No. 04-607

In the Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (doing business as LabCorp),

Petitioner,

v.

METABOLITE LABORATORIES, INC. and COMPETITIVE TECHNOLOGIES, INC.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE AMERICAN CLINICAL LABORATORY ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF THE AMERICAN CLINICAL LABORATORY ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

INTEREST OF THE *AMICUS CURIAE*[1]

The American Clinical Laboratory Association ("ACLA"), a not-for-profit industry association, is the nation's leading organization representing clinical laboratories. ACLA's twenty-four members include local, regional, and national laboratories, and they furnish testing services to patients in all 50 States and the District of Columbia. ACLA estimates that its members supply roughly 60% of all clinical laboratory testing nationwide that is not provided by laboratories affiliated with hospitals or physicians' offices. Founded in 1971, ACLA regularly advocates the interests of its members before the federal and state legislatures and administrative agencies, as well as in dealings with other health care organizations and the public. ACLA previously appeared as an *amicus curiae* in another case before this Court, *Vermont Agency of Natural Resources* v. *United States ex rel. Stevens*, 529 U.S. 765 (2000).

ACLA's mission includes encouraging the highest standards of quality, service, and ethical conduct among its members. Each member company pledges to promote public health and patient welfare by providing the highest quality testing services.

ACLA and its members have a strong interest in the proper resolution of this case. Respondents in effect claim ownership over a natural biochemical relationship. If they prevail, any researcher who discovers a chemical association in the human body will be able to claim a monopoly over any future

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[1] All parties have consented to the filing of this brief. The parties' letters of consent have been lodged with the Clerk of the Court. Pursuant to Rule 37.6, *amicus curiae* states that no counsel for a party has written this brief in whole or in part and that no person or entity, other than the *amicus curiae*, its members, or its counsel, has made a monetary contribution to the preparation or submission of this brief.

diagnostic test based on that association. Petitioner here began using a novel testing technique (the Abbott Laboratories assay) that is not covered by the disputed patent but that measures some of the same substances as the respondents' patented assays. This is not at all unusual. Independent laboratories frequently introduce new tests and improvements on existing tests. These innovations are sometimes developed in house at the independent laboratory company and sometimes developed by outside entities. No matter where they are developed, such innovations typically derive their clinical significance from previously known natural biological relationships.

Under the view of patentability taken in the decision below, these innovations either would not be brought to market at all or would become available only at higher prices and on a limited basis. Either way, laboratories' ability to provide new life-saving tests and patients' access to those tests would suffer. The result would be not just economic harm but also interference with ACLA's and its member laboratories' goal of providing the highest level of testing services.

SUMMARY OF ARGUMENT

Claim 13 of respondents' patent is extraordinary. It recites a "method" for detecting a deficiency of one of two vitamins that consists in its entirety of the following two steps: (1) assay body fluid for elevated levels of the amino acid homocysteine and related molecules, and (2) "correlate" elevated levels of those substances with the existence of a deficiency of one of the vitamins. To infringe claim 13, it is *not* necessary to use respondents' patented methods for performing the assaying step. Thus, the only real content to claim 13 is the scientific insight that deficiencies of certain vitamins are associated with elevated levels of homocysteine. This statistical relationship between chemicals in the human body, however, is a phenomenon of nature and therefore unpatentable.

A ruling for respondents would radically alter the patent regime in this country to the great detriment of clinical labora-

tory testing services. Nearly every clinical laboratory test involves an "assay" followed by the application of some kind of natural correlation. New tests and improvements on existing tests are being developed and introduced all the time. Invariably these innovations – many of which quite properly receive patent protection – build on and derive their significance from previously established biological relationships.

To hold claim 13 valid, however, is to say that the discoverers of those relationships can patent the relationships themselves and thereby gain the right to prevent doctors from using the results of any laboratory assays, even ones not covered by the patent. For example, the researchers who discovered the correlation between risk of coronary heart disease and levels of "bad" cholesterol could have gained the right to prevent doctors from using the results of any "bad" cholesterol measurement to assess risk of heart disease, and the researchers who discovered the correlation between the presence of prostate cancer and levels of prostate-specific antigen, or PSA, could have gained the right to prevent doctors from using the results of any PSA assay to screen for or monitor prostate cancer. That is not, and never has been, the law.

Claim 13 is not saved by following this Court's instructions in *Diamond* v. *Diehr*, 450 U.S. 175 (1981), to examine the method "as a whole." The only information in the claim other than the unpatentable natural relationship is an unspecified "assay" step. But the recital of this step is insignificant in context. To apply a natural correlation between two variables, one must somehow measure one of the variables. Of course, a particular method of measurement might well be the subject of a valid patent. A perfect example is the very patent at issue in this case, which describes novel homocysteine assay techniques in a set of claims that are conceded to be valid. Claim 13, by contrast, does not indicate how to perform the assay before plugging its results into the correlation; it merely directs that some kind of assay is needed. That is profoundly inadequate.

Claim 13 fails as well because it would extend, in violation of patent law and general principles of intellectual property protection, to every practical application of the natural principle it describes. Moreover, contrary to the suggestion of the United States in its earlier brief, the fact that the assay step of the "process" might entail the physical or chemical alteration of a sample of fluid is irrelevant to the claim's validity. The alleged infringement in this case is *doctors'* "correlation" of the assay results with vitamin deficiencies, not the clinical laboratories' performance of the assaying. Petitioner has been held liable for induced, not direct, infringement. Finally, unnecessarily broad language from several Federal Circuit decisions in conflict with this Court's precedents does not support the validity of claim 13.

ARGUMENT

I. The Disputed Patent Claim Is Invalid Because It Seeks To Protect Nothing More Than A Naturally Occurring Biochemical Relationship – A Quintessentially Unpatentable Discovery

This Court has said repeatedly, since at least as far back as the mid-19th century, that "a scientific truth * * * is not patentable invention," *Mackay Radio & Tel. Co.* v. *Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). "Phenomena of nature, though just discovered * * * are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972); accord *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981); *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 116 (1853). A patent claim that recites only scientific truth or natural phenomena is invalid because it does not describe a "process" or any other subject matter patentable under 35 U.S.C. § 101.

It is a matter of basic scientific knowledge that two B vitamins – cobalamin (also known as B_{12}) and folate (also known as

folic acid) – are necessary to break down the amino acid known as homocysteine in the human body's normal metabolic processes. If one of those vitamins is lacking, the body will not properly process homocysteine, and the level of homocysteine will therefore be elevated. The researchers who filed the '658 patent discovered that an abnormally high level of "total homocysteine" – meaning the combination of homocysteine and several related molecules – is a reliable signal of abnormally low levels of at least one of those B vitamins. Or, as the patent puts it: "It has now been discovered that an elevated level of total homocysteine in tissues of warmblooded animals correlates both with cobalamin deficiency and with folic acid deficiency." S.A. 11, col. 4, ll. 17-20.

This knowledge falls squarely in the category of unpatentable natural phenomena. The quantitative relationships between the levels of total homocysteine and the B vitamins are simply observable consequences of certain chemical processes that take place constantly in every cell in the human body. Like the qualities of certain bacteria that were found not to inhibit each other's ability to fix nitrogen in certain plants, see *Funk Bros.*, 333 U.S. at 130, the statistical associations in question here are "manifestations of laws of nature, free to all men and reserved exclusively to none," *ibid.*

There is no content to claim 13 beyond these natural biological relationships. Claim 13 sets forth two steps: (1) assay for – in other words, measure the amounts of – homocysteine, and (2) "correlate" the amounts of homocysteine with the existence of a deficiency in cobalamin or folate.

"Correlate" for present purposes has a meaning different from the word's usual one in research and clinical laboratory science. Normally "correlate" means "to establish a mutual or reciprocal relation" between variables, "to determine, establish, or show a usu. causal relationship between," "to put in relation with each other," "present or set forth so as to show relationship," etc. WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 511 (1986). For example, a researcher who discovers

that elevated levels of cholesterol are statistically associated with increased risk of heart disease has *correlated* cholesterol levels with risk of heart disease. Once that relationship is known, a physician who observes elevated cholesterol in a patient and infers that the patient has an increased risk of heart disease has not correlated the two variables at all but rather *applied* the correlation.

In this case, the relationship between levels of homocysteine and the B vitamins was established through research performed by the inventors of the '658 patent and others. The alleged infringement on the part of doctors is not correlating in its usual sense, because the doctors are not *establishing* the relationship between homocysteine and the B vitamins (each physician is not, for example, performing separate controlled experiments on large numbers of patients) but rather *applying* that relationship in specific instances as part of patient care.

The Federal Circuit interpreted "correlating" in claim 13 to mean "*relating* total homocysteine levels to cobalamin or folate deficiency," Pet. App. 12a (emphasis added) – that is, *applying* in a specific instance the previously established general relationship.[2] Thus correlating for present purposes means only conducting the intellectual exercise of applying the previously established relationship between elevated homocysteine and vitamin B deficiencies to a specific patient's homocysteine levels.

The first step of claim 13 – "assay" – can be performed by any means, whether patented or unpatented. Obviously the use of an assay not specified in the '658 patent cannot be an in-

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[2] The district court effectively interpreted "correlating" in the same way. Although the district court stated that it construed the term to mean "to establish a mutual or reciprocal relationship between," JA 60-61, it, like the Federal Circuit, obviously understood claim 13 to be drawn to the everyday business of applying a relationship rather than the far rarer undertaking of establishing one. See *ibid.* (holding that the term "describes a discrete step in a sequential process").

fringement of that patent, and respondents have never claimed that petitioner committed acts of infringement when it used the Abbott assay.[3] Moreover, homocysteine levels are routinely measured to screen for conditions entirely distinct from vitamin deficiency – in particular, risk of heart attack or stroke. See, *e.g.*, American Association for Clinical Chemistry, "Homocysteine," *in* Lab Tests Online, http://labtestsonline.org/understanding/analytes/homocysteine/glance.html; see also David S. Wald et al., *Homocysteine and Cardiovascular Disease: Evidence on Causality from a Meta-Analysis*, 325 BMJ 1202 (2002) (noting association between elevated homocysteine levels and cardiovascular disease). The patent is not addressed to the correlations between homocysteine and heart disease or stroke. Accordingly, merely assaying for homocysteine or total homocysteine cannot possibly infringe the patent. Thus infringement of claim 13 must occur with the performance of the second step – the "correlating" or "relating." See also Pet. App. 13a ("[T]he parties hinge the direct infringement issue solely on whether the physicians perform the correlating step.").

The relating step, however, as the Federal Circuit explained, "is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a. That is, this step consists of nothing more than applying (unpatentable) fundamental scientific knowledge to the results of an (unspecified) assay. To claim, as respondents have, an exclusive right to engage in that analysis is to arrogate impermissibly the biological relationship between homocysteine and the B vitamins.

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[3] Unlicensed performance of *respondents'* patented assaying methods would be an act of infringement, but only of claims in the '658 patent other than claim 13, and in any event petitioner has paid respondents for every assay it has conducted using their methods.

II. A Holding That Claim 13 Is Patentable Would Cripple Progress In Clinical Laboratory Testing

If respondents succeed in their effort to monopolize the natural statistical relationship between an elevated level of total homocysteine and the existence of a B vitamin deficiency, the harm to clinical laboratory services in this country will be immeasurable. Anyone who discovers any natural correlation in the human body with potential diagnostic significance will be able to block laboratories and physicians from administering tests based on that correlation, even when the tests did not exist at the time the correlation was discovered.

That is precisely what happened in this case. The Abbott total homocysteine assay did not exist at the time the '658 patent was issued. No one suggests that that assay standing alone infringes the '658 patent – just as no one disputes the validity of the claims in the '658 patent directed to the inventors' methods of assaying for total homocysteine. On the contrary, respondents contend that doctors infringed claim 13 of the '658 patent when they analyzed the results of the (non-infringing) Abbott assay. That is, respondents seek to prevent physicians from using any homocysteine assay at all in the diagnosis of the vitamin deficiencies where license agreements are lacking. Accepting respondents' position would pervert the purposes of patent law by stifling innovation rather than encouraging it.

The standard system for coding medical services – Current Procedural Terminology, or CPT, see AMERICAN MEDICAL ASSOCIATION, CURRENT PROCEDURAL TERMINOLOGY (2005) (hereinafter CPT 2006) – contains approximately 1100 codes for clinical laboratory tests. See CMS, 2006 CLINICAL DIAGNOSTIC LABORATORY FEE SCHEDULE (Nov. 16, 2005), available at http://www.cms.hhs.gov/ClinicalLabFeeSched/02_clinlab.asp. Each code corresponds to anywhere from one to dozens of commercially available assays. Nearly all of these at some level – and often at a level of far greater technical and diagnostic sophistication than the "method" in claim 13 – are based on a

"correlation" of some kind. After all, in every case, something must be tested, and the results of that test must be translated into clinically meaningful terms through the application of scientific knowledge about the relationships between variables.

Tests, moreover, are constantly being introduced and improved. See, *e.g.*, Kristian Linnet & James C. Boyd, *Selection and Analytical Evaluation of Methods – With Statistical Techniques*, *in* TIETZ TEXTBOOK OF CLINICAL CHEMISTRY AND MOLECULAR DIAGNOSTICS 353, 353 (Carl A. Burtis et al., eds., 4th ed. 2006) (hereinafter TIETZ TEXTBOOK). The 2006 set of CPT codes includes 29 new ones for laboratory procedures; the number was 19 for 2005. See CPT 2006, at 433; AMERICAN MEDICAL ASSOCIATION, CURRENT PROCEDURAL TERMINOLOGY 408 (2004). The number of new tests actually introduced each year is far greater because codes can correspond to multiple tests. In every instance, the new and improved products are inventive applications of previously discovered laws of nature. And, of course, those innovations are frequently the subjects of patents.

But, if the decision below is affirmed, the availability of new and improved tests would be entirely at the mercy of the person who first discovered the natural correlation that makes the test useful. Progress in clinical laboratory testing in this country never has been, and never should be, subject to such constraints. Several examples should illustrate just how extraordinary it really would be to hold that claim 13 states a patentable process.

Increased risk of coronary heart disease has been correlated with, among other things, elevated levels in the blood of LDL (low-density lipoprotein) cholesterol, also known as "bad" cholesterol. See, *e.g.*, Nader Rifai & G. Russell Warnick, *Lipids, Lipoproteins, Apolipoproteins, and Other Cardiovascular Risk Factors*, *in* TIETZ TEXTBOOK 903, 938. When doctors first began to focus on levels of LDL cholesterol, technology for measuring it directly was not widely available for clinical use. Instead, LDL levels were *estimated indirectly*

using a calculation based on the levels of (a) total cholesterol and (b) other categories of cholesterol besides LDL, all of which could be measured directly. See *id.* at 938, 948.

Today a variety of assays for directly measuring levels of "bad" cholesterol are commercially available. Some of these are "enzyme immunoassays," meaning that they use chemical reactions with substances that react specifically with LDL. Others involve isolating LDL cholesterol using chemicals that either selectively dissolve away the other cholesterol molecules but not LDL, or dissolve away LDL but not the other cholesterol molecules. Rifai & Warnick, *supra*, at 951. All have certain advantages over the indirect method: they can be readily automated, they avoid the distorted estimates that sometimes result from the indirect calculations, and a number of them appear to yield accurate results even when the patient does not fast before the blood is drawn. See *id.* at 942, 949, 952.

It follows from respondents' position that the researchers who established the correlation between elevated levels of LDL cholesterol and risk of coronary heart disease could have gained patent protection for a "method for detecting an increased risk of coronary heart disease comprising the steps of: (1) assaying a blood sample for an elevated level of LDL cholesterol; and (2) correlating an elevated level of LDL cholesterol in said blood sample with an increased risk of coronary heart disease." If that had happened, every time a doctor assessed risk of coronary heart disease using the results of an LDL cholesterol test[4] – including the newer assays that directly measure LDL cholesterol – the doctor would be committing patent infringement. This scenario is absurd, but the hypothetical facts are analytically indistinguishable from the present case. And this

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[4] Congress has specifically directed the Medicare program to pay for cholesterol and other lipid testing – a category that includes measurement of LDL levels – "for the early detection of cardiovascular disease (or abnormalities associated with an elevated risk of cardiovascular disease)." 42 U.S.C. § 1395x(xx)(1); *id.* § 1395x(s)(X).

analysis could be repeated for practically every test conducted by a clinical laboratory in this country.

To take another example, in the late 1980s and early 1990s, it became known that the presence of prostate cancer correlates with an elevated level in body fluids of a protein known as prostate-specific antigen, or PSA. See, *e.g.*, William J. Catalona et al., *Measurement of Prostate-Specific Antigen in Serum as a Screening Test for Prostate Cancer*, 324 N. ENG. J. MED. 1156 (1991). The seminal study, published in 1987, used an assay known as a "double-antibody radioimmunoassay" that was developed by one of the researchers. See Thomas A. Stamey et al., *Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate*, 317 N. ENG. J. MED. 909 (1987). This study demonstrated that PSA could be used to track the progress of prostate cancer in patients already known to have it. *Ibid.*

PSA testing is now a standard screen for prostate cancer. See, *e.g.*, Ian M. Thompson et al., *Prevalence of Prostate Cancer Among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter*, 350 N. ENG. J. MED. 2239 (2004); Michael J. Barry, *Prostate-Specific-Antigen Testing for Early Diagnosis of Prostate Cancer*, 344 N. ENG. J. MED. 1373 (2001). In fact, Congress has specifically required Medicare to cover, for all male Medicare beneficiaries over the age of 50, annual PSA testing (among other tests) "for the purpose of early detection of prostate cancer," 42 U.S.C. § 1395x(oo); *id.* § 1395x(s)(P).

Since the late 1980s, a wide variety of PSA assays have become commercially available. See, *e.g.*, Alexander Haese et al., *Clinical Evaluation of the Elecsys Total Prostate-Specific Antigen Assay on the Elecsys 1010 and 2010 Systems*, 48 CLINICAL CHEMISTRY 944 (2002); Robert L. Vessella et al., *Evaluation of the Abbott IMx® Automated Immunoassay of Prostate-Specific Antigen*, 38 CLINICAL CHEMISTRY 2044 (1992); Sunjay Jain et al., *Improving the Utility of Prostate Specific Antigen (PSA) in the Diagnosis of Prostate Cancer*, 78 POSTGRAD MED. J. 646 (2002); D. Patel et al., *A Comparison of*

Six Commercial Assays for Total and Free Prostate Specific Antigen (PSA), 85 BJU INT'L 686 (2000). Most of these assays are not radioimmunoassays, but other kinds of assays – enzyme immunoassays, "fluoroimmunoassays," and "chemiluminescence immunoassays." See Daniel W. Chan et al., *Tumor Markers*, *in* TIETZ TEXTBOOK 745, 760. The different types of assays are based on somewhat different chemical principles, and each assay uses different materials and equipment. See generally L.J. Kricka, *Principles of Immunochemical Techniques*, *in* TIETZ TEXTBOOK 219, 234-239.

Each assay typically has comparative advantages and disadvantages, including differences in sensitivity and ability to discriminate between different conditions. See Patel, *supra*, 85 BJU INT'L at 688-689. Most have the advantage over radioimmunoassays that they do not use radioactivity and thereby avoid the handling, storage, and disposal difficulties associated with it. Amid the development of all of these tests, however, the basic scientific principle that makes a PSA assay clinically useful – namely, the natural association between elevated PSA levels and prostate cancer – has been the same.

If claim 13 is upheld, the researchers who demonstrated (using a unique assay they had developed) the association between PSA levels and the progress of prostate cancer could have gained a valid patent claiming a "method" for tracking the progress of prostate cancer by (1) assaying a body fluid for the level of PSA; and (2) correlating the level of PSA with the stage of prostate cancer. The owners of that patent would have been able to claim infringement every time doctors use a PSA assay – *any* PSA assay, including all of the immunoassays developed after the hypothetical patent was issued – to monitor the course of prostate cancer or even to screen for it. Such a regime would have severely impeded advances in prostate cancer treatment and screening, if not foreclosed them entirely.

Because those responsible for advances in the diagnosis of risk of coronary heart disease using cholesterol measurements, and in the diagnosis of prostate cancer using PSA measure-

ments, did not attempt to patent claims as broad as claim 13 in the '658 patent, medical science has been able to advance to its current state without the payment of royalties and consequent discouragement of research that such patent claims would have brought about. A decision by this Court upholding claim 13, however, would permit those who make medical advances in the future to patent every potential application of the natural phenomena that underlie their inventions.

Our law does not permit, and never has permitted, such a result. Until now, the patent laws have facilitated innovation in medicine and laboratory science by conferring protection on novel applications of biological phenomena while leaving the phenomena themselves free for other inventors to use. Claim 13, however, arrogates the phenomenon itself. A ruling upholding it would be a major shift in our patent regime, one that would do incalculable damage to the business of ACLA's members and – more important – to the ability and incentives of researchers to make advances in the state of the art of medical diagnosis using laboratory tests.

III. This Court's Precedents Foreclose Any Argument That Claim 13 Discloses A Patentable Process Rather Than An Unpatentable Principle

A. Respondents cannot prevail by arguing that the validity of claim 13 should be determined with reference to the method "as a whole," *Diehr*, 450 U.S. at 188, as opposed to the patentability of individual steps in isolation. There is if anything less to this patent claim than meets the eye.

Viewed in its entirety, claim 13 recites nothing other than that one can ascertain the existence of a cobalamin or folate deficiency by measuring levels of homocysteine. That information, if not a mere reformulation of the natural relationships between levels of homocysteine and the vitamins, at most is a blindingly obvious corollary to those relationships. If it is known that elevated amounts of substance A signify diminished amounts of substance B or C, it follows automatically that one

can determine whether there are diminished amounts of substance B or C by measuring the levels of substance A.

A claim that recites only an unpatentable natural relationship and an additional insignificant step is not a "process" for purposes of 35 U.S.C. § 101. In *Diehr*, this Court squarely stated: "insignificant post-solution activity will not transform an unpatentable principle into a patentable process." 450 U.S. at 191-192. In this case there is no post-solution activity at all, let alone significant post-solution activity. There is an instruction regarding pre-solution activity – namely, "conduct some kind of assay" – but it is "insignificant" within the meaning of *Diehr*. Obviously, to apply the (unpatentable) knowledge that elevated total homocysteine correlates to vitamin deficiencies, one must first somehow measure the amounts of total homocysteine.

This is not to say that an assay itself is an insignificant invention. On the contrary, assay techniques frequently are the product of great ingenuity, and innumerable assays are protected by valid patents. Indeed, this case includes a perfect example. Claims 1 through 12 of the '658 patent are directed to the inventors' novel methods for determining total homocysteine levels. Those methods involve mixing specified substances together, taking readings on a mass spectrometer, and applying specified calculations to those results. By contrast, the "assay" step recited in claim 13 says nothing about how to perform the measurement. It simply says that, somehow, a measurement must be performed.

The *Diehr* patent was upheld even though the claimed process for curing rubber made use of a mathematical formula known as the Arrhenius equation. That is because the inventors did not seek to patent the equation itself, a basic law of chemistry that predicts the rate of a chemical reaction as a function of temperature, see, *e.g.*, NEIL JESPERSEN, GENERAL CHEMISTRY 453-455 (1997), and that had "long been used to calculate the cure time in rubber-molding" processes, 450 U.S. at 177 n.2. Rather, the inventors sought to protect only "the use of that equation in conjunction with all of the other steps in their

claimed process." *Id.* at 187. What made the *Diehr* invention innovative was the continuous measuring of temperature inside the rubber-curing mold, which permitted a computer programmed with the Arrhenius equation to update the cure time continuously, which in turn allowed the computer to open the mold at the right time automatically and thereby achieve a more precise curing time than would otherwise have been possible. *Id.* at 178-179. The *Diehr* patent thus contained a great deal more than the Arrhenius equation itself. By contrast, in *Parker* v. *Flook*, 437 U.S. 584 (1978), the patent failed because, as this Court explained in *Diehr*, it merely recited a mathematical formula with "token postsolution activity." 450 U.S. at 193 n.14.

There can be no serious dispute about which side of the *Diehr-Flook* divide this case is on. From the standpoint of patent law, the correlation between level of total homocysteine and existence of a cobalamin or folate deficiency is equivalent to the Arrhenius equation. Both describe relationships in nature. See *Diehr*, 450 U.S. at 186. In other words, the correlation between elevated homocysteine levels and vitamin deficiency is something like an equation created by the biochemistry of humans and other species. On one side are measurable variables – the levels of homocysteine. On the other side is the variable of ultimate interest – the existence or not of a B vitamin deficiency.

The only information in claim 13 other than the unpatentable scientific relationship is the intellectually insignificant teaching that the quantities of one of the substances must be measured. It is as if, to borrow the *Diehr* context, the claim said only: "A method for calculating the rate of a chemical reaction consisting of (1) measuring the temperature of the reacting substances; and (2) entering the temperature into the Arrhenius equation." Such a claim obviously would fail; it contains in substance nothing other than the unpatentable law of nature. Claim 13 is no different.

The *Flook* patent was defective in part because it recited a mathematical formula without explaining how the values of the variables in that formula were to be determined. See *Diehr*, 450 U.S. at 186 & n.10. Claim 13 has the same fatal flaw. Because it allows the homocysteine assay to be performed by any means at all, it does not specify how the values of the measurable variables are to be determined. It simply recites the insignificant point that one must get those values before using the equation to derive the information of ultimate interest. Again, a great deal of ingenuity may be required to get those values, and testing methods reflecting such ingenuity are the subject of valid portions of the '658 patent and countless others. But claim 13 describes nothing of the kind.

Accordingly, even when claim 13 is viewed as a whole, it still fails to describe a "process" within the meaning of 35 U.S.C. § 101.

B. Claim 13 also runs afoul of the related principle that a "process" claim comprising every "substantial practical application" of a natural principle is invalid because "in practical effect" such a claim "would be a patent on the [natural principle] itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972).

The statistical relationship between levels of homocysteine and the existence of a cobalamin or folate deficiency has "no substantial practical application" other than to diagnose those deficiencies. This relationship by its nature can be used to determine one thing, and one thing only: the possible existence of a deficiency. But that is exactly how broad claim 13 is: it purports to describe a "method for detecting a deficiency of cobalamin or folate." In other words, the claim is tautological and therefore extends to every practical application of the natural relationship that it recites.

A useful analogy here is the "merger" doctrine in copyright law. An axiom of copyright is that it will not protect an idea, only the particular expression of an idea. 4 NIMMER ON COPYRIGHT § 13.03[B][2][a]; 17 U.S.C. § 102(b); cf. *Benson*,

409 U.S. at 71 ("It is conceded that one may not patent an idea."). However, when "a given idea is inseparably tied to a particular expression" such that "there is a 'merger' of idea and expression" – when, in other words, there is but one way of reducing the general idea to a particular expression – courts may deny copyright protection to the expression in order to avoid conferring a monopoly on the idea. 4 NIMMER § 13.03[B][3].

The *Benson* teaching is similar. Only an application of a natural principle may be patented; the principle itself is unprotectable. However, where a patent claims every application of a natural principle (as in copyright when an idea can be expressed in only one way), that patent is invalid (just as in copyright the expression is not protected) because the alternative is to preempt the principle itself (just as in copyright the alternative is to create a monopoly on the idea).

Claim 13 is barred by these principles. It is tautologically constructed so as to claim every conceivable practical application of the natural relationship it discloses: make (by any means) the measurement that correlates with a medical condition and then look at the results to decide whether the medical condition might exist. There is simply no way of applying the statistical correlation between the level of total homocysteine and a deficiency of cobalamin or folate that does not entail "detecting a deficiency [or not] of cobalamin or folate" – and claim 13 by its terms extends to all such acts of detection.

C. There is no merit to any argument that claim 13 is valid because the assay step might, as the United States suggested in its certiorari-stage brief, "entail significant physical or chemical alteration of a sample of blood or bodily fluid." U.S. Br. 9. That is an argument in favor of allowing *assaying techniques* to be patentable – as indeed respondents' technique for assaying homocysteine is. Claims 1 through 12 of the '658 patent are unchallenged here. But a claim that purports to exclude others from making, using, or selling the "invention" consisting of conducting *any* assay and then "correlating" the results stands on a different footing. It bears repeating that the alleged patent

infringers in this case are doctors who *used* the assay results, not petitioner, which performed the assays and is accused of inducing infringement by encouraging the doctors to use the natural relationship between elevated homocysteine levels and vitamin deficiencies in interpreting the assay results.

It is true that this Court has said that "the clue to the patentability of a process claim that does not include particular machines" is the "[t]ransformation and reduction of an article 'to a different state or thing.'" *Benson*, 409 U.S. at 70 (quoting *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877)). But that is far from a holding that any transformation or reduction automatically makes a process patentable.

In *Diehr*, this Court explained:

> [W]hen a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, *is performing a function which the patent laws were designed to protect* (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101.

450 U.S. at 192 (emphasis added). The *Diehr* patent involved a series of steps amounting to a bona fide industrial process. A scientific principle – Arrhenius' equation – was used, but only in the service of a physical or chemical transformation – the curing of rubber. Claim 13 does precisely the reverse. Any chemical or physical transformation involved in the homocysteine assay is merely a means to the end of making a mental connection between levels of homocysteine and the existence of a vitamin deficiency. The entire purpose of the assay, and therefore any transformation it entails, is to collect information for use in the "correlating" step.

"Considered as a whole," therefore, claim 13 does not even come close to "performing a function which the patent laws were designed to protect" – although claims 1 through 12 of the same patent do. "Considered as a whole," claim 13 merely discloses a statistical relationship, albeit one with obvious

clinical relevance. Cf. *In re Warmerdam*, 33 F.3d 1354, 1360 (Fed. Cir. 1994) ("Warmerdam's argument that the claim implies physically measuring the contour of an object misses the point. As a whole, the claim involves no more than the manipulation of abstract ideas."); *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (rejecting patent claims where "[t]he sole physical process step" was performing poorly specified clinical tests on individuals to obtain data; court determined that "applicants are, in essence, claiming the mathematical algorithm"); *In re Meyer*, 688 F.2d 789, 794, 796 (C.C.P.A. 1982) (data-gathering step in claim that recited an algorithm did not satisfy 35 U.S.C. § 101). Because the patent laws were not "designed to protect" natural statistical relationships, the fact that the unspecified assay might involve some physical or chemical transformation is immaterial.

D. Unnecessarily broad language in several Federal Circuit cases is in tension with this Court's own precedents. Whatever the merits of those cases on their own facts, they do not provide legitimate support for the conclusion that claim 13 of the '658 patent describes a patentable process. The Federal Circuit has recently suggested that, for a mathematical algorithm "to be patentable," it need only "be applied in a 'useful' way," *State Street Bank & Trust Co.* v. *Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998); accord *AT&T Corp.* v. *Excel Comm'ns, Inc.*, 172 F.3d 1352, 1357 (Fed. Cir. 1999), or "produce[] 'a useful, concrete and tangible result,'" *State Street Bank & Trust Co.*, 149 F.3d at 1373 (quoting *In re Alappat*, 33 F.3d 1526, 1544 (Fed. Cir. 1994) (en banc)); accord *AT&T Corp.*, 172 F.3d at 1357. There are at least three reasons why the statements in these cases should not be applied to save claim 13.

First, these cases are addressed only to the troublesome subject of inventive algorithms implemented on a computer, as opposed to the kind of naturally occurring phenomena at issue here. Such algorithms are typically the product of technical ingenuity rather than simply a discovery of a relationship in

nature. Indeed, the patents at issue in the Federal Circuit cases have little in common with claim 13. The *State Street Bank & Trust Co.* patent was titled "Data Processing System for Hub and Spoke Financial Services Configuration." It was directed to an intricate investment system – implemented with a complex computer program – whereby mutual funds pool their assets in a portfolio organized as a partnership in order to reduce administrative expenses but gain the tax advantages of a partnership. 149 F.3d at 1370. The *AT&T Corp.* patent was titled "Call Message Recording for Telephone Systems." It disclosed a method for aiding long-distance telephone companies in their billing by allowing the computerized data-recording systems in the public telephone network to identify the long-distance carriers associated with the calling and called parties. 172 F.3d at 1353-1355. And the *Alappat* patent was drawn to a method for processing the input signals to a digital oscilloscope so as to generate a smooth waveform on the display. 33 F.3d at 1537-1539.

Second, even if it were appropriate to apply the Federal Circuit's recent cases on computer-implemented algorithms to claim 13, claim 13 still would fail because it does not disclose "a useful, concrete and tangible result." The only "result" in claim 13 is the ability to diagnosis a vitamin B deficiency – in other words, to apply the very natural correlation disclosed in the claim. This sort of tautology is a far cry from the tangible results in the Federal Circuit cases reviewed above – a novel investment structure that achieves significant cost savings, a key signpost in the electronic traffic that eventually resolves itself into long-distance telephone bills, and a better oscilloscope display.

Finally, to apply the Federal Circuit's standards for computer-implemented algorithms and hold that claim 13 satisfies them would produce a result in conflict with this Court's precedents. Such a holding would essentially say that a natural relationship *can* be patented, so long as it is paired with at least one practical application, no matter how little

inventive content there is in the pairing. As *Diehr*, *Flook*, and *Benson* make clear, that is not the law.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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DECEMBER 2005

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