EXPERIMENTALLY PRODUCED FOCAL INFECTION IN RELATION TO

CARDIAC HYPERTROPHY

From the Department of Medicine University of Oregon Medical School

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S. J. HENSON

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CARDIAG HYPERTROPHY

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S. J. NEWSOM

in the literature an experimentally controlled attempt
to correlate the effect of focal infection with cardiac
hypertrophy and to determine the myocardial response to
toxic injury and infection under stress and strain. This
work represents an attempt to investigate the problem as
accurately as rigidly controlled experimental conditions
will permit. It is the purpose of this paper to deal with
the following five problems: (1) What is the relationship,
if any, between experimentally produced focal (dental)
infection and cardiac hypertrophy? (2) What will be the
relative effects of exercise upon such infected and noninfected dogs? (3) What is the reliability of the various
means of expressing cardiac hypertrophy? (4) What pathological
changes, cardiac and extracardiac, are noted in the experimental

FOCAL INFECTION AND CARDIAC HYPERTROPHY

animals? (5) Have we employed a satisfactorily large population of animals from which to draw results so reliable as to be accepted without question?

Malbe in reviewing the literature finds a general acceptance of the truth that a work hypertrophy exists and concludes that an increased relative and absolute heart weight occurs with exercise without a corresponding increase in body muscle weight. In contrast to this view we find that Horvath 2 denies that hypertrophy is due to increased work. Albrecht3 finds no constant relation between function and hypertrophy. There is, however, an increased connective tissue stroma, vacuolated muscle cells showing a degeneration of the anisotropic portions and an increase of the isotropic portions of the muscle elements with often a doubling of the nuclei. Albrecht considers such changes a response to infection. Stewart4 reports that hypertrophy induced by production of acrtic insufficiency involves all chambers of the heart. The hypertrophy is greatest absolutely in the left ventricle, and is followed in order by the septum, right ventricle and auricles. The greatest relative increase is also seen in the left ventricle, but the auricles show here a greater relative increase then the septum or right ventricle. Herzmann⁵ concludes that the left ventricle has the greatest relative and absolute hypertroph.

POCAL INFECTION AND CARDIAG HYPERTROPHY

Postnote to Page 2.

- 1 Kilbs, Dr., Experimentalles über Herzmuskel und Arbeit., Arch. Exper. Path. U. Pharm. 1906, 55; 288.
- 2 Horvath, A., Ueber die Hypertrophie des Herzens. Vienna & Leipzig., 1897.
- 3 Albrecht, Ehrenfreid, Der Herzmuskel und seine Bedeutung für Physiologie, Pathologie und Klinik des Herzens. Berlin: 1903.
- 4 An Experimental Contribution to the Study of Cardiac Hypertrophy. Jour. Exp. Ned., 1911; 13, 187.
- 5 Herrmann, George R. The Effect of Experimental Aortic Regurgitation on Heart Weight: with a Consideration of some Factors Concerned in Cardiac Hypertrophy and a Summary of Cardiac Manifestations of Experimental Heart Disease. Amer. Heart Jour., 1926; 1, 485.
- 6 Geldenberg, B., Ueber Atrophie und Hypertrophie der Muskelfasern des Herzens., Virchow'e Archiv. 1886; 103, 88.
- 7 Tangl, Franz. Ueber die Hypertrophie und des Physiologiache Wachstaum des Herzen. Virokew's Archiv. 1889; 116, 432.

POCAL INFECTION AND CARDIAG HYPERTROPHY

often refractory to hypertrophy and young dogs show more uniformity; that important contributing factors are the age of the dog and the presence or absence of intracardial infection, and that the solution of the problem of cardiac hypertrophy is still out of reach, probably because a number of factors are active in the process. Goldberger found that the muscle cell of the hypertrophied heart is larger then normal and that the increase is a volume increase. Tangl after using a maceration process on left ventricular wall specimens concluded that the greater the absolute heart weight so the greater the cross diameter of the cells, both in physiological growth and also in pathological hypertrophy.

THE APPROACH

The dogs used in this experimental work were an unselected group with the exception of their age⁵ which averaged nine months, in order that our samples might represent an average group and therefore be comparable to the normal canine standards reported by Herrmann⁶. Thirty six dogs were employed, and these were divided into three groups.

The ineculated group of fourteen dogs were selected at random. These dogs were subjected to a rigidly followed

⁸ Herrmann, G. R., Experimental Heart Disease., Amer. Heart Journ. 1925; l. 213.

FOCAL INFECTION AND CARDIAG HYPERTROPHY

technique by Dr. Frank Miknos⁹, which may be summarised as follows:

(1) Dog anesthetized with other. (2) Lower canine tooth isolated with rubber dam. (3) Distal one-half of exposed canine tooth removed with caisel and mallet. (4) Pulp removed. (5) Pulp cavity dried. (6) Injection with hypodermic syrings of § to c.c. of streptococcus culture deep at base of pulp cavity. (7) Pack pulp cavity with cotton and pulp point. (8) Pack with dental sement. (9) Finish filling with silver amalgam. (10) Repeat process on contralateral lower or homolateral upper camine tooth.

The streptococcus culture employed was isolated by Dr. R. L. Benson 10 from the antra of a patient suffering with chronic bilateral hyperplastic sinusitis and was one of a small series of streptococci cultures used by Dr. Benson in an experimental attempt to produce arterioscleroeis in animals. This organism was identified by cultural and microscopic characteristics as a non-hemolytic green producing type of gram positive streptococcus corresponding to the sugar fermentations of Streptococcus mitis. The injected culture was composed of normal saline washings of a twenty-four pure culture of these organisms.

The central group of mineteen dogs were selected at random. These dogs were, in every way, subjected to the same treatment throughout and after the experimental period

- 9 Attending Oral Surgeon, Multnemah County Hespital.
- 10 Clinical Professor of Rathology, University of Oregon Medical School.

FOCAL INFECTION AND CARDIAC HYPERTROPHY

as that afforded the ineculated dogs with the single exception of the previously described dental ineculation.

The normal dogs, seven in number, were likewise an unselected group. These dogs were secured after death, weighed, autopsied and the fresh heart weighed and kept for further treatment and examination. This series was started with the idea of continuing the inclusions to an indefinite number. It was found that this series of normal dogs corresponded, practically without exception, to the large group of 200 normal dogs reported by Rermann⁸, se the group was discontinued after seven dogs has been thus treated.

The provision that the dogs be examined for effects after being subjected to stress and strain was accomplished by daily exercise to exhaustenn. An electric treadmill having an inclined canvas belt and two screened cages was devised and constructed to provide such exercise. Each dog of the series was exercised for periods of fifteen minutes daily, six days during each week. The tread was inclined at an angle of twenty degrees to the horizontal and moved at a rate of 5.4 miles per hour. The average energy thus expended by each dog in his daily run was 22,600. foet-pounds, and reached the sum total of approximately 3,000,000. foot-pounds

POCAL INDECTION AND CARDIAG HYPERTROPHY

during the entire experimental period. This daily exercise was sufficient to markedly fatigue the dog. This procedure was continued for an average of 1550 minutes of exercise per dog.

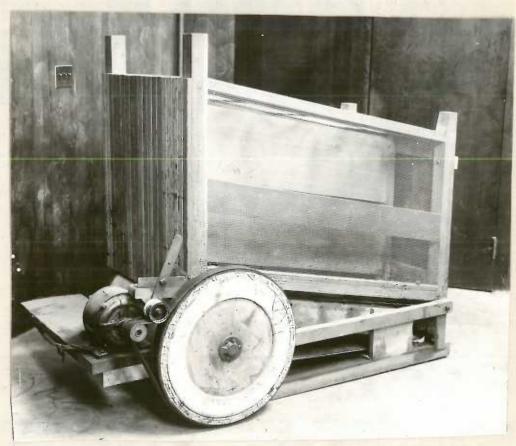


PLATE 1 Electric Treadmill

The dogs were divided into five housing groups, and were kept in pens located on the fourth floor of the University of Oregon Medical School Building. Back pen

FOCAL INFECTION AND CARDIAG HYPERTROPHY

was provided with an ample outdoor runway and a steam
heated room of equal size which was maintained at
approximately 65° F. at all times. The ration provided
was a balanced commercial food product called Ribbled Cakes.



PLATE 2 Bleetric Trendmill

Hamburger was fed at frequent intervals. Water was constantly provided in the pens. Carbon Tetrachloride was used as indicated for tapeworm infestation on diagnosis. The dogs were washed at intervals of a fortnight. Every

FOGAL INFECTION AND CARDIAC HYPERTROPHY

effort was put forth to keep the dogs in the best possible physical condition during the entire course of the experiment. The animals were weighed before running, at intervals during the course of experiment and at death.

Roomigen photographs of the teeth of both the ineculated and control series of degs were made at intervals and informed us of the presence and progress of the dental infections.

Fost mortem examinations of the jaws for infected areas were made.

Animals dying during the course of experimentation were subjected to the same post mortem treatment as animals killed during asphyxia during deep ether anesthesia at the conclusion of the experimental period. An immediate necropsy of the theracic and abdominal viscera was made, noting the presence or absence of gress pathological changes. The upper and lower jaws of the animals were saved for dissection and further investigation. The heart was removed from the pericardial sac and prepared according to the method of Lewis¹¹. This method may be summarized as follows:

⁽¹⁾ Parietal perieardium removed. (2) Vessels cut short. (3) Cavities washed free of clots and drained. (4) Heart weighed. (5) Vessels ligated. (6) Cavities distended with 10% formalis injected through cardiac sail with hypodermic needle. (7) Heart immersed in 10% formalis for five to seven days, depending on size. (6) Grifices opened, heart drained and washed in running water for one to two days. (9) Heart placed in

¹¹ Lewis, Thomas., Observations upon Ventricular Hypertrophy with especial reference to Preponderance of One or Other Chamber, Heart, London, 1913-14; 5, 367.

NOCAL INFECTION AND CARDIAG HYPERTROPHY

70,5 alcohol until its weight reaches normal (Author's note: or until a maximum weight which is still less than hormal is reached.) (10) The epicardium subspicardial fat, coronary vessels, valves and chordae tendiness are removad. (11) Auricles and ventricles separated. (12) Cleaned ventricles separated into lett ventricular, right ventricular and septal portions by a series of cube parallel to and tengential to the septum. (13) Auricle cleaned. (14) Heart portions placed in water and drained. (15) Heart portions weighed individually.

We have investigated four commonly used methods of estimating cardiac hypertrophy in order to adjudge the relative cardiac effects of our experimental method upon both inoculated and non-inoculated dogs; (la) Fresh heart weight to body weight at death ratio; (1b) Fixed and prepared total ventricular weight to body weight at death ratio; (lc) Fixed and prepared left ventricular weight to body weight at death ratio; (ld) Fixed and prepared right ventricular weight to body weight at death ratio; (le) and Fixed and prepared septal weight to hody weight at death ratio; and (1f) Fresh surjoular weight to body weight at death ratio; (2) Fresh heart weight to body area at death ratio; (3) Fixed and prepared left ventricle to right ventricle weight ratio; (4a) Direct measurement of cardiac muscle fibre diameter, using a filar micrometer, from paraffin sections of the apex of the left ventricle; (4b) of the lower t of the interventricular coptumiand - (4e) from macerated teased specimens of the apex of the

FOCAL INPECTION AND CARDIAC HYPERTROPHY

of the left ventricle.

We have instituted the following statistical computations: (5a) Frequency polygons showing for both inoculated and control series the heart weight to body weight at death ratio; (5b) Fixed and prepared total ventricular weight to body weight at death ratio; (Sc) Fixed and prepared left ventricular weight to body weight at death ratio; (5d) Fixed and prepared right ventricular weight to body weight at death ratio: (De) Pixed and prepared septal weight to body weight at death ratio: Fresh auricular weight to body weight at death ratio (5f): (5g) Cardiac muscle fibre diameter from paraffin sections of apax of left ventricle: (5h) Cardiac muscle fibre diameter from paraffin sections of lower & of interventricular septum; (51) Cardiac muscle fibre diameter from macorated apecimens of apex of left ventricle; and (5j) Cardiac muscle fibre diameter from sum of all microscopic muscle fibre dismeter measurements; (6a) Scatter diagrams for both insculated and central series between the following variables; (6aA) Fresh heart weight to body weight at death ratio to Total exercise time in minutes; (6aB) Fresh heart weight to body surface area; (6aC) Body weight at death; (6aD) Fresh heart weight;

FOGAL INFECTION AND CARDIAC EXPERTROPHY

(6all) Average muscle fibre dismeter: (6b) Total exercise time to (6hA) Average muscle fibre diemeter: (6bil) Fresh heart weight to body surface area; (6c) Fresh heart weight to body surface area to (6cA) Fresh heart weight; (GoB) Body surface area; and (GoC) Average muscle fibre diameter: (7) Linear step-interval distribution between inoculated and control groups showing percentage deviation of (7a) Fresh heart weight to body weight at death to the 2/3 power times the constant 0,112, and (b) Fresh heart to body weight at death ratio, to mean values of the same units in the control series: (8a) Pearson product-moment coefficient of correlation between fixed and and prepared total ventricular weights and body weight at death; (8b) Fixed and prepared left ventricular weights and body weight at death; (Sc) Fixed and prepared left ventrioular weight to right ventrioular weight; and (8d) Parcentage body weight lost during experimental period and fresh heart to body weight at death ratio: (Oa) The reliability coefficients of our data were computed by the Mean, minus Mean method of Vsigma (Mean) plus Sigma (Mean) Sigma diff.

and interpreting the obtained results on a table given by H. E. Garrett¹² for the fresh heart weight to body weight at death ratio: (9b) Fixed and prepared total

¹² Garrett, H. E. Statistics in Psychology and Education. New York: Longmans, Green and Co., 1926.

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t to body weight at death ratio; prepared left ventricular weight to at death ratio; (9d) Fixed and prepared atricular weight to body weight at death ratio; (99) Fixed and prepared left ventricular to right entricular weights; (10) Fresh heart weight to body weight ratios for our seven normal dogs were calculated according to the previously described method.

RESULTS

The raw data for all experimental animals are represented in General Data Sheets 1: 2: 3 and 4. The column numbers represent the following values:

- Identification number of deg.
- (2) Cax of dog. Inoculated (I) or control (C) non-inoculated dog.
- 4) Date-Reginning of experimental period.
- (5) Body weight at beginning of experimental period.
- Total exercise time in treadmill in minutes. Running ability-Units of 1 (best) and 4 (poorest).
- (8) Death during course of (C) or end (E) of experimental period.
- Date-End of experimental period.
- 10) Langth of experimental period in days, 11) Dody weight at end of experimental period.
- (10) Percentage of original bodynweight lost during experimental period.
- (13) Cause of death.
- (14) Average muscle fibre diameter-Paraffin sections from apox of left ventricle, in micra.
- (15) Average muscle fibre diameter-Paraffin sections from lower ? interventricular septum, in micra.
- (16) Average muscle fibre dismeter-Tessed macerated stained fibres from apex of left ventricle. in miera.

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ERAL DATA SHRET 1

so deviation of heart weight to body ratio from control average. light (fresh) to body weight at beginning erimental period with own heart weight th taken as standard.

hight to body weight at peginning ratio

assumed normal (Herrmann) heart weight as standard.

POCAL INFECTION AND CARDIAC HYPERTROPHY

(24) Fixed and prepared left ventricular weight to right ventricular weight.

Fresh total heart weight at death. (25)

26]

Fixed and prepared total heart weight.
Fresh heart weight to body weight at death ratio.
Fixed and prepared total ventricular weight. 28)

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GENERAL DATA SHEET 2

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- (30) Fixed and prepared left ventricular weight.
- (31) Fixed and prepared left ventricular weight to body weight at death ratio.
- (32) Fixed and prepared right ventricular weight. (35) Fixed and prepared right ventricular weight to body weight at d eath ratio.

FOCAL IMPROTION AND CARDIAG HYPERTROPHY

(34) Fixed and prepared septal weight.
 (35) Fixed and prepared septal weight to body weight at death ratio.
 (36) Estimated fresh auricular weight.
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GENERAL DATE SHEET 3

(38) Body weight-Normal dog series.

39) Fresh heart weight-Normal dog series.

40) Fresh heart weight to body weight at death ratio-Normal dog series.

FOCAL INFECTION AND CARDIAC HYPERTROPHY

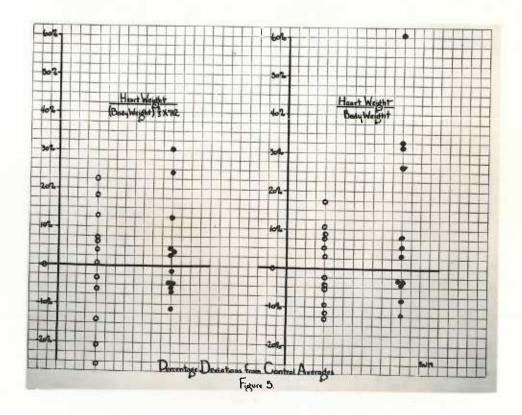
(la) The mean fresh heart weight to body weight at death ratio of our inoculated series is .00883 with a sigma of .000360; of our control series .00792 with a sigma of .000336; and of normal dogs as reported by Herrmann⁸ ..00798 with a sigma of .0001036. Since the

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| | 134 | 159 | 33 | 0.5 | 10 | 6.5 | 16/2 | 00 135 | | _ | 111 |
| - 1 | 12.4 | 12.4 | 134 | 130 | 1 | 101 | 0.00 | | - | + | ++ |
| | 124 | 129 | 30 | Pot | - c | 9.6 | 195 | 00840 | | - | Н |
| Aþical | 141 | (3.0 | 142 | 121 | - 1 | 1 | 11 | | | - | - |
| | 13.1 | 124 | iske | 24 | D | 1.5 | 585 | -00 TB0 | | - | |
| | 134 | 124 | 129 | 22 | 1. | | | 44 | | 11 | 1 |
| | 132 | 134 | 3.3 | 124 | E | - IOo | The | -so-13b | | | 1 |
| | 0.5 | 121 | 44 | | | 92 | 72.0 | 00781 | | | 1 |
| p. 0 - 1 | 133 | 0.5 | 142 | 12.6 | T. | 142 | lu-o | 100 100 | | | 1 |
| | 122 | 129 | Ha . | 1.5 | | Su | 44 | Softon. | | | |
| | 134 | 3.1 | 144 | 23 | G | | | | | | 4 |
| | 22 | (3.3 | 6.2 | (2.6 | Aus | 59 | · u | dffco. | | | ł |
| | 129 | (3.5 | 134 | 0.1 | 77 | | | 1 | | - | |
| | 122 | 13.5 | 0.1 | lo4 | | | | | | | |
| 1 | (5.4 | 842 | 155 | 2.4 | | | | | 1 | | ŀ |
| - 1 | 13.6 | 13.2 | 34 | 11.7 | | +++ | 1 | | 1 | | H |
| - 1 | 13.7 | P30 | 3.2 | aa | C | 13 | 1.19 | et No 4 | | | r |
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| - 4 | 6.58 | 660 | 406 | 600 | | N | Day Se | ers. | | | |
| - 7 | E0. | 62 | 10 | 59 | | | 6 | | | | L |
| - 1 | 58 | 63 | 38 | 59 58 | | | | | | | Ļ |
| 1 | LL | lolo | loa | 4.2 | | | | | | | ŀ |
| | 67 | 61 | 7. | 61 | | | | | | | ł |
| | 63 | li-o | 58 | 71 | | | 1 | | | | ł |
| rased | 61 | 56 | 73 | 61 | | + | 1 | | | | t |
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| | 62 | 62 | 59 | 60 | 1 | - | - | | | | Ì |
| | 1 | 75 | 65 63 | 63 | | 111 | | | | | T |
| | 14 | bb | | 162 | - | 1 | | | 11 | | |
| | 625 | 631 | 652 | 616 | - | | 17 | | | | L |

control dogs were subjected to the same severe and prolonged exercise as the inoculated group, and yet their ratios remained an average of but 0.9% below reported normal values,

NOCAL INFECTION AND CARDIAG HYPERTROPHY

We are forced to conclude that the observed difference is due to unaviodable experimental errors and that severe and prolonged exercise in the absence of toxic injury does not raise the heart weight to body weight ratio. The inoculated



group show a gain of 10.08%, which indicates a definitely demonstrable gross relative cardiac hypertrophy according to this method.

(lb, e, d, e, f) The increased heart weight to body weight

FOCAL INFECTION MED CARDIAG HYPERTROPHY

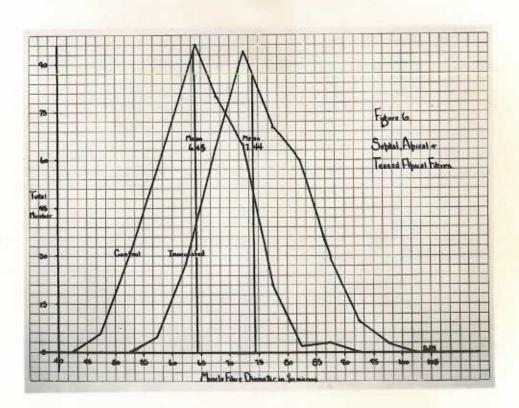
ratio is chiefly due to the increased size of the left ventricle, with the septum, right ventricle and auricle hypertrophied as shown in the following listing:

| F. & P. | TA/SM | I .00786 C .00674 N .00635 | signa | .00068 .00079 .00075 | 3 13 | 20 | N | 24.0% 6.0% |
|---------|-------|----------------------------------|--------|-------------------------------|------|----|-----|----------------|
| F. & P. | LV/BW | I .00394 C .00345 N .00300 | eigna | .000397 .00035 .00028 | 7h | of | *** | 31. % 15. % |
| F.& P. | s/sw | I .00171 C .00165 H .00116 | sigm | .000418 .000306 .000 | % | of | N | 48.5 42.5 |
| P. & P. | RV/BW | I .00235 C .00180 H .00212 | #2 gma | .000238 .000183 .000218 | | 02 | N | 11.5 -15.5 |
| Fresh | A/BW | I .00099 C .00087 N .00078 | elgma. | .000219 .000158 .000 | 1 m | 02 | N | 26.% |

The figures for fixed normal auricles are not given by Hermann⁸ but is estimated from reported figures for the purpose of this paper. From these figures it may be seen that the septum and the left ventricle are increased the most with an apparently smaller involvement of the right chambers of the heart. It is possible that the authors particular dissection of the right ventricular and septal portions might have included more heart in the septal portion at the expense of the right ventricular wieght, a condition which would explain the apparent

FOCAL INFACTION AND CARDIAG HYPERTROPHY

disproportion between these figures. The ratios quoted based upon fresh heart and fixed and prepared total ventricular and left ventricular weights are unaffected by this factor and suggest a moderate gross relative cardiac hypertrophy according to this method of expression.

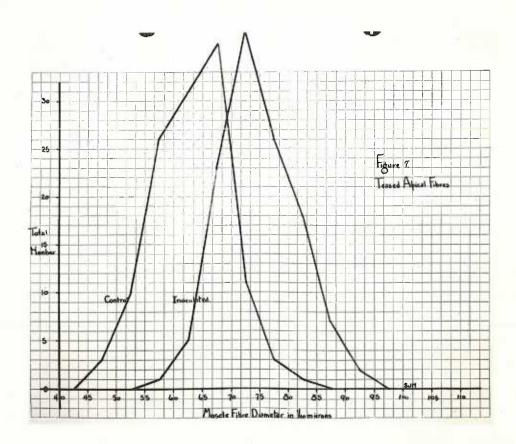


These figures, in the main, correborate the work of Stewart4.

(2) On account of the fact that absolute heart weights are useless for comparison bucause of the

FOCAL INFECTION AND CARDIAC HYPERTROPHY

variations in body size, we are forced to relate the heart weights to some measure of body size. There is ample evidence 13 that in general the heart weight as well as other organ weights of a group of animals in



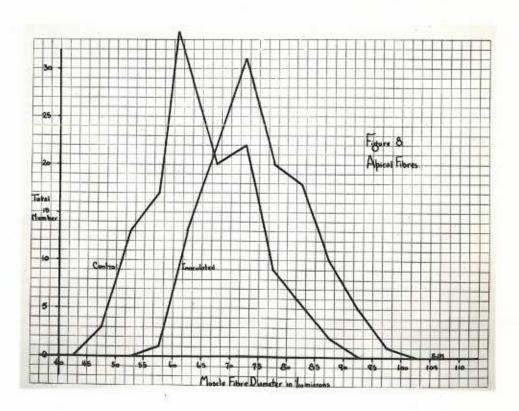
a similar state of nutrition but of varying size shows less variability when expressed as heart weight to body area than when expressed as heart weight to body weight.

¹³ MacKay, L. L., and MacKay, E. M. Factors which Determine Renal Weight. Amer. J. Physiol., 1927, 83, 179.

FOCAL INFECTION AND CARDIAG HYPERTROPHY

To investigate this matter we have calculated body area for each of the dogs according to the formula: 14

Body Area * (Body Weight)** x 0.113, and have calculated the corresponding heart weight to body area ratios.



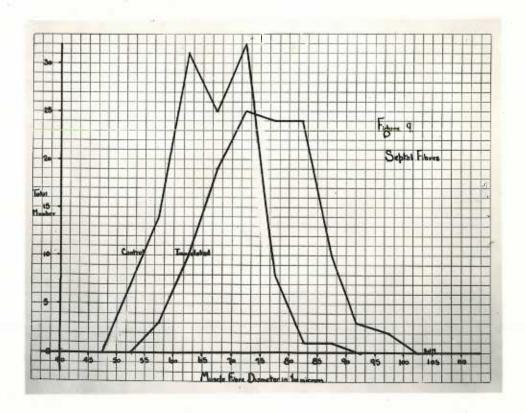
Body Area I 0.417 HW/BA I 149.3 % above C 4.% C 0.469 C 143.9

Percentage deviation of unit figures from control averages

14 Rogers, Charles, G., Textbook of Comparative Physiology., New York: McGraw-Hill Book Co., let Edition, 1927; 357.

POCAL INFECTION AND CARDIAG HYPERTROPHY

as suggested by Dr. Thomas Addis 15 and shown in Figure 5 demonstrates that our inoculated series is definitely less variable and the control series is more variable when expressed as heart weight to body area ratio than



when expressed as heart weight to body weight ratio.

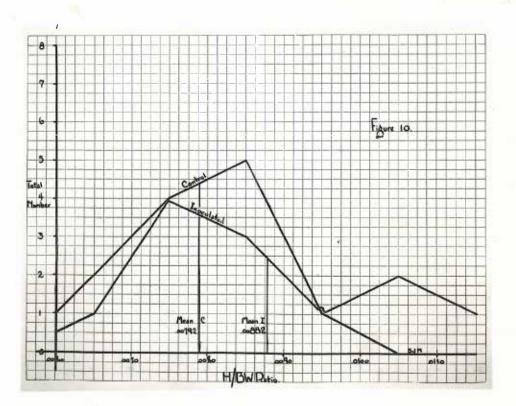
It would therefore appear that, in the absence of more accurate methods of determining body area than we have employed, the heart weight to body area ratio offers a

15 Stanford University.

POCAL INFECTION AND CARDIAC HYPERTROPHY

method no more reliable than the heart weight to body weight ratio.

(3) The fixed and prepared left ventricular to right ventricular weight ratios were found to be:

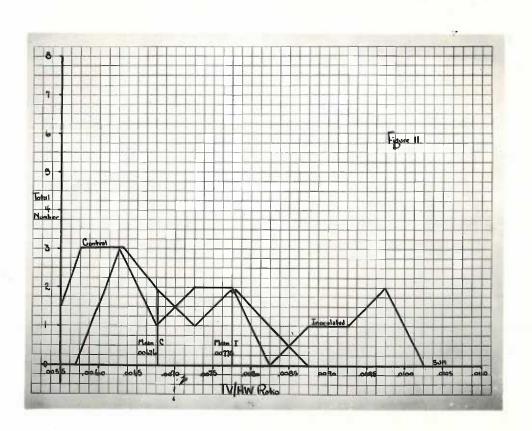


Since the sigma of the means of both the insculated and control groups are so large in comparison to the means of these values, relatively little credence can be placed

FOCAL INFECTION AND CARDIAC HYPERTROPHY

in the apparent increases over the normal values other than indicating a general tendency.

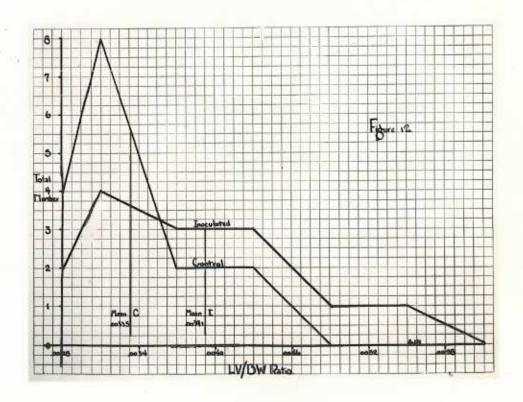
(4a, 45) Direct measurement of cardiac muscle fibre diameter, using a filar micrometer and oil immersion less



upon stained specimens, gives evidence of a microscopic cardiac hypertrophy. This material is shown in Coneral Date Shoots 3 and 4, and in Figures 6, 7, 8, and 9. These results may be summarised as follows:

FOCAL INFECTION AND CARDIAC HYPERTROPHY

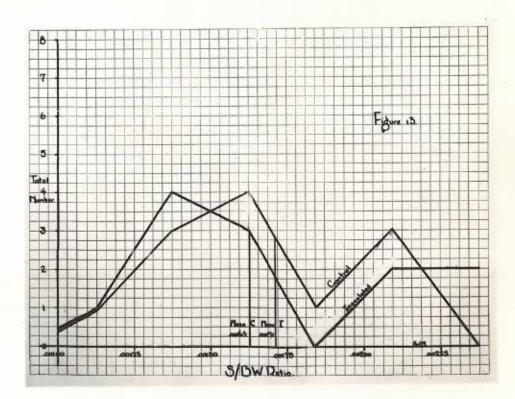
A perusal of the above mentioned figures will show the relatively small proportion of overlap between the frequency polygons for the inoculated and control series. It is this



factor which is responsible for the greatly increased accuracy of this method over the gross methods of expressing cardiac hypertrophy. The fibres from the septum were

FOGAL INFECTION AND CARDIAG HYPERTROPHY

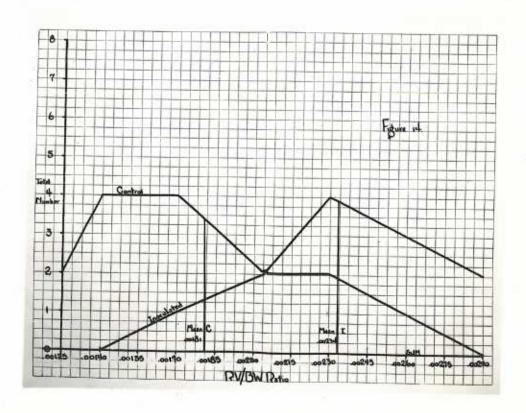
generally found to be slightly larger than the fibres from the apex; a fact which may perhaps find its explanation in the observation that a majority of the heart walls were definitely thinned to 2/3 or 1/2 of



the normal ventricular wall thickness at that particular apical point selected for specimens. The findings of Goldberger we find to be corroborated by this work with the exception of cell volume, which we are unable to

FOCAL INFECTION AND CARDIAG HYPERTROPHY

determine, due to the fact that the present thought upon cardiac muscle 16 considers it a syncytium, with the result that the cardiac muscle fibre length cannot be determined. The findings of Tangl 7 fail to find support



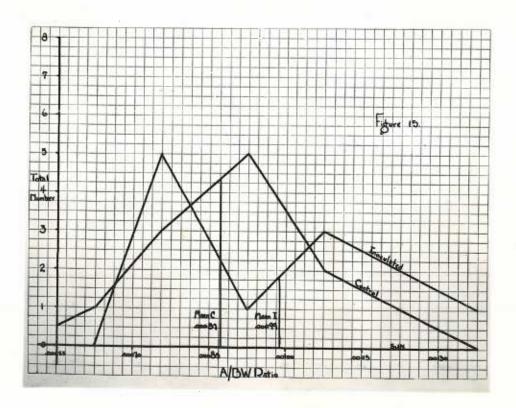
in our results.

(5a,b,c,d,e,f) It is found in an examination of Pigures 10, 11, 12, 13, 14, and 15 that the major difference

16 Strong, O. S., and Elwyn, A., Pailey's Textbook of Histology. New York: William Wood and Co., 7th edition. 1925, 188.

FOCAL INFACTION AND CARDIAG HYPERTROPHY

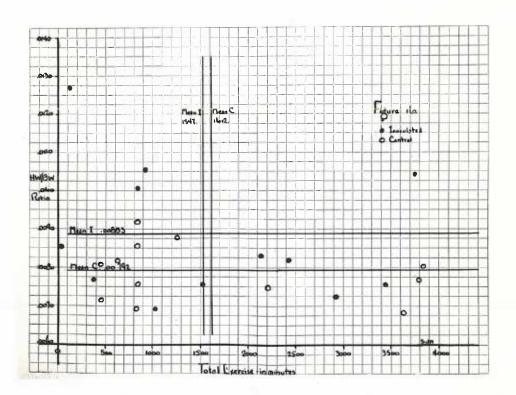
of a skewness of the inoculated curves to the higher ratio values, while the lower limits of the same curves are roughly the same as that shown in the control dogs.



This fact indicates that our cardiac hypertrophy ratios based upon body weight at death, and the body area values deriver therefrom, may perhaps be unduly influenced by the greater body weight loss of the inoculated group. This would make such ratios, under our conditions, fail

POCAL IMPECTION AND GARDIAG HYPERTROPHY

present. Data on the heart weight at the beginning of the experiment is anatomically impossible to obtain, and even telegonograms in dogs are inaccurate for the



above mentioned estimations, with the result that we cannot, mathematically or statistically, estimate the relative effect of the greater weight less upon the above ratios. This matter will be further discussed in (6aA).

FOCAL IMPROFICE AND CAMBIAC HYPERTROPHY

(55,h,i,j) The data relative to these headings has been previously discussed under (4a,b,c).

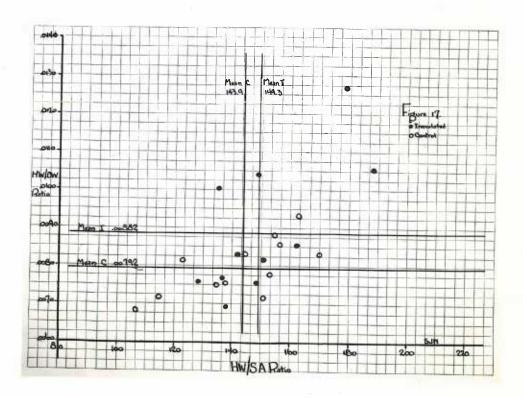
(6aA) Examination of Figure 16 shows an apparent moderate degree of negative relationship between fresh heart weight to body weight ratio and total exercise in minutes. This relationship is most marked in the insculated group. This observation probably finds its explanation in the finding that those dogs dying of an intense toxemia, and therefore not living for the entire experimental period, as a general rule showed the greatest heart weight to body weight ratio.

(6aB) The relationship of heart weight to body weight and heart weight to body surface area (Figure 17) shows a high degree of positive correlation, indicating that these ratios express very nearly the same common factors. This appears to be inevitable from the method used in this work to derive surface area estimations for the various dogs.

between heart weight to body weight ratio and body weight at death, while the inoculated series display a very marked negative correlation. (Figure 18) This fact suggests that the marked loss of body weight in the texemic inoculated dogs may have had an undue influence upon those dogs showing a remarkably high heart weight to body weight ration.

POCAL INFECTION AND CARDIAC HYPERTROPHY

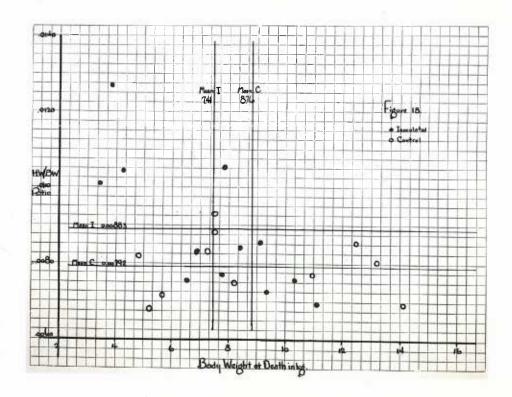
(6aD) A very slight positive relationship is noted in Figure 19 between the factors of heart weight to body weight ratio and gross fresh heart weight in grams.



(Sail) Average muscle fibre diameter, inasmuch as it is a single, definitely delimited measurement, is far less subject to error than a ratio, in which a variation in eigher of its component factors will affect the consequent ratio. It is on this account that the

POGAL INFROTION AND CARDIAG HYPHRYROPHY

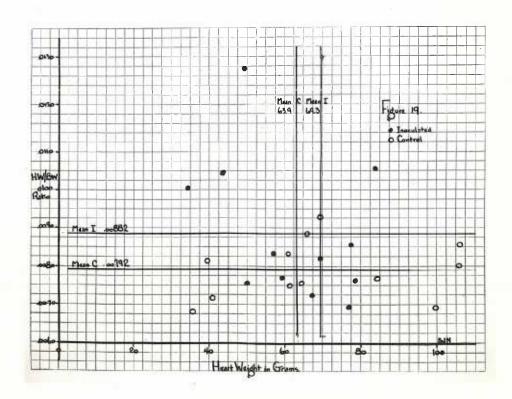
Fact that heart weight to body weight ratio shows only a very slight negative relationship to average muscle fibre diameter (Figure 20) that we conclude that, at least under our particular experimental



conditions, the heart weight to body weight ratio is a less desirable method of expressing cardiac hypertrophy than the microscopic evidences afforded in increased muscle fibre disseter.

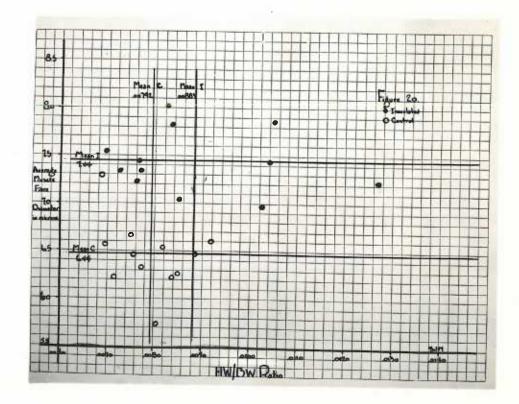
POGAL INFECTION AND CARDIAG HYPERROPHY

(6bA) In contrast to the picture presented by Figure 16, we see in Figure 21 that there is apparently no effect of prolonged exercise upon the central dogs, with the result that their average muscle fibre diameters



remain at practically the same general level regardless of running time. A very definitely moderate degree of positive relationship is noted between length of exercise time and average muscle fibre diameter in the inoculated

series. This shows that those dogs which survived the intense initial toxenia and continued exercise under the effects of a prolonged constant toxenia, responded with a greater increase in average nucle

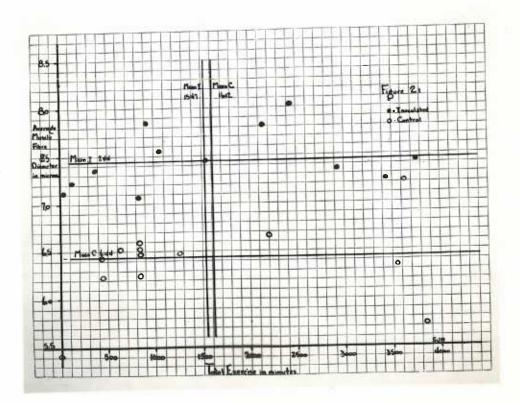


fibre diameter than those dying earlier in the experimental series.

(6bb) Heart weight to body area ratio, when plotted against total exercise time in minutes, as shown in Figure

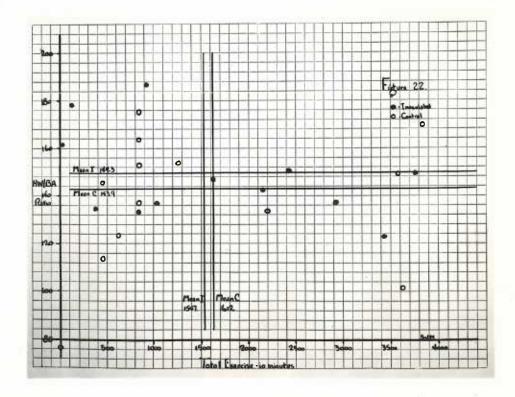
22, shows a scatter so great as to indicate practically no relationship.

(6cA, 6cB) A high degree of positive relationship is noted in Figures 23 and 24, between heart weight to body area ratio and its component factors in the control



series. The inoculated group show the same positive interrelationship to heart weight, but variable when examined in connection with comparison to body surface area in square meters.

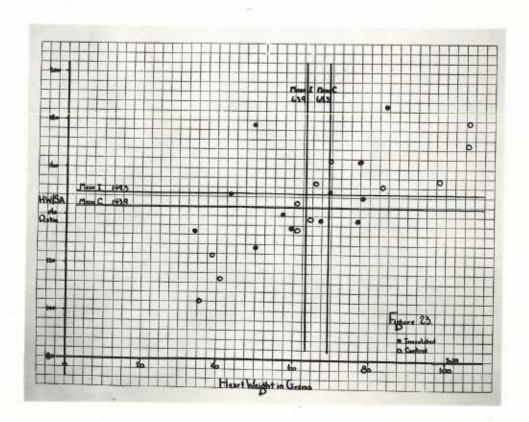
(6eC) When the heart weight to surface area ratio is considered in its relationship to the average muche fibre diameter of the cardiac much calls of that particular animal (Figure 25) we find that the ineculated



Series shows a slight degree of positive relationship.

This indicates that there is a smaller degree of common factors between heart weight to body area ratio and avorage muscle fibre diameter than that shown between heart weight to body weight rationand muscle fibre diameter.

The control series displays a much more marked negative relationship. Under these circumstances the slight positive relation shown by the ineculated group is probably a result of the chance combination of experimental

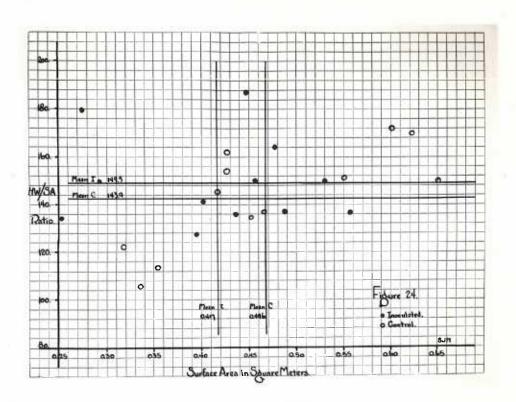


Variables, and therefore unreliable to use as a basis for conclusions.

(?) The data relative to Figure 5 has been previously discussed under (2).

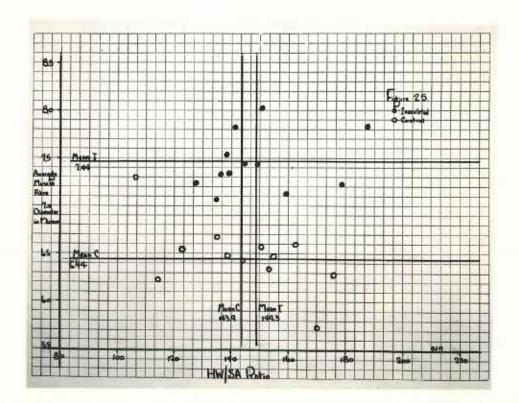
POCAL IMPROTION RED CARDIAC HYPERTROPHY

(8a,b) The Pearson product-moment coefficient of correlation between the fixed and prepared total ventricular weight and body weight at death we find to be .76 £ .2 for ineculated and .90 £ .2 for control dogs. The same coefficients for fixed and prepared left



ventricular weight to body weight are .81 £ .2 for inoculated, .93 £ .2 for control and .91 £ .02 for normal dogs. Since in all cases the value (r) is

practically 4 (PR_T) it can be concluded that a very definite positive relationship exhibts between these factors. The common factors in these measurements we find to be 65 to 87% of the possible total, and such percentages indicate a relatively high degree of elimination of avoidable



experimental error in the entire series.

(So) Fixed and prepared left ventricular to Sight

ventricular weight ratios have an interrelationship represented by a (r) of .66 £ .2 for inoculated, .82 £ .2 for control, and .95 £ .2 for normal dogs. Those figures show a definitely positive relationship, but of less degree than shown by the ratios based upon body weight figures. The common factors are estimated at a minimum of 49%.

(8d) Heart weight to body weight ratio and percentage of original body weight lost during the experimental series have been made the variable factors in a Pearson productmoment coeffécient of correlation in order to determine whether the greater weight less in body weight in inoculated dogs is responsible for the resultant heart weight to body weight ratios. The following coefficients of correlation express the findings:

> I (r) .50 1.15 25% common factors (r) .31 £ .18

15% common factors

An interpretation of these figures indicates that there is a slight positive correlation between heart weight to body weight ratio and percentage body weight loss, greater in the insculated than in the control series. The uncommon factors are markedly predominant in these variables, and are in such excess that the common values

bear little significant relationship to each other.

Further calculations by both the author and Dr. P. E.

Griffin 17 have proved that the increase in heart weight to body weight ratio can be more than accounted for by the greater percentage body weight less in the incculated dogs. These calculations may be summarised as follows:

| The same at the same | .06086 .16602 .00639 .04006 .02500 .35369 .00071 .63683 .64850 .03593 .26774 | tv thet | Combined probability for all Inoculated dogs that Heart Weight Increased Decreased 1.274 × 10 ⁻¹⁴ 1.524 × 10 ⁻² Ratio of likelihood in favor of decrease for all as against increase for all as against increase for all |
|----------------------|--|---------|---|
|----------------------|--|---------|---|

| Increased .16354 .34458 | Weight Decreased .83646 .65542 | CONTROL BOGS Combined probability for all Control Bogs that Heart Weight Increased Becreased |
|--|--|---|
| .64803 .70884 .77637 | .35197 .29116 .22363 | 8.560 x 10 ⁻⁸ 1.191 x 10 ⁻³ |
| .53586 .00734 .10749 .59095 .07214 .15150 | .46414 .99266 .89251 .40905 .92786 .84850 | Ratio of likelihood in favor of decrease for all as against increase for all 1.190 x 10-3 = 763,000 |

¹⁷ Professor of Mathematics, Reed College.

FOCAL INVECTION AND CAPDIAC HYPTETROPHY

We are forced to conclude, as a result of these figures. that the greater heart weight to body weight ratio of the inoculated dogs was either due to an actual decrease in the cardiac musculature during the experimental period or to the preponderant weight less during the same time. The former is at variance with clinical findings, and therefore we assume that the greater percentage body weight loss of the inoculated dogs affects the heart weight body weight ratio in such a manner as to render it relatively unreliable as a criterion of cardiac hypertrophy under our particular experimental conditions. The same conclusion may be applied to heart weight to surface area ratios, inasmuch as they are directly derived from body weight at death values. The above conclusions do not deny that the ratios have no value as estimates of cardiac hypertrophy, but to us seem less reliable than other investigated methods.

shown in Figure 26 are self-explanatory, but are subject to the same criticism as discussed in (8d).

These figures illustrate the fallacy of depending upon rough statistical data without careful analysis as to their exact meaning. The reliability coefficients indicate a great deal of confidence may be placed in the heart weight to bedy weight ratio and other similar ratios. This

conclusion is at variance with the previously given evidence. In view of this fact it appears that if the ratios based upon body weight at death were not unduly influenced by the variable percentage body weight

| | HWIDWRH | TVIEW Rose | LVIBWRSHIS | RVIDW Ratio | LIR Ratio |
|-------------------------------|------------|------------|-----------------|---------------|---------------|
| M. | 0.00883 | 0.00784 | 000394 | 000235 | |
| ec. | Q000360 | 0000 68 | 0000391 | 0000236 | 1765 |
| Me | 0.00792 | 0.00674 | 900345 | 0.001801 | inid |
| 4 | 000036 | 0.000 79 | cmo 35e | 0000185 | ING. |
| Mn | 0.00198 | Q colles | 000300 | 0.002/2 | |
| CH. | 0 000103/6 | 0.00075 | 0.00078 | 0000216 | 937 |
| n _e n _e | 0.000011 | 0.90039 | 0,000045 | 0.000032 | 9503 |
| -COm | 0.000354 | 0.000 344 | 0.000 446 | 0.000285 | 2.02 |
| Disco | 0.515 | 143 | 1.005 | LUD | |
| Chances | 62/100 | 81/100 | 841100 | Ölelloo | 0.25 ke/ke |
| Ma-M. | 0.000058 | 0.00061 | 0.000044 | 9,000025 | 0.504 |
| oC Dan | 0.000335 | 0.000 32 | 0.000486 | 0.000 321 | L82 |
| Dan | 1.95 | 4.73 | 1.93 | 91 | QIT I |
| Chences | 935/100 | 99/100 | 97/100 | 16/100 | 57 /100 |
| m.n. | P-J00000 | 0.00112 | 0.000044 | 0.00055 | |
| dD. | 0.000492 | 0.00033 | 0.000520 | 0.900 30 | 268 |
| Doct | 1.44 | 3.4 | 0.945 | 1.83 | 044 |
| James | 92/100 | 99.9/100 | 83/190 | 99/100 | 65/pp sun |
| H | | Relia | only Coefficien | As . | |
| | | | Figure 26. | + + - - | |
| | | | 0 | | |
| - | | | | | |
| 1 | | | | | |
| | | | | | |
| | | | | | |

less, the resulting ratios would be highly significant. Under our particular experimental conditions these same ratios cannot be accepted as indicating nearly as great a degree of chance that difference is greater than zero

pointed out, a slight positive relationship is present.

Left ventricular to right ventricular weight ratio is

uninfluenced by the above factors, and represents a more

nearly true value of the amount of relationship actually

present. The chance figures are all beard upon chance

selection resulting in a 50/100 selection.

(10) Table 4 shows the results of our nermal series of dogs. A comparison of these figures follows:

Our Normals .00776 sigma .000276 Herrmann's Normals .00796 sigma .0001036

These figures for a gr oup of but seven dogs, in comparison to the larger series of two hundred dogs, show that we have approximated the reported series with a considerable degree of accuracy. On the basis of this check we have concluded that the normal values quoted by Herrmann⁸ are a satisfactory series, and have therefore discontinued our series. Normal values quoted are from Herrmann unless specifically mentioned.

(11) Column 7 in Figure 1 gives an estimation of a four-unit graded system of estimating general running ability. This was done in order that we might know whether the amount of exercise represented by the total exercise time figures in the two groups were approximately equivalent. Using 1 as the unit for best running ability and 4 as

the poorest, we find:

I 2.54

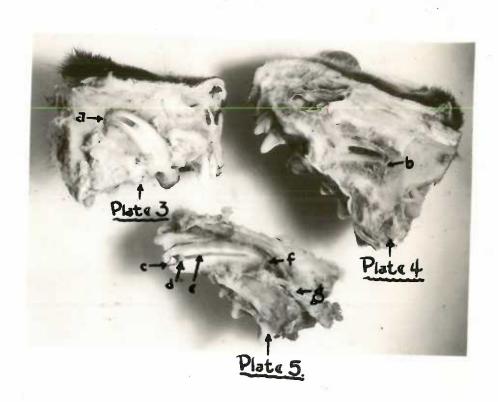
Those average values indicate the groups are largely equivalent to each other in running ability, with a majority of the dogs running satisfactorily. The poorer inoculated series running ability, while relatively slight, has its most logical explanation in the toxicity of this group with the consequent cardiac embarraement during life.

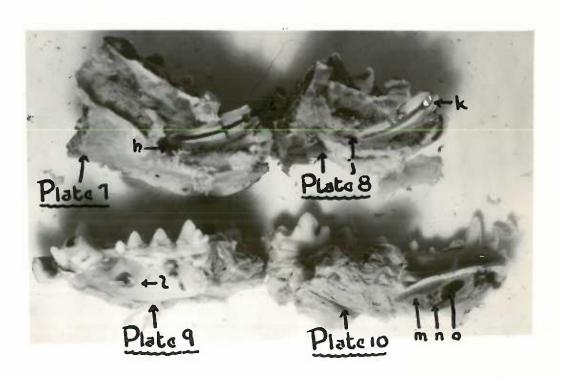
- respresent an unsuccessful attempt to estimate the heart weight to body weight ratio at the beginning of the experimental period by using (a) The animals own fresh heart weight at death as a normal, on the assumption that of any single value this represented the best obtainable estimate of cardiac weight at the beginning of the period, and (b) an average normal heart weight as reported by Herrmann⁶. Inasmuch as he conclusions can be drawn from the resultant figures, we will discontinue the consideration of these ratios.
- (13) The inoculated dogs were more or less toxic, showing more fatigue during the periods of exercise.

 Artificial respiration was necessarily resorted to on

inequiated dogs at eight separate times, and in no instance was this necessary with a control dog. This finding is further strongthened by the fact that only 25% of the ineculated dogs lived through the course of the experimental time, in comparison to 65.6% of the control series.

- (14) The average duration of life in the inoculated group of dogs was 179 days in comparison to 202 days for the control group. This six months period represents roughly one-twentieth of the average life of a dog; a period corresponding to about three years of a human life. Our apparent producation of an average increase of 15% in the heart, without gross insufficiency, indicates that this pathological process proceeded comparably to those cases seen in the cardiologic clinic.
- (15) Cardiac deaths from agute cardiac dilatation were actually known to have occurred in 25% of the inoculated series, while in no case did this happen to a control dog.
- (16) The average weight loss in the control series was 5.9% in comparison to 19.9% among the inoculated dogs.
- (17) Demonstrable apical abscesses at the apex of the ineculated canine teeth were demonstrated with the reentgen plate and by dissection of the jaws after death





Key to Gress Dog Jaw Dissection Plates

PLATE 3

Inoculated Series. Dog # 24. Upper Jaw. (a) Apical Dental Abscess.

PIATE 4

Inoculated Series. Dog # 2. Upper Jaw. (b) Apical Dental Abscess.

PLATE 5

Inoquiated Series. Dog # 18. Lower Jaw.

(c) Silver Amalgam Filling.

(d) Cotton Packing and Rost Point. (e) Root Canal. (f) Apical Dontal Abscess.

(g) Inferior Alveolar Branch of Trigominal Merve.

PLATE 7

Inequiated Series. Deg # 1. Lever Jaw.

(h) Apical Dental Abscess. (i) Filling Recess.

PLATE 8

Inoculated Series, Dog # 16. Lower Jaw.

(j) Apical Dental Abscess. (k) Silver Amalgam Filling.

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Inoculated Series. Dog # 9. Lower Jaw. (1) Apical Dental Abscess eroding outer table of jaw.

PLATE 10

Inoquiated Series. Dog # 17. Lower Jaw.

(m) Apical Dental Abscess.

(n) Mecrotic Peridental Membrane.



PLATE 12

Dog 11. Control Series. January 20, 1928.



FLATE 13

Dog 5. Inoculated Series. February 3, 1928.



PLATE 14

Deg 2. Inoculated Series. April 19, 1928.

(18) The autopsy findings are as follows:

HOGHAND CHARS

(1) Small dental abscess; Very small vegetative mitral endocarditic lesion; No further pathology.

(2) Moderate dental abscess; Small vegetative mitral and aertic endocarditic lesions; No further pathology.

(3) Small dental abscess; Moderate vegetative mitral and aertic endocarditic lesions; No further pathology.

(5) Large dental abscess; Moderate mitral and sertic verrusose endocarditic lesions; Bilateral hilar



PLATE 15

Dog 5.

tuberculosis; Terminal bronchopneumonia; Acute Cardiac Dilatation.

(7) Small dental abscess: Moderate mitral and acrtic vegetative and verrusose endocarditic legions; Tapeworm; No further pathology.

(10) Moderate dental abscess: Very small mitral endocarditic

(16) Moderate dental abscess; Moderate mitral and sortic verruouse endocarditic lesions; Vicerative colitis; Acute cardiac dilatation.

(22) Small dental abscess: Moderate sortic verrusose

endocarditic lesion; Mange; Tapeworm.

(24) Small dental abscess; Moderate verruces and vegetative mitral and aertic endocarditic lesions; Multiple abscesses in Pectoralis Majoris and Minoris, and Rectus Abdominis.

(8) Small dental abscess; Small mitral endocaratic lesion;

Tapoworm.

(9) Moderate dental abscess; Small mitral and aortic vegetative endocarditic lesion; No further pathology.

(17) Moderate dental abscess; Small mitral endocarditic lesion; Terminal bronchopneumonia; Acute cardiac dilatation.

CONTROL SHRIES

(6) Bascistion.

20) No gross pathology. 25) Terminal bronchopneumonia. 26

Mange: Tapeworm. Death by fighting: Eviscerated: Tapeworm.

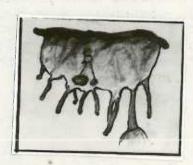


PLATE 16 Dog 24

11) Moderately thin.

14) No gross pathology.

28) No gross pathology. 29) No gross pathology.

30) No gross pathology. (31) No gress pathology.

ENDOGARDITIS CONTROL

(12) No dental abscess: Moderate vegetative mortic and mitral endocarditic lesions; Ulcerative colitis; No demonstrable primary focus of infection noted.

The deg No. 12 was carried in the controllseries until autopay was performed. No dental abscesses were seen, and no primary focus of infection could be identified by a careful necropsy. The causative organism is unknown. This dog showed signs of toxicity during his life. The heart weight to body weight ratio shows an apparent cardiac hypertrophy with a ratio of .00965. The apical cardiac

muscle fibre diameter of this dog is 7.31 microns. This particular dog was not included in either of our series on account of the unknown nature of the



PLATE 17

Dog 5. Inoculated Series.

causative organism,

(19) Three attempts were made to obtain bleed cultures from the hearts bleed of degs belonging to

of the inoculated series. No organisms were isolated in any of the attempts.

(20) The histopathological examination of

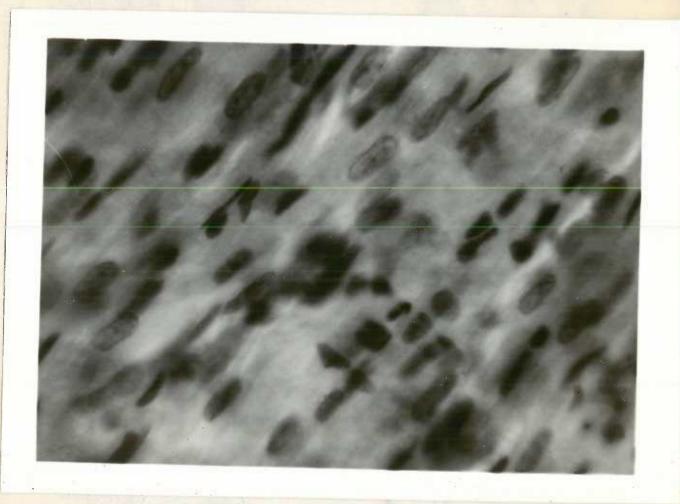


PLATE 18

Dog 17 Inoculated Series.

microscopic sections from inoculated degs generally showed a mild to mederate degree of patchy parenchymatous

degeneration of the individual fibres, which were observably hypertrophied. Individual cell nuclei were found which showed irregularity, pyknosis, a



FLATE 19

Dog 3 Inoculated Series.

deeper concentration of the chromatic material, and in some cases a partial or complete doubling of the nuclei.

A slight diffuse wandering cell of the lymphocyte type was infiltrated in a majority of the specimens, being located particularily in a perivascular manner.



MATH 20

Deg 6 Centrol Series.

Plasma cells were occasionally noted. A slight degree of fatty change, most marked subendocardially, was noted in

- Dog 17. Multiple small focal hasmorrhappe in the myocardium of Dog 3 were noted. There were no abnormal pathological changes noted in any of the myocardial histological examinations of sections from normal or control dogs. The heart muscle of dog 12 was not examined.
- limited to 12 dogs in each series in order that the experimental method not be too cumbersome and unwieldly, the results we have received therefrom appear to be relatively reliable.

 Our experimental error is estimated to be not over 1.5% on an average. Our methods have apparently measured from 49 to 87% of the possible factors concerned in this problem, as noted under the heading (Sa,b). Thus our results can be considered to indicate that we have avoided unnecessary experimental errors and have reduced the unavoidable to a minimum. It appears, therefore, that our twentyfour available animals comprised a population sufficiently large for the purposes of this investigation.
- in the hope that these experimental results will shed some light in the complex field of cardiology. This study, we feel, should be especially important to those cardiologists considering the significance of feeal infection, (especially of the dental variety) in relation to the possible etiology of organic heart disease in humans.

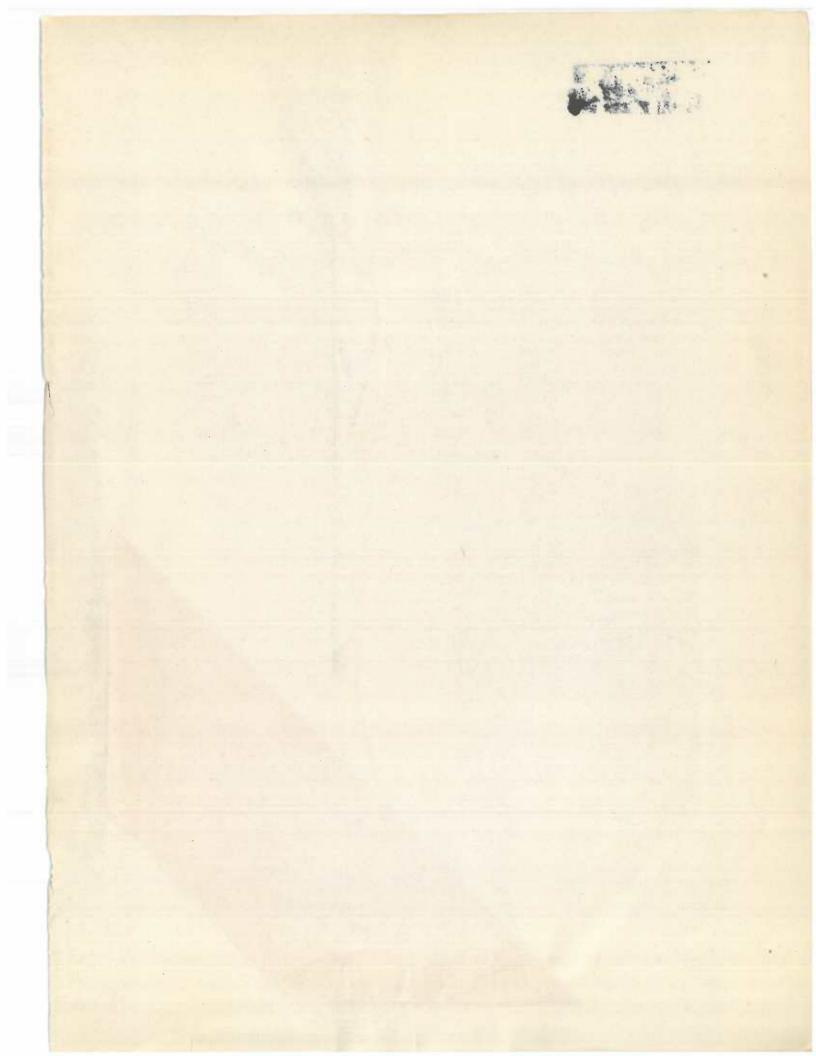
SULLY T

We have found with our experimental method (1) a significantly positive relationship between experimentally produced focal (dental) infection and cardiac hypertrophy as measured by muscle coll dismeters; (2) Stress and strain, in the absence of fogal infection, is without apparent effect in altering the gress or microscopic duracteristics of the heart; (3) Direct measurement of cardiac muscle fibre diameter, under our experimental conditions, is a more reliable criterion of cardiac hypertrophy than any ratio based on heart weight to body weight or heart weight to body area. The ratio of left ventricular weight to right ventricular weight is apparently of the least positive value of the investigated methods; (4) The cardiac changes in the ineculated degs constantly showed vegetative or verrupose mitral and (or) sortic endocarditic lesions, patchy parenchymatous degeneration, nuclear changes, increase in the muscle cell diameter, and a slight round cell infiltration. Dental abscesses were demonstrated in all insculated dogs. There were no other constant cardise or extracardise pathological findings.

University of Oregon Medical School, Portland, Oregon,

The author has pleasure in acknowledging the valuable supervisory assistance given him by Dr. Noble Wiley Jones, Clinical Professor of Medicine, as co-author in carrying out this research. Dr. Clof Lawell, Professor of Anatomy, aided in the management of the problem. Mr. R. Walter Johnson, Photographer and K-Day technician prepared the photographs, microphotographs and roentgen plates.

DUI



FOCAL INVENTITION AND CARDIAC HYPERTROPHY

ventricular waich to body weight at death ratio: (9c) Fixed and Prepared left ventricular weight to body weight at death ratio; (9d) Fixed and prepared right ve atricular weight to body weight at death ratio; and (100) Fixed and prepared left ventricular to right we intricular weights; (10) Fresh heart weight to body weight ratios for our seven normal dogs were calculated according to the previously described method.

RESULTS

The raw data for all experimental animals are represented in General Data Sheets 1, 2, 3 and 4. The column numbers represent the following values:

Identification number of deg.

Cax of dog. Inoculated (I) or control (C) non-inoculated dog.

Date-Beginning of experimental period. Body weight at beginning of experimental period.

Total exercise time in treadmill in minutes. Running ability-Units of 1 (best) and 4 (peorest). (7)

(B) Death during course of (C) or end (E) of experimental period.

(9) Date-End of experimental period.

(10) Length of experimental period in days.

(11) Body weight at end of experimental period. (12) Percentage of original bodynweight lost during

experimental period. (13) Cause of death.

(14) Average muscle fibre diameter-Paraffin sections from apax of left ventricle, in micra.

(15) Average muscle fibre diameter-Paraffin sections from lower t interventricular septum, in micra,

(16) Average muscle fibre diameter-Teased macerated stained fibres from apex of left ventricle. in miera.

(17) Estimated surface area of dog in square meters (18) Fresh heart weight at death to estimated body

(19) Percentage deviation of heart weight to surface area ratio from control average.

(20) Fresh heart weight at death to body weight at

| | 126 | ÷ | - | | wa bu | F.L. | ò | | 4 | 10 | Mus | Jy. | 1 | | (Oil | d | MFO | MEC | MFO | Side | ulma | i. | 14/64 | Zh. | 0.4. | Qui. | R |
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GENERAL DATA SHEET 1

(21) Percentage deviation of heart weight to body weight ratio from control average.

(22) Heart weight (fresh) to body weight at beginning of experimental period with own heart weight

(23) Heart weight to body weight at beginning ratio with assumed normal (Herrmann) heart weight taken as standard.

(24) Fixed and prepared left ventricular weight to right ventricular weight.

(25)Fresh total heart weight at death.

26)

Fixed and prepared total heart weight.
Fresh heart weight to body weight at death ratio.
Fixed and prepared total ventricular weight. 27) (28)

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GENERAL DATA SHIDT 2

| (89) | Fixed and | prepared | total | ventricular | weight |
|------|-----------|-----------|-------|-------------|--------|
| | to body | weight at | deati | a ratio. | 1 N 18 |

Fixed and prepared left ventricular weight. (30)

(31)Fixed and prepared left ventricular weight to body weight at death ratio.

(32) Fixed and prepared right ventricular weight. Fixed and prepared right ventricular weight (33) to body weight at death ratio.