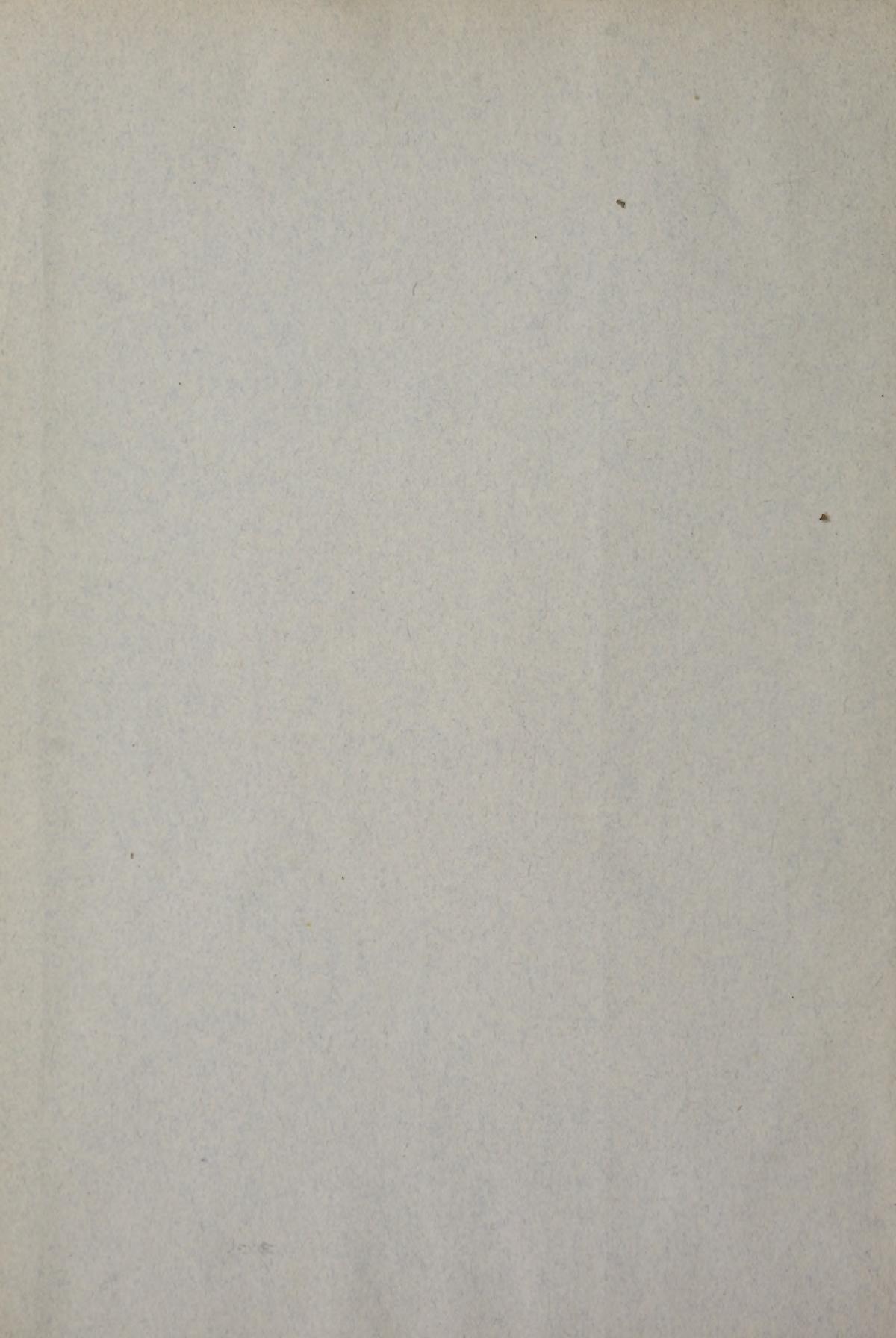
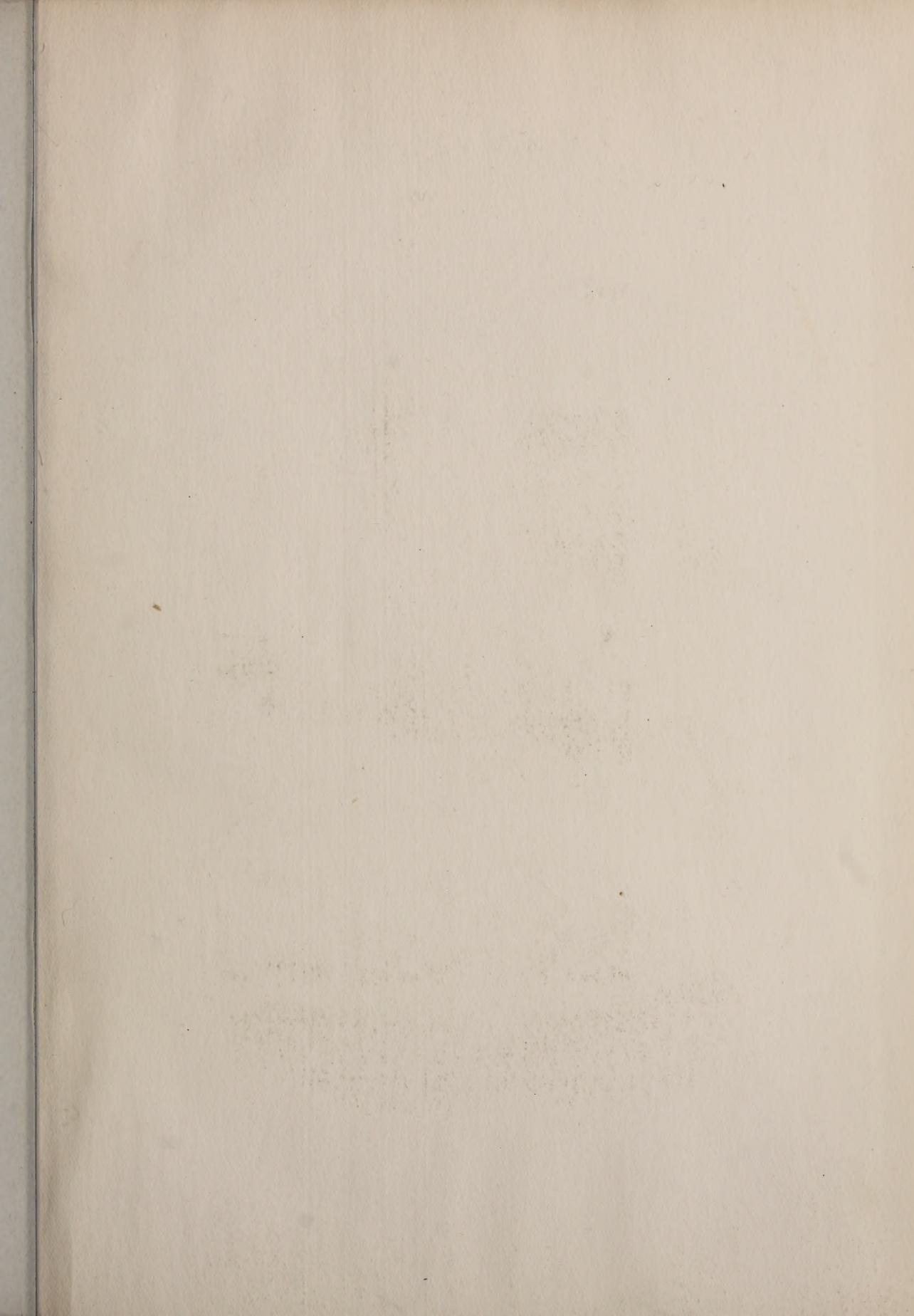


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SCIENTIFIC PROCEEDINGS.

One hundred first meeting.

ABSTRACTS OF COMMUNICATIONS.

Cornell University Medical College, October 15, 1919.
President Calkins in the chair.

I (1461)

The developmental stages at which mutations occur in the germ tract.

By CALVIN B. BRIDGES (by invitation).

[*From the Zoölogical Laboratory, Columbia University.*]

In the fruit-fly *Drosophila melanogaster* about 300 primary mutations have been found, most of which arose in cultures carried on in the laboratory. A study of the critical cases among these mutations has shown that a large majority of them originated at or very near the maturation stage; that a few occurred in the gonial cells some time prior to maturation; and that a few occurred early in the segmentation stage.

The conclusion that most mutations occur at the maturation stage is based largely on the proportion of sex-linked recessives and of dominants that have been first found as a single individual. Approximately half of the sex-linked recessives have been discovered as a single male. This is a surprisingly large proportion and clearly means that in these cases the actual mutation occurred in the mother, and at, or not more than a very few cell generations before, the maturation of the egg. Those sex-linked recessives that did not first appear as a single male have in the main appeared as half the sons of a female already heterozygous for the gene. In these cases the actual mutation had occurred at some indeterminate stage one or more generations previous to the appearance

of the character. There are now about 30 known dominants in *Drosophila melanogaster*, of which fully two-thirds were first found as single heterozygous individuals. This very large proportion of dominants appearing as single individuals means that the actual mutation has occurred very close to the final stage in the formation of the gamete—probably little if any prior to maturation.

That mutations may occur in the oögonial cells prior to maturation is proved by a few cases in which a single female has given rise to more than a single individual of a new sex-linked recessive character. In the first of these cases the mutant called "cut" occurred as six males among the 131 sons of a particular female. The mutation "tiny-wing" occurred as two sons among about 150; "sable-duplication" occurred as three males among 133; and "ivory" as about 10 per cent. of the sons. There are one or two other such cases known. In all of these cases the facts are in accord with the hypothesis that the actual mutation occurred in the oögonial cells of particular females, and from one to a few cell-generations prior to maturation. There has been one case in which a female homozygous for an autosomal recessive was outcrossed to a wild-type male, and produced among 61 offspring 6 flies that were heterozygous for a new allelomorph of the recessive. The mutation responsible for the new allelomorph occurred in the wild-type male in the spermatogonial stage far enough previous to spermatogenesis so that approximately a sixth of the sperm carried the gene. The proportion of gametes that carry the mutant character corresponds to the time previous to maturation at which the particular mutation occurred.

That mutation may occur in the zygote immediately after fertilization is proved by the discovery of nearly a dozen mosaic individuals in which a new mutant has appeared as part of a fly. If the new mutant is a dominant it may appear as part of a female, and if a sex-linked recessive as part of a male. Such mosaics arise by mutation in the zygote, and the parts descended from the mutant cell show the new character while the remainder of the animal shows the original type.

2 (1462)

Contrasting effects of chlorides and sulphates on the hydrogen ion concentration of acid solutions.By **ARTHUR W. THOMAS** and **MABEL E. BALDWIN**.*[From the Laboratory of Food Chemistry, Columbia University.]*

In the course of an investigation upon the effect of neutral salts upon hydrogen ion concentration we have noted a striking contrast in the effect of chlorides, sulphates and magnesium salts on the apparent hydrogen ion concentration of solutions of hydrochloric and of sulphuric acids.

The results of our measurements are given below. In all cases a solution of acid was mixed with a solution of a given salt and diluted to 100 c.c. The concentration of this solution of the mixture was always 0.1 normal with respect to the acid and that particular concentration of the salt whose effect upon the hydrogen ion concentration was to be studied. The hydrogen ion concentrations were measured two days after the solutions were made up.

The effect of chlorides in increasing the hydrogen ion concentration of hydrochloric acid solutions is not new. This has previously been shown by Harned¹ and by Fales and Nelson². Arrhenius³ found that the hydrogen ion activities of acetic and of hydrochloric acids were increased by neutral salts which he thought was due to the salts increasing the dissociation of the acids. It is possible that recent work on the hydration of ions in aqueous solution will offer a more plausible explanation.

When the chlorides are arranged in order of their ability to increase the hydrogen ion activity, we get the following series: $\text{MgCl}_2 > \text{BaCl}_2 > \text{LiCl} > \text{NaCl} > \text{NH}_4\text{Cl} = \text{KCl}$ which, with the exception of magnesium and barium is in inverse order to a series of these cations arranged in order of their equivalent conductivities.

In the above series the salts are arranged in order of the increasing hydration (*i.e.*, number of molecules of water combined

¹ *J. Am. Chem. Soc.*, 37, 2460 (1915).

² *J. Am. Chem. Soc.*, 37, 2769 (1915).

³ *Z. physik. Chem.*, 31, 197 (1899).

with the ions at infinite dilution) of their cations— K^+ , 9.6; NH_4^+ , 10.7; Na^+ , 16.9; Li^+ , 24.0;¹ Ba^{++} , relatively higher;² Mg^{++} , higher than Ba^{++} .³

The contrast in the effect of sodium and ammonium sulphates in decreasing the hydrogen ion concentration as compared with the increasing action of the chlorides is noteworthy.

The peculiar effect of magnesium salts is interesting, especially in that the concentrations for bend in the curves is in each case between 0.5 and 1 molar. We have tried to find an explanation for these peculiarities in Jones' "Hydrates in Aqueous Solutions."³ Jones states, "Magnesium sulphate, like all the other sulphates studied, gives abnormal results. It appears to form no hydrates in aqueous solution, notwithstanding the fact that it crystallized with seven molecules of water of crystallization. It is almost

TABLE I.

EFFECT OF SALTS UPON THE CONCENTRATION OF HYDROGEN ION OF 0.1 NORMAL SULPHURIC ACID.

Conc. Salt.	Log. C_{H^+} .	Conc. Salt.	Log. C_{H^+} .
<i>Sodium Chloride</i>		<i>Ammonium Chloride.</i>	
0 - 1.21	0 - 1.21
1	Molar..... - 0.99	1	Molar..... - 1.08
2	"..... - 0.78	2	"..... - 0.98
3	"..... - 0.57	3	"..... - 0.84
4	"..... - 0.36	4	"..... - 0.72
<i>Magnesium Chloride.</i>		<i>Sodium Sulphate.</i>	
0 - 1.21	0 - 1.21
0.25	Molar..... - 0.84	0.25	Molar..... - 1.60
0.5	"..... - 0.56	0.5	"..... - 1.72
1	"..... - 0.56	1	"..... - 1.80
2	"..... + 0.03	2	"..... - 1.88
3	"..... + 0.60	3	"..... - 1.92
<i>Ammonium Sulphate.</i>		<i>Magnesium Sulphate.</i>	
0 - 1.21	0 - 1.21
0.25	Molar..... - 1.61	0.25	Molar..... - 1.46
0.5	"..... - 1.76	0.5	"..... - 1.52
1	"..... - 1.90	1	"..... - 1.53
2	"..... - 2.04	2	"..... - 1.39
3	"..... - 2.15	3	"..... - 1.15
4	"..... - 2.24		

¹ Smith, *J. Am. Chem. Soc.*, 37, 722 (1915).

² Washburn, *Tech. Quarterly*, 21, 360 (1908).

³ Jones, Carnegie Institution of Washington, Publication No. 60 (1907).

TABLE II.

EFFECT OF SALTS UPON THE CONCENTRATION OF HYDROGEN ION OF 0.1 NORMAL HYDROCHLORIC ACID.

Conc. Salt.	Log. C _{H+} .	Conc. Salt.	Log. C _{H+} .
<i>Sodium Chloride.</i>		<i>Potassium Chloride.</i>	
0 - 1.038	0 - 1.038
1 Molar - 0.88	1 Molar - 0.95
2 " " - 0.72	2 " " - 0.85
3 " " - 0.52	3 " " - 0.75
4 " " - 0.36	4 " " - 0.63
<i>Ammonium Chloride.</i>		<i>Lithium Chloride.</i>	
0 - 1.038	0 - 1.038
1 Molar - 0.94	1 Molar - 0.81
2 " " - 0.87	2 " " - 0.60
3 " " - 0.75	3 " " - 0.35
4 " " - 0.65	4 " " - 0.12
<i>Barium Chloride.</i>		<i>Magnesium Chloride.</i>	
0 - 1.038	0 - 1.038
0.25 Molar - 0.96	0.25 Molar - 0.73
0.5 " " - 0.88	0.5 " " - 0.55
0.75 " " - 0.80	1 " " - 0.55
1 " " - 0.71	2 " " + 0.005
		3 " " + 0.68
		4 " " + 1.37
<i>Sodium Sulphate.</i>		<i>Ammonium Sulphate.</i>	
0 - 1.038	0 - 1.038
0.25 Molar - 1.51	0.25 Molar - 1.52
0.5 " " - 1.65	0.5 " " - 1.72
1 " " - 1.79	1 " " - 1.90
2 " " - 1.86	2 " " - 2.05
3 " " - 1.89	3 " " - 2.14
		4 " " - 2.18
<i>Magnesium Sulphate</i>			
0 - 1.038	1 - 1.47
0.25 Molar - 1.36	2 - 1.34
0.5 " " - 1.45	3 - 1.12

certain that this substance has considerable hydrating power, but this is masked in our results by the large amount of polymerization which the sulphates undergo."

The curve of the freezing point depression of magnesium sulphate plotted against concentration shows a depression to about 0.5 molar, from which point the depression decreases for higher concentrations. In this respect there is a slight similarity to its

effect on hydrogen ion concentration, *i.e.*, it increases hydrogen ion concentration to 0.5 to 1 molar beyond which it decreases it. Magnesium chloride, however, gave a similar effect on freezing point depression, although not so pronounced as magnesium sulphate. We could not find anything in the hydrate theory as developed at present to account for the peculiar bend in the magnesium chloride hydrogen ion curve.

We do not believe that the figures for hydrogen ion concentrations in the presence of salts given in this paper, are the true values. They should be termed apparent concentrations of hydrogen ion as determined by the method in general use at this date.

For the determination of the hydrogen ion concentrations, a Wolff 15,000 bridge with a galvanometer to determine the null point was used. As hydrogen electrode, a No. 16 Browne and Sharp gauge platinum wire (platinized) fused in a glass tube inserted in the Clark¹ cell was used. The calomel element contained 3.5 molar potassium chloride solution saturated with calomel and was the same design as that described by Fales and Vosburgh.² The E.M.F. was determined by means of a Weston cell that had been checked by the Bureau of Standards. The hydrogen contained in a tank under pressure, was carefully washed through saturated mercuric chloride solution, alkaline permanganate, alkaline pyrogallol and a tower of cotton fibers. The measurements were made at room temperatures which varied between 22° and 26° C., the proper corrections being made. No correction for barometric pressure was made since it is so small. (See Harned, *loc. cit.*) No attempt was made to calculate and correct for the solution contact potential because we know of no satisfactory method of doing so, especially where solutions containing divalent ions are concerned. It is emphasized however, that the differences in effects reported in this paper cannot be attributed to solution contact potential. This point was demonstrated by Harned, and Fales and Vosburgh proved there is no contact potential at 25° C., between a saturated solution of po-

¹ Clark, *J. Biol. Chem.*, 23, 475 (1915).

² Fales and Vosburgh, *J. Am. Chem. Soc.*, 40, 129 (1918).

tassium chloride (4.1 M) and hydrochloric acid solutions ranging in concentrations between 0.1 molar and 1 molar.

The salt bridge between the hydrogen and calomel elements used in our measurements was a saturated solution of potassium chloride.

3 (1463)

On the utilization of salep mannan.

By MARY SWARTZ ROSE.

[*From the Department of Nutrition, Teachers College, Columbia University.*]

Some experiments on the utilization of salep mannan were reported in 1911.¹ It was found that this anhydride of mannose was not hydrolyzed by the enzymes of saliva, pancreatic and intestinal juice, nor by malt diastase, but disappeared almost completely from the human alimentary tract when eaten, the coefficient of digestibility in three out of four experiments being 100 per cent. and 94 per cent. in the fourth. Studies of the effect of fecal bacteria indicated that some of them could produce appreciable amounts of sugar from this polysaccharide, and stimulated further research as to its precise fate in the animal organism. Investigations were interrupted in 1914, when the war cut off the supply of salep, and what has been accomplished along several lines is now reported as it is doubtful when these studies can be resumed.

Four more determinations of the coefficient of digestibility were made, two on healthy young women and two on diabetics. The young women, consuming identical and uniform diets, free from cellulose, throughout a fore, mid, and after period, took in the mid period of three days 75 grams of salep mannan, equivalent to 61 grams of glucose. The coefficient of digestibility was 97 per cent. in one case and 95 in the other. A diabetic man given in one day 45 grams of salep mannan, with no other food but broth, coffee and whiskey, had a coefficient of 98 per cent. A diabetic boy fifteen years old, took in three days 33, 65 and 70 grams of

¹ *Trans. Conn. Acad. Arts and Sciences*, XVI, pp. 247-382, 1911.

mannan respectively, and the coefficient of digestibility was 96 per cent. This was the largest amount administered to any subject. There was in no case any discomfort from gas formation, or other evidence of fermentation.

A detailed study of the nitrogen intake and output in the experiments on the two young women showed an increase in the fecal nitrogen accompanied by a marked increase in the volume of dry feces. There was a slight fall in the urinary nitrogen in the salep period and an increase of 16 and 17 per cent. respectively in the after period. This may have been due to decrease in the urine volume in the salep period and a subsequent "flushing out."

There was no evidence of sugar formation in the diabetic organism. In one case 10 grams were given in a day with no other food but broth, coffee and whiskey, and in another 45 grams, the urine in both cases remaining sugar free. For a five-day period a fifteen-year-old diabetic boy was kept on a controlled diet, and salep averaging 56 grams per day given for three days. Salep did not stop the production of β -oxybutyric acid, which rose from 3.4 grams on the day before the salep feeding to 15 grams on the third day.

Glycogen storage in the livers of rabbits could not be demonstrated, though mannose has been shown to form glycogen readily. The animals were starved five or six days, then fed salep by stomach sound for from one to three days. They were killed twelve to fifteen hours after the last feeding, but only traces of glycogen were found after administration of as much as 30 grams of salep in a day. The largest amount was 35 milligrams, whereas a rabbit fed 15 grams starch as a control had 209 milligrams. In two rabbits 16 and 60 per cent. respectively of the mannan was recovered from the alimentary tract and identified.

It was thought that since creatine elimination induced by starvation may be made to disappear by administration of calorically insufficient carbohydrate, carefully controlled experiments with rabbits might afford evidence as to the utilization of this mannan in metabolism. A series of experiments in which rabbits were starved from three to six days, then salep fed by stomach sound for two or three days, showed nothing especially significant

in the output of creatine, creatinine and total nitrogen, when these animals were compared with controls similarly treated, but fed soluble starch alone or combined with maltose or lactose in amounts equivalent to the salep administered. There was a faint tendency for creatine and total nitrogen to fall in the starch period, but the results cannot be considered conclusive.

Salep resembles inulin in its ease of acid hydrolysis, its resistance to digestive enzymes, and its failure to form sugar in the diabetic organism. It is not so fermentable as inulin.

4 (1464)

Growth and reproduction upon simplified food supply.

By **H. C. SHERMAN, M. E. ROUSE, B. ALLEN and E. WOODS.**

[*From the Laboratory of Food Chemistry, Columbia University.*]

Rats were fed rations consisting of white bread (made without milk or butter) either alone or with only one other article of food. Later, ground whole wheat was substituted for white bread in several cases.

In preliminary experiments with animals placed upon the experimental rations at the time of weaning, bread alone resulted in cessation of growth at once and death after about six weeks. With bread and meat there was some growth at first, but the survival period was only slightly longer than with bread alone; with bread and apple there was no growth, but the survival period was considerably longer; with bread and turnip there was continuous slow growth; with bread and milk there was continuous growth at a normal rate. In this case the bread and milk ration consisted of equal weights of fresh bread and market milk, making a food mixture in which the white bread furnished four fifths and the milk one fifth of the total calories. On this ration young rats of both sexes (taken at weaning time from mothers which were receiving mixed food) made normal growth and the males were capable of normal reproduction but the females usually failed to breed and none of them raised any young.

On a ration containing the same proportion of milk (about

one fifth of the total calories) but with whole wheat instead of white read or patent flour, young were successfully suckled (though at the cost of considerable loss of weight on the part of the mother) and are growing at somewhat less than the average rate.

When about two fifths of the total calories were supplied by milk and the rest by whole wheat, the mother has suckled the young without undue loss of weight and the young have made a fully normal rate of growth.

When the market milk used has been replaced by dried milk, or when it has been incorporated into the bread in bread-making and, therefore, subjected to the heating involved in the baking of the bread, there has been no evidence of any serious destruction of either "fat-soluble A" or "water-soluble B." Since the experiments were made upon rats, they would, of course, throw little if any light upon the destruction of the antiscorbutic vitamine. We plan to continue the study of the effects of heating upon the vitamines in some of the staple articles of food.

5 (1465)

The rate of change of hereditary factors in *Drosophila*.

By **H. J. MULLER** and **E. ALTENBURG**.

[*From the Rice Institute, Houston, Texas, and Columbia University, New York City.*]

A knowledge of the rate at which hereditary changes of various sorts occur is the necessary groundwork for an adequate understanding of evolution. The wide recognition given to this fact is attested to by the vast amount of literature on the subject of "variation," but, with our new exact knowledge of the Mendelian and chromosomal method of inheritance of the so-called "variations," it is evident that this literature has very little bearing on the real question of how often changes in the hereditary factors, *i.e.*, mutations, actually occur: for the breeding procedures used in the experiments there considered were not of the type necessary for ferretting out the new mutant factors as they arise, and for distinguishing between them and the apparent variations

caused by the sorting out of old mutant factors into new combinations. There is, to be sure, enough work to show that the real mutations are "rare"—whatever that term may mean; but, so far as an approximate quantitative determination of the rate of factor change is concerned, it is not possible, from the published work, to determine even its general order of magnitude. Some special scheme of crossing is required for this purpose.

In the present series of experiments with *Drosophila*, the X chromosome was chosen as the most convenient one for the detection of mutation, since every hereditary factor in either of the X chromosomes of the female fly stand revealed in the characters of one half of her male offspring, no matter what their father was. Thus, if the female has a new mutated factor in one of her X chromosomes, even though she does not usually show that factor herself, and even though her mate does not contain it, nevertheless one half of her sons are bound to show it and the mutation will thus be recognized. There is reason to believe that by far the commonest type of mutation is that which gives rise to a lethal factor—which kills the organisms containing it—and such lethal factors, also, in the X chromosome of a female, would be revealed; in this case, by the fact that half the male offspring, receiving it, would die before hatching. There would thus be half as many sons hatched as daughters, giving a sex ratio of 2 ♀ : 1 ♂, instead of 1 ♀ : 1 ♂, the usual ratio. In the first set of experiments these lethal factors were looked for primarily, by making a count of the sex ratios.

As a preliminary measure, about 90 females were bred, and the sex ratios of their progeny counted. Those families which gave a lethal, *i.e.*, 2:1, sex ratio (there were three of these) were then discarded, since there was no way of knowing, in this preliminary cross, whether these lethals had just arisen by mutation or were of ancient origin. Females from the normal families (with 1:1 sex ratio) were bred, however, since any lethal later discovered in the descendants of these flies must be due to a really new mutation, inasmuch as the ancestors had been certified as normal. It was necessary, moreover, in selecting females for breeding the next generation, not to breed many females from the same family, but to choose them from as many separate families

as possible, in order to be sure that any mutations that might be discovered later had arisen separately, and were not merely sister representatives of one original mutation. By continuing this method of breeding from separate families over five or more generations after the preliminary tests, the sex ratios in 385 families were counted. Thirteen of these were found to be 2:1 ratios; this is a proportion of one new lethal mutant among each thirty females that are bred. This figure is of a far higher magnitude than any which had been anticipated. It should be noted that at the same time as all these lethals arose, no mutations causing ordinary visible character variations were observed.

The correctness of classification of most of the thirteen lethals was verified by further breeding tests, but there were a few doubtful cases, and it was realized that ratios intermediate between 1:1 and 2:1 are sometimes brought about in other ways. Although the possible error due to these cases was not enough to change the order of magnitude of the frequency found, a new set of experiments was undertaken in which a still more definite test of lethal factors than the sex ratio was used—namely, the test of linkage to known factors in the X chromosome. The breeding procedure—having preliminary tests, breeding from many separate families, etc.—was the same as before, but instead of using pure wild type flies for the work, the following cross was made in each generation:

ratio: $\frac{w^e v f}{W V F} \text{ ♀} \times w^e v f \text{ ♂}$. In this case a lethal arising in either

X chromosome makes itself known not only by the 2:1 sex ratio, but by the practically total absence of all males containing factors on both sides of the lethal. By noting whether any expected class of males was absent, it could thus be determined whether a lethal was present, and, if so, approximately where it was located in the chromosome. 1,062 families were examined in this way, after the preliminary tests, and twenty lethals were found—a ratio of one in fifty-three. Enough work has been done on them thus far to know that they occurred in at least ten different loci scattered along the X chromosome—but this is a bare minimum. Four of the lethals (perhaps five) are more strictly speaking “semi-lethals,” as they occasionally allow the male possessing them to live (and then produce some curious morphological effects in him)

but lethal mutations are so much more frequent than the type of visible character variation ordinarily dealt with, that none of the latter were observed in the whole experiment.

The above figure of 20 in 1,062 has a probable error due to chance of about ± 3 in 1,062. There can, therefore, be no doubt about the correctness of the order of magnitude of the ratio 1:53, so far as any error caused by random sampling is concerned. The ratio 1:53 is, however, a composite result, for the families were kept in two main lots, one at about 66° F., the other at about 80°. The 445 grown at the lower temperature produced five lethals, or one in ninety; the 517 at the higher temperature produced 13 lethals, or one in forty. The other two were new lethals which occurred in the 100 bottles kept at room temperature, in which the lethals found in the two main series were being tested out. In this connection, it should be pointed out that the high ratio of one in thirty observed in the earlier experiment was obtained in bottles kept at room temperature in the warm climate of southern Texas. Although the absolute numbers of lethals are small, the difference between the two series in the later experiment is probably statistically significant,—at least, it may be calculated that if the lots had really been similar, the chances would have been about twenty to one against a difference of this magnitude occurring between figures of the given size. Taking the figures at their face value, we should obtain Q_{10} for mutation between 2 and 3, as is usual for chemical reactions.

If we accept the one in fifty-three ratio as representing the average frequency for the X chromosome, and if, as there is reason to believe, mutation occurs at the same rate in the other chromosomes as in the X chromosome, then, since the X's form about one fourth of the entire chromosome mass, we may figure that about one fly in every thirteen has a new lethal mutation in some chromosome or other. It is evident that, at this rate, without natural selection to weed out the "unfit," the race would soon become filled with lethal factors. For the X chromosome alone, since each female has two X's, and one female in fifty has a new lethal, we may figure that one X chromosome in every 100 contains a lethal factor just arisen in the present generation. Or, to put the matter differently, each X chromosome would, on the

average, tend to contain one lethal factor after 100 generations—which means about four years in *Drosophila*. The rate of change for the X in *Drosophila* is thus about one detectable mutation in four years. This immediately shows us that *Drosophila* must have a different rate from some other organisms—man for example—for if the X chromosome of man mutated at anything like a similar rate, all the X chromosomes in a female would contain several lethal factors by the time she was ready to reproduce, and none of her sons would be viable.

The rate of one mutation in four years is the rate for the whole chromosome. It is of greater interest to know the rate for the individual factors. There is good reason to believe that there are at least 500 factors in the X chromosome of *Drosophila*—probably many times that number. But, taking this undoubtedly much too low minimum figure, it is easy to see that, if 500 factors show only one mutation in four years, each individual factor must on the average show a change in its composition only once in 2,000 years. (Yet this is in the mutable *Drosophila*.) It will be interesting to observe the difference in mutation rate in different organisms and under different conditions.

6 (1466)

The influence of lactic acid upon the metabolism of the dog.¹

By GRAHAM LUSK and H. V. ATKINSON.

[From the Physiological Laboratory, Cornell University Medical College.]

Lactic acid, when given to a dog, causes the same increase in metabolism that is noticed when a similar amount of alanin is administered. It was also noted that the metabolism was increased after giving 500 c.c. of water in which there was 2.5 c.c. of Liebig's extract of beef, whereas the administration of 150 c.c. of water had no influence whatever. When a large quantity of water was given about 100 c.c. per hour were eliminated in the urine. This indicates that for the transport of a large volume of fluid through the circulation increased energy is needed.

¹ A brief report of this work was also published in the *Compt. rendus de l'academie des sciences*, 1919, 168, No. 20, 1012.

7 (1467)

**Rejuvenescence without encystment and without nuclear fusion
in Uroleptus?**

By GARY N. CALKINS.

[From the Department of Zoölogy, Columbia University.]

Experiments made during the last two years on *Uroleptus mobilis* have shown that renewal of vitality follows conjugation, both parents, coming from the same protoplasm and all kept under identical conditions of food and environment. It was also shown that asexual reorganization occurring during encystment, likewise results in rejuvenescence.

It was argued that, since the only Mommon phenomenon in conjugation and encystment is the nuclear dissolution and absorption in the protoplasm, the renewal of vitality after each is due to the chemical and physical changes in the protoplasm set up by the addition of relatively large quantities of nucleoproteins added to it. To test this working hypothesis the following experiments were undertaken last April and May. Individuals of the same ancestry (P series) in the 140th generation, were allowed to conjugate; a normal ex-conjugant was isolated (V series), and this, with the parent P series, were maintained as controls, the latter to show the degree of vitality without conjugation, the former to show the effect of conjugation. Other pairs of conjugating individuals were isolated in a minute drop of culture medium, a pair at a time, and cut with a scalpel across the angle of the V made by the two individuals in conjugation. The detached angle of the V and one of the arms of the V were immediately fixed and stained to determine the stage of conjugation at the time of cutting. The other part was isolated in culture medium and set aside for observation. Seven pairs were successfully cut in this way, and in the desired plane; four of these died within 10 days, three continued to live forming the X series, the X6 series, and the X7 series.

The period required for reorganization of the normal individual after conjugation and prior to the first cell division, varies from

3 to 6 days and the process may be watched in the living cell in which the changes of the nucleus are clearly visible. The individual forming the V series required seven days for this reorganization.

It was most unexpected and interesting to find that the cut individuals invariably went through the same nuclear reorganization states as those of a normal ex-conjugant. If they died, death was always at the last phase of the reorganization process. The individuals destined to live and form the X series, the X6 series, and the X7 series, required eight, nine, and eight days respectively before the first division of the young cells. From the start each series represented by five different lines, was carried on in culture like any normal ex-conjugant series, with similar records of the daily division rate, the average rate for ten days, and the average rate for the first and second sixty day periods. The results for the four months following the operations are given in the following table.

AVERAGE DIVISION RATES IN 10-DAY PERIODS, OF CONTROLS AND EXPERIMENTAL SERIES.

	Parent P Series Non- conju- gant.	Filial V Series Ex-con- jugant.	X Series Cut Conju- gating.	V Series Control Ex-con- jugant.	P Series Control Non- conju- gant.	X 6 Series Cut Conju- gating.	X 7 Series Cut Conju- gating.	V Series Control Ex-con- jugant.	P Series Control Non- conju- gant.
1st " "	13.6	13.8	8.8	13.8	13.2	15.8	17.6	18.2	12.4
2d " "	12.8	16.0	9.4	14.6	10.0	13.3	16.4	16.8	12.2
3d " "	13.2	13.8	13.4	18.2	12.4	15.8	18.6	18.2	16.8
4th " "	10.0	14.6	13.4	16.8	12.2	14.0	15.8	14.8	13.2
5th " "	12.4	18.2	14.2	18.2	16.8	13.2	15.4	17.0	16.4
6th " "	12.2	16.8	12.0	14.8	13.2	14.0	16.8	16.6	14.4
1st 60 "	12.4	15.5	11.9	16.0	12.9	14.3	16.8	16.9	14.2
2d 60 "	14.2	16.3	12.5	14.8	11.5	10.3	12.0	12.9	7.7
Average 120 days.	13.3	15.9	12.2	15.4	12.2	12.3	14.4	14.9	10.9

It has been shown in an earlier paper¹ that the extent of rejuvenescence as indicated by the division rate, varies with the age of the parent series at the time of conjugation. The greater the vitality of the parent series the less is the difference in vitality between parent and filial series. For example, if the filial series starts by a conjugation occurring during the first 60 days (ap-

¹ Calkins, "*Uroleptus mobilis*. II. The Renewal of Vitality through Conjugation." *Jour. Exper. Zool.*, Vol. 29, No. 1, 1919.

proximately 100 generations) the average difference in vitality amounts to only 1.5 divisions in 10 days for the first 60-day period of the offspring. If the filial generation starts from a parent series which is 130 to 200 generations old, the difference in vitality between parent and offspring increases to between 3 and 4 divisions in 10 days, and if the filial generation starts from a parent series that is about 300 generations old, the difference in vitality rises to a maximum of 17 or more divisions in 10 days.

In the present experiments the parent P series was in the 140th generation when the filial V series was started, and in the 160th generation when X6 and X7 were cut. The difference in vitality between the V series and the P series, 3.1 divisions in 10 days for the first 60 days, agrees with the results obtained with all ex-conjugants started at corresponding periods of the parent cycle, and shows the normal rejuvenating effects of conjugation.

The cut conjugants show different results in regard to renewal of vitality. The X series shows no rejuvenescence at all but agrees with the non-conjugant P series throughout. The X6 series agrees with the non-conjugant P series in the first 60-day period but has a higher average division rate for the second 60-day period, while its average for four months is intermediate between the non-conjugant P series and the ex-conjugant V series. The X7 series, on the other hand, shows for the entire period the same vitality as the ex-conjugant V series and gives the same evidence of rejuvenescence.

These three divergent cases are difficult to interpret. Each recovered perfectly after the operation; each underwent reorganization processes apparently identical with those of normal ex-conjugants; each gave rise to a population similar to that of a normal ex-conjugant except that in none of them have I seen a case of encystment; epidemics of conjugation have been frequent in each of these populations.

A possible explanation may be found in the fact that the conjugating pairs which were operated upon to give the X, X6, and X7 series were cut at different phases of the process of conjugation. In none of them had nuclear interchange taken place. One pair was cut at the very outset of conjugation; this gave rise to the X series which showed no rejuvenescence. Another pair was cut

at the stage of the first maturation spindles; this gave rise to the X6 series with evidence of partial rejuvenescence. The third pair was cut at the stage of the second maturation division and this gave rise to the X7 series which showed the same rejuvenescence as the normal ex-conjugant from the same source.

Many more experiments of the same nature are now under way and must be carried out before conclusions can be drawn. These three cases indicate, however, that the absorption of nucleo-proteins in the cytoplasm and which occurred in all cases, is not, by itself at least, the secret of renewed vitality.

8 (1468)

The total carbonate content of the arterial and venous plasma in normal individuals.

By **R. W. SCOTT** (by invitation).

[*From the Department of Medicine, School of Medicine, Western Reserve University, Cleveland.*]

In the course of some observations on the respiratory disturbances seen in certain diseased conditions it became necessary for the sake of comparison to determine the total carbon dioxide of the arterial and venous plasma in individuals with normal cardio-respiratory mechanisms. In all the bloods of nineteen normal individuals at rest have been examined. In each case samples of arterial and venous blood were obtained within a few minutes of each other.

Method.—The arterial blood was obtained by direct puncture of the radial artery using a technique similar to that employed by Stadie.¹ The venous blood was collected without stasis from one of the large veins at the bend of the elbow. To avoid contact with air both samples were carefully delivered under albolene into paraffin coated centrifuge tubes and immediately centrifuged at high speed. One c.c. of the separated plasma was delivered under carbonate free ammonia water contained in a receiving cup

¹ Stadie, W. C., *J. Exp. Med.*, 1919, XXX, 215.

of the Van Slyke apparatus and the total CO₂ content determined by the method devised by Van Slyke.¹ The method adopted was considered to be more advantageous for my purpose than the widely used method of first exposing plasma to 5.5 per cent. of CO₂ and ascertaining the CO₂ combining power.

Results: The results presented in the accompanying table indicate that the total CO₂ content of the arterial plasma is a fairly constant figure, averaging fifty-six volumes per cent. The venous plasma is always a little higher than the arterial in individual cases, the discrepancy being from three to eight volumes per cent. This discrepancy has been found to increase if the individual is allowed to take some light exercise, such as walking, just before the blood samples are taken. Under these conditions the arterial figures remain about normal while the venous are from twelve to fifteen volumes higher.

THE TOTAL CARBONATE CONTENT OF THE ARTERIAL AND VENOUS PLASMA OF NORMAL INDIVIDUALS AT REST.

CO₂ reduced to 0°-760 mm. in 100 c.c. plasma.

Arterial	Venous	Arterial	Venous
c.c.	c.c.	c.c.	c.c.
62.0	66.0	55.0	61.0
57.8	64.4	58.0	61.4
54.0	61.0	57.5	62.8
59.1	67.2	62.8	65.4
54.9	62.2	53.4	60.0
58.1	64.2	59.0	65.7
2.7	59.9	60.3	67.4
57.5	61.5	54.9	62.2
55.7	61.0	60.5	68.9
51.5	59.9		

9 (1469)

The total carbonate content of the arterial and venous plasma in patients with chronic heart disease.

By R. W. SCOTT (by invitation).

[From the Department of Medicine, School of Medicine, Western Reserve University, Cleveland.]

Twenty-eight determinations of the total carbon dioxide content of the arterial and venous plasma have been made on ten

¹ Van Slyke, D. D., *J. Biol. Chem.*, 1917, XXX, 347.

individuals with chronic heart disease. All patients in this group have been carefully selected because they were suffering primarily from a failure of the heart to maintain an adequate circulation. They have been free as far as could be determined from any vascular or renal disease. For the most part they were young patients with chronic rheumatic myocarditis and valvulitis.

In some a normal cardiac mechanism was present, as determined by the electrocardiograph. In others auricular fibrillation usually associated with mitral stenosis was found. Moribund patients and patients with a marked degree of venous stasis and edema have not been included.

Samples of the arterial and venous blood were obtained at the same operation; immediately centrifuged, and the total CO₂ content of the separated plasma determined directly. In all cases the blood was obtained while the patient was at rest in bed. The results are presented in the accompanying table.

THE TOTAL CARBONATE CONTENT OF THE ARTERIAL AND VENOUS PLASMA IN PATIENTS WITH CHRONIC HEART DISEASE.

CO₂ reduced to 0°-760 mm. in 100 c.c. plasma.

Arterial	Venous	Arterial	Venous
c.c.	c.c.	c.c.	c.c.
42.8	50.6	32.0	44.5
33.7	37.3	41.6	48.4
38.2	50.3	48.5	54.2
47.6	52.5	39.7	44.6
46.9	50.6	51.0	63.0

It is seen that both the arterial and venous plasma have a total CO₂ lower than that found in normal individuals. The arterial values for CO₂ show wider variation and the discrepancy between the CO₂ of the arterial and venous plasma is more marked in heart cases than in normal individuals. These differences are attributed to the varying degrees of cardiac efficiency in the heart patients.

In the type of cases studied there has been a certain relation between the integrity of the circulation and the level of CO₂ in the plasma. The more dyspneic the patient the lower has been the CO₂ in the arterial plasma. The following case will serve as an example: A patient walked into the hospital complaining of

shortness of breath. On examination a moderate cardiac enlargement with mitral stenosis and auricular fibrillation was found. The CO_2 of the arterial plasma was thirty-eight volumes per cent. Five days later when he was much improved the CO_2 of the arterial plasma had increased to forty-nine volumes per cent.

The results of this study seem to indicate that when the minute volume of air respired at rest is definitely above normal (10 to 12 liters) the plasma CO_2 is low. With improvement in the circulation and the accompanying fall in the minute volume the CO_2 of the arterial plasma shows a definite increase toward the normal.

10 (1470)

The total carbonate content of the arterial and venous plasma in patients with chronic pulmonary emphysema.

By **R. W. SCOTT** (by invitation).

[From the Department of Medicine, School of Medicine, Western Reserve University, Cleveland.]

This study represents six determinations of the total carbon dioxide content of the arterial and venous plasma over a period of six months on three patients with chronic pulmonary emphysema of the so-called "large lunged" type. The patients were males between forty-five and fifty years of age with definite enlargements in all diameters of the thorax, particularly the anterior-posterior diameter; thus presenting the typical "barrel shaped" chest. They were singularly free from cardio-renal disease so that all their symptoms and signs were attributed to the disturbance in the respiration resulting from the degenerative process in the lung. From observations to be reported in detail elsewhere, it has been found that this type of patient will tolerate an unusually high percentage of CO_2 in the inspired air with little increase in the minute volume over that at room air and without any subjective symptoms of distress. As a rule such patients breath eight to ten per cent. CO_2 for from ten to fifteen minutes with no apparent discomfort. That is, one man who has been under observation for the past nine months had a

respiratory rate of twenty-two and a minute volume of ten liters while breathing room air. During an experiment in which air containing 11.4 per cent. CO₂ was inspired for a period of six minutes, the respiratory rate remained at twenty-two and the minute volume increased to only fourteen liters. At this high concentration of inspired CO₂ the patient complained of a little dizziness and nausea which disappeared when he was allowed to breath room air for a few minutes.

In an attempt to explain the unusual tolerance to CO₂ in the inspired air shown by the type of case described, the CO₂ content of the arterial and venous plasma of three patients have been determined and found to be consistently above normal as indicated by the data in the accompanying table.

TABLE.

THE TOTAL CARBONATE CONTENT OF THE ARTERIAL AND VENOUS PLASMA IN THREE PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA.

CO₂ reduced to 0°-760 mm. in 100 c.c. plasma.

Arterial	Venous	Arterial	Venous
c.c.	c.c.	c.c.	c.c.
76.1	82.7	80.2	88.4
72.4	78.4	70.2	76.4
71.0	76.0	74.5	80.2

II (1471)

Concerning the influence of antipyretics on the acuity of hearing.

By D. I. MACHT, J. P. GREENBERG and S. ISAACS.

[From the Johns Hopkins University, Baltimore, Md.]

In connection with an extensive pharmacological and psychological study of antipyretic drugs, the effect of same was tried on the acuity of hearing. Experiments were performed on normal human subjects, and in a few cases on persons suffering with mild deafness. The tests were made, by means of a watch, in a quiet room, with the subject in a sitting position; and all necessary controls were carried out for the elimination of error. In every experiment the normal limit of hearing was first determined; the drug to be studied was then administered by mouth; and the

acuity was afterwards tested at definite intervals of time. Only therapeutic doses of the drugs were administered. The following substances were studied: acetanilid, acetphenetidin, antipyrin, pyramidon, lactophenin, salol, aspirin, quinin, sodium salicylate, and "melubrin." After studying the effects of individual drugs, certain combinations were administered. The following were among the combinations studied: acetanilid plus sodium bicarbonate, acetphenetidin plus salol, acetanilid plus salol, acetanilid plus acetphenetidin, antipyrin plus aspirin, and antipyrin plus salol.

The results obtained were both interesting and unexpected. It was found that some drugs decrease the acuity of hearing while others increase it. Furthermore, it was found that certain combinations of antipyretics produce synergistic effects not explainable by the simple arithmetical sum of the effects produced by the components individually. Among the agents found to decrease the acuity of hearing were acetanilid, salol, and aspirin. Among those found to increase the hearing were antipyrin, pyramidon, and small doses of quinin. Among the most remarkable combinations studied were those of acetanilid plus sodium bicarbonate and acetanilid plus salol. It was established that whereas acetanilid given alone decreases the acuity of hearing, and ordinary doses of sodium bicarbonate given alone produce no change; a combination of the two produced a definite improvement in the acuity of auditory perception. Again, whereas acetanilid and salol when administered separately, each by itself tends to impair the hearing, a combination of the two actually increases the acuity of perception. The peculiar synergism of acetanilid with sodium bicarbonate recalls the experiments of Hale who called attention to the fact that such a combination is less toxic for animals than the same dose of acetanilid given alone. Experiments are in progress with a view to attempt an explanation of this peculiar synergism, and complete data of the research will be published in due time.

12 (1472)

Serologic method for detecting infection in foods.By **J. BRONFENBRENNER** and **M. J. SCHLESINGER**.

[From the Department of Preventive Medicine and Hygiene, Harvard Medical School.]

The isolation and identification of the infecting organism in contaminated foods is usually beset with difficulties and successful results are not the usual outcome. Negative findings often are due to the fact that it is impossible to examine the whole sample of the incriminated food bacteriologically. Since the pathogenic bacteria are usually few in number, and are not distributed throughout the food, it is more or less a matter of luck if one succeeds in isolating an organism which might justify the suspicions. If one attempts to increase the number of the specific bacteria by enrichment through incubation, he at the same time increases the number of saphrophytes, and thus adds to his difficulties. We find that the entire sample of suspected food can be advantageously analyzed for the presence of any suspected organism, or their split products (in addition to an attempt to isolate individual bacteria), by the following procedure.

The whole of the sample of food is chopped up and an extract made from it. This extract is concentrated so that all the specific bacterial protein is collected in a very small volume of liquid.¹ This concentrated solution is then tested against a set of specific immune sera. We have been able to detect by this method the presence of *B. botulinus* protein in 20 gram samples of artificially inoculated food, where the concentration of toxin was so small that it would have required giving at least 7 grams by mouth or 1.3 grams by injection into a mouse of 15-20 grams to obtain a positive result.

This method enables one to determine the presence of a suspected organism in contaminated food within 24 hours after receiving the specimen. It is, of course, necessary to have on hand a collection of specific sera of high titer.

¹ J. Bronfenbrenner and M. J. Schlesinger, *Jour. Med. Res.* (in press).

(This work is a part of the investigation of food poisoning, conducted under the direction of Dr. M. J. Rosenau, professor of preventive medicine and hygiene, Harvard Medical School. The investigations are done under the auspices of the Advisory Committee of the National Research Council on the Toxicity of Preserved Foods, and under a grant to Harvard University from the National Canners' Association.)

13 (1473)

On methods of isolation and identification of the members of the colon-typhoid group of bacteria. Further studies on *C. R. indicator*.

By **J. BRONFENBRENNER, D. SOLETSKY** and **M. J. SCHLESINGER.**

[From the Department of Preventive Medicine and Hygiene, Harvard Medical School.]

Some time ago we described an indicator for the direct measurement of the hydrogen ion concentration in growing bacterial cultures.¹ This indicator consists of the mixture of China blue and rosolic acid, and covers the range of changes in the hydrogen ion concentration between $C_H = 1 \times 10^{-9}$ and $C_H = 5 \times 10^{-5}$. The choice of the dyes was made on the basis of their possessing suitable turning points coupled with the fact that their respective phases of highest color lie on the opposite sides of the point of neutrality. China blue is colorless at the concentration of hydrogen ions below 1×10^{-7} , and gives graded intensity of blue with the increase in the hydrogen ion concentration up to the point of about $C_H = 5 \times 10^{-5}$, when it reaches its maximum color. Rosolic acid, on the other hand, gives graded intensities of pink beginning with the hydrogen ion concentration close to 1×10^{-7} , and increasing gradually with the increase of the hydroxyl ions concentration reaching its maximum color at the $C_{OH} = 1 \times 10^{-5}$ (or $C_H = 1 \times 10^{-9}$). With the increase in concentration of hydrogen ions above 1×10^{-7} the rosolic acid has a pale yellow (straw) color, which is masked by the color of ordinary culture media.

¹ J. Bronfenbrenner, *Jour. Med. Res.*, XXXIX, I, 25, 1918.

The combination of the two dyes thus offers an indicator which has a faint gray tinge at the neutral point with pure blue and pink on the acid and alkaline sides respectively. Due to the high tinctorial power of the dyes composing it, this indicator is incorporated into the media in very minute quantities. The actual concentrations of China blue and rosolic acid in the medium are respectively 0.0025 per cent. and 0.005 per cent. by weight.

This indicator, however, can be used only for the study of the Gram negative organisms, because the rosolic acid it contains exerts selective bactericidal action against the Gram positive organisms.¹ While this property of the rosolic acid is useful in certain circumstances (as for instance, for the purpose of suppressing Gram positive bacteria while isolating the Gram negative from the mixtures of both)², it limits the usefulness of the mixture as an indicator. In order to permit the use of our indicator in the study of Gram positive as well as Gram negative bacteria, we suggest the substitution of corallin (Harmer) for the rosolic acid (Merk) in the above mixture. The turning point of corallin is the same as that of rosolic acid, and its tinctorial power, as well as the color, are much the same: Corallin (Harmer), however, has no bactericidal action upon Gram positive organisms.

As the supply of either China blue, rosolic acid or corallin of foreign manufacture is very low at present, and as the domestic dyes sold under the same names are manifestly different from the foreign dyes used by us, it was necessary to try a number of related dyes before a suitable choice could be made. While this work is still in progress, we have already found a few preparations which seem to answer the requirements.

(This work is a part of the investigation of food poisoning, conducted under the direction of Dr. M. J. Rosenau, professor of preventive medicine and hygiene, Harvard Medical School. The investigations are done under the auspices of the Advisory Committee of the National Research Council on the Toxicity of Preserved Foods, and under a grant to Harvard University from the National Cannery Association.)

¹ J. Bronfenbrenner, M. J. Schlesinger and D. Soletsky, *Jour. Bact.* (in press).

² J. Bronfenbrenner, M. J. Schlesinger and D. Soletsky, *Jour. Med. Res.* (in press).

14 (1474)

The protein and lipin content of blood serum of nephritic patients.By **MAX KAHN.**

[From the Department of Laboratories, Beth Israel Hospital, New York City.]

It has been reported by Erben,¹ in 1902-3, that in the serum of patients suffering from chronic parenchymatous nephritis, the albumin-globulin ratio (which, normally is about 1.5-2.0 : 1) is entirely disturbed, the figure being 0.2593 of albumin to 7.0352 of globulin. This deviation in the ratio was confirmed by Epstein,² in 1912. The latter author (basing his conclusion on his analyses of nine cases of chronic parenchymatous nephritis, in whom, besides the globulin increase, he also found a huge amount of cholesterol in the serum) propounded the following theory of the etiology of certain cases of chronic parenchymatous nephritis. According to him, there is a group among the cases of chronic parenchymatous nephritis which is due to a constitutional disorder—of a metabolic or endocrinic nature—in which the renal manifestations are concomitant or secondary in point of development and importance. He does not, however, describe cases of chronic parenchymatous nephritis in whom the protein or lipin fractions should vary from the so-called “metabolic” type, and which he should point out as “non-metabolic” in nature.

In the series of cases investigated, the writer did not find one case of the so-called “metabolic or endocrinic” type of chronic parenchymatous nephritis, which would seem to indicate that the type described by Epstein is very rarely met with.³ The albumin-globulin ratio does not seem to be markedly disturbed by various diseases. Feeding of patients suffering with chronic parenchymatous nephritis on a protein-rich, fat-poor diet is a rather risky undertaking.

¹ Erben, *Zeit. f. klin. Med.*, 1903 XLVIII, 450.

² Epstein, *Am. J. Med. Sc.*, 1917, CLIV, 638.

³ Epstein does not state what percentage of the cases of chronic parenchymatous nephritis are of his so-called “metabolic or endocrinic” group.

15 (1475)

Method and results of a study of the distribution of iodine between cells and colloid of thyroid glands.

By **ARTHUR L. TATUM** (by invitation).

[*From the Laboratory of Physiological Chemistry and Pharmacology, University of Chicago.*]

Method.—Use was made of the fact that from frozen sections, as prepared for histological study of fresh unfixed tissues, the colloid of the thyroid gland completely disappears out of the acini when the sections are floated in physiological salt solution. The sections were picked out by means of a needle, washed in another solution of salt solution, dried at 105° C., weighed and analysed for iodine by the technique of Kendall. The iodine in the colloid portion was sometimes determined by evaporation of the salt solution containing the colloid, and at other times differentially by analysis of the whole dried gland.

Results.—In a series of about thirty experiments on dogs' thyroids the thyroid iodine was found in the majority of instances to be wholly in the colloid as the cell portion was free from iodine. In a smaller percentage of cases the cell mass gave only qualitative tests for iodine, which at the present stage of this investigation might be considered due to unopened small acini.

The physiological significance of these findings is being investigated.

16 (1476)

On the certain dietary factors to be considered in the treatment of cases of hyperthyroidism.

By **JACOB ROSENBLOOM**.

[*From the Laboratory of Dr. Jacob Rosenbloom, Pittsburgh, Pa.*]

The writer has obtained clinical evidence that in formulating a diet for patients suffering from hyperthyroidism, two important factors must be considered; first, the diet should contain the minimum amount of protein and second, foods low in iodine content should be selected.

SCIENTIFIC PROCEEDINGS

ABSTRACTS OF COMMUNICATIONS.

One hundred second meeting.

New York Post Graduate Medical School, New York City, November 19, 1919. President Calkins in the chair.

17 (1477)

Blood sugar curves with glucose, lactose, maltose, mannite, and cane sugar.

By **CYRUS W. FIELD.**

These curves were obtained by feeding normal males colored, with 100 grams of the pure sugar, on a fasting stomach. The dose was as a rule given after the first sample of blood had been taken; this was as a rule at 8 A.M. The second, third and fourth samples were taken one, two and three hours after the ingestion of the sugar, which had been dissolved in a large glass of water.

The urines were tested for glucose up to three hours after the last sample of blood had been taken, and in none of the cases did a specimen ever show the slightest trace of a reducing substance with Benedict's qualitative solution.

The glucose curve was that with which all are familiar, that is rising to its highest point one hour after the ingestion, and then dropping to the normal at the end of the next hour or two.

Maltose gave the same curve as the glucose. Mannite gave the same time curve as the glucose, and maltose, but did not rise to the same height as the other two; the average of five cases gave an increase of only 10 milligrams per 100 c.c. of blood, while that for glucose was 40 milligrams, and for maltose 34 milligrams.

Cane sugar showed a curve that reached its height at the end of the second hour after its ingestion, and had dropped to normal at the third hour. Its average rise for 10 cases was 20 milligrams

per 100 c.c. of blood. Lactose shows only a very slight rise, 4 milligrams, and that at the end of the second hour, as was the case with the other disachrade, cane sugar. I have been unable to consult the literature and so will offer the figures for what they are worth.

18 (1478)

The bacteriology of infectious gaseous gangrene.

By **MARSHALL C. PEASE.**

[From the New York Post-Graduate Medical School.]

Infectious gaseous gangrene can no longer be conceived of as being necessarily a monomicrobic disease. On the contrary it is frequently the result of an association of bacteria, not all of which are by themselves pathogenic or even under the most favorable condition of animal inoculation capable of causing a pathological lesion. The causative agents of infectious gaseous gangrene are found in a certain group of anaërobes, all of which are capable of elaborating a powerful toxin which has not only a local but also a systemic action. Death in gaseous gangrene is not the direct result of the local lesion but of the absorption of toxin into the general circulation with a consequent general toxemia.

The spread of the local lesion is dependent upon local tissue necrosis. The tissue necrosis in turn is dependent upon the elaboration of bacterial toxins, which are distributed along the line of the muscle sheaths and fascia, and through the lymph spaces. There is no evidence that the toxin producing the local tissue necrosis differs from the toxin which is the cause of the general toxemia. If for any reason toxins are not elaborated within the wound or are not absorbed from the wound a gaseous gangrene does not develop despite the fact that there may be within the wound a large number of potentially pathogenic anaërobes.

All the aërobes can be dismissed as a cause of infectious gaseous gangrene. Any effects which they produce are in the nature of a complication. At the most their rôle in this disease process is confined to the absorption of oxygen, the turning upon

themselves of the processes which tend to produce an immunity and in causing the death of tissue thus preparing a favorable media for the multiplication of the anaërobes. They have never been isolated in pure culture from a case of infectious gaseous gangrene and have never produced typical lesions when inoculated into animals.

There are a number of anaërobes which cause characteristic lesion in animal inoculations and one or more of which are always isolated from cases of gaseous gangrene. In the following arrangement the organisms that are found in cases of gaseous gangrene are grouped with regard to their importance as causal agents of infectious gaseous gangrene; and there is in addition an indication of their main action toward the carbohydrates and proteids.

GROUP I.

Essential Causal Agents of Gaseous Gangrene.

Saccharolytic:

1. *Vibrion septique.*
2. *B. œdematiens (B. Novyii).*
3. *B. welchii.*

Proteolytic:

- B. histolyticus.*

GROUP II.

Accessory Agents of Gaseous Gangrene.

Comprises organisms capable of causing gaseous phlegmons (even of a severe type). Probably rarely or never an essential agent of gaseous gangrene. Important in association with the essential causal agents and generally unimportant when occurring alone.

I. Anaërobes:

A. Proteolytic group:

- B. sporogenes.*
B. aërofaxidus.

B. Saccharolytic group:

- B. fallax.*

II. Aërobes:

- B. coli.*

B. proteus.

(Both very doubtful as causal agents of true gaseous gangrene.)

GROUP III.

Organisms Merely Present in Gaseous Gangrene.

Never essential causal agents, though they may be capable of causing complications; and may have an importance in symbiosis with other organisms; and may be a cause of a great modification of the clinical picture.

A. Anaërobes:

Proteolytic:

B. putrificus.

B. bifermentans (also has a powerful saccharolytic action).

B. tetani.

B. tertius.

B. Aërobes.

Cocci:

Streptococci, staphylococci and diplococci.

Bacilli. (Gram negative.)

B. proteus, coli, pyocyaneus, etc.

Bacilli. (Gram positive.)

B. anthracoides group

B. subtilis group

B. mesentericus and *myscoides* group, etc.

The pathogenicity of this entire series exhibits great variation. There are strains of *B. welchii* and *B. œdematiens* that have almost no virulence. The *B. welchii* is notable in this respect, a few strains showing great pathogenicity, while many others have little or none; and the average is not sufficiently high to make it an easy matter to produce an antitoxin of high titer. Under exceptional circumstances the *B. sporogenes*, *fallax* and *aërofœtidus* are capable of producing a lesion alone, though as a rule these lesions are of a benign character of a type of a gaseous phlegmon. In infectious gaseous gangrene these organisms are commonly associated with organisms of greater pathogenicity such as the *B. welchii* or *œdematiens*, so that their rôle approaches that of accessory micro-

organisms. In a bacteriological analysis of 308 cases of gaseous gangrene, of which 91 were derived from Weinberg's series and 217 from wounded American soldiers, the percentage of incidence of the various pathogenic anaërobes is as follows:

	Per Cent.
<i>B. welchii</i>	85
<i>B. sporogenes</i>	35.4
<i>B. œdematiens</i>	12.6
<i>Vibrio septique</i>	17.2
<i>B. fallax</i>	6.4

This is not the true incidence of the *B. œdematiens*, *fallax*, *histolyticus* or *aërofœtidus* as the difficulties in the isolation of these organisms in pure culture is great, but it does serve to emphasize the fact that infectious gaseous gangrene is usually a mixed infection.

In this group of 308 cases of infectious gaseous gangrene only 79 were infected with a single pathogenic anaërobes, the remaining 229 having from two to six anaërobes in the local lesion, and nearly always at least two pathogenic anaërobes.

19, (1479)

Hydration effects of amino-compounds.

By D. T. MACDOUGAL and H. A. SPOEHR.

[From Desert Laboratory, Tucson, Arizona.]

The chief interest in the results presented in this brief paper depends upon the following facts and conditions:

A. The amino-compounds furnish the only known solutions in which agar and other pentosans or mucilages undergo a greater hydration than in distilled water. Tentative conclusions to this effect have been confirmed by all of the results obtained during the past year.¹

B. The pentosans, or anhydrides of the 5-carbon sugars are universally and abundantly present in plant cells, originating by transformations of wall-material, starch, etc., in any part of

¹ MacDougal, D. T. and H. A. Spoehr, "The effect of organic acids and their amino-compounds on the hydration of agar and on a biocolloid," PROC. SOC. FOR EXPER. BIOL. AND MED., 1918, xvi: 33-35.

the protoplast, and presumably intimately interwoven into its colloidal mesh. In animals the pentosans seem to be confined to the nucleo-proteins, and the manner of their origin is not so clear in this case.

C. The mucilages, gums and slimes in which form these substances appear in definite masses in syneretic cavities and in layers in the plant cell have a hydration capacity enormously greater than that of the sugars from which they are derived, and show a wide range of solubility and other qualities.

D. The pentosans are subject to digestion in animals to an extent variously assigned by different authors. These substances undergo metabolic changes in the plant but slowly. Wherever they occur they must show changes in volume and form according to the colloidal structure in which they occur and to the nature of the solutions penetrating them.

Our own experimentation has been made principally with agar and some of the common plant gums, separately and in mixtures with albumins. The revised generalizations which we are prepared to support may be briefly stated in the following summary:

1. The pentosans are weak acids which dissociate so slightly that 1 per cent. solutions of agar, acacia and cherry gum showed pH values of 5.1 as determined by the indicator method. The mucilage of *Opuntia* showed a value of 5.8. The swelling of these substances in the amino-acids which dissociate strongly, as aspartic acid which shows a pH of 3 at 0.01 *M* is less than in water.

2. Such acids and other amino compounds as asparagin, pH = 6.2, alanin pH = 7.0, phenyl-alanin pH = 4.8, glycocoll pH = 6.2 at 0.01 *M* as tested by the indicator method, ammonium hydroxide and ethylamine facilitated the hydration of agar so that it showed swellings greater than in distilled water.

3. Other factors than the hydrogen ion concentration are determinative in this action as illustrated by the fact that swellings in phenyl-alanin and glycocoll are fairly equal. The total swelling of agar as compared with that in water as unity was 1.26 in asparagin, 1.52 in alanine, 1.65 in glycocoll and in phenyl-alanin, in ammonium hydroxide and in ethylamine, all in 0.01 *M* solutions. Propionamide the only amide tested did not exert any marked effect on swelling except to retard it slightly at 0.01 *M* and in stronger solutions.

4. Glycocoll was used in extending these experiments, and it was found to exert an accelerating effect on agar when mixed with soy bean albumin, gelatine and similar increases were also shown when the agar was partly replaced by such mucilages as that from *Opuntia*, acacia and cherry gum.

5. Living and dried sections of tomato fruits, growing cell-masses of stems of *Phytolacca*, and joints of *Opuntia*, the cell-sap of which has varying acidity, showed the greatest swellings in alanin, phenyl-alanin, glycocoll and ammonium hydroxide as compared with results in water and organic acids, with but few exceptions. Taking water as unity living sections of *Opuntia discata* showed swellings of 1. in alanin, 1.5 in phenyl-alanin, and an equal increase in glycocoll. Dried sections of the same material showed swellings of 1.3 in alanin, 1 in phenyl-alanin, and 1.4 in glycocoll solutions. Living sections of *Opuntia leptocaulis* swelled 1.4 in alanin, 1.2 in phenyl-alanin, 1.55 in ethylamine, while dried sections of this species gave increases of 2 in alanin and 1.5 in ammonium hydroxide and 2.2 in phenyl-alanin as compared with water.

6. The swellings or increases due to hydration were determined by the use of the auxograph. It has been found that the hydration of dried sections of such pentosans as agar causes changes which are the reverse of those which ensue during desiccation. Plates of this substance poured from a warm 2.5 per cent. solution, which were fastened at the margin in such manner as to prevent shrinkage in area and to allow decrease in thickness only, when swelled showed increases of not more than 4 and generally as little as 2 per cent. laterally, while swelling 4,000 per cent. in thickness.

7. Sections of gelatine from plates cast in the above manner may show a lateral expansion of 8 to 40 per cent. while swelling 500 to 2,000 per cent. in thickness, in water and in acid solutions with a pH value of 2.

8. The swelling of gelatine which showed a pH value of 5.2 in an 8 per cent. solution in nitric and hydrochloric acid at a pH value of 2, in succinic acid (0.01N) at a pH value of 3.05 and in amino-succinic acid (aspartic acid) at a pH value of 3 was much greater than water, but the swelling in alanin, phenyl-alanin and glycocoll was less than that in water.

9. The pentosans on the one hand and the albuminous compounds on the other are intimately intermixed or interwoven in the protoplast of the plant and in the nucleus of the animal cell. The conditions which accelerate the hydration of the first may not affect the volume of the other except to cause a slight shrinkage. The effect of the hydrogen ion is to increase the hydration capacity of albumin and its derivatives, while lessening the hydration of the carbohydrates.

10. In addition to these differential effects of the solutions upon the principal components of the plasmatic colloids, the changes in volume are not isotropic but may be determined by the manner in which the mesh, masses of colloidal material or organs of the protoplast are laid down or fall into place. These two classes of variables may well be considered as prolific sources of differentiation in the procedure of the cell.

20 (1480)

Profound effects of digitalis on the vagus producing severe detrimental subjective symptoms, as shown by simultaneous electro-cardiograms and pneumograms.

By **ROBERT H. HALSEY** (by invitation).

[From the New York Post-Graduate Medical School.]

In a case of syphilis, chronic interstitial nephritis, dilatation and hypertrophy of the heart, auricular fibrillation, arteriosclerosis, periodic breathing, Cheyne-Stokes type, in which because the auricle was fibrillating, digitalis had been given for the purpose of showing the ventricular rate. Counts of the pulse showed the ventricle to be contracting at a rate approximating 100 during apnea and slowing to about half this rate as soon as hyperpnea began. That is, the heart rate was highest while there was no lung ventilation (apnea) and the heart beat less frequently during the period the lung ventilation was greatest (hyperpnea).

As the digitalis was continued the man complained of increasing distress, most severe during his hyperpnea. The ventricle rate did not become slower and evidently the patient was much more uncomfortable. The thought occurred that releasing the heart

from vagus control might give relief, therefore, atropine gr. 1/30 was given by hypodermic injection. Record taken 27 minutes later shows the ventricle beating irregularly at the rate of 150 per minute but uninfluenced by breathing. The patient became comfortable and the cyanosis was less.

Discussion.—As the slowing of the ventricular rate followed the first inspiration after apnea and was maintained until the last part of the hyperpnea stage, it was considered to be due to the inhibition of the vagus which was stimulated by the reflexes from the lung generated by the respiratory efforts of hyperpnea. The average hyperpnea periods were of 37 sec. duration. The reflex from the lung became much less effective as a stimulant to the vagus during the descending phase of the hyperpnea; for, the ventricular rate became accelerated several inspirations before apnea began.

This loss of vagus effect upon the heart rate was due, probably, to the fact that reflex stimuli from the lung tissue when it is contracting are not so strong as when the pulmonary tissue is being distended, but not to true vagus escape of the heart. That the vagus controlled the ventricular rate was shown by absence of alterations of the ventricular rate while the atropine was effective. During atropine effect the hyperpnea persisted for 47 seconds, a ten second increase over the digitalis period.

The distress of the patient was due to the diminished interchange of O_2 and CO_2 between the lungs and blood. This interchange was least during apnea, when the pulmonary ventilation was lowest though the heart rate was highest, but during hyperpnea, when the ventilation of the lung was greatest, the heart rate was slowest. The sensitiveness of the vagus to the pulmonary reflex was increased by digitalis to such a degree that the number of ventricular contractions during hyperpnea were very much less than when digitalis was not given.

To state this in another way; it appears that without digitalis the amount of interchange of O_2 and CO_2 was sufficient, to keep the patient comfortable, notwithstanding the inverse periodic changes in rate of heart and breathing; but, when digitalis was given, the vagus became much more susceptible to the lung reflexes slowed the circulation so as to diminish the interchange of

O₂ and CO₂ between the alveolar air and the blood sufficiently to cause real distress. Relief followed the discontinuance of digitalis and the administration of belladonna.

Conclusion.—In this case of auricular fibrillation digitalis did not improve the circulation because it increased vagus affects which diminished the O₂ and CO₂ interchange between alveolar air and blood.

21 (1481)

The action of camphor on the central nervous system of the squid.

By A. R. MOORE.

[From the Physiological Laboratory of Rutgers College, and the Marine Biological Laboratory, Woods Hole, Mass.]

Newly hatched squid (*Loligo pealii*) if put into a solution of camphor gum in sea water, 1/10 saturation, show characteristic mantle spasms, involving play of the chromatophores, after a latent period which is about 40 seconds at 24° C. This effect, it has been shown, is due to the action of camphor on the stellar ganglia.¹ In appearance, camphor spasms are indistinguishable from those caused by nicotine.² The difference does not lie in the character of the response of the end organs, muscles and chromatophores, but in the locus and the nature of neuronc excitation.

The value of the temperature coefficient Q_{10} for the action of camphor, based on the lengths of the latent periods, is 2.4. The function connecting the velocity of the reaction with the concentration of the drug is, for camphor, expressed by $v = kC^{\frac{1}{2}}$ in which $v = \frac{1}{\text{latent period}}$, $C = \text{concentration}$, and k is a constant whose value is approximately .75.

The camphor spasms soon pass off and the animals lie inert with chromatophores relaxed. This is not due to paralysis of the end organs for the reason that they may again be thrown into activity by treatment with strychnine or nicotine. The absence of any interference between the action of nicotine and that of camphor may be demonstrated by the following experiment. Let

¹ Moore, A. R., *Proc. Nat. Acad. Sc.*, 1917, III, 598.

² Moore, A. R., *J. Gen. Physiol.*, 1919, I, 505.

the specimens of squid be immersed in nicotine solution for 1 minute. They are then put into the solution of camphor. Camphor spasms take place, after which the animals lie quiet for several minutes. At the end of the required latent period¹ nicotine spasms occur just as typically as in animals treated with nicotine alone.

22 (1482)

A method of standardizing bacterial suspensions.

By FREDERICK L. GATES.

[From the Department of Pathology and Bacteriology of the Rockefeller Institute for Medical Research, New York.]

If a wire loop is thrust down into a suspension of bacteria in a test tube, and viewed by looking down into the mouth of the tube, the depth at which the loop disappears will be determined by the opacity of the supervening suspension. If, however, a second suspension of the same organism containing half as many bacteria per cubic centimeter is similarly examined, or if an equal amount of the diluent is added to the original suspension, and the "depth of disappearance" again measured it will be found to be less than twice as great as in the original suspension. In other words, the observed depths of disappearance are not in proportion to the bacterial concentrations or the corresponding volumes.

This discrepancy is due to the presence in each reading of a constant which is apparently related to the size and opacity of the individual organisms. It is found that this constant may be eliminated, thus bringing the opacity observations into inverse ratio with the corresponding bacterial concentrations, and a *corrected* reading (the observed reading minus the constant) for any suspension may be obtained by making two readings at different dilutions of the suspension, and substituting the observed values in the following equation:

$$A = \frac{\text{vol } a (b - a)}{\text{vol } b - \text{vol } a},$$

¹Moore, A. R., *J. Gen. Physiol.*, 1919, I, 505.

in which

A = the corrected reading for the first volume of the suspension = $(a - \text{constant})$

a = first observed reading.

vol a = first volume of the suspension on which reading a is made.

b = second observed reading.

vol b = second volume of the suspension (diluted), on which reading b is made.

A concrete example will illustrate the method. In 4 c.c. (vol a) of a given suspension the loop disappears 1.2 cm. below the meniscus (reading a). The suspension is diluted to 10 c.c. (vol b). The loop now disappears 2.7 cm. below the meniscus (reading b). Then the corrected reading for the opacity of the suspension (A),

is $\frac{4(2.7 - 1.2)}{10 - 4}$ or 1.0 cm.

Such a *corrected* reading may be directly compared with corrected readings on other suspensions of the same organism, since the corrected readings on such suspensions stand in inverse ratio to their bacterial concentrations. Thus, if two suspensions of the same organism are to be compared and the corrected reading for one is half that for the other, the first suspension contains twice as many bacteria as the second. If the actual bacterial count is required, a standard for the given organism must first be established by the correlation of several corrected readings with the corresponding counts, obtained by the usual methods. Thereafter the concentration of the organism per cubic centimeter in suspensions under examination is obtained by inverse proportion:

$$\frac{\text{The required count}}{\text{The standard count}} = \frac{\text{The standard corrected opacity}}{\text{The given corrected opacity}}$$

The simplest possible instrument for making the determinations consists of a piece of 18 gauge nichrome, chromel, or black iron wire about 20 cm. long, bent into a small loop at right angles to one end, and with the other end thrust through a cork, near one side, so that a view may be obtained past the cork into an ordinary test tube, 1.6 × 16 cm. on whose lip it rests. The sterile test tube is partly filled with a measured quantity of the suspension, and the wire loop raised or lowered through the cork until the

point is found at which the loop just disappears from view. The distance of the loop below the meniscus is then measured with a centimeter scale laid along the tube, giving the first reading. A second reading is obtained after the addition of a measured amount of the diluent, and the data required for substitution in the equation for the corrected reading is at hand. The readings and calculations require but two or three minutes. In the zone of most accurate measurement, with suspensions of such opacity that the loop disappears between 1 and 4 cm. below the surface, repeated readings may be made with a variation of about one millimeter, an error of less than 10 per cent. The wire loop, which alone comes in contact with the bacteria, may be flamed after each determination, thus reducing the danger of contamination to a minimum.

A more complete explanation of the method, with a description of the more convenient and accurate instrument shown at the meeting will appear in a forthcoming number of the *Journal of Experimental Medicine*.

23 (1483)

Some studies on the surface layer in the living egg cell.

By ROBERT CHAMBERS.

[From Cornell University Medical College.]

The results recorded here were obtained through the use of Barber's mechanical pipette holder somewhat modified for microdissection purposes.

The cells experimented upon were the egg cells of the starfish and of the sea urchin. The eggs, which are somewhat over 1/10 of a millimeter in diameter, were placed in a drop of sea water hanging from the roof of a moist chamber. The microscopically fine tips of the glass dissecting needles projected into the moist chamber and up into the hanging drop. By manipulation of the screws of the mechanical pipette holder the cells in the hanging drop could be dissected with considerable accuracy and an estimate ascertained of their physical consistency. Detailed accounts

of Barber's apparatus and its application to microdissection have already been published.¹

The egg cells studied consist of a decidedly fluid interior surrounded by a more solid surface layer of appreciable thickness. This surface layer is most solid on its external surface. Internally its consistency seems to merge insensibly into that of the fluid interior. The inner surface of this layer adheres to the touch. This is demonstrated by introducing a microdissection needle into an egg and pushing the needle through until its tip comes into contact with the inner boundary of the surface layer on the side of the egg opposite the puncture. On withdrawing the needle the layer adheres to the needle tip and strands are drawn into the interior of the egg.

If the surface layer be torn while the egg is kept under compression the fluid interior will bulge out through the tear. The cytoplasm, on coming into contact with the surrounding water, tends to establish a definite surface film which prevents the cytoplasm from mixing with the water. If the internal pressure be not too great this film persists and, in time, strengthens into a definite ectoplasmic layer. The bulge then slowly retracts until the original contour of the egg is reestablished. If the neck of the protruding mass of cytoplasm be small it may pinch off a spherule of cytoplasm which to all appearances is normal. If the internal pressure be too great a succession of films may form as, one after the other, they succumb while the escaping cytoplasm disperses and disintegrates in the surrounding water and the film which finally holds out may enclose only a fraction of the original cell but what it encloses will be normal protoplasm.²

Churning of the contents of a mature unfertilized sea-urchin egg causes the ectoplasmic layer to revert to the fluid condition of the interior. The surface film of such an egg is very thin and very easily tears upon which the entire egg disintegrates. On standing, however, the surface film steadily strengthens until the normal condition is reestablished.

That the distribution of substances throughout the egg cell is

¹ Barber, *Philippine Journal of Sc.*, Vol. X, Sec. B, Tropical Medicine, 1914; Chambers, *Biol. Bull.*, Vol. 34, 1918.

² Chambers, *Amer. Journ. Physiol.*, Vol. 43, 1917.

not uniform can be demonstrated by the following experiment on the starfish egg: If the surface of a mature unfertilized egg be torn while the egg is kept under compression almost all of the internal cytoplasm may be made to flow out to form a spherule of cytoplasm which pinches off from the rest of the egg. What is left behind is a collapsed remnant consisting mainly of protoplasm which originally enveloped the egg. This remnant consisting largely of the more solid ectoplasm tends only slowly to round up. The extruded mass, which is very fluid, immediately assumes a shape approximating that of a sphere. This may be termed an endoplasmic sphere. The remnant containing the original ectoplasmic substance of the egg is readily fertilizable and undergoes segmentation. The endoplasmic sphere is unfertilizable. If, on the other hand, the endoplasmic sphere remains for some time connected by means of a bridge of protoplasm with the remnant containing the original ectoplasmic substance it is fertilizable. The ability of the endoplasmic sphere to approximate normal conditions of segmentation is a function of the length of time that it remains in organic continuity with the original ectoplasmic mass. Possibly there exists a substance necessary for development which normally accumulates in the surface layer of an egg. This substance is diffusible and will distribute itself over new protoplasmic surfaces. If a bridge of protoplasm connects the ectoplasmic remnant with the endoplasmic sphere this substance will diffuse into the sphere thereby rendering it fertilizable.

The nature of the surface film produced by cutting an egg cell differs in an unfertilized egg from one which has been fertilized. Before fertilization the needle may be pushed vertically into the side of the egg and moved through the egg from one side to the other without cutting the egg in two. The cytoplasm closes behind the needle thus obliterating the furrow. Shortly after fertilization, however, such a procedure cuts the egg cleanly in two. The sides of the furrow produced by the needle do not fuse although contiguous. The character of the surface film which forms over a cut is thus changed upon fertilization. This change prepares the egg for the ensuing segmentation process by causing the formation of a type of surface film which prevents contiguous blastomeres from fusing with one another.

24 (1484)

Concerning the toxicity of acetanilid and bicarbonate combinations for muscle-nerve preparations.

By DAVID I. MACHT.

Pharmological Laboratory, Johns Hopkins University.]

It is well known, through the work of Worth Hale,¹ that acetanilid when given in combination with small doses of sodium bicarbonate, is less toxic than when administered in the same doses alone. The studies of Macht, Greenberg and Isaacs on the influence of antipyretics on the acuity of hearing² have also shown an interesting difference between the effects of acetanilid when given alone and acetanilid when combined with sodium bicarbonate. The explanations given for the above peculiar synergism are most unsatisfactory. In connection with a pharmacological study of various antipyretics, the author investigated the effect of acetanilid solutions on muscle-nerve preparations which may throw some light upon the above-mentioned phenomena.

Two gastrocnemius muscle-nerve preparations of a frog are immersed simultaneously in physiological sodium chloride solution and the limits of both the muscle and nerve excitability to the electric shocks of an induction coil are determined. One of the preparations is then immersed in a solution of acetanilid in the same saline solution, and the other preparation is immersed in a solution of acetanilid of exactly the same strength but containing some sodium bicarbonate (1-1000 or even weaker). On testing the excitability of the muscles and nerves at regular intervals after treatment with the drugs, it was found that the plain acetanilid solution tends to paralyze and finally kill the sciatic nerve more quickly than the solution of acetanilid plus bicarbonate. The following protocol of an experiment thus performed will serve as an illustration. The slower toxic action of the acetanilid and bicarbonate combination, all other factors being equal would, it is fair to assume, render the drug less poisonous when injected into an

¹ U. S. Hygienic Lab. Bulletin No. 53 (1909).

² PROC. SOC. FOR EXPER. BIOL. AND MED., 1919, xvii, 22, 23.

animal than acetanilid would be if injected alone, for in case of the more slowly acting combination the animal has a longer period of time for the excretion of the poison. The author does not at all presume to offer these experiments as a complete explanation of the above-described synergism, but it is thought that the present findings are at least a little tangible contribution towards the explanation of the peculiar phenomenon.

EXPERIMENT, OCTOBER 28, 1919.

Stimulation of Gastrocnemii Muscles of Rana Clamata.

Time.	Left Side.		Right Side.	
	Stimulation of Muscle. Position of Secondary Coil.	Stimulation of Nerve. Position of Secondary Coil.	Stimulation of Muscle. Position of Secondary Coil.	Stimulation of Nerve. Position of Secondary Coil.
	Immersed in physiological NaCl Sol.		Immersed in physiological NaCl Sol.	
2:45 p.m.	23.0 cm.	37.0 cm.	24.5 cm.	47.0 cm.
2:50 "	23.0 "	37.0 "	24.5 "	43.0 "
3:05 "	23.0 "	39.0 "	24.5 "	44.0 "
3:07 "	Immersed in physiological NaCl Sol. containing acetanilid 1:500 and sodium bicarbonate 1:1,000		Immersed in physiological NaCl Sol. containing acetanilid 1:5000	
3:21 "	20.1 cm.	27.0 cm.	22.5 cm.	23.5 cm.
3:26 "	19.5 "	25.0 "	22.5 "	22.5 "
3:33 "	19.0 "	25.0 "	22.0 "	22.0 "
3:43 "	19.0 "	30.0 "	22.0 "	22.0 "
3:46 "	18.0 "	29.0 "	20.0 "	20.0 "
4:03 "	18.0 "	30.0 "	18.0 "	18.0 "
4:20 "	17.0 "	30.0 "	10.0 "	10.0 "
4:25 "	16.5 "	29.0 "	9.5 "	9.5 "
4:40 "	11.0 "	27.0 "	8.5 "	8.5 "
5:10 "	10.5 "	10.5 "	8.0 "	8.0 "

25 (1485)

A note on the carbohydrates of the root of the cat-tail (*Typha latifolia*).

By ZALIA JENCKS (by invitation).

[From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Conn.]

In a recent communication¹ the root of the cat-tail has been recommended as a valuable food product for man. An analysis is recorded to indicate that the material contains 81 per cent. of carbohydrates. No evidence is presented however, as to the

¹ P. W. Claasen, *The Scientific Monthly*, 1919, Vol. 9, No. 2.

precise identity of the latter. In view of the fact that various roots are known to contain carbohydrates, like inulin, which are by no means identical in physiological value with starch although they have various reactions in common with it, I have separated the most abundant carbohydrate of the cat-tail root for identification.

It gives a blue color with iodine, forms a characteristic paste with hot water, is readily digested (in contrast with inulin) by saliva, and yields on hydrolysis a dextro-rotatory solution from which an osazone, identical with glucosazone, was prepared. The carbohydrate thus corresponds with starch. Our "flour" indicated a carbohydrate content of 56.8 per cent., estimated in the conventional way from the reducing sugar formed by hydrolysis with acid.

To test the innocuousness of the cat-tail root as a food mice were fed for a week on otherwise adequate diets containing 30 per cent. of the "flour" without evident untoward results. The animals gained in weight upon the ration.

26 (1486)

Do fruits contain water-soluble vitamine?

By **THOMAS B. OSBORNE** and **LAFAYETTE B. MENDEL.**

[From the Laboratory of the Connecticut Agricultural Experiment Station, and the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Conn.]

Although fresh fruits have long been classed as valuable anti-scorbutic foods there are comparatively few recorded scientifically planned tests of their potency aside from the familiar studies of the juice of oranges and lemons. With respect to the possible presence, in fruit, of water-soluble vitamine (water-soluble B) comparable to this essential factor in yeast, scarcely anything has been published. We have begun experiments on rats in the otherwise adequate diet of which fruits and fruit juices furnish the the sole source of the water-soluble vitamine. When larger portions (more than 5 grams per day) of fresh apples and pears are fed the characteristic decline in weight observed where vita-

mine-free diets devoid of water-soluble vitamine are used, is averted. The bulky character of such fruits has made it impracticable to feed more than 10 grams per day without decreasing too greatly the intake of other essential nutrients. Ten c.c. of orange juice per day suffice to promote considerable growth. The inner peel of the orange (which Hess has found to be antiscorbutic) seems also to contain some of the other water-soluble vitamine. It is already evident that the proportions of the latter in the fruits tested is not large in relation to the quantities edible.

27 (1487)

Some observations on the biological characteristics of bacillus botulinus.

By PAUL F. ORR (by invitation).

[From the Department of Preventive Medicine and Hygiene, Harvard University Medical School, Boston, Mass.]

In a study of sixteen strains of *Bacillus botulinus*, which have been isolated in connection with outbreaks of food and forage poisoning occurring in different parts of the United States during the past five years, a number of interesting facts have been observed. While a complete report of the findings will be published elsewhere, it seems justifiable to record at this time some of the salient facts; namely:

1. Contrary to the general view that the optimum temperature for growth of *B. botulinus* is about 22° C., we have found that the body temperature 37° C., is most favorable for the growth and spore production of all of the sixteen strains of *B. botulinus* studied. Toxin is readily formed at this temperature.

2. At autopsy of guinea pigs which have been either fed or injected with cultures of *B. botulinus* it has been possible to recover this organism quite frequently from the liver and spleen and also occasionally from the heart's blood, the kidneys and the pancreas.

3. Contrary to the results obtained by previous investigators, guinea pigs, which have been fed or injected with toxin-free spores of *B. botulinus*, Nevin strain, have died with symptoms resembling those of botulinus poisoning. At autopsy of these animals *B. botulinus* was recovered from the liver and spleen.

SCIENTIFIC PROCEEDINGS

ABSTRACTS OF COMMUNICATIONS.

One hundred third meeting.

Rockefeller Institute for Medical Research, New York City, December 17, 1919. President Calkins in the chair.

28 (1488)

The rôle of fat-soluble vitamine in the dietary of infants.

By **ALFRED F. HESS** and **LESTER J. UNGER.**

[From the State Laboratory, Department of Health, New York City.]

It has been shown that the fat-soluble vitamine is an essential constituent of the dietary of rats. There have also been clinical reports attributing marked malnutrition in infants and children to a lack of this dietary factor (Japan, Denmark). As a result of these experiences it has been accepted that this vitamine is highly important for man, and that the lack of it leads to nutritional disorder in children. This has been emphasized all the more as this vitamine is not nearly as widely distributed in nature as is the water-soluble vitamine. In order to study this question five infants, varying in age from 5 to 12 months, were given a diet which was complete except for a very small amount of fat-soluble vitamine. It consisted of 180 g. daily of highly skimmed milk (Krystalak 0.2 per cent. fat), 30 g. of cane sugar, 15 to 30 g. of autolyzed yeast (to supply water-soluble vitamine), 15 c.c. of orange juice, 30 g. of cottonseed oil, and cereal for the older infants.

On this diet the children have done well for a period of eight to nine months. They have shown no anemia, no eye trouble, no bone changes, as seen by the X-ray, nor has their growth in length or in weight suffered. We believe, therefore, that either a very small amount of this vitamine suffices to supply the needs of human nutrition, or that this deficiency has to be maintained

for a period of years in order to bring about any harmful result. Danger from a lack of this dietary factor need not be apprehended if the diet is otherwise complete.

The development of rickets has been attributed by Mellanby, as a result of experiments on dogs, to a lack of fat-soluble vitamine, and Hopkins and Chick have termed this vitamine the "anti-rachitic factor." It was found, however, that infants fed on this "fat-soluble vitamine minimal diet" did not develop the well-established signs of rickets—beading of the ribs, enlargement of the epiphyses, weakness of the muscles, etc. We cannot believe, therefore, that rickets is brought about by a deficiency of this principle; all the more so, as this disorder developed in infants receiving large quantities of milk containing ample fat-soluble vitamine. It may be added that neither cream nor the leafy vegetables, both of which are rich in this principle, were found to be comparable to cod liver oil as growth stimulants.

29 (1489)

A method for the determination of calcium, magnesium, potassium, sodium, chlorides and "acid-soluble" sulfur and phosphorus in one sample (25 c.c.) of blood.

By ISIDOR GREENWALD and JOSEPH GROSS.

[From the Harriman Research Laboratory, The Roosevelt Hospital, New York.]

The blood is laked with eight volumes of water and the protein is then precipitated by the addition of one volume of 1:1 nitric acid. In a portion of the filtrate chlorides are determined gravimetrically by precipitation with silver nitrate and filtering on a Gooch crucible. The excess of silver in the filtrate is removed with hydrochloric acid and the resultant filtrate and the remainder of the blood filtrate are combined and treated with copper nitrate and perchloric acid, evaporated to dryness and then to blackness.¹ The residue is treated with concentrated hydrochloric acid, again evaporated to dryness and then dissolved in dilute hydrochloric

¹ Redness must be avoided, or potassium will be lost. This is a modification of Benedict's method (*Journal of Biological Chemistry*, 6, 363, 1909).

acid. Sulfates are precipitated with barium chloride and the filtrate is made ammoniacal, then acid with acetic acid and phosphates are precipitated with ferric chloride. The precipitate is dissolved in nitric acid and the phosphoric acid is precipitated with ammonium molybdate and the yellow precipitate is titrated. The filtrate from the ferric acetate precipitate is treated with sulphuric acid to remove the barium and with hydrogen sulfide to remove the copper and the filtrate is evaporated to small volume. Calcium is precipitated in a centrifuge tube as oxalate, washed and titrated. The supernatant liquid and washings are evaporated, heated to remove ammonium salts and the magnesium is precipitated in a centrifuge tube as magnesium ammonium arsenate. This is washed and then dried, *in vacuo*, over sulfuric acid. It is dissolved in acid, transferred to a distillation flask and the ammonia determined by distillation and Nesslerization. The supernatant liquid and washings are treated with hydrochloric and hydrobromic acids, evaporated to dryness, freed of ammonium salts and arsenic, sulfuric acid is added and the potassium and sodium are weighed as mixed sulfates in a platinum dish. Potassium is then precipitated as the cobaltinitrite and weighed.¹

30 (1490)

A benign tumor in *Drosophila*.

By MARY B. STARK. (by invitation).

[From the Zoölogy Laboratory, Indiana University.]

In a strain of flies with a lethal tumor, *i.e.*, a tumor occurring in one half of the males and causing their death, another tumor has appeared as a mutation. The new tumor differs from the lethal one in that it is not sex-linked, *i.e.*, it appears in females as well as males, and further in that it does not cause the death of the flies in which it occurs. Linkage experiments show that one at least of the genes essentially for tumor development is in the third chromosome closely linked to *dichaete*.

¹ Garola and Braun, *Annales de falsifications*, 10, 572, 1917.

The tumor may occur in any segment of the larva but seems to occur more often in the twelfth and thirteenth segments. When the tumor occurs in the thoracic region, there may be an ingrowth of tumor cells into the imaginal discs of the appendages checking the development of these parts.

The cells of the tumor are rounded or polygonal in shape and show the presence of pigment.

31 (1491)

The suitability of the "Bachman Test" for water-soluble B.

By **WALTER H. EDDY** and **HELEN C. STEVENSON**.

[From Teachers College, Columbia University, New York City.]

Two recent publications by Drs. Bachman¹ and Williams² dealing with the vitamine requirements of yeasts suggest that the methods developed are adaptable to quantitative measurement of vitamine content (B variety). At the suggestion of the senior author Miss Stevenson has conducted experiments with both methods and in this report are presented some of the results with the Bachman test.

Briefly this method consists in planting yeast cells in a culture medium (Nageli's solution: 100 c.c. distilled water; 10 gms. dextrose; 1 gm. ammonium nitrate; 0.05 gms. calcium phosphate; 0.5 gms. potassium acid phosphate; 0.25 gms. magnesium sulfate) contained in a Durham or Smith fermentation tube and incubating the tubes at 28-32° C. to obtain gas formation. To these tubes are added vitamine "B" extracts from various sources and Dr. Bachman's results showed that in the absence of such extracts gas formation either fails to take place or at least very slowly.

Our experiments aimed to confirm Dr. Bachman's results, to determine whether the method gave promise of use quantitatively and whether it might be used to detect the "B" vitamine qualitatively. The results of our experiments follow:

¹ "The "Vitamine Requirements of Certain Yeasts," by Freda Bachman, *Journ. Biol. Chem.*, XXXIX, 235 (1919).

² "A Simple Biological Test For Vitamines," by R. W. Williams, *Journ. Biol. Chem.*, XXXVIII, 465 (1919).

EXPERIMENT I. To test the applicability of the method to "B" Vitamine extract as prepared by McCollum¹ from Navy Bean.

Contents of Tubes.	Per Cent. of Gas-formation by Days.								
	1.	2.	3.	4.	5.	7.	8.	9.	14.
1. Control tube. Contained Nageli solution and one loopful of yeast cell suspension . .	0	0	0	0	0	0	0	0	0
2. Control tube 2. Contained Nageli solution, loopful yeast cell suspension and 1 c.c. of a dextrin solution made by dissolving 20 gms. dextrine in 150 c.c. of distilled water. The dextrin solution was sterilized in the Arnold machine at 100° C.	0	0	0	0	0	0	0	0	0
3. Control tube 3. Contents same as tube 2 but the dextrin solution was sterilized again, after Arnold treatment, for 20 minutes in the autoclave at 15 lbs. and about 120° C.	0	0	0	0	0	0	0	0	0
4. Tube contained Nageli, loop of yeast and 1 c.c. of a dextrine vitamine extract from Navy Bean (for preparation see explanation below) sterilized in the Arnold at 100° C.	0	90	87	63	18	upset at this point			
5. Same as tube 4 but sterilized in the autoclave in addition to Arnold sterilization . .	0	93	85	58	56	40	38	37	33

Explanation: The vitamine dextrine solutions were obtained by first extracting 86 gms. of Navy bean flour with ether in the Soxhlet for 18 hours. The residue was then extracted for two six hour periods with boiling alcohol (95 per cent.) in a reflux condenser. The alcohol extract was mixed with 20 gms. of dextrine and evaporated to dryness. The solution was made by dissolving this dextrin vitamine in 150 c.c. of distilled water. The control dextrin solution was made by dissolving 20 gms. of dextrine in 150 c.c. distilled water. All the solutions were subjected to two 30 minute periods in the Arnold sterilizer with a 24-hour incubation period intervening. The materials tested in tubes 3 and 5 were then given an additional 20 minutes in the autoclave at 15 lbs. and approximately 120° C. A pure culture of the Fleischman round yeast was used. The suspension was made by transferring to 5 c.c. of sterile water several loopfuls of the agar slant culture and the tubes were inoculated with one loopful of this suspension. Our tubes were incubated at 32° C. The CO₂ is very rapidly reabsorbed by the Nageli solution and sealing the tube with mineral oil was not effective. Consequently readings may be discontinued after the per cent. of gas reaches the maximum.

¹"A Study of the Dietary Essential, Water-soluble B.," by E. V. McCollum, *Journ. of Biological Chemistry*, XXXIII, 55.

EXPERIMENT 2. To determine the effect of variation in the concentration of the dextrine vitamine solution.

Tube Contents	0.1/Cc. Dextrine V.						0.2/Cc. Dextrine V.					
	Arnold.			Arnold Plus Autoclave.			Arnold.			Arnold Plus Autoclave.		
	1.	2.	3.	1.	2.	3.	1.	2.	3.	1.	2.	3.
Days:												
1.....	0	0	0	0	0	0	0	0	0	0	0	0
2.....	0	0	0	0	0	0	16	2	1	50	0	0
3.....	0	0	0	0	0	0	63	35	78	70	18	75
4.....	0	0	0	0	0	0	29	25	99	35	30	67
5.....	0			0			11			72		
7.....	0	1	3	0	0	0	10	8	79	62	7	22
8.....	0			0				5		52		
9.....	0			0			4			48		
14.....	0			0			3			45		
Tube Contents	0.5/Cc. Dextrine V.						1.0/Cc. Dextrine V.					
	Arnold.			Arnold Plus Autoclave.			Arnold.			Arnold Plus Autoclave.		
	1.	2.	3.	1.	2.	3.	1.	2.	3.	1.	2.	3.
Days:												
1.....	0	0	0	0	0	0	0	0	0	0	0	0
2.....	95	95	53	26	60	23	90	99	68	93	99	68
3.....	91	100	95	51	100	100	87	100	100	85	100	100
4.....	85	99	95	58	84	96	63	75	82	58	65	80
5.....	68			25			18			56		
7.....	10	10	10	8	12	8	40	20	8	u	30	28
8.....	8				7		38			u		
9.....	8				7		37			u		
14.....	7			6			33			u		

Explanation: The only variants were the amounts of vitamine solution used and the yeast suspensions.

All the Vitamine solutions were sterilized as in experiment 1 and the second set in the Autoclave for additional 20 minutes. In series 2 and 3 a new yeast suspension was made. The Vitamine solution was the same as used in Experiment 1.

EXPERIMENT 3. To determine the suitability of the test as a qualitative agent in determining the presence and relative amount of "B" Vitamine.

N.B. All tubes contained the Nageli solution and a loopful of yeast suspension as in Experiments 1 and 2. In this experiment only Arnold sterilization was used (two 30-minute periods with 24 hours incubation period intervening).

Tube Contents.	Per Cent. of Gas Formed by Days.						
	1.	2.	3.	4.	5.	6.	7.
1. 1 c.c. of a vitamine extract of a commerical farina. 110 gms. farina was used and the extract made up to 150 c.c.	0	60	100	83	33	28	
2. Vitamine extract from 25 gms. alfalfa. Extract made up to 150 c.c. Using 0.5 c.c.	3	98					
Using 1 c.c.	24	97			48		
4. Protozoa food mixture after Calkins made by boiling 130 gms. flour with 100 gms. timothy hay and 100 c.c. distilled water, allowing to cool and decanting. Used 0.5 c.c.	0	0	0	0	0	0	0
Using 1.0 c.c.	0	0	15	32	12	18	
5. 35 c.c. of the Protein free milk obtained from 1 qt. milk.	0	20	40	53			
6. 1 c.c. Walker Gordon whole milk.	0	100	100	100	100	60	
7. Duplicate of (6) with varying concentrations: Using 1 c.c.	0	68	100	100	86		
Using 0.5 c.c.	0	52	100	88	50		
Using 0.3 c.c.	0	25	60	50	32		
8. Cow's milk to which was added varying amounts of N(NaOH) solution before sterilizing. Using 1 c.c. of solution (25 c.c. milk cont. 1 c.c. N(NaOH))	0	3	70	100			
Using 1 c.c. of solution (25 c.c. milk cont. 0.5 c.c. N(NaOH))	0	4	58	95			
Using 1 c.c. of solution (25 c.c. milk cont. 0.4 c.c. N(NaOH))	0	55	100	100			
Using 1 c.c. of solution (25 c.c. milk cont. 0.3 c.c. N(NaOH))	0	55	100	100			
Using 1 c.c. of solution (25 c.c. milk cont. 0.2 c.c. N(NaOH))	0	60	100	100			
Using 1 c.c. of solution (25 c.c. milk cont. 0.1 c.c. N(NaOH))	0	55	100	100			

9. Breast milk from six different sources. Each specimen used sterilized two 30-minute periods in the Arnold Sterilizer before using. 1 c.c. used in each inoculation. 3 series of experiments. Series 1 used a different yeast suspension from that used for Series 2 and 3.

Sources.	Series 1.						Sources.	Series 2.					Sources.	Series 3.					
	1.	2.	3.	4.	5.	6.		7.	1.	2.	3.	4.		5.	1.	2.	3.	4.	5.
A. 1 c.c. ...	0	12	63	80	100	100	100	1 c.c.	0	0	60	100	68	0.5 c.c.	0	0	0	10	30
B. 1 c.c. ...	0	21	59	70	70	65	65	1 c.c.	0	31	70	72	62	0.5 c.c.	0	0	24	65	90
C. 1 c.c. ...	0	17	47	68	82	68	65	1 c.c.	0	8	82	60	65	0.5 c.c.	0	3	33	50	48
D. 1 c.c. ...	0	21	72	72	72	68	68	1 c.c.	0	65	90	80	70	0.5 c.c.	0	0	28	78	90
E. 1 c.c. ...	0	1	23	56	65	45	44	1 c.c.	0	5	70	90	65	0.5 c.c.	0	0	20	68	64
F. 1 c.c. ...	0	0	20	35	59	55	54	1 c.c.	0	3	78	72	45	0.5 c.c.	0	0	48	68	50

CONCLUSIONS.

The results of the various experiments are obvious from the records. It need merely be pointed out that in none of the duplicates were we able to repeat the gas figures exactly and that for quantitative measurement the test needs further standardization to be efficient in comparing solutions. The great variability of the yeast loopfuls obtained in this method would easily give rise to considerable variation and experiments are being made along this line to be reported later.

As a means of studying presence of "B" Vitamine in large or small quantity and as an index more reliable than rat feeding experiments the test offers such marked advantages in sensitiveness and in speed of observation that it seems well worth while to devote more time to its improvement.

32 (1492)

Two sex-linked lethals of simultaneous appearance in *Drosophila obscura*.By **D. E. LANCEFIELD** (by invitation).

[From the Zoölogical Laboratory, Columbia University, New York City.]

A pair mating in *Drosophila obscura* (Fallén) produced a sex ratio of 106 females to 22 males. This was about a 1:4 ratio and indicated a case of two sex-linked lethals, or lethals at two loci on the X-chromosome. Both lethals (l_1 and l_2) appeared simultaneously in the same culture from a female whose mother did not carry a sex-linked lethal, as was shown by the normal sex ratio produced by her; and the father could not have carried such a lethal and lived.

Three daughters inherited both lethals in the same chromosome with a sex-linked gene producing the character "short" wing veins. These three females produced a total of 352 females to 40 normal and 50 "short" males. Such a count suggested that the gene for "short" was between the two lethals, which were far enough away from it for each to segregate almost independently from it,

that is, giving approximately 50 per cent. crossing over between each lethal and "short." This shows more crossing-over than is known to occur in the X-chromosome of other species of *Drosophila* and may correspond to the greater length of the X-chromosome in *obscura*.

Further breeding tests showed the presence of two separate sex-linked lethals and agreed with the original assumption as to their loci. One (l_2) was found to be very close to the locus for "beaded" and gave 10 cross-overs with it in 155 males. "Beaded" was already known to be far enough from short to show no appreciable linkage to it. The other lethal (l_3) was independent of "beaded" but showed some linkage to "short" by a ratio of 21 "short" to 34 "not-short" males, while the number of "beaded" and "not-beaded" males was equal. That established its locus in the other end of the chromosome from (l_2) with "short" between.

33 (1493)

New methods for the analysis of cytoplasmic structures. With demonstrations.

By **ROBERT H. BOWEN** (by invitation).

[From the Department of Zoölogy, Columbia University.]

The year 1898 marked the recognition of two fundamental cytoplasmic structures,—mitochondria and the Golgi apparatus. The mitochondria soon became of interest to every biologist through Meves' theories concerning their importance in cellular differentiation and inheritance, but we are still very much in the dark regarding many features of their behavior. The Golgi apparatus, on the other hand, was almost forgotten and until recently even its status as an independent cytoplasmic element was in doubt. The last few years have witnessed in Europe a revival of interest in these and other cytoplasmic inclusions, an interest not yet fully reflected in this country. It would seem, then, an opportune time for calling the attention of biologists to these structures, so little reckoned within our physiological concept of the cell.

I have been experimenting with a variety of methods while studying the formation of the insect sperm, more particularly of Hemiptera belonging to the Family Cimicidæ (Pentatomidæ). Two new methods were found which have yielded interesting results.

The first is a modification of the Kopsch method for Golgi bodies, which depends on the reduction of osmic acid by the Golgi apparatus more quickly than by other cell constituents. This modification is more rapid than Kopsch and often gives good fixation of the cell as a whole. The procedure is as follows:

Fix in glass-stoppered bottles for 20 to 30 hours in Mann's sublimate-osmic:—

1 per cent osmic acid solution 1 part
Corrosive sublimate, saturated solution in normal salt 1 part

Wash in water over night, dehydrate and embed. Cut sections four micra thick. Mount directly or counterstain as desired; I find light green very useful. Golgi elements are intense black, mitochondria unstained or light brown. This method, in common with all Golgi technique, is more or less uncertain, due not so much to imperfect impregnation as to variability in general fixation. Since working with this method I have found that Weigl has made use of another sublimate modification for the Golgi apparatus.

The second method bears upon the structure of mitochondria, which, from a chemical standpoint, have been considered as a combination of some lipoid with an albumen. Further, it has been noticed, especially in Lepidoptera and Mollusca, that the mitochondria, occurring as spherical bodies, consist of an outer, intensely staining layer and an unstained medullary substance. Whether any correlation exists between these two facts is unknown. I have found that with Cajal's Golgi apparatus method¹ it is possible in the spermatid Nebenkern of these Hemiptera to demonstrate conclusively a compound structure, especially in those stages where the Nebenkern halves are elongating to form sheaths for the tail filament. Here the medullary substance impregnates intensely, while the chromophilic envelope remains

¹ For a readily accessible statement of this method see A. M. Pappenheimer, "The Golgi Apparatus," *Anat. Record*, 1916, Vol. 11, No. 4.

transparent. The medullary substance is at first arranged in a series of beaded threads running parallel to the long axis of the sheath, the threads undergoing a progressive side by side fusion, until eventually all merge into a single axial core for each of the now considerably elongated sheaths. This Cajal method, though notoriously capricious with the Golgi apparatus, gives some result for the present purpose in perhaps 75 per cent. of trials.

34 (1494)

The excretion of urea.

By J. H. AUSTIN, EDGAR STILLMAN and D. D. VAN SLYKE.

[From the Hospital of The Rockefeller Institute for Medical Research, New York.]

The excretion rate of urea in normal men increases directly as the blood urea concentration, and as the square root of the volume of urine, so long as the latter remains within ordinary limits, under about 5 liters per day. These relations are expressed in the formula, $D = KB\sqrt{V}$, D representing the rate of urea excretion, calculated as grams per 24 hours, B the blood urea concentration (grams per liter), V the rate of urine excretion, calculated as liters per 24 hours. When the size of the individual ($W =$ weight in kilos) is introduced the equation becomes $\frac{D}{W} = KB\sqrt{\frac{V}{W}}$, or

$K = \frac{D}{B\sqrt{VW}}$. $K = 7.5 \pm 3$ for normal individuals. When de-

ciency of the urea-excreting function is present K has a lower value. Increase in volume output beyond the rate of about 200 c.c. per hour, or 5 liters per 24 hours, ceases to accelerate urea excretion, so that for volumes of V in excess of 5, the figure 5 may be inserted in place of the actual V . The above formula gives more consistent results than that of Ambard, which assumes erroneously that the excretion rate increases as the square rather than the first power of the blood urea; and correlates the excretion with the concentration of the urea in the urine rather than with the volume of the urine. In calculating the rate of urine and urea output from short time periods, errors occasionally occur from

failure completely to empty the bladder at either the beginning or end of the period. Such errors may be reduced by basing the output calculations on the creatinine content of the sample, rather than the time over which it is collected, since Shaffer has shown the hourly creatinine output to be constant throughout the 24 hours, *e.g.*, if the creatinine content of the sample analyzed is 1/20 of the individual's known daily creatinine output, the urea and volume output are calculated to a 24-hour basis by multiplying by 20.

35 (1495)

Enzymes of pollen.

By JULIA BAYLES PATON (by invitation).

[From the Osborn Botanical Laboratory, Yale University, New Haven, Conn.]

Pollen enzymes must be very important in rendering stored food available when pollen germinates, in facilitating the passage of the pollen-tube through the pistil, and in stimulating the development of the embryo and maturing of the ovary.

Moreover pollen anaphylaxis is now regarded as the cause of so-called hay-fever and other forms of pollen poisoning. Pollen enzymes may be concerned in these reactions, and the proteolytic enzymes may affect the stability of the pollen-protein solutions used in pollen vaccination.

Yet in spite of the significance of these enzymes few experiments in regard to their nature have been reported, and none recently. Erlenmeyer (1874) found amylase in pine pollen. Van Tieghem (1886) reported invertase in hyacinth, narcissus, wall-flower, and violet. Rittinghaus (1886) made observations which indicate the presence of the cytase. J. R. Green cites amylase in pollen tubes. Strasburger (1905) mentions diastase and invertin in grains prior to germination. Kammann (1912) found proteases, diastases, catalases, and lipases in rye pollen.

Although it has been assumed that pollen tubes digest their way through the style there seems to be no experimental evidence as to the exact nature of this enzyme action. Histological exami-

nation shows that pollen tubes make their tortuous way between the walls of adjacent cells rather than traversing or penetrating the cell. We should expect, therefore, to find not a cytase or cellulose-digesting enzyme, but rather a pectinase, capable of digesting the pectin of the inner lamella. This has been proved in the writer's experiments to be the case.

Twelve kinds of pollen have already been tested, namely, Easter lily, *Lilium rubrum*, red maple, Norway maple, Siberian crab apple, Austrian pine, magnolia, dandelion, goldenrod, ragweed, and corn. Rye, daisy, dock and timothy are now being examined.

The enzymes tested for, both qualitatively and quantitatively, were as follows: amylase, zymase, invertase, erepsin, trypsin, pepsin, lipase, catalase, reductase, cytase, tyrosinase, and pectinase.

So far amylase, invertase, catalase, reductase, and pectinase have been found in all. Several of these reactions are so rapid and striking that they make excellent laboratory demonstrations. Erepsin, pepsin, trypsin and lipase were found active in some and not in others. Cytase, and tyrosinase have not yet been satisfactorily identified in any. Zymase has been found so far only in Siberian crab apple.

36 (1496)

Effect of the anesthetization on the subsequent behavior and intelligence of albino rats.

By **D. I. MACHT** and **C. F. MORA**.

[From the *Pharmacological and Psychological Laboratories of Johns Hopkins University*.]

The behavior of albino rats was studied in Watson's maze.¹ Young adult rats were first trained so as to find their way out of the maze by the shortest distance and in the shortest period of time. After the animals have been thoroughly trained anesthetics were administered and the subsequent behavior after recovery from anesthesia was studied. The effects of a single anes-

¹ Watson, J. B., *Jour. of Animal Behavior*, 1914, IV, 56-59.

thetization and of repeated anesthetizations after several days' intervals of time were noted. The anesthetics studied were nitrous oxide, ether and chloroform. In the different experiments the animals were kept under anesthesia from one to five minutes and observations of their behavior were begun as soon as they were awake and running about.

A difference in the effects of the different anesthetics studied was very early observed. Nitrous oxide, when administered carefully together with sufficient oxygen to prevent asphyxia, produced the least deleterious effects. The animals recovered their normal behavior or intelligence within a few minutes after coming out of anesthesia.

Numerous experiments with ether showed that the rats in this case also were not much affected by the drug. On recovering completely from the anesthesia, about half an hour afterwards, they found their way out of the maze without going astray, but showed occasionally some retardation in the duration of performance. On the following day however the animals were found almost invariably to have recovered completely their intelligence. Even after repeated anesthetizations on different days, or after prolonged single anesthetizations the same results were obtained.

Chloroform was found to be by far the most deleterious anesthetic of those studied. A single administration of the drug for a minute or two was sufficient to impair the intelligence of the animal for that day, and more prolonged anesthesia or repeated anesthetizations produced a greater impairment of intelligence, as manifested by the behavior of the animals in the maze or labyrinth for several days afterwards. In some cases the impairment of the mind and loss of memory were permanent or complete and the animal required to be retrained before it could perform its original tricks. The effect of various opiates on the behavior of rats has been investigated by the authors, and will be reported at an early date.

37 (1497)

On the deterioration of crystalline strophanthin in aqueous solution.By **ROBERT L. LEVY** and **GLENN E. CULLEN**.*[From the Hospital of the Rockefeller Institute for Medical Research.]*

For clinical use, crystalline strophanthin is commonly dissolved in normal salt solution or water and marketed in glass ampules. Sterilization is accomplished by autoclaving after the ampules have been filled and sealed. In making biologic assays, by the cat method of Hatcher and Brody, of several lots of a commercial preparation of "ouabain" (g-strophanthin) wide variations in potency were found. On adding a drop of indicator, phenol red, to the contents of those ampules showing low potency, it was observed that they were decidedly alkaline in reaction, whereas freshly prepared, aqueous solutions of the drug are neutral or slightly acid. Experiments were undertaken to ascertain the cause of the deterioration in relation to the altered hydrogen ion concentration and to devise a method for preparing a stable solution for therapeutic purposes.

Doubly distilled water, pH 6.0, was autoclaved in various types of glass bottles and flasks, chosen at random from the laboratory supply. Immediately after autoclaving, the reaction of the water in the cheaper and softer varieties of container had become quite alkaline, the pH ranging from 6.3 to 9.0. In the hard glass flasks (Pyrex) no significant alteration in reaction occurred.

A similar experiment was done with sixteen types of glass ampules, obtained from a number of pharmaceutical firms, and used by them in marketing their products. The distilled water autoclaved in these ampules in every instance showed a change in pH, which now ranged, in different lots, from 6.2 to 9.0. In order to titrate back to neutrality (pH 7.0) the most alkaline solution in the series, 2.6 c.c. of N/50 HCl per 100 c.c. of water were required.

Next, a 2 per cent. solution of strophanthin was made in standard M/20 phosphate mixtures with pH 7.0, pH 8.6 and pH 5.0.

Biologically tested, the cat unit of these solutions was found to be 0.107 mg. per kg., their optical rotation -0.97° . After autoclaving for 20 minutes at 15 pounds pressure, no alteration in either optical activity or potency was observed in the acid or neutral solutions. The alkaline mixture, however, now had an optical rotation of -0.93° and a cat unit value of 0.152. In short, when strophanthin is autoclaved in alkaline solution (pH 8.6) the molecule is partially decomposed, with resultant alteration in its ability to rotate polarized light and significant reduction in biologic activity.

For bedside use it is convenient to employ crystalline strophanthin in dilute concentration, usually 0.01 per cent. Such a solution autoclaved in a soft glass ampule, which, on heating, gives off enough alkali to alter the reaction of its contents to pH 9.0, becomes biologically practically inert, more than four times the calculated lethal dose having no appreciable effect on the cat's heart. The contents of a hard glass ampule, with no significant alteration in pH after sterilization, retain full potency.

To insure stability of reaction, it is advisable, therefore, to put up solutions of crystalline strophanthin in hard glass (Pyrex) ampules. In order to avoid even slight changes toward the alkaline side, the drug has been prepared for clinical use in *M*/50 standard phosphate solution, at pH 7.0. The buffer action of this mixture can compensate, with a wide margin of safety, for the amount of alkali yielded, on autoclaving, by the softest variety of glass ampule.

SCIENTIFIC PROCEEDINGS

ABSTRACTS OF COMMUNICATIONS.

One hundred fourth meeting.

*College of Physicians and Surgeons, New York City, January 21,
1920. President Calkins in the chair.*

38 (1498)

The relation of the portal blood to liver maintenance.

By **PEYTON ROUS** and **LOUISE D. LARIMORE.**

[From the Rockefeller Institute for Medical Research.]

The occlusion of portal branches to a portion of the rabbit's liver leads to a progressive and ultimately complete atrophy of the parenchyma in the region deprived of portal blood and to hypertrophy of the hepatic tissue elsewhere, which receives such blood in excess. Three fourths of the liver may thus be reduced to a fibrous tag within two months, while the remaining fourth attains the bulk of the entire original organ. The atrophy is simple, unaccompanied by obvious degenerative changes or by the least connective tissue replacement. More important, it is conditional in nature, failing to progress when the bile duct from the proliferating liver tissue is ligated and hypertrophy checked in this way.

Preliminary experiments indicate that these facts hold for the dog, though the changes go on more slowly in the canine liver. After three months the tissue deprived of portal blood has diminished to about one third of its original bulk. That such atrophy is conditional is proven by its relative failure to occur in the absence of a compensating parenchyma, as when the portal stream is completely diverted from the whole liver by way of an Eck fistula.

The bile secreted from a portion of the rabbit's liver far advanced in an atrophy of the sort described, and competing with a large liver mass which received the entire portal stream, is almost colorless and may give but a weak Pettenkofer reaction. Glycogen, though, is present in the atrophic cells in approximately the same amount and distribution as in the hypertrophic parenchyma of the same animal.

The type of local liver destruction here considered, which is dependent upon hypertrophy elsewhere, contrasts interestingly with the local hypertrophy dependent upon destruction which has long been familiar to pathologists.

The fact that a parenchymal shift follows local changes in the portal stream has a bearing on the cause of certain alterations in the shape of the normal liver which have been attributed to pressure from the surrounding organs.

39 (1499)

The utilization of the calcium of carrots by man.

By **MARY SWARTZ ROSE** with the coöperation of **RENA S. ECKMAN**, **EDITH D. BROWNELL**, **EDITH HAWLEY** and **ELLA WOODS**.

[*From the Department of Nutrition, Teachers College, Columbia University.*]

Four healthy young women were given rations with a calcium content approximating their minimum requirement, and calcium balance determined from analysis of food, urine and feces. In two cases the experimental period was about two weeks, and in the other two, about three weeks. In two cases the carrot period was preceded by a period in which the calcium was derived chiefly from milk. In all cases the subjects had had their digestive capacity tested by previous digestion experiments.

About 400 grams of cooked carrot were eaten by each subject daily, furnishing from 55 to 84 per cent. of the calcium ingested. In all cases but one there was a positive calcium balance, and in this case the loss was small. In one case, the balance was nearly the same on a diet in which 55 per cent. of the calcium was derived from carrots as on one in which 70 per cent. was furnished by

milk. The total calcium intake and the per cent. of the intake gained or lost are shown below:

AVERAGE DAILY INTAKE OF CALCIUM AND PER CENT. OF INTAKE RETAINED OR LOST.

Subject.	Diet.	Intake Grams Ca.	Per Cent. Calcium from Carrots.	Per Cent. Gain or Loss.
E. D. B.....	"Milk"	0.383	—	+16
R. S. E.....	"Milk"	0.383	—	+23
E. D. B.....	"Carrot"	0.315	55	+17
R. S. E.....	"Carrot"	0.315	55	- 7
E. H.....	"Carrot"	0.261	84	+ 4
E. W.....	"Carrot"	0.297	82	+27

40 (1500)

Sugar and oxygen relationships in the blood of dogs.

By ERNEST L. SCOTT and A. BAIRD HASTINGS.

[From the Department of Physiology of Columbia University.]

Before subjecting the organism to certain experimental conditions capable of changing the sugar and oxygen relationships of dog's blood, it was thought advisable to determine the variations and relationships which might normally be encountered within the same individual at different times and in different individuals.

The blood sugar was estimated by the MacLean method. The capacity of the blood for oxygen and its actual oxygen content were determined by the Van Slyke technic. Specimens of blood from the external jugular veins of resting dogs were drawn by aspiration without exposure to the air, at intervals of one and one half or two hours over periods of six, or seven and one half hours. To date eleven such series of observations on eight dogs have been completed.

In view of the frequent statement in the literature that even a slight amount of hemorrhage may induce hyperglycemia and because loss of corpuscles would tend to reduce the oxygen-carrying capacity of the blood, the effects of loss of blood on the factors to be studied were examined. The total amount of blood in the body was assumed to be five per cent. of the body weight. Successive samples were drawn until about ten per cent. of the

total amount in the body had been removed before the final sample was taken. Although there were individual instances in which the blood sugar rose slightly above its initial value, it was usually found to progressively decrease. A slight but unmistakable decrease in the oxygen content and capacity of the blood was found following hemorrhage of this extent. Compare columns II and III, VI and VII, X and XI of Table I.

TABLE I.

Dog.	Date.	% Blood Drawn Previous to Final Sample.	Sugar in Mg. per 100 cc.				O ₂ Capacity in cc. per 100 cc.				O ₂ Content in cc. per 100 cc.				VIII-XII.	XII X VIII
			Initial.	Final.	Average for Series.	Dev. from Mean.	Initial.	Final.	Average for Series.	Dev. from Mean.	Initial.	Final.	Average for Series.	Dev. from Mean.		
			I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	XI.	XII.		
<i>A.</i>	II-6	11.6	76	77	75	5	23.1	22.2	23.0	0.8	15.6	14.7	15.2	0.5	7.8	66.1
	I-6	8.3	78	68	73	5	28.7	26.9	26.3	2.5	21.7	18.5	19.0	2.7	7.3	71.6
<i>B.</i>	10-30	16.6	95	83	81	14	17.7	16.1	17.1	1.0	9.3	8.2	9.3	1.1	7.8	54.2
<i>C.</i>	10-31	8.6	63	76	67	14	19.9	15.5	17.9	2.4	13.5	7.4	10.3	3.2	7.6	56.9
	II-7	10.1	72	69	65	11	20.6	16.5	18.1	2.5	9.8	10.2	10.0	1.6	8.1	55.2
<i>D.</i>	II-11	10.8	59	54	55	4	16.4	16.6	16.5	0.3	9.7	8.7	8.4	1.3	8.1	51.0
<i>E.</i>	II-20	14.0	62	51	59	7	22.1	19.7	21.4	1.7	13.3	9.0	11.6	2.0	9.8	54.2
	I-16	8.9	63	66	63	6	23.6	21.0	22.2	1.4	16.4	9.8	12.2	4.2	10.0	54.9
<i>F.</i>	12-18	9.8	72	69	71	2	24.5	23.2	23.4	1.1	16.6	14.0	14.5	2.1	8.9	61.9
<i>G.</i>	12-19	6.9	83	71	77	6	25.0	20.6	22.8	2.2	15.4	14.4	14.9	0.5	7.9	65.4
<i>H.</i>	1-15	7.5	74	71	74	3	27.6	26.6	27.2	0.6	22.0	19.0	19.0	3.2	8.2	69.9

Although the actual amounts of the blood sugar, oxygen content and capacity may vary somewhat when studied at different times in one individual, the average level assumed by each of these factors seems to be characteristic for the individual. See dogs *A*, *C*, and *E*, Table I. On the other hand, when the level of any one factor is compared in different individuals, wide variations are frequently found. Compare the sugars of dogs *A* and *E*, or the oxygen contents and capacities of *A* and *C*. Again variability of blood sugar seems to be characteristic of some individuals while constancy characterizes it in others. Because of this occasional variability, conclusions in the present paper are drawn only from averages of several determinations. The difference between the oxygen capacity and the oxygen content of the blood remains singularly constant from individual to individual under the conditions of our experiments. See column XIV, Table I.

Our experiments do not indicate that any immediate relationship exists between the sugar and either the oxygen capacity or oxygen content of the blood. There is a direct relationship, however, between the ratio of the oxygen content to the oxygen capacity, *i.e.*, the percentage saturation, and the sugar of the blood. From this it will be seen that the sugar varies in the opposite direction to the course which it takes in asphyxial hyperglycemia, which is a well-established phenomenon. This lack of agreement is, to our minds, apparent rather than real since the hyperglycemia of asphyxia is probably due directly, at least in part, to the increased amounts of adrenalin discharged under these conditions and only indirectly to the low content of oxygen. See columns IV and XV, Table I.

In a few experiments the relative volumes of the corpuscles and serum have been determined by a precision hematocrit. The content of oxygen per unit volume of corpuscles was then calculated and was found to bear a direct relationship to the blood sugar. The oxygen capacity per unit volume for the same experiments showed only slight variations. In these experiments the corpuscular volume might be taken as an index of the oxygen capacity of the blood. This confirms the observations noted above that there is a relationship between the blood sugar and the degree of saturation of the blood with oxygen. See Table II.

TABLE II.

Dog.	$\frac{\text{O}_2 \text{ Capacity}}{\text{Corp. Vol.}}$	$\frac{\text{O}_2 \text{ Content}}{\text{Corp. Vol.}}$	Sugar in Mg.	$\frac{\text{IV}}{\text{III}} \times 10.$
A.....	53	38	73	19
E.....	51	28	63	22
F.....	57	36	71	20
G.....	55	36	77	21
H.....	52	36	74	20

41 (1501)

Castration of hen-feathered Campines.By **THOMAS H. MORGAN.**[*From Columbia University, New York City.*]

A few races of domestic fowls, such as the Campines, have two kinds of males, one showing the ordinary cock-feathering, and the other the so called hen-feathering. Three young Campines of a hen-feathered strain were castrated, one before the adult feathers had appeared, one when they had begun to appear, and a third that was like the last but exceptional in certain respects. This bird will not be considered here. Both of the former birds developed cock-feathering after castration. It is evident that removal of the testes in this race produces the same effects as is produced in the hen feathered Sebrights, as reported three years ago before this Society.

42 (1502)

The vermilion gene and gynandromorphism.By **A. H. STURTEVANT.**[*From Columbia University and Carnegie Institution of Washington.*]

Morgan and Bridges (1919, Carnegie Inst. Wash. publ. 278) have recently described and discussed a large number of gynandromorphs of *Drosophila melanogaster*. They conclude that all female parts in gynandromorphs of this animal contain two X-chromosomes, and that all male parts contain only one X. The peculiarities of a given part are thus due to its own constitution, and are not dependent on the rest of the body for their differentiation. The same principle was found to hold for the characters determined by the sex-linked genes, which are carried by the X-chromosomes.

I have recently obtained evidence indicating that the sex-linked character vermilion forms an exception to this rule. A

gynandromorph was obtained in which the male parts showed the sex-linked characters scute, echinus, cut, garnet, and forked. These male parts included the whole head, in which region effects of all five of these sex-linked genes could be identified with certainty. Only one of these genes was present in the mother of the gynandromorph, which was heterozygous for the sex-linked genes eosin, ruby, forked, "vermilion lethal," and perhaps for vermilion. All five of them were known to be present in the single X of the father of the gynandromorph, which must therefore have been the X present in the male parts of the gynandromorph itself. But the X of the father was known to carry also the gene for vermilion, and the eyes of the gynandromorph were not vermilion. The not-vermilion color was, then, apparently determined not by the genetic constitution of the eye-pigment itself, but by that of some other portion of the body.

I have obtained two other gynandromorphs in which vermilion seems to have reacted in the same fashion; but these are not so certain as the case described. One of them can be accounted for by the rare type of "double-nucleus" gynandromorphism described by Morgan and Bridges, and in the other the eye-color, while not vermilion, was still not quite normal.

Among the large number of gynandromorphs described by Morgan and Bridges there are only three in which the male parts were known to be genetically vermilion while the female parts were not genetically vermilion, and in which these male parts included eye tissue. In all of them, however, eosin eye color was also present with the vermilion. Whether the eosin is responsible for the difference between these cases and the one reported here, or whether that difference is due to a difference in the genetic constitution of some other part of the body cannot be determined as yet.

43 (1503)

Age of parents and vitality in *Uroleptus mobilis*.By **GARY N. CALKINS.**

[From the Department of Zoölogy, Columbia University.]

Previous studies on the vitality of *Uroleptus mobilis* have shown that all ex-conjugants start with an initial high vitality as measured by the division rate. From this initial high rate, vitality gradually decreases during the life cycle until the race dies a natural death. After the first fifty days of a cycle endogamous conjugation may occur at any time with a resulting renewal of vitality in the ex-conjugants. Sufficient data have now been obtained to indicate that there is a difference in vitality of offspring given off at different age periods of the parental series, and a summary of such data is shown in the accompanying table.

Line 1 gives the total number of generations, or divisions, in each series; line 2 the total number of days required for those divisions; line 3, compared with line 5, indicates the extent of the renewal of vitality resulting from conjugation; line 4 gives the average division rate for any ten days of the entire life cycle on the assumption that divisions are equally distributed; line 6 gives the age of parents in days, at the time of conjugation which resulted in the offspring series, and line 8 the age in generations; lines 7 and 9 give the number of days and the number of divisions subsequent to the time of conjugation which resulted in the offspring series and represent the vitality remaining in the parental protoplasm.

High vitality in a series is indicated (1) by a high division rate which represents high metabolic activity; (2) by the large number of generations, or divisions, which the series undergoes, indicating a combination of high metabolic activity and endurance or lasting capacity; and (3) by endurance or long length of life of a series in days which may be combined with, or independent of, (1) and (2).

High vitality was shown in all three ways by series *C*, *F*, *I*, *P*, *U*₁, *U*₂, and *V*. Low vitality was shown in all three ways by series *Q*, *R*, and *a*, while series *W* and *H* were low in regard to

		C.	D.	F.	I.	L.	N.	O.	P.	U ₁ .	U ₂ .	V.	H.	J.	Q.	R.	W.	a.	A.	
		(A.)	(A.)	(C.)	(F.)	(I.)	(J.)	(M.)	(L.)	(L.)	(L.)	(P.)	(A.)	(A.)	(I.)	(J.)	(N.)	(P.)	(%)	
Statistics of Parents. of Offspring.	1	349	271	317	322	273	257	268	327	285	301	317	268	253	23	180	207	159	313	
	2	294	215	257	240	210	189	197	287	236	255	265	245	197	35	185	229	148	267	
	3	13.6	14.3	13.4	16.2	16.3	16.6	15.5	12.5	13.9	13.8	13.8	13.8	16.7	17.4	6.7	14.8	10.9	12.4	—
	4	11.8	12.4	12.3	13.4	13.0	13.6	11.4	12.8	11.8	11.8	12.0	10.9	12.8	12.8	6.6	9.7	9.0	10.7	11.7
	5	11.9	12.1	10.8	11.1	13.7	9.0	11.0	11.2	9.3	9.3	10.5	7.8	1.1	1.5	2.1	5.4	4.6	—	—
	6	70	100	50	100	120	120	60	70	140	140	140	90	170	250	200	160	130	210	—
	7	197	167	244	156	90	77	136	140	70	70	197	97	17	40	37	59	77	—	—
	8	78	137	86	143	199	188	108	116	208	208	120	237	311	316	245	225	291	—	—
	9	235	176	263	174	123	65	150	157	65	65	207	76	2	6	8	32	36	—	—

to date

division rate and number of divisions, but high in endurance. The other series were intermediate as regards vitality some of them being high in (1) and intermediate in (2) and (3) as in series *D*, *L*, *N*, *O*, and *J*.

Without exception the series showing high vitality in all three ways came from young parents. Thus the *C* series started when the parent *A* series was 70 days old and in the 78th generation; the *F* series started when the parent *C* series was 50 days old and in the 86th generation; the *I* series was started when the parent *F* series was 100 days old and in the 143d generation; the *P* series and both *U* series came from the *L* series which was 70 days old and in the 116th generation when the *P* series started, and 140 days, or twice as old, and in the 208th generation when *U*₁ and *U*₂ were started; the *V* series, finally, was started from the *P* series when the latter was 90 days and 120 generations old.

Without exception, also, the series showing low vitality in all three ways came from old parents. Thus the *Q* series was started when the parent *I* series was 200 days old and in its 316th generation and should be contrasted with the *L* series which came from the same parent when younger; the *R* series was started when the parent *J* series was 160 days old and in the 245th generation, and should be contrasted with the *N* series which came from the same parent when it was 120 days old and in the 188th generation; the *a* series was started when the parent *P* series was 210 days old and in the 291st generation and should be contrasted with the *V* series which came from the same parents when they were 90 days old and in the 120th generation. The *W* series and the *H* series both of which were weak in respect to division rate and number of generations came from parents that were similarly old, the *W* series from *N* when in its 225th generation; the *H* series from *A* in its 237th generation. The *J* series was exceptional, for, coming from very old parents (*A* series when 250 days old and in the 311th generation) it was weak only in endurance.

44 (1504)

Heredity of twin births.

By C. B. DAVENPORT.

[From the Eugenics Record Office, Cold Spring Harbor, L. I.]

About 1 per cent. of human births are twin births. However, there are certain families in which the proportion rises to 5, 10, or even 15 per cent. There can be little doubt then that, as in sheep, so in man, there are strains having a special tendency toward the production of twins.

It is commonly believed that this tendency toward the production of twins must be wholly a maternal quality, depending upon the inherited tendency to double ovulation.

The study of the heredity of twins is accompanied by certain difficulties, such as the fact that the occurrence of twins is frequently isolated, apparently haphazard, occurring perhaps in only one case in a fairly large fraternity, in which other representatives are single births. It will simplify the matter a little if we consider only those cases in which two or more sets of twins have arisen from a given mating.

The study of twins is still further complicated by the fact that they are of two types, namely twins derived from a double ovulation and twins derived from a single ovulation, there being a subsequent fission or budding of the fertilized egg. Such single-egg twins are easily distinguished clinically by being both enveloped in the same chorion. They are also always of the same sex.

The statement that the mother alone determines the tendency to twins is not, however, supported by the facts. Of the births giving rise to the fraternities of twin-repeating mothers, 4.5 per cent. are twin births. Of the births giving rise to fraternities of twin-repeating fathers, 4.2 per cent are twin births. These figures depend upon 355 and 289 labors respectively.

The sisters of twin-producing fathers have twins in 8.2 per cent. of labors, while the sisters of twin-producing mothers have twins in 5.5 per cent. of labors. Among the children of brothers of twin-producing fathers, 6.5 per cent. are twins, among the

brothers of twin-producing mothers 4.5 per cent of the children are twins. These figures indicate that the twin ratio is increased 4 to 7 times in twin-producing families and that the ratio of twin production is about as high on the father's as on the mother's side of a fraternity which contains 2 or more twins. This result disposes of the statement that fathers play no role in twin production, but at the same time raises the query—How can this be?

It is relatively easy to understand how the sperm may influence the early division of the fertilized egg so as to produce identical or 1-egg twins, and we find indeed that the rate of occurrence of twin production is high, both on the paternal and on the maternal side of such fraternities containing identical twins. The rate in both cases is about 13 per cent. But if one takes only those fraternities producing 2 or more sets of twins of unlike sex, we still find an equality of influence on the paternal and on the maternal side.

The difficulty in the way of understanding the equality of the part played by the father and the mother in the production of 2-egg twins arises from the assumption that such twins are due merely to double ovulation. Were they due merely to double ovulation, then there would be as many sets of twins born as there are double ovulations that occur at the time of conception. That this assumption is false is shown by several lines of evidence.

1. Not all of the eggs that are ovulated are fertilized. In the case of 4 sows' uteri examined the number of embryos (well advanced in development) found was 22 and the number of recent corpora lutea 34. This indicates that fully one third of the eggs laid at these periods of conception were not fertilized. This number is, I think, rather too high for a general statement, probably not more than 10–25 per cent. of eggs ovulated at favorable periods fail of fertilization. In humans also there is evidence based upon counts that have been made on the corpora lutea of non-pregnant and pregnant women that the rate of occurrence of 2.3 corpora lutea in the ovary is much greater than the occurrence of twins. Thus, to cite only a single study, in 33 sets of ovaries with corpora lutea or follicles about to burst, 5 (or 15 per cent) showed that double ovulation was occurring. It seems, therefore, certain that many more cases of double ovulation occur than of twins.

Again, of eggs that are fertilized, a certain proportion are aborted at an early age. This fact is striking in mammals also, where occasionally one finds, as John Hammond, 1914, points out and as I can confirm by numerous examinations of the uteri of swine, one or more embryos degenerate at an early stage. Also the medical literature has abundant references to blighted twin fetuses, and the large number of miscarriages under 3 months is a familiar fact. It is probable, since genetic work has revealed a great number of lethal factors, that a large proportion of these atretic embryos is due to such lethal factors.

The foregoing statements lead to the conclusion that our preconception that twinning is due merely to double ovulation needs revision. It is due to double ovulation combined with some other factors that induces a large proportion of such double ovulations to produce viable twins.

The other factor is the paternal one. It depends upon the capacity of the male to fertilize all of the eggs ovulated with sperm which contain no lethal factors. Now, both the capacity for complete fertilization (high fecundity) and the absence of lethal factors in the male germ cells are hereditary factors.

Attention may be called in passing to the fact that in human matings about 10 per cent. are sterile and, among these sterile matings, a certain proportion are physiologically such or at least no imperfections in the reproductive organs of either member of the pair can be detected.

Summary.—The influence of the male in twin production is determined by the circumstance that twin production does not depend merely upon double ovulation but upon such a quality of the sperm as shall result in a high proportion of fertilization of eggs ovulated and a small proportion of fertilized eggs containing lethal factors.

45 (1505)

The nutritive value of some nuts.By **F. A. CAJORI** (by invitation).

[From the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven, Conn.]

In earlier experiments on the utilization of protein-rich nuts by man, it was found that the "coefficient of digestibility" was practically equivalent to that of the protein coefficient of a mixed diet. The conclusion was drawn that such nuts, when used in the diet with due recognition of their concentrated make-up, are of a physiological value comparable with that of our more common foods.¹

The investigation has been extended to a study of the nutritive value of specific constituents of nuts. Johns' analysis of the nitrogenous components of the peanut and coconut suggest that they are sources of complete protein.^{2, 3} This has been verified by the feeding experiments of Johns with the coconut⁴ and Daniels with the peanut.⁵ Osborne and Mendel have maintained rats over long periods on excelsin, the principal protein of the Brazil nut, as the sole source of protein.⁶ Following the same technique, we have observed satisfactory growth on diets furnishing the almond, English walnut, filbert, and pine nut, respectively, as the essential source of protein in the ration, to the extent of 18 per cent. of the total diet. Experiments with the pecan nut have as yet been less successful.

The presence of abundant quantities of water-soluble vitamine in the coconut and peanut has already been demonstrated,^{4, 5}. We have found that normal growth can be secured when rats are fed upon otherwise adequate diets containing the almond, English walnut, Brazil nut and chestnut as the sole source of water soluble vitamine and that animals which have declined on a diet devoid of

¹ Cajori, F. A., 1918, *J. of Home Econ.*, 10: 304.

² Johns and Jones, 1917, *J. of Bio. Chem.*, 30: 33.

³ Johns, Finks and Gersdorff, 1919, *J. of Bio. Chem.*, 37: 149.

⁴ Johns, Finks and Paul, 1919, *J. of Bio. Chem.*, 37: 497.

⁵ Daniels and Loughlin, 1917, *J. of Bio. Chem.*, 33: 295.

⁶ Osborne and Mendel, 1912, *Zeit. f. Physiol. Chem.*, 80: 307.

water soluble vitamins promptly recover when either the almond, English walnut or filbert is introduced in the diet.

Investigations in this field are being continued.

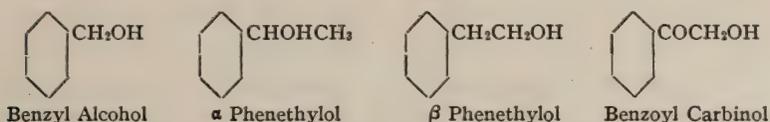
46 (1506)

The local anesthetic properties of benzoyl carbinol.

By AXEL M. HJORT and CHARLES E. KAUFMANN (by invitation).

[From the Department of Pharmacology, Yale University School of Medicine.]¹

Since Macht² observed that benzyl alcohol possessed local anesthetic powers, several of its homologues have been studied for like properties in this laboratory. These consist of α^3 and β^4 phenethylol and benzoyl carbinol. The structural relationship of these substances is:



Hirschfelder⁵ recently reported his observations on a series of compounds closely related to the above. β phenethylol and phenyl glycol were amongst these, the latter being the reduction product of benzoyl carbinol, the subject of this paper.

The relative efficiency of the substances investigated, with respect to their local anesthetic properties, is shown by the following table:

¹ This research has been supported by a grant from the Committee on Scientific Research of the American Medical Association.

² Macht, D. I., *Journ. Pharm. & Exp. Therap.*, 1918, xi, 263.

³ Hjort, A. M., and Kaufmann, C. E., *Ibid.* In press.

⁴ Hjort, A. M., and Eagan, J. T., *Ibid.*, 1919, xiv, 211.

⁵ *Proc. Soc. Pharm. & Exp. Therap.* (Dec., 1919), *J. Pharm. & Exp. Therap.*, 1920.

Substance.	Minimal Lethal Dose per 20-30 G. White Mice Mgms.	Quantity Non-lethal Intravenously in Dogs, Gms. per Kilo.	Minimal Effective Anesthetic Concentration on Rabbits' Cornea, %.	Minimal Effective Anesthetic Concentration in Human Skin, %.
Benzyl Alcohol.	50 ¹	0.2 ¹	1.25 ³	1/30 ²
α Phenethylol.	20 ²	0.1 ²	0.75 ²	1/40 ²
β Phenethylol.	40 ³	0.2 ³	1.00 ³	1/40 ^{3,4}
Benzoyl Carbinol.	40 ²	0.2 ²	0.50 ²	1/40 ²

¹ Macht.

² Hjort and Kaufmann.

³ Hjort and Eagan.

⁴ (1/40) 13 wheals in 21.

Sollmann⁶ found that procaine in the strength of 1/32 per cent. was the minimal concentration which anesthetized human skin when injected intradermally and tested according to the wheal method of Hoffmann.⁷ From the above table, therefore, it is seen that benzoyl carbinol is at least as efficient on the human skin as any known anesthetic.

Benzoyl carbinol is not as irritant on the tongue as the benzyl alcohol and its above mentioned homologues. In the skin, likewise, it does not induce as extensive a local reaction of the tissues. It is soluble in water to the extent of about one half per cent. at 20° C., but when heated to 50° C. a one per cent. solution can be made which does not alter within two hours. Benzoyl carbinol is, therefore, soluble within practical limits.

Summary.—1. Benzoyl carbinol possesses local anesthetic properties which in general are superior to those of its homologues herein discussed.

2. Benzoyl carbinol is less irritant to the body tissues than its congeners.

3. Its solubility in water is sufficient to make it a practicable local anesthetic.

4. It is the most stable of the series.

⁶ Sollmann, T., *Ibid.*, 1918, xi, 69.

⁷ Hoffmann, u. Kochmann, *Beit. Klin. Chir.*, 1914, xci, 489.

47 (1507)

A comparison of the action in patients of g-strophanthin and digitalis.By **ALFRED E. COHN** and **ROBERT L. LEVY**.

[*From the Hospital of The Rockefeller Institute for Medical Research, New York.*]

In the same patients we have compared the action of g-strophanthin given intravenously with the action of digitalis (digipuratum) given by mouth. Both drugs were standardized by the cat method. One cat unit equalled 0.1 mgm. g-strophanthin; one cat unit was equal to 0.1 gm. of digipuratum. The patients selected for treatment were as far as possible sufferers from fibrillation of the auricles. Both drugs were usually given in divided doses, the duration of administration being in several instances comparable.

The effect of the drugs on the speed of action, on the electrocardiogram, and on the duration of the effect on the rate of the ventricles when the auricles fibrillate, we report in brief now. The speed of the action is often faster with strophanthin than with digitalis, though when strophanthin is given in divided doses it may require nearly two hours to obtain an effect. In other instances an effect may be obtained, as is well known, in twenty minutes or less. An effect with digitalis has been observed in a little more than two hours.

With digitalis the effect on the rate of the ventricles outlasts that of strophanthin. It is rare for strophanthin to keep the rate low for more than five days; it did so once for nine days. Digitalis effect endures usually beyond ten days and has lasted as long as twenty-three days.

The effect on the T-wave of the electrocardiogram is absent or slight with strophanthin, and its duration when present transient. The effect with digitalis endures in the manner now familiar. With doses equal, in cat units, to the strophanthin given, the effect on the T-wave is not maximal. Larger doses of strophanthin than 1.1 mgm. were not given, so that the dose of

digitalis in this series was usually low (1.1 gm.). When on occasion we gave larger doses of digitalis, more striking effects on the T-wave were observed.

48 (1508)

The isoagglutinins and isohemolysins of the rat.

By **G. L. ROHDENBURG** (by invitation).

[*From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director.*]

The possibility that some of the irregularities in immunity against transplanted tumors might be correlated with the isoagglutinins or isohemolysins of the respective hosts prompted an investigation of these substances in the blood of rats. The animals tested were derived from three different sources showing rather marked external as well as biological differences. One group, pure white in color, was resistant to the growth of the Jensen rat sarcoma, showing a very high percentage of natural immunity; a second group, red and white in color, was equally resistant to the growth of the Flexner-Jobling rat carcinoma; a third group, hooded black and white, was equally susceptible to both tumor strains.

Fifty animals were tested in the following manner for the presence of either isoagglutinins or isohemolysins. Nine drops of serum were mixed with one drop of a 5 per cent. suspension of washed red cells in a test tube. In the first series of ten animals the serum of each animal was tested against the cells of every other animal, and the cells of each animal were tested against the serum of every other. Five series were carried through in this fashion, each series consisting of three animals of two of the groups and four of a third group.

Tests between animals of the same strain or between animals of different strains showed that neither agglutinins or hemolysins were demonstrable, this being contrary to the well-established phenomena in man, where four distinct groups have been found.

49 (1509)

Latent infection in experimental spirochaetosis.

By JOHN L. TODD.

[From McGill University, Montreal.]

The following observations were made while studying immunity to *Spirochæta recurrentis* in white rats. Since it had been suggested that an immunity might be maintained by persistent latent infection, it was necessary to make careful examinations for spirochætes in all animals exhibiting resistance to infection.

The work was done with strains of spirochætes which usually produced well-marked infection with one or more relapses. During the observation of several hundred animals it was noticed that parasites occasionally reappeared in the peripheral circulation after unusually long absences. It often happened that spirochætes were found in blood films, on one or two days, after they had been absent for from ten to fifteen days; once spirochætes were seen after an absence of twenty-one days. Blood, taken from the tail, was examined for spirochætes in thick dehemoglobinized and stained films. Examinations, throughout the work, were made daily.

It often happens that a normal infection follows when a rat is inoculated with blood from an animal, once infected, although repeated examinations have failed to find spirochætes in it. In many instances, infection resulted when rats were inoculated with blood taken from other rats which were killed from fifteen to twenty days, in one instance twenty-seven days, after spirochætes were last found in them by microscopical examination.

Although the inoculation of blood, and other material, obtained by killing an experimental animal, is sometimes a more efficient method of detecting spirochætal infection, it is not always so and, since it involves the destruction of the animal supplying the material inoculated, it is a method which cannot be repeated. Inoculation of material in which living spirochætes have been seen occasionally fails to infect one of two rats inoculated at the

same time; sometimes, also, the infection produced remains unseen by microscopical examination and is only detected by killing the inoculated animal and by sub-inoculating another rat with blood from it. Inoculations are less likely to fail, or result in unobvious infection when considerable quantities of blood are inoculated.

In order to obtain considerable quantities of material for inoculation from rats in which spirochaetes could not be found by blood examinations, blood was aspirated from hearts and spleens were excised. Of these two methods the aspiration of heart's blood was the more successful. Under chloroform, it is easy to aspirate from 1 to 2.5 ccm. of blood from the heart of an adult rat without injuring the animal. By so doing, spirochaetes were shown, in one instance, to be present in an apparently immune rat thirty-two days after the parasites were last seen by the daily examination of blood films. Previously, this rat had twice been infected by inoculation and had acquired an immunity shown by two unsuccessful inoculations. Two subsequent, also unsuccessful, inoculations showed that the rat was still immune to the strain employed in this experiment.

It should be remarked that several similar experiments did not reveal latent infections in immune rats.

50 (1510)

The influence of water-soluble vitamine on the nutrition of dogs.

By **W. G. KARR** (by invitation)

[From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Ct.]

Studies on a few species of animals have indicated that the water-soluble vitamine is of importance to nutrition during all stages of life and that prolonged absence of it from the diet will lead to a diseased condition. In the present investigation the role of water-soluble vitamins in the nutrition of the dog has been under consideration.

The animals were fed a diet devoid of water-soluble vitamine and consisting of lard, sucrose, inorganic salts, and protein in the

form of casein or wheat gluten. It furnished about 70-80 calories per kg. body weight. Such food mixtures were consumed readily by the dogs during a period from three to nine weeks; thereupon they began to refuse part or all of their food. Characteristic symptoms, similar to those described by Voegtlin and Lake¹ were developed by some of the animals. The ultimate failure to eat was always noted.

Ingestion of as little as 1 gm. of brewer's yeast, which had been previously dried, will cause a quick recovery of the desire to eat. 5 gm. of the dried yeast will bring about the disappearance of the polyneuritic symptoms in 8-12 hrs. and a quick recovery of the animal to its normal condition.

The utilization of the protein nitrogen is not effected by the lack of water-soluble vitamine.

Studies in metabolism on diets with and without vitamine are being conducted.

The fat-soluble vitamine is apparently of less importance than the water-soluble in the nutrition of the adult dog.

¹ Voegtlin and Lake, *Am. J. Physiol.*, 1918, xlvii, 558.

SCIENTIFIC PROCEEDINGS

ABSTRACTS OF COMMUNICATIONS.

One hundred fifth meeting.

*College of the City of New York, New York City, February 18,
1920, Vice-President Wallace in the chair.*

51 (1511)

Pituitary feeding and egg production in the domestic fowl.

By SUTHERLAND SIMPSON.

*[From the Physiological Laboratory, Medical College, Cornell
University, Ithaca, N. Y.]*

Clark¹ found, in 1915, that the egg production of chickens (White Leghorns) was markedly increased by feeding dried pituitary (anterior lobe) in amounts representing 20 mg. of the fresh gland to each hen per day. The effect became evident four days after the feeding began and lasted for several days after the last dosage. The experiments were carried out in May, when the laying curve was on the decline, nevertheless the egg production reached 100 per cent. for the experimental pen (35 hens on two consecutive days laid 35 eggs) or double what it had been before the feeding was begun. He lays emphasis on the fact that the glandular material he used was taken from young, growing animals—calves and lambs.

I have repeated the experiments of Clark when the egg production was low and declining—in June and July, 1917, when low and increasing—December and January, 1917-18, when high (about the maximum)—April, 1918—and again in March and April, 1919, and have been unable to observe any increase from pituitary feeding. The adult gland (ox) was used and also that of the growing animal (calf), and the method of preparation adopted

¹ Clark, L. N., *Jour. Biol. Chem.*, 1915, 22, 485-491.

by Clark was followed as closely as possible. To begin with, the amount given by him was administered, viz, the equivalent of about 20 mg. of fresh pituitary substance (anterior lobe), to each hen individually, in a gelatine capsule, and when no result was obtained the dose was doubled and later trebled. In no case was any distinct effect produced, the egg-laying curves running practically parallel with those of the control pens. Single Comb White Leghorns were employed.

52 (1512)

Some conditions affecting thyroid activity.

By **W. B. CANNON** and **P. E. SMITH.**

[From the *Physiological Laboratory, Harvard Medical School.*]

1. Gentle massage of the thyroid gland in the cat for two or three minutes will cause an increased rate of the denervated heart amounting in some instances to 33 per cent. over the basal rate. The development of the maximal increase of rate is usually slow, requiring from thirty to sixty minutes and passing off in a similarly slow manner.
2. Massage of another gland, *e.g.*, the submaxillary, does not cause this effect.
3. The augmentation of heart rate caused by thyroid massage occurs in the absence of the adrenal glands.
4. Stimulation of the cervical sympathetic trunk as it leaves the stellate ganglion induces a similar augmentation of the rate of the denervated heart: this does not occur if the thyroid gland has previously been removed.
5. If the cardiac fibers from the stellate ganglia are severed, as well as the vagus nerves, and an afferent nerve such as the sciatic or brachial is stimulated under a degree of anesthesia which will permit reflex retraction of the nictitating membrane and dilation of the pupil, there is a primary increase of rate due to adrenal secretion, followed by the slowly developing increase characteristic of the thyroid effect.
6. If the vagi and the cardiac fibers of the stellate are cut,

and the animal is asphyxiated under conditions which permit the eye changes described above, there is a similar primary rise due to adrenal secretion, followed by the secondary thyroid effect.

7. If the thyroid glands have been previously removed, sensory stimulation and asphyxia induce only the increase of rate due to adrenal discharge.

53 (1513)

Studies in the absorption of fats.

By T. F. ZUCKER. (By invitation).

[From the Department of Pathology, College of Physicians and Surgeons, Columbia University.]

The general impression of workers in the field of fat metabolism, with regard to the path of absorption, seems to be that while most of the fat enters the circulation by way of the thoracic duct, a smaller portion can be absorbed directly into the blood stream. The most recent discussion of the subject is by Bloor.¹ The results of previous workers are, briefly, as follows: Walther² recovered in anesthetized animals only a small fraction of the absorbed fat from the lymph of the thoracic duct. Munk and Rosenstein³ recovered from the discharged lymph 60 per cent. of the fat fed to a patient with lymph fistula. Frank⁴ tied off the thoracic duct after feeding fat and still found the fat of the blood to increase during absorption. Hamburger⁵ tied off three equal-sized loops of intestine and in the central loop ligated all lymph vessels. Then after injecting an oil and soap emulsion, he noted that this was absorbed from the central loop despite the tying off of the lymph vessels, although it was distinctly less in amount than in the control loops. Munk and Friedenthal,⁶ in a preliminary communication, describe experiments similar to those of Frank, but use more precautions, such as tying off the

¹ Bloor. *Jour. Biol. Chem.*, 1916, XXIV, 457.

² Walther, *Archiv. f. Physiologie*, 1890, p. 328.

³ Munk and Rosenstein, *Virchow's Archiv*, 1891, CXXIII, 230.

⁴ Frank, *Archiv. f. Physiologie*, 1892, p. 497; 1894, p. 297.

⁵ Hamburger, *Archiv. f. Physiologie*, 1900, p. 554.

⁶ Munk and Friedenthal, *Zentralb. Physiologie*, 1901, XV, 297.

ductus lymphaticus communis dexter, besides the thoracic duct, to avoid possible anastomoses. In general, their findings are the same as those of Frank and they also conclude that the blood can absorb products of fat digestion directly from the intestine.

d'Errico¹ approached the subject from a different angle. He determined the amount of ether extract in simultaneous samples of portal and jugular blood of an animal near the height of fat absorption after a meal. He finds more ether extract in the portal than the jugular blood and concludes that direct absorption by the blood takes place.

In criticizing d'Errico's work we must say that ether extract from blood and blood fat are not the same,² as d'Errico's own results show, since he finds even after feeding fat, not more than a maximum of 412 mg. of ether extract per 100 c.c. of blood, while the "total fat" of fasting blood is usually 600 mg. or more. d'Errico's ether extract was probably principally the cholesterol, plus small quantities of other lipoids. The work of the other authors mentioned above all has this in common, that the conditions of the experiment are far removed from the normal, and in several cases the analytical technique leaves much to be desired.

In connection with another research, our attention was called to the fact that this point had never been settled and we undertook a few experiments similar to those of d'Errico, but using the newer analytical procedures of Bloor¹ for the determination of cholesterol, fatty acids and phosphatides. In the phosphatide determination, Kober's strychnine molybdate reagent was used. Hemoglobin was determined by the acid hematin method using a Dubosq or Kober colorimeter. In the earlier experiments, ether was used as anesthetic, but since ether inhibits the absorption of fats quite markedly, we dispensed with the anesthetic and instead stunned the dog by a quick blow on the occiput. This, when properly executed, is quite humane and very suitable for the requirements of our experiments. The following is the protocol of one of the experiments of which there were five in all.

¹ d'Errico, *Arch. fisiol.*, 1907, IV, 513.

² See Klein and Dinkin, *Zeitschr. physiol. Chem.*, 1914 (XCII), 302; Kumagawa and Suto, *Biochem. Zeitschr.*, 1908, VIII, 212; Hürthle, *Ztschr. physiol. Chem.*, 1895, XXI, 331.

A sample of jugular blood was taken from a dog of 14 kg. weight at 12:45, and then 50 c.c. of olive oil were given by stomach tube. Another jugular sample was taken at 3:45. At 4:45, the dog was stunned, the abdomen was opened and samples of portal and mesenteric blood taken. Then another sample of jugular was taken. The analyses of these samples are given in the table in gms. per 100 c.c. of blood. The cholesterol remains constant. The administration of 50 c.c. of olive oil raised the phosphatides 36 per cent. and the fatty acids 49 per cent. There is no difference, within the limits of error of the method (5 per cent.), between the jugular, mesenteric and portal. The absorption in this particular experiment was moderate. In another experiment, the fatty acids were increased 90 per cent. and still there was no difference between the portal and jugular.

	Cholesterol.	Phosphatides.	Fatty Acids.	Hemoglobin.
12:45. Jugular before giving oil...	.23	.42	.65	125%
3:45. Jugular.....	.22	.52	.93	123%
4:45. Animal stunned, portal.....	.23	.57	.98	126%
Mesenteric.....	.22	.56	.97	122%
Jugular.....	.23	.58	1.02	125%

To sum up the evidence then, we can safely say (1) that d'Erri-co's findings cannot be accepted because of the methods employed, and that they are not corroborated by our own data, (2) that in the experiments in which tying-off of lymph vessels was done, absorption may have been due to the lymph stasis, and (3) that the data here presented preclude the assumption of any very marked participation of the blood vessels in the absorption of fat leaving open the question of absorption of small amounts beyond the detection of the methods used.

54 (1514)

Studies in the diastatic activity of the blood and blood sugar curves indicating a decreased carbohydrate tolerance in hyperthyroidism.

By JOHN A. KILLIAN

[From the Laboratory of Pathological Chemistry, New York Post Graduate Medical School and Hospital.]

In studying the carbohydrate tolerance in hyperthyroidism and other conditions, three methods have been employed, the

diastatic activity of the blood, the fluctuations in the level of the blood sugar, and the sugar excreted in the urine after the administration of a definite amount of glucose by mouth. The diastatic activity was determined by the technic of Myers and Killian,¹ the blood sugar was estimated by the Lewis-Benedict method as modified by Myers and Bailey;² the Benedict-Osterberg³ technic was utilized in the determination of the urinary sugar. It was early appreciated that fasting for twelve hours increased the tolerance for carbohydrate, so that glucose tolerance curves carried out on a fasting stomach did not truly represent the individual's carbohydrate assimilation limit. In our series the patients received in the morning, a standard meal which consisted of one egg in any form, two slices of bread, a cup of coffee, without sugar or milk, or a glass of water. Two hours later, the patient voluntarily emptied the bladder, and then received about 100 c.c. of water to drink. One hour after this, a specimen of blood and a specimen of urine were obtained. These represent the control specimens. The glucose was then administered by mouth in a 50 per cent. solution, 1.75 gm. per kilogram of body weight. At hourly intervals the specimens of blood and urine were obtained, and in these and in the control the sugar was estimated. The diastatic activity was determined only on the control specimen of blood.

The 23 cases presented are from a series of 275 patients examined, representing normal and various pathological conditions.

The control specimen of blood represents the level of blood sugar 3 hours after the standard meal. In normal cases it varied from 0.09 to 0.10 per cent.; in dyspituitarism of the Frölich type, in acromegaly and in Addison's disease a hypoglycemia was noted. In hyperthyroidism, however, the blood sugar ranged from 0.11 to 0.13 per cent. In normal cases the urinary sugar excretion was found to be 20 to 30 mgs. for the control hour; the output in dyspituitarism, acromegaly and in Addison's disease was diminished; the hyperthyroids excreted from 24 to 95 mgs.

Following the intake of glucose, the blood sugar in normal

¹ Myers and Killian, *Jour. Biol. Chem.*, 1917, XXIX, 179.

² Myers and Bailey, *Jour. Biol. Chem.*, 1916, XXIV, 147.

³ Benedict and Osterberg, *Jour. Biol. Chem.*, 1918, XXXIV, 195.

cases reached the maximum from 0.13 to 0.15 per cent. at the end of one hour and in two hours time returned to normal. In hypofunctions of the endocrine system, there was noted practically no increase in the blood sugar; on the contrary hyperfunction of the thyroid produced a pronounced hyperglycemia after the glucose ingestion which persisted for 4 to 5 hours. In the hourly specimens of urine from these cases there was an evident glycosuria, which for a period of 3 hours totaled 1.4 per cent. of the glucose given. These specimens of urine gave positive reactions for sugar with Benedict's qualitative copper solution. The normal cases excreted during 3 hours from 0.1 to 0.2 per cent. of the glucose given and gave negative reactions with the copper reagent.

The diastatic activity of the blood was found to be decreased in dyspituitarism, acromegaly and Addison's disease, but in hyperthyroidism there was a distinct increase ranging from 20 to 34, except in 2 very early cases.

55 (1515)

The influence of systemic changes on local tissue reactions.

By JOHN AUER.

[From the Laboratories of The Rockefeller Institute for Medical Research.]

In order to explain the occurrence of a massive, brawny edema at the site of operative wounds in sensitized, reinjected dogs, the following working hypothesis was formed: Sensitized animals which have circulating ineffective amounts of the antigen, may react locally with anaphylactic changes if through any mechanism (for example, by inflammation and edema) an effective dose of the antigen accumulates in those tissues.

This conception was then tested experimentally in the rabbit.

Rabbits were sensitized by four muscular and intraperitoneal injections of 4 c.c. horse serum at 4 to 5 day intervals. 15 to 21 days after the last injection, 10 c.c. of horse serum were given intraperitoneally. 30 to 45 minutes after the reinjection, none of the rabbits having shown any collapse, the hairy surface of the

ear was moistened with 1 c.c. of commercial xylol in order to produce irritation and edema.

Two groups of control experiments were carried out. In the first group, each normal rabbit received 10 c.c. of horse serum intraperitoneally and after 30 to 45 minutes the ear was treated with the same kind and amount of xylol. In the second group of controls no horse serum was administered, merely one ear was treated with xylol.

The results were strikingly different and support the working hypothesis. In a great majority of the 36 *controls* edema of a fair to good degree developed in six hours; it was generally less in 24 hours, and after 48 hours had largely disappeared, leaving a practically normal ear. No dermatitis with blisters and crusts was observed; nor were hemorrhages or gangrene seen except once among the controls. In this instance the loss of substance was not more than one half millimeter of the ear tip.

In the *sensitized* series (17 rabbits) the edema of the ear developed more slowly and less frequently than among the controls. The maximum was reached generally in 24 hours, and the subsidence was slow, lasting 5 to 9 days. Within 22 to 48 hours, numerous small hemorrhages, blisters and subsequent crusts appeared. In these rabbits (10 out of 17) the ear after a few days showed the picture of an exfoliative dermatitis. This dermatitis involved $1/3$ to $1/2$ of both surfaces of the ear, healed slowly as the deeper tissues were affected, and always caused dry gangrene of the ear tip. The loss from gangrene varied from 1 to 3 centimeters. Healing was usually complete in three to four weeks. The ear stump was bald at first, but slowly became covered with a new growth of white hair.

56 (1516)

The selective effect of the accelerator nerves on ventricular systole.

By C. J. WIGGERS and L. N. KATZ.

[From the Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio.]

Object of Investigation.—Acceleration of the heart in man is chiefly due to a varying balance of control exerted through the

vagi and the accelerator nerves. The only hopeful method of determining which mechanism is at least predominantly concerned is suggested by the observations of Baxt, Pavlow, Frank and Reid Hunt and others¹ that the accelerator nerves exert a predominant effect on the length of systole, whereas the vagi nerves affect chiefly diastole. This, on superficial examination, of course appears contrary to any mechanical conception of the cardiac regulation, such, for example, as the "law of Uniformity of Behavior" advanced by Henderson and his coworkers.²

It is quite obvious that, if, as appears from volume curves recorded by many different investigators, the rate of ejection diminishes late in systole, then, on the basis of the uniformity law enunciated by Henderson, the length of systole will be only slightly altered during the longer cycles but will be progressively more and more abbreviated in a mechanical way as the heart cycles become shorter and shorter. Inasmuch as vagus section and vagus stimulation ordinarily do not alter the heart rate beyond the range where slight variations might be expected, whereas accelerator stimulation quickens the beat so that pronounced shortening of systole might be anticipated, the *mere demonstration that accelerator stimulation shortens the systole is proof neither of any specific influence of these nerves over ventricular contraction, nor does it prove that the heart deviates in its beat from a mechanical scheme. Only if it can be shown that the periods of systole during accelerator nerve stimulation vary materially from those which may be accounted for on the basis of volume curves, can any inference be drawn as to a selective action of the accelerator nerves on the ventricle.* Such proof has, however, not been presented by previous investigators, hence a reconsideration of the subject seemed desirable.

Methods.—As a criterion of the length of systole, we used the interval elapsing between the first and second heart sounds recorded from animals by the direct method described by Wiggers and Dean.³ Sounds were recorded consecutively during the

¹ For literature see Hofmann in Nagel's "Handbuch der Physiologie des Menschen," 1905, I, 269.

² Henderson, *Amer. Jour. Physiol.*, 1909, XXIII, 351.

³ Wiggers and Dean, *Amer. Jour. Med. Sciences*, 1917, CLIII, 666; *Amer. Jour. Physiol.*, 1917, XLII, 476 also Wiggers, *Arch. Int. Med.*, 1918, XXII, 28.

following experimental conditions, the general order being varied only to suit particular occasions:

- (1) during normal cardiac action under morphine and chloretone anesthesia;
- (2) during stimulation of stellate ganglion or accelerator nerves;
- (3) following section of both vagi;
- (4) during stimulation of stellate ganglion with vagi severed and
- (5) during combined stimulation of vagus and accelerator mechanisms.

Using these results, we have found it possible, on the basis of the duration of systole and diastole of a long vagus beat to construct for each animal a theoretical volume curve and to calculate from this the theoretical relations of systole and diastole at all heart cycles in that animal provided the "law of uniformity" applies. With these "theoretical systoles" in different cycle lengths we compared (best in the form of a plot) the actual systole lengths of different cycles during the above mentioned experimental activities.

Results.—We find as follows:

1. The lengths of normal systoles agree very closely with those of theoretical systoles.
2. Vagus section, causing cardiac acceleration, decreases the length of systole slightly but in accordance with its theoretical duration.
3. Vagus stimulation, causing only a moderate slowing, increases the length of the actual systole, practically in accordance with the theoretical values at different rates.
4. Accelerator stimulation shortens the length of actual systole far more than that of the corresponding theoretical systole, indicating that *in some way the accelerator nerves are capable of shortening systole more than can be accounted for by the mechanical operation of the law of "Uniformity of Behavior."*

We append a few data of a single experiment typical of many others to support these conclusions.

Cycle.	Theoretical Systole.	Actual Systole Determined.	
.5422	.23 -.24	Normal controls.
.6723	.23 -.24	
.3419	.135-.14	Accelerators stimulated. Vagus intact.
.50215	.155-.16	
.5622	.215-.22	Vagi cut.
.59225	.22	
.90235	.28	Vagus stimulation.
.98238	.275	
1.5025	.25	
.28175	.125-.135	Accelerator stimulation, vagi cut.
.3319	.14	
.63228	.20	Combined vagus and accelerator stimulation.
.80235	.20	
.83235	.205	
.96238	.20	
1.0824	.20	

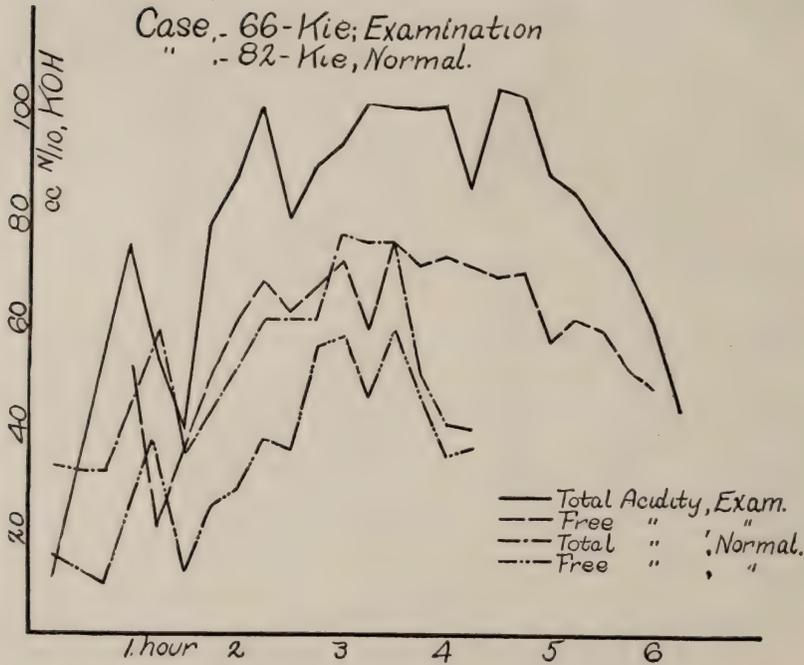
57 (1517)

The influence of anxiety on gastric digestion.

By RAYMOND J. MILLER, OLAF BERGEIM, and PHILIP B. HAWK.

[From the Laboratory of Physiological Chemistry, Jefferson Medical College, Philadelphia, Penna.]

The study of the influence of emotional strain on digestion in man offers some difficulties due to the fact that the emotions cannot be readily controlled, nor are the subjects of extreme emotion readily amenable to experimentation. We were, however, able to obtain an interesting illustration of the profound effect of mental anxiety on gastric digestion in the case of one of our subjects. The man was a first-year medical student who had previously served as a subject of gastric tests. He was given one hundred grams of fried chicken on the morning of an important examination in chemistry, and was asked to write out his answers during the course of the test. He was plainly worried over the outcome of the examination and of his year's work. The resultant effect upon gastric digestion in prolonging evacuation for over two hours with high intra-gastric acidity is charted in the figure. The



same chart gives the normal digestion curve for fried chicken on this subject as obtained a week later under the best mental conditions.

58 (1518)

Is unpalatable food properly digested?

By CLARENCE A. SMITH, RALPH C. HOLDER, and PHILIP B. HAWK.

[From the Laboratory of Physiological Chemistry, Jefferson Medical College, Philadelphia, Penna.]

It is well known that different psychic stimuli promote or retard the secretion of digestive juices. The following experiment was conducted to determine whether the ultimate return to the body from unpalatable food was different from the return from the same food palatably served.

The experimental procedure was simple. A 7-day period during which the subjects were on a uniform diet, served palatably and amid pleasant surroundings, was followed by a 2-day period

during which the same diet was fed in an unpalatable condition and in dirty and unpleasant surroundings. The food was rendered unpalatable and unappetizing by the following treatment. All the food ordinarily used for each meal (meat, biscuits, jelly, corn-starch pudding, oleomargarine, etc.) was stirred together in a large, flat porcelain dish. The dish itself was smeared with animal charcoal, as was the beaker used as a drinking glass. The table was dirty and strewn with dirty dishes. A little indol was sprinkled about under the table. The subjects were kept in ignorance of the constituents of the unpalatable mixture. The food was so unpalatable that one subject vomited his first meal shortly after he had eaten it.

The following table shows the findings on the other subject.

Period.	No. of Days.	Nitrogen.							Percentage Utilization.
		Ingested.		Excreted.			Balance.		
		Daily, Grams.	Period, Grams.	Urine, Grams.	Feces, Grams.	Total, Grams.	Period, Grams.	Daily, Grams.	
Palatable.....	7	10.75	75.25	62.95	10.06	73.01	+2.24	+0.32	86.7
Unpalatable....	2	10.75	21.50	17.03	3.09	20.12	+1.38	+0.69	85.7

The differences in utilization of the palatable and unpalatable foods were quite small as were the variations in nitrogen retention. This short test indicates that flavor is not the outstanding dietetic asset that some people would have us believe.

59 (1519)

Amino-acid synthesis in the organism of the white rat.

By HOWARD B. LEWIS and LUCIE E. ROOT.

[From the Laboratory of Physiological Chemistry of the University of Illinois, Urbana.]

It is generally conceded that the organism of the white rat must be supplied with an adequate amount of lysine if normal growth is to result. The purpose of the present series of experiments was to determine whether α -aminocaproic acid (norleucine), which has been shown to be present in the proteins of the central

nervous system, could replace lysine in the diet. No evidence exists that in the young rat aminization of fatty acids with the resulting formation of aminoacids takes place. It was considered that it might be possible to introduce a second amino group into the caproic acid molecule provided one amino group was already present in the α position. In view of the current idea as to the probable position of the ϵ amino group of lysine in the protein molecule, the possibility also suggested itself that synthesis of a protein without the free amino group of lysine might occur by substitution of norleucine for lysine in the molecule.

Young white rats were fed diets containing 18 per cent. gliadin (wheat), lard, purified butter fat, starch, and protein-free milk. Maintenance or slow growth was observed. That this failure of normal growth was due to protein deficiency was demonstrated by normal growth of young rats on a similar diet in which casein replaced gliadin. Substitution of 0.5 and 1.5 per cents. of norleucine for equivalent amounts of gliadin did not alter the rate of growth. Normal growth occurred, however, when 1 per cent. lysine replaced an equivalent amount of gliadin or was substituted for the norleucine. These results are in agreement with those of Osborne and Mendel in demonstrating the efficiency of lysine as a supplement to a gliadin diet. The experiments with norleucine offer no evidence that this amino acid can replace lysine in nutrition.

60 (1520)

A pharmacodynamic analysis of Straub's morphine reaction.

By DAVID I. MACHT.

[From the Pharmacological Laboratory, Johns Hopkins University and the James Buchanan Brady Urological Institute, Baltimore.]

In 1911 Straub and later his pupil Herrmann described a biological reaction for morphine which they thought was specific for that alkaloid and could possibly be used in forensic work.^{1, 2} They noted that after injections of small amounts of morphine in mice there followed a peculiar stiffening and bending backwards

¹ Straub, *Deutsche med. Wochst.*, 1911, 1426.

² Herrmann, *Biochem. Zeitschr.*, 1912, XXXIX, 216.

or curling of the tails of those animals. No adequate explanation of this phenomena was given by the authors. In May, 1918, Van Leersum¹ described the same phenomenon in the rat and showed that this peculiar stiffening and upbending of the tail was really due to a spasm of the sphincters of the anus and especially of the bladder and that the same phenomenon could be produced by exciting spasm of the sphincters by other agents, chemical or physical. The researches of the present author on the influence of various opium alkaloids on smooth muscle, which were first reported before the Pharmacological Society in December, 1917,² and later, in the PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE in February, 1918, throw additional light on the mechanism of Straub's phenomenon. The author has shown that in respect to their action on plain muscle, the opium alkaloids fall in two groups: the piperidine-phenanthrene group of which morphine is the principal member, and the benzylisoquinoline group, of which papaverin is the principal member. It was shown that morphine stimulates the contractions and increases the tonus of smooth muscle, while papaverin inhibits the contractions and lowers the tonus of the same.³ Injections of morphine in the mouse and rat produce a spasmodic contraction of the bladder and its sphincters, and this probably plays the important rôle in the production of Straub's phenomenon. Van Leersum described the vesical spasm after morphine injections as being of spinal origin. Inasmuch as Macht's experiments were performed on isolated tissues, including the sphincters of the rectum and the bladder, we are forced to regard Straub's phenomenon as being at least in part due to a peripheral effect of morphine.

Further work by the present author sheds more light on the subject. Inasmuch as the morphine molecule structurally is a combination of piperidine and phenanthrene nuclei, experiments were made to determine the effect of phenanthrene and piperidine separately on plain muscle. Experiments with phenanthrene itself revealed that it has no effect on plain muscle. Phenan-

¹ Van Leersum, *Nederland. Tijdscht. voor Genesk.*, 1912, LXII, 1374.

² Macht, *Jour. Pharmacol. and Exp. Therap.*, 1918, XI, 176.

³ Macht, *Jour. Pharmacol. and Exp. Therap.*, 1918, XI, 389.

threne, however, is practically insoluble in water and experiments with it had to be made using alcoholic solutions of the drug. An attempt was therefore made to obtain a simple compound of phenanthrene which is soluble and could be more conveniently employed for tests *in vitro*. Through the kindness of the chemist, Dr. Charles Rouiller, a simple phenanthrene sulphonic acid was prepared and a sodium salt of the same, being neutral in reaction and freely soluble in water, was employed in making the pharmacological tests. It was found that sodium phenanthrene-sulphonate had very little or no effect on the contractions and tonicity of isolated smooth muscle organs. On the other hand, experiments with piperidine hydrochloride revealed at once that piperidine is a powerful stimulant of smooth muscle, causing an increase in the rate and strength of its contractions and an increase in its tonicity. Straub's phenomenon may, therefore, be ascribed to the peripheral effect of the piperidine portion of the morphine molecule: and, indeed, the author has found that when a suitable dose of piperidine hydrochloride is injected into a mouse or a rat, a condition resembling Straub's phenomenon is often produced soon after the injection.

The interesting effect of piperidine upon smooth muscle, mentioned above, has, as far as the author has been able to ascertain, never been described before. A complete study on the action of piperidine on plain muscle is at present the subject of further investigation, and will be published in due time.

61 (1521)

The action of prostatic extracts on isolated genito-urinary organs.

By DAVID I. MACHT and S. MATSUMOTO.

[From the Pharmacological Laboratory, Johns Hopkins University, and the James Buchanan Brady Urological Institute, Baltimore.]

The contractions and tonicity of various surviving excised genito-urinary organs were studied *in vitro*: firstly, under normal conditions, and secondly, after the addition of prostatic extracts

to the medium in which the tissues were suspended. The following organs were examined: Uterus and Fallopian tube, bladder and ureters, and vas deferens and seminal vesicle. Aqueous saline extracts of the ram's, dog's, bull's, steer's and human prostate glands were used. It was found that all of the above organs are stimulated *in vitro* by prostatic extracts, provided a sufficient dose is used; but that different organs require different doses of the glandular extract. The uterus and tubes were found to respond to the smallest quantities of prostatic extract; the bladder and ureters came next in the order of their response to such treatment; while the vas deferens and seminal vesicles required the largest doses of the extracts to give evidence of any physiological effect. As a result of the experiments, the authors conclude that the prostatic extracts cannot be regarded as having any specific or marked influence on the tonus and contractions of the bladder *in vitro*. Fuller data will appear in due time in the *Journal of Urology*.

62 (1522)

Phenol elimination in the dog after intravenous injection of nearsphenamine.

By CHARLES WEISS

[From the *Dermatological Research Laboratories, Philadelphia, Pa.*]

Although Ehrlich himself recognized the importance of discovering the fate of salvarsan in the animal body, it was Sieburg¹ who first approached the solution of this problem. This investigator succeeded in isolating from the urine of a syphilitic patient who had received repeated intravenous injections of salvarsan the following substances: *p*-aminophenol, *o*-acetylamino phenyl hydrogen sulphate, oxycarbanil, an aminohydroxyphenylarsonic acid, $C_6H_8O_4N$ As, and a hydroxyphenylarsonic acid, $C_6H_7O_4As$, besides inorganic arsenates and arsenites. He concludes that salvarsan is broken down in the system in the following way (Chart 1):

¹ Sieburg, E., *Zeitschr. physiol. chem.*, 1916, 97, 53-108. Abstr. in *Chem. Abstracts*, 1917, 2, 270-1. (Original article not available in U. S. A.)

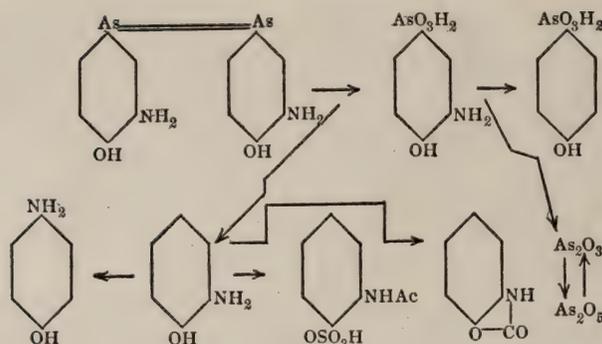


CHART I.

"Apparently *o*-aminophenol is to a comparatively small extent converted into the isomeric, highly toxic *para* compound, while the remainder is conjugated either with H_2SO_4 with the introduction of an acetyl group, or with urea with the subsequent elimination of 2 N H_3 radicals."

Sieburg also studied the behavior of *para*-arsenobenzoic acid and of 3-amino-arsenobenzoic acid in the body of the calf and concludes that in all cases a cleavage of the toxophoric $-As=As-$ linking in 'arseno' compounds occurs in the living organism, whereby not only is the toxicity reduced, but transformation takes place into compounds which are more soluble in water and less easily soluble in other media. The characteristic effects are due to the small proportion of the substance which escapes oxidation to the arsenic acids, and to the subsequent liberation of the As_2O_3 and As_2O_5 ."

Sieburg's discovery of conjugated phenol derivatives resulting from the metabolism of salvarsan as well as our independent investigations on the causes of the reactions following intravenous injections of arsphenamine and neo-arsphenamine¹ led us to direct our attention to the mechanism of detoxication which the body possesses,—the power of rendering innocuous various aromatic toxic substances by conjugation with sulphuric acid, *d*-glucuronic acid, urea, glycocoll, bile acids, etc. It seemed plausible to venture the hypothesis that in those patients in whom severe reactions are observed within a few hours or days after intravenous injection of arsphenamine or neo-arsphenamine,

¹ Schamberg, J. F., Kolmer, J. A., Raiziss, G. W., and Weiss, Charles, *Arch. Dermat. & Syph.*, 1920, 1, 235-256.

detoxication is subnormal, owing to injury sustained during the course of the infection by the hepatic, renal and other cells concerned in this mechanism. Of course, normal variations in this process cannot be overlooked as a possible factor.

We have, therefore, studied, in a preliminary way, the elimination of free and conjugated urinary phenols after the intravenous injection of a single large tolerated dose (50 mg. per kilo) of neo-arsphenamine into the dog.

Method.—A normal healthy female dog (16.82 kilo) was employed and was kept on a constant diet. The technique followed was that of Folin and Denis¹ with the modifications described by Dubin.²

Results.—The results are summarized in Table I and indicate the following:

TABLE I.
PHENOL ELIMINATION AFTER A SINGLE INTRAVENOUS INJECTION OF NEO-ARSPHENAMINE (0.841 Gr.).¹

Daily Elimination	Control Period.		1st Neo Period.		2d Neo Period.		3d Neo Period.		Summary.					
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Periods of Exp.	Free.	Total.	Conj.	% Free.	% Conj.
1st day	106	156	117	158	95	147	90	127	Normal	528	734	206	72	28
2d "	117	187	96	125	115	173	108	143	1st neo	506	673	167	75	25
3d "	78	110	82	109	105	140	119	173	2d neo	581	875	294	66	34
4th "	106	149	106	143	152	238	88	138	3d neo	511	728	217	70	30
5th "	121	132	105	138	114	177	106	147	Total 3 neo periods	1,598	2,276	678	70	30
Total 5 days	528	734	506	673	581	875	511	728	15 days "Extra" phenols	14	74	60	19	81
									15 days					

¹ All figures refer to milligrams unless otherwise indicated.

1. The elimination of "normal" free and conjugated phenols is quite uniform from day to day, if the animal is kept on a constant diet. The work of Folin and Denis is thus confirmed.

2. After a single intravenous injection of neo-arsphenamine, no appreciable variation in phenol elimination is observed during the first period of five days. During the next period there is an increase in both the free and conjugated phenols. During the

¹ Folin, O., and Denis, W., *Jour. Biol. Chem.*, 1915, 22, 305-308.

² Dubin, Harry, *Jour. Biol. Chem.*, 1916, 26, 69-91.

third period of five days there is a return to practically normal excretion.

3. The injection of a dose of 0.841 gr. of neo-arsphenamine results in the elimination of a total of only 74 mg. "extra" phenols during a period of 15 days; 81 per cent. of this is in the conjugated state. Of the "normal" phenols only from 10 per cent. to 30 per cent. is conjugated. Since in the colorimeter 1 mg. of neo-arsphenamine reacts like 0.466 mg. phenol, we have the striking observation that only 9.2 per cent of the dose of the drug injected is eliminated in the urine in the form of a phenol or phenol derivative. This suggests the following possibilities: (a) Some of the drug is eliminated as phenols in the feces; (b) a portion of it is burned; (c) a portion is retained or "fixed" by the various tissues, notably the liver, for a period much longer than 15 days; (d) most of the drug is oxidized to the stage of *inorganic* arsenic and eliminated as such; (e) a portion is eliminated as nitro-phenols which do not react with the Folin reagent. The latter suggestion seems the most improbable but not impossible.

TABLE 2.

PHENOL ELIMINATION AFTER INJECTION OF NEO-ARSPHENAMINE AND AMMONIUM PERSULPHATE.¹

Daily Elimination.	Normal Control Period.		Persul. Control Period.		1st Period Neo. and Persul.		2d Period Neo and Persul.		Summary.					
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Periods.	Free.	Total.	Conj.	% Free.	% Conj.
1st day...	99	154	137	188	136	190	235	265	Normal period	523	775	252	68	32
2d " ...	91	154	128	181	191	272	263	301	5 days with persul. only .	604	834	230	73	27
3d " ...	106	152	106	135	137	188	320	365	1st period after neo and persul...	885	1,163	278	76	24
4th " ...	113	153	124	173	212	265	275	331	2d period after neo and persul...	1,426	1,630	204	88	12
5th " ...	114	162	109	157	209	248	333	368	Total 10 days neo and persul...	2,311	2,793	482	83	17
Total 5 days ...	523	775	604	834	885	1,163	1,426	1,630	"Extra" phenols 10 days....	1,103	1,123	21	98	2

¹ All figures refer to milligrams.

Since the administration of sulphates is known to counteract the effects of phenol poisoning, and particularly in view of the work of Bufalini,¹ we studied the phenol elimination in the same dog after a single intravenous dose of neo-arsphenamine during the time that she was receiving daily subcutaneous injections of ammonium persulphate.

Method. The animal was kept on the same constant diet. Phenol elimination was studied for five days (control period); ammonium persulphate was now given subcutaneously twice daily in 2.5 per cent. solution in physiological saline in doses of 10 c.c. and phenol excretion was measured during this period. A single intravenous dose of 0.841 g. of neo-arsphenamine was now given and persulphate injections and estimation of urinary phenols was continued for ten more days.

Results are summarized in Table 2, and indicate the following:

1. The subcutaneous injection of ammonium persulphate which theoretically would furnish the organism with additional sulphuric acid for phenol conjugation, does not result in the elimination of any "extra" conjugated "normal" phenols. During a period of five days, only a slight increase in the free "normal" phenols was observed.

2. After the intravenous injection of a single dose of 0.841 g. of neo-arsphenamine and the daily subcutaneous administration of the persulphate, an enormous increase in the output of "extra" free phenols was observed. Simultaneously, a marked diminution in the excretion of "extra" conjugated phenols was noted. The animal also showed definite symptoms of intoxication. We must, therefore, conclude that the "extra" free phenols were due entirely to tissue destruction resulting from the toxic effects of the persulphate.

The writer is indebted to Dr. John A. Kolmer, Head of the Department of Pathology, for his encouragement and unfailing kindness throughout the course of this work.

¹ Bufalini, G., *Archives ital. de Biol.*, 1903, 40, 131-140.

63 (1523)

The influence of hunger and temperature upon the utilization of food substances.

By **EDUARD UHLENHUTH.**

[From the Laboratories of the Rockefeller Institute for Medical Research.]

In the larvæ of amphibians when the thyroid glands begin to excrete the thyroid hormone, metamorphosis of the larvæ into adult animals takes place. Since larvæ with fully developed thyroid glands frequently do not metamorphose, and since in the thyroid gland of the normal larvæ, large quantities of "colloid" are present in the follicles for a considerable time before metamorphosis, it is very probable that the thyroid gland cannot begin to excrete its hormone unless a second factor is present in the larvæ. It seems that this factor is elaborated during the process of growth and must be present in a definite quantity in order that the thyroid function may begin. This is shown in two tables in which for several series of the marbled and the tiger salamanders, the age at which metamorphosis took place and the rate of growth were recorded. The greater the rate of growth the shorter the length of the larval period. As a consequence the product of the rate of growth into the duration of the larval period gives a fairly constant value K . The maximum deviations observed can be traced back to certain causes which will be discussed immediately.

Hence it is evident that metamorphosis not only depends upon the thyroid hormone but also on a second substance, the quantity of which increases in the same ratio as growth. This second substance must be present in a certain quantity in order that metamorphosis can take place. The rate at which it is formed from the same kind of food and for the same rate of growth is distinctly influenced by two factors; by the quantity of food available to the larvæ, and by the temperature.

A series of the marbled salamanders (*A* 1916) required 186 days to metamorphose, when they grew at a rate of 0.21; K was 39. Another series (*C* 1916), which was fed the same food but kept

at a temperature lower by 10 degrees, needed at the same rate of growth 243 days to metamorphose. K was therefore higher than for series *A* (51). The same was true for other series of marbled as well as tiger salamanders; in all of these series the length of the larval period was increased more than the rate of growth was decreased, and consequently the product K increased. In short, during the same amount of growth less of the substance was produced at low temperature than at high temperature, though the same kind of food was given to all the larvæ.

If one diminishes the quantity of food instead of lowering the temperature, the rate of growth decreases as in the case of lowered temperature, and the length of the larval period increases, as is shown in the record of four series of marbled salamanders. All four series were kept at the same temperature and fed the same kind of food, but Series *D* received only one half, Series *E* only one quarter the amount of food which was given to Series *C*, and *A* received still less food. Consequently, as in lowered temperature, the rate of growth was decreased with the diminution of food, and the length of the larval period was increased. But while in lower temperature the length of the larval period was increased more than the rate of growth was decreased, hunger increased the length of the larval period less than it decreased the rate of growth, and consequently K decreased instead of increasing as in lowered temperature.

When the same kind of food is available to the amphibian organism, a certain substance required for metamorphosis is elaborated, at the same rate of growth, the more easily the less food there is available, and the less readily the more the temperature is lowered.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF COMMUNICATIONS

One hundred sixth meeting

College of the City of New York, Presbyterian Hospital, N. Y. City,

March 17, 1920

64 (1524)

A case of lipuria associated with chronic nephritis.

By **L. BAUMAN** and **G. H. HANSMANN.**

[From the Department of Internal Medicine, State University of Iowa.]

Clinical, pathological and chemical data of a case of lipuria associated with chronic nephritis which terminated in uremia. The lipuria was influenced by the amount of fat in the diet. The absence of coagulated protein, the scarcity or absence of cells in the urine and the apparent absence of a fistulous communication between the urinary passages and the lymphatics at autopsy indicate that the lipuria was due to an altered permeability of the renal cells. The available evidence makes it probable that there are at least two types of lipuria, the one associated with a fistulous communication, the other entirely due to an abnormal condition of the kidney cells.

65 (1525)

Calcium in the blood in diseases of the skin.

By **WILLIAM C. THRO** and **MARIE EHN.**

[From the Laboratory of Clinical Pathology, Cornell University Medical College, New York City.]

Before proceeding with experiments on the efficacy of calcium in the treatment of furunculosis it was thought advisable to deter-

mine the amount of calcium in the blood of patients with boils. We proceeded on the idea that the calcium might be decreased in such patients. As it happened, we first examined a number of patients with acne and we were much surprised to find the amount of calcium markedly increased in such. After testing about ten patients with acne we examined our first patient with boils and found the calcium was slightly below normal in amount. In one other patient with a large boil on the arm the amount of calcium was extremely low; that is, 5 mg. per 100 c.c. of plasma. Thus it is seen that in most of the patients with acne the amount of calcium in the blood was markedly increased while in some of the patients with furunculosis the amount of calcium was very low.

So far as we have searched the literature we have not found any results reported on the amounts of calcium in the blood of patients with acne and furunculosis. The amounts of calcium found by us in the blood of patients with acne were so extremely large that we determined to subject the gravimetric method, which we used, to a careful investigation. We ran through six blanks by the ashing method, which we used, with negative results. In one test we used 20 c.c. of our distilled water and found it free from calcium. In case No. 2, 22 c.c. of plasma were obtained at one time and divided into two portions of eleven c.c. each. In one portion the calcium was determined by Mr. Osterberg and in the other by Thro. The results disagreed by only 1.8 mg. per 100 c.c. of plasma. In case No. 6, Mrs. Ehn divided the whole blood into two lots of 25 c.c. each and her determinations of calcium agreed exactly. Six times the titration method, as given by Halverson and Bergeim¹, was used as a control. While the results were not in strict agreement with those obtained by ashing, it was noted that if high results were obtained with one they were also obtained with the other. It is our opinion that the ashing method is more accurate with large amounts of plasma than with small amounts. It is also believed that it is better to use blood plasma or serum than whole blood, since results are obtained sooner and variations in corpuscular volume do not affect the results. In every one of our patients the volume of corpuscles was greater than the volume of plasma.

¹Halverson, J. O., and Bergeim, O., *Jour. Biol. Chem.*, 1917, 32, 159-170.

As is well known, the giving of a diet low in carbohydrate^{1,2} tends to eliminate the calcium from the body. This was tried twice on patients with acne, resulting in the lowering of the calcium in the blood.

TABLE I.

Case No.	Name.	Diagnosis.	Quantity Used, C.c.	Mg. Ca in 100 C.c.	
				Ashing.	Titration.
2	N. W. C.	Acne	Plasma, 11	19.9 ¹	
	"	"	" 11	18.1	
5	Miss C.	" Jan. 7, 1920. ²	Whole blood, 25	24.5	
	"	"	" " 25	13.6	
6	E. G. C.	" Jan. 19, 1920.	" " 25	17.6 ³	
	"	"	" " 25	17.6	
7	M. C.	"	" " 25	12.0	
8	Mr. A.	"	Plasma, 15	17.8	
11	Mary F.	"	" 19	17.8	
12	Mr. R.	"	" 12	10.7	
17	Mrs. V.	"	" 19	25.4	
18	Miss M.	"	" 10	25.7	
20	L. R.	"	" 18	25.6	
24	Mr. L.	"	" 12.5	14.4	
25	Mr. S.	"	" 10	15.0	17.4
3	Mrs. R. V.	Furunculosis	Whole blood, 25	13.6	
13	Dr. B.	"	Plasma, 10	8.2	
23	J. D.	"	" 14	5.0	6.0
22	R.	"	" 18	11.8	14.4
27	Mr. Mc A.	"	" 20	11.5	
21	M. T.	Folliculitis barbae	" 12.5	22.24	20.83
15	— —	Epilepsy	Whole blood, 25	12.4	
16	— —	"	" 25	8.0	
26	G. C.	Diabetes	Plasma, 12	20.4	17.6

¹ Mr. Osterberg ascertained the Ca in one lot of 11 c.c. and Thro in another portion of 11 c.c.

² Between the two dates the carbohydrate intake was low.

³ 50 c.c. of blood divided into two portions of 25 c.c. each.

H. J. Schwartz has found that in acne there is a carbohydrate fermentation of the feces when examined by the Schmidt method. He has also reported that in skin diseases there is an increase in the blood sugar³ The blood of one diabetic was tested for the calcium content but the amount was not decreased.

¹ Thayer, W. S., and Hazen, H. H., *Jour. Exper. Med.*, 1907, 9, 1-17.

² Mendel, L. B., and Benedict, S. R., *Am. Jour. Physiol.*, 1909-10, 25, 25.

³ Schwartz, H. J., Heimann, W. J., and Mahnken, H. C., *Jour. Cutan. Dis.*, 1917, March.

The pathologic lesion of acne is in the sebaceous glands of the hair follicles, while in furunculosis the sweat glands become infected. It is of interest, then, to note that in one patient with folliculitis barbae, in which the hair follicle is involved, the amount of calcium in the blood was increased.

GRAVIMETRIC METHOD USED.

The blood was collected in a flask containing 90 mg. of sodium citrate. After centrifugalization the plasma was drawn off and evaporated in a platinum dish; ashed with addition of nitric acid. The ash was taken up with dilute hydrochloric acid. The solution was made alkaline with ammonia and then faintly acidulated with acetic acid. The iron was precipitated with 20 per cent. sodium acetate. The calcium was precipitated from the filtrate with 4 per cent. ammonium oxalate. The solution was allowed to stand over night. Gooch crucibles packed with asbestos were used. The calcium was weighed as calcium oxide.

66 (1526)

The preparation of animal nucleic acid.

By **EMIL J. BAUMANN.**

[From the Chemical Laboratory of the Montefiore Home and Hospital, New York City.]

The proposed method depends on the following properties of nucleic acid: (1) that it is separated from its protein combination by treatment with sodium hydroxide, (2) that it is soluble in dilute acetic acid and, (3) that it is precipitated by hydrochloric acid, or in the case of dilute solutions, by hydrochloric acid in the presence of magnesium sulphate.

Fresh, trimmed glandular tissue, finely hashed, is mixed well with twice its weight of tap water and 100 c.c. of 50 per cent. sodium hydroxide is then added for each kilogram of tissue. The material is then heated until all except the connective tissue is dissolved (40° C.-70° C.). Neutralize hot and at once with strong acetic acid; the reaction should finally be distinctly acid to litmus. Bring to a boil and filter hot on large folder filters.

When the filtrate has cooled an aliquot of 200 c.c. is taken and

concentrated hydrochloric acid diluted with an equal volume of water is added from a burette until precipitation is complete, carefully avoiding an excess. If the nucleic acid does not flock out after the solution has been quiescent for several minutes, the same process should be repeated upon another aliquot after first adding 5 per cent. of magnesium sulphate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$). Magnesium sulphate renders nucleic acid more insoluble. A proportionate quantity is then added to the bulk of the solution. The nucleic acid, which forms large flocks and slowly settles, is washed successively with 60, 80, and twice with 95 per cent. alcohol by decantation, filtered on hardened filter paper, washed again with 95 per cent. alcohol and finally with ether and then rapidly dried at about 70°C .

The yields from different glandular tissues vary from 0.8 per cent. to 1.5 per cent.

67 (1527)

Some human digestion experiments on raw white of egg.

By **MARY SWARTZ ROSE** and **GRACE MACLEOD**.

[*From the Department of Nutrition, Teachers College, Columbia University.*]

Experiments to determine the relative digestibility of raw and cooked white of egg in the human subject were carried out with four young women students in two periods of five days each. As they all had practically the same food requirements, they took the same diet, quantitatively and qualitatively, throughout the experiment, the only variation being the change from raw whites to cooked whites for half the time, and some differences in the ways in which the whites were prepared. The egg whites furnished 48 grams of protein per capita per day out of a total of 67 grams. Besides the eggs the diet consisted of rice, cream, saltines, butter, olive oil, fruit juice and a small amount of lettuce. The cooked eggs were never subjected to a temperature or method of cooking which would toughen them unduly; the raw whites were taken unbeaten by one person, all beaten light by another, and about half and half by the other subjects.

The coefficients of digestibility for the two diets have been calculated for the total protein and for the egg white protein alone.

COEFFICIENTS OF DIGESTIBILITY FOR RAW AND COOKED EGG WHITES.

Subject	For Protein of Whole Ration.			For Protein of Whites of Eggs Only.			Remarks.
	Eggs Cooked, %.	Eggs Raw, %.	Diff. (in Favor of Cooked).	Eggs Cooked, %.	Eggs Raw, %.	Diff. (in Favor of Cooked).	
G. S. .	85.7	82.6	+3.1	85.4	81.0	+ 4.4	½ beaten
L. S. .	86.2	82.5	+3.7	86.0	80.8	+ 5.2	½ beaten
M. K. .	83.2	83.9	-0.7	81.8	82.8	- 1.0	All beaten
M. F..	83.3	75.7	+7.6	81.9	71.2	+10.7	All unbeaten

In these experiments the raw white was as well digested as the cooked if beaten light, and the difference between the two was not striking when taken half beaten and half unbeaten. The greatest difference was observed when the whites were swallowed with no subdivision whatever, and even then the difference between the cooked and the raw was only 11 per cent. when as many as ten or twelve whites were taken per day. The effect of beating on the coefficient of digestibility is under further investigation.

68 (1528)

A study of the sugar and oxygen relationships in the blood of dogs during exercise.

By **ERNEST L. SCOTT** and **A. BAIRD HASTINGS**.

[From the Department of Physiology, Columbia University, New York.]

As a phase of our investigation of the chemical changes in the organism resulting from exercise, the following study of the sugar and oxygen relationships in the blood of dogs was undertaken.

Samples of blood amounting to about 1 per cent. of the body weight were drawn from the external jugular vein. Determinations of the blood sugar by the MacLean method, of the oxygen by the Van Slyke technique, and of the volume of the corpuscles by a precision hematocrit were made every two hours during the course of six-hour working periods. During these periods the dogs ran on an electrically-driven, horizontal treadmill at the rate of about five miles per hour. For each such experiment, we made a corresponding series of control observations on the same

dog similar in all respects save that the exercise factor was eliminated. The figures given in the table are the averages of the data obtained from five dogs.

The fact that the averages of the initial samples are so nearly identical for each constituent, indicates that our series is sufficiently long to permit the attaching of significance to subsequent variations.

Since it is desirable to compare figures which were obtained under conditions identical except for the added element of exercise, we wish to point out that in studying the table the figures given for exercise should be compared with the figures for the corresponding periods of rest, rather than with the initial values for the exercise experiments. This is indeed necessary in the interpretation of the effect of work because variations of significant magnitude in the control series make comparisons between initial and successive periods unjustifiable for this purpose.

	Experimental Conditions.	Number of Experiments Performed.	Elapsed Time in Hours.			
			0.	2.	4.	6.
Oxygen content c.c. per 100 c.c. blood.....	Rest	12	16.5	13.7	14.5	14.0
	Work	13	16.1	17.3	17.0	16.6
Difference due to work.....			-0.4	+3.6	+2.5	+2.6
Oxygen capacity c.c. per 100 c.c. blood.....	Rest	12	24.6	23.8	23.6	23.1
	Work	13	24.8	25.6	26.4	26.4
Difference due to work.....			+0.2	+1.8	+2.8	+3.3
Volume of corpuscles expressed as per cent.....	Rest	8	49.9	47.1	46.9	47.9
	Work	10	49.1	50.6	51.0	51.5
Difference due to work.....			-0.8	+3.5	+4.1	+3.6
Sugar as glucose mg. per 100 c.c. blood.....	Rest	12	69	68	70	66
	Work	13	69	66	64	60
Difference due to work.....			0	-2	-6	-6

From the table it will be seen that the oxygen content of the blood rises during the first period of work as compared with the first period of rest and falls slightly thereafter. These results may be due among other things, to increased aeration in the lungs, increased oxygen capacity of the blood, and to an increased rate of blood flow through the tissues.

The oxygen capacity of the blood rises progressively, but at a decreasing rate, throughout the period of work. This phenomenon

is correlated with a parallel rise in corpuscular volume as indicated in the table.

The concentration of sugar falls steadily throughout the work period. It should be noted, however, that the variations during the first period in work and those during the same period in rest are almost identical, but from this point on there is a divergence which becomes quite pronounced in the later stages of the experiment.

It is perhaps worthy of notice that there is a rather distinct change in the magnitude of the effects of work after the first period. This we have interpreted as indicating that the day's work falls into at least two phases; first, one in which certain augmenting effects of exercise apparently predominate, second, one in which fatigue phenomena are relatively more prominent.

69 (1529)

Further studies in the measurement of vitamine content.

By WALTER H. EDDY and HELEN C. STEVENSON.

[From the Department of Physiology Chemistry, Teachers College, Columbia University and the Department of Pathology, New York Hospital.]

During the past year two papers have appeared in the *Journal of Biological Chemistry*, one by Dr. Bachman¹ and the other by Dr. Williams², which postulate the requirement of the water-soluble B vitamine in yeast growth. Both these papers suggest the use of yeast cells as a means for the measurement of vitamine content and present a technique that may be used to that end.

In an earlier number of the PROCEEDINGS³ we reported on a study of the suitability of the Bachman test for vitamine measurement and some of the difficulties encountered. Since that time we have carried out similar studies of the Williams technique and as a result have devised a method which employs features of both

¹ Bachman F., Vitamine requirements of certain yeasts. *Journ. Biol. Chemistry* 1919, xxxix, 235.

² Williams, Roger J., The vitamine requirement for yeast. A simple biological test for vitamine. *Journ. Biol. Chem.*, 1919, xxxviii, 465.

³ PROCEEDINGS SOC. EXPER. BIOL. AND MED., 1919, xvii, 52.

authors but seems to permit of better control and to be at the same time more easily handled than the Williams method. This method is presented herewith, not as a finished product for we are still experimenting with certain details of standardization, but with a view to stimulating criticism and suggestion.

The Bachman test measures the vitamine activity in terms of gas generated; it is really a measure of enzyme activity. This fact makes it difficult to be sure that the stimulus is a growth stimulus or merely an enzyme control in any given test. The Williams test measures the effect of the vitamine in growth of yeast cells and this seems to us a more reliable indicator than the gas production. On the other hand the hanging drop method of Williams makes difficult the control of concentration during incubation and we found the preparation of drops containing single yeast cells far from easy to prepare. We believe that our method obviates both these difficulties while retaining the yeast cell count as an indicator.

The Method.—The illustration shows the tools used, being essentially those of the opsonin technique. The first step is the preparation of two capillary pipettes by drawing out in the flame a 5 mm. glass tube as shown in *A*. This tube is marked at the center with a pen point (1) and with the aid of a drop of mercury accurately calibrated into units of equal volume on each side of the center point (2) and (3). The two halves are then separated at the point (1) into two pipettes. Each pipette is then heated at the large end and a constriction made to permit a flame seal later, the end plugged with cotton and the pipette sterilized. After sterilization and by fitting a rubber bulb to the end as in *B* the pipette is ready for use. After filling as described below the tip and constriction point are sealed in the flame and the tube is ready for incubation, *C*.

The materials necessary for the test are the pipette described above, a dilute suspension of yeast cells in Nageli solution, and the vitamine extract to be tested. These are prepared as follows: A pure culture of Fleischman round yeast is maintained on an agar slant. Two days before the test a transfer is made to a fresh slant and in all our tests, cells of 48 hour growth are used. From such a slant the smallest amount of yeast that can be taken up on a

needle point is transferred to 10 c.c. of Nageli solution in a sterile test tube and the tube shaken from 1¾ to 2 hours on a shaking machine. At the end of that time the uniformity of the emulsion is tested by removing ten units of the suspension with the pipette, blowing them out on a microscope slide, staining and counting. If the counts are uniform the suspension is used, if not it is shaken further. This uniformity of the emulsion is extremely important in comparing results. Having secured a uniform emulsion the pipettes are prepared as follows: Two units of a sterile extract of vitamine are first drawn up into the pipette (the unit we have used is about 1/800 c.c.). We have prepared our extracts in various ways but in all cases they have been sterilized for two 30-minute intervals in the Arnold Sterilizer with a 24-hour interval. Next two units of yeast suspension are drawn up. By manipulating the bulb a bubble of air separates the yeast and vitamine in the tube and permits accurate measurement. When both materials are in the tube they are drawn up to the large part of the tube and mixed. The tube is then sealed as described above. The control tube contains the yeast cells in the Nageli solution (two units) but no vitamine. Our Nageli solution is the same as used by Dr. Bachman, being a sterilized solution of the following components: 100 c.c. distilled water; 10 gms. dextrose; 1 gm. ammonium nitrate 0.05 gms. calcium phosphate, 0.5 gms. potassium acid phosphate; 0.25 gms. magnesium sulfate.

After the tubes are filled and sealed they are incubated at 35° Cent. for the time necessary, usually 18–24 hours. At the end of that time the ends are broken off, the rubber bulb adjusted and the contents blown out on a specially prepared counting slide, fixed and stained and can then be counted at leisure. For this purpose we prepare common microscope slides by etching 7 mm. squares on them, experience having shown that such a square will hold the contents of a tube. In this way it is possible to get a series of the contents of ten or twelve pipettes on one slide. Counting is done under the high power with the aid of a mechanical stage.

Results with the Method.—The methodology reported above has been arrived at by experiment. The necessity for accurate calibration, the need for uniform suspensions of yeast, the size of

the units etc. are the result of preliminary trials and tests that need not be reported here in detail. Certain questions however arise at once and some of our results to date are presented here as partial answers to these questions pending the accumulation of more complete data. The first question that arises is naturally as to the specificity of the test. Bachman and Williams have gone into this matter somewhat but we believe that our results with the above technique demonstrate additional evidence that this test is specific for the so-called antineuritic vitamine or water-soluble B. Dr. Funk kindly supplied us with a specimen of his purified antineuritic vitamine prepared after his well-known method in 1913. A water solution of this material sterilized in the Arnold sterilizer was tested with the results given below. We also made comparative studies of an extract of navy bean made after the McCollum method⁴ before and after shaking with Lloyd's reagent. This reagent⁴ is supposed to remove quantitatively the B and apparently with little effect upon the other constituents of the extract. The results follow:

TABLE I.

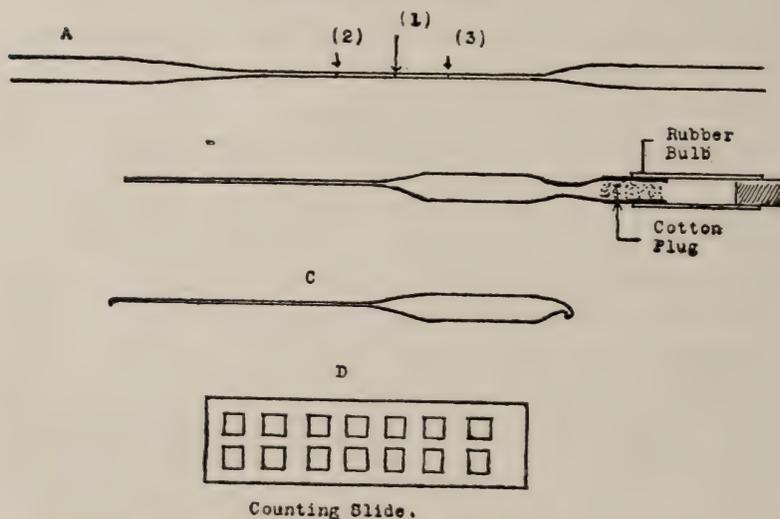
Vitamine Preparation Tested.	No. Yeast Cells in Unit.	Incubation Period.	Cell Count of Incubated Tubes.	
			Vitamine Tube.	Control Tube.
Water sol. Navy bean (a).	7-8	20 hours	11,237	113
Water sol. Navy bean (b).	2	20	672	15
Water sol. Navy bean (c).	2	20	633	15
Same after shaking with Lloyd reagent (a)	7-8	20	100	113
Same after shaking with Lloyd reagent (b)	2	20	2	15
Same after shaking with Lloyd reagent (c)	2	20	0	15
Funk 1913 preparation	7-8	20 hours	404	11
	2	20	31	2
	2	20	68	2

These results seem to demonstrate that what Funk calls the antineuritic vitamine as prepared by him and what we call water-soluble B as prepared by the McCollum method both respond to the test whether they are identical in character or not. The absence of salts and other substances present in the crude navy

⁴ McCollum and Simmonds, A study of the dietary essential, water-soluble B. *Journ. Biol. Chem.* 1918, xxxiii, 55.

bean extract resulting from the Funk method seems to indicate that it is the vitamine and not the impurities that is responsible for the action. Many more experiments are of course necessary to settle this point fully but these preliminary ones justify faith that we are here dealing with a specific test for vitamine. We hope to confirm them in much greater detail later.

DIAGRAM OF APPARATUS.



A (2) (1) (3) B Rubber Cotton C D Counting Slide
Bulb Plug

The second question that arises is as to whether it is possible to compare solutions by this test and actually measure vitamine content quantitatively. Experiments in this direction have consumed most of our time to date and have led to the technique presented, since the earlier tests showed the necessity for rigorous control in each feature of the test. We have not yet attained satisfactory results in this respect but believe it is attainable by improvement in technique. In this connection it must be borne in mind that aside from uniform yeast suspensions, accurate calibration and other mechanical details the test is biological. Yeast cells like rats vary in metabolic activity, the vitamine necessary to stimulate growth does not vary directly with concentration but exhibits an optimum and minimum effect which must be

established in the comparative standard used. These factors complicate the problem. The following results show some of these difficulties and are given rather to suggest the problems than as conclusions. All these features are under study and we hope soon to present a report of progress toward their solution:

TABLE II.

Vitamine Preparation Used.	Concentration.	Period of Incu- bation.	Count of Incubated Tubes.	
			Vitamine Tube.	Control Tube.
Water sol. vitamine from Navy bean, F24.....	c/1	24 hours	5312	5
F24.....	c/2	24	3192	28
F24.....	c/1	18	6161	14
	c/2	18	472	58
	c/8	18	59	20
F24.....	c/1	18	9724	123
	c/2	18	362	60
	c/8	18	85	9
F24.....	c/1	18	6248	48
	c/2	18	729	60
F24.....	c/1	18	8531	97
F24.....	c/1	6	24	2
	c/2	6	147	6
	c/4	6	119	3

The above were made with the first pipettes before accurate calibration or standardized suspensions were made. The following were results with calibrated pipettes but the suspensions were not entirely uniform as shown by a count of 25 units of the suspension used. These units were taken after an hour shaking and varied as follows: 18-37-12-1-3-2-2-0-15-35-46-78-57-6-27-31-33-12-11-17-34-21-60-29 cells.

F24.....	c/1	6	27	15
	c/2	6	9	one control
	c/4	6	14	for series
	c/1	6	20	6
	c/2	6	16	one control
	c/4	6	60	for series
	c/8	6	12	

The following were made with calibrated pipettes and a suspension for which eight counted units resulted as follows (2 hours shaking): 4-2-3-1-3-5-2-3 cells.

F24.....	c/1	22 hours	492	1
	c/2	22	660	one control
	c/4	22	102	for series
	c/8 +	22	11	

It is unnecessary to suggest the various fields of application for the test in testing the effect of heat, alkali, quantity, etc. The above represents merely a preliminary communication and we hope soon to report such modifications as will meet the defects that have shown in the preliminary study outlined here.

70 (1530)

A study of local anesthetics in respect to their antiseptic properties.

By **D. I. MACHT** and **Y. SATANI**.

[*From the Pharmacological Laboratory, Johns Hopkins University, and the James Buchanan Brady Urological Institute, Baltimore, Md.*]

An inquiry into the antiseptic properties of local anesthetics is interesting for two reasons: Firstly, in relation to the healing of post-operative wounds and secondly in connection with genito-urinary practice, where these drugs are introduced into the bladder cavity and may thus directly influence its bacterial flora. The following local anesthetics were studied by the authors: cocain, novocain, alpha-eucain, beta-eucain, stovain, holocain, alypin, apotesine and benzyl alcohol. Bacteriological tests were made in three ways. Firstly, the growth of bacteria in bouillon containing small amounts of the anesthetics was studied. Secondly, bacteria were suspended in weak solutions of the anesthetics for definite periods of time, then washed, and planted in various media in order to determine whether they will grow, or not. Thirdly, bacteria were planted on agar impregnated with the various drugs and their growth in this medium was noted.

It was found that some local anesthetics possess definite antiseptic properties, while others are entirely devoid of such. It was interesting to find that the chief local anesthetics in use, namely, cocain and novocain, possess no antiseptic properties. On the other hand, some of the other bodies studied and in particular, benzyl alcohol, beta-eucain and holocain, showed distinct antiseptic properties. The fuller data will appear in due time in the *Journal of Pharmacology and Experimental Therapeutics*.

71 (1531)

**Comparison of the catalase content of the tissues of the mother
and of the offspring.**By **W. E. BURGE** (by invitation).[From the *Physiological Laboratory of the University of Illinois.*]

Hasselbalch¹ found that oxidation or metabolism is very low in the infant during the first month of life, and Magnus-Levy and Falk² that it is high during childhood. As a result of the work of these three observers and of Bailey and Murlin³, Murlin and Hoobler⁴, Howland⁵, Benedict and Talbot⁶, Benedict, Emmes, Roth and Smith⁷, Palmer, Means, and Gamble⁸, and others, it is now considered that oxidation or metabolism is low during the first month of life, high during childhood, and low after the onset of old age. Warburg⁹ found that during the process of fertilization, oxidation was greatly increased in the sea-urchin egg. It is also known that oxidation is greatly increased in the greening of tubers and the germinating of grain. The present work is an attempt to find an explanation for the variation in the intensity of oxidation under the conditions named.

Since we¹⁰ had found that whatever increased oxidation in the body, the ingestion of food, for example, produced an increase in catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxide, by stimulating the alimentary glands, particularly the liver, to an increased output of this enzyme, and that whatever decreased oxidation, narcotics for example, diminished catalase by decreasing its output from the liver and by direct destruction, we naturally turned to catalase for an expla-

¹ Hasselbach, *Bibliotek for læger*, Copenhagen, 1904, 8, 219.

² Magnus-Levy and Falk, *Arch. f. Anat. u. Physiol.*, 1899, Suppl. 315.

³ Bailey and Murlin, *Am. Jour. Obst.*, 1915, lxxi, 1.

⁴ Murlin and Hoobler, *Am. Jour. Dis. Child.*, 1915, ix, 81.

⁵ Howland, *Ztschr. f. physiol. Chem.*, 1911, lxxiv, 1.

⁶ Benedict and Talbot, Carnegie Institution of Washington, Pub. 201, 1914. *Am. Jour. Dis. Child.*, 1914, viii, 1.

⁷ Benedict, Emmes, Roth and Smith, *Jour. Biol. Chem.*, 1914, xviii, 139.

⁸ Palmer, Means and Gamble, *Jour. Biol. Chem.*, 1914, xix, 239.

⁹ O. Warburg, *Zeitschr. f. physiol. Chem.*, 1908, lvii, 6.

¹⁰ Burge, *Am. Jour. Physiol.*, 1918; xlv, 4, 1918; xlvi, 1, 1918. xlvi, 3,

nation of the increase or decrease in oxidation under the conditions enumerated.

On examination of the literature, it was found that Winternitz¹¹ had already shown that the unfertilized hen's egg showed no catalytic activity even after prolonged incubation, whereas the incubated fertilized egg rapidly acquired the power of decomposing hydrogen peroxide. We repeated and confirmed these observations of Winternitz. Doubtless if Winternitz had determined the intensity of oxidation in the fertilized hen's egg, he would have found that this increased parallel with the increase he observed in catalase, and if Warburg had determined the catalase content of the fertilized sea-urchin egg, he would have found this enzyme increased parallel with the increase he observed in oxidation. J. Loeb¹² attributes the development of the fertilized sea-urchin egg to the increase in oxidation, and the increase in oxidation to a change in the cortex of the egg which makes the entrance of oxygen, and hence oxidation possible, while R. Lillie¹³ holds that the cortical layer of the unfertilized egg prevents the diffusion of CO₂ from the egg and this CO₂ prevents oxidation, and hence development. A more plausible explanation for the increased oxidation or metabolism in the fertilized egg, and hence for the development of the egg, would seem to be that the spermatazoön furnishes a substance which stimulates the egg to an increased formation of catalase. Further evidence in support of this view is afforded by the fact that the very same chemicals (amines, alkalies, acetates, butyric acid, etc.) which Loeb found would bring about increased oxidation and artificial parthenogenetic development of the egg, we found when introduced into the alimentary tract of animals, stimulated the alimentary glands, particularly the liver, to an increased output of catalase with resulting increase in oxidation.

Battelli and Stern¹⁴ found that the catalase content of most of the tissues and particularly of the liver of newly born pigs is lower than the corresponding tissues of the mother, but that the

¹¹ Winternitz and Rogers, *Jour. Exper. Med.*, 1910, xii, 12.

¹² Loeb, *Artificial Parthenogenesis and Fertilization*. University of Chicago Press, 1913.

¹³ Lillie, *Am. Jour. Physiol.*, 1910, xxvii, 289.

¹⁴ Battelli and Stern, *Arch. di Fisiol.*, 1905, ii, 471.

catalase activity rapidly increased until at the end of the seventh or eighth day it was as high as that of the adult. We repeated and confirmed these observations using the dog and newly-born puppies. We also determined the catalase content of the tissues of puppies that were about ten weeks old and found that the tissues generally were richer in catalase than those of the mother. The catalytic activity of the liver, for example, of the ten week old puppies was about thirty per cent. greater than that of the liver of the mother. The catalase was determined by adding one gram of the hashed tissue to hydrogen peroxide and the amount of oxygen liberated in ten minutes was taken as a measure of the amount of catalase.

Appleman¹⁵ found that there was an increase in catalase parallel with the increase in oxidation in the greening of potato tubers, but that the oxidase activity was not increased and, in fact, was slightly decreased. He also found that the exposure of potatoes to ethyl bromide gas increased the catalase of the potato parallel with the increase in oxidation, while it had no effect on the oxidases.

The low metabolism or oxidation in the newly-born is attributed to the low catalase content of the tissues, due undoubtedly to the small output of this enzyme from the liver, while the high metabolism in youth is attributed to the richness of the tissues in catalase brought about by a large output of this enzyme from the liver. Likewise, the increase in oxidation or metabolism in the sprouting of grain or of potatoes is attributed to an increase in catalase. The increase in oxidation or metabolism and hence the development of the fertilized egg is attributed to the increase in catalase brought about by the stimulation of the egg by the spermatozoön to an acceleration in the formation of this enzyme.

¹⁵ Appleman, The Maryland Agricultural Experiment Station, 1915, Bull. 191.

72 (1532)

The effect of compression on tissue enzymes.By **BERT HOLMES HITE** and **WITHROW MORSE**.

[From the West Virginia Experiment Station Laboratories of Chemistry and the School of Medicine, Department of Biochemistry, Morgantown.]

The senior author (B.H.H.) has studied various enzymes when subjected to great compression in a special hydraulic press, capable of delivering pressure of over $(10)^5$ pounds per square inch. As a rule, these enzymes are inhibited or destroyed. At the same time, there is generally lee-way between the destruction of enzymes and the total destruction of bacteria included in the preparations. It is well known from the work of investigators, such as Wolbach, Sakai and Jackson,¹ that it is difficult if not impossible to obtain aseptic autolytic digests by employing the most rigid asepsis in operations of removing organs from mammals, for included bacteria are practically always present. The junior writer (W.M.) has abundantly verified this conclusion, although there exist reports of investigations, as those of Magnus-Levy,² where the work was controlled by aërobic and anaërobic cultures and aseptic organ suspensions seem to have been obtained. We have no suggestion to make regarding this discrepancy.

In order to determine whether the lee-way mentioned above is of sufficient extent to warrant an attempt to study tissue enzyme action apart from bacteria, the following experiments were conducted, rabbits being used as subjects, the livers being excised, sieved, weighed to 20 per cent. digest, 10 g. and 25 g. portions being transferred to special blocked tin tubes, resembling vaseline tubes, which were tightly stoppered by means of screw-caps, each tube then being introduced into the cylinder of the press surrounded by a jacket of water. The following table gives the number of the sample, the pressure involved, the time of exposure to this pressure and the Kjeldahl data utilized to follow the rate of digestion, if any³; the term "initial" refers to the non-protein

¹ Wolbach, Sakai and Jackson, *Journ. Med. Res.*, 1909, 21, 267.

² Magnus-Levy, *Hofmeister's Beiträge*, 1902, 2, 261.

³ For details see Bradley and Morse, *Journ. Biol. Chem.*, 1915, 21, 209.

nitrogen analyzed immediately after removal of the tubes from the press and "48 hrs.," that nitrogen found in aliquots after remaining in a thermostat at 37° for that period.

Sample Number.	Pressure.	Time.	Initial.	48 Hours.
Control (septic).....	xx	xx	0.50 c.c. 0.1 N.	0.80 c.c. 0.1 N.
I. septic.....	75(10) ³	5 mins.		.90
II. sterile.....	16(10) ⁴	2 hrs.		.50
III. sterile.....	(10) ⁵	16 hrs.		1.40
IV. sterile.....	(10) ⁵	1 min.		.50

The explanation of number III being at variance with number IV, where both are at the same degree of compression, doubtless lies in the fact that during the longer period of exposure (16 hrs.), some enzyme action may proceed before inhibition sets in, especially as the temperature rises somewhat⁴ during this prolonged time of exposure.

It is evident that the method can be used only with the greatest care to adjust the pressure so that complete inhibition does not occur, while at the same time, all bacteria⁵ are killed, which is of doubtful practicability.

At these pressures, egg albumen is coagulated (B.H.H.), but in the case of the tissue from the rabbit's liver, there is little evidence of change in the colloidal dispersion, although the Ringer's Solution used to make up the liver mass to 20 per cent. suspension separates in the tubes during compression from the semi-solid mass.

73 (1533)

The relation between the disappearance of foreign proteins from the circulation and the formation of antibodies.

By WARFIELD T. LONGCOPE and GEORGE M. MACKENZIE.

[From the Presbyterian Hospital, New York City.]

Some observations which Dr. Rackemann and one of us made a few years ago indicated that when serum disease followed the injection of horse serum in human beings anti-bodies, such as

⁴ The cylinder is cooled during the period of compression.

⁵ This probably lies near (10).³

precipitin, anaphylactic antibodies, and skin hypersensitiveness to horse serum appeared as a rule toward the termination of the serum sickness. It was considered that the excessive production of antibodies followed the cellular reaction which was made evident by the serum sickness. In two of the cases that were studied, serum disease did not follow the injection of horse serum and anti-bodies did not appear in the circulation. The reason for this variation in susceptibility, a condition that has long been puzzling, has not been satisfactorily explained.

The object of the present investigation was to determine, if possible, whether the presence of antigen, namely, horse serum, bore any relation to serum disease or to the production of antibodies. It is known that by the method of specific precipitation a reaction for horse serum may be obtained in the blood, both of animals and of human beings, for many days after the injection of horse serum. Since reactions for horse serum cannot be obtained in the urine, it is improbable that horse serum is secreted as such by the kidneys.

The method employed has been to estimate by means of specific precipitin reactions the presence of horse serum at given intervals after its injection into human beings for therapeutic purposes in pneumonia and at the same time to follow the appearance and curves of precipitin for horse serum. Preliminary observations on rabbits showed that when 5 c.c. of horse serum per kilo body weight was injected intravenously, reactions for horse serum could be obtained in the blood of the rabbit over a period of from 7 days to three weeks. Precipitin for horse serum appeared in from 6 to 10 days and persisted for from 4 to 7 weeks. It is well known that animals differ widely in their ability to form antibodies, and observations on six rabbits showed considerable variation in the rate of precipitin formation, and in the duration of the reaction for horse serum in the circulation.

By this same method we have studied 14 individuals who have received from 100 to 500 c.c. of antipneumococcus horse serum intravenously. An analysis of these cases shows that they fall into two groups: In one group of eight cases the curve of precipitin formation and the persistence of horse serum was much the same as that observed in rabbits. The persistence of

the reaction for horse serum was somewhat longer, 18 to 39 days, and the appearance of the precipitins slightly slower than in rabbits, since they were not obtained in human beings until the 6th to the 15th day after injection. The injection of horse serum in all these cases was followed by severe serum disease, lasting from 11 to 28 days, and as a rule the precipitins appeared first or their concentration increased markedly towards the end of the serum disease. On the other hand, the reaction for horse serum diminished rapidly towards the termination of the serum disease and disappeared shortly thereafter. The intensity of the serum disease and the persistence of the reactions for horse serum in the circulation bore no direct relationship to the amount of serum injected.

In the second group were five cases to whom 300 to 500 c.c. of horse serum were given. In this group the results differ entirely from those obtained in rabbits and in the patients of the first group. One characteristic of these cases is the persistence in the blood of the reaction for horse serum over a very long period of time which ranged from 49 to 67 days. Practically all of these patients were lost to observation before negative reactions for horse serum were obtained. Secondly, the precipitin formation was either of extremely short duration or entirely absent. In the third place, these patients either had very mild serum disease lasting from one to five days or had none at all.

There was one other case receiving 630 c.c. of serum who showed the persistence of the reaction for horse serum in the circulation for over 75 days; he also showed precipitins and he had severe serum disease lasting 12 days. This is an exception to the cases in both groups.

An analysis of these observations shows that the reaction for horse serum disappeared fairly promptly from the blood of individuals who had severe serum disease and who formed precipitins towards horse serum, and that the disappearance of the antigens, that is the horse serum, came shortly after the subsidence of the serum disease, and when the precipitins were present in the largest concentrations. On the other hand, in the second group the reaction for horse serum persisted in the blood over long periods of time. In these patients the precipitin reaction was absent or slight and serum disease was absent or of very mild type.

It is known that individuals vary within very wide limits in their reactions to injections of foreign proteins. These observations suggest that those individuals who are relatively insusceptible have some protective mechanism either in the serum or in the cells of the body which prevents or delays the union of the antigen, in this case horse serum, with the cells of the body.

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74 (1534)

The determination of calcium in blood and plasma.

By **GUY W. CLARK** (by invitation).

[*From the Department of Biochemistry and Pharmacology, University of California.*]

The method consists in a direct precipitation of the calcium without removal of the blood proteins. The only reagents necessary are ammonium chloride (to prevent the precipitation of magnesium), and ammonium oxalate, both adjusted approximately to P_H 7.4.

Blood.—Citratd blood (5 c.c. in a 50 c.c. centrifuge tube), is hemolyzed by the addition of four volumes (20 c.c.) of warm water and after standing 15 to 20 minutes is centrifuged to remove the stroma. An aliquot (20 c.c.) of the clear, red liquid is transferred to a 50 c.c. centrifuge tube. One c.c. of 5 per cent. ammonium chloride is added and, after mixing, 3 c.c. of 3 per cent. ammonium oxalate are added. The oxalate should be added slowly and the contents of the tube must be well mixed. After standing at least 16 hours (the much shorter time recently reported by de Waard¹ results in an incomplete precipitation of the calcium), the mixture is centrifuged and the supernatant liquid siphoned off. The tube is washed by the addition of 25–30 c.c. of cold water

¹ de Waard, D. J. *Biochem. Z.*, 1919, 97–98, p. 186.

and immediately centrifuged. After removal of the wash water the precipitate is dissolved in 5 c.c. of approximately normal sulfuric acid and, after heating in a water bath to 75° C., the contents are titrated with 0.01 normal potassium permanganate. (After precipitation of the calcium the method follows, with minor modifications, that described by Halverson and Bergeim.²

Plasma.—Citrate plasma (5 c.c. in a 50 c.c. centrifuge tube) is diluted with an equal volume (5 c.c.) of one per cent. ammonium chloride and 10 c.c. of one per cent. ammonium oxalate are slowly added. After standing 16 hours the precipitate is centrifuged, washed and titrated as in the procedure for blood.

The method has been checked by:

1. The determination of known amounts of calcium in solutions having approximately the same mixture of salts as is found in the blood.

2. The ashing of whole blood and plasma in platinum dishes and precipitation of the calcium by a modification of McCrudden's³ method.

3. The addition of known amounts of calcium to plasma and recovery by the above method.

The advantages of this method are:

1. The small amount of sample necessary, 5 c.c. blood and 3 to 5 c.c. of plasma.

2. The few reagents necessary and the relative ease of preparing them free from calcium.

3. The precipitation of the calcium in the presence of the proteins. Methods^{2, 4} now in common use require either ashing or removal of the proteins by precipitation, operations which greatly add to the chances for mechanical losses.

The accuracy of this method lies between five and seven per cent.

² Halverson, J. O., and Bergheim, O. *J. Biol. Chem.*, 1917, 32, p. 159.

³ McCrudden, F. H. *J. Biol. Chem.*, 1909-10, 7, p. 83; *J. Biol. Chem.*, 1911-12, 10, p. 187.

⁴ Lamers, A. J. M. *Z. Z. Gebürts. u. Gynäk.*, 1912, 71, p. 393.

Lyman, H. *J. Biol. Chem.*, 1917, 29, p. 169.

Marriott, W. McK., and Howland, J. *J. Biol. Chem.*, 1917, 32, p. 233.

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75 (1535)

Outline of a classification of the lipoids.

By W. R. BLOOR.

[From Department of Biochemistry and Pharmacology, University of California.]

At the meeting of the American Society of Biological Chemists in December, 1919, the matter of a classification of the fats and related substances was brought before the members for discussion. It was decided that the available knowledge on the subject was insufficient to justify a classification at that time. While admitting the truth of the conclusion it has seemed to me since, that something might be gained by an attempt at classification,—in clarifying our ideas and in bringing the newer developments in the field into connection with the old—even though the scheme might later have to be radically changed or even abandoned. It is becoming more and more apparent, for example, that the fats and the substances ordinarily grouped under the name of lipoids are so intimately related both chemically and in metabolism—all being directly connected with the metabolism of the fatty acids—that they should be considered together, and when so considered they form a group which is believed to be as distinct and well defined as that of the carbohydrates and proteins. The following is an outline of proposed classification:

THE LIPOIDS.

The higher fatty acids, their naturally occurring compounds and certain substances found naturally in chemical association with them.

The group is characterized in general by insolubility in water and solubility in 'fat solvents'—ether, chloroform, benzol, etc.

Simple Lipoids.

Esters of the fatty acids with various alcohols.

Fats.—Esters of the fatty acids with glycerol. (fats which are liquid at ordinary temperatures are called oils.)

Waxes.—Esters of the fatty acids with alcohols other than glycerol. Beeswax, lanolin, cholesterol oleate.

Compound Lipoids.

Compounds of the fatty acids with alcohols but containing other groups in addition to the alcohol.

Phospholipoids.—Substituted Fats containing phosphoric acid and nitrogen—lecithin, cephalin, etc.

Glycolipoids.—Compounds of the Fatty acids with a carbohydrate and nitrogen but containing no phosphoric acid.—Cerebron, etc.

(Aminolipoids, Sulpholipoids etc.—Various groups which may be added as soon as they are sufficiently well characterized.)

Derived Lipoids.

Substances derived from the above groups by splitting, which have the general properties of the lipoids.

Fatty Acids of various series.

Sterols.—Alcohols, mostly large molecular solids, found naturally in combination with the fatty acids and which are soluble in "fat solvents"—Cetyl Alcohol ($C_{16}H_{33}OH$), Myricyl Alcohol ($C_{30}H_{61}OH$), Cholesterol ($C_{27}H_{43}OH$), etc.

NOTES ON THE CLASSIFICATION.

The group is specifically limited and defined in two ways;

1. Only substances are included which are chemically and metabolically related to the fatty acids.
2. Only naturally occurring substances are included.

The definitive chemical entity of the group is the fatty acid and it is intended to include only those substances which are closely concerned with the metabolism of the fatty acids. The second limitation—"naturally occurring" is intended to exclude organic compounds which have no relation to the metabolism of the fatty acids but which would otherwise be included owing to composition or physical properties.

The name "Lipoid" has been chosen for the group because

1. By derivation it is suitable.
2. When limited as above it is sufficiently definite for the purpose and yet general enough to include all necessary substances.

3. It is already in considerable use on the continent in approximately this (Bang, Czapek and most French investigators in the field).

The term "Lipin," introduced by Gies, although by derivation equally suitable, is believed to be less desirable because of the present practice among biochemists of making little or no distinction between—in and—ine (signifying the presence of nitrogen). For example MacLean uses the term lipin to mean lipid substances containing nitrogen.

Very little originality can be claimed for the above classification and the writer freely acknowledges the help obtained from a study of earlier classifications, notably those of Bang, Leathes, Gies and MacLean. At the same time it is believed to be an improvement on preceding classifications in that it provides a definite chemical and metabolic basis which has hitherto been lacking.

76 (1536)

Sodium citrate and scurvy.

By HAROLD K. FABER.

[From the Stanford Medical School, San Francisco, California.]

An Italian child ten months old was brought to the Children's Clinic, Stanford Medical School, in October, 1919, suffering from severe scurvy. The child had been fed from birth on raw certified milk to which had been added sodium citrate in the proportion of one grain to each ounce of modified milk.

A series of seventeen guinea pigs was fed on oats and milk. In the case of nine of these guinea pigs sodium citrate was added to the milk in the following proportions: 2 animals, 0.25 per cent.; 2 animals, 0.50 per cent.; 3 animals, 1 per cent.; 1 animal 1.3 per cent.; 1 animal 2.0 per cent. The period of feeding in this series was ten to forty-six days. Of the animals to which sodium citrate was given all except one, to which 0.50 per cent. was given for forty-six days, developed scurvy. Of the eight animals to which milk and oats only were given two developed scurvy. These control animals were observed for periods of forty to forty-six days. The average milk intake was 39.1 c.c. of milk per day for the control animals and 41.6 c.c. for the sodium citrate animals.

The incidence of scurvy in the latter series was 88.9 per cent. and in the control series, 25 per cent. The results of the control series are not in accordance with those of Chick, Hume and Skelton who state that guinea pigs receiving less than 50 c.c. milk per day invariably develop scurvy but indicate that with Inspected Milk used in this laboratory the lower limit is about 32 c.c. The average intake in the two series reported was approximately the same.

A series of electrometric determinations performed through the courtesy of Dr. E. C. Dickson showed the following changes in fresh Inspected Milk when sodium citrate in varying amounts was added:

Fresh milk.....	pH	6.45
0.25 per cent. sodium citrate added.....		6.50
0.50 per cent. " " "		6.95
1.0 per cent. " " "		7.05
1.25 per cent. " " "		7.15
2.0 per cent. " " "		7.35

The results of these experiments indicate that sodium citrate even in concentrations of 0.25 per cent diminishes or destroys the anti-scorbutic substance normally present in small amounts in raw cow's milk.

SCIENTIFIC PROCEEDINGS.

One hundred seventh meeting.

ABSTRACTS OF COMMUNICATIONS.

University and Bellevue Hospital Medical College, April 21, 1920.
Vice-President Wallace in the chair.

77 (1537)

Effect of underfeeding on ovulation and the œstrous rhythm in guinea-pigs.

By **GEORGE N. PAPANICOLAOU** and **CHARLES R. STOCKARD.**

[From Cornell University Medical College, New York City.]

Under well-regulated food conditions the œstrous cycle in the guinea-pig is almost uniformly 16 to 17 days in duration.

Underfeeding with a diet of 20 grams of carrots per day produces a prolongation of the diœstrum and, at the same time, a congestion in the ovary and uterus and a degeneration of developing graafian follicles.

The extent of prolongation of the diœstrum depends upon the stage at which an animal is underfed.

Underfeeding during the first 5 to 7 days of the diœstrum has only a slight effect, postponing the next œstrus for one or two days, while underfeeding during the later part of the diœstrum gives much more marked results.

When an animal is underfed for 5 days, from the 12th to the 17th day after an ovulation and œstrus, the next ovulation and œstrus is delayed for about 7 days, being expressed at the 23d to 25th day instead of at the 17th.

Should an animal be underfed for 7 days, from the 10th day to the 17th day after œstrus, the next ovulation and œstrus is postponed for 10 to 11 days, arriving at the 27th to 28th day, instead of the 17th day.

This variation in the effect of the underfeeding when applied at different periods of the diœstrum is associated with the fact that the conditions of the ovary differ at the different times.

Shortly after an ovulation the ovary contains almost entirely small primary follicles. These follicles are not so unfavorably affected by food conditions as are the large graafian follicles, which begin their growth and development during later stages of the diœstrum.

A large follicle at the height of its development seems to require much better nutrition than a small primary follicle, and the lack of proper food arrests its progress very readily. Thus a late underfeeding has a more injurious effect than an early one, and the postponement of the next œstrus is correlated with a postponement of the development of new ripe follicles in the ovary. The entire œstrus activity depends chiefly upon the conditions prevailing in the ovary.

The fact that following a late and long underfeeding the next ovulation is delayed about 11 days after the underfeeding has been stopped is in accord with the results of operation experiments which Papanicolaou has performed on the corpora lutea in guinea-pigs.

These experiments show that after removal of all young corpora lutea following an ovulation, the next ovulation arrives in about 11 days instead of 16 to 17 days as would be expected. This acceleration of 5 to 6 days is due to the absence of the corpora lutea, which if present evidently inhibit the maturation, or prolong the time necessary for the development, of ripe follicles in the ovary.

These experiments all demonstrate the sensitiveness of the follicles within the ovary to environmental conditions and when considered in more detail than is here possible, they throw light on many peculiar reproductive phenomena observed in nature. The extreme variations in the œstrous cycles recently recorded for the rat by Long and Evans (Proc. Am. Ass'n of Anatomists, Anatomical Record, April 1920) may be in part, at least, due to the variations in the diet taken by the individuals. When rats are fed a mixed diet no doubt certain individuals receive a ration quite different from that eaten by certain other members of the colony.

78 (1538)

The effect of varying pressures upon the abdominal musculature in the cat.

By HELEN C. COOMBS.

[From the Department of Physiology, Columbia University.]

Sherrington¹ has summarized rather completely our knowledge of tonus for smooth and striated muscle. He believes that muscle fiber is not to be considered as an elastic string, for it has the property of exhibiting different lengths with one and the same degree of tension. This doctrine is of special interest in the case of the abdominal musculature, which is of necessity subject to many changes in pressure due to the many variations which occur in the abdominal contents. We should therefore expect to find the muscle fibers of the abdomen showing different lengths with the same degree of tension, or, to put it conversely, to exhibit a fairly constant pressure with varying increments of volume.

The object of these experiments has been to determine whether this regulation of inter-abdominal pressure is essentially a function of the nervous mechanism of the abdominal walls or of the intrinsic musculature itself.

Cats were used in these experiments under the several conditions of light and deep anesthesia and decerebration. A cannula introduced into the abdominal cavity was connected by a 3-way stopcock with a manometer and a burette filled with 0.9 per cent. sodium chloride solution kept at a temperature of 38 degrees centigrade. Costal respiration was recorded throughout the experiment. The warmed saline was admitted to the abdominal cavity at the rate of 10 c.c. a minute. With each increment of fluid the pressure was read from the manometer and plotted against the volume. A curve was thus obtained for the entire experiment, which, in about fifty cases was found to be typical. There was a slow increase of pressure in proportion to volume until a certain point was reached, from which pressure rose much more rapidly. At this point also, costal respiration increased very greatly in depth to effect a compensation for the lack of adequate abdominal

¹ Sherrington, *Brain*, 1915, xxxviii, 191.

respiration. In many cases the experiments were continued until there was a failure of respiration which was likely to occur when the pressure had risen to from 250 to 300 millimeters of saline. In other cases they were intermitted when respiration was observed to be labored. The curve always had much the same form indicating a slow rise in pressure in proportion to the volume up to a critical point, after which the pressure increased much more rapidly, as though such a point indicated the end of the ability of the musculature to lengthen with a minimum increase in pressure and thereafter exhibited only elasticity.

The anesthesia, when neither very light nor very deep, had no effect upon the pressure, volume remaining constant. Very light anesthesia sent the pressure up, and very deep anesthesia sent it down a little. Decerebration had no effect upon it.

The next step was to determine whether ablation of the motor nerves of the abdominal musculature would have any effect upon the pressure curve. After the control curve had been taken, therefore, the fluid was removed from the abdominal cavity and no further procedures were undertaken for an hour. The three branches of each phrenic nerve were then removed and the filling of the abdominal cavity was repeated.

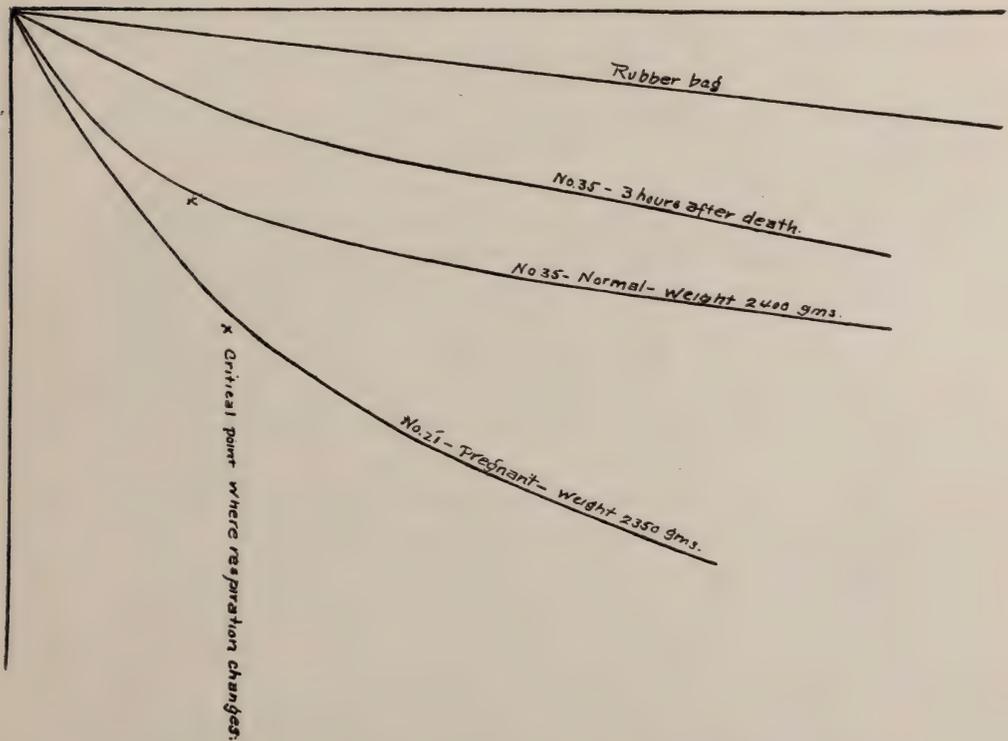
In a similar manner, after obtaining the normal curve in other cats, the ventral roots of the spinal nerves from the mid-thoracic through the lumbar region were destroyed (laminectomy having previously been done) and another curve obtained.

Removal of the phrenics with paralysis of the diaphragm was in all cases found to cause a slight increase in pressure proportionate to volume, and the same was the case with removal of the spinal nerves. The curves, however, were so closely parallel to the normal curve as to be hardly significant. In order to obtain the effect of isolation of the muscle from all motor impulses, curare was injected into the femoral vein of a number of cats and artificial respiration was maintained. There was little variation from the control curve.

After the death of the animal, curves were taken of the pressure at intervals of one and three or two and four hours in order to determine the rôle played by the intrinsic elasticity of the musculature in the maintenance of this curve. With each succeeding

hour after death the pressure curve more closely approximated the straight line exhibited by any elastic body.

The condition of pregnancy is of interest in connection with these experiments. Many cats in varying stages of pregnancy were examined. They all, in proportion to their weight, exhibited a greater degree of extension of the abdominal musculature, with a lesser amount of pressure in proportion to volume, than the non-pregnant cats. Even when the abdominal musculature was greatly distended, these cats appeared capable of the accommodation of a relatively large volume of fluid.



Grey² has pointed out that time is an essential factor in the expression of this lengthening of the muscle fiber with no greater degree of tension. It is probable that the conditions of pregnancy, with the lengthy time factor involved, are far more ideal for demonstrating this particular form of muscular activity than a laboratory experiment can ever be; it is significant that the abla-

² Grey, Ernest G., *Amer. Jour. Physiol.*, 45, 272.

tion of the motor nerves of the abdominal musculature in pregnancy is not more effective in causing alterations of the pressure curve than in the non-pregnant cat. The function appears to be part and parcel of the musculature itself rather than of the extrinsic nerves, although some slight nervous regulation and coördination does undoubtedly exist.

79 (1539)

Coli fever and blood volume in dogs.

By **H. G. BARBOUR** and **A. J. HOWARD**.

[*From the Pharmacological Laboratory of the Yale University School of Medicine.*]

For the continuation of work on the mechanism of fever reduction by drugs we have been seeking a satisfactory method of producing fever in dogs. In these animals a predictable curve of neurogenic fever is very difficult if not impossible to obtain. A few injections of peptone have given us a maximum rise of less than 1° C. with a rapid return to normal within two or three hours (maximum dose employed: 7 c.c. per kilo of 67 per cent. "bactopeptone.")

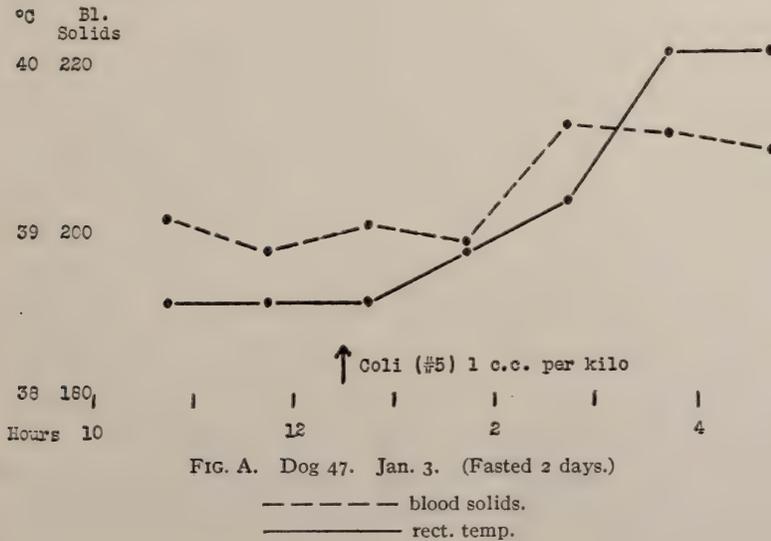
Turning to injections of killed cultures of colon bacilli we made nineteen experiments with subcutaneous injections of a vaccine containing 325,000 million bacilli per c.c. and in fourteen of these obtained a temperature the following morning (that is, after 15 hours), varying from 0.4° to 1.7° C. above normal. In the other five, no elevation of temperature was seen.

The next procedure was to inject in the morning, following the curve throughout the day. For this purpose a more concentrated vaccine was selected, containing 1,625,000 million bacilli per c.c. In five uncomplicated experiments in which this vaccine was used, maximum temperature increases of 2.4° to 1.5° C. (with hourly readings) were obtained with doses of 1 c.c. per kilo. With ½ c.c. per kilo the maximum increase was 2.4°. A smaller dose (0.2 c.c. per kilo) gave, however, an increase of only

0.6° C. A third strength of vaccine used contained one million bacilli per c.c.; doses of ½ and 1 c.c. per kilo, gave maximum increases of 1.0° and 1.2° C. respectively. In all of the experiments with the last two vaccines the maximum temperature was attained by either the second or the third hour after the subcutaneous injection. At the end of the day (6-8 hours after injection) the temperature elevation was usually reduced by about one half.

The last two strengths of vaccine mentioned were therefore considered suitable for further studies. On the second day the temperature was usually found somewhat elevated, but thereafter not at all. The dogs could not as a rule be used for more than one injection each as repetition of the same or larger doses after four days gave a less pronounced effect, indicating that some degree of immunity had been produced.

In all experiments the injections gave sterile abscesses developing to a considerable size and breaking down several days after the injection. About half of our dogs were fasted for two days before being injected, the others being kept on a constant adequate diet of meat, lard, and bread; water ad libitum was always allowed. No essential differences were noted between fed and fasted animals.



Changes in the blood volume of coli fever dogs were followed by means of hourly determinations of hemoglobin and blood solids. In uncomplicated experiments the blood solids showed constantly an increase running parallel with the increase of body temperature. This increase varied at the maximum point from 3.3 to 7.6 per cent. in five different animals. It is illustrated in the accompanying figure (A) as well as in Figures 2 and 3 of the following paper on dextrose plethora. Similar hemoglobin changes were quite definite in some cases.

The increase in the percentage of the blood solids is interpreted as a diminution in the volume owing to loss of water. We are not yet prepared to discuss the fate of this water, but have noted no significant increases in the amount of urine. The loss of water from the circulation is probably the chief factor in the decreased heat dissipation which accompanies the initial rise of temperature in infectious fevers.

80 (1540)

Dextrose plethora and its antipyretic effect in coli fever.¹

By H. G. BARBOUR and A. J. HOWARD.

[From the Pharmacological Laboratory of the Yale University School of Medicine.]

The antipyretic action of dextrose was pointed out by one of us in the PROCEEDINGS of this Society about one year ago in connection with observations upon rabbits with peptone fever, and febrile human individuals to whom the sugar had been administered by mouth.² In view of the experiments reported some

¹ The assistance of an appropriation from the Bache Fund of the National Academy of Sciences in support of the researches reported in this and in the preceding paper is gratefully acknowledged.

The authors desire to thank Dr. George H. Smith, of the department of bacteriology, for valuable assistance in the preparation of the greater part of the coli vaccines used in this work.

² "The Antipyretic Action of Dextrose," PROC. SOC. EXP. BIOL. AND MED., 1919, XVI, 136.

In connection with the demonstration that antipyretic drugs increase the blood sugar this has been interpreted as a potent factor in their action. See Barbour and Herrmann, "On the Mechanism of Fever Reduction by Drugs," *Proc. Nat'l. Acad. of Sci.*, 1920, VI, 136.

years ago from Dr. Lusk's laboratory by Fisher and Wishart¹ it was believed that our observations could be correlated with the dextrose plethora described by the last mentioned investigators.

To this end dextrose was first given to dogs by mouth in doses varying from 1 to 10 gms. per kilo with quantities of water, usually sufficient to make about a 30 per cent. solution. Observations were made upon dogs which had just been fasted for two days subsequent to receiving an adequate daily ration of meat, bread, and lard. Two dogs showed a maximum increase of 15-20 per cent. in the hemoglobin and 6.6-8.6 per cent. in the total blood solids. In no case was there any indication that the blood volume was increased.

The maximum rises of temperature in these two experiments were 0.6° and 0.2° C. respectively, the minimum temperatures noted being 0.2° respectively above and below normal, (hourly observations after injection of dextrose). In two similar experiments with normal dogs, no variation greater than 0.2° C. was observed in the course of the day.

In two dogs which had been given a coli injection (325,000 million bacilli per c.c.) on the previous day, reductions in temperature of -0.2° and -0.5° C. respectively were noted (at the end of three hours). From the above it was concluded that it is difficult to give dextrose by mouth in such a dose as constantly to affect the temperature either of normal or of fever dogs.

The changes in the blood above described must be attributed to a tendency of the sugar to enter the circulation slowly or else to leave it rapidly, in either case abstracting water. To confirm the observations on this blood concentration may be cited three experiments in which dextrose was given per os simultaneously with a coli injection. In one of these was noted an exaggeration of the usual (3-7 per cent.) increase in blood solids produced by such coli injections. In the hemoglobin content, 23, 29 and 15 per cent. increases were noted.

Knowing that a plethora could be induced by dextrose if introduced into the circulation in the proper amounts and at the proper rate, intravenous injections² were next instituted. Two

¹ Fisher, G. and Wishart, *J. Biol. Chem.*, 1912, xiii, 49.

² Starling, E. H., *Jour. Physiol.*, 1899, 24, 317.

normal dogs and two dogs with coli injections were carefully studied, being kept in a comfortable recumbent position throughout the day without anesthesia. The following table illustrates the results:

TABLE I.

SINGLE INTRAVENOUS INJECTIONS OF DEXTROSE IN QUIET UNANESTHETIZED DOGS.

Date.	Dog.	Condition.	Dextrose, Dose Gms. per Kilo.	Water, C.c. per Kilo.	Normal.		With Fever.		With Plethora.		With Secondary Rise.	
					Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.
1/24	41	Normal. . .	3.4	6.8	38.7	20.9	—	—	38.7	20.0	39.1	20.7
1/31	49	Normal. . .	2.2	4.4	37.2	18.5	—	—	37.2	17.5	37.5	19.2
1/24	47	Coli fever.	3.6	7.2	39.0	18.1	40.6	19.3	40.2	16.7	41.1	20.7
1/31	41	Coli fever.	4.3	8.6	38.1	19.7	39.0	21.1	38.4	19.4	39.0	22.5

From the table it is obvious that dextrose given intravenously in fever dogs produces a plethora. The volume change is approximately two to three times as extensive as that produced by corresponding injections in normal dogs. The normal dogs (Fig. 1) showed no diminution in temperature, but after about half an hour the curve began to rise, maximum increases of 0.4° and 0.3° respectively, having been noted. The return to normal occurs after about three hours. In the fever dogs (Fig. 2), on the other hand, the temperature was depressed within fifteen minutes in the one case falling 0.4° and in the other case 0.6° . This was followed by a prompt return to and above the former level. In

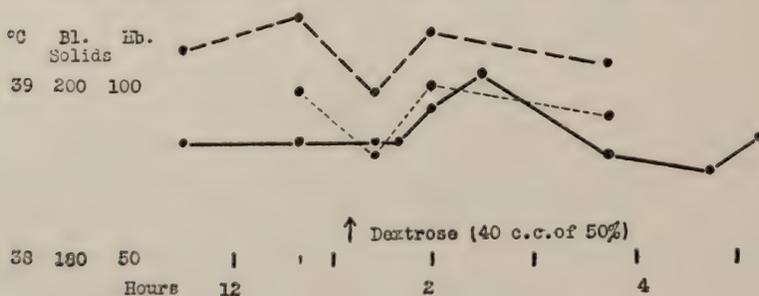


FIG. 1. Dog 41. January 24, 5.9 kilos.

— — — — blood solids.
 hemoglobin.
 ————— rect. temp.

both of these experiments the curves for hemoglobin and total solids ran qualitatively parallel to the temperature curve, both in changing from normal to fever, from fever to antipyretic effect, and from antipyretic effect back to the new high level.

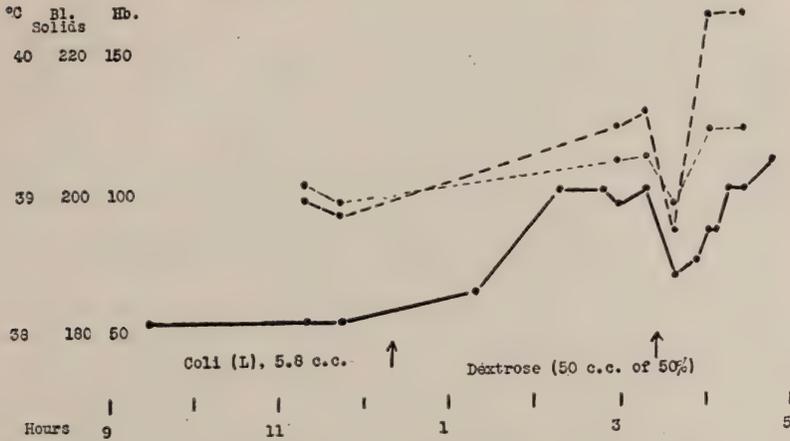


FIG. 2. Dog 42. January 31, 5.8 kilos.

----- blood solids.
 - - - - - hemoglobin.
 _____ rect. temp.

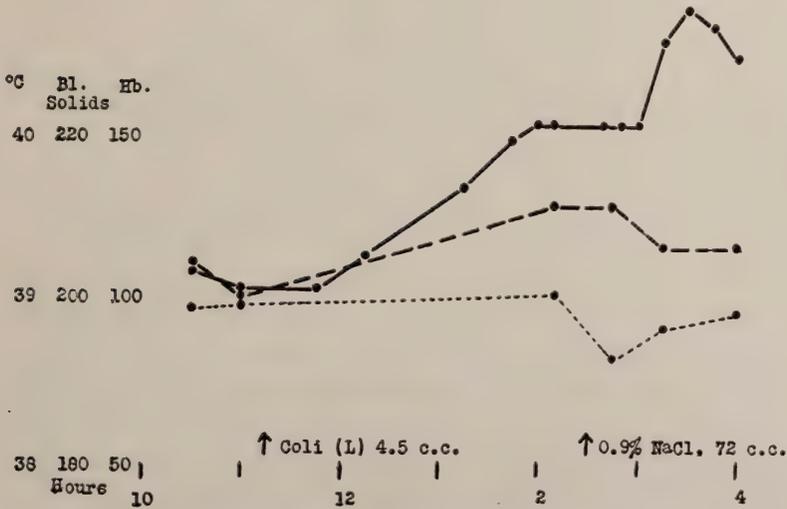


FIG. 3. Dog 53. April 2, 8.9 kilos.

----- blood solids.
 - - - - - hemoglobin.
 _____ rect. temp.

As a control to the above experiments, intravenous injections were made of 0.9 per cent. sodium chloride, of which was given 8 c.c. per kilo to each of two dogs exhibiting a typical coli fever. In the first fifteen minutes there was observed no change whatever in the temperature which subsequently ascended to points 0.7° C. and 0.4° C. respectively higher than the former febrile level. The blood solids on the other hand showed a slight diminution after half an hour, and the hemoglobin fell within the first quarter of an hour. (See fig. 3). The control experiments therefore showed that isotonic NaCl in amounts comparable to the dextrose injections is not able to reduce the temperature of coli fever dogs, nor is the increase in blood volume as marked as when the dextrose was given either to the normal or the fever dogs.

It is therefore concluded that the antipyretic effect (not noted in health) of intravenous dextrose injections is due to osmotic action by which in fever dogs an unusually profound increase in the fluids of the blood results for a short time. This increase in fluid is of value to the animal in promoting heat elimination. The tissues in coli fever appear to contain a higher percentage of "available water" than is normally present. Sensitivity to antipyretic drugs can thus be accounted for.

81 (1541)

Preparation and refining of diphtheria toxin-antitoxin.

By EDWIN J. BANZHAF.

[From the Bureau of Laboratories, Department of Health.]

The mixture has been readjusted so that after standing eight months and longer, late paralysis will occur when the mixture is injected into guinea pigs. This is done by adding to each L+ dose one unit of a properly aged antitoxin. When five mils of this mixture is injected into guinea pigs acute death occurs within four or five days. The mixture is then stored in a refrigerator for a month to six weeks for stabilizing.

On reinjecting five mils, after storage, the guinea pigs die of late paralysis after twenty to twenty-five days. It is then properly

balanced and safe for distribution. Prepared as stated it retains its balance eight months and possibly much longer and its practically full immunizing value at least a year. What slight deterioration occurs takes place equally in the toxin and antitoxin and therefore there is no danger of the mixture becoming toxic.

Constitutional disturbances are frequent. They are usually observed in adults, especially in those who give a pseudo Schick reaction. These disturbances are mostly due to the bacillary substances which are present in the diphtheria toxin.

Methods for refining the mixture for the complete removal of the bacillary substances have not been found. Considerable of these reacting substances can be eliminated through the use of ammonium sulphate, sodium chloride and alcohol.

82 (1542)

Further observations upon reflex gastric hypermotility.

By W. HOWARD BARBER and GEORGE D. STEWART

[From the Department of Surgery, New York University and Bellevue Hospital Medical College.]

Increase in the force or rate or change in the direction of gastric contractions have followed irritation of the gallbladder, duodenum, or appendix, experimentally, and these motor changes have been associated with pathological gallbladders, duodenums, and appendices, clinically.¹ It may be assumed, subject to further experimental proof, that these organs constitute three of the possible foci of reflex gastric stimulation. Were the nerve paths known along which these impulses travel, it might be possible to explain these motor responses and group other possible causes of gastric motor unrest.

Other observations of abnormal reflex gastric activity in which the pyloric and fundic parts functionate separately are the following:

1. Prostalsis of the pars pylorica, alone, occurring in the course of irritation of the above organs and after thoracic vagus section.
2. Anastalsis of the pars pylorica, alone, associated with traumatization of the gallbladder.

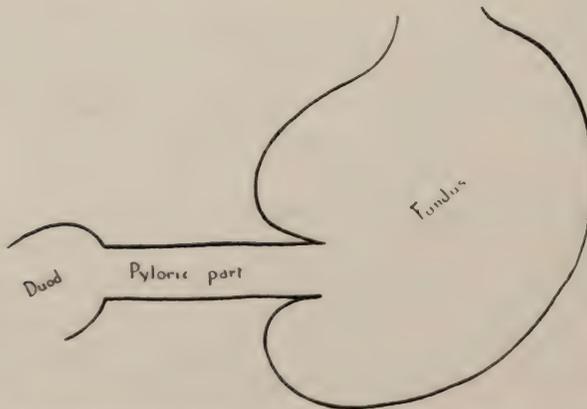
¹ PROCEEDINGS SOC. EXP. BIOL. AND MED., Vol. XVI., No. 7.

3. Pro- and anastalsis of the pars pylorica, alone, after extra-gastric traumata before the stomach appears to settle down to definite rhythmical contractions and is produced mechanically by dividing or blocking the stomach at the junction of the pyloric part and the fundus. It also follows thoracic division of the vagi.

4. Pylorospasm, diffuse, with fundic relaxation resembling a pylorofundic intussusception (see diagram).

This fourth type has been observed repeatedly under experimental traumatization of the gallbladder, duodenum, or appendix and once in the human with evidence of appendical and gallbladder disease. It can be produced by direct stimulation of the lesser curvature at the junction of the descending and horizontal arms. The subjective evidence, associated with this motor state, is anorexia, vomiting, and epigastric pain. The objective signs are mass and tenderness over the stomach, present at times and absent at other times. This form of motility, as appears to be the rule with the reflex types, disappears with parietal peritoneal irritation.

Experimental data, to date, indicate the total hypermotility to be of probable vagus and the pyloric hyperactivity, alone, to be of probable vago-sympathetic origin.



SCHEMATIC REPRESENTATION OF DIFFUSE PYLORIC SPASM AND FUNDIC RELAXATION RESEMBLING A PYLORO-FUNDIC INTUSSUSCEPTION.

83 (1543)

The behavior of crown gall on the rubber tree (*Ficus elastica*).By **MICHAEL LEVINE** (by invitation).

[From the Montefiore Hospital, Cancer Research Laboratory,
New York City.]

Smith (1911-12) in his extensive studies on crown gall and its resemblance to animal cancer shows that the physiological effects of these tumors vary from species to species and also within the species and are generally less pronounced and speedy than one might expect. He holds that it is difficult to show conclusively that the substances produced in the tumor by the parasite are absorbed and act as slow poisons. This is especially difficult in view of the fact that the galls are often soaked by rains and become infected with other parasitic and saprophytic organisms.

Levin and Levine (1918) in a preliminary report on the malignancy of the crown gall and its analogy to human cancer pointed out that a number of the phenomena in both diseases are analogous. They contend that the neoplasms in plants produced by *Bacterium tumefaciens* are sometimes benign, though some are true malignant growths. The latter generally dwarf the plant so affected and cause the necrosis of the tissue above and below the gall.

These studies and those of other workers were carried out on annuals, biennials or deciduous trees in which the period of growth of the host as well as the crown gall is normally interrupted. The difficulty in determining the effects of crown gall, is made greater by the intervention of natural death, caused by changes in temperature and its concomitant factors, and second, by the occurrence of infections caused by fungi and even insect grubs, the eggs of which are deposited in the soft tissue of the young crown gall.

The purpose of this report is to bring forward further evidence on the malignancy of the crown gall experimentally induced on mature evergreen perennials such as the common rubber tree, *Ficus elastica*. In such plants where the growth is rather active all the year round, when kept under uniform, green house

conditions the effect of the crown gall organism and the neoplastic growth on the host can be kept under observation for an extended period. Drenching rains and destructive insects are avoided and very often other parasitic and saprophytic fungi. In this way and in such plants as *Ficus elastica* it is possible to show definitely whether and in what degree the crown gall has an effect upon the adjacent normal tissue of the host.

It was found that *Bacterium tumefaciens* inoculated into the apical internode of the branches, into the leaves or main stem of the rubber tree, *Ficus elastica*, stimulates the development of a neoplasm in the region of inoculation of a benign or malignant nature. The crown galls so formed, in this plant, are of two kinds, one in which growth is uniform and appears to be a swelling, the other is the characteristic convoluted type indicating a peripheral growth of isolated nodules. The early stages in the development of the crown gall in *Ficus elastica* does not interfere with the nutrition of the plant as a whole nor does it interfere with the growth of the inoculated branches. The crown gall in *Ficus elastica* after a number of months of active growth becomes hard and dry and finally dies. This is associated with the differentiation of the tissue which converts the gall into a mass of parenchymatous cells and nodules of woody fibers. The central portion of the crown gall which generally lies near the wood cylinder disintegrates.

The invasion of the stem by the new growth does not destroy the entire conducting system of the stem, yet that portion of the stem above the gall dies as well as considerable portion of the stem below. Cultures made from pieces of the crown gall and stem above and below the gall yield only a shizomycete which in appearance is not unlike *Bacterium tumefaciens* and which when inoculated into the stems of young geraniums and rubber plants produce crown galls in the region of inoculation. It is altogether possible that substances of the disintegrating crown gall or products of the crown gall forming organism are carried into the circulation of the stem and are responsible for the progress of the death of the stem from the gall upward and downward. The death of the plant due to crown gall is at least suggestive of the death caused by the invading and disintegrating malignant growths in animal cancer.

84 (1544)

- A. Vicious activity of the gall bladder during biliary stasis.
- B. The determining factor in the causation of white stasis bile.

By PEYTON ROUS and PHILIP D. McMASTER.

[*From the Rockefeller Institute for Medical Research.*]

Ligation experiments in dogs, cats, and monkeys show that under stasis conditions the gall-bladder and bile-ducts act very differently. The gall-bladder, continuing to exercise functions that are normal to it, effects a great concentration of the stasis bile and adds mucus thereto in quantity. As result, when an obstruction is produced below the entrance of the cystic duct all of the extralobular biliary channels come at length to be filled with a thick, greenish-black fluid. The ducts, on the other hand, have no concentrating faculty, and their lining secretes but little mucus. In an obstructed duct system blocked off from the gall bladder, or connecting with one so changed as to be incapable of functioning, there regularly accumulates a limpid, watery fluid devoid of pigment and bile salts even when the animal is heavily jaundiced. This is the "white bile" of the surgeons. The passages soon become so distended with it that true bile ceases to enter them.

The facts as given relate to uninfected and uninflamed bile passages. So far as they go they point to cholecystectomy as a wise measure in gall stone cases, and notably when the gall-bladder is but little damaged. For an abnormal concentration and thickening of the bile such as the gall bladder can effect must act both to promote the formation of stones and to render obstruction by them more complete. The frequent rapid increase in size of stones partially obstructing the common duct (Naunyn) is attributable to the concentration of stasis bile by the gall bladder.

85 (1545)

The effect of therapeutic doses of digitalis on the contraction of heart muscle.By **ALFRED E. COHN** and **ROBERT L. LEVY**.

[From the Hospital of the Rockefeller Institute for Medical Research,
New York, N. Y.]

That digitalis causes alterations in the heart resulting in changes in the form of the electrocardiogram is now well known. Robinson and Wilson have estimated in experiments on cats that the quantity of digitalis which can induce a change is about 30 per cent. of the calculated lethal dose. So far, however, no evidence has been presented to show that this amount of digitalis is beneficial—except in cases of fibrillation of the auricles in which block of auricular impulses, mainly through stimulation of the vagus nerves, takes place.

A beneficial action must be based on the ability of the drug to increase the volume output of the heart, and it must be able to do this in therapeutic doses, that is to say, in doses which influence the T wave of the electrocardiogram or reduce the rate in auricular fibrillation. We have accordingly injected this amount into the veins of dogs, 11 of which received the tincture of digitalis and 19 of which received *g*-strophanthin; and into cats, 5 of which received *g*-strophanthin, and 9, the tincture of digitalis.

Alterations in volume output were studied in curves obtained by the use of the Roy and Adami myocardiograph. The curves represent longitudinal linear alterations in the form of ventricles and may, under the conditions of cardiac contraction, represent changes in volume of the cavities and consequently of volume output. The results are reported as changes in the degree of contraction. The animals were anesthetized with ether only. The chest was opened in the median line. Other details of the technical procedure, which are important, will be given in the full report of these experiments.

The significant results concern the effect of these two drugs on the T wave and on the degree of contraction (Table I). In

TABLE I.

No.	Drug.	Rate.	P-R Time.	T-Wave.	Con- traction.	B-P.	Result.
Dogs, 19..	g-Strophanthin...	9	0	0	1	1	Decrease.
		8	4	11	14	4	Increase or change.
		2	15	8	4	0	No change.
11..	Tr. Digitalis.....	4	2	0	0	0	Decrease.
		5	1	6	10	2	Increase or change.
		2	8	5	1	0	No change.
Cats, 5..	g-Strophanthin...	3	1	0	1	1	Decrease.
		2	0	4	2	3	Increase or change.
		0	4	1	2	0	No change.
9..	Tr. Digitalis.....	7	0	0	5	3	Decrease.
		0	2	7	2	6	Increase or change.
		2	7	2	2	0	No change.

30 dogs, the T wave changed 17 times, and remained uninfluenced 13 times; the degree of contraction increased 24 times; decreased in 1; and remained unchanged 5 times. The degree of contraction changed, then, in the greater number of animals; the T wave, in more than half. In 14 cats, the T wave changed 11 times and remained uninfluenced in 3; the degree of contraction increased 4 times, decreased 6 times, and remained unaltered 4 times. That is to say, the T wave usually changed; the degree of contraction decreased in more than half. The effect on contraction differed, therefore, in cats and dogs.

In 7 dogs and 13 cats the record of the blood pressure in the femoral artery was added to the other records. Except in one dog and 4 cats, the blood pressure usually rose. With the tincture of digitalis a significant fall of pressure often preceded a rise.

Anesthesia and operative procedures, it was thought, might disturb the electrocardiogram. Experiments were therefore done on dogs in which electrocardiograms and blood pressure records were taken without anaesthetic and without operation. The electrocardiograms were taken in the usual way. The blood pressure curves were obtained in dogs previously prepared by a method described by van Leersum. By this method a long stretch of one carotid artery was enclosed in a stretch of skin included between two parallel incisions. The tube containing the artery lay free of the neck, and surrounded by a small rubber cuff. Water transmission to a mercury manometer permitted the taking of records. Minimum and maximum oscillations after the manner of Erlanger indicated systolic and diastolic pressures. It has

been found in the few experiments which have so far been done that T wave changes occurred uniformly and that the blood pressure usually rose, the increase varying from 20 to 66 mm. Hg.

Data on the effect of the drugs on rate and on conduction are reserved for later publication and likewise detailed descriptions of differences between the two drugs.

CONCLUSIONS.

With doses of therapeutic range equal to 30 per cent. of the calculated lethal dose, digitalis and strophanthin (1) increased the contractile power of the cardiac muscle, and by so doing increased the volume output. This effect supplies a firm basis for the statement that these drugs may exercise a beneficial action. (2) At the same time, the T wave is usually altered, and (3) there is a transient elevation of blood pressure.

86 (1546)

A method for the estimation of lactic acid in blood.

By **GEORGE A. HARROP, JR.** (by invitation).

[From the Chemical Division of the Medical Department of Johns Hopkins Hospital, Baltimore.]

The procedure is based upon the observation of Denigès¹ that lactic acid, in the presence of concentrated sulphuric acid, is converted into acetaldehyde, and can then be detected by certain reagents, particularly phenols and morphine alkaloids.

5 c.c. of untreated whole blood or serum is delivered directly into 15 c.c. of acidified copper sulphate solution, the flask being in the meanwhile gently shaken. It is heated 4-5 minutes on the water bath, cooled, and an excess of powdered calcium hydrate is added. It is then allowed to stand for 30 minutes and filtered. A water-clear solution is obtained which is free from sugar and other aldehyde forming substances, and which does not char appreciably during the subsequent treatment with sulphuric acid. One part of filtrate is added cautiously to 4 parts of pure concentrated sulphuric acid, the mixture being meantime shaken and

¹ G. Denigès, *Ann. de Chem. et de Phys.* (8), 18, 149.

cooled in a dish of ice water. It is then placed in the boiling water bath for 2 minutes and immediately cooled in ice water, after which 3 drops of 5 per cent. solution of guaiacol are added. With pure lactic acid solutions a rose color is developed which remains stable and clear for some time. The maximum color is developed in the blood filtrates in about 20 minutes and it must then be read against standards prepared with known amounts of lactic acid (conveniently prepared from zinc or lithium lactate). An appreciable color is produced by 0.01-0.02 mg. of lactic acid. The colors may be compared in small flat-bottomed Nessler tubes, or the concentrated acid solutions may be compared in the Duboscq colorimeter without injury to the cups. On prolonged standing a turbidity develops in the blood filtrates which renders it impossible to read them accurately.

87 (1547)

Effect of opiates on memory and behavior of albino rats.

By **D. I. MACHT** and **C. F. MORA**.

[From the Pharmacological and Psychological Laboratories of the Johns Hopkins University.]

Studies were made by the authors on the behavior of white rats in Watson's circular maze. A total number of eighteen rats was used. The animals were trained to find their way through the intricate labyrinth of the maze in the shortest period of time without making any error. They were then injected with the various drugs studied, and their behavior, both immediately after injection and for some time afterwards, was observed. The experiments on the rats in the maze gave data concerning the memory habit of the animals, their activity, and the coordination of their movements after the administration of the narcotics. A large number of experiments was performed on different rats, and the effects of the following opiates were studied: Morphin, codein, thebain, narcotin, narcein and papaverin. In addition to the individual alkaloids, the following combinations were also administered: pantopon (total opium alkaloids) and narcophin (morphin plus narcotin).

It was found that morphin, in both large and small doses, impaired the memory and the behavior of the rats. In the case of only one of the animals was there an excitation or stimulation noted after small doses of the drug. After large doses of morphin, the impairment was long-lasting, continuing for several days. In most cases, however, the animals eventually completely recovered from the effects of the narcotic.

In regard to the comparative effects of morphin alone and morphin given in combination in the form of pantopon or narcophin, the following interesting observations were made: Out of 26 experiments with pantopon and morphin, in 22 the effects of morphin were found to be more depressant than those of pantopon.

Out of 9 experiments with morphin and narcophin on the same animals, 7 experiments showed that morphin was more depressant than narcophin. In all the experiments with the opium alkaloids, the effects were noted on both the time in which the rats went through the maze and the total distance traversed or the number of errors made.

Codein, in 9 experiments out of 11, produced impairment, as indicated by both the time and the distance. Narcotin, in 5 experiments out of 7, produced also a depression. Narcein, out of a total number of 10 experiments, produced a slight depression in 4, and no effect in 6. Thebain indicated a slight retardation in 10 experiments out of 11. In the case of papaverin, it was found that very little effect was produced by small doses of the drug, but that after large doses (10 or 15 mgs.), a depression was noted. The complete data of this research will appear in due time in the *Journal of Pharmacology and Experimental Therapeutics*.

88 (1548)

On the generalization of *treponema pallidum* in the rabbit following local inoculation.

By LOUISE PEARCE and WADE H. BROWN.

[From the Laboratories of the Rockefeller Institute for Medical Research, New York.]

That a widespread dissemination of *Treponema pallidum* may be produced in the rabbit by local inoculation has been shown

by the recovery of the organisms in isolated instances from the blood, lymphnodes or other organs as well as by the occasional occurrence of generalized lesions in infected animals. However, there is no evidence to show either the time or frequency with which this dissemination occurs or whether the organisms thus distributed over the body are capable of sustaining the infection in these animals.

With these questions in mind, a series of experiments was undertaken, the object of which was to determine the frequency of invasion of the regional lymphatics and the general circulation following inoculation in the scrotum or testicles and how soon a self-sustaining generalized infection might be established.

Time and Frequency of Invasion of Regional Lymphatics.—An examination was made of the inguinal lymphnodes in a series of 29 rabbits which had been inoculated by the introduction of a bit of infected tissue beneath the skin of the scrotum. The nodes were excised under ether anesthesia at intervals of from 61 days down to 48 hours after inoculation and the presence or absence of *Treponema pallidum* determined by dark field examination or by animal inoculation.

The first group of nodes studied included those showing well marked enlargement and induration and these gave positive results in all cases. Nodes were then taken 5 days after inoculation and after the lapse of only 48 hours. Positive results were again obtained in all cases.

Invasion of the Blood Stream.—A similar series of experiments was carried out to determine the time and frequency of blood stream invasion and something of the character of the blood stream infection with relation to processes of reaction in the primary lesions. With a few exceptions, the animals used for these experiments were inoculated in the testicles. The mode of determining the presence of *Treponema pallidum* in the blood of infected animals was by bleeding from the heart, defibrinating and injecting 0.5 c.c. of blood into each testicle of 2 normal rabbits.

A total of 81 bleedings was made on a series of 37 rabbits at intervals of from 7 to 99 days after inoculation. The earlier bleedings were all spaced with reference to some phase of the testicular infection and from these it was found that organisms

could be recovered from the circulating blood from the time an infection could first be detected clinically (12 to 14 days) until regression of the primary lesions took place. The number or the virulence of the organisms as indicated by the incubation period and the constancy of infection in subinoculated animals varied, however, according to the stage of development and the state of the reaction in the primary lesions.

A small series of animals was then bled arbitrarily one week after inoculation and it was found that even as early as this, the number of organisms in the circulating blood was sufficiently great for each 0.5 c.c. of blood to constitute an infecting dose. In view of these facts, there seemed to be no immediate object in further reducing the time limits.

The Establishment of a (True) Generalized Infection.—When it had been shown that *Treponema pallidum* appeared to be widely distributed through the body within a very short time after inoculation, it was considered necessary to determine whether a true generalized infection had been established in these animals or whether the organisms proved viable only because they were transferred to such a favorable medium as the testicles of normal rabbits. For this purpose, 10 rabbits were inoculated in the right scrotum only (using implants), and 48 hours later, the entire right scrotum and testicle were amputated under ether anesthesia. In spite of the complete removal of a wide zone surrounding the area of inoculation, 9 of the 10 rabbits showed well-marked infections by the end of the seventh week and the tenth developed lesions at the end of 2½ months after inoculation.

Conclusions.—These experiments show that following a local inoculation of well adapted strains of *Treponema pallidum*, there is an immediate invasion of the tissues of the animal and that within a very short time, organisms may be recovered from both the regional lymphatics and the circulating blood. They also show that the blood stream infection tends to pursue a course parallel with that of the primary lesions. Finally it was shown that within 48 hours or less, a true generalized infection had been established which was capable of maintaining the infection in the animal independent of that at the site of inoculation.

89 (1549)

On the production of generalized syphilis in the rabbit by local inoculation.

By WADE H. BROWN and LOUISE PEARCE.

[From the Laboratories of the Rockefeller Institute for Medical Research, New York.]

Two of the most striking features of the infection usually produced in rabbits by testicular or scrotal inoculations of well-adapted strains of *Treponema pallidum* are the marked reaction at the site of inoculation and the total absence of generalized lesions. In fact, these features of the reaction to infection are so conspicuous as to suggest a casual connection between the two, especially when it has been shown that the failure to produce generalized lesions can in no wise be attributed to the absence of a generalized infection or to an insusceptibility on the part of the animal's tissues to react to such organisms. Specifically, it appeared to us that in all probability, the failure to produce generalized lesions was due in a large measure to an inhibitory influence arising from the reaction at the primary focus of infection and that the reduction or suppression of this reaction might be sufficient in itself to permit the development of generalized lesions.

In order to test this hypothesis, three types of experiments were carried out which were intended to compare the effects produced by unilateral and bilateral inoculations, the effects of castration and the effect of suppression of the primary lesions by the use of therapeutic agents. The castrations were done under ether anesthesia.

Effects of Unilateral and Bilateral Inoculation and of Castration.—In the first series of experiments, there were 27 rabbits inoculated in one testicle and 20 inoculated in both testicles, giving a total of 47 rabbits. These were divided into two groups, one of which was castrated soon after the appearance of the primary lesion and the other held as controls. Both groups were kept under observation for a period of 4 months after inoculation.

Of the 27 rabbits inoculated in one testicle, 14 were castrated

and 13 were held as controls. Generalized lesions developed in 8 of the 13 controls and 13 of the 14 castrated animals.

Of 20 rabbits inoculated in both testicles, 6 were held as controls and 14 were castrated. Generalized lesions occurred in 1 of the 6 controls and in 13 of the 14 castrated animals.

Several other experiments of a similar character gave essentially the same results. In one of these, 46 rabbits were given a heavy inoculation with a testicular emulsion—half of them unilaterally and the other half bilaterally. With these animals, the influence of castration at different periods of the infection was studied and the effects of suppression of the local infection by the use of a therapeutic agent. Only the results of the therapeutic experiments can be given here.

Effects of Suppression of Primary Lesions by Therapeutic Agents.—In carrying out these experiments, a drug was chosen from among those studied by us in collaboration with Dr. W. A. Jacobs and Dr. Michael Heidelberger whose effect in inducing resolution of lesions was much greater than its spirocheticidal action. This substance was arsenophenylglycyl dichloro-*m*-aminophenol.

Twelve rabbits, 6 of them inoculated unilaterally and 6 bilaterally, were given a single intravenous injection of this drug 14 days after inoculation and the results were controlled by 6 untreated rabbits from each of the respective groups.

In the unilateral series, the lesions present were almost completely resolved and the local reaction suppressed for between 2 and 3 weeks. At the end of 3 months, all of these animals had developed generalized lesions as contrasted with 3 of the 6 controls. The effect of the drug upon the animals inoculated in both testicles was less marked and lasted for only 7 to 10 days. At the end of 3 months, generalized lesions had developed in 4 of the 6 treated animals and in 1 of the 5 surviving controls.

Effects of Complete Prevention of a Primary Reaction and Early Removal of the Medium of Inoculation.—An experiment originally carried out for the purpose of determining the time at which a true generalized infection became established in the rabbit proved to be a remarkable demonstration of the effects which might be obtained from complete prevention of the develop-

ment of a primary lesion plus an effect which appeared to be attributable to the early removal of even the small bit of syphilitic tissue used in the process of inoculation by the implantation of a small piece of infected testicle beneath the skin of the right scrotum. 48 hours later, the entire scrotum and testicle were amputated under ether anesthesia. By the end of the 7th week, 8 of the 10 rabbits had developed marked generalized syphilis while the other 2 showed a definite lymphadenitis. One of these developed slight generalized lesions at the end of 2 months and the other 2½ months after inoculation. As a whole, however, the generalized infection was the most pronounced which we have seen in any single group of animals.

Conclusions.—The conclusions to be drawn from these experiments are: That the marked character of the reaction which takes place in the rabbit following local inoculation of old strains of *Treponema pallidum* is in a large measure responsible for the absence of generalized lesions; that an inhibitory influence is exerted upon the development of other lesions which is proportionate to the reaction taking place at the site of inoculation and that the reduction, suppression or prevention of this reaction will remove this influence to a sufficient extent to permit the development of a generalized disease analogous to that which occurs in man.

90 (1550)

Blood changes in ether anesthesia.

By DONALD D. VAN SLYKE, J. HAROLD AUSTIN and GLENN E. CULLEN.

[From the Hospital of the Rockefeller Institute for Medical Research, New York.]

During light ether anesthesia the bicarbonate content of the arterial blood falls, the carbon dioxide tension (determined directly by the tonometric method on the blood) rises, as does the hydrogen ion concentration. These phenomena indicate a state of uncompensated acidosis. The oxygen saturation increases, indicating that ventilation is accelerated in response to the stimulus

of increased carbon dioxide tension. The acceleration does not, however, as under normal conditions, reach the height necessary to keep CO_2 tension and hydrogen ion concentration down to normal limits. It therefore appears that even in light etherization the respiratory center is markedly deadened.

In deep etherization the carbon dioxide tension rises still higher (over 80 mm. has been observed) and the P_H may fall to below 7.2. Respiration not only fails to be accelerated in response to the increased CO_2 tension but may even be so retarded that the oxygen saturation of the arterial blood falls below that normally found in venous. The blood tends to become concentrated.

Conductivity and chloride determinations on the serum indicate only minute changes. The only striking electrolyte changes appear to be the increase in hydrogen ions and the replacement of part of the bicarbonate HCO_3 anions by the anions of acids as yet unidentified.

SCIENTIFIC PROCEEDINGS.

ABSTRACTS OF COMMUNICATIONS.

One hundred eighth meeting.

Osborn Memorial Laboratory of Zoölogy, Yale University, New Haven, Conn. May 22, 1920.

Vice-President Wallace in the chair.

91 (1551)

Additional experiments showing the production of fat from protein.

By **GRAHAM LUSK.**

[From the Physiological Laboratory, Cornell University Medical College, New York City.]

A dog, which had been fed for two days with 1,000 gm. of meat daily at 8 a.m. and which had had at 5 p.m. on the same two preceding days the usual standard diet containing about 70 gm. of carbohydrate, was given 1,000 gm. of meat at 8 a.m. The respiratory quotients for the fifth, sixth and seventh hours after giving this quantity of meat were 0.842, 0.845 and 0.845. Computed on the basis of the metabolism of protein which is the equivalent of 1.44 gm. of urinary nitrogen per hour, there appeared to be a retention of material derived from protein which, if it had been burned, would have shown respiratory quotients in the successive hours of 0.708, 0.688 and 0.685. This indicates that the carbon-containing material derived from protein which was retained in the body had a respiratory quotient approximately the same as that of fat.

For the three hours by direct calorimetry 85.32 calories were found. By indirect calorimetry, if the retained carbon be calculated as having been deposited in the form of fat, 83.58 calories may be calculated as the heat which should have been expected to

arise under those circumstances. Had the carbon been retained as glycogen the calculated heat production would have been greater (about 4 calories per hour).

This work confirms in three successive hourly periods the work previously published by Atkinson and Lusk¹ concerning the formation of fat from protein under experimental conditions similar to the ones here described.

The experimental data follow:

DOG XVIII.

Experiment 68—Basal metabolism—April 14, 1920.

Indirect = 14.25 calories
 Direct = 14.31 "
 R. Q. = 0.82

Experiment 70—After 1,000 grams meat.

5th hour:	N—CO ₂13.46	N—O ₂12.17	N—cals.....38.17
	Resp.—CO ₂10.10	Resp.—O ₂8.72	Deposit cals.....11.32
	3.36	3.45	Indirect cals.....26.85
	R. Q. of deposit = 0.708		Direct cals.....27.52
6th hour:	N—CO ₂13.46	N—O ₂12.17	N—cals.....38.17
	Resp.—CO ₂10.45	Resp.—O ₂8.99	Deposit cals.....10.43
	3.01	3.18	Indirect cals.....27.74
	R. Q. of deposit = 0.688		Direct cals.....29.07
7th hour:	N—CO ₂13.46	N—O ₂12.17	N—cals.....38.17
	Resp.—CO ₂10.56	Resp.—O ₂9.09	Deposit cals.....10.10
	2.90	3.08	Indirect cals.....28.07
	R. Q. of deposit = 0.685		Direct cals.....28.73
	Total indirect	= 82.66 calories	
	" direct	= 85.32 "	
	" indirect		
	as calculated:		
	on C retained as		
	fat	= 83.58 "	
	on C retained as		
	glycogen	= 96.8 "	
	Urine nitrogen	= 1.44 gm. per hour	

¹ Atkinson, H. V., and Lusk, Graham, "On the Problem of the Production of Fat from Protein in the Dog," *Proc. National Academy of Sciences*, 1919, V, 246.

92 (1552)

An observation of the effect of a protein meal given to a man at the end of an 8-day fast.

By **WILLIAM S. McCANN** (by invitation).

[From the Russell Sage Institute of Pathology and the Second Medical Division (Cornell) of Bellevue Hospital.]

In an observation of the effect of a protein meal on a man at the end of an eight day fast a rather unexpected result was obtained which throws light on the fate of the carbohydrate portion of the protein cleavage products.

The subject was a normal man, 23 years old. Height 180 cm., weight 70.4 kgm. At the time of observation he had a marked odor of acetone on his breath. Respiration was normal. The CO₂ combining power of the blood plasma was 50 volumes per cent.

He was placed in the respiration calorimeter for a basal observation of 2 hours. He was then given a meal which consisted of 350 gm. of lean beef and 10 gm. of butter. One hour after taking the meal a second observation was started and continued for 3 hours. During the first two hours of this latter observation respiratory quotients were obtained of .687 and .681. During the third hour the quotient was .740. The first two quotients are similar to those found in severe diabetes, or in phlorhizin glycosuria. During the basal periods the quotients were normal for the fasting state, .733 and .723 respectively. Following the meal there was very little increase in heat production. The nitrogen excretion was not increased.

As evidence that the subject was not diabetic his tolerance for 100 gm. of glucose was normal. The fasting level for blood sugar was .086 per cent. After glucose it rose to .137 per cent. There was no glycosuria.

One week after the first observation the experiment was repeated. During the interval the subject took a normal diet. The basal heat production was lower, as was the basal nitrogen excretion. After the meal a marked rise in heat production oc-

curred (17-28 per cent.), but the hourly heat production is practically the same after the meal as it was in the first observation. The nitrogen excretion was much increased after the meat. The quotients are normal throughout and higher than after fasting.

The explanation of the diabetic respiratory quotient has been made by Lusk¹ who estimates the amount of oxygen and carbon dioxide exchanged in respiration for each gram of urinary nitrogen in severe diabetes ($D : N = 3.65$). In the case of a dog with phlorhizin glycosuria, and the cases of two diabetic men, diabetic quotients were obtained, but non-protein quotients were found to closely approximate that for fat. In the present case the non-protein quotients are below that for fat, due to a failure of all of the nitrogen metabolized to appear in the urine.

It seems probable that the diabetic quotients in this case were obtained by the same mechanism as in diabetes, except that the glucose instead of being excreted in the urine, was stored as glycogen.

TABLE I.

EFFECT OF 350 GM. MEAT ON A FASTING MAN, AGE 23, WT. 70.4 KG., HT. 180 CM.

Hours.	Before—Basal.		Eating.	After.		
	1.	2.		3.	4.	5.
CO ₂ gm.	22.92	22.46		23.02	23.73	24.34
O ₂ gm.	22.73	22.60	PROTEIN	24.38	25.36	23.91
R.Q.733	.723	70 gm.	.687	.681	.740
N. per hr.639	.639	FAT	.637	.637	.637
Cals. per hour.	73.85	73.36	28 gm.	78.77	81.98	77.89

Observation 391 made at the end of an 8 day fast.

TABLE II.

BEHAVIOR OF THE SAME INDIVIDUAL ONE WEEK LATER, HAVING BEEN ON A NORMAL DIET IN THE INTERVAL.

Hours.	Basal.		Eating.	After.		
	1.	2.		3.	4.	5.
CO ₂ gm.	20.67	29.88		23.89	26.60	25.97
O ₂ gm.	19.09	19.53		22.82	24.96	24.91
R.Q.788	.778		.762	.775	.758
N per hr.599	.599		1.020	1.020	1.020
Cals. per hour.	62.81	64.11		74.08	81.38	80.98

The same meal was given after a basal observation.

¹Lusk, Graham, "On the Diabetic Respiratory Quotient," *Arch. Int. Med.*, 1915, 15, part II, p. 939.

TABLE III.

	CO ₂ gm.	O ₂ gm.	Calories.
In diabetes 1 gm. urinary N =	4.00	4.56	13.04
In periods 4-5, 0.637 gm. N =	2.55	2.90	8.31
Period 4. Total	23.02	24.38	R.Q.
Deduct for N	2.55	2.90	.687
Non-protein	20.47	21.48	.693
Period 5. Total	23.73	25.36	.681
Deduct for N	2.55	2.90	
Non-protein	21.18	22.46	.686
Compare with	D : N	R.Q.	Non-protein R.Q.
Phlorhizinized dog	3.54	.687	.704
Diabetic man G. S.	3.5	.697	.700
Diabetic man C.K.	3.97	.687	.699

93 (1553).

Experiments on a quantitative and qualitative test for anti-beriberi vitamine.

By CASIMIR FUNK and HARRY E. DUBIN.

[From the Research Laboratory of H. A. Metz, New York City.]

In 1912 one of us (C.F.) experimented with the anti-beriberi vitamine to see if it could not act as coferment in alcoholic fermentation. The experiments failed at that time, but now the subject through the work of Williams, Bachmann and Eddy has attained a new interest. Their results seem to prove that vitamine activity can be measured by growth of yeast cells and would permit of dispensing with animal experimentation in the initial stages of vitamine fractionation.

Because of the uncertainty of the Bachmann fermentation test, and the complicated procedure of Eddy's test, it was thought desirable to develop a simple macro method. Our procedure is as follows: A yeast suspension is prepared according to the method of Eddy by shaking a loopful of 48 hours yeast culture in a definite amount of Naegeli's solution for 4 hours on a shaking machine. Duplicate tubes are then prepared containing: (1) yeast suspen-

sion + Naegeli, (2) vitamine sol. + Naegeli, and (3) vitamine sol. + yeast suspension + Naegeli. The tubes are incubated for 20 hours at 30° and the fermentation then interrupted by heating to 70° for a few minutes. The contents of the test tubes are then transferred to special centrifuge tubes, the bottom part of which ends in a capillary 2½ cm. in length and divided in mm. The tubes are centrifuged at 2600 r.p.m. for 15 min. and the reading made without much delay as there is a tendency for the yeast cells to swell up slightly after a time. Sterility during the entire process, excepting centrifugation, is of paramount importance. The results obtained with this method were as follows: The procedure was so well standardized that the controls with yeast suspension alone were practically constant. Duplicate experiments checked very well so that the method was applicable for a quantitative determination. In developing the test, autolyzed yeast was used as a source of vitamine. It was noticed, however, that the amount of cells obtained, as shown by the reading on the centrifuge tube, does not increase double if the vitamine amount is doubled. By trying varying amounts of vitamine a curve was established, using autolyzed yeast as standard, which permits of comparison between an unknown vitamine content and our standard. The sensitivity of the method is .0001 c.c. of autolyzed yeast, and the amount to be tested is best made so that it corresponds to our curve between 0.01 and 0.1 c.c. of autolyzed yeast. In this interval the curve climbs up abruptly and small differences can be read with facility. It was found also that contrary to the method of Eddy, where the number of cells incubated varies the controls to an undesirable extent, this is not the case in our method. The variation of cells in our yeast suspension has very little effect on the final result.

First of all, we were interested to know in how specific this test is for B-vitamine. Among the substances found negative in their action were allantoin, hydantoin, nicotinic acid, several purine and pyrimidine bases and several aminoacids. Pilocarpine found by Dutcher to be curative in pigeon beriberi was found inactive, while thyroid gland was active, as it contained the cellular constituents. An extract of pituitary gland was also found active for the same reason. In a second series the substances isolated

from the vitamine fraction from yeast in 1912 and 1913 were tested. Those of 1913 were analyzed at that time and their formulas established. These substances showed an attenuated but definite activity. Polished rice was entirely negative as opposed to the statement of H. H. Green. Saliva was found inactive and urine as already reported by Muckenfuss was active. The latter test may prove of clinical value later on, but possibly blood could be used to greater advantage for diagnostic purposes. A few discrepancies were found however; for instance, yeast treated with Lloyd's reagent still retained a large portion of its activity and also it was found that corn and wheat, separated from the germ by the method of Voegtlin and Myers, still exhibited a large activity, although several times less than the germ containing portion. Further experimentation is under way to clear up these matters.

By comparing the method of extraction of Osborne and Wake-man from yeast with an extract prepared from autolyzed yeast and then heated over 50° to coagulate proteins (we found some heat coagulable protein in autolyzed yeast) we found that Osborne's preparation contains only one-fifth of the nitrogenous substances but exhibits only one-fifth of the activity of the autolyzed yeast extract. It remains to be seen therefore whether it is advisable to use very purified extracts for vitamine fractionations, since it appears that the concentration of vitamins in such crude extracts as above varies with the amount of impurities present.

94 (1554)

The site of the cardiac lesion in two instances of intraventricular heart block.

By **B. S. OPPENHEIMER** and **H. E. B. PARDEE**.

[From the Physiological and the Pathological Laboratories, Columbia University.]

The hearts of two cases were examined in order to determine the site of the lesion associated with electrocardiograms suggesting partial block of either the right or the left branch of the auriculo-

ventricular system. As the main deflections in the two sets of electrocardiograms were in opposite directions, it was to be expected that the lesions, if any, in the two instances, would be found on opposite sides of the heart. There has been considerable theoretical discussion as to which type of electrocardiogram is associated with right-sided and which with left-sided block.

The first case showed electrocardiographically a main deflection inverted in lead I, upright in leads II and III, a marked widening of the foot-points of the Q.R.S. complex, and only moderate voltage; in addition there was auricular fibrillation. Microscopic examination of serial sections of the A.-V. system, showed that the right bundle branch became attenuated almost immediately after its origin from the main stem, and was surrounded by connective tissue. This diminution became more pronounced until at a distance of 7.5 mm. from the bifurcation, scarcely one or two doubtful muscle fibers could be seen. Below this the right branch increased in size again until at 4 cm. below the bifurcation it was of normal dimensions. There was marked fibrous myocarditis of the septum, involving chiefly the left side, especially the sub-endocardial region. The left branch presented no lesion.

The second case showed, on two examinations at an interval of six weeks, electrocardiograms in which the main deflection was upright in lead I, inverted in leads II and III, was notched, and its foot-points abnormally separated. Wave *P* was present throughout. Serial sections showed the A.-V. node, stem and right branch intact. The left bundle branch was imbedded in dense fibrous tissue throughout its course, and at a distance of 3.5 cm. below its origin, its posterior (dorsal) half was replaced by connective tissue continuous with an adherent, organized mural thrombus. There was also a thrombus within the apex of the right ventricle, partially adherent to its right lateral wall, but not involving the septum. In addition, there was a general fibrous myocarditis which predominated in the left side of the septum, and an intense thickening of the endocardium on the left side only.

The direct application of the published electrocardiograms associated with experimental bundle branch lesion in dogs to the interpretation of bundle branch block in man is rendered somewhat doubtful by certain anatomical peculiarities of the dog's

heart and its relation to the thorax. If the results in these two human cases are corroborated repeatedly by similar findings in other instances, it is possible that the usually accepted electrocardiographic interpretation of right and left bundle branch block may have to be revised.

95 (1555)

Studies in pyrimidine metabolism.

By **D. WRIGHT WILSON** (by invitation).

[*From the Laboratory of Physiological Chemistry, Johns Hopkins University, Baltimore.*]

By partial hydrolysis of yeast nucleic acid, preparations containing pyrimidines as the only nitrogenous constituents were prepared and administered to rabbits. Uracil nucleoside when administered per os, subcutaneously or intraperitoneally caused an increased excretion of urea often much more than enough to account for the nitrogen administered. The undetermined nitrogen (the difference between the total nitrogen and the urea nitrogen) was always increased. A part of the increase in the undetermined nitrogen was due to the excretion of free uracil which was isolated in pure crystalline form. As much as 20 per cent. of the uracil fed as the nucleoside was recovered free in the urine.

When a mixture of cytosine and uracil nucleosides was administered to rabbits, there was an increased excretion of urea and usually no increase in the undetermined nitrogen. Uracil was isolated from the urine of one animal and was barely detected by a color reaction in another. No increase of creatine, creatinine, or purines was detected after feeding either preparation. Not even a color reaction for pyrimidines was obtained by using the same procedures on the urine obtained after feeding yeast nucleic acid.

Mendel and Myers were unable to find a trace of pyrimidine in the urine after feeding yeast nucleic acid but found that uracil, when fed, was excreted unchanged. Taken together, the data show that increasing quantities of uracil appear in the urine as simpler complexes containing the uracil group are fed. The con-

clusion may therefore be drawn (at least in respect to uracil), that, in the metabolism of yeast nucleic acid before the pyrimidine is liberated and even before the nucleoside is formed, the pyrimidine is altered in such a way that it may be further broken down and its nitrogen converted into urea.

96 (1556)

**The variable acidity of hemoglobin and the distribution of chlorides
in the blood.**

By **FRANKLIN C. MCLEAN, H. A. MURRAY, JR.**
and **L. J. HENDERSON.**

[From Boylston Chemical Laboratory, Harvard University.]

We have undertaken an investigation of the shift of chlorides between the serum and corpuscles of the blood described by Koeppe and by Hamburger, and have studied this phenomenon particularly in its relation to the heterogeneous acid-base equilibrium between hemoglobin, oxygen, carbon dioxide, bicarbonate, and the concentration of hydrogen ions.

Such a shift in chlorides may be easily produced, *in vitro*, by disturbing, in any way, the acid-base equilibrium, and is observed, under physiological conditions, between arterial and venous blood.

For the purposes of the investigation we have used fresh defibrinated ox blood, expelling the oxygen from combination with hemoglobin by first passing through carbon dioxide at 38° and then by boiling *in vacuo* at the same temperature. This can be accomplished with only very slight hemolysis. The blood has then been brought into equilibrium, at constant temperature and at atmospheric pressure, with various tensions of carbon dioxide, first in an atmosphere free from oxygen and then in an atmosphere with oxygen present at the tension at which it is present in atmospheric air. The whole blood has then been analyzed for oxygen and carbon dioxide, free and combined, and the serum, obtained by immediate centrifugalization under oil, analyzed for carbon dioxide and chlorides. The atmosphere

with which the blood has been brought into equilibrium has in each instance been analyzed for carbon dioxide and oxygen after equilibrium has been reached.

From the data obtained the hydrogen ion concentration has been calculated from the ratio of free dissolved carbonic acid to bicarbonate. When the concentration of bicarbonate has been plotted against the hydrogen ion concentrations, curves similar to those given by L. J. Henderson in a recent paper¹ have been obtained, showing an isohydric shift of base between hemoglobin and the other constituents of the blood, according to whether the hemoglobin was oxygenated or reduced. When the bicarbonate was plotted against the logarithm of the figure obtained for the hydrogen ion concentration a linear relationship was found.

On plotting the serum chlorides against the hydrogen ion concentration an isohydric shift of chlorides has been noted in every experiment—*i.e.*, at the same hydrogen ion concentration the concentration of chlorides in the serum is higher in the case of oxygenated blood than in the case of reduced blood, which is the reverse of the condition in the case of bicarbonate. The total isohydric shift of chloride amounts to about two thirds that of base under the same conditions.

On plotting the serum bicarbonate against the serum chlorides it was found that they have a linear relationship, in the case of both oxygenated and of reduced blood, and that an increase in the concentration of bicarbonate in the serum is accompanied by a decrease of chlorides, corresponding to somewhat more than one half of the increase of bicarbonate. These curves appear to be straight lines, and are apparently parallel, indicating a constant difference between oxygenated and reduced blood at all hydrogen ion concentrations. This constant difference, accompanying the change in the state of hemoglobin, and not dependent on the change in concentration of bicarbonate, we are inclined to attribute to the change known to occur in the relative volumes of the red cells and serum. Of the total shift of chlorides at an isohydric point, this constant difference makes up only a small part.

Since the shift of chlorides, from or to the cells, accounts for

¹ L. J. Henderson, "The Equilibrium between Oxygen and Carbonic Acid in Blood," *J. Biol. Chem.*, 1920, XLI, 401.

two thirds of the shift of base, and since other anions, chiefly HCO_3' but also SO_4'' , shift in the same direction as Cl' , it seems improbable that there is any considerable migration of kations in and out of the cells, with the exception of hydrogen ions. This is in accord with the older ideas on this subject. We are at present investigating also the extent of migration of HCO_3' ions.

As a general conclusion it may be stated that when the heterogeneous acid-base equilibrium is disturbed, from any cause, the new equilibrium is established by the migration of acids in and out of the cells, and that about two thirds of this acid is hydrochloric acid.

Further confirmation of the mechanism of the chloride shift is obtained from the fact that the shift is produced by varying the tension of oxygen as well as by varying the tension of carbon dioxide. The fact that the chloride shift occurs isohydrally provides additional evidence as to the change in the acidity of hemoglobin at varying tensions of oxygen.

In all of our experiments we have obtained data pointing to an extremely constant relationship between the various factors studied—*i.e.*, hemoglobin, oxygen, carbon dioxide, bicarbonate, chlorides, and hydrogen ion concentration—for different samples of ox blood. We are proceeding with the investigation in the hope of reducing these relationships to precise mathematical form.

We have obtained evidence to the effect that the buffer action of the serum under physiological conditions as compared with isolated serum is increased at least ten times by the change in acidity of hemoglobin.

It should be noted that we have studied the hydrogen ion concentration on the alkaline side of the isoelectric points of hemoglobin and serum proteins. At these hydrogen concentrations, as has been shown by Loeb,¹ the amphoteric colloids dissociate entirely, or almost entirely, as acids, so that we have disregarded, for the present, the possibility of combination of chloride and other anions with the colloid substances present.

¹ Jacques Loeb, "Emphoteric colloids. I. Chemical influence of the hydrogen ion concentration," *J. General Physiol.*, 1918, I, 39.

97 (1557)

The determination of small quantities of sugar in urine, including observations on the polysaccharide content of human urine.

By **STANLEY R. BENEDICT.**

[*From the Department of Chemistry, Cornell University Medical College, New York City.*]

Conditions have been found for carrying out the reaction between sugar and picric acid which render it possible to determine sugar in the presence of three or four times its weight of creatin or creatinine without affecting the results. When this reaction is applied directly to urine, figures for sugar are obtained which are only a few hundredths of a per cent. higher than those obtained after precipitation with mercuric nitrate as described by Benedict and Osterberg. After treatment of the urine with a suitable purified bone-black the figures obtained duplicate very closely those found with the mercuric nitrate method. The procedure recommended will be described in detail in the near future.

Using the new technique, observations have been made on the increase in reducing substance of normal urine which results from mild hydrolysis with hydrochloric acid. The increase in reducing substance thus obtained amounts to about 0.5 gm. per day calculated as glucose, for the 24 hour elimination of a normal human adult. Very much higher figures (several grams per day) have been observed in cases of diabetes mellitus which were under treatment, and where the glucose eliminated amounted to from 3 to 20 grams per day.

98 (1558)

Disturbances in the development of mammalian embryos caused by radium emanation.

By **J. F. GUDERNATSCH** and **H. J. BAGG** (by invitation).

[*From the Department of Anatomy and the Memorial Hospital, Cornell University Medical College, New York City.*]

As has been shown by various observers, the exposure of living tissues to the influence of radium rays leads to a severe injury and

ultimate destruction of these tissues. In our work an attempt was made to study this destructive influence on mammalian embryos in utero, in the hope that a partial or complete destruction of one or more tissues might lead to definite abnormalities or malformations in these fetuses.

Bagg had lately used a method of applying radium, which was described in the *Journal of Cancer Research*, Vol. V, 1920. Radium emanation, carried in a very small amount of saline solution, was injected in measured quantities into adult rats, either subcutaneously or intravenously. This solution contained all the properties of the radium metal itself, and, no doubt, the resulting physiological changes were due mainly to the activity of α -rays. Such an injection produced peculiar destructive changes in the inner organs of the animals.

The same method was used in our experiments. After long experimentation we found that a dose of 5 mc. (= milli-curies, a standard unit in radium experimentation) was about the optimal dose. Such an amount was injected into female rats, pregnant and non-pregnant, with the purpose of either injuring the ovarian or uterine tissues, or, in case of pregnancy, the embryonic tissues. While the results were not those which we expected, viz., the production of various types of monstrosities, yet a definite influence of radium on the fetal and placental tissues was noticeable. Radium-treated rats were killed at different periods of pregnancy, so as to procure a series of fetuses of various ages.

The most destructive results of radium emanation, injected subcutaneously, were seen in a number of pregnant females, in which the embryos were killed in the uterus and, instead of being aborted, remained attached to the uterine wall and were gradually absorbed (group I). Whether the embryos were killed primarily, or their death was due to the destructive influence of the radium on the maternal, placental tissues, cannot, of course, be determined. Probably the first assumption is correct, since other findings (group II) showed, that the toxic agent *does* pass the placenta and affects the embryos directly.

A number of such partially absorbed embryos were found, the age of which, naturally, could not be determined. Judging from the sizes of their respective placenta, however, development must

have proceeded to some extent before the radium was applied. The remnants of the embryos were small, nodular bodies attached to the placenta (figures were shown) and had lost all resemblance to properly developed fetuses.

In one case a small, ovoid shaped sac was found, attached by a thin stalk to the uterine wall (figure shown). This apparently represented the remnants of a former embryo and placenta, although neither one could be recognized any longer. In the sac extravasated blood and cell detritus were found. A great many large cells of an epithelioid nature probably belonged to the former embryonic syncytium. The wall of this cyst was formed by fibrous connective tissue.

In a number of other cases (group II), the fetuses were not killed by the radium emanation, but peculiar macroscopic lesions appeared in their skin vessels.

When the fetuses were removed from the uteri, peculiar hemorrhagic areas were noticeable, in some cases just along the dorsal midline, in other cases, spreading over the entire body with the exception of the ventral surface. These extravasations took place in the vessels of the subcutaneous connective tissue and along the meningeal sinuses. In all cases, one or more hemorrhages appeared in the midline, mainly in the head and thoracic region. It seems that the vessels in this dorsal median zone are especially liable to injury. In one instance, there was a large area of hemorrhage extending over the thoracic and lumbar region. Its outline was just symmetrical to the dorsal midline (figure shown). In other cases, a great number of such hemorrhagic areas, some extremely small, were found over the lateral aspects of the head and body. Probably these affected fetuses would have died, if left longer in the uterus, and would have undergone absorption. In many animals which we killed in the early parts of the experiments we failed to find any fetuses, although we definitely believed that these animals had been pregnant before. We probably waited too long after treatment, so that the embryos were completely absorbed, when the animals were opened.

Not all of the fetuses of one litter are affected in the same degree. In one case, for instance, we found among 7 fetuses 3 showing hemorrhagic lesions, 2 beginning to macerate and 2 in the process

of absorption. This difference in resistance may be due either to the higher or lower vitality of the embryos themselves or to the amount of radium which passes the placenta. In another case the fetuses, although injured, were carried to full term and among 6 young of one litter we found two normal and four showing hemorrhagic spots on head, face and along the dorsal midline.

In one very remarkable instance the female had been treated 22 days previous to conception and yet the fetuses, approximately 16 days old, showed areas of extravasation (one of considerable size shown in figure). These lesions were much more widely distributed than in previous cases, extending over both lateral and dorsal surfaces (figure shown). These results cannot be explained at present. It would seem as if the treatment of the mother previous to conception had lessened the faculty of the later embryos to form proper endothelial walls. The wide distribution of the lesions would seem to substantiate such a view. This is in accordance with findings in adult animals treated with radium in which the extravasations in the organs are due not only to increased blood pressure, as would seem at first, but to the actual breaking down of the endothelial tubes. In other words, the effect of radium on endothelium might be selective.

When the radium was injected intravenously (group III) instead of subcutaneously, the same lesions resulted along the vascular channels. Females of about 19 days pregnancy were injected intravenously and the young, born dead 24 hours later, showed the hemorrhagic lesions along the dorsal midline (figures shown). In one case we found a striking difference in the size of the placenta of different fetuses. One fetus, for instance, had a markedly enlarged placenta completely filled with blood, so that it had the appearance of a large hemorrhagic sac. This fetus did *not* show any hemorrhagic lesions, while their placenta were of normal size and moderately filled with blood. It would seem as if in the first case the placenta functioned as an effective "shock-absorber," while in the other cases the radium emanation passed through the placenta to the fetuses.

Lately Bagg exposed pregnant females, near full term, directly to the action of γ -rays (group IV). This radiation of the fetuses in utero, through the abdominal walls produced hemorrhagic

lesions of the same nature as described above. However, the lesions did not appear until about 10 days after exposure. The young were born 2 days after treatment and appeared normal. After about a week they began to fail considerably, hemorrhagic areas appeared along the mid-dorsal line, especially in the head region and death followed. The hemorrhages in these animals were mainly along the meningeal sinuses (figures shown), in some cases frontal and occipital hemorrhages were just beginning, in others they extended considerably over the cerebral hemispheres. Additional lesions on the dorsal side of the thorax were found.

The interval of 10 days after treatment strictly corresponds to the time at which a primary skin erythema develops in radium treated patients. Again it seems as if the endothelial walls had been injured at the time of exposure and gradually gave way to the blood pressure.

In the course of the experiments, we also found numerous hemorrhagic areas in the uteri and especially in the ovaries (figures shown). Congestion of the uterine vessels always was pronounced.

While in experiments on adult animals reported by Bagg before, the injection of radium emanation led to considerable injuries in the internal organs, in our experiments the weaker doses did not produce any macroscopically visible effects on the *maternal* tissues. However, the *embryonic* differentiating tissues were easily affected. This fact might be of some biological significance, when one remembers that radium rays have a decided effect on fast growing tumor and cancer tissues.

99 (1559)

The influence of phenylcinchoninic acid and its methyl derivative on the uric acid and urea content of the blood.

By V. C. MYERS, J. A. KILLIAN and G. E. SIMPSON.

[From the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital.]

It has been recognized now for some time that the administration of salicylates and phenylcinchoninic acid (cinchophen)

resulted in an increased excretion of uric acid in the urine. Quite recently it has been shown by Folin and Lyman,¹ and Fine and Chace,² in particular, that this action was accompanied by a marked drop in the uric acid content of the blood, and later the same was shown to be true of salicylates by Fine and Chace,³ and Denis.⁴ It has been assumed that these drugs induce an increased output of uric acid by endowing the renal cells with an increased power for eliminating uric acid. Fine and Chace⁵ have pointed out that, in the last stages of interstitial nephritis cinchophen has little influence on the excretion of the uric acid, indicating that the renal cells can no longer be stimulated to increased activity.

INFLUENCE OF PHENYL CINCHONINIC ACID AND ITS METHYL DERIVATIVE ON THE URIC AND UREA CONTENT OF THE BLOOD.

Case.	Date 1920.	Uric Acid Mg. to 100 C.c.	Urea N Mg. to 100 C.c.	Creatinine Mg. to 100 C.c.
1. M.G.....	3/26	6.0	29	1.5
	3/28	5.2	29	2.4
	3/31	trace	16	2.0
	4/ 5	3.0	24	2.2
	4/12	3.5	18	3.0
	4/13	3.9	15	2.4
2. M.D.....	3/16	2.8	26	2.6
	3/18	2.8	22	2.6
	3/22	trace	13	2.7
	3/25	2.6	20	2.4
	3/29	2.6	19	2.2
	4/ 9	2.8	16	2.4
	4/12	0.7	13	2.6
	4/15	2.0	17	2.4

Case 1, male, aged 58; clinical diagnosis, chronic interstitial nephritis, arteriosclerosis; 50 grains tolysin daily 3/28 to 4/3.

Case 2, female, aged 53; clinical diagnosis, neurasthenia, visceroptosis; vegetable diet; 50 grains tolysin daily 3/19-22; 50 grains cinchophen daily 4/9-12.

We have been endeavoring to obtain further light on the mechanism of the action of these drugs by experiments upon both man and animals. Setting aside cases of advanced interstitial nephritis where the action of cinchophen is comparatively slight, we have been struck by the fact that this drug and its methyl

¹ Folin and Lyman, *Jour. Pharmacol. and Exper. Therap.*, 1912-13, IV, 539.

² Fine and Chace, *Jour. Pharmacol. and Exper. Therap.*, 1914, VI, 219.

³ Fine and Chace, *Jour. Biol. Chem.*, 1915, XXI, 371.

⁴ Denis, *Jour. Pharmacol. and Exper. Therap.*, 1915, VII, 255, 601.

⁵ Fine and Chace, *Arch. Int. Med.*, 1915, XVI, 401.

derivative show quite different ability to lower the blood uric acid in different individuals, the action being very pronounced in some cases and comparatively slight in others.

In their experiments Folin and Lyman noted the interesting fact (in two cases) that cinchophen not only brings about a diminution of the uric acid in the blood but also seems to lead to a diminution of the nonprotein nitrogen and urea whenever these are present in the blood in unusual amounts. Unfortunately these two experiments were not followed by a control after period.

Data are given in the table above on two cases in which we believe there is unmistakable evidence of a drop in the blood urea as well as in the uric acid. It will be noted that the action on the uric acid was very pronounced in both cases, the first case having a high and the second a normal initial uric acid.

100 (1560)

The purification and concentration of antigens by new methods of adsorption.

By **AUGUSTUS B. WADSWORTH** and **FRANK MALTANER**.

[From the Division of Laboratories and Research, New York State Department of Health, Albany.]

The results of recent studies of complement fixation in tuberculosis suggest that the test might be of considerable diagnostic value if satisfactory antigens could be prepared.

Three strains of tubercle bacilli were selected: one a virulent, another a non-virulent, human strain and a third bovine strain. Immune serum sufficient for titration with all the antigens was obtained from inoculated horses.

The antigens were prepared from cultures by various methods of fractioning and extraction similar to those used by other observers. The culture filtrates were so anticomplementary that they could rarely be used. The glycerine and distilled water extracts gave the most active antigens. These active antigens and also the culture filtrates for comparison were selected for further study by methods of adsorption.

Animal charcoal and globulin (horse serum) were used to adsorb the substances possessing antigenic action from the filtrates. When animal charcoal was added, the antigenic properties were removed, and could not be recovered by extraction of the charcoal. The adsorption with globulin was a more complicated procedure. The technique was briefly as follows: The original antigen was dialyzed and horse serum, one part to twenty of antigen, was added and allowed to stand in the incubator half an hour. The globulin was then precipitated by passing purified CO₂ gas free from HCl through the mixture for one half an hour at 37° C. The globulin precipitate was collected and by shaking it with alcohol the antigenic substances were extracted. The alcoholic extract was concentrated in a vacuum.

The preliminary dialysis of the culture filtrate eliminated practically all of its anticomplementary action. The adsorption with globulin removed the antigenic substances from the culture filtrates and the aqueous extractions so that they were easily obtained in greatly purified and concentrated form.

In preliminary studies the antigens which are used in the diagnosis of syphilis by complement-fixation were also purified and concentrated by similar methods. This method thus allows more precise study of many phases of infection and immunity than has hitherto been possible.

101 (1561)

Observations on the immunization of rabbits with single strain and combined multiple strain vaccines.

By **W. C. NOBLE, JR.** and **RUTH A. THOMAS.**

[*From the Department of Bacteriology, New York University (University and Bellevue Hospital Medical College).*]

Previous to 1916, the Army and the National Guard were immunized with typhoid vaccine. During the late summer and early autumn of that year, numerous cases of paratyphoid fever developed among the troops along the Mexican border, and the Army medical authorities therefore felt it desirable to substitute a triple vaccine, of typhoid bacilli combined with the paraty-

phoids A and B, for the single strain typhoid vaccine then being issued. Similar experience with paratyphoid in the British Army in Flanders in the same year had also resulted there in the adoption of a combined vaccine.

This immediately brought up the question as to the basis for the use of combined vaccines for prophylactic inoculation and led to the initiation, in the winter of 1917, of the experiments here presented. Other workers in this field had preceded us. Castellani¹ in 1903, showed that on injecting an animal with two different organisms at the same time, agglutinins were produced for both, and that the amount of agglutinin for each of the two organisms was about the same as in those animals inoculated with but one type of organism only. Subsequently he stated that as many as six different types of bacteria might be combined in a single vaccine with this same result, but that if more than six types were combined, a diminished amount of agglutinin for each type resulted. The problem has been attacked by other investigators, who have followed the methods of Castellani, by comparing the agglutinin formation when single and combined vaccines were employed. As we have long known that agglutinin formation is not a real index of the degree of immunity, it has seemed desirable that further study of the problem should be made, in observing the relative amounts of bacteriolysins produced.

Four series of from four to five rabbits each, were immunized; one series was immunized with combined triple vaccine of typhoid and paratyphoid bacilli A and B; three other series with single strain vaccines,—one series each with typhoid, paratyphoid A, and paratyphoid B. At the beginning and end of the experimental period, the blood serum of each rabbit was tested for specific and group bacteriolysins and also for agglutinins. In the series immunized with the single strain typhoid vaccine, all the animals show a sharp rise in immunity, but an interesting paradox is to be observed in the excessive production of the (group) para A lysin beyond the specific typhoid lysin (the highest lytic dilution for para A being 1-700,000, for typhoid 1-75,000; and for para B 1-400.) In the series immunized with para A vaccine, the highest lytic dilution for the homologous strain is 1-20,000; for typhoid it

¹ Castellani, A., *Zeitschrift f. Hyg.*, 1902, 40, p. 1.

is 1-3,000; and for para B 1-300. The third series immunized with para B shows its highest lytic dilution with a heterologous strain, typhoid (1-950); while for para A and para B the corresponding dilutions are 1-380 and 1-350 respectively.

The fourth series of rabbits was immunized with combined triple vaccine, and the degree of immunity reached for each organism (as measured by the highest lytic dilution) would appear to be lower than the degree of immunity obtained for the same organism by inoculation with the single strain vaccine. This result was not wholly anticipated, from the previous work of Castellani¹ and also of Davison.² The latter in a series of very completely worked out experiments with agglutinins, reports that the combined vaccine when injected, gives for each organism as good and usually a greater immunity response than if it had been injected alone. Davison, and likewise Bull³ have also observed some tendency in respect to the heterologous strains to lead to an added formation of the specific agglutinin, a phenomenon somewhat comparable to that of "summation" in muscle contraction. Our results with bacteriolysins, in a small series of animals, if confirmed, would *appear* to differ from Davison's observations with agglutinins. Further experimentation along these lines is desirable, and it is our hope to amplify our own work with improved methods.

102 (1562)

Studies on intestinal implantation of *Bacillus acidophilus*.

By HARRY A. CHEPLIN and LEO F. RETTGER.

[From Yale University, New Haven, Conn.]

B. acidophilus (Moro) is a common inhabitant of the intestinal tract of the albino rat and of man. Ordinarily it is present in very small numbers, however, and often may escape detection.

Diet exerts a profound influence on the character of the intestinal flora. Lactose and dextrin, when fed in sufficient amounts, bring about a marked transformation in bacterial types.

¹ Ibid. and Centralbl. Bakt., 1909, Ab. I, 52, p. 92.

² Davison, W. C., *Arch. of Inter. Medicine*, 1918, XXI, 437.

³ Bull, C. G., *Jour. Exp. Med.*, 1916, XXIII, 419.

The present investigation has shown, also, that the ingestion of pure cultures or suspensions of *B. acidophilus* results in a similar change.

The administration of 2 grams of either lactose or dextrin to white rats, in connection with a basal diet of bread and meat, caused within three to six days a complete transformation of the fecal flora from the ordinary mixed type to one strongly dominated by *B. acidophilus*, while the same amounts of maltose, sucrose and glucose failed to exert any transforming influence. The ingestion of 1 gram of lactose or dextrin brought about a partial change, whereas the addition of 1 c.c. (nephelometer 5) of living cultures of *B. acidophilus* to the 1 gram of carbohydrate effected a complete simplification of the intestinal flora. Identical results were obtained by the administration of 2 c.c. of the *B. acidophilus* culture or suspension alone. Post-mortem examinations of the different sections of the alimentary canal of rats harboring a simplified flora of the aciduric type revealed a general distribution of *B. acidophilus* throughout the length of the intestine.

The implantation of *B. bulgaricus* was not effected by the ingestion of even 5 c.c. of *B. bulgaricus* suspension of the same concentration as those of *B. acidophilus*, either with or without accompanying lactose. However, when *B. bulgaricus* and lactose were given simultaneously a transformation of the intestinal flora took place corresponding to that obtained with the feeding of 2 grams of lactose alone.

In feeding experiments with human subjects it has likewise been shown that either lactose or dextrin, when added in sufficient amounts to the ordinary diet, causes a pronounced transformation of the intestinal flora within four to six days, with a marked predominance of *B. acidophilus*. With a single exception thus far, the ingestion of 300 grams of either of these carbohydrates led to such a proliferation of *B. acidophilus* that it entirely dominated the flora and effected an almost complete suppression of all other viable bacterial types. The simple character of the flora tended to remain permanent so long as the ingestion of these carbohydrates was continued. The administration of 400 grams was necessary in the one exception noted.

No radical suppression of the commonly prevailing types was observed when but 150 grams of lactose or dextrin were ingested, barring two notable exceptions. The addition of 150 c.c. of living cultures of *B. acidophilus* to the 150 grams of lactose or dextrin caused a very pronounced transformation of the fecal flora from the usual mixed type to one strongly dominated by *B. acidophilus*. The daily ingestion of 300 c.c. of *B. acidophilus* suspension alone effected simplification of the flora, reducing it to the aciduric type.

The striking results obtained from the use of milk soured with *B. acidophilus* bring to view a new avenue of approach to the field of *B. acidophilus* implantation within the alimentary canal. The administration per os of one liter of *B. acidophilus* milk, in conjunction with the ordinary daily diet, exercised in every instance a telling effect upon the complex flora, which was clearly manifested within one to six (usually less than three) days in the establishment of a non-gas-producing intestinal flora dominated by *B. acidophilus*. On the other hand, the ingestion of a similar amount of *B. bulgaricus* milk offered no encouragement whatever to the aciduric type of organisms. In a few instances the consumption of only 500 c.c. of *B. acidophilus* milk was sufficient to establish a *B. acidophilus* flora. The addition of 100 grams of lactose or dextrin to 500 c.c. of *B. acidophilus* milk resulted in a rapid simplification of types in those subjects who did not respond readily to the ingestion of the 500 c.c. of milk culture alone.

There appears to be a definite correlation between the rate of absorption in the alimentary canal of a utilizable carbohydrate and its tendency to effect a transformation of the intestinal flora. This relation was indicated in the observation that the feces of lactose- and dextrin-fed rats contained reducing substances at the times when *B. acidophilus* was present in preponderating numbers, while the feces of the animals receiving maltose, sucrose or glucose gave negative results with Benedict's solution and presented no change in the types of bacteria. With the human subjects results were obtained after lactose ingestion similar to those furnished by the albino rats.

No definite relation could be established, on the other hand,

between the hydrogen ion concentration of the feces and the bacterial flora. That is to say, the hydrogen ion concentration limits remained essentially the same during the preliminary and the transforming periods of the different experiments.

103 (1563)

An unrecognized pathway for bacterial invasion of the respiratory tract.

By **M. C. WINTERITZ, G. H. SMITH** and **E. S. ROBINSON** (by invitation).

[From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine, New Haven, Conn.]

Normally, the ciliated, mucus-secreting epithelium is a mechanism competent to protect the lungs against infection by way of the upper respiratory tract. When this epithelium is injured by toxic gas or when the mechanism is otherwise incapacitated, as for example, in aspiration pneumonia, the lumen of the trachea undoubtedly is the pathway traveled by the agent responsible for the pulmonary inflammation. Pneumonia may occur, however, and this is especially true of the lobar type, without demonstrable gross lesion of the upper respiratory tract, and in these circumstances some route other than the above must have been provided.

Experimentally, the introduction of pneumococci by intratracheal instillation or by needle puncture of the tracheal wall through the neck, may result in pneumonia. With either of these methods of inoculation, local damage to the mucosa of the trachea occurs. When the needle method is employed, an opportunity is at hand, not only for infection of the submucosa, but of the peritracheal tissue as well. When the organisms are introduced by insufflation into the rabbit, damage to the mucosa of the larynx or upper trachea can hardly be avoided. In either case, an atrium of invasion for the submucosa of the trachea is provided, and histologically infection of the submucosa is evident at the point of inoculation. From here it may be traced throughout the submucosa of the trachea and larger bronchi to the hilum of the

lung by way of the peribronchial and periarteriolar structures into the pulmonary tissue. Infection of the lung occurs under these conditions even though cultures from the lower trachea are sterile.

An abundant lymphatic system can be demonstrated by the injection of India ink into the submucosa of the trachea. This plexus extends from the epiglottis downward as far as the bifurcation of the trachea and connects directly with similar plexi in the submucosa of each bronchus. With further subdivisions of the bronchi, the condition noted above is duplicated. At the points of bifurcation throughout the cartilage-bearing bronchi, anastomotic branches connect the plexi with the periarteriolar lymphatics, and other branches pass directly to the regional lymph glands. Thus a short circuit around the valves of the deeper pulmonary lymphatics is provided.

The distribution and extension of these tracheal lymphatics can be demonstrated equally well by Gram-stained sections prepared from an animal inoculated through the submucosa of the trachea by injection or insufflation of virulent pneumococci. The presence of the organisms shows the distribution of the infection through the lymphatics of the submucosa of the trachea, past the hilum of the lung, into the pulmonary parenchyma. Thus a direct pathway of infection is provided. On the other hand, the manner in which the lymphatic plexi are sharply demarcated at the bifurcations of the trachea and bronchi suggests that this lymphatic system may also serve as a protective mechanism, since, undoubtedly, many of the invading bacteria are, at these points, diverted to the protective regional lymph glands.

104 (1564)

The life of the white mouse.

By **W. B. KIRKHAM** (by invitation).

[*From the Osborn Zoölogical Laboratory of Yale University, New Haven, Conn.*]

White mice may give birth to young every month in the year, but most of the litters come during the warmer months. Males

and females are both sexually mature when about six weeks old, and in females of that age, ovulation occurs regardless of whether or not there has been a previous pairing. The gestation period of non-suckling mice is from 18 to 21 days, so that the first litter may be born when the parents are about two months old, and in all cases of normal, paired animals a litter has appeared before they were three months of age. This first litter may be large (12) or small (2). If the first litter includes more than five young (the average size of litters among white mice) the succeeding litters from that female are usually above the average number of young, but the reverse of this proposition is sometimes true and at other times not. Sixteen litters seems to be the limit for one female to bear, and some stop before reaching that number. The total number of young produced may reach 80, and appears to bear no relation to the size or the total number of litters. Females which are allowed to suckle their young, cease to bear at 18 to 22 months of age, after producing 12 to 16 litters, while those females whose young are removed as soon as found usually die before they cease to bear, but in the rare instances where such females survive, their litters come nearer together, but reproduction stops at an earlier age, so that the total number of litters produced is within the limits stated above. Females appear to be somewhat shorter lived than males, but animals of both sexes if healthy at birth, given reasonably good care, and protected from contagious diseases, have an expectation of life of about two years.

Females suckling young frequently fail to at once again become pregnant, due to some influence from the mammary glands which inhibits ovulation, and in all cases where more than two young are being suckled and the female becomes pregnant, the implantation of the embryos is retarded for about nine days, until the young cease to suckle, and a corresponding prolongation of the gestation period occurs, as compared with that of non-suckling females. Both of these phenomena appear to be protective for the parent organism, since females whose young are removed at birth usually bear litters in such rapid succession that they die of exhaustion before the termination of the reproductive period.

Males and females which were never allowed to pair have lived the same length of time as other animals, and have shown no peculiarities of behavior or appearance.

Healthy animals, for experimental work, are only to be secured by individual selection, as not all members of a litter are equally healthy, but too rapid breeding of healthy animals is sure to produce weak offspring. Extreme heat will kill mice quicker than cold. Pulmonary diseases must be guarded against by rapid removal of infected animals. Sarcomas have also caused the death of a number of animals in the course of this investigation, usually not appearing in animals less than a year old. Tape-worm cysts have been found in the livers of some mice, but seemed to have been without effect on the general health and reproductive activity of their hosts.

A few female white mice have shown a peculiarity common in yellow mice, sterility accompanied by extensive laying down of fat, after having four to six litters. The cause of this behavior is at present unknown.

105 (1565)

Reaction of cells to the galvanic current in tissue cultures.

By SVEN INGVAR (by invitation).

[From the Osborn Zoölogical Laboratory, Yale University, New Haven, Conn.]

By applying a weak constant galvanic current (strength 2-4 billionths of an ampere, density approximately 1/1000-1/2000 δ , nonpolarizable electrodes) to tissue cultures made according to Harrison's method, the following observations were made:

The galvanic current has a directing influence upon the *cell and fiber outgrowth in the cultures* so that this occurs almost entirely *along the lines of force* in the galvanic field. Whereas in the control preparations the outgrowth occurs in all directions, cell movements under the influence of a galvanic current take place toward the anode and the cathode. The cell processes growing toward the anode show morphological differences from those growing toward the cathode. A new biological cell character may in this way be revealed.

If a weak electric current by means of a single conductor is drawn through the culture, the outgrowth of the fibers and cells

always takes place *perpendicular to the conductor*. Bok has called attention to the fact that in the living organism the nerve fibers grow out from the spinal cord *perpendicular to the long fiber paths* growing down from the brain stem. Kappers has tried to explain this as a galvanotropic phenomenon. To this observation, an interesting analogy is thus found in tissue cultures.

The hypothesis of Kappers, as the main result of this author's work on "neurobiotaxis," that electrical forces are determining factors in the outgrowth and distribution of the different constituents of the nervous system, has been proved to be a fact in pieces of the central nervous system of the chick cultured in vitro.

As several authors (Hyde, Mathews, Pfeffer) have pointed out, electrical currents flow in developing organisms. The currents successfully employed in our experiments correspond in range in electromotive force with those found in various embryos. From this it may be concluded that electrical forces play a rôle in the formative processes in morphogenesis.

106 (1566)

Experiments on the lens in amblystoma.

By ROSS G. HARRISON.

[From the Osborn Zoölogical Laboratory, Yale University,
New Haven, Conn.]

The embryo of *Amblystoma punctatum* has been reported as one of those in which the ectoderm normally giving rise to the lens is dependent upon the continued influence of the optic vesicle to effect its differentiation.¹ It was surprising, therefore, to find that in certain experiments, directed toward the study of the gills, lenses developed from the proper ectoderm when transplanted to regions far from the eye.

There are obviously two ways of testing the independence of lens differentiation: one is to take away the eye rudiment as has been done in previous experiments (Spemann, Lewis, Le Cron); the other is to transplant the lens-forming ectoderm to another

¹ Wilbur L. Le Cron, "Experiments on the Origin and Differentiation of the Lens in *Amblystoma*," *Am. Journ. Anat.*, 1906-7, VI.

region of the embryo. The present experiments upon *Amblystoma* show that the results may be different in the two cases.

Excision of the eye rudiment in the medullary plate stage is followed by suppression of the lens. Likewise, if the optic vesicle is removed immediately or shortly after closure of the medullary folds, the lens fails to develop, as shown by Le Cron.

If, however, this same lens ectoderm is transplanted to other regions of the head, a well differentiated lens will develop, provided the ectoderm is taken from the eye region after closure of the medullary folds. Contact between optic vesicle and ectoderm has at this time been established, though the two are not adherent and may be readily separated without cells from one layer sticking to the other. If the lens ectoderm is taken in earlier stages, small and not fully differentiated lenses are sometimes but not always formed.

Barring one or two questionable cases, there is no evidence that, in *Amblystoma*, ectoderm from other parts of the head or from the trunk can give rise to a normal lens. When such ectoderm is transplanted to the eye region, even before closure of the medullary folds, abnormalities in the optic cup, due to irregular infolding, frequently arise and no lens develops. When a circular piece of ectoderm, having the diameter of the optic vesicle, is removed from the eye region, the surrounding ectoderm, which pushes in and covers the wound, usually gives rise to a lens, as Spemann found to be the case in *Triton*. When larger pieces of ectoderm are removed, the lens usually does not develop.

These experiments show that *Amblystoma* must be added to those forms in which the lens ectoderm is capable of self-differentiation. Why this power is manifested only when it is removed from its normal position and not when it is left in place after removal of the optic vesicle is problematical. The difference in behavior can scarcely be referred to differences in the degree of injury to the cells, but it is apparent that at times secondary circumstances of some unknown character may dominate more fundamental ones and thus lead to mistaken conclusions.

107 (1567)

The effect of solutions of certain salts and colloids on the permeability of the capillary walls.

By **ARTHUR H. SMITH** and **LAFAYETTE B. MENDEL.**

[From the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven, Conn.]

In order to study the permeability of the capillary walls for various substances, the material was injected, in isotonic solution, intravenously into rabbits, the diffusion out of the circulation being estimated by the relative concentration of the blood as indicated by the hemoglobin. The rate of injection was such that a volume of fluid equal to the estimated blood volume was introduced in two minutes.

When the chloride, bromide, sulfocyanate, nitrate or acetate of sodium was used, the blood volume returned to normal in thirty minutes. When the tartrate, citrate or sulfate was used the blood volume remained somewhat higher than normal throughout the experiment which usually lasted more than two hours.

The injection of M/15 hydrochloric acid, calcium chloride or colloidal silver (Solargentum, Squibb) produced no delay in the removal of fluid from the circulation. Acacia, however, markedly sustained the increased blood volume at a point one third above the normal for more than two hours.

Under the conditions of these experiments, there was no evidence of edema or of increased water content of the muscles even after repeated injections. The excess of fluid was eliminated through the gastro-intestinal tract, the kidneys and to a slight extent, into the serous cavities.

108 (1568)

Observations on the physiology of the otic labyrinth. The influence of prolonged rotation on the duration of post-rotatory nystagmus.

By ALEXANDER L. PRINCE.

[From the *Physiological Laboratory, Yale School of Medicine, New Haven, Conn.*]

Rotation of the head in space is accompanied by ocular movements of a definite type. These ocular movements (nystagmus) present two phases: a slow deviation of the eyes opposite to the direction of rotation, followed by a quick return to the initial position.

On cessation of rotation similar movements are observed. In the post-rotatory nystagmus, however, the slow deviation phase is in the direction of the preceding rotation.

The deviation phase as shown by Wilson and Pike¹ is dependent on labyrinthine stimulation whereas the quick return is due to a proprioceptor reflex arising from the stretched antagonist ocular muscle during the deviation phase. These ocular movements can be especially well studied in the post-rotatory period.

The duration of the post rotatory nystagmus is dependent on the intensity of the labyrinthine stimulus and therefore on the speed of rotation and up to a certain point on the number of revolutions at any given speed. Using a standard of ten turns in twenty seconds, the duration of post rotatory nystagmus in man has been utilized as an index of labyrinthine efficiency.

This test has been applied extensively in the examination of candidates for the U. S. Aviation Service.

The post rotatory nystagmus under the standard rotation test has an average duration of 23 seconds. This figure is based on a large number of determinations made by investigators in the otological department of the Air Service.² On the other hand, according to members of the psychological department of this Service²

¹ Wilson and Pike, *Philosophical Transactions of the Royal Society*, London, 1912, Series B, CCIII, 127.

² Manual of the Medical Research Laboratory, War Department, Air Service, Division of Military Aeronautics, Washington, D. C.

the nystagmus time decreases progressively with practice. They find that in four persons subjected to frequent periods of rotation over an extended period (20 days) the average post-rotatory nystagmus time fell from 24.9 to 6.3 seconds.

The question then arises as to whether the nystagmus time can be taken as an absolute index of labyrinthine efficiency.

In experiments on animals it has been shown that the nystagmus following unilateral extirpation of the otic labyrinth disappears a few days after operation and that the ocular symptoms (deviation) recur after ablation of the cerebrum. This seems to indicate that the disappearance of nystagmus under these circumstances is dependent on the activity of a compensatory mechanism localized in the cerebrum.¹

In order to decide whether such compensation occurs after repeated rotation I have tested the matter as follows: Cats were subjected to interrupted horizontal rotation over a prolonged period and the nystagmus time observed. The rotation tests (20 turns in 20 seconds) were applied 50 to 60 times daily at intervals of two minutes and were repeated for twenty consecutive days.

The duration of post-rotatory nystagmus under these conditions was found to vary slightly in different animals. With 20 revolutions in 20 seconds the maximal variations in the post-rotatory nystagmus time observed in six animals were from 12 to 19 seconds.

The ocular responses to rotation for each animal remained fixed within narrow limits and were unaffected by prolonged rotation. It may be concluded therefore that rotation tests give an adequate index of labyrinthine activity.

¹ Prince, A. L., PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1917, XIV, 133.

109 (1569)

Variations in the affinity of hemoglobin for carbon monoxide in health and disease.

By **ALEXANDER L. PRINCE.**

[From the *Physiological Laboratory, Yale School of Medicine, New Haven, Conn.*]

It is known that the affinity of hemoglobin for carbon monoxide varies slightly in different individuals and even more in the blood of various species. But the possibility of variations in human blood under conditions of health and disease has not received special consideration.

Bloods from normal individuals and selected hospital cases in whom the percentage of hemoglobin varied from 38 to 110 per cent. were examined.

In each case the blood was equilibrated in vitro at 20° C. with known concentrations of carbon monoxide in atmospheric air and the carbon monoxide-hemoglobin dissociation curve of the blood determined.

From the curves the oxygen-carbon monoxide affinity ratio was computed by the following formula:

$$\text{Affinity CO} = \frac{\text{TO}_2 \times \text{CO per cent.} \times \text{affinity O}_2}{(100 - \text{CO per cent.}) \times \text{TCO}}$$

when TO_2 = the tension of O_2 (2,100 when expressed in parts per 10,000 of air).

TCO = the tension of CO (expressed in parts of carbon monoxide in 10,000 of air) at any given point in the carbon monoxide dissociation curve of the blood.

CO per cent. = percentage saturation of the blood at a given tension of CO.

Affinity O_2 and affinity CO = the relative affinity of O_2 and CO for the blood when affinity for $\text{O}_2 = 1$.

The results obtained are shown in the following table. It will be noted that (1) the carbon monoxide variations in the oxygen-

carbon monoxide affinity ratio of all bloods examined fall between 1 : 254 and 1 : 378, and (2) these variations bear no relation to the hemoglobin percentage of the blood nor to the age and condition of the subject.

Subject.	Age.	Sex.	Condition.	Hemoglobin.	Affinity at 20° C.
				Per cent.	
H. S.....	59	Male	Pernicious anemia	38	1 : 310
M. G.....	27	Female	Pernicious anemia, recent transfusion	60	1 : 323
W. F.....	38	Male	Diabetes mellitus	60	1 : 310
J. B.....	28	"	Pulmonary tuberculosis	80	1 : 286
M. H.....	3	Female	Broncho pneumonia	80	1 : 298
H. C.....	31	Male	Chronic endocarditis	85	1 : 323
E. K.....	12	"	Lobar pneumonia	85	1 : 254
M. M.....	14	Female	Diphtheria (convalescent)	85	1 : 275
M. B.....	48	"	Tumor of spinal cord	85	1 : 364
F. B.....	53	"	Mucous colitis	85	1 : 323
S. C.....	8	"	Tuberculosis of hip joint	90	1 : 275
E. G.....	30	Male	Diabetes mellitus	100	1 : 323
F. W.....	20	"	Normal	100	1 : 286
M. G. T.....	30	"	"	100	1 : 378
R. M. W.....	23	Female	"	100	1 : 378
A. L. P.....	36	Male	"	105	1 : 364
Y. H.....	46	"	"	110	1 : 275
H. W. H.....	28	"	"	110	1 : 323

110 (1570)

The elimination of carbon monoxide and a method of acceleration.

By HOWARD W. HAGGARD (by invitation).

[From the *Physiological Laboratory, Yale University Medical School.*]

Carbon monoxide combines with hemoglobin with an affinity about 300 times as great as that of oxygen for hemoglobin. Blood is deprived of its oxygen-carrying power by combining with CO and the organism suffers from a corresponding degree of anoxemia. The severity of the damage done to the victim is dependent upon the degree of anoxemia and especially upon the duration. Evidently the rate of elimination is extremely important.

A study has been made of the normal rate of elimination in dogs gassed to 60 to 80 per cent. saturation of the hemoglobin with

CO. If the animals survived, the blood was practically free of CO in from two to three hours.

The curve so obtained was relatively flat for the first half of the period of elimination. A dog with 80 per cent. of the hemoglobin combined with CO, at the end of an hour still showed 60 to 70 per cent. During the remainder of the elimination period the drop in the curve was rapid.

It is evident that considerable damage may be wrought even after the inhalation of CO has stopped.

The elimination of CO was studied in animals inhaling oxygen, carbon dioxide, and oxygen-carbon dioxide mixtures following gassing.

With the inhalation of oxygen the rapidity of elimination was increased to approximately double. The curve of elimination of CO from the blood still maintained its normal shape. Deaths from respiratory failure still occurred.

Inhalations of 6 per cent. carbon dioxide in air, increased the pulmonary ventilation, and thus accelerated greatly the period of elimination to one half or less of the normal. The curve of CO-hemoglobin in the blood tended to approach more nearly a straight line.

Inhalations of oxygen containing 6 per cent. carbon dioxide resulted in complete elimination of the CO from the blood in from 15 to 20 minutes. The curve obtained was a straight line.

With the inhalations of carbon dioxide death from respiratory failure was prevented.

III (1571)

The influence of oxygen in expelling CO₂ from the blood.

By **YANDELL HENDERSON** and **H. W. HAGGARD** (by invitation).

[From the Physiological Laboratory, Yale University Medical School.]

Considerable theoretical significance attaches to the interaction of oxygen and CO₂ in blood. That variations of CO₂ tension influence the capacity for oxygen is generally accepted. There has not been, however, universal agreement among observers

as to the influence of variations in oxygen tension upon CO₂ capacity.

Our experience has led us to believe that the quality of exhibiting this reaction depends upon the previous treatment of the blood. Thus in our hands freshly drawn dog's blood shows it when defibrinated, but not when oxalated. The following is typical of our results.

Equilibrating Gas Mixture	Defibrinated Blood	Oxalated Blood
Air plus 5.6% CO ₂ ...	53.5 volumes per cent. CO ₂ ...	55.0 volumes per cent. CO ₂
Nitrogen plus 5.6% " "	58.5 " " " "	55.0 " " " "

Experiments are under way to determine whether the influence of CO₂ upon oxygen capacity is likewise lacking in oxalated normal blood.

Variations within the body in respect to the capacity of the blood for interaction of the two gases would afford a possible ground for reconciling some otherwise difficult discrepancies.

112 (1572)

Observations on the connective tissue ground substance in living amphibian embryos.

By **GEORGE A. BAITSSELL.**

[From the Osborn Zoölogical Laboratory of Yale University.]

Results obtained from a study of the development of connective tissue in amphibian embryos, as presented in a previous communication,¹ show that the process is essentially in agreement with the intercellular theory of connective tissue formation.

The previous observations were made on preserved amphibian material. It has been found possible this spring to demonstrate the presence of a primary ground substance in various stages of living amphibian embryos. Living embryos, ranging from a late gastrula stage up to the free-swimming embryo, have been dissected under the binocular microscope and it has been possible in all stages to show, as was previously demonstrated in the prepared

¹ A report of this work was presented at a meeting of the National Academy of Sciences held at New Haven, November, 1919, and an abstract appears in the *Proceedings* of that Society, 1920, VI, 77.

material, that an homogeneous, intercellular, gelatinous material, permeates various regions of the embryo. This substance as seen in a living embryo is perfectly transparent and is, therefore, difficult to detect under the binocular or under a compound microscope equipped for ordinary illumination. It can, however, be readily studied with a microscope equipped for dark field illumination and numerous observations on this material have been made in this manner.

The present observations on the ground substance in living amphibian embryos, therefore, confirm those previously obtained with prepared material and show conclusively that the primary substance in connective tissue formation is a secreted, intercellular material.

113 (1573)

Effects of pilocarpine upon salivary fistula dogs before and after coli injection.

By **H. G. BARBOUR** and **B. P. FREEDMAN**.

[From the Department of Pharmacology, Yale University School of Medicine.]

In each of two healthy dogs was made a fistula of Wharton's duct. After several weeks a standard dose of 0.5 mgm. per kilo pilocarpine hydrochloride was injected at intervals of two or three days. After each dose the curve of secretion was followed for two hours by weighing the saliva on cotton pledgets by five minute periods.

Contrary to expectation, a normal curve was not readily established. The secretion increased with each experiment until both the total for two hours and the figure for the maximum individual five-minute period were approximately doubled in one case and trebled in the other. After six to eight injections the results became more constant. This gradually increasing sensitivity to pilocarpine has not yet been explained.

After a fairly constant degree of sensitivity to the drug had been established each of the above animals received an injection of $\frac{1}{2}$ c.c. per kilo of a coli vaccine (one million million killed coli

per c.c.). At the height of the ensuing fever (*i.e.*, after three or four hours) was injected the standard dose of pilocarpine. In both cases the secretion curves exhibited an unusually slow onset and a much diminished maximum as well as total secretion. The saliva was of a much thicker consistency than normal.

These experiments were made at a stage of fever in which Barbour and Howard¹ have demonstrated a thickening of the blood. It is suggested that the latter is the chief causative factor in numerous cases of diminished secretion which have been reported in fevers.

114 (1574)

Temperature changes induced by gum acacia injections in normal and fevered animals.

By **H. G. BARBOUR** and **L. H. BARETZ.**

[*From the Department of Pharmacology, Yale University School of Medicine.*]

The effects of gum acacia upon the body temperature have been studied in both normal and fevered rabbits and dogs. Solutions were made in water redistilled from glass and given intravenously. In the following experiments upon rabbits 20 c.c. of fluid per kilo were injected unless otherwise stated.

Intravenous injections of control fluids (Locke's solution or physiological saline) gave an increase in temperature of 1° C. or more, subsequent to a brief depression of 0.2° C. This temperature increase could be superimposed upon the rise induced by bacto-peptone injections.

Similar amounts of 7 per cent. acacia (also 10 c.c. of 20 per cent.) gave a slight depression in normal rabbits by a few tenths of a degree centigrade, never an increase.

In five bacto-peptone rabbits in which the temperature had reached a level of about 1° C. or more above normal within 4 or 5 hours, an injection of acacia (7-10 per cent. or 10 c.c. per kilo of 20 per cent.) brought the temperature back to approximately

¹ Barbour, H. G. and Howard, A. J., *Proceedings of the Society for Experimental Biology and Medicine* 1920 XVII.

the normal level in 20-40 minutes. A rabbit in which fever was induced by puncture of the corpus striatum gave a very rapid fall (average 1.1° C. in 20 minutes) of temperature on three different days as a result of 7 per cent. acacia injections.

In rabbits, therefore, acacia injections induce a mild temperature depression in health but a marked antipyretic effect in fever.

Four dogs responded to 4 c.c. per kilo of 20 per cent. acacia injected intravenously by increases in body temperature varying from 0.9 to 1.8° C. In one of these, however, a preliminary depression of one half degree was observed. The normal temperature was regained within from 3 to 8 hours after injection.

Two dogs were given coli fever (method of Barbour and Howard) and the usual increase in blood solids was noted. Following an intravenous injection of 4 c.c. per kilo of 20 per cent. acacia in each dog reductions of 0.4 and 0.7° C. respectively were noted within 20 minutes, with a corresponding diminution in the total solids of the blood. This was followed however by a renewed temperature rise in both cases.

Intravenous acacia injections therefore raise the temperature of normal dogs but in fever dogs exert a brief though marked antipyretic action, accompanied by increased blood volume. The latter phenomenon is obviously parallel to the antipyretic effect of intravenous injections of 50 per cent. dextrose.

115 (1575)

Studies on salt action. III: The effect of hydrogen ion concentration upon salt action.

By I. S. FALK (by invitation).

[From the Department of Public Health, Yale School of Medicine.]

Our recent studies of the effect of electrolytes upon the viability of bacteria have indicated the important influence of even slight variations in hydrogen ion concentration upon such phenomena. Working with *Bact. coli* we find that hydrogen ion concentrations above $\text{pH} = 6.0$ or below $\text{pH} = 7.0$ give a much more rapid death rate than occurs when the pH is maintained within these limits. Our experiments suggest that a very careful

control of hydrogen ion concentration is absolutely essential before valid conclusions can be drawn as to the influence of electrolytes, alone or in combination.

Furthermore, it is essential to follow with care the changes which go on in a suspension of living and dead cells as well as to determine the initial conditions which are provided. We find that a bacterial suspension in 5 isotonic NaCl solution quickly reverts to a pH of about 7.2 whether its initial hydrogen ion concentration be above or below this value. A similar change takes place in a balanced solution of 5 isotonic NaCl + isotonic CaCl₂ but at a much slower rate as indicated by the table below.

HYDROGEN ION CONCENTRATION OF SUSPENSIONS OF *Bact. coli* IN THE PRESENCE OF ELECTROLYTES.

Initial.	5 Isotonic NaCl.			Initial.	5 Isotonic NaCl + Isotonic CaCl ₂ .		
	4½ Hrs.	9 Hrs.	30 Hrs.		4½ Hrs.	9 Hrs.	24 Hrs.
4.0	7.0	7.0	7.2	4.0	4.8	4.8	5.8
5.0	7.3	7.2	7.2	5.0	6.5	6.5	7.2
6.0	7.5	7.2	7.2	6.0	7.2	7.2	7.1
7.0	7.2	7.0	7.4	7.0	7.2	7.2	7.5
8.0	7.2	7.2	7.2	8.0	8.0	8.0	8.0

116 (1576)

Discrepancies in blood oxygen analyses by the methods of Van Slyke and Henderson-Smith.¹

By Arthur H. Smith, J. A. Dawson and Barnett Cohen.

[From the Sheffield Laboratory of Physiological Chemistry, Osborn Zoölogical Laboratory and the Laboratory of Public Health, Yale University, New Haven.]

Loosely bound oxygen is liberated from the hemoglobin in blood by the addition of potassium ferricyanide. In the Van Slyke method,² all the gases are exhausted by means of a Toricellian vacuum from a laked blood-ferricyanide mixture and measured directly. In the Henderson-Smith method,³ the oxygen is evolved

¹ This work was initiated in the Laboratory of Intermediary Metabolism, Chemical Warfare Service, Yale Station, under Lt.-Col. F. P. Underhill.

² Van Slyke, D. D., *Jour. Biol. Chem.*, 1918, XXXIII, 127.

³ Henderson, Y., and Smith, A. H., *Jour. Biol. Chem.*, 1918, XXXIII, 39.

into a fixed volume of air, a portion of which is analyzed directly for oxygen by absorption with alkaline pyrogallate. After application of all the corrections suggested by the authors of these methods, the results are not identical,—analyses by the Van Slyke method yielding 4 to 10 volumes per cent. more oxygen than those by the Henderson-Smith method. The divergence between the results from each method may represent a variation of 17 to 64 per cent. A few typical figures are cited in Table I.

TABLE I.

Sample.	Van Slyke Vol. Per Cent. O ₂ .	Henderson- Smith Vol. Per Cent. O ₂ .	Difference.	
			Amount.	Per Cent.
18a. Venous content	12.9	10.4	2.5	19.4
18b. Venous capacity	18.5	12.8	5.7	30.8
18c. Arterial content	20.1	14.6	5.5	27.4
18d. Arterial capacity	20.0	15.5	4.5	22.6

It is clear that there is a constant factor or factors at play, inherent in the methods of analysis employed, which ought to account for this discrepancy.

The gas evacuated by the Van Slyke procedure is not all oxygen but probably contains in addition to nitrogen, minute amounts of carbon monoxide, hydrogen, methane and the rare atmospheric gases. Bohr¹ states that blood contains 1.23 volumes per cent. of nitrogen (incorrectly quoted by Van Slyke as 0.9 vol. per cent.) and 0.22 volumes per cent. of the other gases—a total of about 1.45 volumes per cent. of gas not oxygen. We have absorbed with alkaline pyrogallate, the oxygen from the gas extracted in the Van Slyke procedure and have found in all cases a residue of 0.055 to 0.082 c.c. from 2 c.c. of blood—an average of about 3.3 volumes per cent. This residue does not contain CO₂, and we have reason to believe that it is practically all nitrogen. It occurs to the same extent in aerated blood as in venous. Since this residue is almost constant within narrow limits, its value may be subtracted from the total Van Slyke gas volume as an average correction. We have applied this correction in Table II, and have thereby reduced the level of the Van Slyke figures by about two volumes per cent. A further refinement would be to deduct

¹ Bohr, C., in Nagel, W., "Handb. Physiol. d. Mensch.," 1909, I, 117.

the amount of oxygen physically held in the blood if the analysis is intended to show the amount of oxygen loosely held in the oxyhemoglobin.

In the Henderson-Smith method a small correction should be applied for water vapor pressure. This is however of theoretical interest for it is only 0.1 to 0.3 volumes per cent. in amount. Much more important is the fact that the oxygen content of the air in the diffusion tube has been considered without regard to the amount physically held in the 3 c.c. of blood-ferricyanide mixture. The volume of air in the diffusion tube is constant at about 10 c.c. When 0.5 c.c. potassium ferricyanide is injected through the rubber stopper, this volume is reduced, and the pressure within the tube correspondingly increased by about 5 per cent. As a result of the chemical reaction oxygen is liberated, and the pressure further increased by one per cent. Consequently, the 3 c.c. of fluid within the tube will absorb oxygen in proportion to its increased partial pressure. This physically held oxygen should be added to that determined analytically to give the total contained in the sample of blood.

We have calculated the amount of oxygen that the blood-ferricyanide mixture would hold on the basis of the gas laws (assuming that the mixture has 90 per cent. the absorption capacity of water), and it will be seen from Table II that the level of the Henderson-Smith figures has been raised about 1.5 volumes per cent.

TABLE II.

Sample.	Van Slyke Method.		Henderson-Smith Method.		Difference Between VS and H-S Corrected Values.
	Volumes Old Value.	Per Cent. O ₂ Corrected Value.	Volumes Old Value,	Per Cent. O ₂ Corrected Value.	
18a.	12.9	10.7	10.4	11.7	-1.0
18b.	18.5	16.7	12.8	14.1	2.6
18c.	20.1	18.0	14.6	16.0	2.0
18d.	20.0	18.4	15.5	16.9	1.5

From Table II it is evident that our corrections have brought the Van Slyke and Henderson-Smith values for blood oxygen much closer together than they were originally. The figures are however not identical, and we are now engaged in testing out other factors that may be involved.

117 (1577)

On the comparative toxicity of some alcohols with especial reference to isomers.

By **DAVID I. MACHT.**

[From the Pharmacological Laboratory of the Johns Hopkins University, Baltimore.]

While the comparative toxicology of various alcohols belonging to the aliphatic series has been studied by various authors, very little is known concerning the comparative pharmacological properties of some of their isomers. The present author, during the past winter, had occasion to determine the relative toxicity of methyl, ethyl, propyl, butyl and amyl alcohols, and, in that connection made a comparative study of isopropyl, isobutyl, and isoamyl alcohols, together with the normal propyl, butyl and amyl alcohols. The lethal dosage of the various alcohols was first determined by the cat method, that is, by injections intravenously of 5 or 1 per cent. solutions at regular intervals, and determining the amount of drug per kilo required to kill the animal. It was found, in these acute experiments, that the lethal dose of the normal alcohols followed the well-known Richardson's law, that is, decreased with the increase in molecular weight of the alcohol, as has been shown already by many observers. On comparing the toxicity of propyl, butyl and amyl alcohols, however, with their isomers, the secondary alcohols, it was found that in every case the secondary alcohols were less poisonous than the primary ones. Following the determination of the lethal dosage, experiments were made on isolate frogs' hearts, and here again the same relationship was noted. A third series of observations on the effects of the different alcohols on surviving plain muscle (ureter), also showed that the secondary alcohols were less toxic than the primary ones.

118 (1578)

The concentrating activity of the gall bladder.

By PEYTON ROUS and PHILIP D. McMASTER.

[From the Rockefeller Institute for Medical Research.]

In a previous paper we have noted the fact that the fluid which collects in bile ducts experimentally obstructed is an inspissated, tarry bile when the ducts communicate with the gall-bladder, whereas in ducts unconnected with this viscus the fluid is thin and soon becomes free from pigment and cholates. It has long been recognized that the gall-bladder must have a concentrating function, since bladder bile is more concentrated than duct bile from the same animal; and continued functioning during stasis will explain the tarry bile then found. The inspissation occurs so rapidly as to raise the question whether concentration of the bile in periods of intermittent or partial stasis may not be an important favoring element in the formation of gall-stones.

To determine the rate of concentration advantage has been taken of the arrangement of the hepatic ducts in the dog. There are three of these, which unite to form a common duct, with the cystic duct emptying high up into the central one. Through an opening near the lower end of this last a catheter was pushed into the neck of the gall-bladder, which was emptied and washed with salt solution; and the duct was ligated after the catheter had been withdrawn. The bile from the middle lobes of the liver had now no way of escape save into the gall-bladder. That from the lobes to either side still reached the common duct, but from this it was collected into a rubber balloon placed in the peritoneal cavity. The laparotomy incision was completely closed. The dogs tolerated the operation well. Control experiments in which a second balloon was substituted for the gall-bladder showed that the separated portions of bile differed little in their pigment content, which was taken as the index to concentration.

On examination after twenty-four hours the gall-bladder, still undistended, was regularly found to contain only one sixth to one tenth as much fluid as should on calculation have reached

it, but this, thick and dark, was six to ten times as concentrated in pigment as the control specimen in the rubber balloon. The results were the same when, without other variation in the experiment, the gall-bladder was filled to the normal distension with sterile bile of known character prior to withdrawal of the catheter. The contents of the branches of the hepatic duct connecting with the gall-bladder were always examined at autopsy. Here a thin bile, like that in the balloon, was obtained, a direct proof that the thick contents of the gall-bladder had not come as such from the liver.

It is evident that the normal gall-bladder can concentrate bile with very great rapidity.

119 (1579)

Osmosis as a factor in the local accumulation of leucocytes in the animal body.

By **FRANK MALTANER** and **E. N. HOPPE** (by invitation).

[From the Division of Laboratories and Research, New York State Department of Health, Albany.]

Chemical forces have generally been held responsible for the chemotaxis of leucocytes. Some of the early classical experiments which led to this belief were repeated. The results showed that the work had been misinterpreted, and also indicated that the forces which were active in producing the phenomenon were physical in character.

These physical forces are the forces responsible for osmosis and diffusion. In a solution not at concentration equilibrium they will act in directions counter to each other.

In the aqueous solutions examined, leucocytes are shown to move in the direction of the osmotic force and opposite to the direction of the diffusing substances in solution.

This motion is explained as being due to the greater permeability of leucocytes for water and the fact that their total mass is negligible as compared to their content of water.

120 (1580)

Alterations of intracranial tension by salt solutions in the alimentary canal.

By HARVEY CUSHING and FREDERICK E. B. FOLEY.

[From the Laboratory of Surgical Research, Harvard Medical School, and the Surgical Clinic, Peter Bent Brigham Hospital].

In two interesting and suggestive papers¹ Weed and McKibben demonstrated the significant physiological fact that it is possible to reduce the cerebrospinal fluid pressure and diminish the bulk of the brain by injecting a hypertonic solution into the blood stream. Conversely they found that hypotonic solutions had the opposite effect: a rise of cerebrospinal fluid pressure and an increase of brain bulk. In the course of our studies their work has been repeated and their general conclusions confirmed.

The clinical bearing of these facts is obvious. Particularly they concern the states commonly referred to as "pressure symptoms." By similar methods it has been found possible to secure these same results in patients with increased degrees of intracranial tension. It was felt that the undesirable effects on pulse, respiration and blood pressure of such intravenous injections might contraindicate their use. For this reason the effects of gastrointestinal doses of hypertonic solutions were studied.

In a large series of animal experiments it has been found that practically the same effects may be obtained by the gastrointestinal route of administration. By this method the intracranial changes are not attended by disturbances of pulse, respiration or blood pressure, also the possible alterations of the cellular elements of the blood are avoided.

Twenty to thirty cubic centimeters of a saturated sodium chloride solution introduced into the duodenum or rectum of an average-sized cat produced a maximal fall of cerebrospinal fluid pressure precisely comparable to that which occurred when the solution was given intravenously. Following such doses the

¹"Experimental Alterations of Brain Bulk," *Am. Journ. Physiol.*, 1919, XLVIII, p. 531; "Pressure Changes in the Cerebrospinal Fluid following Intravenous Injection of Solutions of Various Concentrations," *Ibid.*, p. 512.

average fall of pressure in a large series of experiments was 258 mm. normal saline. The changes were roughly proportionate to the concentration of the salt and the size of the dose. Two per cent. sodium chloride solution in large doses or a saturated solution in doses as small as 5 c.c. gave corresponding though less marked effects. Non-absorbable salts gave similar reductions though slower in occurrence and less in extent. Dextrose solution caused still less striking results though identical in nature.

The converse results seen after the ingestion of hypotonic solutions (water) were not great in extent nor well sustained. A previous dose of a hypertonic solution rendered more extensive the rise of pressure in these cases.

The changes observed were independent of blood pressure and were not attended by significant alterations of pulse or respiration.

These effects on cerebrospinal fluid pressure and brain volume were investigated in patients. An excellent opportunity for this was afforded by patients with brain tumor and cerebral hernia subsequent to decompression operations. In these patients there was a lowering of tension when hypertonic salines were given by mouth. Occasionally very striking results could be obtained in which case the tense convex protrusion became a soft concave area over the decompression site.

121 (1581)

Some results with a new technique in vitamine measurement.

By **WALTER H. EDDY** and **HELEN C. STEVENSON**.

[From the Department of Physiological Chemistry, Teachers College, Columbia University and the Department of Pathology, New York Hospital, N. Y. City.]

By means of a technique described in detail in the March, 1920 number of the PROCEEDINGS certain results have been attained that seem to indicate the specificity of the test for the "B" vitamine. These results are briefly as follows:

(a) Application of the test to three specimens of Funk's antineuritic vitamine prepared in 1912 and '13 showed that the

two 1913 preparations were active, though one was markedly more so than the other, and that the 1912 preparation was inactive. These specimens were supplied by Dr. Funk and represent the products of greatest purity as obtained by his fractional precipitation method. The only known impurity present was nicotinic acid and pure synthetic nicotinic acid failed to respond to the test.

(b) Lloyd's reagent was shown by Seidell and Williams to remove the B vitamine and by Harden and Silva to have little if any action upon the C vitamine. This point was tested with the new method and orange juice obtained by sterile puncture was shown to be deprived of its powers of responding to the test by shaking with the Lloyd reagent. This showed that the reagent removes the cause of the test reaction. Through the kindness of Mr. La Mer working in Professor Sherman's laboratory orange juice shaken with the Lloyd reagent and then filtered, was used in the treatment of a guinea pig suffering from scurvy. The filtrate was curative in fifteen days. It was also used as a protective agent in the diet of a pig started on a scurvy-producing diet. The symptoms had not appeared in twenty days. From these two experiments we can conclude that the test is not affected by the C vitamine and that the cause of the response is removed by Lloyd's reagent. The power of the Lloyd reagent to remove the cause of the test was confirmed by experiments with other vitamine extracts. Such experiments are not conclusive evidence but since the effects are so striking and the Lloyd has been demonstrated to remove the B type they seem to justify the belief that the causative agent in the test is the anti-neuritic or water voluble B vitamine.

(c) Results were also presented showing that the test is applicable to blood. Specimens of blood plasma furnished by Dr. N. R. Blatherwick representing bloods from the jugular and the mammary veins of a cow were poured into alcohol, the alcohol filtered off, evaporated to dryness and the residue taken up with enough water to restore it to the original plasma volume (10 c.c.). Repeated tests showed the mammary vein plasma residue to be markedly richer in the B vitamine than that from the jugular veins, indicating drainage from a mobilizing (?) point of the vitamine.

Aside from the particular interest in the bloods examined, the sensitiveness of the test to amounts present in blood suggests the use of the test in localizing the distribution of the substance in the blood streams and possibly in pellagra investigations etc.

(d) The value of the test in comparisons of vitamine concentrations was demonstrated and the point made that there is an optimum amount which must first be established by diluting the extracts studied. Below this optimum amount the test varies approximately with the concentration. Amounts above the optimum cannot be detected except by this method of applying the test. By such a method it was shown that autoclaving for three hours at 15 lbs. and approximately 120° temperature produces some destruction of the vitamine. Alkali was shown to be definitely destructive in concentrations of N/20 to N/40 NaOH. Concentration lower than N/40 seemed to have little effect.

(e) The results of applying the test to water extracts of some ten sources of the B vitamine confirmed the feeding experiments with these substances.

The detailed counts upon which these conclusions are based were presented but need not be recorded here.

122 (1582)

Dietaries of infants in relation to the development of rickets

By **ALFRED F. HESS** and **LESTER J. UNGER**.

[*From the Home for Hebrew Infants, New York City.*]

For the past two years we have been observing the effect of various diets on the development of rickets in infants. The babies received orange juice to exclude the possibility of latent scurvy. All have been on the diet for at least six months, and were followed clinically as well as controlled by means of the X-ray. It was found that many diets supposed to be eminently conducive to rickets resulted in normal nutrition. Condensed milk, for example, only exceptionally induced rickets. The one food which almost regularly led to marked rickets was a "protein milk" prepared by precipitating buttermilk with heat (not with rennin).

This preparation contained about 3.3 per cent. protein; 2.5 per cent. fat; and 6.6 per cent. carbohydrate. Its ash was about 0.44 per cent., of which the calcium and phosphorus stood about midway between that of human milk and cow's milk; its sodium content was even higher than that of the latter. Its fat-soluble vitamine content was high, its water-soluble vitamine low. Judged from the clinical standpoint, this must be regarded as a diet markedly productive of rickets.

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McMaster, Philip D.

1544. See Rous, Peyton.

1578. See Rous, Peyton.

MacDougal, D. T.

1479. [with H. A. Spoehr.] Hydration effects of amino-compounds.

Macht, David I.

1471. [with J. P. Greenberg and S. Isaacs.] Concerning the influence of antipyretics on the acuity of hearing.

1484. Concerning the toxicity of acetanilid and bicarbonate combinations for muscle-nerve preparations.

1496. [with C. F. Mora.] Effect of the anesthetization on the subsequent behavior and intelligence of albino rats.

1520. A pharmacodynamic analysis of Straub's morphine reaction.

1521. [with S. Matsumoto.] The action of prostatic extracts on isolated genito urinary organs.

1530. [with Y. Satani.] A study of local anesthetics in respect to their antiseptic properties.

1547. [with C. F. Mora.] Effect of opiates on memory and behavior of albino rats.

1577. On the comparative toxicity of some alcohols with especial reference to isomers.

Mackenzie, George M.

1533. See Longcope, Warfield T.

MacLeod, Grace.

1527. See Rose, Mary Swartz.

Maltaner, Frank.

1560. See Wadsworth, Augustus B.

1579. [with E. N. Hoppe.] Osmosis as a factor in the local accumulation of leucocytes in the animal body.

Matsumoto, S.

1521. See Macht, David I.

Mendel, Lafayette B.

1486. See Osborne, Thomas B.

1567. See Smith, Arthur H.

Miller, Raymond J.

1517. [with Olaf Bergeim and Philip B. Hawk.] The influence of anxiety on gastric digestion.

Moore, A. R.

1481. The action of camphor on the central nervous system of the squid.

Mora, C. F.

1496. See Macht, David I.

1547. See Macht, David I.

Morgan, Thomas H.

1501. Castration of hen-feathered Campines.

Morse, Withrow.

1532. See Hite, Bert Holmes.

Muller, H. J.

1465. [with E. Altenburg.] The rate of change of hereditary factors in *Drosophila*.

Murray, H. A., Jr.

1556. See McLean, Franklin C.

Myers, V. C.

1559. [with J. A. Killian and G. E. Simpson.] The influence of phenylcinchoninic acid and its methyl derivative on the uric acid and urea content of the blood.

Noble, Willis C., Jr.

1561. [with Ruth A. Thomas.] Observations on the immunization of rabbits with single strain and combined multiple strain vaccines.

Oppenheimer, B. S.

1554. [with H. E. B. Pardee.] The site of the cardiac lesion in two instances of intraventricular heart block.

Orr, Paul F.

1487. Some observations on the biological characteristics of *Bacillus botulinus*.

Osborne, Thomas B.

1486. [with Lafayette B. Mendel.] Do fruits contain water-soluble vitamine?

Papanicolaou, George N.

1537. [with Charles R. Stockard.] Effect of underfeeding on ovulation and the oestrous rhythm in guinea pigs.

Pardee, H. E. B.

1554. See Oppenheimer, B. S.

Paton, Julia B.

1495. Enzymes of pollen.

Pearce, Louise.

1548. [with Wade H. Brown.] On the generalization of *Treponema pallidum* in the rabbit following local inoculation.

1549. See Brown, Wade H.

Pease, Marshall C.

1478. The bacteriology of infectious gaseous gangrene.

Prince, Alexander L.

1568. Observations on the physiology of the otic labyrinth. The influence of prolonged rotation on the duration of postrotatory nystagmus.

1569. Variations in the affinity of hemoglobin for carbon monoxide in health and disease.

Rettger, Leo F.

1562. See **Cheplin, Harry A.**

Robinson, E. S.

1563. See **Winternitz, M. C.**

Rohdenburg, G. L.

1508. The isoagglutinins and isohemolysins of the rat.

Root, Lucie E.

1519. See **Lewis, Howard B.**

Rose, Mary Swartz,

1463. On the utilization of the salep mannan.

1499. [with **Rena S. Eckman, Edith D. Brownell, Edith Hawley and Ella Woods.**] The utilization of the calcium of carrots by man.

1527. [with **Grace MacLeod.**] Some human digestion experiments on raw white of egg.

Rosenbloom, Jacob.

1476. On the certain dietary factors to be considered in the treatment of cases of hyperthyroidism.

Rous, Peyton.

1498. [with **Louise D. Larimore.**] The relation of the portal blood to liver maintenance.

1544. [with **Philip D. McMaster.**] A. Vicious activity of the gall bladder during biliary stasis. B. The determining factor in the causation of white stasis bile.

1578. [with **Philip D. McMaster.**] The concentrating activity of the gall bladder.

Rouse, M. E.

1464. See **Sherman, H. C.**

Satani, Y.

1530. See **Macht, David I.**

Schlesinger, M. J.

1472. See **Bronfenbrenner, J.**

1473. See **Bronfenbrenner, J.**

Scott, Ernest L.

1500. (with **A. Baird Hastings.**) Sugar and oxygen relationships in the blood of dogs.

1528. [with **A. Baird Hastings.**] A study of the sugar and oxygen relationships in the blood of dogs during exercise.

Scott, R. W.

1468. The total carbonate content of the arterial and venous plasma in normal individuals.

1469. The total carbonate content of the arterial and venous plasma in patients with chronic heart disease.

1470. The total carbonate content of the arterial and venous plasma in patients with chronic pulmonary emphysema.

Sherman, H. C.

1464. [with **M. E. Rouse, B. Allen and E. Woods.**] Growth and reproduction upon simplified food supply.

Simpson, G. E.

1559. See **Myers, V. C.**

Simpson, Sutherland.

1511. Pituitary feeding and egg production in the domestic fowl.

Smith, Arthur H.

1567. [with **Lafayette B. Mendel.**] The effect of solutions of certain salts and colloids on the permeability of the capillary walls.

1576. [with **J. A. Dawson and Barnett Cohen.**] Discrepancies in blood oxygen analyses by the methods of Van Slyke and Henderson-Smith.

Smith, Clarence A.

1518. [with **Ralph C. Holder and Philip B. Hawk.**] Is unpalatable food properly digested?

Smith, G. H.

1563. See **Winternitz, M. C.**

Smith, P. E.

1512. See **Cannon, W. B.**

Soletsky, D.

1473. See **Bronfenbrenner, J.**

Spoehr, H. A.

1479. See **MacDougal, D. T.**

Stark, Mary B.

1490. A benign tumor in *Drosophila*.

Stevenson, Helen C.

1491. See Eddy, Walter H.

1529. See Eddy, Walter H.

1581. See Eddy, Walter H.

Stewart, George David.

1542. See Barber, W. Howard.

Stillman, Edgar.

1494. See Austin, J. H.

Stockard, Charles R.

1537. See Papanicolaou, George N.

Sturtevant, A. H.

1502. The vermilion gene and gynandromorphism.

Tatum, Arthur L.

1475. Method and results of a study of the distribution of iodine between cells and colloid of thyroid glands.

Thomas, Arthur W.

1462. [with Mabel E. Baldwin.] Contrasting effects of chlorides and sulphates on the hydrogen ion concentration of acid solutions.

Thomas, Ruth A.

1561. See Noble, W. C., Jr.

Thro, William C.

1525. [with Maria Ehn.] Calcium in the blood in diseases of the skin.

Todd, John L.

1509. Latent infection in experimental spirochaetosis.

Uhlenhuth, Eduard.

1523. The influence of hunger and temperature upon the utilization of food substances.

Unger, Lester J.

1488. See Hess, Alfred F.

1582. See Hess, Alfred F.

Van Slyke, Donald D.

1494. See Austin, J. H.

1550. [with J. Harold Austin and Glenn E. Cullen.] Blood changes in ether anesthesia.

Wadsworth, Augustus B.

1560. [with **Frank Maltaner.**] The purification and concentration of antigens by new methods of adsorption.

Weiss, Charles.

1522. Phenol elimination in the dog after intravenous injection of neoarsphenomine.

Wiggers, C. J.

1516. [with **L. N. Katz.**] The selective effect of the accelerator nerves on ventricular systole.

Wilson, D. Wright.

1555. Studies in pyrimidine metabolism.

Winternitz, M. C.

1563. [with **G. H. Smith** and **E. S. Robinson.**] An unrecognized pathway for bacterial invasion of the respiratory tract.

Woods, Ella.

1464. See **Sherman, H. C.**

1499. See **Rose, Mary Swartz.**

Zucker, T. F.

1513. Studies in the adsorption of fats.

EXECUTIVE PROCEEDINGS.

MAIN SOCIETY.

One Hundred First Meeting.

Cornell University Medical College, October 15, 1919. President Calkins in the chair.

Members present: Baumann, Calkins, Eddy, Fine, Funk, Gies, Greenwald, Jackson, Jobling, Kleiner, Lusk, MacNeal, Muller, Myers, Rose, A. R., Rose, M. S., Salant, Sherman, H. C., Uhlenhuth, Wallace.

Members elected: I. J. Kligler, Marshall C. Pease, Charles Weiss.

One Hundred Second Meeting.

New York Post-Graduate Medical School, November 19, 1919. President Calkins in the chair.

Members present: Auer, Calkins, Field, Gates, Gies, Githens, Greenwald, Harris Isaac, Jackson, H. C., Jobling, Killian, Kligler, MacDougal, MacNeal, Moore, Morgan, Myers, Olitsky, Rose, A. R., Scott, Senior, Wallace, Wilson.

Members elected: Robert A. Gesell, Jean Redman Oliver, Oscar M. Schloss, R. W. Scott.

One Hundred Third Meeting.

Rockefeller Institute for Medical Research, December 17, 1919. President Calkins in the chair.

Members present: Auer, Austin, Burton-Opitz, Calkins, DuBois, Eddy, Field, Funk, Gies, Githens, Greenwald, Hess, Jackson, H. C., Kahn, R. L., Meltzer, Mosenthal, Muller, Myers, Riddle, Rose, A. R., Salant, Sherwin, Thro, Torrey, Uhlenhuth, Van Slyke.

Members elected: S. C. Brooks, B. M. Duggar, H. A. Spoehr.

One Hundred Fourth Meeting.

College of Physicians and Surgeons, January 21, 1920. President Calkins in the chair.

Members present: Auer, Burton-Opitz, Calkins, Davenport, Eddy, Gies, Greenwald, Jackson, H. C., Lee, MacNeal, Morgan, Muller, Myers, Pike, Rose, A. R., Rose, M. S., Salant, Scott, E. L., Stockard, Sturtevant, Wallace.

One Hundred Fifth Meeting.

College of City of New York, February 18, 1920. Vice-President Wallace in the chair.

Members present: Auer, Cannon, Edwards, Fine, M. S., Goldfarb, Hess, Jackson, H. C., Jobling, Kahn, R. L., Killian, MacNeal, Moore, Myers, Pappenheimer, Riddle, Rose, A. R., Salant, Thro, Uhlenhuth, Waksman, Wallace.

Members elected: Helen C. Coombs, E. C. Fleischner, Samuel Goldschmidt, Henry G. Mehrstens, George W. Raiziss, A. H. Ryan, Mary B. Stark.

One Hundred Sixth Meeting.

Presbyterian Hospital, March 17, 1920. Vice-President Wallace in the chair.

Members present: Bauman, L., Coombs, Eddy, Edwards, D. J., Funk, Gies, Greenwald, Hess, Jackson, H. C., Killian, Lee, F. S., Longcope, Myers, Pappenheimer, Rose, A. R., Rose, M. S., Scott, E. L., Sherman, H. C., Thro, Wallace.

Members elected: Emil J. Baumann, A. Baird Hastings.

One Hundred Seventh Meeting.

University and Bellevue Hospital Medical College, April 21, 1920. Vice-President Wallace in the chair.

Members present: Banzhaf, Barber, W. H., Barbour, Chambers, Coombs, Eddy, Funk, Hess, Levin Isaac, Myers, Park, W. H., Rous, Sherman, H. C., Uhlenhuth, Van Slyke, Wallace, Williams, Anna, Zingher.

Members elected: W. C. Boeck, W. W. Cort, R. W. Hegner, Byron M. Hendrix, F. M. Root, W. H. Taliaferro.

One Hundred Eighth Meeting.

Osborn Memorial Laboratory of Zoology, New Haven, Conn., May 22, 1920. Vice President Wallace in the chair.

Members present: Bailey, C. V., Baitsell, Barbour, Baumann, E. J., Chittenden, Cohen Barnett, Cohen Martin, Cushing, Donaldson, DuBois, Eddy, Fine, Funk, Gies, Githens, Goldschmidt, Harrison, Hartwell, Hatai, Hess, Howe, Jackson Holmes, Killian, Laurens, Lusk, McLean, Meltzer, Mandel, Myers, Noble, Osborne, Pappenheimer, Rettger, Ringer, Rose, A. R., Rose, M. S., Smith Arthur, Underhill, Wadsworth, Wallace, White Benjamin, Winslow, Woodruff.

PACIFIC COAST BRANCH.

Twenty-third Meeting.

San Francisco, California, October 8, 1919.

Members present: Addis, Alvarez, Barnett, Bloor, Burnett, Dickson, Evans, Hewlett, Kofoid, Ophüls, Schmidt, Walker, Watanabe, Whipple.

Twenty-fourth Meeting.

San Francisco, California, February 11, 1920.

Members present: Addis, Alvarez, Crawford, Dickson, Evans, Faber, Hewlett, Holmes, Lucas, Oliver, Ophüls, Schmidt, Walker, Whipple.

Twenty-fifth Meeting.

San Francisco, California, April 21, 1920.

Members present: Alvarez, Bloor, Crawford, Dickson, Faber, Gesell, Hewlett, Mehrtens, Ophüls, Schmidt, Walker, Watanabe, Whipple.

REGISTER OF NAMES AND ADDRESSES OF THE MEMBERS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE

ABBOTT, ALEXANDER C.....	University of Pennsylvania.
ABEL, JOHN J.....	Johns Hopkins University.
ADAMI, J. GEORGE.....	University of Liverpool, England.
ADDIS, THOMAS.....	Leland Stanford University, San Francisco.
ADLER, HERMAN M.....	Juvenile Psychopathic Institute, Chicago.
ALLEN, BENNET M.....	University of Kansas.
ALSBERG, CARL L.....	U. S. Department of Agriculture, Washington, D. C.
ALVAREZ, WALTER C.....	University of California.
AMOSS, HAROLD L.....	Rockefeller Institute for Medical Research.
ANDERSON, JOHN F.....	Rutgers College, New Brunswick, N. J.
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AUSTIN, J. H.....	Rockefeller Institute for Medical Research.
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ONE HUNDRED FIRST MEETING

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OCTOBER 15, 1919

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TWENTY-THIRD MEETING

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OF THE
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ONE HUNDRED FOURTH MEETING

COLLEGE OF PHYSICIANS AND SURGEONS

NEW YORK CITY

JANUARY 21, 1920

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SOCIETY FOR
EXPERIMENTAL BIOLOGY AND MEDICINE

ONE HUNDRED FIFTH MEETING
COLLEGE OF THE CITY OF NEW YORK
NEW YORK CITY
FEBRUARY 18, 1920

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No. 5

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PROCEEDINGS
OF THE
SOCIETY FOR
EXPERIMENTAL BIOLOGY AND MEDICINE

ONE HUNDRED SIXTH MEETING
PRESBYTERIAN HOSPITAL
NEW YORK CITY
MARCH 17, 1920
AND
TWENTY-FOURTH MEETING
PACIFIC COAST BRANCH
SAN FRANCISCO, CALIFORNIA
FEBRUARY 11, 1920

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Dates of the next two meetings:

February 18, 1920—March 17, 1920.

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ONE HUNDRED SEVENTH MEETING

UNIVERSITY AND BELLEVUE HOSPITAL
MEDICAL COLLEGE

NEW YORK CITY

APRIL 21, 1920

AND

TWENTY-FIFTH MEETING

PACIFIC COAST BRANCH

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APRIL 21, 1920

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ONE HUNDRED EIGHTH MEETING

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YALE UNIVERSITY

NEW HAVEN, CONN.

MAY 22, 1920

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Dates of the next two meetings:

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Members present at the twenty-fifth meeting of the Pacific Coast Branch:

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Dates of the next two meetings:

May 22, 1920—October 20, 1920.

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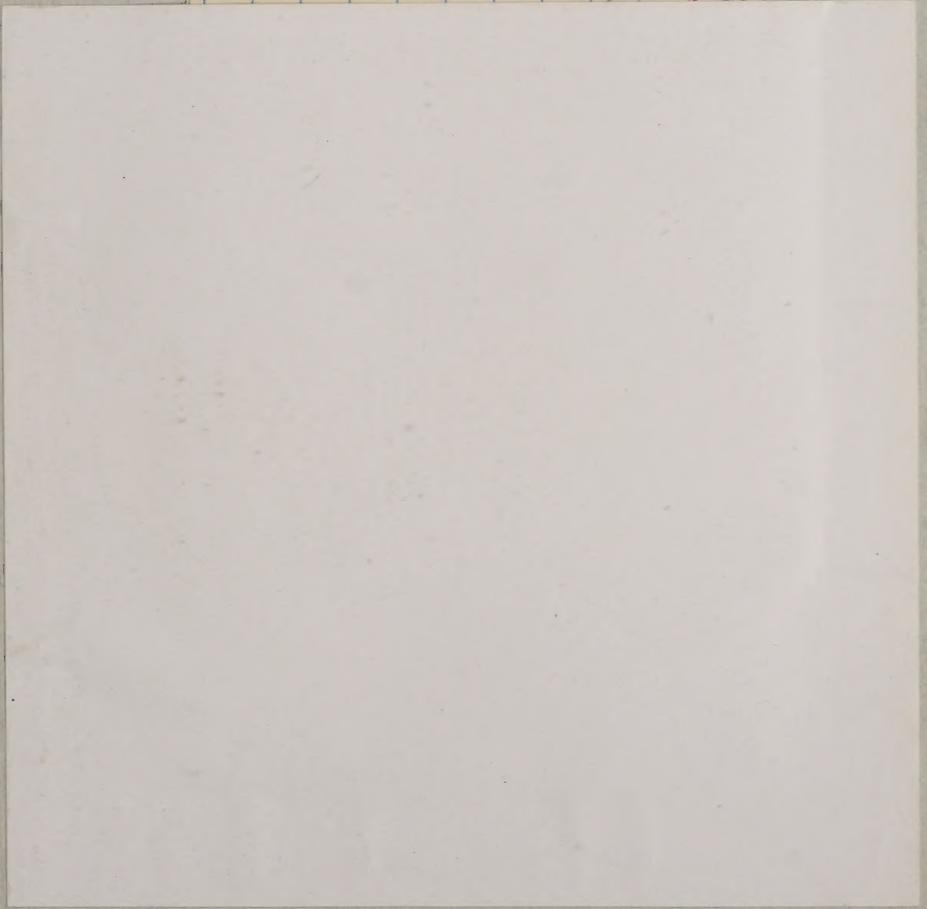
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