THE RELATIVE STRENGTH OF FRESH AND OLD SAMPLES OF THE FLUIDEXTRACT OF ERGOT.

CHAS. C. HASKELL AND CHAS. R. ECKLER.

The importance of having medicinal preparations of constant strength can not be overestimated. Many factors over which the physician has no control of necessity arise when patients are treated with drugs, and if the drugs administered are of unknown and variable strength, truly rational therapy is impossible. Fortunately, chemical investigation has been so fruitful of results that most of the important drugs used in therapeutics can now be standardized with great accuracy.

Even if preparations are of definite strength at the time of manufacture, however, the question arises as to whether deterioration can not occur before their employment. It is well known that in aqueous solutions some of the alkaloids rapidly decompose. Careful examination [18] has shown, however, that most galenical preparations which are susceptible of chemical assay retain their strength undiminished for a number of years.

Unfortunately, there is a group of drugs for which no chemical assay method is commercially practicable. Most important of this group are the cardiac tonics while ergot is of scarcely less moment.

Since ergot can not be standardized by chemical means, it is easy to understand why attempts have been made to estimate its strength by observation of the effect of the drug upon lower animals. The question of deterioration being so obviously dependent upon standardization, it seems necessary to consider briefly the three methods commonly employed in the attempt to produce preparations of uniform strength.

Practically all recent investigators have observed that fresh ergot preparations have a distinct pressor activity. Dixon,[6] apparently, was the first to utilize this action to measure the therapeutic efficiency of the drug. He states: "I have found, however, that rise in blood-pressure in mammals is proportional to the effect upon the uterus." He advocates the use of rabbits, injecting the drug into the femoral vein and recording the carotid blood-pressure by means of a mercury manometer.

While Dixon's paper was very brief and incomplete, Wood and Hofer [20] have studied the pressor activity of a number of commercial samples of ergot with great thoroughness. They, too, consider that the actions upon the blood pressure and upon the uterus are parallel. They believe that: "There can be little doubt but that the increased contractions of the uterus and the vasomotor stimulation are part of a widespread effect of the drug, involving all involuntary muscle. * * * and the changes in the circulations, in the intestines, and in the uterus are but a part of one general action." This being the case, they maintain that a measure of the pressor action of ergot enables us to estimate the value of the drug as an oxytoxic.

In an earlier paper, Wood and Hofer [21] pointed out that the use of ergot need not be limited to obstetrical practice. It is certainly true that a measure of the

pressor activity of the drug upon lower animals would probably be a measure of the value of ergot as a circulatory stimulant for man, but it would seem that, in the light of both recent and early research, the objection to the use of an observation on the vasomotor action of ergot as a criterion of its oxytoxic power is decidedly a valid one.

Dale [4] has found that there is no constant relation between blood-pressure and uterine effects when the drug was administered to a monkey. "In the cat, too, there is no distinct relation between the two sets of effects; some cats in which the blood-pressure effect was comparatively small, showed marked uterine effects and vice-versa."

In examining a number of commercial preparations of ergot, Goodall [9] also found that the absence of pressor activity did not justify one in assuming absence of power to affect the uterus. He concludes: "Whereas 42 per cent. of commercial samples caused contraction of the uterus without effecting a rise of blood-pressure, the action on the uterus might be regarded as a more satisfactory test by the manufacturer."

Finally, Edmunds and Hale,[7] after making a very careful comparison, have come to the conclusion that there is no essential parallelism between the two actions.

While Goodall's work is open to adverse criticism, the results secured by such men as Edmunds, Hale, and Dale must be considered as reliable and it would seem that some investigators have acted rather hastily in establishing arbitrary standards and making wholesale condemnations of commercial preparations without reporting a single experiment in support of their statements as to the parallelism between blood-pressure and uterine effects.

The recent work of the English investigators offers an explanation as to why ergot may cause uterine contractions and yet fail to show pressor activity. Ergotoxine, para-hydroxyphenylethylamine, and B-isoamylamine excite the uterus to contractions and bring about an elevation of the blood-pressure. B-iminazolylethylamine, however, is capable of causing intense uterine tetany, and, under proper conditions, a marked *fall* of systemic blood-pressure.

While not essential, it is certainly advantageous to observe on lower animals the therapeutic action of the drug to be standardized. It seems most rational to attempt the standardization of the cardiac tonics by noting their effects upon the heart of the experimental animals; and, likewise, if the effect of ergot upon the uterus of a cat or some other suitable animal could be satisfactorily recorded, it would probably furnish a rational means for standardizing this drug. Numerous investigators have studied the action of ergot upon the uterus in various functional conditions, but, at present only two uterine methods are employed commercially.

Kehrer [13, 14] believes that the isolated uterus of a virgin cat offers an ideal object on which to standardize ergot. His method is simple in technic, but it would be extremely difficult to secure suitable animals in sufficient numbers for commercial standardization. Moreover, the light which recent chemical and physiological work has thrown upon the ergot question, enables us to see grave objections to Kehrer's method. In the first place, the important alkaloid, ergo-

toxine, in a pure state is insoluble in water, and Kehrer's test is, of necessity applicable only to the water-soluble constituents. Then, of the amines present, two have an action similar to adrenaline in causing inhibition of the non-pregnant uterus. Edmunds and Hale [7] have found that there are serious practical disadvantages in the use of the excised uterus, the chief one arising from an increasing irritability of the organ, so that the employment of a solution of ergot which was too weak to have any effect at the beginning of the experiment later on would cause distinct contractions.

Edmunds [8] was the first to make practical application of the method in which the movements of the uterus in situ are recorded. This method is obviously not simple and introduces the same theoretical disadvantages which were mentioned in discussing the isolated uterus method. Edmunds and Hale [7] find, however, that quite accurate results can be secured by perseverance and are inclined to consider this the most reliable method employed; an opinion in which Cushny [7] apparently concurs.

Finally, there is the much used and much abused cock's-comb method. As far back as 1824, Lorinser [14] noted the production of cyanosis in the comb of cocks to which ergot had been administered, and Kobert, Grünfeld,[10] and others made use of this phenomenon in studying ergot. Houghton,[11] however, was the first to make a practical application of it in attempting to standardize commercial preparations of the drug.

The cock's-comb method has, apparently, been employed by two classes of men in recent years. First, those who, believing implicity in the efficiency of it as a method of standardization, have used it blindly without carefully investigating its worth. Second, a number of investigators who seemed to have paid too little attention to the attempt to secure uniform conditions, a factor of such great importance in any method of physiological assay.

Wood and Hofer [20] are inclined to consider the cock's-comb test of no value. They point out that there is "a wide biological gap between man and the chicken and the fact that the effect studied is a toxic one." Later, they say that they have made fifty experiments upon the rooster with such unsatisfactory results as to convince them that this method is too inaccurate to be of utility.

Cronyn and Henderson [3] concur in this opinion. They do not adduce any experimental evidence of their own in support of this contention, except reports of tests by them of preparations "of the one large pharmaceutical house whose preparations are supposed to be standardized by the same method."

The objection that "a wide biological gap exists between man and chicken" can have force only with those who fail to grasp the underlying principle of standardization. We wish to measure the oxytoxic principle in ergot, and it does not matter in what way it is measured if the measure be accurate. It certainly would seem that "a wide biological gap" exists between man on the one hand and the analytical balance on the other, yet this is not considered a sound reason for discarding methods of chemical assay.

Nor does it seem to us that the fact that the action upon the cock's comb is a toxic one proves the method defective. Lethal dose methods are sometimes accurate, and moreover, it is not so evident that the cyanosis of the comb is any

more a "toxic" effect than an elevation of blood-pressure 50 millimeters or stimulation of the uterus to marked contractions.

As Edmunds and Hale [7] have pointed out, Cronyn and Henderson are in error concerning Dale's statements as to variation in individual fowls of the same variety, since Dale [5] evidently used no one variety exclusively. The fact that preparations standardized by the cock's comb method seem inert when tested by Cronyn and Henderson is obviously no reason for criticizing the method, because there is apparently no way of knowing how old these preparations were when tested the second time.

In Wood and Hofer's fifty experiments, no mention is made of the number of fowls used; of the age, breed, or method of administration. It would certainly seem advisable for them to present full data before recommending the elimination of a method which has so much in its favor.

It remained for Edmunds and Hale [7] to take the first important step toward a solution of the question as to the best method available for commercial standardization of ergot. In their paper already quoted from, a careful comparison of various methods was made, and a striking similarity was found to exist between the results of tests upon the cat's uterus in situ and of tests upon fowls.

As would be expected, varying results have been secured when the question of deterioration of ergot was investigated by different methods. It is very surprising, however, to find that when presumably the same method was used by different men, variations fully as great appear in the results.

Grünfeld [10] was, so far as we can learn, the first to report systematic observations bearing upon the keeping qualities of ergot. His tests were made upon fowls and pigs, the drug being given per os. As the result of his experiments, he concluded that ergot, either powdered or in a natural state rapidly lost its activity and was practically worthless six months after the harvest. He also draws attention to the fact that the outbreaks of "ergotism" usually occur in the summer and autumn, when the ergot is fresh.

There are several features of Grünfeld's work, however, which allow opportunities for error. In the first place, his method of administration introduces the question of absorption from the gastro-intestinal canal. Secondly, he did not secure a stock of ergot and age it himself, making tests at various intervals, *but secured small lots as he needed them for testing,* assuming that their activity was the same throughout originally. Then, he disregarded the fact that seasonal variation may play an important part in the susceptibility of animals to poisons. Thus, Hunt [12] has shown that guinea pigs and mice vary in their resistance to acetonitrile according to the season of the year, and Südmersen and Glenny [19] find that the susceptibility of guinea pigs to poisoning by diphtheria toxin shows a similar variation. In our own laboratory, we have found a seasonal variation in guinea pigs and frogs when the heart tonics are used as toxic agents. While fowls may not show this seasonal variation, still the suspicion exists. Finally, he seemed to consider the death of the fowl as the end point, often disregarding temporary bluing of the comb.

Using practically the same method, Meulenhoff [15] reached very different conclusions. He believes that ergot kept under suitable conditions retains a considerable amount of activity for as long as five years.

Kehrer,[14] using the isolated uterus method, reaches conclusions approximating Grünfeld's. He states: "From this comparative investigation, it is evident that ergot, as preserved by the apothecary, in one year detereriorates 7-8 times; in two years, about 15 times."

Wood and Hofer [20] also find that ergot rapidly loses strength. By observations upon the blood-pressure and by determination of the "sphacelotoxin content" these authors conclude:

"8. A fluidextract of ergot exposed to the air deteriorates extremely rapidly.

"9. The deteriorations of fluidextract of ergot may be much retarded by protecting it against contact with the air, but under the most favorable conditions there is a loss of strength approximating 10 per cent. a month."

If ergot loses in strength as rapidly as some of these authors believe, it is obvious that little can be expected of commercial preparations of the drug. When it is realized that Russian ergot does not reach the American manufacturers usually under six months after the harvest, and it is quite possible that it is mixed with ergot of the preceding year's harvest, it is evident that Grünfeld's statements being accepted would mean that ergot should be eliminated from the Pharmacopœia.

This state of affairs has existed for a number of years, and yet there are obstetricians who believe that satisfactory results follow the clinical use of ergot. Sharp [16] obtained a "liquid extract" of ergot which he kept under ordinary conditions for twelve months, using it, as the occasion offered, on patients in labor or who had just completed labor and in whom there was a "loss of uterine tone." He concluded that this liquid extract was apparently as active at the expiration as it was at the beginning of the year.

Wood and Hofer [20] and Crawford [2] apparently attach little value to the results of clinical observation in studying the question of the deterioration of ergot. It is certainly true that it is the tendency of some clinicians to draw conclusions from their experience in very limited numbers of cases, in which they have failed to consider adventitious circumstances. Such may have been true with Sharp, for he does not, unfortunately, give full enough details in regard to his study.

Bischofberger,[1] however, seems to have carried out his experiments with such care and thoroughness as to leave small room for questioning the results that he reports. In 1896, he tested lots of ergot, fresh, one year old, and two years old respectively, by administering the drug in powdered form to thirty patients. These patients had all been confined a short time previously and their abdominal walls were lax enough to permit of easy palpation of the uterus. In a number of instances, different lots of drug were tried upon the same patient, so that a comparison of activity could be made. He concludes: "If we take the mean of all experiments * * * it results that the activity of ergot of 1895 and 1896 is almost identical while that of 1894 * * * shows a plain, if only moderate decrease in activity." In comparing, more specifically, the results of experiments dealing only with fresh (1896) ergot and that one year old, he was able to see in the year-old specimen slightly less activity than in the fresh specimen.

As was said, Bischofberger's results seem entitled to acceptance, but, like Grünfeld he makes the mistake of assuming the same initial activity for his three

lots of ergot. It is quite possible that his older ergot may have been considerably stronger when fresh than was the ergot of 1896, so his inferences as to the rate of deterioration are not justified. One point, however, seems established: namely, that ergot two years old has a decided influence upon the uterus of a woman when the drug is administered per os.

To study properly the question of the deterioration of ergot, it is necessary to secure a lot of the drug and determine its strength in reference to a definite standard, and then test it at stated intervals thereafter. Edmunds and Hale [7] seem to have shown that the cock's comb method, carried out with proper precautions, is a satisfactory test method, and they suggest ergotoxine, a definite chemical compound, as a standard. An investigation of this nature is now being carried out in our laboratory, but it seemed to us that information of value could be obtained by examining fresh and old preparations of ergot with a view to determining their relative activity. Unfortunately, in our earlier work of the routine testing of ergot, we simply determined that the preparations tested were sufficiently active to cause bluing of the comb when injected intramuscularly in the dose of 1 cc. per kilo fowl, so the possibility remains that the older preparations were originally more active than the recent ones. We can not believe that this will be the case throughout the large number of samples tested, but would rather think that the more recent samples possess greater activity than those made several years ago, owing to the greater care in manufacture.

The samples were, at about the time when the preparation was made, placed in small one-ounce, amber bottles. Ordinary cork stoppers were used, the samples were stored on shelves in a well-lighted room and subjected to wide variations in temperature; in fact, they were kept under conditions similar to those in many retail pharmacies, except that for practically all of the samples the stoppers had not been removed during the time they remained in storage. In the few instances where the stoppers had been removed it was for the withdrawal of a small portion of the liquid for examination and occurred only once or twice in any instance.

Blood pressure experiments were carried out on dogs, using, in most cases, morphine anæsthesia, supplanted by ether for operation—the method proposed by Wood and Hofer.[20] The morphine was given subcutaneously one-half to one hour before the operation was begun. At the end of this period the animal was etherized, the common carotid artery was attached to a mercury manometer, and last the trachea was connected with the artificial respiration apparatus. After allowing the animal about ten minutes to recover from the ether, and when a constant blood pressure record had been secured, the injection was made. Artificial respiration was used in all experiments except one.

The systolic pressure (as recorded by the ordinary mercury manometer) was measured. Measurements were made in millimeters, and fractions of millimeters were dropped.

Table A gives the actual elevations of blood pressure at the beginning of the experiments, and for the several periods following. Table B gives the changes in pressure after the injection of the drug from that at the beginning of the experiments.

(+ = above, — = below.)

TABLE A.

Blood Pressure Records on Dogs.

Date of test.	No. of preparation.	Date when made.	Sex of dog.	Wt. of dog in Kgms.	Anaesthetic and amount given per Kgm. of body weight. Stated in fraction of gram.	No. of injection.	Dose per Kgm. stated in fractions of a c.c.	Blood pressure when inj. was made.	Initial pressure (1-3 min. after inj.)	Pressure 5 min. after injection.	10 min. after.	15 min. after.	20 min. after.
5-29-11	421352	5-29-11	M	6.6	Morph. S. 0.008	1	0.10	136	170	169	172	164	161
						2	0.15	160	178	168	158	150	
3-29-11	415330	3-26-11	M	17.0	Morph. S. 0.006	1	0.08	132	159	157	151	141	151
						2	0.16	150	164	173	172	174	180
2- 8-11	411173	2- 8-11	M	9.0	Morph. S. 0.005	1	0.08	145	166	171	160		
						2	0.15	160	175	168			
2- 7-11	409578	2- 7-11	M	7.2	Morph. S. 0.009	1	0.08	140	173	170	167		
						2	0.15	166	204	164			
12-21-10	406559	12-21-10	M	18.0	Morph. S.	1	0.14	163	234	226	215	200	190
					Atrop. S.								
12-18-10	406556	12-15-10	M	8.8	Morph. S. 0.010	1	0.05	114	218	214	187	187	166
					Atrop. S. 0.00014								
11-18-10	401649	11-18-10	F	10.0	Morph. S. 0.0064	1	0.08	124	174	174	180	160	148
					Atrop. S. 0.00017								
10-28-10	401646	10-28-10	M	13.6	Morph. S.	1	0.10	110	210	194	203	150	129
					Atrop. S.								
6-28-10	386647	6-28-10		12.0	Morph. S.	1	0.08	70	132	118	152	152	148
					Acetoform (No ether.)								
5-29-11	320659	9- 8-08	M	7.6	Morph. S. 0.008	1	0.10	128	176	191	189	172	160
					Acetoform .025								
5-14-11	316825	8-24-08	M	6.3	Morph. S. 0.006	1	0.10	159	173	179	188	200	200
4- 3-11	310299	6- 7-08	M	18.6	Morph. S. 0.007	1	0.08	124	151	120	129	141	140
						2	0.15	140	153	155	150	147	149
3-27-11	306389	5- 3-08	F	9.0	Morph. S. 0.007	1	0.08	134	167	165	146	139	138
						2	0.15	137	177	161	158	146	142
3-27-11	306389	5- 3-08	M	11.8	Morph. S. 0.008	1	0.08	132	165	213	Clot		152
3-23-11	277009	4-29-07	F	5.7	Morph. S.	1	0.08	95	135	115	122	132	137
						2	0.15	137	160	137	146	122	120
3-23-11	277008	4-29-07	F	12.2	Morph. S. 0.008	1	0.08	126	Clot	163	168	167	160
3-22-11	277007	4-23-07	M	15.4	Morph. S. 0.007	1	0.08	174	201	138	207	216	148
6-24-11	272572	3-12-07	M	15.8	Morph. S. 0.0037	1	0.10	118	149	128	111	106	102
					Curare 0.0026	2	0.15	101	164	159	151	141	132
6-23-11	272572	3-12-07	F	18.4	Morph. S. 0.006	1	0.10	148	240	232	268	193	187
					Atrop. S. 0.0001	2	0.15	170	242	222	199	188	184
					Curare 0.0015								
5- 5-11	261770	2-26-07	M	22.0	Morph. S. 0.150	1	0.10	90	127	110	112	110	110
						2	0.15	107	116	116	111	110	111
6-23-11	261766	12-22-06	M	20.0	Morph. S. 0.006	1	0.10	142	160	167	165	157	153
					Curare 0.0015	2	0.15	154	182	192	187	177	
6- 2-11	261766	12-22-06	F	7.1	Morph. S. 0.0021*	1	0.10	146	178	178	171	166	167
						2	0.15	169	188	193	181	177	176
4- 4-11	255660	8-28-06	M	9.0	Morph. S. 0.007	1	0.08	146	166	152	154	146	140
						2	0.15	140	176	150	137		
4-12-11	254053	8-16-06	M	19.5	Morph. S. 0.010	1	0.10	122	181	170	140	136	130
4- 5-11	251604	8- 3-06	M	8.6	Morph. S. 0.006	1	0.10	92	118	119	119	118	122
						2	0.15	124	135	135	141	140	140
4- 5-11	251604	8- 3-06	F	4.3	Morph. S. 0.0035	1	0.10	112	132	106	113	114	109
4- 5-11	251603	8-28-06	M	7.2	Morph. S. 0.006	1	0.10	150	177	149	160	169	169

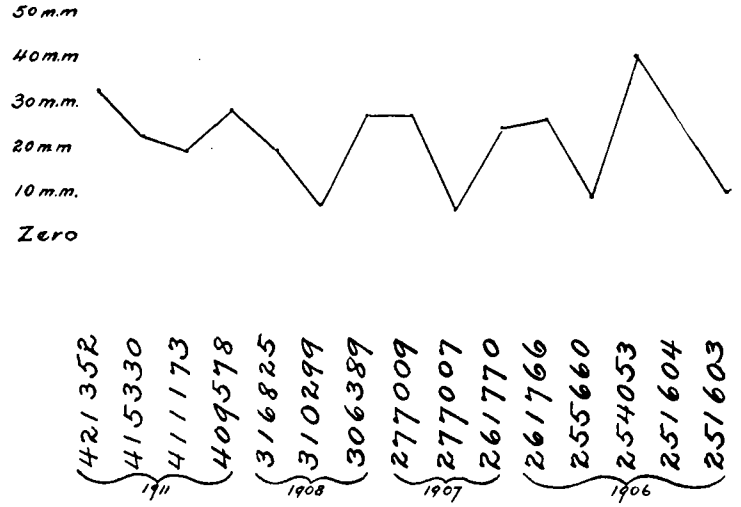
*Natural respiration.

TABLE B.

No. of preparation.	Age. (Fractions of months were dropped.)	Anaesthetic.	No. of injection.	Initial change.	Change at end of 5 min.	10 min.	15 min.	20 min.	Average change of initial, 5 and 10 min. periods.
421352	Fresh	Morph. S.	1	+34	+33	+36	+28	+25	+34
			2	+42	+32	+22	+14		+22
415330	Fresh	Morph. S.	1	+27	+25	+19	+9	+19	+24
			2	+34	+41	+40	+42	+48	+38
411173	Fresh	Morph. S.		+21	+26	+15			+21
409578	Fresh	Morph. S.		+33	+30	+27			+30
406559	Fresh	Morph. S. Atrop. S.		+71	+63	+52	+37	+27	+62
406556	Fresh	Morph. S. Atrop. S.		+104	+100	+73	+73	+52	+92
401649	Fresh	Morph. S. Atrop. S.		+50	+50	+56	+36	+24	+52
401646	Fresh	Morph. S. Atrop. S.		+100	+84	+93	+40	+19	+92
386647	Fresh	Morph. S. Acetoform (No ether)		+62	+48	+82	+82	+78	+64
320659	32 mo.	Morph. S. Acetoform		+48	+63	+61	+44	+32	+57
316825	32 mo.	Morph. S.		+14	+20	+29	+41	+41	+21
310299	33 mo.	Morph. S.	1	+27	—4	+5	+17	+16	+9
			2	+29	+31	+26	+23	+25	+29
306389	34 mo.	Morph. S.	1	+33	+31	+12	+15	+4	+29
			2	+43	+27	+24	+12	+8	+31
306389	34 mo.	Morph. S.		+33	+81	Clot	Clot	+20	
277009	46 mo.	Morph. S.	1	+40	+20	+27	+37	+42	+29
			2	+65	+42	+51	+27	+25	+53
277008	46 mo.	Morph. S.		Clot	+37	+42	+41	+34	
277007	47 mo.	Morph. S.		+27	—36	+33	+42	—26	+8
272572	51 mo.	Morph. S.		+31	+10	—7	—12	—16	+11
		Curare		+46	+41	+33	+23	+14	+40
272572	51 mo.	Morph. S.	1	+92	+84	+120	+45	+39	+99
		Atrop. S.	2	+94	+74	+51	+40	+36	+73
		Curare							
261770	50 mo.	Morph. S.	1	+37	+20	+22	+20	+20	+26
			2	+26	+26	+21	+20	+21	+24
261766	54 mo.	Morph. S.	1	+18	+25	+23	+15	+11	+22
		Curare	2	+40	+50	+45	+35		+45
261766	53 mo.	Morph. S.*	1	+32	+32	+25	+20	+21	+30
			2	+42	+47	+35	+31	+30	+41
255660	55 mo.	Morph. S.	1	+20	+6	+8	0	—6	+11
			2	+30	+4	—9			+8
254053	55 mo.	Morph. S.		+57	+48	+18	+14	+8	+42
251604	56 mo.	Morph. S.	1	+26	+27	+27	+26	+30	+27
			2	+43	+43	+49	+48	+48	+45
251604	56 mo.	Morph. S.		+20	—6	+1	+2	—3	+5
251603	55 mo.	Morph. S.		+27	—1	+10	+19	+19	+12

* Natural respiration.

The average rise for the first three periods, in those experiments where morphine alone was used (with ether for operation), may be seen in plotted curve No. 1. The dots connected by lines represent pressures obtained from first



CURVE NO. 1.

injections. The separate dots represent pressures obtained from second injections (where second injections were made), and show the increase or decrease in pressure from that following the first injection. The vertical figures are the serial numbers of the fluidextracts. The dates at the bottom show when the preparations were made.

Five blood pressure experiments were carried out on spinal preparations, prepared according to the directions of Sherrington.[17] Data and results may be seen in Table C.

TABLE C.

Blood Pressure Records on Spinal Preparations.

Date of test.	No. of preparation.	When made.	Animal.	Wt. in Kgms.	No. of injection.	Dose of drug per Kgm. in fractions of a c.c.	Blood pressure at beginning of inj.	Blood pressure 4-3 min. after injection.	5 min. after.	10 min. after.	15 min. after.	20 min. after.	Average rise of first three periods.
4- 5-11	251603	8-28-06	Cat	3.5	1	0.10	104	161	167	165	152	134	+60
3-25-11	277007	4-23-07	Cat	2.6	1	0.08	130	136	Clot		141	132	
					2	0.16	132	162	168				
3-18-11	306389	5- 3-08	Cat	2.9	1	0.15	120	159	138	122	113		+20
					2	0.15	104	152	129	100			
5-14-11	316825	8-24-08	Cat	2.6	1	0.10	100	118	110				
					2	0.10	96	139	125	88			+21
					3	0.10	87	114	86				
3-10-11	411176	2- 8-11	Dog	5.6	1	0.08	138	153	158	151	158		+16

The results secured by the blood-pressure experiments are surprising in view of the experience of Wood and Hofer. As may be seen from the table and from

the chart, no definite information could be obtained by this method, for while some of the old samples failed to have the desired pressor activity, others appeared to be very active in this respect. In most of the experiments we followed the procedure of Wood and Hofer and are at a loss to account for the difference in the results.

Cock's-comb tests were carried out on stock samples of fluidextract (previously described). White Leghorn fowls from 7-10 months old were used except in a few cases where otherwise mentioned. All doses were calculated per kgm. of body weight. The drug was injected into the breast muscles and the fowls were observed at intervals for one and a half hours.

Fowls having well developed combs, of a deep red color and thickly covered with papillæ, have seemed to be the most susceptible, and will, nearly all of them, show the characteristic bluing of the comb provided the drug has been given in sufficient quantity.

Occasionally, however, fowls are found which will not show a bluing of the comb even after receiving large doses of the drug. In such chickens a blanching of the comb usually results, although in others there may be almost no change in color. Fowls of this kind were excluded. Some of those used may have partaken of this tendency in a slight measure. Certainly, some seemed more resistant than others. In some, considerable blanching of the comb would precede the bluing, while in others the comb would gradually become darker until a distinct bluing was visible Of the fowls used, we made no selection for any given tests, but simply injected them in the order they happened to be brought to the laboratory by the assistant.

Tables D, E, and F show the results secured. In table D the samples were tested in a dose of 0.75 c.c.; in table E all samples failing to cause any bluing when administered in a dose of 0.75 c.c. were given in a dose of 1 c.c.; in table F those failing to cause bluing in 1 c.c. were administered in 1.5 c.c. per kgm.

The different results are designated in these tables as follows:

Marked bluing = Where larger part of comb was very distinctly blue.

Very faint bluing = Where the tips of points and back tip were very faintly though distinctly blue.

Faint bluing = A stage between the two preceding.

Darkening = Where comb seemed darkened but showed no distinct bluing.

Blanching = Where blanching occurred without any darkening or bluing.

TABLE D.

Tests on Stock Samples of F. E. Ergot by the Cock's Comb Method, Using White Leghorns. Dose per Kgm. of body weight=0.75 cc.

Date of test.	No. of preparation.	When made.	No. of fowl.	Wt. in Kgms.	Result.	
11-14-11	434060	11-14-11	203	1.676	Marked bluing	+
10-20-11	434057	10-20-11	194*	1.849	Faint bluing	+
10-10-11	429539	9-23-11	183	1.498	No coloring	O
10-28-11	429539	9-23-11	191*	1.965	No coloring	O
11- 7-11	429539	9-23-11	195*	1.735	Faint bluing	+
11- 8-11	429539	9-23-11	186	1.511	Faint bluing	+
11- 7-11	425456	9- 4-11	194*	1.909	Blanching	O
11- 8-11	425456	9- 4-11	187	1.250	No coloring	O

* Fowl at least one and a half years old.
+ Where bluing in any degree was obtained.
O No noticable bluing.

TABLE D.—(Continued.)

Date of test.	No. of preparation.	When made.	No. of fowl.	Wt. in Kgms.	Result.	
10-10-11	425453	8- 8-11	172	1.224	Marked bluing	+
10-10-11	421335	7-10-11	184	1.253	Marked bluing	+
10-10-11	421352	6-11-11	181	1.231	Faint bluing	+
10-11-11	415333	5-18-11	169	1.293	Marked bluing	+
10-11-11	415330	4-27-11	171	1.207	Marked bluing	+
10-11-11	411176	3-18-11	173	1.464	Marked bluing	+
10-11-11	409575	2-10-11	168	1.105	Very faint bluing	+
10-28-11	409575	2-10-11	192*	1.912	Very faint bluing	+
11- 7-11	409575	2-10-11	197*	1.709	Darkening	O
10-11-11	406559	1-19-11	182	1.412	Faint bluing	+
10-13-11	401649	12-15-10	187	1.425	Faint bluing	+
10-13-11	401646	11-22-10	186	1.420	Marked bluing	+
10-13-11	397483	10-24-10	194	1.194	Marked bluing	+
10-16-11	393872	9- 9-10	181	1.189	No coloring	O
10-28-11	393872	9- 9-10	192*	1.712	Very faint bluing	+
10-16-11	393869	8-19-10	172	1.318	Marked bluing	+
10-16-11	386647	7-17-10	184	1.146	Marked bluing	+
10-16-11	382975	6- 4-10	183	1.438	Faint bluing	+
10-17-11	382972	5- 6-10	186	1.579	Marked bluing	+
10-17-11	380930	4-18-10	182	1.378	Faint bluing	+
10-17-10	375495	3- 5-10	173	1.458	Faint bluing	+
10-17-10	375491	2-19-10	171	1.151	Very faint bluing	+
10-18-11	375488	1-28-09	187	1.400	Very faint bluing	+
10-18-11	369507	12-10-09	190	1.218	Very faint bluing	+
10-18-11	361919	11-14-09	189	1.339	Very faint bluing	+
10-18-11	359337	9-12-09	188	1.231	Very faint bluing	+
10-21-11	353756-7-8	8-21-09	185	1.106	Darkening	+
10-30-11	353756-7-8	8-21-09	189	1.385	No coloring	+
11-11-11	353756-7-8	8-21-09	198	1.565	No coloring	+
10-21-11	353728	7-10-09	189	1.327	Very faint bluing	+
10-21-11	351522	6-14-09	172	1.304	Very faint bluing	+
10-21-11	347870	5-13-09	188	1.265	Marked bluing	+
10-21-11	340670	4-10-09	173	1.341	Darkening	O
10-30-11	340670	4-10-09	188	1.264	Darkening	O
10-21-11	340668	3-22-09	190	1.234	Very faint bluing	+
10-21-11	337592	2-27-09	187	1.380	Darkening	O
10-21-11	337588	1-30-09	186	1.475	Darkening	O
10-26-11	330033	12-23-08	183	1.480	Darkening	O
10-26-11	323359	11-23-08	173	1.408	Very faint bluing	+
10-26-11	323356	10-19-08	186	1.423	Faint bluing	+
10-26-11	320661	9-20-08	185	1.100	Darkening	O
10-26-11	316822	8- 3-08	190	1.269	Darkening	O
10-26-11	316821	7-19-08	188	1.292	Faint bluing	+
10-26-11	310300	6- 7-08	187	1.311	Darkening	O
10-26-11	310298	5-15-08	189	1.380	Faint bluing	+
10-28-11	306387	4-17-08	196o	1.983	Darkening	O
10-30-11	306387	4-17-08	186	1.372	No coloring	O
10-28-11	303460	3-15-08	197o	1.764	No coloring	O
10-30-11	303460	3-15-08	185	1.065	No coloring	O
10-30-11	300827	2- 4-08	183	1.461	No coloring	O
10-30-11	300824	1- 4-08	187	1.249	No coloring	O
10-30-11	294875	12- 6-07	169	1.085	Very faint bluing	+
10-30-11	294874	11-23-07	172	1.306	No coloring	O
10-30-11	291699	10-11-07	173	1.319	No coloring	O
10-30-11	289208	9-13-07	190	1.200	No coloring	O
10-30-11	286684	8-17-07	192*	1.822	No coloring	O
10-30-11	286682	7-14-07	191*	1.804	No coloring	O
10-30-11	280986	6-23-07	193*	1.564	No coloring	O
11- 4-11	277010	5-23-07	187	1.291	Darkening	O
11- 4-11	277009	4-29-07	173	1.329	No coloring	O
11- 4-11	272572	3-12-07	188	1.233	Darkening	O
11- 4-11	261770	2-26-07	190	1.114	Darkening	O
11- 4-11	261766	12-22-06	189	1.364	Darkening	O
11- 4-11	255664	10- 8-06	172	1.295	No coloring	O
11- 4-11	254053	8-16-06	183	1.479	No coloring	O
11- 4-11	251604	8- 3-06	186	1.443	No coloring	O

o Brown Leghorn at least one and one-half years old.
* Fowl at least one and one-half years old.
+=as above.
O=as above.

TABLE E.

Tests on Stock Samples of F. E. Ergot by the Cock's Comb Method, Using White Leghorns. Dose per Kgm. of body weight=1 c.c.

Date of test.	No. of preparation.	When made.	No. of fowl.	Wt. in Kgms.	Result.	
11-11-11	425456	9- 4-11	182	1.394	Marked bluing	+
11-11-11	409575	2-10-11	173	1.298	Marked bluing	+
11-11-11	353756-7-8	8-21-09	198	1.565	No coloring	O

TABLE E.—(Continued.)

Date of test.	No. of preparation.	When made.	No. of fowl.	Wt. in Kgms.	Result.	
11-11-11	353756-7-8	8-21-09	186	1.455	Very faint bluing	+
11- 7-11	340670	4-10-09	192*	1.886	Very faint bluing	+
11-11-11	340670	4-10-09	188	1.229	Marked bluing	+
11-11-11	337592	2-27-09	187	1.218	Darkening	O
11-11-11	337588	1-30-09	189	1.311	Marked bluing	+
11-11-11	330033	12-23-08	185	1.089	Darkening	O
11-11-11	320661	9-20-08	172	1.216	Very faint bluing	+
11-11-11	316822	8- 3-08	190	1.117	Marked bluing	+
11-11-11	310300	6- 7-08	181	1.298	Very faint bluing	+
11-16-11	306387	4-17-08	182	1.423	Darkening	O
11-16-11	303460	3-15-08	185	1.145	Darkening	O
11-16-11	300827	2- 4-08	190	1.060	Faint bluing	+
11-16-11	300824	1- 4-08	187	1.163	Darkening	O
11-16-11	294874	11-23-07	188	1.173	Faint bluing	+
11-16-11	291699	10-11-07	183	1.504	Blanching	O
11-16-11	289208	9-13-07	181	1.276	Darkening	O
11-16-11	286684	8-17-07	186	1.452	Faint bluing	+
11-16-11	286682	7-14-07	189	1.262	Marked bluing	+
11-16-11	280986	6-23-07	191*	1.567	Very faint bluing	+
11-16-11	277010	5-23-07	173	1.218	Very faint bluing	+
11-16-11	277009	4-29-07	172	1.293	Darkening	O
11-16-11	272572	3-12-07	192*	1.687	Blanching	O
11-18-11	261770	2-26-07	200	1.376	Blanching	O
11-18-11	261766	12-26-06	199	1.793	Very faint bluing	+
11-18-11	255664	10- 8-06	219	1.351	Darkening	O
11-18-11	254053	8-16-06	220	1.390	Darkening	O
11-18-11	251604	8- 3-06	198	1.715	Darkening	O

* Fowl at least one and a half years old.
+=Bluing in any degree.
O=No noticable bluing.

TABLE F.

Tests on Stock Samples of F. E. Ergot by the Cock's Comb Method, Using White Leghorns. Dose per Kgm. of body weight=1.5 c.c.

Date.	No. of preparation.	When made.	No. of fowl.	Wt. in Kgms.	Result.	
11-22-11	337592	2-27-09	188	1.210	Very faint bluing	+
11-22-11	330033	12-23-08	187	1.206	Darkening	O
11-22-11	306387	4-17-08	220	1.423	Very faint bluing	+
11-22-11	303460	3-15-08	200	1.359	Very faint bluing	+
11-22-11	300824	1- 4-08	202	1.522	Very faint bluing	+
11-22-11	291699	10-11-07	173	1.260	No coloring	O
11-22-11	289208	9-13-07	189	1.297	Darkening	O
11-22-11	277009	4-29-07	186	1.532	Very faint bluing	+
11-22-11	272572	3-12-07	182	1.430	No coloring	O
11-22-11	261770	2-26-07	190	1.089	Darkening	O
11-22-11	255664	10- 8-06	181	1.298	Very faint bluing	+
11-22-11	254053	8-16-06	172	1.366	Very faint bluing	+
11-22-11	251604	8- 3-06	183	1.568	No coloring	O

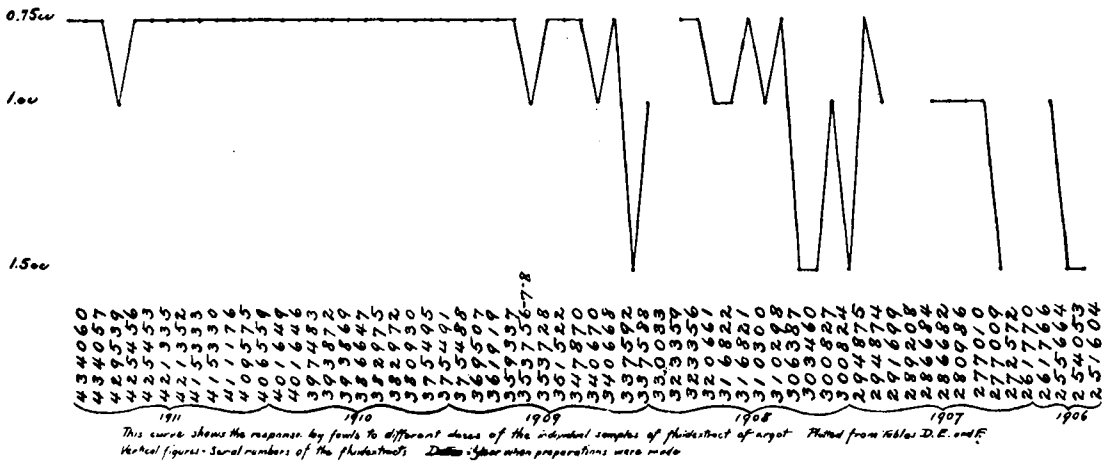
+=Bluing in any degree.
O=No noticable bluing.

Curve 2 was plotted from the results given in Tables D, E, and F and shows the response of fowls to the different doses of the fluidextracts.

The gaps are due to the fact that preparations corresponding to those numbers did not cause bluing in a dose of 1.5 c.c. per kilo, that being the largest dose used in this series.

TESTS OF MIXED SAMPLES MADE FROM STOCK SAMPLES BY THE COCK'S COMB METHOD, USING WHITE LEGHORNS.

Sixty of the stock lot samples previously tested individually were divided into five groups of twelve each. A mixed sample was made from each group. Since the individual samples were taken, one for each month, extending back over



CURVE No. 2.

approximately sixty months, each mixed sample represented the lots made during a given year. The sample from the oldest group was labeled 1, the next 2, 3, 4, and 5 respectively. Data and results may be seen in table G, or plotted in curve 3.

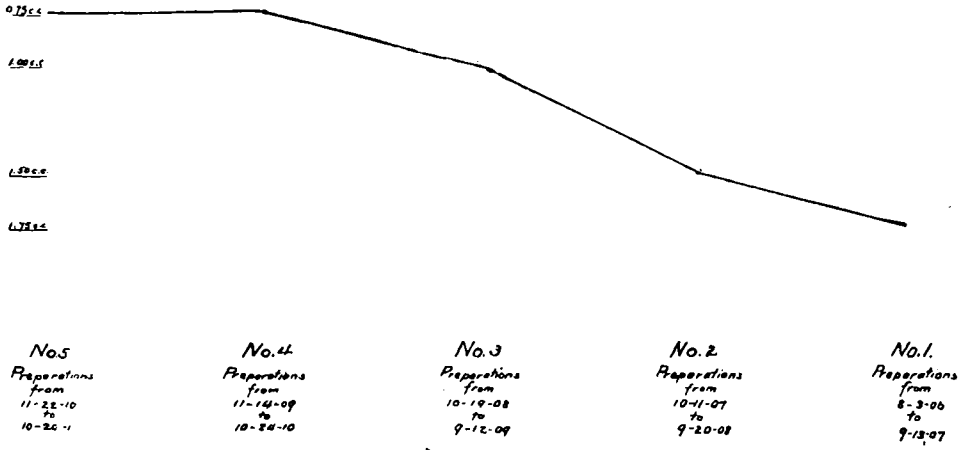
TABLE G.

Date of test.	Sample and age.	No. of fowl.	Wt. in Kgms.	Dose per Kgm.	Result.
11-14-11	1.	202	1.469	0.75 c.c.	No coloring O
11-22-11	Preparations	198	1.704	0.75 c.c.	Blanching O
11-18-11	from	233	1.865	1.00 c.c.	Darkening O
12- 5-11	8- 3-06	199	1.953	1.25 c.c.	Very faint bluing +
12- 5-11	to	224	1.368	1.25 c.c.	Darkening O
12- 9-11	9-13-07	223	1.850	1.25 c.c.	Darkening O
11-28-11	inclusive	226	1.586	1.5 c.c.	Faint bluing +
12-12-11		202	1.558	1.5 c.c.	Darkening O
12-12-11		225	1.793	1.5 c.c.	No coloring O
12-21-11		201	1.460	1.5 c.c.	Very faint bluing +
12-21-11		237	1.437	1.5 c.c.	No coloring O
12-21-11		220	1.475	1.63 c.c.	Very faint bluing +
12-21-11		187	1.392	1.63 c.c.	Very faint bluing +
12-21-11		226	1.500	1.63 c.c.	Darkening O
12-15-11		203	1.796	1.75 c.c.	Very faint bluing +
12-21-11		204	1.371	1.75 c.c.	Faint bluing +
11-14-11	2.	201	1.507	0.75 c.c.	Darkening O
11-14-11	Preparations	226	1.726	0.75 c.c.	Darkening O
11-18-11	from	222	1.396	1.00 c.c.	Darkening O
12- 6-11	10-11-07	223	1.907	1.00 c.c.	Darkening O
12- 6-11	to	198	1.725	1.00 c.c.	Blanching O
12- 9-11	9-20-08	219	1.397	1.00 c.c.	No coloring O
12-12-11	inclusive	204	1.478	1.25 c.c.	Very faint bluing +
12-15-11		202	1.418	1.25 c.c.	Faint bluing +
12-15-11		226	1.514	1.25 c.c.	Darkening O
12-28-11		222	1.398	1.50 c.c.	Faint bluing +
12-12-11		199	1.916	1.50 c.c.	Very faint bluing +
12-12-11		237	1.541	1.50 c.c.	Very faint bluing +
12- 6-11	3.	200	1.348	0.50 c.c.	Darkening O
12- 6-11	Preparations	202	1.559	0.63 c.c.	Darkening O
12- 9-11	from	226	1.558	0.63 c.c.	No coloring O
11-14-11	10-19-08	200	1.418	0.75 c.c.	Very faint bluing +
11-22-11	to	202	1.721	0.75 c.c.	Faint bluing +
12-12-11	9-12-09	200	1.493	0.75 c.c.	Darkening O
12-12-11	inclusive	226	1.550	0.75 c.c.	No coloring O
12-15-11		223	1.841	0.87 c.c.	No coloring O
12-15-11		224	1.384	0.87 c.c.	No coloring O
12-21-11		225	1.764	0.87 c.c.	Darkening O
12-21-11		223	1.878	0.87 c.c.	Darkening O
12-21-11		182	1.689	0.87 c.c.	Very faint bluing +
11-18-11		201	1.477	1.00 c.c.	Faint bluing +
12-21-11		219	1.327	1.00 c.c.	Very faint bluing +
12-21-11		224	1.419	1.00 c.c.	Very faint bluing +

TABLE G.—(Continued.)

Date of test.	Sample and age.	No. of fowl.	Wt. in Kgms.	Dose per Kgm.	Result.
12- 6-11	4.	226	1.576	0.5 c.c.	No coloring O
12- 6-11	Preparations	225	1.806	0.5 c.c.	No coloring O
12- 9-11	from	224	1.355	0.63 c.c.	Darkening O
12-15-11	11-14-09	225	1.739	0.63 c.c.	Very faint bluing +
12-15-11	to	187	1.333	0.63 c.c.	Darkening O
12-21-11	10-24-10	229	1.193	0.63 c.c.	Very faint bluing +
12-21-11		199	1.908	0.63 c.c.	No coloring O
12-21-11	inclusive	199	1.738	0.75 c.c.	Very faint bluing +
11-22-11		225	1.933	0.75 c.c.	Very faint bluing +
11-18-11		221	1.566	1.00 c.c.	Marked bluing +
12- 6-11	5.	203	1.775	0.5 c.c.	No coloring O
12- 6-11	Preparations	219	1.387	0.5 c.c.	No coloring O
12- 9-11	from	225	1.744	0.63 c.c.	Darkening O
12-15-11	11-22-10	201	1.429	0.63 c.c.	No coloring O
12-15-11	to	219	1.367	0.63 c.c.	No coloring O
12-21-11	10-20-11	186	1.669	0.63 c.c.	Very faint bluing +
12-21-11	inclusive	228	1.465	0.63 c.c.	Very faint bluing +
11-14-11		198	1.760	0.75 c.c.	Very faint bluing +
11-22-11		201	1.473	0.75 c.c.	Faint bluing +
11-18-11		203	1.647	1.00 c.c.	Marked bluing +

From an examination of Table D, it is seen that, with a few exceptions, the samples back to April 10, 1909 (that is, two years and six months), seem to cause bluing of the comb in a dose of 0.75 c.c. per kgm. From that time back, of the 31



This curve shows the amount of the different mixed samples of fluidextract of ergot required to produce bluing of the cock's comb Curve plotted from Table G.

CURVE No. 3.

samples tested, only six had any visible effect upon the comb when given in this dose.

From Table E, it may be seen that, with quite a number of exceptions, there is no distinct evidence of diminished strength until April 29, 1907 (sample No. 277009), or about four years and six months.

Table F does not give information of any value, because the sample five years old gave as much bluing in the dose of 1.5 c.c. as did the one only two years old.

The results given in Table G are, we believe, the ones of most value. By mixing

together all of the samples of one year, variations of individual samples become less important and the resulting diminution in the number of preparations enables fairly accurate comparison of strength.

For mixture No. 1, we may put the effective dose at 1.75 c.c.; or, may say that a mixture of preparations about four and one-half years old causes bluing of the cock's comb when given in that dose. Mixture No. 2 approximately three and one-half years old, produced about the same effect when given in a dose of 1.5 c.c. Mixture No. 3, about two and one-half years old, produces bluing in a dose of 1.00 c.c.; while mixture No. 4, about one and one-half years old, and mixture No. 5, about six months old, were effective in a dose of 0.75 c.c. The last two mixtures showed an almost identical degree of activity, so far as we could determine, and it is exceptional to find a fresh preparation that will cause bluing in a smaller dose than this. Edmunds and Hale* find that 1 c.c. of a fresh fluidextract of ergot per kgm. fowl should cause distinct bluing of the comb, and suggest that 5 mgms. of ergotoxine phosphate be considered equivalent to 2 c.c. of such a fluidextract. On our chickens, we have found that our effective dose of 0.75 c.c. is about equivalent to 1.87 mgms. of ergotoxine phosphate; or, in other words, samples of fluidextract of ergot two years old possess an activity approximately equal to this provisional standard.

The mixture two and one-half years old had to be given in a dose 33 1-3 per cent. larger; the three and a half year old mixture had to be given in a dose 100 per cent. larger; while the four and one-half year old mixture was effective only in a dose about 133 per cent. larger than the mixtures made up of comparatively fresh preparations.

As we have said, inferences as to the exact rate of deterioration can be drawn from these experiments only on the assumption of an initial activity the same for all preparations. This is, of course, not justified, but it does seem to us that the large number of preparations examined affords ground for making approximations as to the keeping quality of the fluidextract of ergot. It would seem to us that, if the cock's-comb method is considered reliable, preparations of the fluidextract of ergot kept in well-stoppered, small vials under ordinary conditions will retain their activity practically unaltered for at least two or two and one-half years, but from this time on there is an appreciable deterioration which, at the end of four or five years, would necessitate the administration of more than double the dose in order to secure the same effect as from a fresh preparation. It is probable that deterioration is taking place from the time of manufacture, but in the samples examined by us, this did not become evident under two and a half years.

It has been frequently suggested that commercial preparations of ergot should bear the date when tested, but it seems to us that such procedure would be of value only when information is possessed concerning the probable rate of deteri-

* These authors do not state distinctly that the dose was per kgm., but from the context we assume this.

oration. The experiments which we report are suggestive, but we hope that others will take up the investigation so that a definite conclusion can be reached.

PHARMACOLOGICAL LABORATORY ELI LILLY & CO., INDIANAPOLIS, IND.

BIBLIOGRAPHY.

(1) Bischofberger—"Geburtshulflich-klinsche Untersuchungen über die Haltbarkeit des Mutterkorns." Inaug. Dissert, 1897.
(2) Crawford—American Journal of Pharmacy, Vol. 83, p. 147.
(3) Cronyn and Henderson—Jour. Pharmacology and Exper. Ther., Vol. 1, p. 203.
(4) Dale—Jour. of Physiology, Vol. XXXIV, No. 3, p. 163.
(5) Barger & Dale—Bio-Chem. Jour., Vol. 2, p. 240.
(6) Dixon—Pharm. Jour., Vol. 75, p. 155, July 29, 1905.
(7) Edmunds and Hale—Bulletin No. 76, Hygienic Lab., U. S. Public Health and Marine Hosp. Service.
(8) Edmunds and Roth—Jour. Am. Med. Assoc'n, Vol. LI, p. 2130.
(9) Goodall—Edin. Med. Jour., 1909, Vol. 3, p. 20.
(10) Grünfeld—Arb. des Pharm. Inst. zu Dorpat, Vol. VIII, p. 109.
(11) Houghton—Therapeutic Gazette, Vol. XIV, p. 433.
(12) Hunt—Bulletin No. 67, Hyg. Lab., U. S. Pub. Health and Mar. Hosp. Service.
(13) Kehrer—Arch. of Gyn., Vol. 81, No. 1.
(14) Kehrer—Arch. für Exper. Path und Pharm., Vol. 58, p. 366.
(15) Meulenhoff—Abstr., Pharm. Rundschau, Vol. XXXVI, pp. 738, 772.
(16) Sharp—Pharm. Jour., Vol. 80, p. 82.
(17) Sherrington—Jour. of Physiology, Vol. XXXVIII, p. 375.
(18) Report of Committee of Pharm. Chemists—Stability of Drug Extracts.
(19) Sudmersen and Glenny—Jour. of Hyg., Vol. 9, No. 4, p. 399.
(20) Wood and Hofer—Arch. of Int. Med., Vol. 6, p. 388.
(21) Wood and Hofer—Univ. Pennsylvania Bulletin, Vol. XXI, p. 341.

THE BACON BILL.*

GEO. F. PAYNE.

"To promote the efficiency of the Medical Department of the United States Army.

"Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That the Hospital Corps of the United States Army shall hereafter be known and designated as the Medical Corps, shall constitute the enlisted personnel of the Medical Corps now authorized by law, and shall consist of sergeants major, at seventy-five dollars per month; sergeants, first class, at sixty-five dollars per month; sergeants, at thirty-six dollaars per month; corporals, at twenty-four dollars per month; cooks, at thirty dollars per month; privates, first class, at twenty-one dollars per month; and privates, at sixteen dollars per month, with such increase for length of service and other allowances as are or may hereafter be established by law."

The purpose of this Bill is to remedy as far as possible the present and long standing condition which makes it actually impossible to secure for the Medical Department the class of men necessary for the efficient performance of duties connected with the care of the sick and the sanitary service in general. Inasmuch as all branches of the Army are practically in competition with each other for men possessing the necessary qualifications, it is obvious that efficiency can only be maintained by offering equal opportunities for advancement in all branches, or, as in this case, by a compensatory increase in the rate of pay in those branches

*Indexed as S. 5725, and as H. R. 22263, 62d Congress, 2d Session.