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The Shape of Medicine

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ABSTRACT: Biochemical phenomena are usually reported as abnormally high, with some exceptions such as the white blood cell count. In most instances, little consideration is given to the value being reported as too low. For example, a high blood uric acid is associated with gout, but nobody has any information as to the significance of it being found below the normal range. Evidence is presented here to show that all physiologic and biochemical measurements are governed by a curvilinear or parabolic distribution. The extremes of the curve are abnormally high and abnormally low, each being a variation away from the norm which is represented at the apex of the curve.

Introduction

In an orthodox medical viewpoint, an increased serum cholesterol is considered to be physiologically bad. If it is in the moderate range, that is regarded as an improvement. It is thus implied that a linear relationship exists from low, which is good, to high which is bad. Many people are left with the impression that their blood cholesterol should therefore be as low as possible (1). This is hardly common sense when other measurements of body function are compared. For example, nobody would argue with the fact that it is just as disadvantageous to be too tall as it is to be too short, or too fat versus being too thin. Other extremes are being too hot or too cold, excessive anger and euphoria, each of which exacts its pathologic price. Hard data exist in the medical literature that emphasize the need for avoidance of extremes, including biochemical factors like blood glucose and uric acid. We examined the phenomenon and reported on it as long as 25 years ago (2). Common sense would suggest that low blood cholesterol must be just as clinically significant as when it is too high.

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The Cholesterol Curve

For a long time now it has been fashionable to associate lipid metabolism, expressed in several different ways, with a variety of cardiovascular problems. A prime example is that of the National Cooperative Pooling Project Study (3), in which risk factor data were collected at initial examination and again at a ten-year follow-up, with regard to disease incidence and mortality. The data from 5 studies are reproduced in Figure 1 and included 7594 white males aged 30-59 years who were ostensibly free of signs of definite coronary heart disease (CHD) at entry. It is abundantly clear that the incidence of cardiac events increases in proportion to the increase in serum cholesterol. From these apparently linear data, the general concensus was formed that it is desirable to maintain serum cholesterol concentrations as low as possible to prevent CHD.

On the other hand, is well known that although mortality rates for CHD and total serum cholesterol levels are lower in Japanese than in people in Western countries, the mortality rate for cerebro vascular

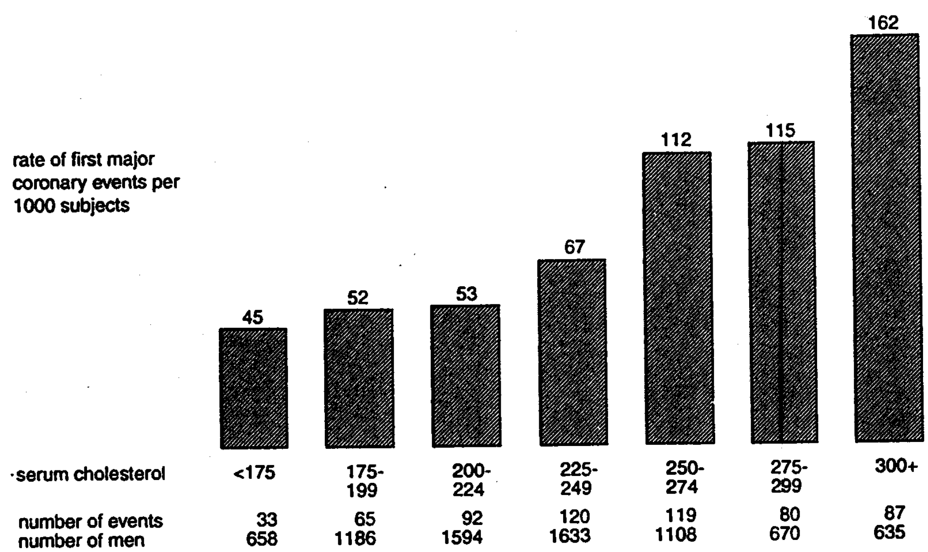

FIGURE 1

National cooperative pooling project with serum cholesterol level at entry and ten-year age-adjusted rate per 1000 men for any major coronary event. (Stamler, J. and Epstein, F. H. *Coronary heart disease: risk factors as guides to preventive action.* Prevent. Med. 1: #1-2, 27-48, March 1972.)

accident (CVA) is higher. Ueshima and associates (4) performed a ten year study based on several epidemiologic surveys of cerebrovascular and cardiovascular disease in various populations of 6500 men with different lifestyles. One group, mainly farmers betweeen the ages of 40 and 59 years, had the highest incidence of strokes and the lowest mean levels of serum cholesterol (155 md/dL).

Both groups of industrial manual workers and clerks showed the lowest incidence of strokes and their average serum cholesterol levels were between 180 and 200 mg. A group of executives with the highest total mean serum cholesterol concentration (200 mg/dL) had the highest incidence of CHD among all the study subjects. Figure 2, repro-

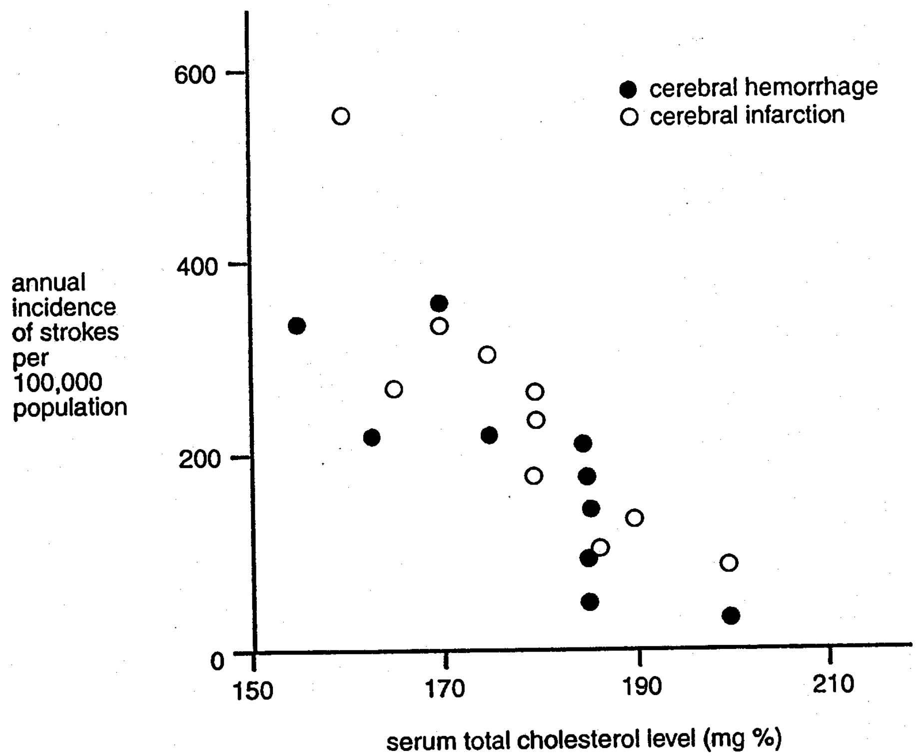

FIGURE 2

Annual incidence of cerebral strokes plotted against serum total cholesterol levels in 40-69 year old males. (Ueshima, H., Lida, M., Komachi, Y. *Is it desirable to reduce total serum cholesterol level as low as possible?* Prevent. Med. 8: #1, 104-105, Jan. 1979.)

duced from this study, shows the inverse relation of serum cholesterol to the incidence of CVA. These investigators concluded that a desirable serum cholesterol should be somewhere between 180 and 200 mg/dL.

One thousand two hundred and eighty one doctors and their spouses were evaluated in terms of their nonfasting serum cholesterol (5). Clinical state was graded by the Cornell Medical Index Health Questionnaire (CMI), a self-administered test consisting of 195 questions. Each item is answered by circling the word "yes" or "no." Questions are phrased so that affirmative answers referring to clinical symptoms and sign, indicate pathologic findings. Thus, the higher the score, the more abnormal is the clinical status.

Table 1, taken from this study, clearly demonstrates that higher CMI scores are associated with a wider range of serum cholesterol from high to low extremes. The lowest CMI scores were seen in those subjects with the narrowest range and a mean in the moderate or intermediate concentration of serum cholesterol.

The evidence suggests that the ideal concentration is approximately 200 mg/dL, a conclusion which is consistent with the earlier

TABLE 1

Relationship of Nonfasting Serum Cholesterol and Clinical Findings in a Presumably Healthy Male and Female Sample

Line	Group	Sample Size	Clinical Findings (Affirmative CMI* Responses) Range	Mean	Nonfasting Serum Cholesterol Level (mg/dl) Range	Mean ± S.D.
1	entire group	1281	0-125	16	110-520	224 ± 4
2	CMI<20	930	0-19	10	110-520	223 ± 4
3	CMI<10	474	0-9	6	122-520	221 ± 5
4	CMI<5	157	0-4	3	122-456	216 ± 4
5	CMI<4	100	0-3	2	122-456	213 ± 4
6	CMI<3	66	0-2	2	158-456	211 ± 4
7	CMI<2	23	0-1	1	166-290	214 ± 4
8	CMI 0	7	0	0	176-239	207 ± 3

***Cornell Medical Index Health Questionnaire**
(McDonagh et. al. Medical Hypotheses 1981; 7: 685-694.)

Japanese finding. Blood cholesterol appears to be a marker of wellness representing an intermediate balance between extremes.

Much the same phenomenon was seen in our studies that we reported in dental patients in 1960 (6). Xerostomia, stomatopyrosis and gingival tenderness, symptoms that are less well known in diabetic subjects, were found to be least in evidence when the fasting blood sugar was in the 70-79 mg/dL range. These symptoms were in greater evidence with lower as well as higher fasting blood sugar concentrations. Figure 3, reproduced from this study, demonstrates what

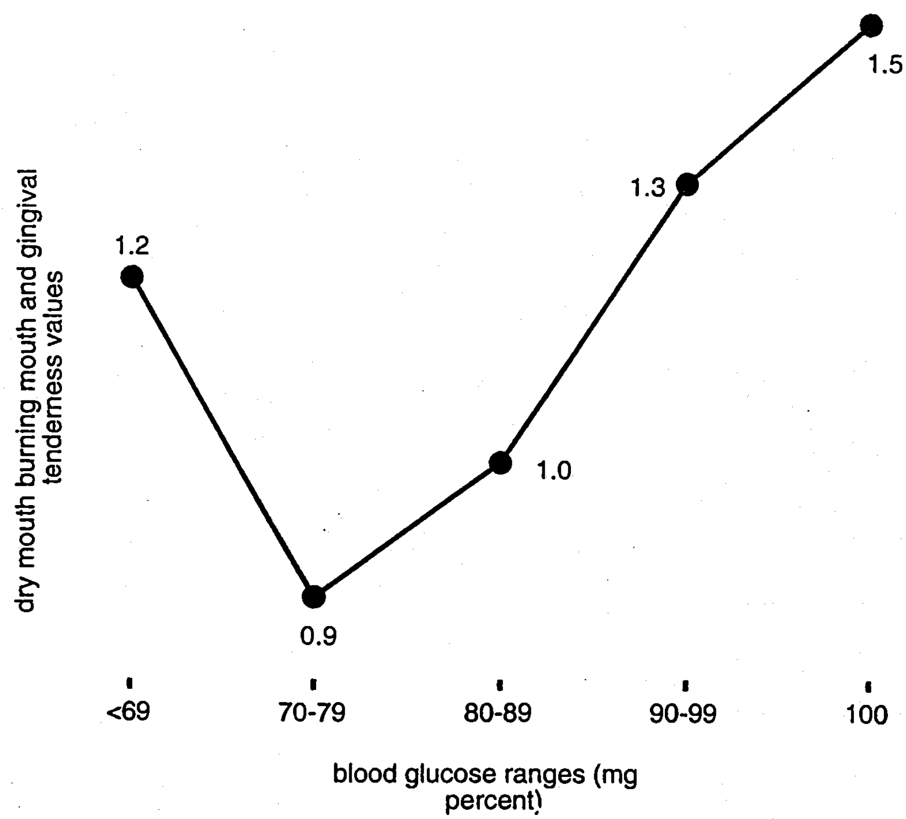

FIGURE 3

Relationship of fasting blood glucose to dry and burning mouth and gingival tenderness (100 routine dental patients). (Cheraskin, E. and Brunson, C. *The relationship of fasting blood glucose to oral symptoms.* J. of Applied Nutrition 13: #1, 2-19, May 1960.)

is sometimes referred to as a J-shaped curve, the nadir of symptom scores being found at a fasting blood sugar between 70 and 79 mg/dL.

A more detailed study of these three individual symptoms, and in various combinations in terms of fasting blood glucose, essentially supported these data (7,8). In addition, observations have been made on dental signs and roentgenographic findings both under fasting and nonfasting conditions and the J-shaped curve described here is constant (9-14).

Body Weight

Body weight is a sensitive barometer of health and disease. Approximately 20% of Americans are at least 20% overweight according to the 1983 Metropolitan Life Tables. These figures represent classic obesity and do not reflect the countless numbers of individuals who are marginally overweight. Most of the published information regarding "desirable" weight is derived either from mortality studies or specific morbidity analyses. Strikingly little information is available regarding underweight.

We attempted to examine the phenomenon of ideal body weight by studying 621 apparently healthy physicians and their spouses, using the CMI questionnaire (15,16). The Body Mass Index (BMI) is calculated from weight in kilograms divided by the square of the height in meters. The larger the number, the heavier the individual. For purposes of this discussion, only the BMI results for the female group will be considered. Table 2 makes it clear that the women with the lowest score in the CMI have the narrowest range in the BMI. Thus the parabolic curve once again demonstrates the fact that the healthiest subjects, as judged by this study, are within the intermediate weight range.

Nineteen thousand, two hundred and ninety-seven Harvard University alumni with an average age of 46.6 years, with self-reported physician-diagnosed CHD, stroke or cancer, participated in an interesting study (17). They completed questionnaires on weight, height, cigarette smoking and physical activity. The BMI was calculated. In multivariate analysis, adjusting for age, cigarettes and physical activity, a J-shaped relation between BMI and mortality was discovered, not unlike our study with presumably healthy physicians and their spouses.

TABLE 2

An Analysis of the Body Mass Index in a Progressively Healthier Female Sample

Line	Groups	Sample Size	Clinical Findings Range	Clinical Findings Mean	Body Mass Index Range	Body Mass Index Mean & S.D.
1	entire sample	270	0-125	21	18.0-43.1	23.7 ± 3.1
2	CMI<30	204	0-29	15	18.0-34.7	23.4 ± 2.7
3	CMI<10	60	0-9	6	19.0-30.5	22.9 ± 2.6
4	CMI<5	17	0-4	3	19.4-27.0	21.7 ± 1.8
5	CMI<4	12	0-3	2	19.4-23.3	21.2 ± 1.0
6	CMI<3	7	0-2	1	19.4-21.9	20.7 ± 0.8
7	CMI<2	3	0-1	1	19.4-21.9	20.5 ± 1.1

(Cheraskin E. A different methodologic approach to "ideal" weight: A study of body mass index. Alabama Medicine 1988; 58: 17-20.)

The White Blood Cell Count

Without exception, all of the standard hematology texts have suggested for a long time that the normal total white blood cell (WBC) count is approximately 4000 to 11000 cells per cubic millimeter. This means that, in the usual clinical circumstance, the total leukocyte count is a limited diagnostic or predictive instrument and only becomes useful with extremes of leucopenia or leukocytosis.

Recently there has been a burgeoning interest in the predictive potential of relatively small differences in the circulating WBC count (18). For example, the relationship of the WBC to fatal and non-fatal CHD incidence has been assessed in a subset of the participants of the Multiple Risk Factor Intervention Trial (MRFIT). It was discovered that for each decrease of 1000 cells/cu mm in the WBC count below the baseline, the risk for CHD decreased by 14%, controlling for confounding risk factors like smoking, blood cholesterol, and diastolic blood pressure. Additionally, in this same set of middle-aged men, there appeared to be a significant predictive relationship of the WBC for carcinomatosis and all causes of death. It was found that the average total WBC count in smokers was 7750 and 6080 in nonsmokers.

TABLE 3

Relationship of Total Number of Clinical Findings (Cornell Medical Index Health Questionnaire, CMI) and WBC Count in a Presumably Healthy Male and Female Sample

Line	Group	Sample Size	CMI Score Range	CMI Score Mean	White Blood Cell (WBC) Range (per CU MM)	White Blood Cell (WBC) Mean ± S.D. (per CU MM)
1	entire sample	1227	0-125	16	3500-21000	6600 ± 1843
2	CMI<10	443	0-9	8	3500-13900	6414 ± 1608
3	CMI<5	140	0-4	3	3500-11700	6339 ± 1471
4	CMI<4	88	0-3	2	3500-11100	6227 ± 1376
5	CMI<3	59	0-2	2	3500-11100	6242 ± 1391
6	CMI<2	19	0-1	1	4000-11100	6532 ± 1778
7	CMI 0	6	0	0	4000- 6900	5683 ± 1216

(Reproduced from Cheraskin E, et al. Nutritional Perspectives 1978; 1: 41-44.)

We have studied the ideal total WBC count from a different perspective (19,20).

Using data from the same group of asymptomatic physicians and their spouses, Table 3 shows that the WBC ranged from 3500 to 21000 cells/cu mm, with an average of 6600 ± 1843. It is clear that the narrowest range of WBC is in the group that registers zero score on the CMI and the parabolic curve is again evident. The overall average for the WBC count declined by approximately 14% and the variance decreased about 44% in the totally asymptomatic subjects compared with those with the highest CMI scores. It is possible that the WBC count is a more sensitive predictor of overall health when it is used in this manner.

The Parabolic Curve

A practical application of the parabolic curve is the APACHE system (APS), a physiologically based classification for measuring severity of illness in groups of critically ill patients. The system, which has been modified (APACHE II and III) and subsequently simplified (SAPS I and II), was reported recently (21). A value of 0 to 4 is assigned to each variable according to its degree of abnormality. Four represents the

TABLE 4

Scoring Values for Heart Rate

Variable SAPS Scale	Heart Rate (beat/min)
4	≥180
3	140-179
2	110-139
0	70-109
2	55-69
3	40-54
4	<40

(Reproduced from LeGall J.R., et al. JAMA 1993; 270: 2957-2963.)

greatest deviations at both extremes as demonstrated by tachycardia and bradycardia (Table 4).

This report summarized the experiences in 137 intensive care units in 12 countries embracing 13,152 patients. The investigators concluded that this scoring system provided a convincing estimate of the risk of death without having to specify a primary diagnosis.

Obviously, a curve of this type is not necessarily symmetrical. An excellent example is provided by the J-shaped curve of blood sugars as seen in Figure 3. Since the range of blood glucose can extend from a low of 20 to a high of 1500 mg/dL (22), the hyperglycemic range is much greater than that of hypoglycemia.

The curve may be changed by considering age as a factor. Hammond studied one million subjects (23). Of particular relevance is the relationship between number of hours of sleep and mortality. The evidence seems clear that the highest death rate occurs in the subjects with the fewest (less than five) and greatest (more than ten) hours of sleep (Figure 4). The lowest death rate occurs in those with a seven hour sleep pattern per night. Additionally it is clear that in the relatively younger age group (50 to 59 years) the curve is flatter than that in the 80+ year group.

The configuration of the curve is also a function of the range of values chosen to describe normo-, hypo-, and hyper- (Figure 3). The more restricted the physiologic range, the more sharply defined is the parabolic pattern.

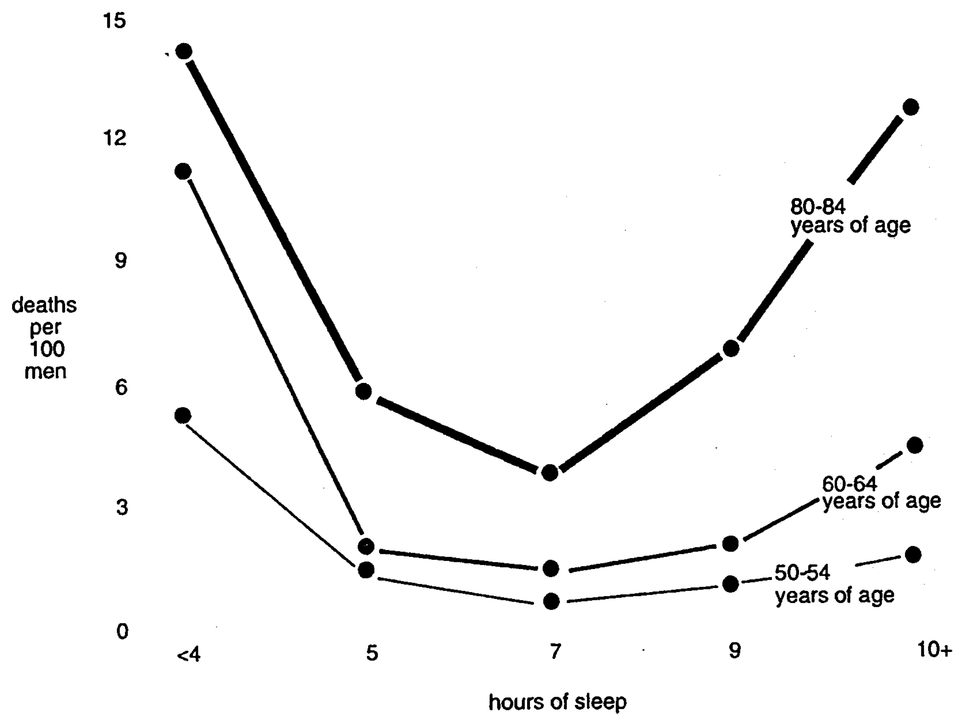

FIGURE 4

Hours of sleep per day and mortality in men. (Hammond, E. C. *Some preliminary findings on physical complaints from a prospective study of 1,064,004 men and women.* Am. J. Public Health 54: #1, 1-23, January 1964.)

Summary and Conclusions

Clinical, physiologic and biochemical phenomena are rarely viewed in this manner. When plotted from one extreme to another the distribution is curvilinear rather than linear.

Documentation in support of the parabola is cited as it relates to blood sugar, total WBC count, serum cholesterol, weight, sleep, oral cavity symptoms, mortality and morbidity in general. Perhaps the sharpness of each of these curves can give an appropriate pointer to the state of ideal health.

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