Higher Mathematics

In Todays Medicine

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AS WORKERS in biological and medical sciences have broadened their understanding of the advanced branches of mathematics, many phenomena associated with life have been analyzed, and then defined in the language of mathematics. Numerous occurrences presently defy rigorous mathematical treatment, but eventually will yield to at least some extent to elucidation by analytical means, while others will no doubt forever remain enigmas.

It is the intent of this discussion to enumerate several broad fields of mathematics and to show application of them to various phenomena encountered by biologists and medical workers.

I. *Algebra*

Definition

Algebra is a branch of mathematics in which arithmetical operations are studied by the use of generalizing symbols. These symbols in turn represent factors which interact in a system or situation. Once the relationships between the symbols have been assembled into a formula or equation, then specific quantities can be substituted in order to solve individual problems.

Examples

A. The Henderson-Hasselbach equation expresses the relationship of the pH of blood plasma to the buffer systems of the blood[3]. The principal buffer system which maintains the plasma pH within a narrow range near pH $= 7.4$ is the bicarbonate system. Both acidic and alkaline substances are neutralized by this buffer system. The algebraic expression which designates the relationship between the pH and the concentrations of the components of this buffer system is:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

where $[HCO_3^-]$ is the concentration of bicarbonate ion in plasma and $[H_2CO_3]$ is the concentration of carbonic acid in plasma. Figure 1 shows the graphic expression of this equation.
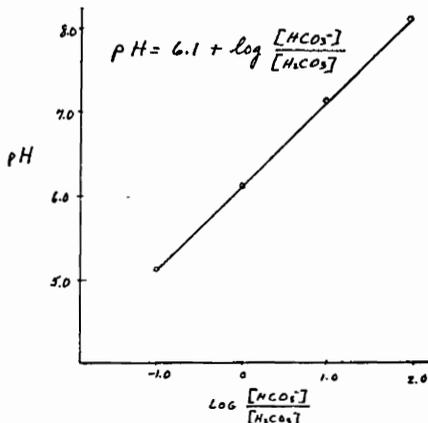
Micromoles of pyruvic acid formed in 20 minutes	$\frac{1}{V}$	Pyridoxal phosphate Concentration $(X10^5M)$	$\frac{1}{[S]}$
0.150	6.6 X10⁶	0.20	.5 X10⁶
0.200	5.0	0.40	.25
0.275	3.6	0.85	.118
0.315	3.18	1.25	.08
0.340	2.94	1.70	.06
0.350	2.86	2.00	.05
0.360	2.78	8.00	.0125

Figure 1

Figure 2

B. The Michaelis-Menten equation[5] relates the reaction velocity of an enzyme-substrate system to the amount of substrate present:

$$Vi = \frac{V_m \, [S]}{[S] + K_m}$$

Vi is the initial reaction velocity
V_m is the maximum reaction velocity
$[S]$ is the concentration of substrate
K_m is the Michaelis constant

The equation as expressed above is difficult to interpret when represented graphically. Lineweaver and Burk[2] recommend transformation into a linear equation as below:

$$\frac{1}{V_i} = \frac{1}{V_m} + \frac{K_m}{V_m \, [S]}$$

Thus $1/V_i$ can be plotted versus $1/S$ to give a straight line relationship. The resulting straight line provides a much simpler means of checking the validity of the theory against laboratory data. Figure 2 shows this relationship in the case where d-serine is acted upon by the hydrase of *Neurospora crassa*, in the presence of the coenzyme pyridoxal phosphate, to form pyruvic acid and ammonia.
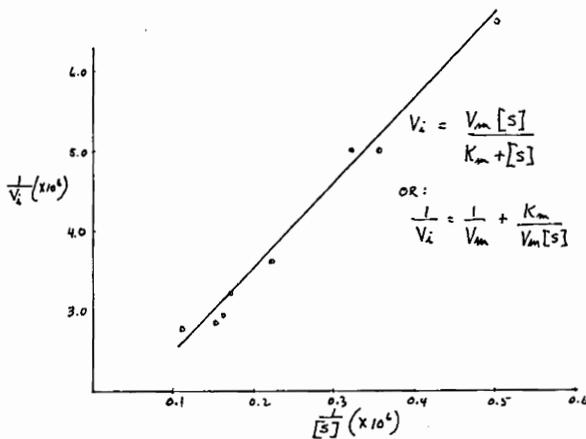
II. Trigonometry

Definition

Trigonometry is a science which deals with the definitions, properties and relations of lengths and angles. It uses the methods of algebra and its principal goal is to give numerical answers.

Examples

A. The power expended on a treadmill whose platform angle can be varied is expressed by the equation[4]:

$$P = P_o + P_h$$

where,
$P_o =$ power normally expended when walking along level surface
$P_h =$ power expended in lifting the body vertically

In the case where the treadmill is horizontal, the power expended is expressed as:

$$P = P_o$$

A rough approximation of P_o can be made, assuming that an average adult man (70 Kg.), while walking on a horizontal surface at a rate of 4 kilometers per hour,

would expend energy at the rate of 2400 calories (kilocalories) per day or 100 kilocalories per hour, or 116 watts, or 42.7 kilogram-kilometers per hour. The relations between the above units are as follows:

$$1 \text{ watt} = 1 \text{ joule/second}$$
$$1 \text{ kilocalorie} = 4185 \text{ joules}$$
$$100 \text{ kilocalories/hour} = \frac{418500 \text{ joules}}{3600 \text{ seconds}} = 116 \text{ watts}$$
$$116 \text{ watts} = \frac{116 \text{ joules}}{\text{sec}} = 116 \times 10^2 \frac{\text{dyne-kilometers}}{\text{second}}$$
$$= \frac{116 \times 10^2 \times 3600}{980} \frac{\text{gram-kilometers}}{\text{hour}}$$
$$= 42.7 \frac{\text{kilogram-kilometers}}{\text{hour}}$$

When the platform is tilted upward, the additional power expended in lifting the body vertically can be expressed as:

$$P_h = WV \sin \phi$$

where W = weight of the subject
V = velocity of subject on treadmill
ϕ = slope of the treadmill
V sin ϕ = velocity in the vertical direction

The total power expended when the treadmill is slanted upwards at various angles is indicated in the following table:

platform slope		power	
ϕ	sin ϕ	kg-km/hr	watts
0	.000	42.7	116
5°	.087	66.7	181
10°	.174	91.7	250
15°	.258	114.7	312
20°	.342	138.7	378
25°	.423	160.7	438
30°	.500	182.7	498

III. Analytical Geometry

Definition

Analytical geometry is the field of mathematics in which the methods of algebra, geometry and trigonometry are utilized to simplify and clarify problems which arise in any of the three respective fields and to portray in accurately plotted coordinates interrelationships among 3 variables.

Examples

A. Bacterial growth and destruction can be expressed as a complex curve composed of several phases[7]. When plotted on a semilog plot (logarithmic for bacterial numbers and linear for time intervals), the following general curve in figure 3 results:
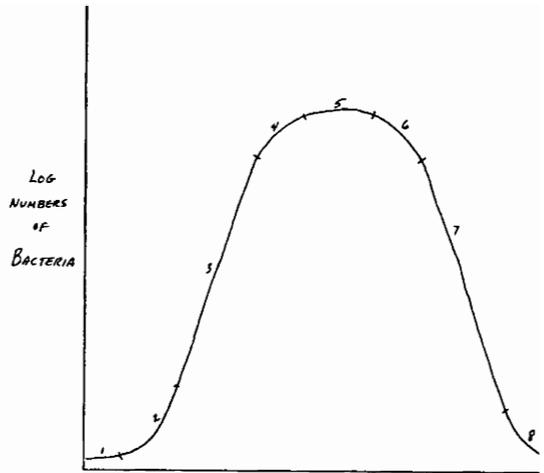

Figure 3

The phases are:

1. latent or initial stationary phase
2. lag phase
3. logarithmic growth phase
4. negative acceleration phase
5. stationary phase
6. accelerated death phase
7. logarithmic death phase
8. final phase of decline

1. The growth of a bacterial strain in broth culture is shown in the following table.

time	log [bacteria/cc]
0 hours	6.3
1	6.3+
2	6.3−
2.5	6.6
3	6.9
4	7.2
5	7.7
6	8.2
7	8.4
8	8.5
9	8.5+
11	8.5+
25	8.6

These data are plotted on figure 4. The curve which results is S-shaped, or sigmoid. Fortunately, a curve of this shape can be reproduced when the equation, log y = tanh x is plotted, making allowances for translation of axes and scaling factors. In figure 4 the equation $\log y = 7.45 + 1.15 \tanh \dfrac{(x-4.5)}{2}$ is also plotted. It approximates very closely the experimental data.
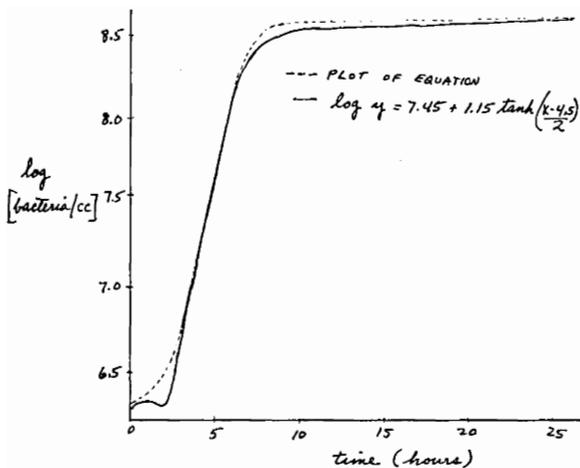
Figure 4

2. Figure 5 illustrates the logarithmic death phase of a culture of bacterial spores. Here the use of a three cycle semilog plot gives a linear representation of the following data:[8]

Mean number of Bacteria per drop	Time (hours)
439.0	0
275.5	0.5
137.5	1.25
46.0	2.0
15.8	3.0
5.45	4.1
3.6	5.0
0.5	7.0

Appropriate analysis of the analytic geometry of the straight line drawn to fit the data reveals that the mean number y of bacteria per drop is related to the time t (in hours) by the equation $y = 439e^{-t}$, where $e = 2.71828$ is the base of the natural logarithm system.
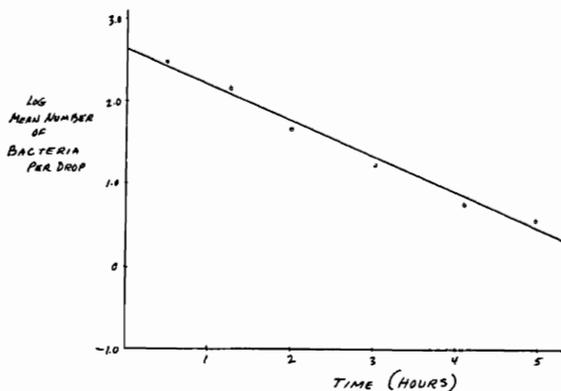

Figure 5

B. Hill Equation for muscle. When a muscle contracts under a load, the speed or velocity at which it contracts is maximum initially and decreases as the tension on the muscle increases[10]. The following equation accurately portrays the relationship,

$$(P + a)(v + b) = (P_o + a)_b = k$$
$$\text{(a constant)}$$

where P_o = initial tension on the muscle
P = tension at any time during contraction
a = a constant having the same dimension as P
v = velocity of contraction = change in length per unit time
b = a constant having the same dimension as v.

Graphically, the relationship appears as in figure 6. The curve shown is one branch of a hyperbola, and it can be said that contraction velocity decreases hyperbolically with tension in an isotonic contraction. The Hill equation, and its related curve, has been shown to accurately represent the contraction characteristics of nearly all skeletal muscle, regardless of the warm-blooded species.
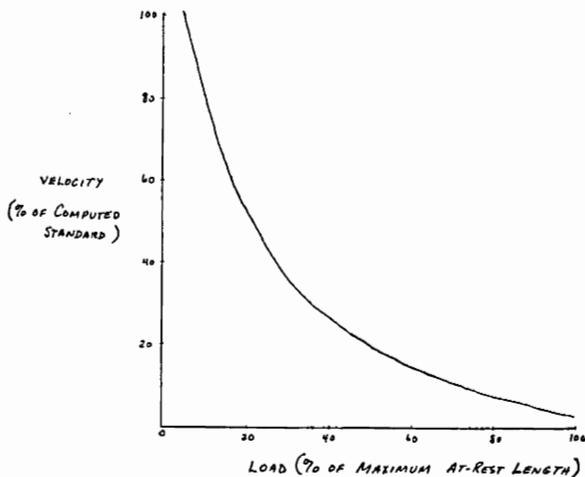

Figure 6

IV. Differential Calculus

Definition

Differential calculus deals with continually varying quantities, and especially problems which relate the rate of change of one variable with respect to another.

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Examples

A. Body temperature rise in an environment where heat cannot be lost (external temperature near normal body temperature, relative humidity near 100%).

If an animal, for example a 75 Kg. pig, is placed in the above-specified environment, the time for the body temperature to increase by a given amount can be calculated:

For a 75 Kg. pig the resting metabolic rate r is

$$r = 1.55 \text{ Cal./Kg./hr.}$$

By definition, one Calorie is the amount of heat required to raise the temperature of 1 kilogram of water 1° Centigrade. The body temperature rise per hour, in the environment which prevents heat loss, is calculated as follows:

If: **M** = resting metabolic rate of pig (in Cal./hr.)

dT = amount of t e m p e r a t u r e change

dt = time interval for the temperature to rise by the given amount (dT)

w = weight of animal (in kilograms)

c = mean effective specific heat of the body tissues = 0.85

then:

$$\frac{M}{w} = c\frac{dT}{dt}$$
$$dT = \frac{M}{cw} dt$$

For example, to estimate the time interval for the temeprature of a resting 75 Kg. pig to rise by 5° C., direct substitution in the formula gives:

$$(0.85)(5) = 1.55 \text{ dt}$$
$$dt = 2.73 \text{ hours}$$

Recent laboratory experiments indicate that this prediction is reasonably well confirmed.[6]

V. *Integral Calculus*

Definition

Integral calculus is that branch of mathematics which, from the relations among the infinitesimal (small) changes or variations of quantities, de-

duces relations among the quantities themselves.

Examples

A. Cardiac output from a dye dilution curve. In determining the flow rate of blood from the heart, one method involves the use of a known quantity of dye which is rapidly deactivated (i.e., indocyanine green). If the dye is rapidly injected into the right atrium, is allowed to mix with the blood in the lung, and the concentration of dye in the aorta is monitored by photometric means, a curve resembling that in figure 7 is obtained. The solid line indicates the concentration of the dye as sensed by the photosensitive transducer.
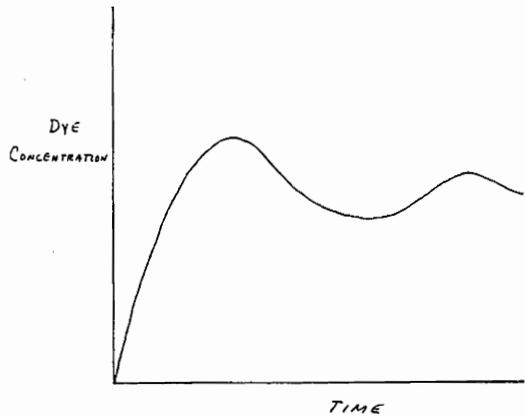

Figure 7

The phenomena represented by the curve may be explained as follows: Shortly after the dye is injected it mixes with the blood in the lung, and it is soon found in maximum concentration in the arterial blood. As the heart continues to beat, fresh dye-free blood dilutes the dye in the lung and its concentration decreases. The second peak on the curve results when the arterial blood containing the dye has returned as venous blood to the lung. In analyzing the data, the useful portion of

the curve is that part showing decline in concentration of the dye following the initial peak. This part is found to be linear on a semilog plot (as shown in figure 8a and therefore represents a simple exponential decay on the linear plot.
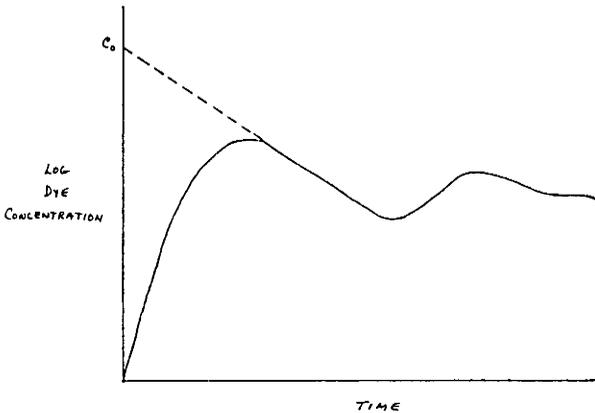

Figure 8a

A dependable value of the initial dye concentration C_0 is easily found by extrapolation to zero time on the semilog plot, as shown by the dashed line. The value of the "time constant" t, for the exponential decay is found by extrapolating, on the linear plot, the initial slope of the curve, as shown by the dashed line in figure 8b.
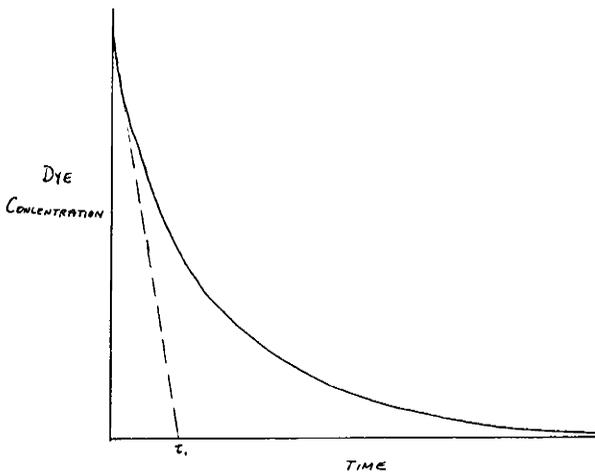

Figure 8b

The decrease in dye concentration is expressed in mg./ml./minute, and is taken from the linear portion of the curve. It is designated as:

$$\int_o^t C_o(t)dt$$

and equals Ct where C is the average concentration of the dye during the first circulation.

The flow rate, or cardiac output, is calculated from the equation:[9]

$$F = \frac{Q}{\int_o^t C_o(t)dt} = \frac{Q}{Ct} = \frac{mg}{mg/liter/min} = \frac{liters}{min.}$$

where $F =$ flow rate
$Q =$ quantity of dye injected

The equation representing the concentration C of dye in the aortic blood following the initial peak is:

$$C = C_o\, e^{-\left(\frac{F}{V}\right)t}$$

where $V =$ the volume of the m i x i n g chamber (lung capillaries)
$F =$ the blood flow rate
$e = 2.71828 = $ t h e base of natural l o g a - rithms.

Integrating this equation with respect to time t gives:

$$\int_o^\infty C_o e^{-\left(\frac{F}{V}\right)t}\, dt$$

$$= \left(\frac{V}{F}\right) C_o$$

Now, the product VC_0 is equal to the total quantity Q of dye injected, and the integral $\int_o^\infty C\, dt$ is equal to the total area A under the idealized exponential-decay curve (figure 8b), i.e.,

$$VC_o = Q$$

$$\int_o^\infty Cdt = A$$

But the result of the above integration indicates that:

$$A = \frac{Q}{F}$$

Consequently the simple equation,

$F = \dfrac{Q}{A}$ gives the blood flow rate F

(in liters per minute) in terms of the total quantity Q (in milligrams) of dye injected and to the area A (mg.-minutes/liter) under the idealized curve representing the concentration C (in mg./liter) in the aortic blood as a function of time t (in minutes).

B. Electronic integrator for use in calculating hormone feedback. In an analog computer, integration is accomplished rapidly and with precision limited only by the tolerance of its components. The basic integrating unit is an operational amplifier with specific coupling impedances, as shown in figure 9.
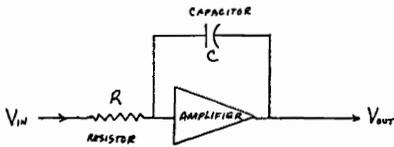

Figure 9

Any voltage fed into this unit will be integrated with respect to time. A specific voltage input V_{in} is used to represent experimental data, the output voltage V_{out} will be related to it in the following way:

$$V_{out} = \frac{1}{RC} \int_o^t V_{in}\ dt$$

This may be verified as follows:
The charge Q across a capacitance C is expressed as $Q = CV$ where V is the voltage across it. When it discharges, the current i that flows is

$$i = \frac{dQ}{dt} = \frac{(\text{change in charge})}{(\text{change in time})}$$

is in turn equal to $C \left(\dfrac{dV}{dt} \right)$ where

dV is the change in voltage. Rearranging the equation:

$$i = C\ \frac{dV}{dt}$$

to read:

$$dV = \frac{i}{C}\ dV$$

and integrating, gives:

$$V = \frac{1}{C} \int_o^t i\ dt$$

The high gain amplifier with its feedback capacitor always acts to maintain its input voltage near zero. Writing the circuit equations for the system shown in figure 9 gives:

$$\frac{V_{in}}{R} = -C\ \frac{dV_{out}}{dt}$$

This is equivalent to stating that:

$$V_{out} = -\frac{1}{RC} \int_o^t V_{in}\ dt$$

Integrating amplifiers of the type shown in fig. 9 are widely used in groups to solve systems of differential equations, which are frequently necessary for adequate description of physiological phenomena.

Bibliography

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4. Hauseman, E., and Slack, E. P. Physics. 2nd edition. p. 145. New York, N. Y., D. Van Nostrand. 1939.
5. Hawk, P. B., Oser, B. L., and Summerson, W. H. Practical Physiological Chemistry. 13th edition. p. 314. New York, N. Y., The Blakiston Company, Inc. 1954.
6. Juszkiewicz, T. 1960, unpublished data. Department of Physiology and Pharmacology,, College of Veterinary Medicine, Iowa State University, Ames, Iowa.

Dean I. A. Merchant attended a meeting of the Advisory Committee on Veterinary Medical Specilties to the Council on Education, American Veterinary Medical Association, for the purpose of discussing those groups who wish to form a specialty board under the sponsorship of the AVMA.

Dr. D. L. Baker presented two papers at the Missouri Veterinary Medical Association's meeting on February 20–21, 1961 at St. Louis, Missouri. The papers were entitled, "The Diagnosis and Treatment of Heart Diseases" and "Diseases of the Urinary System."

Dr. R. A. Packer, Head of the Department of Veterinary Hygiene, attended a national meeting on bovine mastitis and the Conference of Research Workers in Animal Diseases on November 28-December 1, 1960, in Chicago, Illinois.

On January 4–6, 1961, Dr. B. W. Kingrey, Head of the Department of Medicine and Surgery, attended the 53rd annual New York Conference for Veterinarians at New York State Veterinary College at Cornell University. Ithaca, New York. While there, Dr. Kingrey presented a paper entitled "Cattle Surgery."

At the annual convention of the Iowa Veterinary Medical Asociation, January 17–19, 1961, Des Moines, Iowa, Dr. B. W. Kingrey presented a paper, "Cattle Practice" and participated in the "Disease Forum."

Dr. M. J. Swenson was recently appointed to the Research Committee of the Iowa Heart Association.

Dr. Harry W. Yoder of the Veterinary Medical Research Institute presented a report of the research on "Control of Infectious Sinusitis of Turkeys" at the convention of the National Turkey Federation in Chicago, Illinois, January 3–7, 1961.

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placed within a larger ice packed container. The package should be labeled as a rabies suspect on the outside as a safety precaution for laboratory personnel.

The diagram is a suggested mode of packaging for all specimens requiring refrigeration.
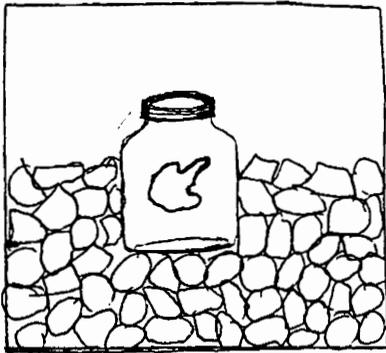
Sample jar packed in container of ice

The Becton-Dickinson Company, suppliers of laboratory equipment, states: "A laboratory diagnosis is no better than the specimen submitted and the specimen is no better than the manner in which it was collected."

7. Porter, J. R. Bacterial Chemistry and Physiology. p. 103. New York, N. Y., John Wiley and Sons, Inc. 1946.
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9. Shumway, N. E., Johnson, J. A., and Stish, R. J. Quantitative analysis of a direct writing method for dye dilution curves. J. Applied Physiol. 10:297–300. 1957.
10. Stacy, R. W., Williams, D. T., Worden, R. E., and McMorris, R. B. Essentials of biological and medical physics. p. 90. New York, N. Y., McGraw-Hill Book Co., Inc. 1955.

Dates for State Board Examination Are Announced

The state board examination will be given at the State Capitol Building Des Moines, Iowa. They will be held June 1 and 2. The tests will be given commencing at 8:00 a.m. in the House Chamber.

Each applicant should be advised that he must present a diploma showing that he is a graduate of a recognized school of Veterinary Medicine.