solutions, and the same may be said of solutions used on the fifth day after their preparation.

Reverting to the conclusion stated on p. 115, that both albino and pigmented animals are more resistant to nucleo-proteids derived from glands of individuals of the same race, and less resistant to those obtained from the alternative source, it must be borne in mind that this is a mean result.

But an inspection of the curves in fig. 2 (upper and lower), shows that upon analysis this result apparently holds true for a part only of the range of gland-weight. If the conclusion were generally true, the curve for pigmented animals injected by "albino" nucleo-proteid should be lower throughout its range than for those injected by "pigmented" nucleo-proteid; and the curve for albino individuals injected with "pigmented" nucleo-proteid should also be lower throughout its range than that for those injected by "albino" nucleo-proteid. But this is not wholly the case. With the albino individuals (fig. 2, upper) the two curves are relatively as they should be throughout the greater part of their range, the lower one crossing the upper one towards the left. But this crossing obviously may be due to the absence of any data for "pigmented" testis weighing 1 gramme, and to that for "albino" testis weighing 0·6 gramme. The same considerations hold for the pigmented animals (fig. 2, lower); had data been available for "pigmented" testes of 1 gramme and 4·2 grammes, the "pigmented" curve may have been lowered at these two points, and they would then have followed a uniform course throughout their range, the "albino" line being the higher.

(B) *Variation in the Activity of Solutions of Nucleo-proteids with Increasing Age.*

In the experiments described in this paper, most of the injections were made on the same day that the solutions of nucleo-proteid were prepared, some of them two days later (so that the solution, inclusive of the day of its preparation, was then three days old), and some of them five days later (the solution then being six days old), and a few at still later periods. If we examine the results obtained by using the same solution on different days it is found that the mean dose per kilogramme of body weight required to clot varies with the age of the solution. There were seven different solutions, *i.e.*, I, K, O, P, R, S, and T, each of which were used on different days. Four of these, *i.e.*, R, S, T, and K, which were derived from heavier glands (*cp.* p. 122 and figs. 1 and 2), gave a continuous fall of strength with increasing period of keeping, but three of them, *i.e.*, I, O, and P, which were derived from lighter glands, gave different results (fig. 3).

The R, S, and T solutions were tested on the day of preparation and on the second and fifth days after, and the K solution on the day of preparation and on the second day after. All these solutions fell in strength with each successive period, but the S solution fell markedly on the fifth day. With respect to the T solution, experiment 172 has to be eliminated, owing to idiosyncrasy; how marked it is can be seen by comparison with experiment 171.

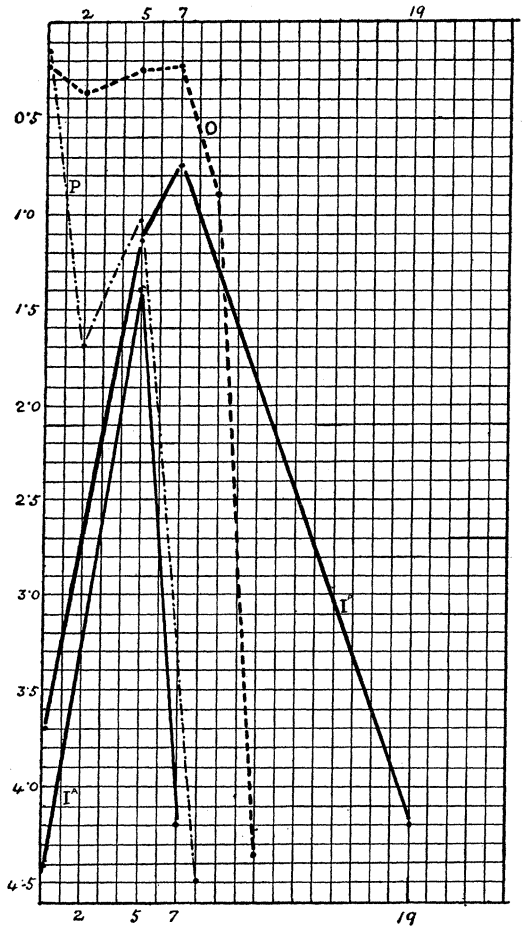

FIG. 3.—Curves showing the fluctuation in activity of solutions of nucleo-proteids with increasing period of keeping. The abscissæ show the age in days of the solutions, and the ordinates the amount of the injection in cubic centimetres of the solution per kilogramme of body weight to produce death by intravascular coagulation. The solutions used (*cp.* p. 122) are indicated by the letters attached to the curves. The curves marked I^A and I^P are for albinoes and pigmented individuals respectively. The curves for O and P are for pigmented individuals only.

The behaviour of Solutions I, O, and P is graphically represented in fig. 3. With Solution O, the mean dose required to clot on the day of its preparation was 0·24 c.c. per kilogramme of body weight; on the second day afterwards (third day old solution) the activity had fallen, and a mean dose of 0·38 c.c. per kilogramme of body weight was required to clot; on the fifth day after preparation the strength had increased to 0·252 c.c.; this increase continued until the seventh day of preparation, when it was

slightly stronger, *i.e.*, 0·236 c.c., that is, nearly as active as on the day of its preparation; on the ninth day it had fallen in activity considerably, *i.e.*, to 0·9 c.c., and on the 11th day the loss of strength was very great, to 4·36 c.c. The same fall on the second day, with a subsequent rise in strength on the fifth, is shown in a yet more marked manner by the curve for Solution P.

In the case of the I solution, for which two curves are shown, one for the albino animals (I^A) and one for the pigmented animals (I^P), no examination of its strength on the second day was made. But for both pigmented and albino animals there is a very marked rise in activity on the fifth day after the preparation of the solution. In the case of the albinoes the strength of the solution falls on the seventh day, but rises for the pigmented animals; this difference may be due to the fact that only one pigmented rabbit was injected on the seventh day; but, bearing in mind the curve for Solution O, it is possible it may have still retained its present form if more experiments had been performed. On the 19th day the activity of the solution, when used on pigmented animals, fell very markedly. It is very probable that had Solution I been tested on the second day, that it would have shown, like Solutions O and P, a fall in activity. My experiments, however, at this period were not designed to investigate this problem, and I did not consequently test the solution on the second day.

Summary of Conclusions.

1. When albinoes are injected with a solution of nucleo-proteid derived from a pigmented animal, a certain number of them, about 9 per cent., absolutely fail to clot, while about 7 per cent. give a qualified clotting, the remainder giving a typical intravascular coagulation of more or less extensive development.

2. When albinoes are similarly injected with a solution of nucleo-proteid, but derived from albinoes, no absolute failure of coagulation occurs, and it is very doubtful if any qualified ones do. The great majority clot as distinctly as do pigmented individuals.

3. When pigmented rabbits are injected with solutions of nucleo-proteids, derived from albinoes or with those derived from pigmented individuals, no failures of coagulation occur.

4. The Himalayan rabbit, in respect of its reaction to injected nucleo-proteids, behaves like the complete albino. This rabbit, though resembling the Norway hare in its winter coat, in which condition Pickering failed to obtain intravascular coagulation, differs from it in having pink

(unpigmented) instead of pigmented eyes and in never becoming periodically wholly pigmented. It cannot, therefore, be used as corroborative evidence of Pickering's conclusion with respect to the Norway hare.

5. That failures to coagulate, when they occur, are due to inherent qualities of the individuals and not to weakening in the activity of the solutions used.

6. Albinoes require a larger mean dose per kilogramme of body weight of injected nucleo-proteid to cause death by intravascular coagulation than do pigmented animals, the relative resisting powers of the pigmented and albino individuals being as 1 to 1·5 respectively.

7. Both albino and pigmented individuals are more resistant to nucleo-proteids, obtained from individuals of their own race, than they are to those obtained from the alternative source.

8. The activity of a solution of nucleo-proteid, prepared from spermatic glands, decreases (but not quite uniformly) as the maturity (weight) of the gland increases.

9. Solutions of nucleo-proteids, prepared from heavier (maturer) spermatic glands, undergo a progressive loss of activity with increasing period of keeping, *i.e.*, from 1 to 20 days. But solutions derived from lighter (immature) glands undergo a fluctuating variation in activity, falling off on the second day after preparation and rising again on the fifth to seventh, and thence exhibiting a progressive fall.

NATURE OF SOLUTIONS USED.

W.G. = weight of gland ; D. = dissolved in 1-per-cent. solution of anhydrous Na_2CO_3. The amount of solution used in each case is indicated in cubic centimetres. Unless otherwise stated, all the solutions were prepared by pressing the glands through finely meshed iron wire gauze into 1-per-cent. solution of Na_2CO_3.

Sol. A.—(1) Thymus glands from four albino rats, 6 weeks old, descended from albino parents. (2) Testes from albino rat of unknown parentage. (3) Thymus from albino rat, 8 weeks old, from black and white parents. W.G. = 4·2 grammes, D. in 65 c.c. = 1 gramme in 15·5 c.c.

Sol. B.—Thymus gland of a black and white calf. Portion of organ minced and ground in a mortar with an equal volume of sodium chloride. Separated the nucleo-proteid by addition of distilled water, and collected into 1-per-cent. solution of Na_2CO_3. Strength of solution was not ascertained, but was probably nearly saturated.

Sol. C.—Testes from albino rabbit. W.G. = 6 grammes, D. in 100 c.c. = 1 gramme in 15·5 c.c.

Sol. D.—Thymus glands from four young pigmented rabbits, with much unpigmented coat. Glands crushed in distilled water, macerated for 36 hours, and the nucleo-proteid then precipitated by 0·2-per-cent. acetic acid. Dissolved in 70 c.c. of 1-per-cent. solution of Na_2CO_3.

Sol. F.—Testes from two albino rats of albino parentage. W.G. = 3·6 grammes, D. in 50 c.c. = 1 gramme in 14 c.c.

Sol. G.—Testes from Himalayan rabbit. W.G. = 2·2 grammes, D. in 32 c.c. = 1 gramme in 14·5 c.c.

Sol. H.—Thymus glands from three black and one brown rabbit. Dissolved in 1-per-cent. solution of Na_2CO_3.

Sol. I.—Testes from five brown (grey), one black, one silver grey, one fawn and one brown and white rabbits. The glands from the five brown rabbits weighed 8 grammes, and those from the remaining four rabbits 19 grammes. Total W.G. = 27·2 grammes, D. in 423 c.c. = 1 gramme in 15·5 c.c.

Sol. J.—Testes from a black and white rabbit, a blackish-grey, and a brown one. W.G. = 11 grammes, D. in 170·5 c.c. = 1 gramme in 15·5 c.c.

Sol. K.—Two testes from a brown rabbit. W.G. = 5·5 grammes, D. in 85 c.c. = 1 gramme in 15·5 c.c.

Sol. L.—Testes from albino rabbit. W.G. = 3·2 grammes, D. in 49 c.c. = 1 gramme in 15·5 c.c.

Sol. M.—Testes from albino rabbit. W.G. = 4·2 grammes, D. in 65 c.c. = 1 gramme in 15·5 c.c.

Sol. N.—Testes from two grey (brown) rabbits. W.G. = 1·2 gramme, D in 18·6 c.c. = 1 gramme in 15·5 c.c.

Sol. O.—Testes from a grey (brown) rabbit. W.G. = 2·9 grammes, D. in 45 c.c. = 1 gramme in 15·5 c.c.

Sol. P.—Testes from an albino rabbit. W.G. = 1 gramme, D. in 15·5 c.c.

Sol. R.—Testes from one fawn and one grey rabbit. W.G. = 7·8 grammes, D. in 121 c.c. = 1 gramme in 15·5 c.c.

Sol. S.—Testes from Himalayan rabbit. W.G. = 5 grammes, D. in 77·5 c.c. = 1 gramme in 15·5 c.c.

Sol. T.—Testes from black rabbit. W.G. = 5·2 grammes, D. in 80·6 c.c. = 1 gramme in 15·5 c.c.

EXPLANATIONS OF THE ABBREVIATIONS USED IN THE TABLES I—V.

"Albino" solution and "pigmented" solution mean a solution of nucleo-proteid derived from albino and from pigmented animals respectively.

The capital letter in the column headed "Solution used" refers to the nature of the solution used. A description is to be found on p. 122. The small numeral at the top right-hand side of the capital letter indicates the age of the solution when used. Thus L^0 means that it was prepared and injected on the same day: and I^5 that it was injected on the fifth day after its preparation, exclusive of the day of preparation. The solutions were kept in an ice safe, gave no signs of putrefaction, and retained their physical characters at the time of using.

V.P. = Very pronounced. All the vessels examined; *i.e.*, right and left precavals, right and left external jugulars, the whole length of the postcaval (that lying in the thorax, and for brevity called "thoracic portion," and that lying in the abdominal cavity and called "abdominal portion" or "abdominal postcaval"), and the hepatic-portal veins, being filled solid with continuous axillary strands.

P. = Pronounced. The clot in the vessels either fills it solid, as above, or does not quite fill it, but in either instance is absent from the "thoracic postcaval," or from the portal vein, or from both.

F.P. = Fairly pronounced. The clot is axillary and continuous, but thin, and is absent from the "thoracic postcaval" or portal vein, or from both.

F. = Faint coagulation. The clot is a mere cotton-like thread, and is more or less continuous and axillary, but is absent from the "thoracic postcaval" and portal vein.

V.F. = Very faint coagulation. The chief feature of this condition is in its limitation, for the clot may be a mere cotton-like thread or fairly thick (nearly as thick as in P). The clot is limited, however, to one or other of the two jugulars and associated precavals, or is confined to any other one vein; and small clots may or may not be present in the chambers of the heart.

A.B. = Coagulation almost absent. Only a few *colourless* clots of fibrin specks or filaments are present in the ventricles of the heart, and usually attached to the chordæ tendineæ. There are no clots of any kind in any of the veins.

A.B'. = Like A.B., but the clot in the chambers of the heart is red (not colourless) and is fairly large, varying from a tenth of an inch to a clot which fills the chamber.

A. = Absence of coagulation absolute.

The above definitions of conditions are based upon actually occurring states, and are not therefore wholly arbitrary; but in a few of the experiments it is difficult to assign the observed state to any one of the above defined groups. Such instances are indicated in the tables by the interrogative sign.

No result = Means that as much of the solution that could be spared was injected, but was not sufficient to kill the animal. It was then killed by an overdose of chloroform.

No P.M. exam. = A *post-mortem* examination was not made. In the few cases in which the examination was omitted (owing to the lateness of the hour) the symptoms were typically those of death by intravasculation coagulation. The object of the experiment in these cases was not to ascertain the extent of coagulation, but the amount of the minimum lethal dose.

Table I.

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No. of experiment.
			(A) Albino rabbits injected with "albino" solution.			
	kilos.	c.c.				
16·0	0·6	10·0	In one dose	C^2	V.P.	3
12·5	0·8	10·0	„	F^7	V.P.	12
0·28	1·75	0·5	In 0·25 c.c. doses at 2′ intervals...	L^0	P. ?	77
0·6	0·5	0·3	In one dose, slowly	L^0	F.P.	78
0·27	0·9	0·25	„ „	L^0	A.B′.	80
0·31	0·8	0·25	„ „	L^0	V.F.	81
0·83	0·6	0·50	In 0·25 c.c. doses at 2′ intervals...	L^0	V.F.	82
0·45	0·55	0·25	In one dose, slowly	M^0	V.F. ?	85
0·294	1·70	0·50	In 0·25 c.c. doses at 2′ intervals...	M^0	V.F. ?	87
0·50	0·5	0·25	In one dose, slowly	M^0	F.P.	88
0·45	2·2	1·0	In 0·25 c.c. doses at 2′ intervals...	M^0	V.F.	91
0·4	0·5	0·2	In one dose, slowly	M^0	V.F.	93
0·28	1·75	0·5	In 0·25 c.c. doses at 2′ intervals...	M^0	V.F. ?	95
0·23	0·43	0·1	In one dose	M^0	V.F.	97
0·32	1·55	0·5	In 0·25 c.c. doses at 2′ intervals...	M^0	F.P.	99
0·50	0·5	0·25	In two 0·1 + one 1·5 c.c. doses at 2′ intervals	M^0	V.F.	100
0·235	1·7	0·4	In 0·2 + 0·1 + 0·1 c.c. doses at 2′ intervals	P^0	A.B.	140
0·64	0·85	0·55	In one 0·1 + three 0·15 c.c. doses at 2′ intervals	P^0	V.F.	141
0·91	0·55	0·50	In one dose	S^2	F.P. ?	164
1·1	0·45	0·50	In 0·1 c.c. doses at 2′ intervals ...	S^2	A.B. ?	165
			(B) Albino rats injected with "albino" solution.			
20·0	0·5	10·0	In one dose	A^2	V.P.	2
	—	8·0	„	C^7	V.P.	5
	—	7·0	„	C^7	V.P.	7
33·0	0·12	4·0	„	F^2	P.	10

Table II.

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No. of experiment.
			(A) Albino rabbits injected with "pigmented" solution.			
	kilos.	c.c.				
5·0	2·0	10·0	In one dose, slowly	I^0	P.	24
4·0	2·0	8·0	„ „	I^0	P.	25
2·5	2·8	7·0	„ „	I^0	A.	26
6·1	1·8	11·0	„ „	I^0	P.	27
1·0	1·5	1·5	„ „	I^5	A.B.	29
2·0	1·3	2·6	„ „	I^5	A.B.	30
2·1	1·9	4·0	„ „	I^5	V.P.	31
1·25	1·6	2·0	„ „	I^5	P.	33
1·15	1·3	1·5	„ „	I^5	P.	35
1·0	1·7	1·7	„ „	I^5	P.	37
4·66	1·2	5·6	„ „	I^7	F. ?	40
0·5	2·0	1·0	„ „	I^7	P.	41
7·69	1·3	10·0	„ „	I^7	V.P.	42
0·52	1·9	1·0	„ „	J^2	A.	53
15·7	0·7	11·0	In 0·25 + 0·5 c.c. doses at 2′ intervals	J^2	V.F.	54
5·9	1·95	11·5	In 1 c.c. doses at 2′ intervals	J^2	V.F.	56
0·41	1·2	0·5	In one dose	K^0	A.B. ?	65
1·0	1·5	1·5	In two 0·5 + one 0·25 + three 0·75 c.c. doses at 2′ intervals	K^0	V.F.	66
4·1	1·7	7·0	In 0·25 and 0·5 c.c. doses at 2′ intervals	K^0	F.	67
2·82	0·85	2·4	In 0·3 and 0·5 c.c. doses at 2′ intervals	K^2	V.F.	68
6·8	0·8	5·5	In 0·5 c.c. doses at 2′ intervals	K^2	V.F.	69
5·7	0·7	4·0	„ „ „	K^2	A.B. ?	70
21·4	0·7	15·0	In 1·0 and 0·5 c.c. doses at 1′ intervals	K^2	A.	71
4·28	0·7	3·0	In 2·0 + 1·0 c.c. doses at 1′ intervals	K^2	A.B.	72
12·5	0·6	7·5	In 1·5 and 1·0 c.c. doses at 1′ intervals	K^2	V.F.	73
23·6	0·55	8 of K + 5 of J	Continuously, but very slowly	K^2 & J^7	V.F.	74
10·0	0·6	6·0	„ „ „	J^7	V.F.	75
9·0	0·5	4·5	In one dose, quickly	J^7	V.P. nearly	76
0·31	0·8	0·25	„ slowly	N^0	V.F. ?	101
0·13	1·8	0·25	„ „	N^0	V.F.	103
0·38	1·7	0·65	In 0·35 + 0·3 c.c. doses at 2′ intervals	N^0	V.F. ?	105
0·5	1·0	0·5	In 0·25 c.c. doses at 2′ intervals	N^0	V.F.	107
0·41	1·2	0·5	„ „ „	O^0	V.F. ?	109
0·14	0·9	0·13	In one dose	O^0	V.F.	111
0·31	0·8	0·25	„	O^0	V.F.	115
0·58	0·6	0·35	In 0·2 + 0·15 c.c. doses at 2′ intervals	O^2	V.F. ?	121
0·40	0·5	0·20	In one dose	T^0	A.	173
3·80	2·85	11·0	In 0·25 c.c. doses at 1′ intervals	T^0	V.F. ?	174
			(B) Albino rats injected with "pigmented" solution.			
	Not weighed	Not recorded	In one dose	B^5	A.B. ?	6
	„	4·0	„	B^5	F.P.	13
	„	5·0	„	H^0	P.	14
	„	6·0	In 4 + 2 c.c. doses	D^{12}	P.	17
	„	8·0	In small doses at 20″ intervals	D^{12}	P. or V.P.	18

Table III.—Pigmented Rabbits injected with "Albino" Solution.

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No. of experiment.
	kilos.	c.c.				
21·0	2·0	42·0	In doses of 10+10+11+11 c.c., quickly	A^2	F.P.	1
9·09	1·1	10·0	In one dose	C^2	V.P.	4
12·5	0·4	5·0	„	F^2	V.P.	11
0·35	1·4	0·5	In 0·25 c.c. doses at 2′ intervals	L^0	P ?	83
0·34	1·45	0·5	„ „ „	L^0	V.F.	84
0·31	0·8	0·25	In two equal doses „	M^0	V.F.	86
0·185	1·35	0·25	In one dose	M^0	A.B′.	89
0·28	0·85	0·24	In two equal doses at 2′ interval	M^0	F.P. ?	90
0·19	1·3	0·25	In one dose	M^0	A.B′. ?	92
0·2	2·5	0·50	In 0·25 c.c. doses at 2′ intervals	M^0	V.F.	94
0·19	1·3	0·25	In one dose	M^0	V.F.	96
0·5	1·0	0·5	In 0·25+1·25+1·25 c.c. doses at 2′ intervals	M^0	V.F.	98
0·089	1·12	0·1	In one dose	P^0	Nearly A	136
0·083	1·2	0·1	„	P^0	Nearly A	137
0·19	1·3	0·25	In 0·1+0·15 c.c. doses at 2′ intervals	P^0	V.F.	138
0·19	1·05	0·20	In 0·1 „ „	P^0	V.F. ?	139
2·0	1·5	3·0	„ „ „	P^2	No result	145
1·3	0·75	1·0	„ „ „	P^2	V.F. ?	146
1·56	0·8	1·25	In 0·25 „ „	P^5	F. ?	149
0·57	1·3	0·75	„ „ „	P^5	V.F.	150
4·5	1·0	4·5	In 0·25+0·2 „ „	P^8	No result	151
0·13	1·1	0·15	In one dose	S^0	V.F.	154
1·77	2·25	4·0	In 0·2 c.c. doses at 2′ intervals	S^0	V.F. ?	155
0·7	1·0	0·7	In 0·1 „ „	S^0	V.F.	156
0·5	0·6	0·3	„ „ „	S^2	V.F. ?	161
6·3	0·95	6·0	In 0·1 c.c. and then 0·5 c.c. doses at 2′ intervals	S^2	No result	162
0·41	0·6	0·25	In one dose	S^2	Nearly A	163
11·0	1·8	20·0	In 2·0 c.c. doses at 2′ intervals	S^5	No result	169
20·0	0·55	11·0	In 1·0 „ „	S^5	No P.M. exam.	170

Table IV.—Pigmented Rabbits injected with "Pigmented" Solution.

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No. of experiment.
	kilos.	c.c.				
9·0	0·5	4·5	In one dose	B^{10}	F.P. ?	16
2·8	2·1	6·0	„ slowly	I^0	V.F.	19
4·6	1·5	7·0	„ „	I^0	P. ?	20
4·0	2·5	10·0	„ „	I^0	V.F. ?	21
4·0	2·7	11·0	„ „	I^0	P.	22
3·0	2·0	6·0	„ „	I^0	F.P.	23
1·07	1·4	1·5	„ „	I^5	F.P.	32
1·5	2·0	3·0	„ „	I^5	A.B′.	34
0·97	1·85	1·8	„ „	I^5	F.P. ?	36
0·76	1·3	1·0	„ „	I^7	P.	43
3·8	1·3	5·0	„ „	I^{19}	F.P.	46

Table IV—*continued.*

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No of experiment.
	kilos.	c.c.				
4·6	1·5	7·0	In one dose, slowly	1^{21}	V.P.	47
0·52	1·9	1·0	,, ,,	J^{2}	V.F.	57
4·28	2·1	9·0	In 1 c.c. doses at 2′ intervals	J^{5}	V.F. ?	58
0·5	1·0	0·5	In one dose, slowly	K^{0}	P.	59
0·55	0·9	0·5	,, ,,	K^{0}	V.P.	60
0·5	1·0	0·5	,, ,,	K^{0}	F.P. ?	61
0·37	0·8	0·3	,, ,,	K^{0}	V.F.	62
3·1	0·8	2·5	In 0·25 + 0·5 c.c. doses at 2′ intervals	K^{0}	V.F.	63
0·5	1·0	0·5	In one dose, slowly	K^{0}	P.	64
0·12	2·05	0·25	,, ,,	N^{0}	V.F.	102
0·25	0·8	0·2	In 0·1 c.c. doses at 2′ intervals	N^{0}	V.F. ?	104
0·25	1·0	0·25	In 0·1 + 1·5 c.c. doses at 2′ intervals	N^{0}	V.F. ?	106
0·26	1·9	0·5	In 0·25 c.c. doses at 3′ intervals	O^{0}	V.F. ?	108
0·30	1·2	0·37	In 0·25 + 0·12 c.c. doses at 2′ intervals	O^{0}	V.F.	110
0·20	1·0	0·20	In 0·1 c.c. doses at 2′ intervals	O^{0}	V.F.	113
0·12	0·8	0·1	,, ,, ,,	O^{0}	V.F.	114
0·45	0·55	0·25	In 0·1 + 0·15 c.c. doses at 2′ intervals	O^{2}	V.F. ?	116
0·24	1·25	0·30	In 0·15 c.c. doses at 2′ intervals	O^{2}	V.F. ?	117
0·41	0·6	0·25	In 0·1 + 0·15 c.c. doses at 2′ intervals	O^{2}	V.F. ?	118
0·38	0·65	0·25	,, ,, ,,	O^{2}	V.F. ?	119
0·5	0·6	0·3	In 0·1 c.c. doses at 2′ intervals	O^{2}	V.F. ?	120
0·31	0·8	0·25	In 0·1 + 0·15 c.c. doses at 2′ intervals	O^{2}	V.F.	122
0·41	0·6	0·25	,, ,, ,,	O^{5}	V.F.	128
0·27	0·9	0·25	,, ,, ,,	O^{5}	V.F.	129
0·173	1·15	0·2	In 0·1 + 0·1 ,, ,,	O^{5}	V.F.	130
0·158	0·63	0·1	In one dose	O^{5}	V.F.	131
0·25	2·0	0·5	In 0·1 c.c. doses at 2′ intervals	O^{5}	V.F.	132
0·28	1·25	0·35	In two equal doses at 2′ intervals	O^{7}	F.P.	133
0·178	1·4	0·25	,, ,, ,,	O^{7}	F.P.	134
0·25	0·6	0·15	In one dose	O^{7}	V.F.	135
0·8	0·5	0·4	In three equal doses at 2′ intervals	O^{9}	V.F.	142
1·0	0·6	0·6	In five ,, ,, ,,	O^{9}	F.P. ?	143
0·91	0·55	0·5	In three ,, ,, ,,	O^{9}	V.F. ?	144
1·22	1·43	1·75	In 0·25 c.c. doses at 2′ intervals	O^{11}	V.F.	147
7·5	1·0	7·5	,, ,, ,,	O^{11}	V.F.	148
0·37	1·35	0·5	In 0·1 ,, ,,	R^{0}	V.F.	152
0·26	0·95	0·25	In 0·1 + 0·15 ,, ,,	R^{0}	V.F.	153
16·8	1·48	25·0	In 0·1 + 0·25 + 0·5 + 1·0 c.c. doses at 2′ intervals	R^{2}	No result	157
0·71	0·7	0·5	In 0·25 c.c. doses at 2′ intervals	R^{2}	F.P. ?	158
0·73	1·7	1·25	,, ,, ,,	R^{2}	V.F.	159
1·3	0·75	1·0	In 0·1 ,, ,,	R^{2}	V.F.	160
1·29	0·85	1·1	,, ,, ,,	R^{5}	No P.M. exam.	166
2·9	1·7	5·0	In 0·25 ,, ,,	R^{5}	,,	167
13·3	0·6	8·0	In 0·1 + 0·25 ,, ,,	R^{5}	,,	168
0·41	1·95	0·8	In 0·1 ,, ,,	T^{0}	P ?	171
3·1	0·86	2·75	,, ,, ,,	T^{0}	V.F. ?	172
1·18	1·9	2·25	In 0·25 ,, ,,	T^{2}	P ?	175
1·6	1·4	2·25	,, ,, ,,	T^{2}	V.F.	176
2·32	1·4	3·25	,, ,, ,,	T^{5}	No P.M. exam.	177
1·13	1·1	1·25	,, ,, ,,	T^{5}	,,	178
2·6	1·05	2·75	,, ,, ,,	T^{5}	,,	179
3·0	0·75	2·25	,, ,, ,,	T^{5}	V.F.	180

Table V.

Dose per kilogramme of body weight.	Weight of animal.	Total dose injected.	Method of injection.	Solution used.	Result.	No. of experiment.
			(A) Himalayan rabbits injected with "pigmented" solution.			
	kilos.	c.c.				
0·43	2·3	1·0	In one dose	I^5	A.	28
4·34	2·3	10·0	„	B^8	A.B	8
4·10	1·7	7·0	In 0·7 c.c. and in 0·5 c.c. at 2′ intervals	J^2	V.F.?	49
0·52	1·9	1·0	In one dose	J^2	F.	50
1·57	1·9	3·0	In one 1 c.c. and in 0·5 c.c. at 1′ intervals	J^2	V.F.	51
1·87	1·6	3·0	In one 0·8 c.c. and in 0·2 c.c. at 2′ intervals	J^2	V.F.	52
0·18	2·7	0·5	In 0·25 c.c. at 2′ intervals	O^2	V.F.?	112
0·62	0·4	0·25	In two 1·5 + 1 c.c. at 2′ intervals	O^2	V.F.?	123
			(B) Himalayan rabbits injected with "albino" solution.			
4·76	2·1	10·0	In one dose	G^2	V.P.	9
0·5	0·5	0·25	„	L^0	P.	79

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