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Wrongful Life and Wrong Rules:

Abuse of the Normal Range Concept

James W. Winkelman, M.D.

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Blood tests from a clinical laboratory are generally reported on a form that shows the result and, next to it, a normal range. This form has the apparent advantages of being direct, simple, and easy to use. But in fact, it is none of these, and failure by physicians to understand the significant underlying assumptions behind the concept of normal range leads to some awful consequences in patient care. Beyond that, lack of understanding of the same assumptions by lawmakers and the regulation-writing bureaucrats who follow behind them leads to terrible stupidities that threaten to institutionalize improper medical practices.

I recently have been involved in two topical, that is to say (with academic hyperbole), intensely controversial examples of abuse of the concept of normal range. In one case a child suffered being born with the prospect of certain death in infancy. In such situations the human issues never really are resolved. But the scientific, social, and economic aspects of the case were discussed in a court of law. During the legal procedings I was one of several "expert" witnesses asked to testify. In the second instance, new legislation is being implemented which is likely to worsen the very problem it ostensibly addresses. The problem relates to the manner in which physicians distinguish between health and disease. As a pathologist, it is my business first to identify the signs of ill health, and second to alert a patient's attending physician to the presence of dangerous or potentially dangerous findings. Therefore, the legislation of which I speak affects me directly, as well as every other pathologist in every hospital in the country. More important, it affects the utilization of diagnostic procedures which in human terms can translate into continued life or death of patients. Both cases were precipitated by a failure to examine the implications of the concept of normal range beyond the most superficial impression it conveys. This concept is taught in medical school but is readily within the grasp of

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any generally educated person who may profit as a patient, or a citizen, from such understanding.

Tay-Sachs test results and the normal range

Among the most impressive and valuable achievements in medical diagnosis is the ability to detect the carrier state for Tay-Sachs disease in prospective parents. With a specimen of blood from the arm and a sophisticated chemical test in the clinical laboratory a couple can know whether they are at no risk or have a 25% chance of giving birth to an afflicted child.

Tay-Sachs disease is an inherited disorder characterized by the inexorable accumulation of an abnormal metabolite, the GM_2 ganglioside, in brain cells of afflicted newborns. It produces in infants a degenerative disorder that is manifested by a failure to grow, mental retardation, blindness, loss of voluntary motor ability, and death by the age of three or four. The ganglioside is normally metabolized by two enzymes, hexosaminidase A and B (hex A and B). Newborns with Tay-Sachs have almost no hex A. To express this trait, the newborn must be homozygous for the defective gene (it must therefore have inherited a recessive gene from each of its parents). The parents are thus both heterozygous for the gene, meaning that they possess a normal gene paired with the defective one. The normal gene is "dominant," meaning that the trait is not expressed. The recessive gene is not revealed by abnormal signs or symptoms. But such an individual is a carrier, and if two carriers mate they transmit their genes according to simple Mendelian patterns.

If either parent is not a carrier of the recessive gene, their offspring could not possibly be homozygous and express the disease. If both parents are heterozygous, then one in four times their offspring will be homozygous for the Tay-Sachs gene and express the full disorder, two in four times it will be heterozygous, and one in four times the child will not inherit the gene from either parent.

Although no outward evidence of the carrier state is apparent, a laboratory test has been developed which segregates homozygous normals, heterozygous Tay-Sachs carriers, and homozygous Tay-Sachs–afflicted subjects.[1] The value of knowing the results of such a test is obvious.

1. J. S. O'Brien et al., "Tay-Sachs Disease: Detection of Heterozygotes and Homozygotes by Serum Hexosaminidase Assay," *New England Journal of Medicine* 283 (1970): 15.

The laboratory test can also be performed on amniocentesis fluid from a pregnancy occurring as the result of a union of heterozygous carriers. It can determine whether the fetus will express the full-blown disease or not. The choice of abortion is then available. A couple with this knowledge can attempt again to produce a healthy baby with a 75% chance of doing so. Their success can be confirmed by application of the same test procedure.

To prevent the birth of Tay-Sachs children, a series of events must fall into place. A couple must seek testing or be advised to have it. The laboratory tests must be done properly. They must be interpreted properly. All subsequent diagnostic and therapeutic steps must be properly executed under expert medical guidance. While all this does not seem so problematic, in fact, Tay-Sachs children continue to be born. Most often such occurrences do not follow from the desire of parents to complete the pregnancy with the outcome known to them in advance, but because of a breakdown somewhere in the sequence.

Tay-Sachs disease appears among Ashkenazi Jews with a frequency

of 1 in 900 births. The recessive gene conferring carrier status exists in 1 out of 30 adults of such origin (1/30 x 1/30 = 900). In the general population, its frequency is vastly lower. The carrier rate, for example, is estimated at 1 in 300 non-Jewish Americans, and therefore the frequency of Tay-Sachs offspring from that population is only 1 in 90,000 (1/300 x 1/300 = 1/90,000).[2] The Jewish population has therefore been identified as being at a relatively high risk. Attempts are made to test Jewish couples by alerting physicians to their special risk status and by going directly to the people themselves in programs operated through synagogues. This approach is considered to be more or less adequate in the United States. Given the relative rarity of the disease, the cost-benefit ratio is thought to be too low to justify testing the broad base of the population. Whether it is or not could be debated. There is little argument for mandatory testing for Tay-Sachs in, for example, the People's Republic of China. Yet the disorder is known there[3] and interest in it is widespread.[4] Doctors there are curious about the dispersion of the once flourishing communities of Chinese Jews in Kai-feng-fu, Tungming, and Sungchiang, later subsumed into the Han majority and thus not overtly identifiable for more than sixty years.[5]

2. S. M. Aronson and B. W. Volk, "Genetic and Demographic Considerations concerning Tay-Sachs Disease," in *Cerebral Sphingolipidoses,* ed. S. M. Aronson and B. W. Volk (New York: Academic Press, 1962), p. 375.

3. Z. F. Tang, *Practical Pediatrics* (Peking: Chinese People's Printing Co., 1981), pp. 131–32.

4. Personal communication from M. C. Boa, Director of Metabolic and Endocrine Diseases, Children's Hospital, Tiaujin, China, 14 September 1982.

5. W. C. White, *Chinese Jews,* 2d ed. (New York: Paragon Book Reprint Corp., 1966).

The case in point

In one celebrated case the neat working of the diagnostic and therapeutic program broke down in a most unexpected place—in the interpretation of the laboratory test results vis-à-vis the quoted normal range. As a consequence of a failure to understand this concept, two inauspicious births occurred. One was of an afflicted child. The other was of a new legal basis for malpractice suits, the cause of action being "wrongful life." Reporting of the case in both lay and medical literature has either ignored or failed to deal properly with the fundamental abuse of the normal range concept that gave rise to the unfortunate consequences in the first place.

The facts of the case are as follows. A couple in southern California decided to conceive a child. Both were descendants of Eastern European Jews. Having learned of their high-risk status from a community-directed educational campaign they themselves initiated the request for carrier status testing by going to their family physician. He authorized blood testing and referred them to the modest clinical laboratory in his medical office building. The specialized test was not performed by that laboratory, but specimens were drawn there and sent to a larger reference laboratory in the same city. Each specimen was tested and the results were returned to the originating laboratory, which transmitted them to the physician.

The form for the results of this test is more complicated than those of more common tests, but the format is essentially the same. The analytic results are reported, the normal range is quoted, and notes are made which help the physician interpret the results.

The reports in this case gave the information shown in Table 1 (all names, demographics, specific identification numbers, dates, and other miscellaneous requirements of a complete laboratory report are omitted). On the basis of this information the family physician told the couple that the wife could not be a Tay-Sachs carrier and, therefore, that they need have no fear of conceiving a Tay-Sachs child. Pregnancy occurred. The obstetrician accepted the verbal assurance of the couple

that they were at no risk. He did not review the results, discuss the testing with the family physician, or request confirmatory testing. A Tay-Sachs child was born. Within the appropriate time, a malpractice suit was brought on behalf of the child on the basis of "wrongful life." In other words, the child was suing for having been born. The suit named the physicians and the laboratories.

It is helpful to draw attention to the aspect of this report that is most important for assessment of carrier status, viz, the result "hexosaminidase A, % of total." The "hexosaminidase, total" is not so valuable because of the very wide, overlapping ranges between controls, heterozygotes, homozygotes, and individuals with other conditions. Only the percent of total result provides some discrimination between the populations of interest. The husband's percent of total result places him squarely in the middle of the heterozygote's range. The wife's percent of total result is at the very lower limit of the range given for controls.[6]

The limits of the normal range and data interpretation

Since the ultimate outcome differed from the intended one, it is reasonable to inquire where the error occurred. The issue is, What is the proper way to think about results very close to the quoted normal range limit?

TABLE 1

EDITED COMPOSITE REPORT OF TESTS FOR TAY-SACHS CARRIER STATUS

Patient Name: Husband — Referring Physician: Dr. XYZ

Test	Result	Units	Adult normals
Serum hexosaminidase, total	980	nmol/ml/hr	See "Ranges" below
Serum hexosaminidase A	38	% of total	

Patient Name: Wife

Serum hexosaminidase, total	360	nmol/ml/hr	See "Ranges" below
Serum hexosaminidase A	50	% of total	

RANGES

	Total Hexosaminidase Range	Hexosaminidase A % of Total Range
Controls	333–775	49–68
Heterozygotes	288–644	26–45
Children with Tay-Sachs disease	284–1232	0–4
Other patients	401–2652	19–79

Note: 20% of women on birth control pills, pregnant women, patients with diabetes, myocardial infarct, hepatitis, or pancreatitis may have a high total hexosaminidase with low percentage of hexosaminidase A. Heterozygotes have about 65% of normal levels of hexosaminidase A. However, the gap between values from normals and heterozygotes is narrow; thus as more individuals are studied, an overlap in values may occur.

Source: This report form is based on J. S. O'Brien et al., "Tay-Sachs Disease."

6. O'Brien et al., "Tay-Sachs Disease," on which the report form is based, presented total hexosaminidase activity in activity units, and hexosaminidase A only as a percent of total (that is to say, hexosaminidase A was not presented in activity units). Whereas the range of hexosaminidase A of heterozygotes expressed as a percent of total does not overlap with the range for controls in that series, the range of hexosaminidase A in activity units does overlap with that of controls, as is shown in later reports from other laboratories. See M. M. Kaback et al., "Automated Thermal Fractionation of Serum Hexosaminidase: Effects of Alteration in Reaction Variables and Implications for Tay-Sachs Disease Heterozygote Screening," *Progress in Clinical and Biological Research* 18 (1977): 197–212. This latter point does not obviate the diagnostic use of hexosaminidase A as percent of total, but it should serve as a further cautionary note in the diagnostic use of complicated laboratory data.

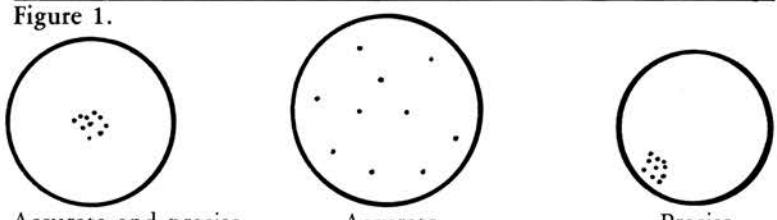
First, was the laboratory test result wrong? It is possible for an out-and-out error to occur in any procedure. There are certain safeguards that a laboratory builds into its routine to prevent that. Over and above the observance of good laboratory practice a laboratory is required to perform internal quality control checks every time a patient specimen or batch of specimens is run. The laboratory did test serum from normal controls and a Tay-Sachs carrier in this way. The hexosaminidase A, percent of total results with these controls clustered within an acceptable dispersion around the target values of 55% and 40%, respectively. In addition, an artificial standard with a target value of 25 nmol/ml was analyzed with each batch, and it, too, was accurately determined. There was no drift or wide fluctuation of results during the period before, during, and after the specimens of interest were tested, indicating the absence of systematic or random error occurring with the test at that time. Therefore it can be assumed, there being no evidence to the contrary, that the results on the specimens were correct.

The concept of "correctness" subsumes the concepts of accuracy and precision. It is best to be accurate and precise, but it is possible to be either one or the other. This is illustrated by Figure 1. These terms have very specific meanings in laboratory science. Accuracy refers to the approximation of the analytic result to the true value. The use of standards and controls described above satisfies the usual criteria for accuracy in this case. Precision refers to the repeatability of an analytic procedure.

Each laboratory test has a known precision, or imprecision. In the case of hexosaminidase levels it is approximately ± 15%. This is the 2 standard deviation (2 S.D.) spread of results around the mean from repeated analysis of the same specimen. Two S.D.'s are defined as the limits that include 95% of the observations. It translates to this kind of understanding of any particular result: If a test has a precision of ± 15%, an analytic determination of, for example, 100 arbitrary units is really 100 ± 15 units with 95% probability. That is, if the same specimen were analyzed repeatedly, 95% of the time the result would fall between 85 and 115. The 15% imprecision of the hexosaminidase test is about at the state of the art. It is not as good as many tests, but it is much better than others. What it means in this particular case is that the result of "50% hexosaminidase A" is really 50% ± 7.5%; i.e., if the same specimen were tested 100 times, 95% of the results would be between 42.5% and 57.5%. The more precise a test, the more confidence can be placed in a result close to a normal range limit. The less precise the test or the closer to the normal range limit, the less significance can be attached to results. So, in this particular case, with a result that is not analytically wrong and is as good as a laboratory can perform, a definitive conclusion about the subject's carrier status cannot be made because of the intrinsic precision limits of the test procedure itself.

Second, what is the meaning of normal range anyway? First note that

Figure 1.



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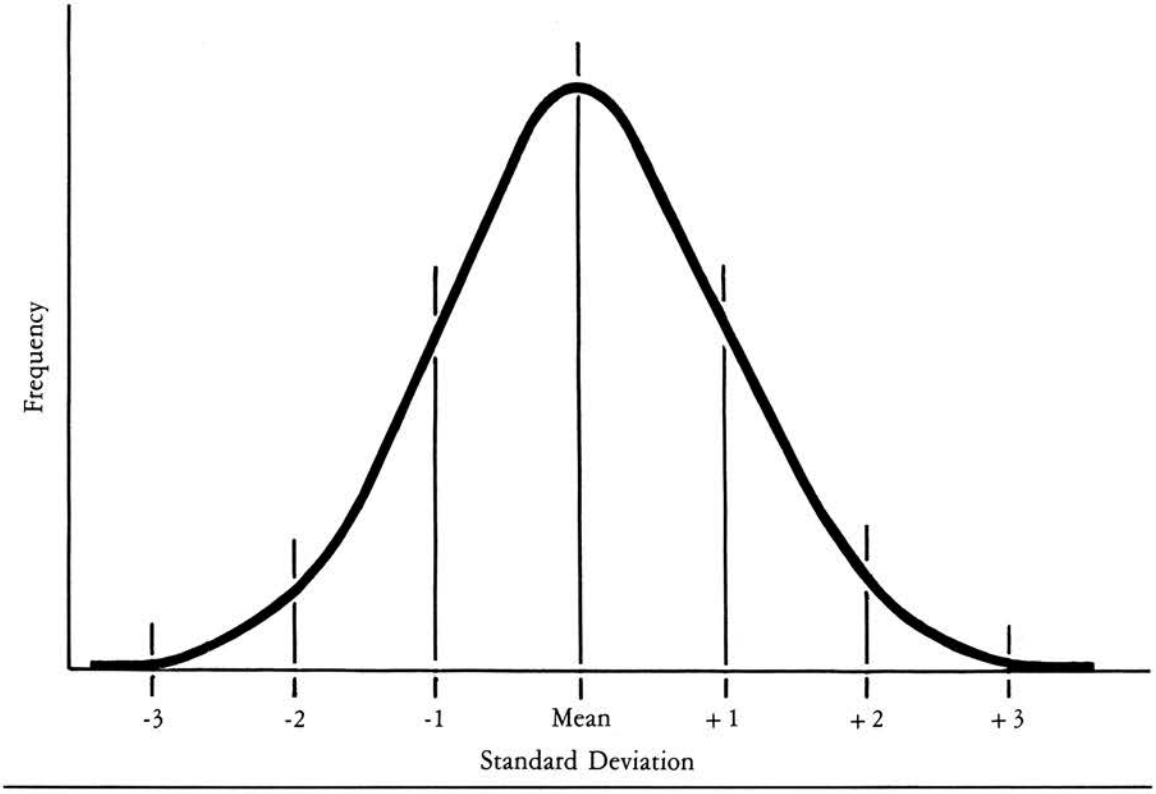
even the laboratory report shown in Table 1 does not use the term "normal range," but "adult normals." Another phrase that replaces "normal range" on the report form of some laboratories is "reference interval." Each version aims to avoid the suggestion that the quoted range is synonymous with normality in the sense of desirability or that it is indicative of good health.

The normal range is a statistical concept, and the words themselves are derived from the most fundamental property of populations, the normal distribution. It is not wasted printer's ink to display a normal distribution in its classic form (see Figure 2). Any measurable characteristic will distribute about a calculable mean. If the values form a "bell-shaped" curve, as shown in the figure, or if they are skewed as in a nonparametric distribution, the standard deviation can still be calculated. These measures quantify nothing more or less than the individual variations that characterize almost every property in biology. By definition, 1, 2, and 3 standard deviations are the limits around the mean that embrace 66.3%, 95.4%, and 99.7%, respectively, of all the values that were measured. By convention, the normal range in clinical laboratories, and in many other fields, is taken as the 2 S.D. limit. An example may be helpful: Serum uric acid levels are highly diagnostic of gout. By definition, 95 of 100 individuals who do not have gout will have blood uric acid levels within the stated normal range limits. This also means that 5 in 100 people without gout will have blood uric acid results outside the normal range. A range of blood uric acid results can also be obtained for gouty patients. It will have a mean and, by definition, a normal range limit that embraces 95% of the population studied. Also, therefore, by definition, 2.5% of all people with gout will have blood uric acid results below the lower limit of that

Figure 2. Normal range distribution curve.



range.

The ranges of results actually found for any constituent of blood almost always show overlap between those without and those with the disease of interest. A blood uric acid slightly higher than the quoted normal range could be from one of the 2.5% of nongouty people who, by definition, fall above the limit. Or a blood uric acid just below the upper limit of the quoted normal range could be from one of the 2.5% of gouty patients who, by definition, fall below the range limit that was defined to include only 95% of all patients with gout. Since the ranges overlap, a blood uric acid just at or within the upper limit of the normal range could be from a gouty *or* a nongouty subject.

It is intuitively obvious, and has been rigorously proved,[7] that the closer a result is to the stated normal range limit, the more likely it is to come from an abnormal individual, i.e., one with the disorder of interest and who is therefore part of the diseased population that was not evaluated precisely in order to establish the normal range. If a test has any diagnostic discriminatory value, it must have ranges that do not totally overlap between people with and without the disease. It follows that the closer a result is to the middle of the normal range, the more confidently one can assert that it came from a person without the disease. Quantitative statements can be made for expressing such probabilities, but they require knowledge of the number of normal and diseased persons in the overall population. For example, if diabetics and nondiabetics were in exactly equal numbers in a hypothetical population, and the upper limit of the normal range for nondiabetics corresponded exactly to the lower limit of the normal range for diabetics, then a result exactly at that common range limit would have a 50% chance of coming from a diabetic and a 50% chance of coming from a nondiabetic. If the result were slightly lower than the upper limit of the normal range, the probability would increase that it came from a nondiabetic and proportionately decrease that it came from a diabetic, and so on.

7. R. J. Henry and A. H. Reed, "Normal Values and the Use of Laboratory Results for the Detection of Disease," in *Clinical Chemistry, Principles and Technics,* 2d ed., ed. R. J. Henry, D. C. Cannon, and J. W. Winkelman (Hagerstown, Md.: Harper & Row, 1974), pp. 343–73.

Since in most cases overall population frequencies are not known and such probability statements cannot be made, physicians are taught to recognize the consequences of the general principles, look at each case individually, and act accordingly.

Third, what is the proper interpretation of the findings in this case? A full interpretation of the result "50% hexosaminidase A" for the wife should *not* have simply noted it to be within the low end of the quoted range for controls, above the high end of the quoted range for heterozygotes, and concluded that therefore the sample came from someone who could not be a heterozygous carrier of Tay-Sachs. On the basis of the intrinsic imprecision of the tests alone, it should have been appreciated that the result could well fall into the range for heterozygotes. On the basis of the definition of normal range alone, it should have been recognized that a substantial number of heterozygotes fall outside the quoted limits. The note included on the report form was intended to alert the family physician to the overlapping of ranges that was predicted, and which was later substantiated, between proved heterozygotes and noncarrier controls. An informed and prudent approach, considering the great significance attached to this particular result, would have been at least to repeat the test. If just about the same result was obtained, judicious counseling would have emphasized the possibility that the wife was a carrier. Other steps could

then have been taken to establish whether the subsequent embryo was afflicted with Tay-Sachs disease, and a "wrongful life" could have been avoided.

The legal precedent: Wrongful life

In the legal suit under discussion, the clinical laboratory became the prime target of the plaintiffs. Why? It had very large liability insurance coverage. The physician's malpractice insurance would have covered only a fraction of the amount of damages sought. The suit, brought in 1978, was the first based on this version of the "wrongful life" theory. A lower court in California ruled that the afflicted child could sue on that basis, and the decision was allowed to stand by the state supreme court. Neither court ruled on the particulars of the case, either to establish responsibility or to determine damages. But before those very issues were brought before the Superior Court of the State of California a settlement was made. The laboratory paid the plaintiffs $1.5 million.

The consequences of this case are uncertain at this time. Bad reporting in the medical and lay press has also beclouded the issue. For example, *Newsweek* reported this case in an article entitled "Suing for Being Born."[8] It stated, "A genetic laboratory analyzed their blood and declared that neither was a Tay-Sachs carrier. The lab was wrong." In fact, and unfortunately for the cause of truth, *Newsweek* was wrong. The lab did not declare anything. It reported numbers to a physician who had requested a test, and there is no evidence that "the lab was wrong" in the results they rendered. *Newsweek* went on to note that other cases based on wrongful life can be expected. It mentioned the case of a normal birth following an unsuccessful vasectomy. It also mentioned a child who was born deaf after an apparently inaccurate assessment of a hereditary factor in an older sibling. The *American Medical News* has recently reported the award in a wrongful life suit of $625,000 to a 3-year-old boy with multiple birth defects.[9] He was born to an Air Force recruit whom military physicians failed to advise properly about measles.

8. *Newsweek*, 8 March 1982, 53.

9. *American Medical News*, 3 July 1981, 7.

Especially in the case of a failed vasectomy, the theory of wrongful life threatens to undo precedents of many years standing which hold that damages are not recoverable in the case of the birth of a normal child. Basic legal theories are involved. Is there a breach of contract or breach of implied warranty for insured sterility after a vasectomy or tubal ligation? Is life an overriding value and awarding damages even for the costs of pregnancy and delivery contrary to public policy? Even if such damages are allowed, should they be extended to include the costs of raising and educating a normal child? If so, is there a definable and recoverable dollar amount that balances the benefits of raising and enjoying a child and the costs and problems associated with that experience? These questions have been well discussed in an article by the general counsel of the American Medical Association.[10]

10. V. R. Greenfield, "Wrongful Birth, What is the Damage?" *Journal of the American Medical Association*, 27 August 1982, 926-27.

Further complicating the issue is legislative action in California. According to a recent article,[11] a measure has been approved that would bar a child with birth defects from suing his parents for being born. But the bill "does not prevent a child from suing a laboratory in a similar case," i.e., a case in which the parents had known they were carriers of a heritable disorder and had gone ahead with the birth anyway. "It also bars the laboratory from using the parent's knowledge and refusal

11. *American Medical News*, 11 September 1981, 16.

to get an abortion as a defense against a suit by the child." This kind of convoluted legislative thinking should make any laboratory director without a deep self-destructive tendency discontinue testing for inheritable disorders. Can this be progress?

Legislative abuse of the normal range

It is now in vogue to identify medical care costs as a target for reduced support by government. Overall, medical costs are demonstrably rising by every measure: percent of GNP, $/year, patient cost/hospital day, etc. The cost of medical care is increasing faster than the inflation rate, which is, after all, merely the average of many components. But it was not very long ago that the government, presumably representing the people it serves, chose to support more medical care for more people through increased expenditures. Medicare, Medicaid, Workmen's Compensation, and numerous programs directed at particular diseases, e.g., kidney disorders (via renal dialysis funding), cancer, and hypertension, were brought into being. After all, until two decades ago our government provided virtually no such support, while socialist and even democratic states who did were perceived as doing the right thing. Even now, on a per capita basis our government support for direct medical care is less than many other nations. Regardless, medical care costs are now subject to critical review with the objective of reducing current levels of support by the very bureaucracy that was brought into being to deliver that support not so long ago. I, for one, am not clear whose bidding is being done now. There has never been anything like a national referendum on the subject of the relative level of funding desired for medical care. It has not been openly discussed in election debates, in letters of inquiry from congressmen to their constituents, or by other means of soliciting the opinion of a broad base of the population.

Nonetheless, deep in section 108 of the Tax Equity and Fiscal Responsibility Act of 1982, Section 1887, the Social Security Act is modified for the purpose of reducing medical care expenditures. Rules were drafted to implement these changes by the Health Care Financing Administration (HCFA) and published in the *Federal Register* on 1 October 1982. Some of these rules reveal an appalling ignorance of the practices they will regulate. Particularly meretricious are regulations ostensibly intended to limit unnecessary medical consultations in the interpretation of laboratory tests. These regulations flagrantly abuse the concept of normal range. Far from being an arcane detail of little importance to society in general, it directly and adversely affects the approximately 4 million of us who, each day, have laboratory tests. I will explain and illustrate this issue which, I submit, is within the intellectual reach of any thoughtful person, even the Federal rules writers who have neglected, ignored, or misunderstood it.

In order for a pathologist, who is a specialized physician responsible for laboratory testing, to be reimbursed for his professional services relating to a patient's test result, a consultation with the physician who ordered the test must meet four new conditions. Among them, according to the rules put forth in Section 405.556 (*b*), are that the consultation "must . . . relate to a test outside normal range(s)." Now, pathologists can no more be expected to perform without compensation than any other member of society would be expected to deliver

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goods or services without pay. So as written the new rules would effectively deny payment for, and therefore eliminate consultation on, results that are not outside the nominal normal range.[12]

Consider some of the consequences of this restriction. The entire constellation of suffering and expense described previously in the case of the child with Tay-Sachs disease would all have been avoided if proper interpretation had been obtained of laboratory tests that were *not outside* the normal range. In the discussion of that case, I emphasized the arbitrary limit setting that, by a formal convention only, has designated certain values as normal range limits. The term normal range is technical and not intuitive. It does not mean that medical desirability or the absence of disease is limited to results within the normal limits. It does not necessarily attribute abnormality or medical undesirability to results outside the normal limits. It is a purely statistical concept that has meaning in a special sense that may or may not be important for a particular patient. I also emphasized that the significance that can be attached to any numerical result from a quantitative test is dependent on the intrinsic error of the method. *Therefore, test results that fall within the nominal normal range limits can well lead to an important medical diagnosis of disease and consequent therapeutic decisions.*

12. At the present time it appears that this rule will be included in those finally published by HCFA. Its impact cannot be gauged until we see whether some modifications are introduced and the manner and extent of its enforcement.

Other fundamental concepts involved in the interpretation of laboratory tests are also violated by the simplistic rule written by HCFA. The first of these is individual variation.[13] The range of results with any particular test is much narrower for a single individual than for a large group of individuals. This truism follows from the inescapable workings of statistics but translates into very direct human consequences. For example, one may have a blood urea nitrogen (BUN) level of 12 mg/dl ± 2 mg/dl day in, day out for years. The BUN reflects the effective function of the kidneys in removing nitrogenous wastes left over from the metabolism of protein and the breakdown of tissue that is constantly occurring in the wear and tear of life. Other perfectly healthy people with perfectly well-functioning kidneys may show BUNs of 8, 10, 15, or 20 mg/dl with a similar narrow range of day-to-day fluctuation. This is predictable on the basis of individual variation. It is characteristic of virtually all biological phenomena and leads to the bell-shaped parametric or other nonparametric distributions from which means and standard deviations are calculated for whole populations. Normal range limits for BUN are defined to include, arbitrarily, 95% of all people without kidney disease. That normal range is substantially wider than the range of results within which any single healthy individual fluctuates. Therefore, a significant change from normal kidney function to abnormal kidney function will first elevate a person's BUN above *his* normal range *but within the population's normal range*. Only the few individuals in the healthy population with BUNs at the upper end of the normal range will show elevation beyond the normal range limit at the first appearance of kidney disease. Doctors know the values for many constituents of their patients' blood or urine from previous tests. "Screening" testing has been widely advocated for that very purpose. Therefore, it is incorrect, improper, and counterproductive to construe what may well be a significant change for an individual as ineligible for review by an expert because it still falls within the normal limits of the broader population.

What is normal in a general population may nevertheless be abnormal in some individuals.

13. D. S. Young, "Biological Variability," in *Chemical Diagnosis of Disease*, ed. S. S. Brown, F. L. Mitchell, and D. S. Young (Amsterdam: Elsevier/North Holland, 1979), pp. 1–115.

Trending patterns... Since disease originates in a healthy body, the first indication of illness occurs in the normal range, just as occasional sneezing may indicate the beginnings of a bad case of flu.

Another basic phenomenon observed in the monitoring of a patient's laboratory results that deserves, but would be denied, consideration is "trending" within normal limits. Even within the narrower range of results found for a single individual, important trends may occur that need to be further investigated and understood. It is intuitively obvious that a change big enough to place a result outside normal limits begins with small changes that move in that direction. Astute observation of such trends is the hallmark of good medical practice. From it the physician can be proud and the patient saved much suffering. For example, in the field of endocrinology it is now possible to perform very precise measurements of circulating thyroid hormones. Disorders of the thyroid usually develop over relatively long time spans. Thyroid hormone levels are regulated by feedback inhibition systems so that very rapid changes are rarely seen. There is little diurnal or other periodic fluctuation in the serum levels of those hormones. Therefore a slow but steady increase or decrease in thyroid hormone levels, even if small, can constitute objective evidence in support of an early diagnosis of hyper- or hypothyroidism. All the advantages of modern therapy can then be employed. This example is not a rarity or a fiction concocted to support weak arguments. Along with the others already mentioned it occurs often enough in the ordinary practice of clinical pathology that its prohibition by regulation needs to be exposed as contrary to science and to the best interests of patients.

In blood banking there are no such things as normal or abnormal ranges.

HCFA's rules ignore even much simpler realities than those mentioned above. For example, in the field of blood banking there is no such thing as a normal range. Yet it is in this area that some of the most important consultations between pathologists and clinicians occur. Modern blood banking has responded to the requirements of daring new forms of surgery. Laboratory tests are of the utmost direct importance in the care of such patients. But the concepts of normal range are not applicable at all to such testing. Characterization of the antigen composition of donor and recipient blood allows for compatible transfusions entirely without reference to normal ranges. By definition, no blood banking result, including workups of transfusion reactions, can be outside the normal range.

A further example is provided by the need for a laboratory specialist's appropriate consultation in the field of coagulation. Specific components are now available from blood banks for the correction of coagulation disorders that only recently led to fatal bleeding. This is a complicated and rapidly progressing field. New aspects of the reaction cascade of more than a dozen factors that culminates in a successful clot are being discovered and named every year. A defective or deficient component can influence many steps, each tested separately, that occur in this cascade. Few practitioners can keep abreast of the latest information, and they rely on the clinical pathologist. In the workup of a "bleeder" many tests are usually performed, and an interpretation is made on the basis of the entire picture they provide. Perhaps only one of ten will be abnormal, but all ten must be performed and considered to identify where and how to intervene with the correct component replacement therapy. It is patently impossible to limit a consultation in such a situation to the abnormal result only.

Perhaps the most common laboratory test for clotting, the prothrom-

bin time, is indicative of a serious problem *precisely when the result is normal and not when it is abnormal.* This is not semantic sleight of hand. The prothrombin time is ordered to monitor the effectiveness of anticoagulant therapy that is commonly employed in patients with heart attacks, strokes, and thromboses. The danger represented by normal clotting in these conditions is treated by prolonging the coagulation of blood as measured by this in vitro test. The therapeutic objective is, therefore, to regulate the dose of anticoagulant to keep the test result outside the normal range. Under these conditions, a result within the normal range is an indication of a true medical emergency. The literal application of HCFA's rule in such circumstances would certainly invite a form of negligence no one really wants.

In many medical emergencies, test results characteristically fall in the normal range.

The entire field of toxicologic testing and therapeutic drug monitoring employs definitions of normal range, therapeutic range, and toxic range that have everything to do with good medicine and nothing to do with HCFA's regulation. Drugs, of course, have no normal range in untreated, well populations. Therapeutically active substances that are naturally present in very low concentrations, such as lithium (which is used in pharmacologic doses for control of manic depression), have a normal range of no particular interest. Toxic materials such as alcohol are important at some concentrations but not at others. Especially important in the proper utilization of such test results is recognition of the patient's individuality. Often pathologists act as consultants on particular patients and particular circumstances. For example, idiosyncratic reactions are particularly common with some drugs and in some patients. It is inconceivable that regulations could ever be properly drafted to cover what constitutes a consultable result in the case of a drug whose blood level varies several orders of magnitude in the course of its cycle of absorption and excretion. A given blood level found early after administration and the same level found at the time expected for it to peak would obviously have enormously different implications. For example, an acetaminophen (Tylenol) level of 100 μg/ml is five times the upper limit of the quoted therapeutic range, but well below the level ordinarily found within four hours of ingestion of nontoxic amounts of the drug. Many drugs or toxins can be tolerated by some individuals at levels that would be deadly to others. This happens because of idiosyncratic reactions that go beyond ordinary interindividual variations. Such reactions represent some distinctly different metabolism of the agent in one person or class of persons than in the majority. Certain disease states inhibit normal processes of detoxification. Just these kinds of problems are reviewed by the pathology staff day by day and patient by patient in our and probably every good clinical laboratory. The pathologist knows individual patients by their reactions and susceptibilities even if he never sees them face-to-face.[14] His consultation on behalf of such problem patients would be noncompensable by HCFA rules because it defies codification.

In the case of drug therapy, it is dangerous to ignore the patient's individuality by applying the normal range concept.

In microbiology testing, the concept of normal range is also totally inapplicable. Laboratories may quote "normal flora" for particular body sites, but the same organisms that are innocuous under some conditions can be serious pathogens under others. Consider that pneumococcus and hemophilis influenza are found in the throat cultures of many healthy people. But in a debilitated or immunocompromised host they can cause fulminant disease. Almost every opportunistic fungus can be

14. P. Winkel, "Reference Values," in *Clinical Diagnosis and Management by Laboratory Methods,* ed. J. B. Henry (Philadelphia: Saunders, 1979), pp. 29-53.

found in normal people, where it is held in check. The same organism can disseminate and kill the susceptible host.

Conclusions

Normal range is a meaningless concept in so many areas of the clinical laboratory that one is tempted to deal with HCFA's misuse of it by an evasive semantic mechanism. Since the definition of normal range has arbitrarily been set at 2 standard deviations to encompass 95% of the population, why not change the definition to 1 standard deviation? Then only 66% of the population would be normal, and the opportunity to consult would extend to a larger potential number of problem cases. Similarly, pathologists could adopt new conventions to state the normal range for infectious organisms as "none" and escape any restrictions on consulting about any microbiological results. The same could be done for all toxicology and therapeutic drug monitoring results. Certainly the profession could outdefine the regulators in blood banking, coagulation testing, or any other part of the clinical laboratory's repertoire. But such exercises would go against the proper scientific understanding and good medical practice that should be advocated by organized medicine on behalf of its members and their patients.

After all, it is the legislator who should comprehend and deal with reality, no matter how complicated. The misapprehension of reality manifested by a small but important phrase buried in the depths of a bill that nobody will study or complain about is, perhaps, indicative of a more general shortcoming in society. I refer not only to the too easy way in which we grant powers and acquiesce to the published word provided that it appears in the *Federal Register*. We passively accept civil authorities that go beyond the intent of statutes, exceed their knowledge, and establish harmful public policies. Our acceptance betrays a deeper, more dangerous set of attitudes characteristic not only of our authorities and lawmakers but also of the public whom they serve, ourselves, in other words. The life of the body is no less complex than the life of the mind. While it would be reassuring and convenient to solve problems simply and neatly, be they physical or metaphysical, most problems do not admit of simple solution. Life, whether of the individual cell or of the body politic, is not governed by a system of sharp contrasts in black and white, but by a continuum of shades of gray. Except in a statistical sense, there is no such thing as normalcy; there is only a range of behavior—biological, psychological, intellectual—which under specific circumstances may be described as desirable and, under others, as undesirable. To insist on simple distinctions when circumstances dictate complexity and even ambiguity is to abuse the scientific concepts. In the hospital this attitude can result in incalculable personal suffering. In the world of ideas, this attitude constitutes the very denial of the richness of life itself.