Chapter 6

The Historic Ruling in the Patent Dispute

Should natural constituents formed in our own bodies be patentable? This was a particularly taxing problem for legal experts, and the first answer is believed to be that given by Learned Hand, the American judge who presided over the lawsuit involving infringement of the patent for the manufacture of adrenaline.

Jokichi Takamine, who wrote the patent for the manufacturing process himself, was instructed by the authorities to divide the patent claims into separate patent applications, and his work as a patent attorney to divide the original patent was well regarded. Judge Hand inspected the applications and passed the judgment that Takamine's manufacturing method was patentable, and he commended Takamine's research results in the courtroom as something that no one else had achieved until that time.

1. Unreliable nineteenth century medicines

In the latter half of the 19th century, the jobs of pharmacists and physicians were made harder by the fact that the activity of commercially available medicines, and particularly medicinal extracts of animal organs or herbal medicines, was very unpredictable.

Product quality varied enormously—some of these products had so little activity that they were virtually useless, while others were so strong that they put the lives of patients in danger. Needless to say, no pharmaceutical company wanted one of its products to be responsible for the death of a patient, so there was inevitably a tendency for the activity of medicines to become weaker.

As a result, physicians either made up their own prescriptions or dealt only with pharmacists they knew and trusted. Techniques for analysis and testing had yet to be developed, and so it was extremely difficult for sellers, buyers, or users to have any confidence in medicines.

George S. Davis, the charismatic proprietor of Parke, Davis & Co., had a shrewd grasp of the situation. He gathered together chemists and set about finding a way to solve this

problem. In 1879, he developed standardization processes using chemical assays, and the world's first "standardized medicine" went on the market. By 1883, the company's product list included 20 different types of "normal liquid."

At the start of the 1890s, pharmacological researchers began to notice that animal gland tissues were potential raw materials for new medicines. Parke, Davis & Co. was quick to respond to this new development, and in 1893 released dried thyroid for therapeutic use in treating hypothyroidism.

The techniques available at the time did not allow for even the most basic chemical analysis to be performed on medicines made from animal products, so in 1897 the company began introducing standardized assays for physiological activities that used experimental animals. We saw in the previous chapter how this quality control system was started on the understanding of Davis, the owner, with Dr. Houghton in charge.

Twenty years after the first system was introduced, the 1,100th product was standardized using this method (6-1). Doctors were particularly stringent in their demands for reliable quality control with useful products such as adrenaline, in which a mistaken dose could be life threatening, and this was of utmost importance for ensuring confidence in the pharmaceutical industry [Note 6-1].

Note 6-1.
Obtaining crystals of a substance does not necessarily guarantee its purity. However, if after repeated purifications the results of elemental analysis do not change and the numerical values for physiological activity do not rise any further—in other words, both sets of values reach a plateau—you can be more or less certain that you have the active principle in its pure form.

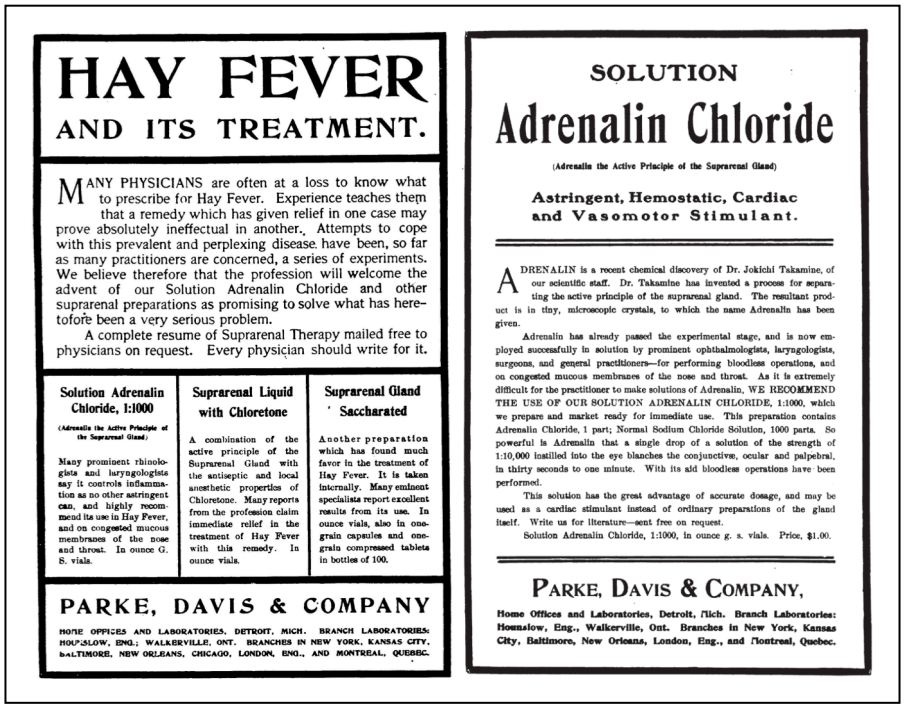
Abel gave the impression he was right at the fore front of the race to isolate the active principles of the adrenal glands. Inferring from his reports, it appears that he was receiving economic support for things like experimental materials from companies (6-2), but none of his research reports give an accurate description of activity, expressed as numerical values, corresponding to the purification stage.

2. Smooth commercialization

Parke, Davis & Co. steadily put its system of biological activity tests in place from around 1897 onward, and to make absolutely sure, the company also put together a chemical group for adrenal extracts under the leadership of Aldrich. The company launched its product "Solution Adrenalin Chloride" in 1901, the year after Wooyenaka and Aldrich successfully crystallized adrenaline. Aldrich wrote in a report that same year that he and Takamine had already collected samples of sufficient quantity for thorough research in the future (6-3), and it appeared that he was confident in the manufacturing method that had already enabled the company to put the product on the market.

The parent patent and the manufacturing expertise accumulated during that time were extremely valuable to Takamine and to Parke, Davis & Co. from the point of view of both social responsibility and business development. At the same time, the company was aggressively marketing its adrenaline products with publicity campaigns aimed at hospitals and doctors.

An advertisement from that time shows not only the ordinary preparations of the adrenal gland (saccharated) that had already been on sale, but also two other products: 0.1% adrenaline solution and this solution combined with chloretone (chlorobutanol) for its preservative and local anesthetic effects (6-4) [Figure 6-1].



HAY FEVER
AND ITS TREATMENT.

MANY PHYSICIANS are often at a loss to know what to prescribe for Hay Fever. Experience teaches them that a remedy which has given relief in one case may prove absolutely ineffectual in another. Attempts to cope with this prevalent and perplexing disease have been, so far as many practitioners are concerned, a series of experiments. We believe therefore that the profession will welcome the advent of our Solution Adrenalin Chloride and other suprarenal preparations as promising to solve what has heretofore been a very serious problem.

A complete resume of Suprarenal Therapy mailed free to physicians on request. Every physician should write for it.

Solution Adrenalin Chloride, 1:1000
(Adrenalin the Active Principle of the Suprarenal Gland)

Many prominent rhinologists and laryngologists say it controls inflammation as no other astringent can, and highly recommend its use in Hay Fever, and on congested mucous membranes of the nose and throat. In ounce G. S. vials.

Suprarenal Liquid with Chloretone

A combination of the active principle of the Suprarenal Gland with the antiseptic and local anesthetic properties of Chloretone. Many reports from the profession claim immediate relief in the treatment of Hay Fever with this remedy. In ounce vials.

Suprarenal Gland Saccharated

Another preparation which has found much favor in the treatment of Hay Fever. It is taken internally. Many eminent specialists report excellent results from its use. In ounce vials, also in one-grain capsules and one-grain compressed tablets in bottles of 100.

PARKE, DAVIS & COMPANY

HOME OFFICES AND LABORATORIES, DETROIT, MICH. BRANCH LABORATORIES: HOUNSLOW, ENG.; WALKERVILLE, ONT. BRANCHES IN NEW YORK, KANSAS CITY, BALTIMORE, NEW ORLEANS, CHICAGO, LONDON, ENG., AND MONTREAL, QUEBEC.

SOLUTION
Adrenalin Chloride
(Adrenalin the Active Principle of the Suprarenal Gland)

Astringent, Hemostatic, Cardiac and Vasomotor Stimulant.

ADRENALIN is a recent chemical discovery of Dr. Jokichi Takamine, of our scientific staff. Dr. Takamine has invented a process for separating the active principle of the suprarenal gland. The resultant product is in tiny, microscopic crystals, to which the name Adrenalin has been given.

Adrenalin has already passed the experimental stage, and is now employed successfully in solution by prominent ophthalmologists, laryngologists, surgeons, and general practitioners—for performing bloodless operations, and on congested mucous membranes of the nose and throat. As it is extremely difficult for the practitioner to make solutions of Adrenalin, WE RECOMMEND THE USE OF OUR SOLUTION ADRENALIN CHLORIDE, 1:1000, which we prepare and market ready for immediate use. This preparation contains Adrenalin Chloride, 1 part; Normal Sodium Chloride Solution, 1000 parts. So powerful is Adrenalin that a single drop of a solution of the strength of 1:10,000 instilled into the eye blanches the conjunctive, ocular and palpebral, in thirty seconds to one minute. With its aid bloodless operations have been performed.

This solution has the great advantage of accurate dosage, and may be used as a cardiac stimulant instead of ordinary preparations of the gland itself. Write us for literature—sent free on request.

Solution Adrenalin Chloride, 1:1000, in ounce g. s. vials. Price, $1.00.

PARKE, DAVIS & COMPANY,

Home Offices and Laboratories, Detroit, Mich. Branch Laboratories: Hounslow, Eng., Walkerville, Ont. Branches in New York, Kansas City, Baltimore, New Orleans, London, Eng., and Montreal, Quebec.

Figure 6-1. On the left is an advertisement for Solution Adrenalin Chloride from the year following the successful crystallization (*Homœopathic News*, May 1901). The advertisement states that the product is the invention of Dr. Jokichi Takamine, a member of the technical staff of Parke, Davis & Co., and it gives the conditions for which the product is indicated, the directions for use, and the content of the active ingredients. The price of a one-ounce bottle is one dollar. The advertisement on the right (*Homœopathic News*, August 1901) introduces two new products from adrenaline crystals alongside the suprarenal extract medicine that was already on sale. As we saw in Chapter 3, America was a country of vast grassy plains with many sufferers of hay fever—this was a market that no drug company could overlook. (Courtesy of HathiTrust)

A subsequent Parke, Davis & Co. medicine information magazine disclosed the composition of the basic Solution Adrenalin Chloride 1:1,000 solution, which was hydrochloric acid salt of adrenalin dissolved in physiological saline solution with 0.5% chloretone added (6-5).

Parke, Davis & Co. provided doctors with a detailed technical document, the introduction of which stated, "A member of our scientific staff, Dr. Jokichi Takamine, had finally perfected a process for separating the active principle of the suprarenal gland, to which he gave the name 'Adrenalin.'" The conditions for which the medicine was indicated were divided into 24 separate items. There was an introduction to clinical use of the medicine for each item that included the very latest information released the same year. These items were coryza, tonsillitis, eye disease, nasal surgery, epistaxis, hay fever, heart disease, surgery, otitis media, rhinitis, chronic hypertrophic, uterine inertia, metrorrhagia, hematuria, hemoptysis, post-partum hemorrhage, chloroform syncope, opium and morphine poisoning, rachitis, exophthalmic goiter hematemesis, pain, Addison's disease, laryngeal papilloma, and miscellaneous (6-6).

The information on the launch of a new product with guaranteed quality had a tremendous impact on doctors and researchers, who either prepared adrenal gland extract themselves or used medicinal extracts of animal organs such as the "Supra-renal Tabloid" of the British company Burroughs, Wellcome & Co.

Very soon, these doctors and researchers began to switch their allegiance to the new product from Parke, Davis & Co. A good example of this transition phase is the treatment report of the Late House Surgeon of New York City Hospital. This report includes three clinical cases, with a freshly prepared suprarenal emulsion used to treat two of these, and a 1: 5,000 adrenalin solution used to treat the other. The report states that the positive effects that were expected were found in all three cases (6-7).

3. The appearance of a rival product

The label of Solution Adrenalin Chloride lists the efficacy of the medicine, noting that it sustains the heart and prevents depression, and is effective for bloodless operations, congested mucous membranes, and hay fever among others. The list also included asthma from the initial launch onward.

We have seen in previous chapters that adrenal extract was known to be effective for all these conditions before adrenaline was crystallized, but when Parke, Davis & Co. made high-quality adrenaline available to doctors, cases of clinical treatment using the drug were reported in rapid succession.

An example of these is a report of the treatment of asthma by two doctors at Montefiore Home for Chronic Invalids, a hospital in New York.

The paper gives an explanation of the mode of action of adrenaline and then details the clinical treatment of five cases, three women and two men ages 17 to 63. In one case in particular, adrenaline brought great relief to an asthmatic patient (6-8, 6-9): "Male, aged sixty years; peddler; Wheezing and sonorous râles all over the chest. Five minutes after the injection of 6 minimus of adrenalin chloride, the respiration dropped to 30, and the pulse to 100; all râles disappeared and the patient slept quietly. A number of other cases were treated with adrenalin chloride hypodermatically with precisely the same results." The paper concludes, "In conformity with the angioparetic theory of an attack, the dose must be such as will cause prompt general vasoconstriction."

A new medicine with so many benefits was, of course, an irresistible target for pharmaceutical companies. It was only a matter of time before companies such as the German pharmaceutical manufacturers Hoechst A. G. and Bayer A. G. attempted to respond with their own synthetic compounds, while other companies rapidly developed similar products using manufacturing techniques that did not infringe on the patent for the production of adrenaline.

However, this was no easy matter—as we will discuss in more detail in Chapter 8, manufacturing a synthetic product for marketing as a medicine requires a high level of technological development.

In 1906, an academic report on a method of extraction and purification of adrenal gland extract was published by the chemical laboratory of the American company H. K. Mulford Co. (6-10). This was a complex process, in which the proteins were removed using trichloroacetic acid and then lead compounds, in order to extract the active principles. The references cited in this report included papers by Abel and von Fürth, but even though the authors were evidently aware of Parke, Davis & Co., no mention at all was made of the research results of Takamine or Aldrich. While no documents have been found to show exactly when this was, H. K. Mulford Co. began to market a dry powder preparation of the active principle of adrenal glands under the brand name "Adrin." One can easily suppose that the company did not make it a liquid preparation in order to avoid similarity to the products of Parke, Davis & Co.

4. The Patent dispute and a landmark ruling

Takamine had already transferred the patent license to Parke, Davis & Co., and the company naturally filed a lawsuit to prevent infringement of their patent. Presiding over the

patent infringement lawsuit was Judge Learned Hand of the Circuit Court of the Southern District of New York, who passed his ruling on April 28, 1911 (6-11): the lawsuit was won by Parke, Davis & Co. Takamine's method was ruled to be patentable, and the method of H. K. Mulford Co.was found to infringe upon the patent rights of Parke, Davis & Co.

This lawsuit called for an extremely difficult legal judgment, as it addressed the common understanding of the legal field of the day—that a product of nature could not be patented. At the same time, a challenging question such as this could not be tackled without a sound understanding of organic chemistry.

Judge Hand had no background in chemistry; nonetheless, he presided over the court and the judgment paper he read out was extremely detailed and showed a deep understanding of the science, clearly indicating the extent to which he had studied chemistry and other related fields to prepare himself for this lawsuit.

The paper ran to about 12,000 words, citing the work of Moore, von Fürth, and Abel, and was of a very high scientific level. The highlight is Judge Hand's declaration, "For he has been author of a valuable invention and has succeeded where the most expert have failed." The "he" in this case naturally referred to Takamine.

The judgment paper notes that Takamine was instructed by the patent office to divide the original patent (U.S. Patent No. 730,175), and even includes the details of the difficult negotiations he conducted during the application process. The original U.S. patent was divided into four patents (marked * in Table 6-1), and Hand acknowledged Takamine's work as a patent attorney [Note 6-2].

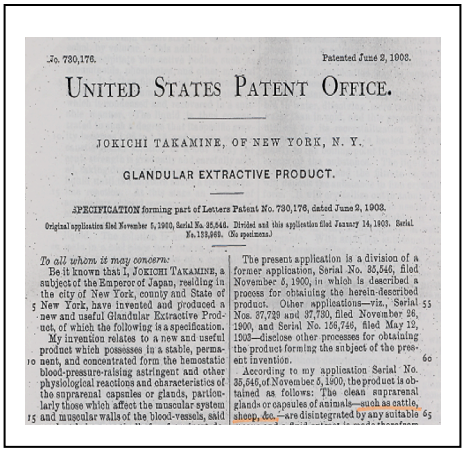
Note 6-2 Judge Hand found that H. K. Mulford Co. had infringed upon nine of the patent claims of U.S. Patent No. 730,176 (6-12) and four of the patent claims of U.S. Patent No. 753,177. The other four patents were not covered by the lawsuit (6-13), because "Adrin" was a dry powder preparation, and therefore only patents that corresponded to this were considered for possible infringement.

This was an historic ruling in the field of natural sciences that gave patent rights to a substance containing natural products, and has been the subject of numerous treatises. Since the discovery of the structure of DNA, the ruling is still studied by legal experts even today in relation to natural products that control life. Most recently, in November, 2010 the U.S. Patent and Trademark Office wrote in a brief that it would not recognize patents for DNA, and on June 13, 2013 the U.S. Federal Supreme Court ruled that patents for human genes would not be recognized.

Table 6-1. U.S. Patents applied by Jokichi Takamine

Patent No.	Date of application	Patented date	Divided patent		Summary of patent contents and sentence treatments
			Date of Acception	Patented date	
730,175 (Serial No. 35,546)	Nov. 5, 1900	June 2, 1903			This is the original patent which was asked to divide. This was patented with 4 other divided patents on the same date. In this patent, methods to extract crystals by combining such as extraction of impurities by using solvent, by changing pH of solution and so on. Number of claims: 9.
730,176* [Fig 6-2]	Nov. 5, 1900		Jan. 14, 1903	June 2, 1903	This is the patent divided from the patent No. 730,175. This was designated as the mother patent in the patent dispute. This has the suprarenal activity and show the characteristic color reactions and free from the inactive glandular tissues. Off white powder or crystal. Melting point: ca 207 °C. This shows alkalinity. This has blood pressure raising and hemostasis activities. 9 out of 16 patent claims were awarded as patent infringement.
753,177 Serial No. 156,747	May12, 1903	Feb.23, 1904			The patent applied on 1903 separately from the original patent and adopted as the patent in the patent suit. A stable method for the preparation of adrenaline aqueous solution. 4 claims out of 8 were recognized as patent infringement.
730,196*	Nov. 5, 1900		Nov. 26, 1900	June 2, 1903	Minerals and proteins were removed with alcohol. After removing pigments with ether, adrenaline was separated by using alkali, especially ammomia. Number of claims: 9.
730,197*	Nov. 5, 1900		Nov. 26, 1900	June 2, 1903	Minerals and proteins were removed with alcohol. After removing pigments with ether, adrenaline was separated from its alkaline solution by using neutralizing agents favorably with carbon dioxide. Number of claims: 9.
730,198*	Nov. 5, 1900		Jan. 8, 1901	June 2, 1903	Methods of preparation of aqueous crude extracts of suprarenal gland by using precipitation agents such as alcohol. Number of claims: 5.

The mark * indicates divided patents. Two patents under gray zone are the patents discussed in the patent suit together with the mother patent.



No. 730,176. Patented June 2, 1903.

UNITED STATES PATENT OFFICE.

JOKICHI TAKAMINE, OF NEW YORK, N. Y.

GLANDULAR EXTRACTIVE PRODUCT.

SPECIFICATION forming part of Letters Patent No. 730,176, dated June 2, 1903.

Original application filed November 5, 1900, Serial No. 35,546. Divided and this application filed January 14, 1903. Serial No. 138,969. (No specimens.)

To all whom it may concern:

Be it known that I, JOKICHI TAKAMINE, a subject of the Emperor of Japan, residing in the city of New York, county and State of New York, have invented and produced a new and useful Glandular Extractive Product, of which the following is a specification.

My invention relates to a new and useful product which possesses in a stable, permanent, and concentrated form the hemostatic blood-pressure-raising astringent and other physiological reactions and characteristics of the suprarenal capsules or glands, particularly those which affect the muscular system and muscular walls of the blood-vessels, said

The present application is a division of a former application, Serial No. 35,546, filed November 5, 1900, in which is described a process for obtaining the herein-described product. Other applications—viz., Serial Nos. 37,739 and 37,730, filed November 26, 1900, and Serial No. 156,746, filed May 12, 1903—disclose other processes for obtaining the product forming the subject of the present invention.

According to my application Serial No. 35,546, of November 5, 1900, the product is obtained as follows: The clean suprarenal glands or capsules of animals—such as cattle, sheep, &c.—are disintegrated by any suitable

Figure 6-2. The patent for adrenaline in the U.S. (U.S. Patent No. 730,176, shown in Table 6-1).

Learned Hand was an ideal judge, an outstanding man with a broad understanding of legal theory coupled with profound common sense. After he passed judgment in the adrenaline lawsuit, he went on to state his own personal philosophy in the courtroom.

"There is no surer way to misread any document than to read it literally," he once aptly said, and as a true patriot, he was worried about the confusing administration of justice in America and always encouraged efforts to improve it (6-14) (see Column 6-1 at the end of this chapter).

Hand was never appointed to be one of the nine Justices of the Supreme Court, but he was often seen as the "tenth justice" and has a place in American legal history as one of the country's most influential judges. After a lifetime in which his influence came to be felt across America, he passed away on August 18, 1961.

5. Maintaining the manufacturing method and product quality that were praised

When Judge Hand gave his opinion in the courtroom after ruling in favor of Parke, Davis & Co., it must have been an unexpected compliment for the two researchers, Takamine and Wooyenaka. As well as encouraging the two men, it must have given momentum to use the judgment in favor of the plaintiff, Parke Davis & Co., to the maximum to expand the company's business.

The quality and stability of "Adrenalin chloride (Takamine)" were highly regarded not just in the medical field but also among researchers. For example, a well-known research report by the American physiologist W. B. Cannon and his associates clearly describes this (6-15).

As a natural consequence of this, Parke, Davis & Co., which had a monopoly on the market with their product bearing the name of the active principle as "Adrenalin chloride (Takamine)," constantly paid large sums in patent and technical fees to Takamine.

Combined with the income from Taka=Diastase, this made him a very wealthy man. In his later life, his activities contributing to non-governmental diplomacy between Japan and the United States earned him the title of "Unofficial Ambassador."

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Jokichi Takamine studied the basics of patent law in the United Kingdom, and researched the latest information on the American patent system after the close of the exposition in New Orleans (1885). He continued his efforts even after that, and Judge Hand showed his

appreciation with the comment, "The applicant, after some struggles with the Patent Office, decided voluntarily to divide out the product claims."

However, as we shall see in the next chapter, the patent rights for which Takamine fought and won had a big impact on a ruling involving trademark rights.

Column 6-1.

Hand's philosophy

Judge Learned Hand's philosophy, which he put forward in the courtroom, was as follows:

"Whatever confusion the intricacy of the subject-matter causes, one fact stands out, which no one ought fairly to forget. Before Takamine's discovery the best experts were trying to get a practicable form of the active principle. The uses of the gland were so great that it became part of the usual therapy in the best form which was accessible. As soon as Takamine put out his discovery, other uses practically disappeared; by that I do not mean absolutely, but that the enormous proportion of use now is of Takamine's product. There has been no successful dispute as to that; hardly indeed any dispute at all. What use remains is, so far as the evidence shows, of the old dried glands, which everyone concedes to have been dangerous, at least for intravenous use. All this ought to count greatly for the validity of the patent, and Takamine has a great start, so to speak, from such facts. It is true that he overstates the degree of stability of his acid solution without any preservative. Strictly it is not in that form fit for sale about in drug stores where it may be kept for long even in a stoppered bottle; but commercial or practical stability is a somewhat elastic term, and this is a case where he should be entitled to a lenient construction, for he has been author of a valuable invention and has succeeded where the most expert have failed.

I cannot stop without calling attention to the extraordinary condition of the law which makes it possible for a man without any knowledge of even the rudiments of chemistry to pass upon such questions as these. The inordinate expense of time is the least of the resulting evils, for only a trained chemist is really capable of passing upon such facts, e.g., in this case the chemical character of Von Furth's so-called 'zinc compound,' or the presence of inactive organic substances. In Germany, where the national spirit eagerly seeks for all the assistance it can get from the whole range of human knowledge, they do quite differently. The court summons technical judges to whom technical questions are submitted and who can intelligently pass upon the issues without blindly groping among testimony upon matters wholly out of their ken. How long we shall continue to blunder along without the aid of unpartisan and authoritative scientific assistance in the administration of justice, no one knows; but all fair persons not conventionalized by provincial legal habits of mind ought, I should think, unite to effect some such advance." (6-11).

Judge Hand showed tremendous ability, and Hand's formula, which was the classic source of defect standards for planning defects, was used as a method for calculating liability for defects. It became the keystone of the Product Liability Law.

He was a strong protector of freedom of speech, and left behind many written works that encapsulated the spirit of the United States of America. *The Spirit of Liberty* (6-16), a collection of his essays and lectures, and *The Bill of Rights*, edited from a series of lectures, are his major legacy to the United States.

A short but moving oratory Hand gave in New York's Central Park on May 21, 1944 left his audience of thousands entranced. He spoke on faith, explaining that liberty lies in our minds and that when it dies, the constitution, the laws, and the courts can do nothing to save it.

"The spirit of liberty is the spirit which is not too sure that it is right; the spirit of liberty is the spirit which seeks to understand the minds of other men and women," he said.

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(6-13) US Patent No. 730,175; No. 730,196; No. 730,197; No. 730,198 (these were patented on June 2, 1903). No. 753,177 (patented on Feb. 23, 1904).

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