One of the effects of plowing back earnings is that the base upon which rate of return is computed grows, which requires a company to make increasing dollar profits to show the same profit rate on investment. For example, given an initial net worth of $20 million, and an annual net profit of $10 million (assumed retained for the purpose of this example) the rate of return would start at 50 percent and decline to 33⅓, 25, 20, 16.7, 14.2, 12.5, 11.1, and to 10 percent in the ninth year. When plowing back of earnings takes place, this type of calculation does not reveal the limited amount of time in which total profits may equal the investment.

Several charts designed to display the rapid recovery of investment through profits were introduced in the hearings and are reproduced here; these charts simply compare the net worth of a company as of a given year with its total profits made each year thereafter. No differentiation is made between the share of the profits reinvested in the company and the share paid out in dividends, as that is a matter of company policy. The question here is how the profits compare with the investment as of a few years earlier, regardless of how they are distributed between retained earnings and dividends.

The first of these charts relates to the Schering Corp. Schering had been seized by the Alien Property Custodian in 1942, and operated under Government control for 10 years. In March 1952, the Government sold the corporation to a syndicate headed by Merrill Lynch, Pierce, Fenner & Beane for $29,152,000. Through the first half of 1957 the corporation had shown net profits totaling $31,959,000 or $2.8 million more than the whole corporation had sold for only 5½ years earlier.

Growth of profits was faster for American Home Products Corp. and Smith Kline & French Laboratories. At the beginning of 1949 American Home Products had a net worth of $54,166,000. In the following 5 years, it earned $54,861,000, after allowing for some nonoperating income. In the next 3 years, 1954–56, net profits totaled $68 million. In the following 3 years, 1957–59, the company showed net profits of $127.7 million. Thus, as against an original net worth of $54 million, the company made net profits of a quarter of a billion dollars in 11 years.

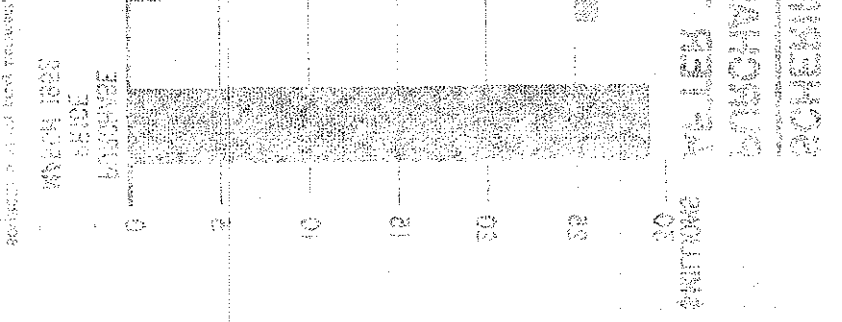
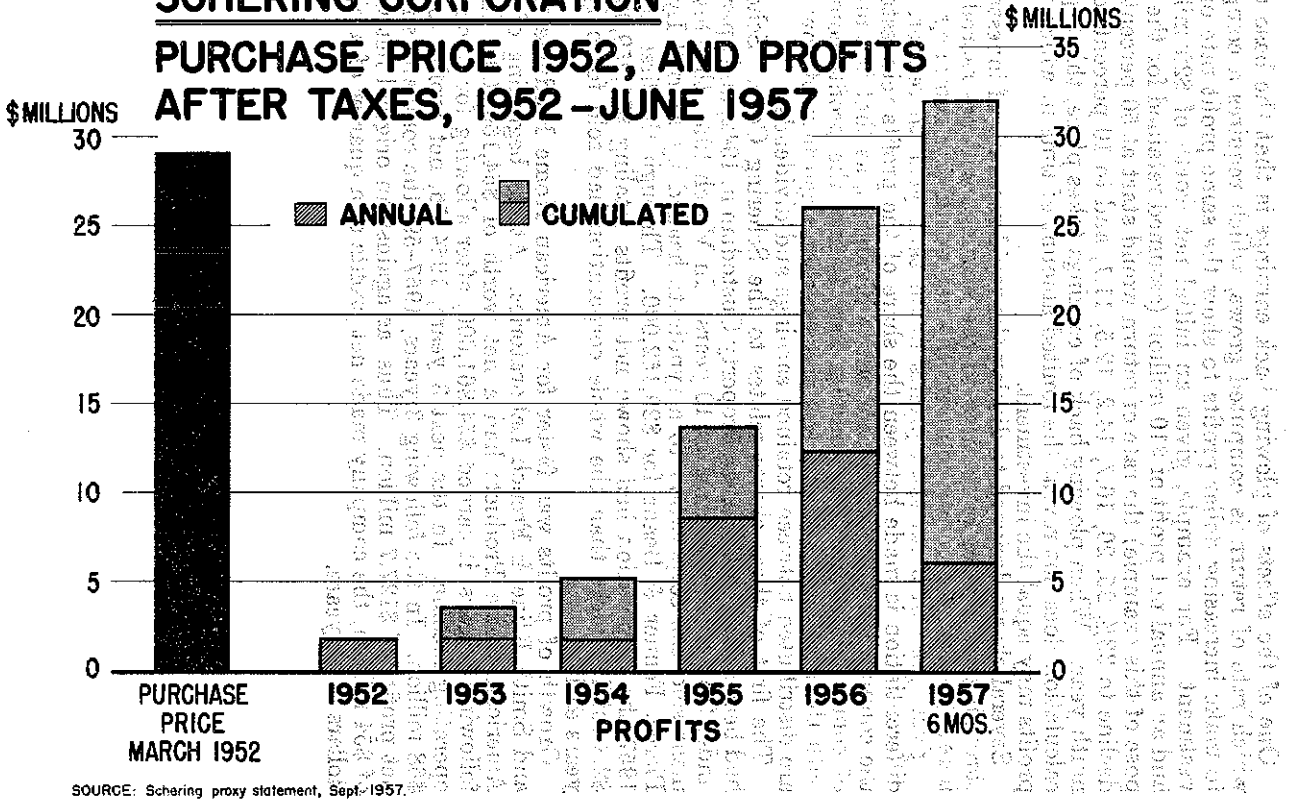


CHART 5

SCHERING CORPORATION

PURCHASE PRICE 1952, AND PROFITS AFTER TAXES, 1952–JUNE 1957

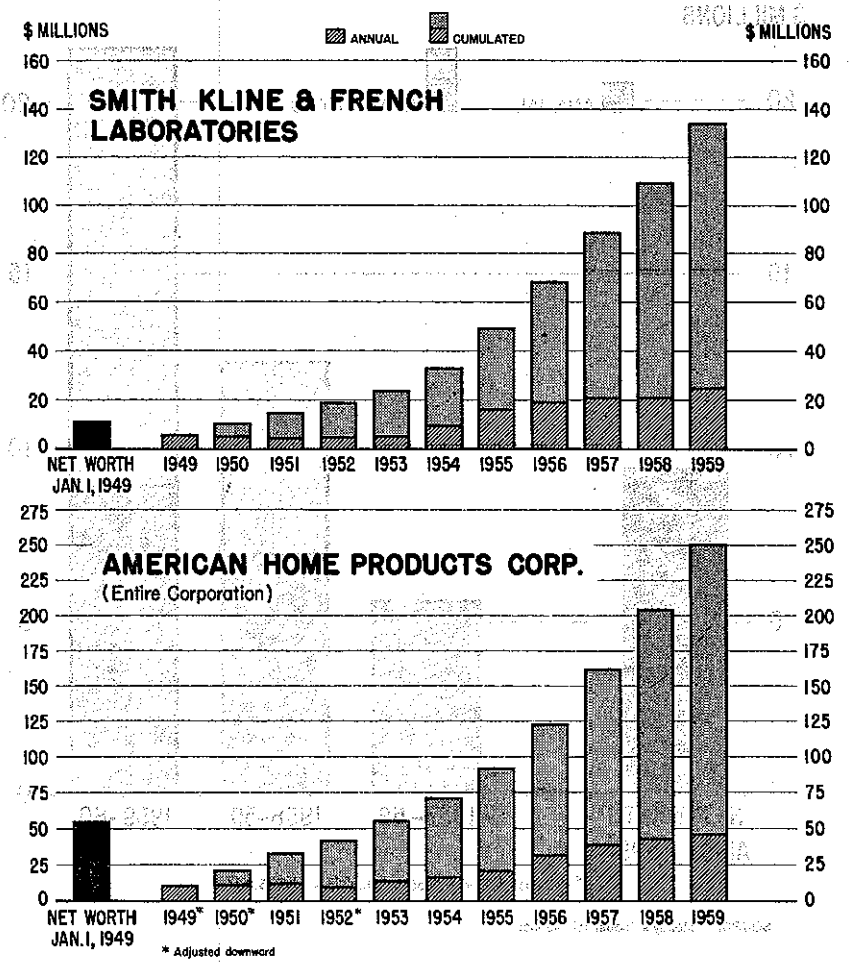


SOURCE: Schering proxy statement, Sept. 1957.

For Smith Kline & French the rate of net profit growth was even faster. It had a net worth of $10.8 million at the beginning of the period, which was nearly equaled by profits of $10.3 million in just the next 2 years. In 3 more years the company earned an additional $13.4 million profits. Thereafter profits moved up even more rapidly. Through 1959 total net profits had amounted to $134.2 million—12 times the net worth of $10.8 million of 11 years earlier.

CHART 6

NET WORTH JAN. 1, 1949, AND PROFITS AFTER TAXES, 1949-1959



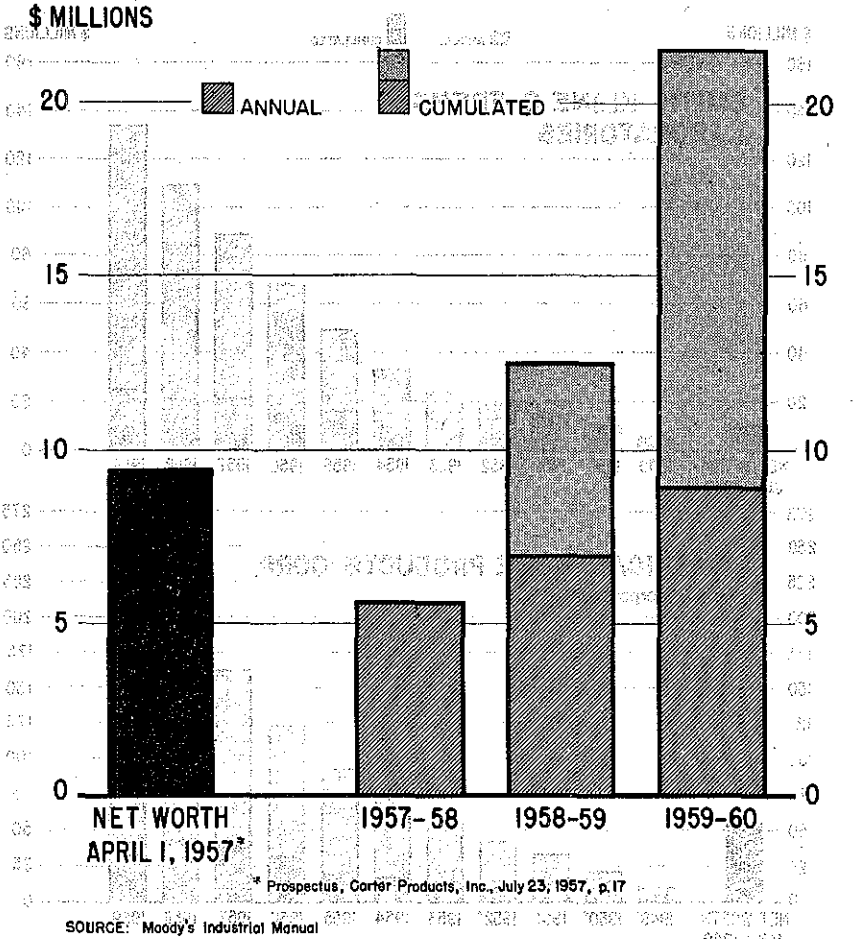
SOURCE: Moody's Industrials, Standard & Poor's, and FTC

The public record for Carter Products, Inc., is shorter, but the pattern is the same. Carter's net worth, published for the first time as of April 1, 1957, was $9.5 million. In 3 years its net profit has aggregated $21.5 million, well over double its net worth in April 1957.

CHART 7

CARTER PRODUCTS, INC.

NET WORTH APRIL 1, 1957, AND PROFITS AFTER TAXES, 1957-58 TO 1959-60



* Prospectus, Carter Products, Inc., July 23, 1957, p. 17

SOURCE: Moody's Industrial Manual

STOCK PRICES AND DIVIDENDS

With such a capacity for profitmaking, it was inevitable that the investing community would come to look with favor on the stocks of drug companies. Regardless of whether the profits were paid out in dividends or retained for further expansion—which would tend to make the securities all the more attractive to later investors—the investors in drug company stocks stood to gain. Since World War II this sequence of developments has certainly not been peculiar to the drug industry. What has been unusual is the extent of the gain. That drug companies well deserve the sobriquet of "Wall Street's Favorite" is illustrated by three exhibits introduced during the hearings. They are based on an assumed purchase of $10,000 worth of stock, at the market price, for three of the companies just discussed—American Home Products, Smith Kline & French, and Carter—for the same time periods as nearly as could be matched in public quotations.[77]

TABLE 23.—*American Home Products Corp.—Stock prices and dividends, 1949–59*

Stock opened on New York Stock Exchange on Jan. 3, 1949, at 25:[1] 400 shares could have been purchased for	$10,000
The stock was split 2 for 1 on Nov. 14, 1957.[2]	
Market value of 800 shares at closing price on Dec. 31, 1959 of 171½[3]	137,200
Gain, 11 years	127,200
Dividends:[2]	
1949, $1.70×400 shares	680
1950, $2×400 shares	800
1951, $2×400 shares	800
1952, $2×400 shares	800
1953, $2.30×400 shares	920
1954, $3×400 shares	1,200
1955, $3×400 shares	1,200
1956, $5×400 shares	2,000
1957, $6×400 shares	2,400
1958, $3.50×800 shares	2,800
1959, $3.60×800 shares	2,880
Total dividends, 11 years	16,480

[1] "Bank & Quotation Record," William B. Dana Co., February 1949.
[2] "Moody's Industrials."
[3] Wall Street Journal, Jan. 4, 1960.

[77] Hearings, pt. 16, pp. 8936, 9307.

TABLE 24.—*Smith Kline & French Laboratories—Stock prices and dividends, 11 years, 1949–59*

Stock quotations, Dec. 31, 1948, bid 41, asked 44: [1] At asked price, 225 shares could have been purchased for	$9,900
The stock was split, 2 for 1 on Sept. 13, 1950; 3 for 1 in November 1954; and 3 for 1 on May 29, 1959; or a total of 18 for 1 over this period. [2]	
Market value of 4,050 shares (225×18) at closing price on Dec. 31, 1959, of 60¼ [3]	244,013
Gain, 11 years	234,113
Dividends: [2]	
1949, $2.50×225 shares	562
1950, $1.50×225 shares	338
1950, $0.75×450 shares	338
1951, $1.50×450 shares	675
1952, $1.60×450 shares	720
1953, $1.75×450 shares	788
1954, $1.30×450 shares	585
1954, $0.50×1,350 shares	675
1955, $1.75×1,350 shares	2,362
1956, $2×1,350 shares	2,700
1957, $2.20×1,350 shares	2,970
1958, $2.60×1,350 shares	3,510
1959, $1.35×1,350 shares	1,822
1959, $0.50×4,050 shares	2,025
Total dividends, 11 years	20,070

[1] "Bank & Quotation Record," William B. Dana Co., February 1949.
[2] "Moody's Industrials".
[3] Wall Street Journal, Jan. 4, 1960.

TABLE 25.—*Carter Products, Inc.—Stock prices and dividends, 1957–59*

Public offering (secondary), July 23, 1957 [1]	$22.00
455 shares could have been purchased for	10,010
Market value on Dec. 31, 1959, 455 shares at closing price of 78½ [2]	35,718
Gain, 2½ years	25,708
Dividends: [3]	
1957, $0.15×455 shares	68
1958, $0.80×455 shares	364
1959, $1×455 shares	455
Total dividends, 2½ years	887

[1] Carter Products, Inc., prospectus, July 23, 1957.
[2] Wall Street Journal, Jan. 4, 1960.
[3] "Moody's Industrials."

In 11 years, American Home Products Corp. stock would have returned $16,480 in dividends for $10,000 invested. In addition, the capital value of the stock, as reflected in quotations on the New York Stock Exchange, would have risen to $137,200 at the end of 1959. Such a rise represents nearly 14 times the initial investment. Between 1949 and 1959 Smith Kline & French paid in dividends more than double the initial cost; its stock appreciated over 24 times. The stock was split 18 for 1 during this 11-year period (which incidentally, was in addition to a 20 for 1 stock split in 1947). The original investment of $10,000 at the beginning of 1949 was worth $244,000 at the end of 1959—an appreciation of $234,000—and the investor would in addition have received $20,000 in dividends.

The Carter record shows appreciation of 2½ times in 2½ years. Ten thousand dollars worth of stock in July 1957 was worth $35,718 in December 1959, and had yielded $887 in dividends in the process. No stock splits took place during this short period; Carter had split its stock 100 for 1 only 3 weeks before the secondary public offering.

DRUG OPERATIONS VERSUS NONDRUG BUSINESS

The profits made on sales in their drug operations alone, as shown above, were substantially higher than the companies made on their other activities. This can be seen by subtracting the data on their drug operations only from the corporate totals for income and expenses. Ten of the twenty-two companies classified themselves wholly as drug companies, with no other business.[78] The other 11 companies reported varying amounts of nondrug sales; i.e., they are to a greater or lesser extent "conglomerate" corporations. Table 26 compares for each of these companies the profits (after taxes) on sales for their drug operations only with the rates for the corporation as a whole minus its drug activities.

TABLE 26.—*11 conglomerate drug corporations*[1]*—Profits after taxes as percent of sales: Drug operations only versus corporation as a whole minus drug operations, 1958*

Company	Profits as a percent of sales	
	Drug operations only	Total corporation less drug operations
Carter Products, Inc	20.4	0
Olin Mathieson Chemical Corp	6.8	0.3
Eli Lilly & Co	13.3	1.7
Smith Kline & French Laboratories	17.2	2.7
American Cyanamid Co	15.6	3.8
Mead Johnson & Co	11.3	4.0
Bristol-Myers Co	9.9	5.2
Warner Lambert Pharmaceutical Co	13.4	6.4
Sterling Drug	10.1	7.4
American Home Products Corp	14.7	8.4
Vick Chemical Co	10.4	9.7

[1] No exact separation provided by Pfizer.

Source: Reports to subcommittee by companies on form I, "Comparative Statement of Income and Expense" and Moody's Industrials.

The extreme case is provided by Carter Products which made about $7 million profit on $31 million of drug sales plus $3 million of drug royalties; this put it at the top of the "drug operations only" list, with 20.4 percent net profit on sales of drugs. On $17 million sales of other business it lost $1,000, thus having a zero profit margin on nondrugs.

Olin Mathieson just about broke even on half a billion dollars worth of receipts from its combined operations in industries other than drugs. While it made 6.8 percent on its drug sales, its profits on its other activities averaged only one-third of 1 percent.[79]

[78] Pfizer simply estimated a flat 95 percent of each of its receipts and expenditures as applying to drugs, leaving a noncommittal and unusable 5 percent for other business. (Cf. hearings, pt. 18, p. 10527.)

[79] Prior to allocation of some $3.4 million in expenses, the drug divisions apparently made all the profit for the whole Olin Mathieson complex and earned 8.3 percent on drug sales. Cf. also footnote 41, p. 29.

The subcommittee was unable to obtain from these conglomerate firms data showing net worth devoted to drug operations. Consequently, it is impossible to compute rates of return on net worth for drug operations in contrast with other operations of the same companies. Inasmuch as the capital investment requirements in drugs as compared to the other industries in which these companies are engaged are not particularly high, there are reasonable grounds for assuming that the showings in terms of this measure would also be more favorable for their drug operations than their other activities.

Clearly, since it is the same management which governs the activities of these corporations in all of the industries in which they are engaged, the uniformly more favorable showings in drugs cannot be due solely to the greater efficiency of management in this industry, but must reflect other factors as well, such as the greater control of the market.

PART II

THE CONTROL OF THE MARKET

The extraordinary margins and profit rates in ethical drugs, as shown in part I of this report, are made possible by the existence of extremely high levels of concentration, with one or at most three large firms accounting for all of the output of most of the industry's products. A correlative condition is the poor position of smaller producers who probably face greater problems in getting their products distributed and used than in any other manufacturing industry. In some lines, small manufacturers are able to put their products on the market; but even though offered at prices substantially below those of the large firms, they usually are able to capture only a very small proportion of the market. There are a few lines, however, in which the price competition stemming from smaller enterprises has been sufficiently important to break down the rigid price structures of the large firms. Such price behavior is in striking contrast to that of similar products sold only by the major companies. Where effective competitive influences are absent, the methods of price determination followed by the large companies will inevitably yield margins and profit rates of the magnitudes shown earlier. This part of the report will be concerned with the concentration of the industry and the type of price behavior which results therefrom.

Chapter 4. Economic Concentration in Ethical Drugs

At the outset a differentiation should be made between concentration of production and concentration of sales, or "control of the market" as it is often termed. It happens that in this industry there is an unusually high degree of specialization on particular products among the industry's major companies. Thus, the nine principal hormone products are produced by only 7 of the 20 largest companies. The diabetic drugs are produced by only 5 of the 20, the tranquilizers by only 6. In sulfas there are only three producers, in vitamins only six, in antibiotics other than penicillin eight, and in penicillin seven. More often than not a large company which markets a broad line of ethical drugs will itself produce less than half of the products, buying the remainder from other major companies, or in some instances from small specialty houses. In such arrangements the drug is usually purchased in bulk form, with the buying company performing the functions of tableting and bottling. An inevitable consequence is that concentration in terms of sales is lower than in terms of production.

But this should not be taken to mean that the latter type of figure is wholly without significance. As long as the legal doctrine prevails that sellers are free to select their own customers, the producing firm is in an advantageous position vis-a-vis its competitors who also happen to be its customers. Although the degree of dependence may

be mitigated by purchase contracts, most contracts have a terminal date. If the supplying firm does not wish to renew the contract and there are only one or two other producers, the buying firm may have difficulty in securing a new source of supply. This may be particularly true if he has made substantial inroads on the producers' sales or has failed to adhere to an established price structure. If, as is true more often than not, the supplier is a monopolist, the buying firm may not wish to duplicate the plant, equipment, and know-how necessary for production; he may also encounter a patented intermediate, a process patent, or other legal barrier to production. Hence, it can be seen that figures on concentration of production, while usually overstating concentration in the market as of a given time, nevertheless have a unique significance with respect to the concentration of economic power in the long run.

Concentration of production

During the hearings, concentration ratios prepared by the subcommittee staff were placed in the record for 51 products in the major product groupings—hormones, diabetic drugs, tranquilizers, sulfas, vitamins, and antibiotics. These ratios, presented in chart 8, show the percentage share of total U.S. output in 1958 accounted for by each of the 15 major drug companies which produce 1 or more of these products.[1] The 51 products represent at least two-thirds of the total value of all ethical drugs in 1958.[2] In addition to indicating the percentage of output accounted for by each of the major companies, the chart shows with an "X" those instances where a company sells a product but does not produce it; where for some reason a company produces a product but does not sell it to the drug trade, a circle is drawn around the concentration ratio.

There are in all 87 instances in which the 15 major drug companies produce and sell the 51 products shown on the chart. There are 127 *X*'s on the chart representing instances where the drug company sells the drug but does not produce it; there are 14 instances of the anomalous situation where the company produces the drug but does not sell it.

Representing one extreme is Parke, Davis which sells 20 of the 51 products but produces only one (chloramphenicol), or a ratio of products sold to products produced of 20 to 1. At the other is Pfizer which also sells 20 products but manufactures 14, for a ratio of 1⅓ to 1.

[1] In addition, the subcommittee sent its questionnaire to seven other companies, each a major factor in the drug industry. None reported that it manufactured any of these 51 products. These companies are Mead Johnson, Norwich Pharmacal, G. D. Searle, Sterling Drug, U.S. Vitamin & Pharmaceutical, Vick Chemical, and Warner Lambert (hearings, pt. 21, p. 11742).

[2] Hearings, pt. 19, pp. 10772–10783. On the basis of information presented by Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, certain revisions in the original percentage figures were made; in addition, the information presented in the chart was expanded to indicate whether sales were made by a company which did not produce the product and whether sales were not made by companies which produced it (hearings, pt. 19, pp. 10773–10774, 10825; pt. 21, pp. 11740–11745).

CHART 8

SELECTED ETHICAL DRUGS

SALES BY, AND CONCENTRATION OF PRODUCTION OF, 15 MAJOR DRUG COMPANIES

NAME OF DRUG	ABBOTT	AM CYAN	AM HOME	BRISTOL-M	CARTER	CIBA	HOFFMANN LA R	LILLY	MERCK	OLIN-MATH.	PARKE, DAVIS	PFIZER	SCHERING	SMITH K&F	UPJOHN	PRODUCERS	SELLERS
HORMONES:																	
HYDROCORTISONE									33			28	X		39	3	4
CORTISONE									39				33		28	3	3
METHYLTESTOSTERONE	X					100		X			X	X	X		X	1	7
PREDNISOLONE									33			22	X		45	3	4
PREDNISONE									9				89		2	3	3
PROGESTERONE	X		X					X	X	X	X	X	X		100	1	9
TRIAMCINOLONE		17							83							2	2
DEXAMETHASONE									74				26			2	3
6-METHYL PREDNISOLONE						X									100	1	1
DIABETIC DRUGS:																	
INSULIN								77	4	19						3	3
DIABINESE												100				1	1
ORINASE															73	2	1
TRANQUILIZERS:																	
RESERPINE						56		X	X	X	X			X	X	2	7
HYDROXYZINE												100				1	1
CHLORPROMAZINE														100		1	1
PROCHLORPERAZINE														100		1	1
PERPHENAZINE													100			1	1
PROMAZINE			100													1	1
MEPROBAMATE			X		100[a]											1	2
SULFAS:																	
SULFISOXAZOLE							100									1	1
SULFADIAZINE	X	100						X	X	X	X			X	X	1	6
SULFAMETHOXYPYRIDAZINE		100									X					1	2
SULFAPYRIDINE		(100)						X	X		X					1	3
SULFAPYRIDINE, SODIUM		(100)							X							1	1
SUCCINYLSULFATHIAZOLE									100							1	1
PHTHALYLSULFATHIAZOLE									100							1	1
SULFATHIAZOLE	X	(73)	X					X	27		X		X		X	2	7
MADRIBON							100									1	1
VITAMINS:																	
A	X	X	X				28	X	(2)	X	X	36	X		X	5	10
B1	X	X	X				(44)	X	56	X	X	b		X	X	3	10
B2	X						(53)	X	30	X	X	(37)				4	5
B6	X	6					(46)	X	48	X	X	X		X	X	3	9
B12	X	X	X	X		X		X	100	X	X	X	X	X	X	1	13
E	X	X					X	X	100	X	X				X	1	8
BIOTIN							(100)	X								1	1
FOLIC ACID	3	65					X	X	X	X	X	X	X	X	32	3	11
ASCORBIC ACID	X	X	X				35	X	27	X	X	38	X	X	X	3	12
ANTIBIOTICS:																	
CHLORAMPHENICOL											100					1	1
AUREOMYCIN		100														1	1
DIHYDROSTREPTOMYCIN	X	(5)	X					10	(44)	25	X	16			X	5	7
ERYTHROMYCIN	35							65							X	2	3
NYSTATIN										100		X			X	1	3
OLEANDOMYCIN			X				X					100				1	3
TERRAMYCIN												100				1	1
STREPTOMYCIN		(6)	X					2	(15)	46	X	30			X	5	6
TETRACYCLINE		33		36						X		31			X	3	5
PENICILLIN:																	
BENZATHINE G			99									1				2	2
BENZATHINE V			100													1	1
POTASSIUM G	2		23	9				6	22	28	X	10	X		X	7	10
POTASSIUM V	17							83								2	2
PROCAINE G	1	X	16	1				22	(6)	28	X	26	X		X	7	10

LEGEND: Numerals – Produces and Sells
X – Sells Only
Circled Numerals – Produces Only

Numbers Represent Percentage of Production

[a] Carter controlled all production by license under patent although producing none itself

[b] Less than 1/2 percent

SOURCES: Producers: Reports by companies to the Subcommittee, for 1958

Sellers: Exhibit 263 of Dr. Austin Smith P.M.A., 1958-60, as adjusted

The ratio of products sold to products produced for each of the companies is as follows: [3]

Pfizer	1⅓ to 1.
Merck	1⅓ to 1.
Bristol-Myers	1⅓ to 1.
American Cyanamid (Lederle)	2 to 1.
CIBA	2 to 1.
Hoffmann-LaRoche	2 to 1.
Lilly	3 to 1.
American Home Products (Wyeth)	3 to 1.
Olin Mathieson (Squibb)	3 to 1.
Upjohn	3 to 1.
Abbott	3 to 1.
Schering	4 to 1.
Smith Kline & French	5 to 1.
Parke, Davis	20 to 1.

Thus, insofar as the 51 products are concerned, only 6 companies produce as many as half of the drug products which they sell. About half of the companies are faced with the possibility that their supplier may discontinue sales on at least two out of every three products which they market. In the degree of dependence by major companies upon others and particularly upon their competitors for their supplies, the ethical drug industry is unique among manufacturing industries.

There is still another way in which the concentration of production in this industry appears to be unique. It is an accepted maxim that among highly concentrated industries concentration typically takes the form of oligopoly (control of the few) rather than monopoly. Insofar as production is concerned, the drug industry represents a striking exception. This can be seen in the summary tabulation prepared from the preceding chart. It shows for the 51 products the number of firms required to produce 100 percent of the U.S. output:

TABLE 27.—*51 ethical drugs—Number of companies required to produce total U.S. output*

Type of drug	Number of drugs	Number of companies					
		1	2	3	4	5	7
Hormones	9	3	2	4			
Antidiabetics	3	1	[1] 1	1			
Tranquilizers	7	6	[2] 1				
Sulfas	9	8	1				
Vitamins	9	3		4	[3] 1	[4] 1	
Antibiotics (excluding penicillin)	9	5	1	1		2	
Penicillin	5	1	2				2
Total	51	27	8	10	1	3	2

[1] Includes Hoechst, not on table (Orinase).
[2] Reserpine: includes producer not among 22 major companies.
[3] Includes a producer of B-2 not on table.
[4] Includes 2 producers of A not on table.

In 27 of the products, or more than half, the entire U.S. output is produced by 1 of the 15 companies shown on chart 8. In sulfa drugs one company accounts for 100 percent of the output in eight of the nine products. In tranquilizers the condition of monopoly prevails

[3] The listing omits the unusual case of Carter which sells only one of the products, which, incidentally, is made for it.

in six of the seven products. In antibiotics (other than penicillin) the total output is produced by one company in five out of the nine products, and in hormones and vitamins, each, in three out of the nine. In 8 additional products concentration takes the form of "duopoly"—control by 2, while in 10 others the entire output is produced by 3 companies. Against the typical structure of concentration in manufacturing industries, it is indeed remarkable that in only 6 of the 51 products are there as many as 4 producers.

CONCENTRATION OF SALES

While the concentration of production reflects the underlying control of resources, it is the concentration of sales which indicates the control of the market. Where different products made by competing firms are substitutable for each other or where, because of buying and selling contracts among competitors, there are more sellers than producers, the concentration of sales will be lower than the concentration of production. Both of these conditions are exemplified in the broad spectrum antibiotics. Three of the broad spectrums are produced and sold exclusively by one company—Aureomycin by American Cyanamid, Chloromycetin by Parke, Davis, and Terramycin by Pfizer. Within the range of ailments for which they are substitutable for each other, the control of the market will be considerably less than the concentration of their production. There are, however, some ailments for which one or the other of these products may be considered to be the drug of choice, e.g., in the use of Chloromycetin to treat typhoid fever. Here the concentration in the market would tend to be identical with the concentration of production. An example of the second factor which results in a lower concentration of sales than of production is tetracycline, which is produced by three companies—American Cyanamid, Bristol-Myers, and Pfizer—but sold by five (the three producers plus Squibb and Upjohn).

Because of the importance of these two factors in the broad spectrum antibiotics, the subcommittee obtained, under subpena, data prepared by a recognized market research firm showing the concentration of sales for all broad spectrum antibiotics. Chart 9 presents this information, broken down between new prescriptions (i.e., sales made to the drug trade) and hospital purchases.

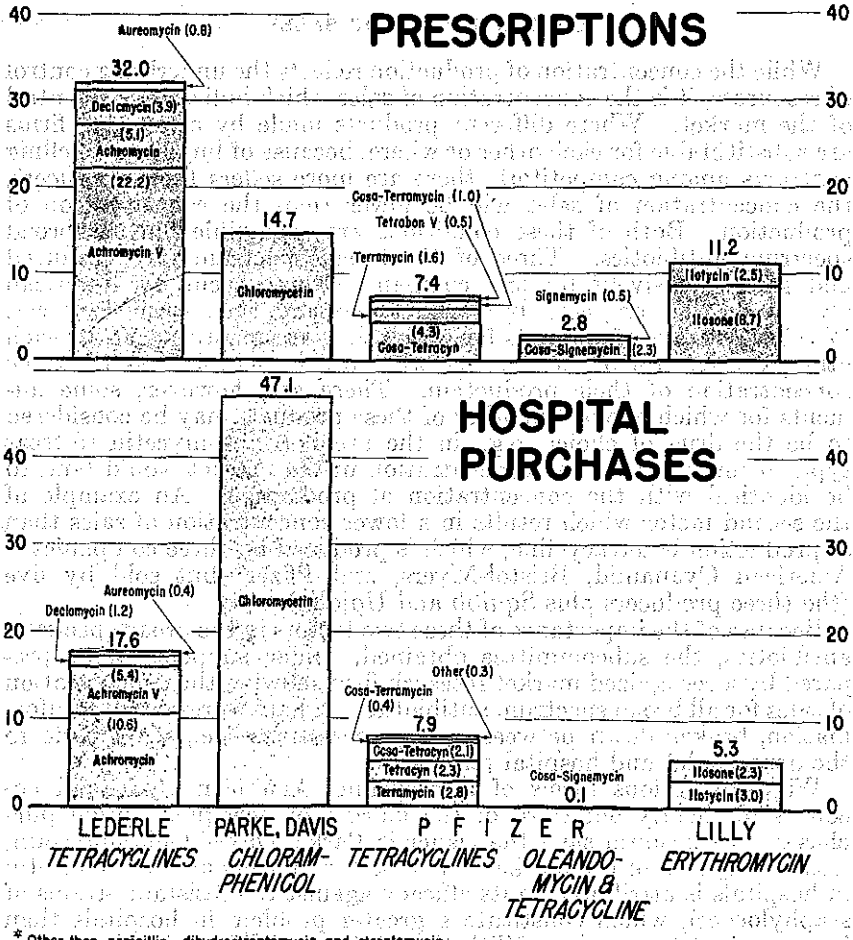
With its various forms of tetracycline, American Cyanamid accounts for nearly one-third of the market of new prescription purchases. In hospital sales the leader is Parke, Davis' Chloromycetin, with nearly half of the market. The better showing of Chloromycetin in hospitals is attributed to its efficacy against the resistant strains of staphylococci, which constitute a greater problem in hospitals than in outpatient treatment. With the addition of Pfizer the three companies—American Cyanamid, Parke, Davis, and Pfizer—account for 57 percent of the new prescription market and 73 percent of the hospital market. Such control of the market in the hands of only three companies represents by any standard a relatively high level of concentration, particularly in view of the breadth of the product grouping and the magnitude of its sales.

It is probably no mere accident that these three companies were the first to develop and market the broad spectrum antibiotics—American Cyanamid with Aureomycin (chlortetracycline) in 1948, Parke, Davis

CHART 9

LEADING ANTIBIOTICS—1959

PERCENT OF MARKET*



* Other than penicillin, dihydrostreptomycin and streptomycin

with Chloromycetin (chloramphenicol) in 1948, and Pfizer with Terramycin (oxytetracycline) in 1949. They were the first to promote broad spectrums with costly advertising and sales campaigns, and the first to introduce slight variations in their products designed to give the appearance of novelty and improvement. And of course they were the first in this area to obtain patents, which not only eliminated competition on these particular products but gave them much of the resources with which at least two of the three have been able to maintain their position against the challenges of newer broad spectrums.

Another product grouping for which statistical information is available on the concentration of the market is corticosteroids. During the hearings Merck supplied figures showing new prescriptions for all types of corticosteroids broken down by leading brands.[4] This information for the first 9 months of 1959, together with the generic name of the product and the identity of the company, is shown in the following table:

TABLE 28.—*Corticosteroid plain tablets—leading brands by percent total new prescriptions (January–September 1959)*

Brand	Product	Company	Percent total	Cumulative
Decadron	Dexamethasone	Merck	26.9	26.9
Aristocort	Triamcinolone	American Cyanamid	18.8	45.7
Medrol	6 Methyl Prednisolone	Upjohn	17.2	62.9
Meticorten	Prednisone	Schering	13.5	76.4
Kenacort	Triamcinolone	Squibb	5.5	81.9
Deronil	Dexamethasone	Schering	4.8	86.7
Sterane	Prednisolone	Pfizer	2.0	88.7
All others			11.3	100.0

Source: Supplied to subcommittee by Merck & Co.

Four brand name products accounted for over three-fourths of the market. The leading company was Merck with Decadron (its brand of dexamethasone). Virtually tied for second are American Cyanamid, which markets triamcinolone under the trade name of Aristocort, and Schering with two products, its brand of prednisone (Meticorten) and of dexamethasone (Deronil). Sales to the trade by small companies comprise only part of the "all other" figure of 11.3 percent. And these sales may soon be a thing of the past, since under contracts now in effect bulk sales of prednisone to small firms will cease if the patent is awarded to any of the major firms involved in the current interference proceedings at the Patent Office. Again the importance of being first is evident. The first corticosteroid was cortisone, introduced by Merck, while prednisone, the most improved of the earlier steroids, was first marketed in this country by Schering.

The control of the market is also relatively high in the other major categories of drug products. The diabetic patient who cannot be transferred to the new oral antidiabetic drugs will probably obtain his requirements of insulin from Lilly, which has 77 percent of the production, or the Squibb division of Olin Mathieson which accounts for 19 percent. Aside from Merck, which has only 4 percent of the production, none of the other 15 major drug companies offers insulin for sale. Patients who can be placed on oral medication are virtually limited to two drugs—tolbutamide (Orinase) and chlorpropamide (Diabinese); a complete monopoly of U.S. sales of the former is enjoyed by Upjohn and of the latter by Pfizer.[5] In diabetic drugs as in antibiotics the leading firm was the first on the scene. Although the basic patent on insulin held by the University of Toronto expired more than 20 years ago, through a series of improvement patents and licensing arrangements with Danish firms on newer types of insulin the international structure of patent control still remains largely

[4] Hearings, pt. 14, pp. 8174-8175.

[5] As compared to the other two, sales of a third oral antidiabetic drug, DBI, produced and sold entirely by U.S. Vitamin, are quite small.

intact. In this country where Lilly was the first and for a time the sole licensee, its dominant position has been unassailable for almost 40 years.

Among the "potent" tranquilizers, Smith Kline & French with its Thorazine and Compazine accounts for the major share of the sales, while in the "mild" drugs there is no close rival to meprobamate sold only by Carter Products and American Home Products.

Eight of the nine sulfa drugs are produced entirely by one or another of three firms—American Cyanamid, Hoffmann-LaRoche, and Merck. In four of the products, including the important new product Madribon, none of the other 15 major drug companies sells the product. And in two additional sulfa drugs, sales are made only by the producer and one of the other major companies. After earlier developments in Germany, France, and Italy, American Cyanamid entered the sulfa field in the midthirties. By 1936 it had a pilot plant in operation and shortly thereafter sulfathiazole was synthesized. American Cyanamid was also involved in the early development of sulfadiazine, sulfapyridine, and others. It is therefore not surprising that Cyanamid accounts for 100 percent of the production of four of the sulfas and 73 percent of a fifth.

The difference between concentration of production and of sales is probably greater in vitamins than in any of the other product groupings. Of the nine vitamins shown in chart 8, three are produced exclusively by Merck, while in three others Merck together with Hoffman-LaRoche produce 100 percent of one, 95 percent of another, and 89 of a third. In still another, Merck shares the entire output with Hoffman-LaRoche and Pfizer. But all of the vitamins are sold by at least one major company in addition to the producer. The inexplicable situation of production without sales is dramatized by Hoffman-LaRoche, long known as "Mr. Vitamin," which is a leading producer of four vitamins that it does not sell to the trade.

THE POSITION OF SMALL BUSINESS

As is obvious from the high levels of conentration in production and sales, small manufacturers are a relatively unimportant factor in the etnical drug industry. In three of the four leading steroid hormones, there is no small business [6] participation whatever, while in the fourth (the "predni" drugs) the small manufacturers presently engaged in the business will be deprived of their supply unless Syntex is awarded the patent. Small manufacturers are completely excluded not only from insulin but from the oral antidiabetic drugs as well. There is no small business participation in any of the broad spectrum antibiotics nor in the newer forms of penicillin. Neither meprobamate nor any of the "potent" pbenotbiazine tranquilizers is offered for sale by a small company. Perhaps because of competition with rauwolfia serpentina, of which it is a derivative, or a lack of confidence by CIBA in its patent, reserpine is the one tranquilizer sold by small companies. Drug industry spokesmen frequently emphasize the existence of "over 1,300" firms in the industry. Quite apart from the possible inaccuracy of this estimate, what is not emphasized is the relatively small (or more often nonexistent) share of the market occupied by small firms in most of the industry's leading products.

[6] For purposes of convenience, a small business in this industry is regarded as any firm other than the 22 major companies.

During the hearings, representatives of small firms engaged in the manufacture of ethical drugs described their difficulties in some detail which they attributed chiefly to patent restraints and to vast expenditures on advertising and sales promotion by their large rivals. It was emphasized, however, that this is an industry in which the amount of capital required to engage in production (as distinct from distribution) is not a significant deterrent. On this point Dr. Philip Berke, vice president of Formet Laboratories, Roselle, N.J. (which is itself a supplier of bulk prednisone) testified that with a capital expenditure which would be regarded as extremely small in most industries he could supply the prednisone requirements of the entire world:

> Mr. DIXON. Dr. Berke, if it were possible for you to obtain all of the patent rights and facilities to fully engage in the cortical steroid market, what would you say that the investment would take? Would you give me an opinion as to what investment it would take for you, or for a very small business firm, to go into this manufacturing process fully?
>
> Dr. BERKE. Well, of course, that depends on the quantities you want to produce, and if the research has been accomplished, the sum wouldn't be too large.
>
> Mr. DIXON. Would you say that you could do this on an investment of, say $4 or $5 million?
>
> Dr. BERKE. Oh, I could do it very well on that. We could do very well on $5 million. I would say that we could probably produce all the prednisone and prednisolone that is required in the world for a $5 million investment.[7]

In Dr. Berke's view it is not the amount of capital required but rather patent restrictions which constitute the chief barrier to small firms. He specifically objected to (*a*) the failure of large companies to license small firms when they license other large firms, (*b*) the right of a patent holder of an intermediate to prevent its use to produce a different finished product, and (*c*) the right of an owner of a product patent to prevent the sale of the product when manufactured by a new and improved process:

> If the holder of a patent issues a license or cross license to another firm, and by his own volition gives up his monopoly on the product, then it should be compulsory for him to license all other companies wishing a license regardless of the size of the company.
>
> In order not to retard research and development of new products, I would also suggest mandatory issuance of licenses in the case of compounds that are not to be marketed as such, but are to be used as intermediates for the production of other compounds.
>
> For example, a company receives a patent on product A which it markets as such. It should of course not be mandatory for the company to issue a license on product A to another firm who wishes to market the same product.
>
> However, it another company wishes to produce product A as an intermediate for producing an entirely different product,

[7] Hearings, pt. 14, p. 8056.

say product B, it should certainly be able to obtain a license from the holder of product A patent.

We also believe that the Patent Office should provide a more critical examination of patent applications, and in the case of steroids, which is a very complicated field, should request a sample of a new steroid claimed in the application, including all physical and chemical data to prove the compound structure so that if questioned at some future date, one could easily refer to the file sample for a recheck.

Another point of interest is the issuance of a product patent on a new steroid regardless of the yields obtained, and hence eventual cost to the consumer.

Let us assume a hypothetical case of a firm obtaining a product patent on a new steroid in which the reported yield is say 1 percent or even less of the starting material.

Let us further assume another firm, say a small manufacturer, is able to produce this new steroid at say a 90-percent yield. This latter firm can of course obtain a process patent, but unless it receives a license from the product patent holder, it can do absolutely nothing with its superior process. Such a condition stifles improved process research and can create high prices for the consumer.

I certainly do not know what legislation would be appropriate, but it seems to me that here too some compulsory licensing would be in order.[8]

One of the practices objected to by Dr. Berke—the licensing of other large companies but refusal to license small concerns—was illustrated by the case of meprobamate; Carter licenses one large firm, American Home Products, for sales in the U.S. market and another large company, American Cyanamid, for sales abroad, but no small firm is licensed to sell either at home or abroad.

The subcommittee obtained copies of voluminous correspondence between Carter and companies seeking licenses on meprobamate. Firms of all sizes, located in the far spots of the globe, sought the opportunity to share in this lucrative business. The smaller companies merely received a brushoff with a form letter. Negotiations with the large companies proceeded on the basis of whether they held patent monopolies on other drugs which could be combined with meprobamate in marketable mixtures. Indeed the marketability of combinations—where both products were subject to patent control—appeared to be more decisive in awakening interest in Carter Products than therapeutic usefulness. Dr. Paul Maney, of Maney Laboratories, informed the subcommittee that he approached Carter with a proposed combination of Neothylline, a theopyhlline derivative, with meprobamate, after he had received favorable reports from professors at the University of Iowa and medical experts on the therapeutic usefulness of the combination in the treatment of hypertension.[9] Carter was not interested in his proposal. Questioning by Senator Kefauver disclosed that the second drug proposed was not a patent monopoly, and was sold by many companies under generic name. This fact in itself would, under Carter's policy, make the com-

[8] Hearings, pt. 14, p. 8058-8059.
[9] Hearings, pt. 16, pp. 9339-9340.

bination unacceptable—no matter how useful it might be to the medical profession.

The evidence submitted to the subcommittee indicates that few of the smaller companies even attempt to secure licenses from the larger manufacturers, either under patent applications or issued patents.[10] The policy of polite refusal has become such an established practice in the drug industry that as Mr. Seymour N. Blackman, executive secretary of Premo Pharmaceutical Laboratories, put it, he didn't ask because "Mostly we knew it was futile, but we tried here and there." This witness had just testified: "I cannot tell you of any significant patent in the pharmaceutical field that we, and several of the smaller drug firms, have been licensed under." [11]

Even when a small company is the discoverer of an important new drug and has an excellent research organization, it still may encounter insurmountable difficulties. Such a case is provided by the example of Syntex Corp. of Mexico which is credited by the Pharmaceutical Manufacturers Association as being the originator of prednisone and is a party to the current interference proceeding on the basis of its discoveries in 1950. Being uncertain of the ultimate outcome of these proceedings in the Patent Office, Syntex approached Schering, the largest seller of prednisone, for a license and was refused. Beginning in 1956, Syntex then began to ship bulk prednisone into the U.S. market in substantial quantities, mostly to smaller companies who engaged in active price competition in sales to Government agencies and private hospitals. Schering then instituted an infringement action, which was countered with an infringement action by Syntex.[12]

At the time Mr. Francis Brown, president of Schering, appeared before the subcommittee, Senator Kefauver inquired about the current Schering-Syntex relationship and was informed an agreement had been reached. A request was made by the subcommittee for a copy of the agreement. In substance, the agreement provides that if Schering secures the patent, Syntex may sell in bulk only to Schering licensees, although it may sell "in pharmaceutical dosage form under its own label" (which, lacking a distribution organization, it has never done).

Syntex represents the case of a small independent company which gambled heavily on research. According to one expert, this company has one of the finest research groups in steroids in the world.[13] It applied for and received numerous important patents. It was the source of supply of smaller companies who injected competition into the prednisone market. With the import of the Syntex product an accomplished fact, Merck and Pfizer also began to make bulk sales. Bulk prices fell rapidly from 1955 to 1960.

Mr. Seymour N. Blackman of Premo told the subcommittee:

> I assure you there is no free ride in this industry, given by any of the big manufacturers. If they are selling, to us, in

[10] The single exception in the subcommittee's hearings was meprobamate (Miltown and Equanil) where hundreds of companies—large and small—from all over the world sought licenses to market this product.

[11] Important patents under which Premo requested a license, which was refused, are tetracycline (from Pfizer) and dexamethasone (from both Merck and Schering, who are involved in an interference). Neither company accepted Premo's offer to take a license under the application, despite an offer to pay royalty both before and after the issuance of a patent, and neither granted Premo's request for a bulk price.

[12] Apparently infringement of process patents held by each.

[13] Applezweig, "Steroid Research II," Drug and Cosmetic Industry, July 1958.

bulk; it is only because we can buy it from somebody else at the same price, in bulk.

If Merck sells prednisone to us at $2.35 a gram, it is because the same product is being offered by Syntex or Organon. All of them have contributed research work, and all of them make it back when they sell both in bulk and in specialty form.[14]

Whenever Syntex made a commercially significant development, an attempt was made to interest one of the large manufacturers in a license. Parke, Davis' steroid, Norlutin, is a product of Syntex research. However, the discouragements and difficulties encountered in attempting to break into the market itself or to make advantageous arrangements seemed insurmountable to the founders of the company. Syntex was acquired in 1958 by a U.S. investment company, and policies changed. In August 1959 an agreement was entered into between Syntex and Eli Lilly & Co. under which all new discoveries from the Syntex laboratories are exclusively licensed to Lilly, with Syntex retaining the right to sell in packaged form only under its own label. Thus it would appear that the kind of active price competition supplied by Syntex on prednisone in the midfifties has little likelihood of repetition on future products developed in the Syntex laboratories.

The experience of Syntex illustrates the difficulty of the small drug company in trying to compete successfully against the large drug producers. With a flying start from its research accomplishments of 1950, Syntex made the effort and for a time appeared to have a fighting chance. But its vitality was short lived; one blow followed another from 1955 onward until its demise as a competitive factor in the steroid field with the Lilly agreement in mid-1959.

Mr. Blackman stated that new products and processes have also been introduced by his company:

> Premo's trademark has been in use for 40 years. Over 100 Premo products have been approved for advertising, by the AMA Council on Pharmacy and Chemistry.
>
> Premo has contributed to the advancement of the pharmaceutical industry through modest and constant research and development of new and useful products.
>
> In brief, I shall mention a few developments:
>
> Penicillin aerosol, procaine penicillin, injectable suspensions.
>
> We introduced the first soluble penicillin tablet. We introduced the first Heparin syringeable at room temperature. Premo owns 37 patents.
>
> The Premo drain-away feature, which is used in all procaine penicillin suspensions today, is a patent which we have been proud to share by licensing other manufacturers such as Pfizer, Lilly, Merck, Abbott, Squibb, and Upjohn.
>
> Currently, we have a patent pending which covers a brand-new concept in the field of time-release formulation, and may be of significant importance to the entire industry.[15]

[14] Hearings, pt. 14, p. 8232.
[15] Hearings, pt. 14, p. 8211.

He went on to add, however, that because of the difficulties faced by the small company in promoting a new product or engaging in a patent controversy with a large concern, it was their general practice to sell the patent rights to their development on a "lump basis":

> Mr. BLACKMAN. Also, we have sold, outright, some of our patents because we just don't have the money to promote them.
>
> * * * * * * *
>
> When we issue licenses, we receive what is known as a paid-up royalty, one lump sum.
>
> Mr. PECK.[16] Then you have virtually sold your licenses?
>
> Mr. BLACKMAN. We have sold them, chiefly, because we know that a patent is little more than a piece of paper and a license to fight your competitors in court. I would much rather take a small return, if you would call it a gratuity, than to go into court and battle my larger competitors. If they are willing to take a license, under the patent, at a nominal fee, and we have received, for example, on this drain-away feature, some $70,000 in royalties, paid-up patents, both here and abroad, we are happy.[17]

In Mr. Blackman's opinion, the principal problem faced by the small drug manufacturer is the difficulty of competing in the face of the "tremendous" amounts spent by the large drug companies on advertising and promotion:

> As this investigation proceeds, it will become evident to you that the only real competition that we have in our field is the tremendous competition for the eye and ear of the physician, how many pages of advertising we can put out, how many samples we can distribute, how many detail men we can put in the field.
>
> These and these alone govern the ultimate acceptance of the product.[18]

The small company, according to Mr. Blackman, simply cannot afford to pay for the type and quantity of advertising now required for successful promotion. "Advertising costs", he said, "are so disproportionately expensive small companies cannot afford to make their way in the marketplace."[19] He gave as evidence the cost of the type of advertisements now appearing in medical journals and the expense of maintaining a force of detailmen:

> The smaller manufacturer, even if he had the means of applying additional research, to develop unique products for the market, would still lack the funds to properly propagandize and promote such items.

---

[16] Theodore Peck, former subcommittee minority counsel.

[17] Hearings, pt. 14, pp. 8253-8254.

[18] Hearings, pt. 14, pp. 8205-8206. As evidence of the volume of advertising and promotional effort, Mr. Blackman cited an article by Walter L. Griffith, director, product advertising and promotion, Parke, Davis & Co. which appeared in "Proceedings of Program, Mid-Year Conference, American College of Apothecaries," 1959:

"Today, the builder of better mousetraps will sell more mousetraps, only if he builds a path to the world and presents the advantages of his trap with more ingenuity and impact than his competitor.

"It is such activity as this which, in the aggregate, has caused the ethical pharmaceutical industry of this country to provide during the past year 3,790,908,000 pages of paid journal advertising; 741,213,700 direct mail impressions; and well in excess of 18 to 20 million physician and pharmacist calls" (ibid, p. 8215).

[19] Hearings, pt. 14, p. 8210.

As an illustration, Mr. Tobias Wagner, advertising director of Smith Kline & French, stated that his company spent $130,000 on eight mailings to physicians, merely devoted to the discussion of the hazards attending the use of a product called Thorazine.

From this, you might imagine the program attendant to advertising the attributes of this product, and then add additional costs for direct mailing, sampling, detailing, and various general advertising and you get a fantastic picture.

The tendency today is for the pharmaceutical company who, a few short years ago, considered a full-page journal ad, in color, sufficient to gather the physicians' attention, now uses 4-, 8-, and 16-page inserts. Some of these inserts actually assume the proportion of exhaustive monographs. Business is so good in the medical journal field that there are over 300 different journals which exist on the basis of paid advertising of ethical pharmaceutical specialties. It is estimated that in today's market, journal advertising, direct mail advertising, and sampling would require an expenditure of approximately $1 million to do an effective job in partially promoting a single ethical specialty.

This, however, is not the most expensive part of the advertising program. According to a speech delivered by Mr. Tobias Wagner, at a recent national pharmaceutical forum for pharmacy educators, he states:

"The well-trained detail man can do what medical ads and direct mail cannot do. The pharmaceutical company spends between $9 and $10 for every physician visit."

Couple this with the 200,000 physicians in the United States and we get a cost of $2 million for making only 1 detail call on each physician.

Well, it is not necessary to cover every physician with 1 detail, so, let us cover only one-half. It is therefore my conservative estimate that it has taken, in some cases, $2 and $3 million of initial advertising to bring certain new products into the marketplace, in the light of the tremendous pressure and competition for the physician's eye and ear.[20]

According to Mr. Blackman, Premo did try, without success, to emulate the larger companies; it established its own detail force, gave cocktail parties for physicians, etc.:

> These detail men were actually carefully schooled. They were headed up by experienced elder statesmen, as it were. They were given what we called the "canned detail." They were exercised in the pros and cons as to the merits and disadvantages of the products which they were advertising. And they were schooled, intelligently, as to how to answer questions on any given item that we were detailing, at any given time.
>
> * * * * *
>
> Senator HART. So far as the detail men who were employed by you are concerned, you would say that they con-

[20] Hearings, pt. 14, pp. 8218-8219.

tributed to the knowledge of a physician and his understanding of the product, is that right?

Mr. BLACKMAN. To a limited extent. Let's not beg the question. They were out there to sell our products to the physician.[21]

While the company's expenditure on journal advertising, sampling and detailing nearly tripled between 1948 and 1953, its net sales, while rising from $1.9 million in 1948 to $2.8 million in 1951, had by 1953 nearly fallen back to the 1948 level. In the next 2 years, despite a further increase in advertising and promotion, sales continued to decline.

By the end of the year 1956, the handwriting was on the wall, without doubt. The program, which we had inaugurated, while meeting initial success, fell through even though advertising expenses increased percentagewise and dollarwise.

I attribute the failure of this program to the tremendous increase in the advertising dollars spent by our large competitors, to the extent that our efforts appeared, in the market place, as a mere spark in a vast conflagration.[22]

Noting that the pharmaceutical industry had come to be referred to as Wall Street's "fair-haired boy," Mr. Blackman referred to new stock issues of the large companies and the existence of "a lot of money that could be spent in advertising pharmaceuticals":

Mr. KITTRIE.[23] I would like to learn more about your experience several years back, before 1956. I noticed in your old folder that you were advertising the fact that you have detail men. You were advertising the fact that you will make cocktail parties and other facilities available to anybody that would come to your place. You were making known the fact that you will invite groups from pharmaceutical colleges.

Now weren't you trying to do the same things that these large corporations are doing?

Mr. BLACKMAN. The answer is "Yes"; we tried, desperately, to emulate these large manufacturers, and, as I stated before, we didn't make it.[24]

Mr. Blackman estimated that three-quarters of a billion dollars a year is spent on drug promotion, much of which he regarded as pure waste in view of the nature of the demand:

I personally feel that the American public is overpaying at least three-quarters of a billion dollars, at wholesale prices, annually, for the medication which they purchase on prescription.

I arrive at this figure by examining the cost of approximately three-quarters of a billion dollars annually spent on advertising and sales promotion, coupled with almost another three-quarters of a billion dollars in net profits.

[21] Ibid., p. 8222.
[22] Hearings, pt. 14, p. 8215.
[23] Nicholas N. Kittrie, subcommittee minority counsel.
[24] Hearings, pt. 14, p. 8255.

> Spending three-quarters of a billion dollars in advertising to produce $2½ billion in sales seems to me to be excessive, especially since the products being propagandized are absolutely necessary and an artificial demand need not be created. It is my personal opinion that at least one-half of the sum spent on advertising and promotion is totally wasted.
>
> Likewise, I feel that the three-quarters of a billion dollars in net profits, before Federal corporate taxes, is excessive by at least 50 percent.
>
> This brings us to the figure of three-quarters of a billion dollars which the public pays unnecessarily.
>
> * * * * * * *
>
> I say that the market does exist. When we are sick, we must buy medication. This doesn't fall into the category of advertising for a washing machine, for example, to create a false demand, or to make a new car stylish. This field is something we need. It is like electricity or clothing. We don't have to create a false market; the market exists.[25]

Mr. Myron Pantzer, vice president of the Panray Corp., agreed that in the drug industry "advertising * * * costs a lot of money," and that his firm did not have the resources "to put several million dollars into the promotion of a product." That the necessity of making such outlays may actually impede the introduction of new and better drugs was implicit in his answer to the following question:

> Mr. DIXON. Suppose you came up with product X, a steroid hormone, that was, we will say, more potent than even dexamethasone, and actually had no side effects, none whatever. How would you get the message to the doctor?
>
> Mr. PANTZER. We as a company would, frankly, be stuck; we couldn't get the product off the ground.[26]

CHAPTER 5. THE BEHAVIOR AND DETERMINATION OF PRICE

THE BEHAVIOR OF PRICE

The difference in the behavior of administered versus market-determined prices, which has been noted in the subcommittee's earlier reports and hearings,[27] is nowhere more dramatically illustrated than in the drug industry. Where the only sellers consist of one or a few of the major companies, prices tend to be unchanged over long periods of time, with the different companies selling at identical prices. Where there is an "uncontrolled" bulk supply to which small manufacturers serving the trade can secure access, not only does the bulk price tend to be flexible, but the drug in packaged form will be offered at widely varying prices. This is true of both of the markets for drug products—sales to the regular trade (i.e., the retail drug store) and sales to institutional buyers (e.g. governmental bodies, hospitals, etc.). The difference in prices to the drug

[25] Hearings, pt. 14, pp. 8204-8205.
[26] Hearings, pt. 16, p. 9373.
[27] Cf. e.g., Subcommittee on Antitrust and Monopoly, "Administered Prices: Steel" S. Rept. 1387, 85th Cong., 2d sess., p. 8; and hearings, pt. 10, "Administered Price Inflation: Alternative Public Policies," pp. 4997-5013.

trade will be examined here in two of the few areas in which small firms are able to enter the market—penicillin and prednisone.

SALES TO THE DRUG TRADE

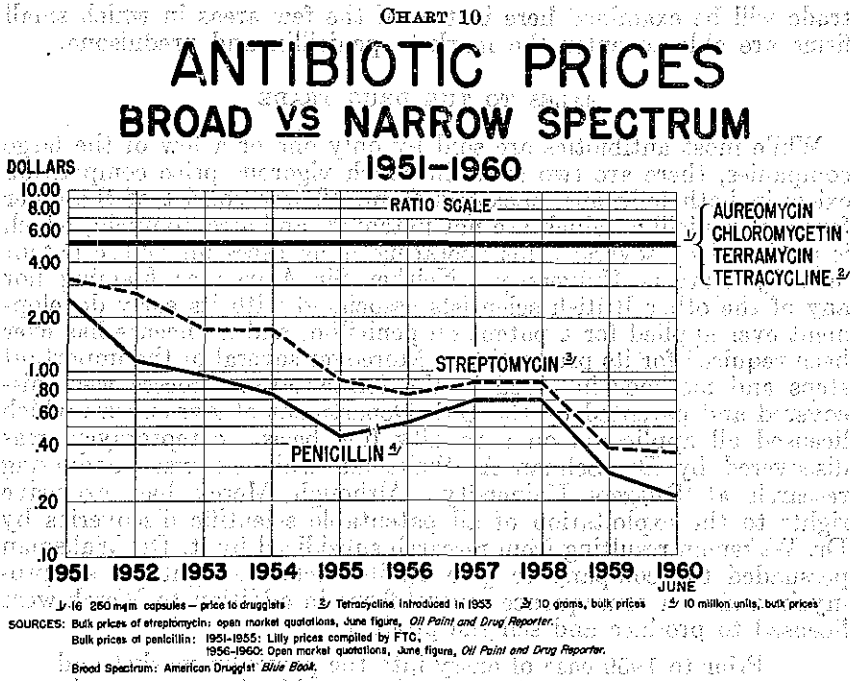
While most antibiotics are sold by only one or a few of the large companies, there are two areas in which vigorous price competition exists in both bulk and packaged form. These consist of the older forms of penicillin, which are not patented, and streptomycin, which is produced by several firms operating as licensees under the patent held by Rutgers University. Neither Sir Alexander Fleming nor any of the other British scientists associated with its early development ever applied for a patent on penicillin, and no license has ever been required for its production. Moreover several of the important steps and methods involved in the fermentation process were discovered and patented by the U.S. Department of Agriculture which licensed all applicants on a royalty free basis. Streptomycin was discovered by Dr. Selman A. Waksman while he was conducting research at Rutgers University. Although Merck had exclusive rights to the exploitation of all patentable scientific discoveries by Dr. Waksman resulting from research subsidized by it, Dr. Waksman persuaded the company to give up its exclusive rights to streptomycin and as a consequence several firms in addition to Merck were licensed to produce and sell the product:

> Prior to 1950 ease of entry into the penicillin market and ease of entry into the streptomycin-dihydrostreptomycin market existed in the antibiotics industry. This was an important factor in the development of price competition among the producers of streptomycin and dihydrostreptomycin, as well as among the producers of procaine penicillin. No restrictions existed with respect to production of sodium and potassium penicillin, as far as can be determined.[28]

The broad spectrum antibiotics, introduced in late 1948–50, were subject to a few price reductions during that early period. By 1951, however, the price of each had stabilized at the identical figure of $5.10 to the druggists,[29] where it has been maintained through the third quarter of 1960. What appears to be a straight black line near the top of chart 10 is the price trend of the broad spectrums during this 10-year period.[30] In contrast to the complete rigidity of the broad spectrums the bulk prices of penicillin and of streptomycin have fallen during the 10-year period about 90 percent—from $2.50 to 21 cents and from $3.24 to 36 cents, respectively.

[28] Federal Trade Commission, "Economic Report on Antibiotics Manufacture", 1958, p. 230.
[29] Federal Trade Commission, op. cit., p. 192.
[30] The type of quotation used for the broad spectrums is the price to the druggists for 16 capsules of 250 milligrams each, whereas the quotations used for penicillin and streptomycin are bulk prices. With the exception of sales by Bristol to Upjohn and Squibb there are no bulk sales of broad spectrum antibiotics. After an initial decline, Bristol's prices to Squibb and Upjohn have not fluctuated and of course are not a matter of regular public record.

CHART 10



During the hearings it was emphasized that any increases in costs affecting the broad spectrums should also have affected penicillin and streptomycin:

> Dr. BLAIR. Penicillin, streptomycin, and these broad-range antibiotics are all produced, with some modifications, by the same basic production method, except that Chloromycetin is now produced by an even cheaper process, being produced synthetically. This basic method is the fermentation process. From this chart, it is obvious that certain reductions in the cost of production have developed in the use of the fermentation process. Changes in production methods, greater efficiency, lowering costs, have in fact been reflected in lower prices of penicillin and streptomycin, but obviously, to the extent that they occurred in the production of the broad-spectrum antibiotics, have not been manifested in lower prices there.[31]

A similar contrast between administered and market-determined prices appears in chart 11, which compares the price trend of one of the newer patented forms of penicillin (V–Cillin), with the trends of the unpatented forms both in bulk and package. All of the prices relate to one company, Eli Lilly. To facilitate comparison they have been expressed on the basis of a common measure, 1 billion units.

As was true of the broad spectrums, the price trend of the patented penicillin is represented since its introduction in 1956 by a straight

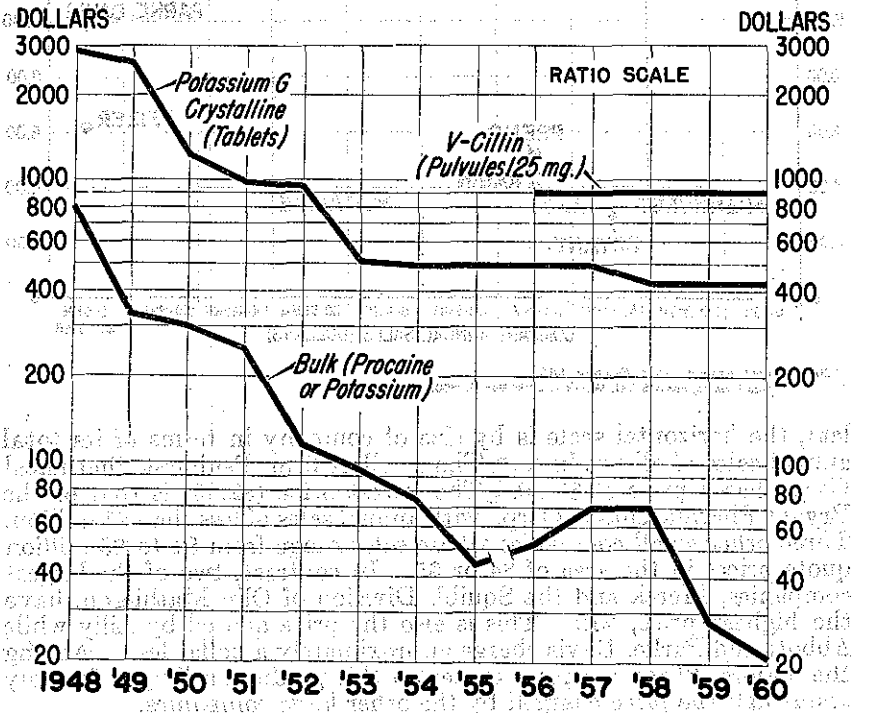
[31] Hearings, pt. 24, p. 13659.

CHART 11

PENICILLIN-LILLY

BULK PRICES COMPARED WITH PRICES TO DRUGGISTS

PER BILLION UNITS, 1948-1960

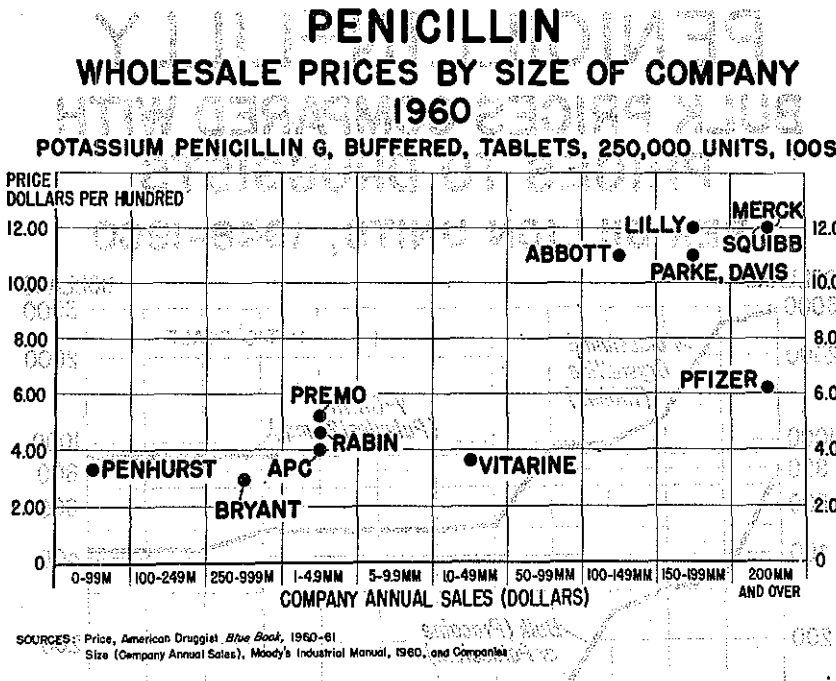


SOURCES: Bulk: 1948-1955, Lilly prices compiled by FTC.
1956-1960, Open market quotations, June figures, *Oil, Paint and Drug Reporter*
Dosage Forms: 1948, Drug Topics *Red Book*
1949-1960, American Druggist *Blue Book*, annual quotations

line. During that same period Lilly's price of the older type in tablet form declined by 14 percent while the bulk price dropped by 60 percent after an increase. The chart also reveals that up to very recent years the price trend of the older type closely paralleled that of the bulk price, after about a 1-year lag. Such parallelism, however, has recently been conspicuous by its absence, as the bulk price showed a further price decrease between 1958 and 1960 while the tablet price remained unchanged.

Small manufacturers sell the unpatented penicillin in finished form at prices substantially below those of the major companies. This is evident from chart 12 which shows the price differences between selected small companies and large concerns for penicillin potassium G tab-

CHART 12



SOURCES: Price, American Druggist *Blue Book*, 1960-61
Size (Company Annual Sales), Moody's Industrial Manual, 1960, and Companies

lets; the horizontal scale is by size of company in terms of its total annual sales of all products. The smallest firm, Penhurst Pharmacal Corp., has a price of $3.30. The lowest price ($2.95) is that of the Bryant Pharmaceutical Corp., with annual sales of less than $1 million. Three other small companies whose sales range from $1 to $5 million quote prices in the area of $4 or $5. In contrast, two of the largest companies, Merck and the Squibb Division of Olin Mathieson, have the highest price, $12. This is also the price quoted by Lilly while Abbott and Parke, Davis charge approximately a dollar less. Among the majors, Pfizer is a price cutter on this product, selling it for only about half the price charged by the other large companies.

During the hearings, Mr. Seymour N. Blackman of Premo contrasted Squibb's price for penicillin tablets [32] of $14.85 per hundred with his price of $3.75. On the question of possible differences in quality between the products of large and small companies the following exchange with Senator Hart took place:

> Mr. BLACKMAN. All antibiotic products, which would take this particular product within its scope, are controlled by your Food and Drug Administration.
>
> Not only in the usual way products are controlled, that is, by picking up shipments in interstate commerce and examining them for their labeled potency, but the Food and Drug Administration, on antibiotic products, requires that before a pharmaceutical manufacturer releases the product for sale, he must present the sample to the Food and Drug Administration plus an analysis, and the product is not released for sale until the Food and Drug Administration runs their own

[32] A different dosage form from the previous example.

parallel analysis and certifies that the product is actually what the label says it is.

So, it is fortuitous that the product which you pick is not only the same because I say so, but it is the same because your Food and Drug Administration says so, and has proved it.

Senator HART. Does the Food and Drug Administration say that both of these meet minimum standards, and does it also express any opinion as to how far one or the other exceeds the minimum?

Mr. BLACKMAN. The Food and Drug Administration will not allow either Squibb or Premo to exceed or come under the requirements. There are definite specifications as to how much penicillin you may have in a tablet. It can't be more or less, within certain limits, of the labeled requirements. These limits are close, and if, for example, we have 1 or 2 percent more penicillin in our tablet than Squibb, it would be inconsequential as far as the therapeutic efficacy of the product is concerned.[33]

The price differences among the major companies on unpatented penicillin are not to be found in the patented broad spectrum antibiotics. This is brought out by table 29, which shows for the various dosage forms of tetracycline, Aureomycin and Terramycin, the price to the druggist of each of the sellers.[34]

TABLE 29.—*Identity of prices to druggists—Tetracycline, Aureomycin, and Terramycin*

	Tetracycline					Cyanamid Aureomycin	Pfizer Terramycin
	Cyanamid Achromycin	Pfizer Tetracyn	Bristol Polycycline	Squibb Steclin	Upjohn Panmycin		
Capsules:							
100 mg. 25's	$3.61	$3.61	$3.61	$3.61	$3.61	$3.61	$3.60
100 mg. 100's	13.77	13.77	13.77	13.77	13.77	13.77	13.77
250 mg. 16's	5.10	5.10	5.10	5.10	5.10	5.10	5.10
250 mg. 100's	30.60	30.60	30.60	30.60	30.60	30.60	30.60
Intramuscular: 100 mg. vial	.94	.94	.94	.94	.94	----------	.94
Intravenous:							
250 mg. vial	1.62	1.62	1.62	1.62	1.62	1.62	1.62
500 mg. vial	2.91	2.91	2.91	2.91	2.91	2.91	2.90
Ped. drops: 100 mg./cc. 10 cc	1.47	1.47	1.47	1.47	1.47	1.47	1.47
Oral susp.: 250 mg./5 cc., 1 oz	2.54	2.55	2.54	2.54	2.55	----------	2.55
Syrup:							
125 mg./5 cc., 2 oz	2.54	2.55	2.54	2.54	2.55	----------	2.55
125 mg./5 cc., 16 oz	18.36	18.36	18.36	----------	18.36	18.36	18.36

Source: FTC, "Proposed Findings of Fact and Conclusions of Fact and Law" (June 1960), p. 375.

For each of the dosage forms the five companies selling tetracycline charge the same price, which also happens to be the price charged by American Cyanamid for Aureomycin and by Pfizer for Terramycin. From the 94 cents which each charges for a 100-milligram vial for intramuscular injection to the $18.36 for 16 ounces of 125-milligram syrup to the $30.60 for 100 capsules of 250 milligrams, not a single variation of more than 1 cent among the companies is to be found.

[33] Hearings, pt. 14, pp. 8208–8209.
[34] Hearings, pt. 24, p. 13667.

Similar identity within 2 cents is to be found in the suggested resale prices to consumers.[35]

TABLE 30.—*Identity of suggested resale prices to consumers, Tetracycline, Aureomycin, and Terramycin*

	Tetracycline					Cyanamid Aureomycin	Pfizer Terramycin
	Cyanamid Achromycin	Pfizer Tetracyn	Bristol Polycycline	Squibb Steclin	Upjohn Panmycin		
Capsules:							
100 mg. 25's	$6.02	$6.02	$6.02	$6.02	$6.02	$6.02	$6.00
100 mg. 100's	22.95	22.95	22.95	22.95	22.95	22.95	22.95
250 mg. 16's	8.50	8.50	8.50	8.50	8.50	8.50	8.50
250 mg. 100's	51.00	51.00	51.00	51.00	51.00	51.00	51.00
Intramuscular: 100 mg. vial	1.56	1.56	1.56	1.57	1.57		1.57
Intravenous:							
250 mg. vial	2.70	2.70	2.70	2.70	2.70	2.70	2.70
500 mg. vial	4.85	4.85	4.85	4.85	4.85	4.85	4.85
Ped. drops: 100 mg./cc. 10cc.	2.45	2.45	2.45	2.45	2.45	2.45	2.45
Oral susp.: 250 mg./5 cc. 1 oz.	4.24	4.25	4.24	4.23	4.25		4.25
Syrup:							
125 mg./5 cc. 2 oz.	4.24	4.25	4.24	4.23	4.25		4.25
125 mg./5 cc. 16 oz.	30.60	30.60	30.60		30.60	30.60	30.60

Source: FTC "Proposed Findings of Fact and Conclusions of Fact and Law" (June 1960), p. 372.

Senator Kefauver inquired of Dr. W. G. Malcolm, president of American Cyanamid, how these identities of price came about:

> Senator KEFAUVER. [The table] shows the prices of all the companies, regardless of the size of the order, regardless of the way you use it—capsules, drops, sirup, intravenous—you all have exactly the same prices, and you all suggest the same price for the drugstore to sell to the consumer.
>
> How do you get together? How do you work that out, Dr. Malcolm?
>
> Dr. MALCOLM. Mr. Chairman, Mr. Duncan is the general manager of the Lederle Laboratories Division. Would you kindly permit him to read this statement that he has, which I think will save a great deal of time?[36]

The patent fight over prednisone (and its companion prednisolone) has now been raging at the Patent Office for several years, during which time there has developed a bulk market in the drug somewhat similar to that in the unpatented penicillins. This market has been supplied by small producers such as Syntex and Formet Laboratories, by foreign concerns such as Organon of Holland and also by some of the major companies. As in the case of penicillin, competition in a free market has resulted in a substantial decline in price. Although there are no publicly reported bulk prices for these products, the fact that they have declined is demonstrated by purchase contracts in the subcommittee's files.

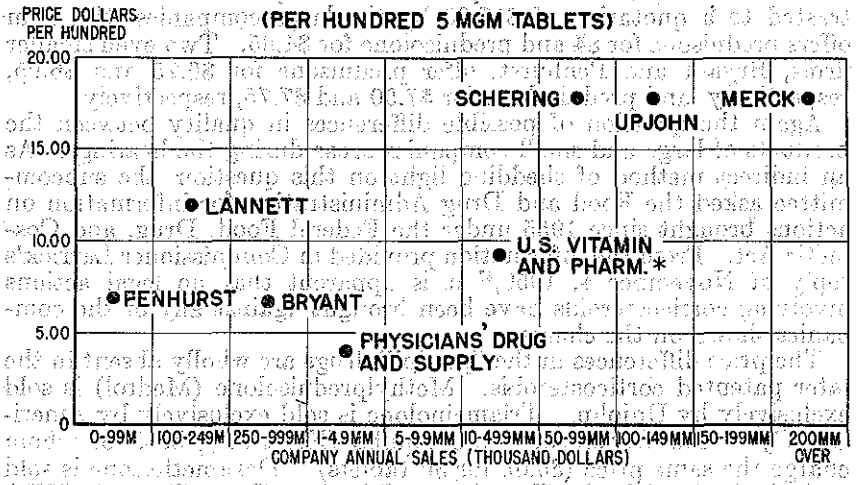
The availability of this free supply has made it possible for small manufacturers to sell the "predni" drugs in package form to drugstores and institutional buyers. Again, as in the case of penicillin, substantial differences exist between the prices of the small and the large companies. Charts 13 and 14 contrast for prednisone and prednisolone, respectively, the prices of the leading firms in this area with those of a number of smaller enterprises.

[35] Hearings, pt. 24, p. 13668.
[36] Hearings, pt. 24, p. 13667.

CHART 13

PREDNISONE

WHOLESALE PRICES BY SIZE OF COMPANY 1959



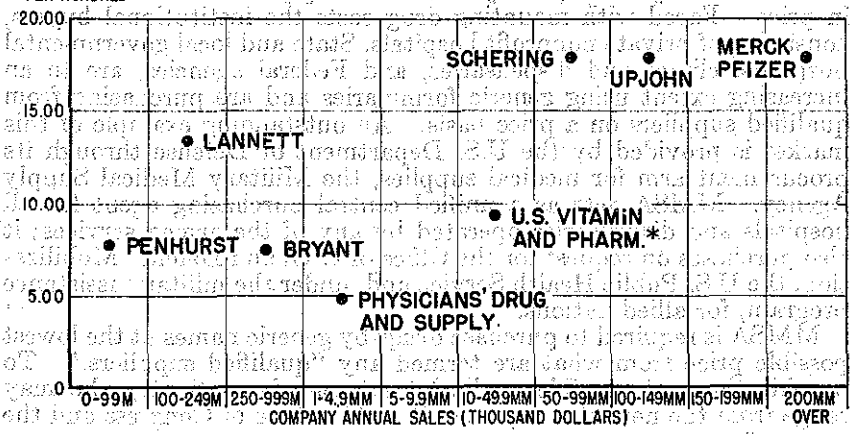
SOURCE: PRICES, AMERICAN DRUGGIST BLUE BOOK, 1959-60, AND UPJOHN CATALOG. SIZE, MOODY'S INDUSTRIAL MANUAL, 1959, AND COMPANIES.

* ARLINGTON-FUNK DIVISION

CHART 14

PREDNISOLONE

WHOLESALE PRICES BY SIZE OF COMPANY 1959



SOURCE: PRICES, AMERICAN DRUGGIST BLUE BOOK, 1959-60, AND UPJOHN CATALOG. SIZE, MOODY'S INDUSTRIAL MANUAL, 1959, AND COMPANIES.

* ARLINGTON-FUNK DIVISION

In these products the pricing pattern differs in one respect from that of penicillin; there is absolute price identity among the majors, including Pfizer. Insofar as the difference between large and small companies is concerned, however, the pattern is the same. With total annual sales in the $1 to $5 million range, Physicians Drug & Supply has the lowest price for both prednisone and prednisolone. As contrasted to a quotation of $17.90 by the large companies, this firm offers prednisone for $4 and prednisolone for $4.85. Two even smaller firms, Bryant and Penhurst, offer prednisone for $6.75 and $6.95, respectively, and prednisolone for $7.50 and $7.75, respectively.

Again the question of possible differences in quality between the products of large and small companies arose during the hearings. As an indirect method of shedding light on this question, the subcommittee asked the Food and Drug Administration for information on actions brought since 1955 under the Federal Food, Drug, and Cosmetic Act. From the information provided in Commissioner Larrick's reply of November 4, 1959,[37] it is apparent that no legal actions involving corticosteroids have been brought against any of the companies shown on the charts.

The price differences in the "predni" drugs are wholly absent in the later patented corticosteroids. Methylprednisolone (Medrol) is sold exclusively by Upjohn. Triamcinolone is sold exclusively by American Cyanamid (Aristocort) and Squibb (Kenacort), both of whom charge the same price ($5.65 for 30 tablets). Dexamethasone is sold exclusively by Merck (Decadron), Schering (Deronil), and CIBA (Gammacorten), all of whom have a price of around $8.10 for 50 tablets.[38]

SALES TO INSTITUTIONAL BUYERS

In addition to the usual prescription market, substantial quantities of drugs are sold to institutional buyers. In the regular market the customer, being limited to the brand name product usually prescribed for him, has little freedom to shop around for a lower price. This is true even where a product is sold by small manufacturers at prices substantially below those of the major companies. The essential difference between the two markets is that, unlike the physician, the institutional buyers frequently and increasingly have an acute interest in price. Faced with mounting drug costs the institutional buyers, consisting of private nonprofit hospitals, State and local governmental hospitals, clinics and dispensaries, and Federal agencies, are to an increasing extent using generic formularies and are purchasing from qualified suppliers on a price basis. An outstanding example of this market is provided by the U.S. Department of Defense through its procurement arm for medical supplies, the Military Medical Supply Agency. MMSA acts as a unified central purchasing agent for all hospitals and dispensaries operated by any of the armed services; it also purchases on request for the Office of Civil and Defense Mobilization, the U.S. Public Health Service and, under the military assistance program, for allied nations.[39]

MMSA is required to purchase drugs by generic names at the lowest possible price from what are termed any "qualified suppliers." To provide the best possible medical treatment for patients, who may range from the newest Army recruit to Members of Congress and the

[37] Hearings, pt. 15, p. 8359.
[38] Merck's Decadron is sold at a price of $16.11 for 100 tablets of 0.75 mgm.
[39] Hearings, pt. 24, p. 13775.

President, MMSA insists that suppliers meet exacting standards. Not only must the quality of the particular product being delivered conform to rigid specifications but inspection is made of the supplier's entire operation including the "housekeeping" facilities of his plant, his production and quality control techniques and performance, his records system, the technical proficiency of his staff, and the competency and knowledge of the management itself.[40] In short, every effort is made to assure that any company, large or small, which sells drugs to MMSA is capable of providing pharmaceutical products of fully acceptable quality. Given quality, MMSA endeavors to fill its requirements at the lowest possible cost.

The agency has provided the subcommittee with a complete record of its contracts, dating back as far as 1954, in a variety of areas (antibiotics, sulfa drugs, polio vaccine, steroids, insulin, tranquilizers, and vitamins). Here, also, a sharp differentiation between administered and market-determined prices emerges. The differentiation exists not only among drugs as a whole but within given product groups which are characterized by a general similarity of production methods and thus of costs.

MMSA has had little success in securing price concessions in the patented broad spectrum antibiotics. A case in point is Chloromycetin available only from Parke, Davis. From May 1954 to February 1958, MMSA negotiated 16 contracts with the company; despite a wide variation in quantities, the price was rigid at $12.50 per bottle.[41] In April 1958, MMSA's purchase officer persuaded Parke, Davis to reduce the price to $11.25; from that date through June 1959 there were 11 additional procurements—all at this same price, although there was again a wide range in quantities.

A similar pattern is presented by Aureomycin, also available only from a single supplier, American Cyanamid. From May 1954 to February 1956, MMSA made nine procurements in widely varying quantities, all at a price of $12 per bottle.[42] In April 1956 the price was reduced but only to $11 a bottle, which has prevailed for 11 procurements of widely varying quantities.

MMSA has had its greatest procurement difficulties with tetracycline, which is sold by five companies, though one of them (Upjohn) has not sought MMSA orders. Rear Adm. William L. Knickerbocker, USN, executive director of MMSA, described to the subcommittee his experience in trying to secure lower prices for this important drug:

> When the Government first purchased these tablets, it paid $11 per bottle of 100 in a procurement involving 94,176 bottles. Six months later in May 1957, the unit price (from a different supplier) was still $11, even though the quantity purchased was about one-seventh that of the previous procurement. On the third procurement, 9 months later, the price rose, inexplicably, to $17.24—a 57-percent increase over the previous $11 price. As a matter of fact, in this latter procurement the low offeror refused to take more than one-half the quantity required by the Government, and the remainder had to go to the second low offeror at a price of $19.19 per bottle—or an increase of 74 percent over the initial low price.

[40] Hearings, pt. 21, pp. 11547 ff.
[41] 250 mgm. capsules in bottles of 100.
[42] 250 mgm. capsules in bottles of 100.

During 1958 there were 3 additional procurements of tetracycline hydrochloride for 93,476, 41,904, and 25,632 bottles, respectively. For the first two of these procurements, the price remained at $17.24 and for the third it was $17.15. In June 1959, it seemed that this price "freeze" finally had been broken when the Government was able to buy 46,512 bottles at a unit price of $14.36. But no. This "thawing out" process was illusory, because 2 months later, in August 1959, a solicitation for 28,000 bottles again produced an offered low price of $17.15 with 3 suppliers offering the identical price. This was the same price as quoted before the so-called price break. When this occurred, MMSA felt that it had no alternative but to cancel the procurement because of the unreasonably high price.

Over a period of 3 years, four independent suppliers participated in the Government procurement of this item. Nevertheless, in that time the price rose to a high of 174 percent of the initial low price, and, thereafter, with one exception, became constant in the $17 bracket. Moreover, all price quotations to the Government bore no relationship to the quantities ordered * * *.

Aside from the foregoing peculiar pattern of cost to the Government, there are other characteristics in the procurement history of tetracycline hydrochloride tablets which should be noted. On a number of procurements, more than one supplier initially offered the identical low price. Furthermore, even when only one supplier was low, others came in at higher but identical prices (i.e., either the specific prices offered were the same, or they became identical when the prompt payment discount was applied).[43]

While Admiral Knickerbocker refused to hazard any guess as to the reason for this strange price behavior, an explanation was proffered by Mr. Lyman Duncan, manager of the Lederle Laboratories Division of American Cyanamid. According to his testimony the first MMSA tetracycline procurement was announced at a time when Mr. Duncan was still learning the drug business (shortly after his transfer to Lederle from Cyanamid's Organic Chemicals Division). As a result, he made a mistake and simply bid for the tetracycline contract at the same $11 price at which Cyanamid had been supplying Aureomycin to MMSA for some months:

> As I recall the circumstances, up to that time I think the buying had been entirely Aureomycin or Terramycin with some Chloromycetin, but the real competing products there were Aureomycin and Terramycin.
>
> Now what happened there was I was not fully aware of this, being new in the business, that the Army had never before bought tetracycline.

[43] Hearings, pt. 24, p. 13779-80.

It was brought to my attention that they had an order for tetracycline. Well, I guess I did not give it a great deal of consideration.

* * * * *

So far as I can remember when this came up, I said: "Well, I suppose we have been bidding $11 on Aureomycin. It is too low a price, but I guess we might as well bid the same price." [44]

Mr. Duncan's uncertainty as to what Lederle should charge for tetracycline is surprising in view of the fact that for a full 2 years prior to the MMSA procurement, his company had been selling the same product to the Veterans' Administration at a price of $19.58, less 2 percent for prompt payment.[45]

On the second procurement Pfizer apparently made a "mistake" in bidding $11 on the assumption that Cyanamid would be in that range. Since Cyanamid actually bid $19.58, the contract of course went to Pfizer. Thereafter, prices rose as described by Admiral Knickerbocker. As the subcommittee counsel pointed out: "I notice that $11 mistake never occurred after the first two times." [46]

In a discussion of subsequent identical bids by several companies, Mr. Duncan was asked specifically about the MMSA procurement in September 1958, for which Cyanamid, Pfizer, and Squibb all bid $17.24; he explained that this was a coincidence which "astounded" him.

I had not the faintest idea, Mr. Dixon—it is very easy looking back, but in looking ahead, I had not the faintest idea. Actually, I was astounded that they bid $17.24. I expected someone to bid, with a different situation, to bid $15 or $16. I had no idea what those bids would be.[47]

Another "astounding" coincidence is the mathematically precise division of the MMSA market for tetracycline. For the 3-year period, November 1956–October 1959, the patent-holder, Pfizer, had 46.6 percent of the MMSA purchases of this drug.[48] The remaining 53.4 percent was split almost exactly evenly among the other sellers, with the Lederle Division of American Cyanamid getting 17.8 percent, Bristol 17.6 percent, and Squibb 17.5 percent. (See table 31.)

TABLE 31.—*MMSA procurement of tetracycline, all forms, November 1956–October 1959*

[In dollars]

	Pfizer	Lederle	Bristol	Squibb	Upjohn	Total
Tetracycline hycrochloride:						
Tablets, 250 milligram, 100's	3,572,922	1,397,148		1,330,219	42,000	6,342,289
Oral suspension	178,434		1,377,335	86,298		1,642,067
Powder, 250 milligram	56,131	7,540	74,313	33,408		171,392
Powder, 100 milligram	44,155	67,923				112,078
Total	3,851,642	1,472,611	1,451,648	1,449,925	42,000	8,267,826
Percent	46.6	17.8	17.6	17.5	.5	100.0

Source: MMSA (Sept. 2, 1960).

[44] Hearings, pt. 24, p. 13690.
[45] Veterans' Administration purchase records provided to the subcommittee.
[46] Hearings, pt. 24, p. 13691.
[47] Hearings, pt. 24, p. 13692.
[48] Hearings, pt. 24, p. 13700. Upjohn obtained only a very small procurement, amounting to only 0.5 percent of the total.

The division of the business in the two principal products, 250-milligram capsules and tetracycline for oral suspension, represents at the least an unusual coincidence. Pfizer supplied approximately 60 percent of MMSA's dollar purchases of tablets, while the remaining percentage was divided almost exactly evenly between Lederle and Squibb; none was furnished by Bristol. On the other hand, Bristol supplied the greater part of MMSA's requirements for the drug in oral suspension form, with relatively modest participation by Pfizer and Squibb and none at all by Lederle.[49] This division of the oral suspension contracts cannot reflect any form of product specialization. Bristol, of course, makes tablets, while Pfizer, Lederle, and Squibb sell the oral suspension form to the regular trade and, indeed, entered bids on it during this period to the MMSA.[50] What is most unusual is that the dollar volume of Bristol's oral suspension sales to MMSA is almost identical to the dollar shares of Lederle and Squibb in the procurement of tablets in which Bristol has not participated successfully.

Just as there is a sharp difference in the price structure between the broad spectrum antibiotics and the older penicillins in sales to the regular drug trade, so also is there a similar difference in sales to the Military Medical Supply Agency. As has been noted, penicillin G is sold to the retail druggist by most of the large companies at around $12 a bottle, with small companies quoting as low as $3.30.[51] In contrast to these prices, MMSA's first reported procurement was a negotiated contract with Bristol calling for a series of deliveries in 1954 at a price of $1.61 a bottle. Since 1956, procurements have been made for the most part on an advertised bid basis, with small as well as large companies participating, and prices have declined sharply. Since early 1959 the price to MMSA has ranged between 67 and 77 cents a bottle.

Another unpatented antibiotic is bacitracin, most often administered in topical ointments. Typical of the major companies, the price to the druggist for Pfizer's product is $10.20 a package.[52] With as many as eight firms of varying sizes bidding in individual procurements, the price has been $2.35 or less except for a few months in 1956. Seven of the contracts have been won by Pfizer, itself, at bids between $1.65 and $1.99 a package, while on five other occasions Pfizer has been unsuccessful with bids below $2 a package.

As in sales to the drug trade, the large manufacturers of prednisone and prednisolone encounter price competition from small companies. MMSA has made a number of procurements of these products, with from 8 to 15 qualified suppliers, both large and small firms, bidding on each. On none of the procurements did the bids, even by large firms, remotely approach the $170 paid by the retail druggist for the major brand-name items.[53] Further, under the pressure of competition the trend of prices has been steadily downward. The first prednisone procurement by MMSA reported to the subcommittee,

[49] MMSA reported procurements of tetracycline for oral suspension in 1957, 1958, and 1959. Only Bristol bid successfully in 1957 and 1958. Sales of this dosage form shown in the table for Pfizer and Squibb reflect the two 1959 procurements, which exhibit an interesting sequency of bids. Bristol's 1958 price had been $1.64 a bottle. In June 1959 Pfizer bid $1.267 a bottle, while Bristol, Squibb, and Lederle were in the $1.60-$1.64 range. But in December it was Squibb which bid $1.267, while Pfizer was back up with Lederle and Bristol in the $1.60-$1.63 range.

[50] MMSA purchase records and American Druggist Blue Book.

[51] 250,000 unit tablets in bottles of 100.

[52] 1960 Drug Topics Red Book: Ointment containing 500 units of bacitracin per gram, sold to the druggist in packages of a dozen ½-ounce tubes.

[53] 5-milligram tablets, bottles of 1,000.

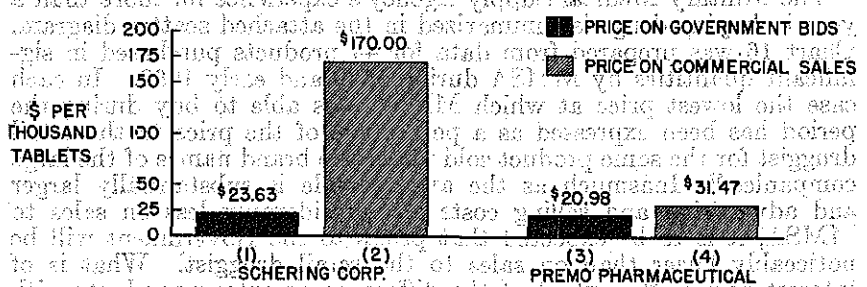
March 1958, went to Chase Chemical Co. for $41.50; Schering, one of the largest sellers, bid $79.74. The last reported procurement, January 1960, was awarded to Premo Pharmaceutical Laboratories at a price of $11.79 per bottle of 1,000 tablets. By the time of the same procurement, Schering had reduced its bid price to $17.97—or approximately one-tenth of the price for which it sells the identical product to the retail druggist.[54]

The contrasting price structures of large and small companies are illustrated by chart 15, which shows prices to the commercial trade and to MMSA of Schering and Premo; the period is February 1959, which is about halfway through MMSA's experience in procuring prednisone.

CHART 15

SCHERING AND PREMO PRICES ON GOVERNMENT BIDS AND ON COMMERCIAL SALES

PREDNISONE
PRICE PER THOUSAND 5 MG. TABLETS



(1) SCHERING'S BID TO MILITARY MEDICAL SUPPLY AGENCY, FEBRUARY 1959.
(2) SCHERING'S PRICE TO DRUGGISTS (AMERICAN DRUGGIST BLUE BOOK, 1958-59).
(3) PREMO'S BID TO MILITARY MEDICAL SUPPLY AGENCY, FEBRUARY 1959; CONTRACT AWARDED TO PREMO.
(4) PREMO'S ESTIMATED PRICE TO DRUG STORE BASED ON ABOVE BID PLUS ITS NORMAL SELLING AND DISTRIBUTION EXPENSES AND NOMINAL PROFIT (LETTER TO SUBCOMMITTEE, OCTOBER 27, 1959).

In this particular instance, Premo outbid Schering ($20.98 versus $23.63). But what is more important is the fact that Premo's price to the commercial trade, $31.47, was only 50 percent above its bid price, whereas Schering's commercial price, $170, was 620 percent above its MMSA bid. Commenting on the difference between the commercial prices of large and small companies, Mr. Francis Brown, president of Schering, stated: "I have no doubt, Senator, that our overhead is 8 to 10 times the overhead of any of these smaller companies."[55] If the difference between their commercial and their

[54] The first reported prednisolone procurement, January 1959, was given to Panray Corp. at a price of $25 per bottle of 1,000 tablets. Interestingly, Parke, Davis, Pfizer, and Schering were all bidding in the $25 to $35 range, a marked contrast to the $170 paid by the retail druggist for the identical product offered by the same companies. A year later, January 1960, the last reported procurement went to Premo at a price of $14.29 per 1,000—just about one-twelfth of the price for major brands to the retail druggist.
[55] Hearings, pt. 14, p. 7898.

MMSA prices could be regarded as a rough measure of "overhead" (assuming similar profit rates), Mr. Brown's estimate in this particular case is somewhat low: Schering's overhead would be 14 times that of Premo.

The patented tranquilizers purchased by the MMSA—meprobamate, promazine, and chlorpromazine—have been offered at rigid prices only 25 to 35 percent below the price to the retail druggist. Reserpine, on the other hand, although developed by CIBA Pharmaceutical Co., has been widely licensed. Some 20 sellers have made bids at one time or another, with as many as 14 firms bidding in a single procurement. MMSA's first reported procurement, February 1956, was won by Eli Lilly with a bid of $1.39 per bottle of 1,000, which is one twenty-fifth of Lilly's price to the druggist. Since that time MMSA's reserpine price has steadily fallen. In February 1959, CIBA won a contract with a bid of 60 cents a bottle (only 1.5 percent of CIBA's price to the retail druggist of $39.40).[56] And by the date of the last reported procurement, April 1960, the price had dropped to 51 cents a bottle. MMSA was buying 1,000 tablets at about the cost of 15 tablets to the civilian druggist. On one or more occasions, each of the four major sellers of this product—CIBA, Lilly, Squibb and Merck—made bids which were less than one-twentieth of their price to the retail druggists.

The Military Medical Supply Agency's experience for more than a year in buying drugs is summarized in the attached scatter diagram. Chart 16 was prepared from data for 44 products purchased in significant quantities by MMSA during 1959 and early 1960. In each case the lowest price at which MMSA was able to buy during the period has been expressed as a percentage of the price to the retail druggist for the same product sold under the brand names of the large companies.[57] Inasmuch as the average sale is substantially larger and advertising and selling costs are considerably less on sales to MMSA, it is to be expected that prices to the Government will be noticeably lower than on sales to the retail druggist. What is of interest here is the extent of the difference as among products with differing numbers of bidders.

The scatter diagram clearly shows the existence of an inverse relationship between MMSA prices and the number of bidders; the greater the number of available suppliers, the lower the price.[58] A freehand curve has been fitted to the plotted points to show the approximate relationship between MMSA prices and the number of bidders for contracts to supply the various products. It will be observed that the curve tends to fall sharply as the number of sellers rises—i.e., the effectiveness of competition in reducing prices when drugs are purchased by generic name is clearly illustrated. When its sources of supply are limited to a single firm or a very few companies, MMSA's procurement advantage over the retail druggist is far smaller than is the case when 10 or 12 firms are competing for the agency's

[56] See hearings, pt. 16, p. 9430. Mr. T. F. Davies Haines, president of CIBA's U.S. subsidiary, testified: "When we bid 60 cents for bottles of 1,000 here, we didn't anything like recover our out-of-pocket costs. * * * In retrospect, it was perhaps a mistake that we did that." If this is correct, it is rather surprising to note that in MMSA's procurement of March 6, 1959, CIBA bid 58 cents per 1,000 and in October 1959 the company bid 52 cents; incidentally, in neither of these was CIBA the low bidder.

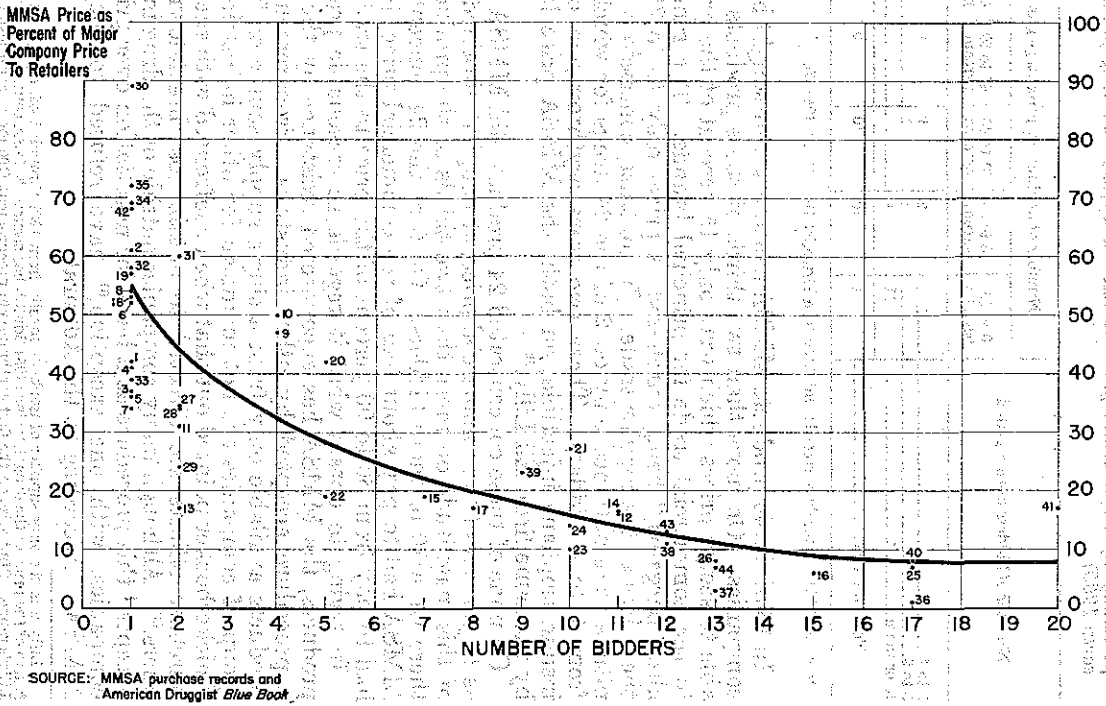
[57] In the case of tetracycline capsules the lowest domestic price was used. In December 1959 MMSA awarded a contract to Farmochimica Cutolo-Calosi (Italy) at $8.15 per 100, less than half of the lowest price ($16.76 per 100 capsules) bid on this contract by a domestic manufacturer.

[58] The number of "available suppliers" has been considered to be the number of firms which actually entered bids for MMSA contracts during the period covered by the tabulation. See appendix B, table A-13 for identification of products.

CHART 16

MMSA DRUG PROCUREMENT

RELATIONSHIP OF NUMBER OF BIDDERS TO MMSA PRICE EXPRESSED AS PERCENT OF COMMERCIAL PRICE, 1959 AND EARLY 1960



SOURCE: MMSA purchase records and American Druggist *Blue Book*

contracts. The curve appears to break definitely at about five sellers. With fewer sellers the difference between the MMSA price and the commercial price may be noticeable, but arbitrary; with more sellers, a fairly uniform pattern of relatively low prices appears. The inverse relationship can also be seen in the following summary tabulation.

TABLE 32.—*Number of suppliers compared to lowest MMSA price expressed as percentage of major brand prices to retail druggists—44 drug products (1959 and early 1960)*

Number of bidders during period	Number of products in percentage groups					Total
	0 to 15 percent	16 to 30 percent	31 to 45 percent	45 to 60 percent	Over 60 percent	
1 to 4	----------	2	9	9	4	24
5 to 9	----------	4	1	----------	----------	5
10 or more	11	4	----------	----------	----------	15
Total products	11	10	10	9	4	44

Source: MMSA purchase records and American Druggist Blue Book, 1959-60.

In 15 of the 44 products MMSA contracts were sought by 10 or more companies. On more than two-thirds of these products MMSA was able to secure prices which were only 15 percent of the prices charged to the commercial trade for principal brands. The remainder were also "bargains," being purchased at prices only 16 to 30 percent of the prices to the regular trade. In contrast, concessions of this magnitude were obtained only on 2 of the 24 drugs for which there were from 1 to 4 bidders. These two were erythromycin capsules and insulin isophane injectible; on both, the MMSA price level was set by the same firm, Eli Lilly.[59]

On none of these concentrated 24 products did MMSA pay as little as 15 percent of the commercial price, although it obtained concessions of this magnitude on more than two-thirds of the products in which there were 10 or more bidders. On 9 of the 24 concentrated drugs MMSA had to pay about half of the commercial price; for 4 more it had to pay from 60 to 90 percent of the price to the trade.

In trying to obtain what it regards as reasonable prices for drug products, the MMSA has encountered resistance by the industry to a procedure accepted by other industries. Procurements involving products available only from a single supply source or from a small group of companies are not unknown for other industries. Admiral Knickerbocker pointed out that when confronted with such situations, purchase officers are directed to obtain cost breakdown from suppliers.[60] Although many companies outside of the drug industry have accepted this procedure as a basis for negotiation over price, the drug companies, with one exception,[61] have refused to cooperate with MMSA. According to the Admiral:

[59] Lilly was the only supplier of isophane insulin from 1952 through 1954, charging approximately one-fourth of the price to the druggist; since 1954 Squibb has secured MMSA contracts, but only by bidding in Lilly's range. Similarly, on the first erythromycin procurement (100 mgm. capsules), one of the two bulk manufacturers, Abbott, bid $12.32 per 100 capsules, while Lilly offered to supply them at $3.31 per 100. As in the case of the insulin, Lilly has kept its erythromycin prices at a reasonable level, which Abbott has been forced to meet on MMSA contracts.

[60] Since the drug and pharmaceutical products sold by the industry to MMSA are the same as the commercial "shelf" items sold to the civilian market, Government contracts for these products are excluded from statutory renegotiation provisions.

[61] Armour Pharmaceutical Co., Kankakee, Ill.

The Armed Services Procurement Regulation urges that, where a question arises as to whether the offered price is fair and reasonable, steps should be taken to resolve that question by obtaining a cost breakdown or price analysis from the potential contractor.

The Navy Department has negotiated the purchase of billions of dollars of supplies and has obtained from suppliers cost and price analyses by which a determination could be made that the prices offered to the Government bore a logical relationship to the contractor's overall costs. *This is not our experience, however, with the drug and pharmaceutical industry.* Generally, MMSA has been unable to obtain such cost analyses from its suppliers, and there is no way under the present law in which these suppliers can be required to produce such analyses if they are confident they can sell their products without doing so.[62]

The relationship between fewness of suppliers and price was concisely pointed up in the testimony of Dr. E. Gifford Upjohn. Upjohn's Orinase (tolbutamide) was the only oral antidiabetic drug purchased by MMSA during the period for which reports are available. As the sole supplier, Upjohn charges the Government 90 percent of the price to the direct-buying retailers.[63] When Upjohn competes against other suppliers, however, the company is both willing and able to lower its prices considerably.

Mr. DIXON. The record shows, in our previous hearings, that when you won the bid on hydrocortisone tablets, 20 milligram tablets in bottles of 100 on May 22, 1958, your bid to MMSA was for $4.63 a bottle. The price to the druggist for that same bottle would have been $18.64. On cortisone acetate tablets, Upjohn bid as low as $1.86, almost meeting Merck's winning bid which was for $1.85 for 20 milligram tablets in bottles of 40. This was 1956, and your price to druggists was $6.56 * * *.

* * * * * * * * *

On the items I talked about you had competition?

Dr. UPJOHN. I expect you are right.

Mr. DIXON. You did not have any competition on Orinase because you were the exclusive manufacturer?

Dr. UPJOHN. That is right. If they specify our product then it would be filled with our product; that's right.[64]

THE DETERMINATION OF PRICE

In previous hearings the subcommittee has concerned itself with the standards employed by large corporations in concentrated industries to establish prices. This important issue, which has received considerable attention in economic literature, was also examined during the course of the drug inquiry. In the other industries examined by the subcommittee—steel, automobile, and bread—price leadership

[62] Hearings, pt. 24, pp. 13789–13790 (emphasis added).
[63] Testimony of Dr. E. Gifford Upjohn, hearings, pt. 20, p. 11057.
[64] Ibid., p. 11058.

was found to be generally observed.[65] Even though they might be more efficient, have lower costs, and show higher profit margins, companies in those industries tend to change their prices only after the leader has changed.

The same practice has been found to prevail in the drug industry, with, however, an important further dimension. This is the extension of the principle to the introduction of new drugs. In an industry such as steel, price "followership" usually takes the form of matching the leader's prices on the industry's existing products. In drugs the practice is followed not only on existing products but on new drugs as well. When a new product is put on the market, the customary procedure is to introduce it at or very near the price charged for an existing drug used to treat the same general type of ailment. Inasmuch as most ailments are treated with a drug of some kind, there is usually no great difficulty in finding a product whose price can be matched. The practice, which is referred to by industry representatives and their legal spokesmen as "meeting competition," is the essence of simplicity; this, incidentally, makes it rather irrelevant to speculate on the complex of variables that businessmen might have in mind in setting their prices. Whether so intended or not, the practice has the effect of automatically eliminating price rivalry. As long as a new drug is introduced at the same price as its predecessor, the manufacturer of the older drug is not faced with the necessity of lowering his price, which in turn might provoke a further price reduction of the new product, culminating in "disastrous" competition.

The broad spectrum antibiotics provide a striking example of the manner in which "meeting competition" resulted in price identity on different, though competing, products, as well as among the different sellers of a given product. Less than 3 years after the introduction of the first of these antibiotics, the price of each of the three broad spectrums then on the market, Aureomycin, Terramycin, and Chloromycetin, had been stabilized. On September 27, 1951, Pfizer adopted a price of $5.10 for Terramycin;[66] 4 days later both American Cyanamid and Parke, Davis announced the same price for Aureomycin and Chloromycetin, respectively. A little more than 2 years later American Cyanamid became the first company to introduce the new broad spectrum, tetracycline; the price which it adopted was the same as that of the earlier broad spectrums, $5.10. Shortly thereafter the four other sellers of tetracycline put their products on the market at the same price.[67]

The corticosteroids provide a similar case in point. Describing the manner in which Schering arrived at the prices for Meticorten and Meticortelone (its brands of the "predni" drugs), Dr. Upjohn testified:

> When prednisone and prednisolone came out they had to be priced in respect to the then existing competition, which was hydrocortisone and cortisone. So the price level selected for those originally by Schering was obviously based on the corresponding price of those other commodities.[68]

[65] 85th Cong., 2d sess., S. Rept. No. 1387, "Administered Prices: Steel, Report of the Senate Subcommittee on Antitrust and Monopoly," 1958, pp. 73–106; 85th Cong., 2d sess., "Administered Prices: Automobiles, Report of the Senate Subcommittee on Antitrust and Monopoly," 1958, pp. 52–75; 86th Cong., 2d sess., S. Rept. No. 1923, "Administered Prices: Bread," 1960, pp. 146–178.

[66] 16 capsules of 250 mgm.

[67] Federal Trade Commission, "Economic Report on Antibiotics Manufacture," 1958, p. 192.

[68] Hearings, pt. 14, p. 8298.

The "predni" drugs in turn became the basis for the pricing of the more recent corticosteroids. In 1957 Upjohn introduced methylprednisolone under the trade name, Medrol. During the same year Squibb and Lederle introduced triamcinolone under the respective trade names, Aristocort and Kenacort. All were introduced at the price charged by Schering for Meticorten and Meticortelone, 18 cents a tablet to the druggist.

A third advantage is that the steady advance in science and technology frequently makes it possible for the new product to be produced more cheaply than its predecessor. The most dramatic savings occur when the new product is of an entirely different character and can be produced by much simpler processes. An example is the substitution of the oral antidiabetic drugs for insulin. These are synthetic chemicals which can be produced at little cost. As has already been shown, the computed production costs for Orinase are only 0.7 cent per tablet, and including royalty only 1.3 cents. This compares to a price paid by the druggists of 8.3 cents and by the consumer of 13.9 cents. Although the cost of production of insulin is not known, there can be little doubt that it is well above this figure. The essential raw materials, pancreas, must be purchased from slaughterhouses and are undoubtedly more expensive than the basic chemicals from which the oral forms are made. In Great Britain it was found that, "The cost of pancreases is an important item in the cost of insulin, representing in recent years approximately 45 percent of factory costs".[69] Refining and purification, quality control, are all exacting steps. On what basis then was the price of Orinase, the first of the oral antidiabetic drugs, arrived at? In his testimony before the subcommittee, Dr. E. Gifford Upjohn, president of the Upjohn Co., stated that the price for Orinase was determined by the market price for insulin. The following exchange occurred:

> Mr. DIXON. How did you arrive at your price on Orinase in this country?
>
> Dr. UPJOHN. Well, that was arrived at on the basis of competition of course. Diabetic patients can be treated by diet or by insulin.
>
> Senator KEFAUVER. What?
>
> Dr. UPJOHN. With insulin, and insulin had been on the market for many years, during which time its price had come down very markedly, and even though the price of insulin was at quite a low level, it was necessary for us to consider that as our competition. So in arriving at any price you consider what the competitive situation is going to be.
>
> Now the competition does not necessarily fix the point at which the pricing will be made, because there are other things to be considered, such as competitive advantages that one might have.
>
> * * * * *
>
> Mr. DIXON. You stated then, if I understand you correctly, that when you established this price, you took into consideration the competitive product insulin?
>
> Dr. UPJOHN. Yes, sir.
>
> Mr. DIXON. And you figured that the price you set was a competitive price with insulin?

[69] The Monopolies and Restrictive Practices Commission, "Report on the supply of Insulin," 1952, p. 28.

Dr. UPJOHN. That is right.

* * * * *

Mr. Dixon. Figuring this out on a dosage formula, we understand that a diabetic who can shift from insulin to an oral drug normally is one who must take 30 units of insulin daily, usually 10 units shortly before each meal. Regular insulin is sold in 10 cubic centimeter vials containing 40 units per cubic centimeter or a total of 400 units per bottle. According to the Blue Book, the price to the consumer is $1.40, and, as I stated, I believe that price has been unchanged since 1947. Thus, every time the patient gives himself an injection of 10 units of insulin, the cost of the drug to him for such injection is about 14 cents. This is the same price also for an Orinase tablet, I believe.

* * * * *

Senator KEFAUVER. Apparently you priced it just about the same as the injectible insulin, as I understand your testimony. Maybe it is a little different, but just about the same.

Mr. UPJOHN. Senator, that would be a very difficult thing to say one way or another because there are so many variables.

Senator KEFAUVER. The point is, isn't insulin in injectible form a much more expensive product to manufacture than a tablet of oral insulin? I understood the injectible insulin had to be made out of animal pancreas of which there is a shortage, and it is a very difficult process, whereas Orinase is a chemical combination which is comparatively much cheaper and much easier to make.

Dr. UPJOHN. I haven't any information about that at all. I don't know anything about the production costs of insulin. We do not manufacture insulin.

Senator KEFAUVER. But it is true that insulin is made out of the pancreas of animals?

Dr. UPJOHN. That is right.

Senator KEFAUVER. In setting your price, it would seem that you were bringing out a new product which is to take the place of insulin in certain limited cases where it can be used. It would seem that instead of trying just about to match the price of a product already on the market, that if you had a lower manufacturing cost—it would cost you less, it would be less expensive to manufacture—you would bring your price down and thereby gain some advantage by having a lower competitive price.

Dr. UPJOHN. You asked me how the price of insulin was set.

Senator KEFAUVER. No.

Dr. UPJOHN. I mean how the price of Orinase was fixed.

Senator KEFAUVER. My question was, Why didn't you set Orinase at a lower price? Why did you just set it the same as insulin which was already on the market?

Dr. UPJOHN. That was our competition, Senator.[70]

[70] Hearings, pt. 20, pp. 11037-11039.

A somewhat similar cost-saving innovation took place in the production of Chloromycetin. In its early history it was discovered that Chloromycetin could be manufactured not only by the fermentation process used in the production of other antibiotics but by a cheaper synthetic chemical process. To use the chemical process, Parke, Davis constructed a new plant, and since that time, most if not all of its output has been produced by the synthetic chemical process. While its cost advantage may have narrowed with the increase in yields of the fermentation process, Chloromycetin has at no time been sold at a price below that charged for the other broad spectrums, all of which are produced by the fermentation process.

Another case in point is the discovery by Upjohn in 1952 of the microbiological process of producing corticosteroids. Up to that time the manufacture of these products had been an expensive and complex undertaking. The starting raw material of the older method had been oxbile, which required hundreds of slaughtered animals to yield a few grams of cortisone. Moreover this could be secured only by a complex chemical process which originally took 37 steps and as late as August 1952 still required 20.[71] The effects of the new process on costs were two-fold; to reduce the steps involved in production from 20 down to 1 and to open up a relatively inexpensive and abundant vegetable source of supply in place of the costly and restricted supply of oxbile. In a letter dated August 28, 1957, to Mr. John McKeen, president of Pfizer, Dr. Upjohn referred to the new method as constituting "the most economical and versatile steroid processes presently available anywhere in the world today."[72] In contrast Dr. Upjohn described the older process in these words:

> Now oxbile is not a readily available commodity on the market in large quantities. It was scarce. It was expensive. The process * * * had some 40 steps or more. It was an extremely complicated chemical synthesis, as you have said. The costs of the material were very high.[73]

Yet neither when Upjohn in 1952 introduced its brand of hydrocortisone (Cortef), nor when in 1955 it introduced its brands of the "predni" drugs (Deltasone and Delta-Cortef), nor when in 1957 it introduced methylprednisolone (Medrol) did Upjohn's price ever depart from that of its "competition," part of which was produced by the older and more costly process.

By being introduced at its predecessor's price, a new drug may tend to enlarge the margin between production costs and price in still another way. This is where the active ingredient is more "potent," which reduces the quantity required. Thus, when the Lederle Division of American Cyanamid introduced a new form of tetracycline, Declomycin, it was priced at the same level as Cyanamid's older form, Achromycin, although its content of active ingredients had been reduced by 40 percent. Referring to the fact that Declomycin and Achromycin are sold to the druggist at around 30 cents and to the

[71] Chemical Week "Cortisone Quest: The Right Process Bug," August 23, 1952.
[72] Hearings, pt. 14, p. 8291.
[73] Hearings, pt. 14, p. 8292.

consumer at 45 cents a capsule, Mr. Seymour Blackman, executive secretary of Premo Pharmaceutical Laboratories, said:

> Declomycin is a 150-milligram capsule, whereas tetracycline is a 250-milligram capsule. The cost for Declomycin should be 60 percent that of the cost of tetracycline capsules * * *. If Premo were allowed to sell the tetracycline drug; that is, if we had not already been refused a license, we could offer this very same product, to the pharmacists, at approximately 9 cents per capsule and it would retail to the consumer for 18 cents giving the pharmacists a legitimate markup and the consumer a legitimate cost.[74]

The practice of the drug companies in using the increased "potency" of new products as the basis for promotional campaigns was strongly criticized before the subcommittee by Dr. Louis Lasagna of Johns Hopkins University:

> Now for the parade of steroids—let me put it this way. In coming up with one new steroid after another, I think various pharmaceutical firms have tried to enlist doctors' support by one of two devices. The first is what I like to call the pharmaceutical numbers racket. This is where a compound is alleged to be better than another, more potent because one can give, let us say, 2 milligrams instead of 15 of a rival product.
>
> Now this is like saying that a dime is more potent than two nickels, because you can use one coin instead of two.
>
> It may be more convenient to carry dimes than to carry nickels, but in regard to steroid preparations, where one has just a few milligrams involved and where one usually has to add many more milligrams to make a tablet that can be found in a pillbox, the problem of convenience of taking such preparations doesn't even come into the picture.
>
> I am ashamed to say physicians do fall for this pharmaceutical numbers routine and are somehow convinced that drugs are better if one can give them in smaller amounts.[75]

To the extent that physicians do "fall for this pharmaceutical numbers routine" the price received by the drug companies per unit of active ingredient will of course rise unless the price per tablet is correspondingly reduced, which for patented drugs is rarely the case. The manner in which the successive introduction of increasingly "potent" corticosteroids has tended to result in an increased realized price per gram as well as an increase in the margin above direct costs was brought out in the following table introduced during the hearings:[76]

[74] Hearings, pt. 14, p. 8204.
[75] Hearings, pt. 14, p. 8189.
[76] Hearings, pt. 14, pp. 8324–8327; the table, as shown here, excludes a potential new product discussed in the hearings only "for illustrative purposes."

TABLE 33.—*Prices for corticosteroids to consumers and druggists, and computed cost, 1959*

	Tablet size (milligram) (1)	Number tablets per gram (2)	Price to consumer per tablet (3)	Price to consumer per gram (4)	Price to druggist per gram (5)	Computed cost based on bulk price, includes wastage, tableting and bottling, but excludes selling and distribution costs [1] (6)
Cortisone	25	40	$0.23	$9.13	$5.48	$1.50
Hydrocortisone	20	50	.27	13.32	7.99	1.63
Prednisone	5	200	.30	59.66	35.80	3.12
6-methyl prednisolone	4	250	.30	74.60	44.75	
Triamcinolone	4	250	.30	74.60	44.75	
Dexamethasone	.75	1,333	.27	358.00	214.80	72.69

[1] Based on lowest bulk prices as published or reported to subcommittee: Cortisone, $1.30 per gram, Oil, Paint and Drug Reporter, Sept. 21, 1959; hydrocortisone, $1.40 per gram, Oil, Paint and Drug Reporter, Sept. 21, 1959; prednisone, $2.36 per gram, Syntex sales, 3d quarter, 1959; dexamethasone, $65 per gram, Merck sale to Ciba, 1958.

Source: Cols. 1 to 5: "American Druggist Blue Book," 1959–60.

Since the price of each of these different corticosteroids, with the exception of cortisone, differs by no more than 10 percent per tablet, since their potency has tended to rise (col. 1), and since the number of tablets per gram has correspondingly tended to increase (col. 2), there has been a steady increase from one corticosteroid to the next in the price per gram (cols. 4 and 5).

Unless there is a corresponding increase in costs, there would be a progressive widening of the margin between direct costs and prices, moving from one corticosteroid to the next more potent one. Column 6 shows derived production costs including wastage, tableting, and bottling but excluding selling and distribution costs, computed on the basis of bulk sales prices. It can be seen that such a widening has taken place. For hydrocortisone the margin above direct costs was $6.36 per gram; for dexamethasone (also sold at the same price per tablet) it was $142.11 per gram.

The knowledge that price determination usually takes the form of matching the price of a predecessor product leaves unanswered the question of how the price of the original drug was determined. At some time there had to be a drug which served as the basis for setting the price of possibly a whole series of successive products. In some cases the history of the price of the original drug is shrouded in the mists of antiquity. The price of Diabinese was based on the price of Orinase; the price of Orinase was based on the price of insulin. The question then becomes, how did the price of insulin get where it was at the time that Orinase was introduced? For about a decade prior to that time the price of insulin had remained unchanged; following World War II it was 20 percent above its 1939 level. The price history can be extended back to 1922 when insulin was discovered. Even if all of the cost, demand, and other factors influencing the price of insulin throughout its history were known, how relevant would such knowledge be to understanding the factors involved in determining the price for the oral drugs? The one relevant fact is that, although manufactured at lower costs by an entirely different process using

entirely different raw materials, they were priced "to meet" the competition of insulin.

In some cases knowledge of the factors involved in stabilizing prices at a given level—which has then served to govern the prices of successive products—may become available with the completion of antitrust cases. Some of the considerations which Pfizer and American Cyanamid had in mind in stabilizing the price of the early broad spectrum antibiotics at $5.10 may become known when the current price-fixing case of the Federal Trade Commission against the sellers of tetracycline is brought to an end.[77]

But while knowledge of the price-determining process for the original product would be interesting, the important fact is that a good majority of today's drugs which by any standard would be regarded as important, have had their prices established on the basis of the price of a predecessor product. The necessity of giving attention to cost and demand factors has thus been obviated by the simple act of "meeting competition."

[77] Federal Trade Commission, *In the Matter of American Cyanamid et al.* docket No. 7211.

PART III

PATENTS AND RESEARCH IN DRUGS

To what are the extraordinary margins and profits in the U.S. drug industry, as shown in the preceding section, to be attributed? Essentially, they stem from the control over the market, and the manner in which that control is exercised. But on what does the control of the market rest? Although it derives from many factors, its principal bases would appear to be (*a*) the granting in this country of product patents on drugs, (*b*) intensive and costly advertising and sales efforts directed to the physician, and (*c*) the success of the drug companies in persuading the physicians to write their prescriptions in terms of brand names rather than generic names. Each of these sources of market power will be discussed in the succeeding parts of this report, the first of which will be concerned with patents.

Chapter 6. Patents and Prices in World Markets

PATENT PROTECTION IN FOREIGN COUNTRIES

The single most important fact concerning patents on pharmaceutical products is that most countries do not grant them. In this sense the patent situation on drugs is unique. As a general rule, patents on the processes of producing drugs are granted, though even here there are some exceptions, e.g., Italy grants no patents on drug processes and Switzerland grants none on "natural" processes, such as the fermentation process which yields antibiotics. Therefore, whenever in this discussion reference is made to the absence of patent protection, what is meant is the refusal to issue patents on drug products, *per se*. It happens that in drugs, as indeed in most chemical industries, process patents are a relatively weak form of protection because of the comparative ease with which, by a slight change in the process, the patent can be evaded. Probably more than any other industrial area, the chemical industries lend themselves to the manufacture of a given product by several, and often numerous alternative methods or processes; the result is that process patents in drugs are commonly referred to in the trade as constituting only a "basis of litigation" or a "source of employment for patent attorneys."

The basis for withholding patents on new pharmaceutical products is the simple moral belief that no one should have the right to withhold from the public products which relieve suffering and may spell the difference between life and death. No one, it has been felt, should make a monopoly profit on the sale of such products. In contrast, by granting process patents, inventors would be encouraged to develop constantly better and cheaper methods of production, which would result in lower prices of the products themselves:

> The limitation of protection for chemical products in general as well as pharmaceutical products in particular, to

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process claims, is essentially a continental European conception, and is tied up with social thinking in the 19th century during the industrial revolution. It became a matter of practically unassailable dogma that if the public is to receive the benefit of new chemical or pharmaceutical products at a reasonable price and in amounts sufficient to meet the demand, that this could only be accomplished by restricting the inventor to his process, so that others will be encouraged to invent new and improved processes which will make the product cheaper and available in greater quantities.[1]

The facts are thus quite in conflict with the impression which one might have obtained from the testimony of drug company spokesmen concerning Italy. That country, one might have inferred, formerly followed the customary practice of granting patent protection on drugs, but that Mussolini in a dictatorial decree in 1934 abruptly ended this protection, since which time that country has been alone among the great powers in this respect, harboring a "nest of pirates." [2] In actual fact, Italy has never granted product patents (or for that matter, process patents) on drugs. Modeled after the earlier French statute of 1844, the original Italian patent law of 1859 resembled its French counterpart in specifically denying patent protection on pharmaceutical products.[3] The action by Mussolini was only an interpretation, affirming the original statute.

Although in very recent years a few countries have modified their laws to allow patents on drug products, this is still not the case in the great majority of countries. Out of 77 countries for which information has been obtained, only 28 grant product patents in the pharmaceutical field. And some of these 28 specifically exclude patents on "combination" drugs which are a mixture of known ingredients. Others limit the protection to products prepared by means of the process revealed by the patent holder, while still others contain compulsory licensing requirements. Of the 17 foreign countries for which usable price information was obtained for the subcommittee by the Department of State, 6 grant patents on pharmaceutical products, while 11 do not. The 6 countries which do are Australia, Belgium, Canada, Great Britain, India, and Panama, together of course with the United States; the 11 which do not are Argentina, Austria, Brazil, France, Germany, Holland, Iran, Italy, Japan, Mexico, and Venezuela.[4] Of the six foreign countries for which price information has been obtained and which do grant product patents, four (Australia, Canada, Great Britain, and India) have compulsory licensing provisions.[5] Moreover, two of these countries

[1] Leonard J. Robbins, "Pharmaceutical Patents in Foreign Countries," Journal of the Patent Office Society, vol. 37 (1955) (Langner, Parry, Card & Langner, New York).

[2] Hearings, pt. 24, p. 13723.

[3] G. Bergami in "Legislazioni Farmaceutiche D'Europa," Istituto Superiore Di Sanita, Rome, 1959, p. 233.

[4] If a country grants product patents except on combinations of known ingredients, or except where the product is not prepared through the process revealed by the patent holder, the country is included among those granting patent protection since the exceptions are of relatively limited significance. Although France enacted a statute granting patent protection on drug products in February 1959 it is classified among the countries without patent protection. The price information which was obtained during the spring of 1959 reflected the price structure prevailing before the enactment of this law; rigorous price control would have prevented any significant change during the intervening period of approximately 2 months.

[5] In Australia and Canada, compulsory licensing may be invoked after 3 years. In India compulsory licenses may be applied for at any time for patents on foods, medicines, insecticides, germicides, or fungicides or on any surgical or curative device, even when there is no abuse of the patent or failure to work it. In Great Britain compulsory licensing may be invoked after 3 years for all products except foods and medicines for which it may be invoked at any time.

(Australia and Great Britain) will not issue patents on any mixtures of known ingredients. Thus, of these countries only Belgium, Panama, and the United States grant product patents on drugs without imposing any of these limitations or safeguards to the public welfare.

PRICES IN COUNTRIES WITH AND WITHOUT PATENTS

The fact that some countries do not award patents on pharmaceuticals, while others do, raises the question of the difference in drug prices as between the two groups of countries. The policy of withholding patents on drugs has been based in part upon the assumption that prices would thereby be lower. In contrast, spokesmen for the drug industry have long maintained that, by stimulating research, patents result in lower costs and thus lower prices. What are the facts on this critical issue?

As has been noted, the State Department obtained for the subcommittee price information as of the spring of 1959 in leading cities of 17 foreign countries. This price information was introduced in the hearings for each of the four major product areas examined by the subcommittee—corticosteroids, tranquilizers, oral antidiabetics, and antibiotics. The number of countries for which such information was obtained ranged from 8 (Penicillin B) to 17 (tetracycline). Information relating to the status of their patent laws on drugs has also been obtained for each of these countries and is summarized in appendix I.

The comparison is, of course, complicated by the fact that the price level of a given product in a given country is affected by many forces. One of the inherent difficulties of the social sciences is the impossibility of holding constant all factors except the one under examination. However, some of these other factors, such as differences in wage costs, have already been shown to be of very limited significance in this particular industry. Others would tend to raise the average level of drug prices in countries which do not award patents relative to those which do.

As an example of the latter, it happens that underdeveloped countries constitute a larger proportion of the nations which do not award drug patents than of those which do. In most of the underdeveloped countries the drugs themselves are imported, either in finished or bulk form. To whatever are the costs of manufacture where the drug is produced, an importing country must add the further costs of freight, insurance, import duties, and charges. Moreover, if both the country of manufacture and the importing country have price controls on drugs (as is frequently the case), the presumption would be, other factors being equal, that they would be lower in the former, not merely because of the noninclusion of the freight and import charges but also because the price control authorities would have access (at least in theory) to the cost and profit figures of the manufacturers. To the authorities of the country of import, the laid-down price of the imported drug must be regarded as a given datum; their efforts at price control must largely be restricted to limiting markups by wholesalers and retailers. Obviously, these considerations would tend to give greater force to any showing that prices are lower in countries without patent protection.

In table 34 the average [6] prices of countries without product patents are compared with the corresponding figures of countries with product patents for 12 major drug products. It was on these products that foreign price data were introduced in the hearings. The table shows both the generic and brand names of the product, the latter in parentheses. The brand name cited is what appears to be the most widely known brand in the United States. Where no price information for an American company was available, the price used was that of the highest-priced leading European manufacturing seller; the table does not include prices of distributors or of little-known manufacturing firms, United States or foreign. When prices from several U.S. firms in a given foreign country were supplied, the price used is that of what appears to be the leading American seller of the product.

TABLE 34.—*Comparison of average prices in countries without and with patent protection on drug products, Spring 1959*

Product	Average price in countries		b/a
	Without product patents (a)	With product patents (b)	
			Percent
Prednisone (Meticorten)	$14.75	$22.36	151.6
Chlorpromazine (Thorazine)	1.24	1.89	152.4
Prochlorperazine (Compazine)	.80	2.84	355.0
Promazine (Sparine)	1.57	1.98	126.1
Meprobamate (Miltown)	2.53	3.31	130.8
Reserpine (Serpasil)	1.73	2.79	161.3
Tolbutamide (Orinase)	2.03	3.02	148.8
Chlorpropamide (Diabinese)	3.81	4.87	127.8
Penicillin V	10.87	13.19	121.3
Chloramphenicol (Chloromycetin)	3.17	3.77	118.9
Chlortetracycline (Aureomycin)	4.68	5.53	118.2
Tetracycline (Achromycin)	4.63	5.68	122.7

Source: Foreign prices obtained by Department of State through U.S. Embassies abroad in the spring of 1959. U.S. prices obtained from American Druggist Blue Book, 1959–60.

As can be seen, the average priees are higher for countries with than for those without patents in each of the 12 products. At one extreme is prochlorperazine (Compazine), with an average price for countries with patent laws of 255 percent above that of countries without such protection. Even in the product with the smallest difference, Aureomycin, the average price is 18 percent higher in countries with patent protection. In no fewer than 4 of the 12 products, the average price is more than 50 percent higher in countries with product patents and in all products except the antibiotics it is more than 25 percent higher. The fact that the difference is more limited in the case of the antibiotics is not to be unexpected in view of the restrictive cartel agreements entered into between American patent holders and firms in countries which do not have patent protection, e.g., Italy. These agreements, which are described in chapter 8, go to unusual lengths in enhancing prices in countries without patents by restricting the areas in which the foreign companies can sell,

[6] The averages are simple averages. Had the prices for the various countries been weighted by some factor designed to reflect the quantity of drugs consumed, the difference between the average prices for countries with patents as against those without such laws would have been widened owing to the greater importance thereby given to the United States, which with Canada has the highest prices for drugs of any nation in the world.

prohibiting them from selling in bulk form and in some cases requiring them to police the selling prices of their buyers.[7]

Because of the inherent presence of other factors, this table, by itself, should not be construed as demonstrating beyond doubt that prices are higher in countries with patent protection. It is, however, one of a number of pieces of evidence which, *in toto*, are strongly suggestive that such is the case.

The next table presents the same type of comparison but on a somewhat different basis. Here the contrast is limited to prices of what appears to be the leading U.S. seller.[8] For example, the first item does not represent the average prices for prednisone as such (as is the case of the preceding table), but rather the average prices for prednisone as sold in different countries by Schering under its brand name, Meticorten. This type of comparison is limited to fewer products since necessarily excluded are those products (e.g., Thorazine) for which the U.S. seller is only a licensee of a foreign firm and does not sell the product abroad under its brand name.

TABLE 35.—*Comparison of average prices in countries without and with patent protection in drug products patented by U.S. firms and sold abroad by U.S. firms, Spring 1959*

Product	Countries		b/a
	Without product patents (a)	With product patents (b)	
			Percent
Meticorten (Schering)	$15.10	$21.55	142.7
Miltown (Carter-American Cyanamid)	2.52	3.31	131.3
Diabinese (Pfizer)	4.82	4.87	101.0
Penicillin V (Eli Lilly & Co.)	10.97	13.80	125.8
Chloromycetin (Parke, Davis)	3.46	4.08	117.9
Aureomycin (American Cyanamid)	4.71	5.53	117.4
Achromycin (American Cyanamid)	4.68	5.68	121.4

Source: Foreign prices obtained by Department of State through U.S. Embassies abroad in the spring of 1959. U.S. prices obtained from American Druggist Blue Book, 1959–60.

As can be seen, American firms, in selling their own products under their own trade names, charge higher prices in countries which have patent protection than in countries which do not.

Another piece of evidence is a direct comparison of the actual prices for the same drugs in the highly industrialized nations of North America and Western Europe.[9] The purpose would be to ascertain whether among nations which are in an advanced state of technological development patents appear to have an important influence on price. There are seven such countries for which information on prices and patents is available—United States, Canada, Belgium, France, Germany, Great Britain, and Italy.

Before the comparison can be made, however, it is essential to obtain information on one additional variable which in an industrialized country may have a very real effect on manufacturer's prices.

[7] See p. 148, ff.

[8] Miltown is a unique case; it is sold in the United States by Carter Products; abroad it is sold under the trade name Miltown exclusively by American Cyanamid. Carter's prices are used for the United States and American Cyanamid's for foreign countries.

[9] This comparison is limited to 11 products since price information for one of the products included in table 34, prednisone, was available for only 1 of these 7 countries.

This is the vexatious matter of price control, which unfortunately does not lend itself to any form of mechanistic treatment. Some countries have formidable legislation on the statute books, but enforcement is a different matter. In contrast is a country such as Great Britain in which informal control over manufacturers' prices is in fact exercised without the existence of any specific enabling legislation. Under its "voluntary" price control scheme, the Ministry of Health establishes a maximum price, based on specific standards, which the industry "agrees" to abide by, with the entire operation being subject to "the spotlight of publicity" through annual appearances of the Ministry of Health before the Committee on Public Accounts of the House of Commons.

In table 36 the seven countries have been classified into one or another of four categories:

(*a*) Countries without product patents [10] and with price control (Italy and France).

(*b*) Countries without product patents or price control (West Germany).

(*c*) Countries with product patents and price control (Great Britain).

(*d*) Countries with product patents and without price control (Belgium, Canada, and United States).

TABLE 36.—*Prices of leading seller in 7 industrialized countries grouped according to status of patent protection and price control, Spring 1959*

Product	Countries without product patents and with price controls (*a*)		Countries without product patents or price controls (*b*)	Countries with product patents and price controls (*c*)	Countries with product patents and without price controls (*d*)		
	Italy	France	Germany	Great Britain	Belgium	Canada	United States
Chlorpromazine (Thorazine)	$1.22	$0.51	$0.97	$0.77	$1.37	$3.75	$3.03
Prochlorperazine (Compazine)	----------	.80	.80	2.24	1.61	3.60	3.93
Promazine (Sparine)	1.32	----------	.83	.85	----------	3.15	3.00
Reserpine (Serpasil)	1.83	.83	1.05	1.06	1.89	2.70	4.50
Meprobamate (Miltown-Equanil)	1.77	2.65	1.38	1.48	3.25	3.60	3.25
Tolbutamide (Orinase)	2.35	----------	1.85	[1] 1.87	2.45	3.75	4.17
Chlorpropamide (Diabinese)	1.41	----------	[2] 2.22	3.32	4.45	4.77	5.40
Chloramphenicol (Chloromycetin)	3.90	[3] 2.33	[4] 3.70	2.67	3.36	5.61	5.10
Chlortetracycline (Aureomycin)	5.86	3.26	4.31	4.56	----------	5.61	5.10
Tetracycline (Achromycin)	5.86	[5] 2.94	4.31	4.57	6.87	5.66	5.10

[1] Rastinon by Horlicks.
[2] Nadisan by Boehringer.
[3] Chloramphenicol by Opolabo.
[4] Leukomycin by Bayer.
[5] Tetracyne by Clin.

Source: Foreign prices obtained by Department of State through US Embassies abroad in the spring of 1959. U.S. prices obtained from American Druggist Blue Book, 1959–60.

[10] The phrase "without product patents" refers to the absence of product patent protection o pharmaceuticals.

The most striking conclusion to be drawn from the table is the noticeable difference between price levels in groups (*a*) and (*b*) on the one hand and in group (*d*) on the other. Prices in countries without product patents, regardless of whether they have price control, are significantly lower than in countries with patent protection. Moreover, the fact that prices in Germany are relatively similar to those in Italy and France would tend to suggest that it is the absence of patents more than the presence of price controls which is the more important factor in accounting for the lower level of prices. Indeed, the performance of West Germany is of particular interest. Of the seven countries, West Germany has the lowest price for prochlorperazine, promazine, meprobamate and tolbutamide and the second lowest price for reserpine, chlortetracycline, and tetracycline. Prices in Great Britain, which has both patent protection and price control, tend on the majority of products to be somewhere between the levels of countries without patents and those which grant patents but do not exercise price control.

Closer inspection of the data reveals some interesting differences in prices by the same company in countries with, as contrasted to those without, patent protection. Thus Rhone-Poulenc which discovered and patented chlorpromazine (marketed in the United States as Thorazine) sells the product for $1.37 in Belgium but for only $0.51 in France. Similarly, Rhone-Poulenc sells prochlorperazine (Compazine) for $1.61 in Belgium but for only $0.80 in France. American Home Products sells Promazine (Sparine) at a price of $3 in the United States and $3.15 in Canada but for only $1.32 in Italy. American Cyanamid, which holds the exclusive foreign rights to Miltown, sells the product for $3.25 in Belgium and for only $1.38 in Germany. Cyanamid's price in Canada is $3.60 whereas in Italy it is $1.77.

CIBA sells Serpasil for $1.89 in Belgium and for only $0.83 in France; its price in the United States is $4.50 as contrasted to $1.05 in Germany.

Hoechst, the discoverer and patent-holder of tolbutamide (Orinase) has a price of $2.45 in Belgium but only $1.85 in Germany. The other leading oral antidiabetic, chlorpropamide (Diabinese) is sold by Pfizer for $5.40 in the United States and $4.45 in Belgium but for only $3.77 in Holland, another country which does not grant product patents on drugs.

Parke, Davis' price for chloramphenicol, sold under the trade-name of Chloromycetin, is $5.61 in Canada and $5.10 in the United States but $3.90 in Italy. Its price in Belgium is $3.36 but only $2.98 in Holland.

Chlortetracycline is sold by American Cyanamid under its trade name Aureomycin for $5.61 in Canada and $5.10 in the United States but for only $4.31 in Germany. The same company sells tetracycline under its brand name, Achromycin, for $6.87 in Belgium but for only $4.31 in Germany.

A further contrast is provided by the differences in prices between Brazil and Panama—both relatively underdeveloped countries within fairly close proximity of each other. Both have price control laws on drugs, which, however, are not too relevant to manufacturer's prices since both countries import most of their requirements. The one outstanding difference is that Brazil does not award patents on pharmaceutical products while Panama does. The prices to druggists

for the eight products for which price information from both countries is available are shown below:

Product	Brazil	Panama	Product	Brazil	Panama
Prednisone (Meticorten)	$14.15	$22.99	Penicillin V (V-Cillin)	8.67	15.00
Meprobamate (Miltown-Equanil)	2.20	4.79	Chloramphenicol (Chloromycetin)	3.21	5.05
Tolbutamide (Orinase)	2.43	3.64	Chlortetracycline (Aureomycin)	3.40	5.40
Chlorpropamide (Diabinese)	4.59	6.40	Tetracycline (Achromycin)	3.40	5.40

In seven of the eight products prices are more than 50 percent higher in Panama than in Brazil; in two of the eight they are more than 75 percent higher. Broad-spectrum antibiotics which are sold for $3.40 in Brazil cost $5.40 in Panama. The druggist pays $14.15 for prednisone in Brazil but $23 in Panama. And the tranquilizer, Miltown, costs more than twice as much in Panama as in Brazil.

India, which does grant patents on drug products, provides an interesting case example. The prices in India for the broad-spectrum antibiotics, Aureomycin and Achromycin, are among the highest in the world. As a matter of fact, in drugs generally, India ranks among the highest priced nations of the world—a case of an inverse relationship between per capita income and the level of drug prices.

A final comparison involves products discovered by a foreign firm in which the foreign company holds the U.S. patent and which are sold in the United States under license by a leading American drug company. Here, the price of the inventing company in its home country is contrasted with the price of the American licensee in the United States. The purpose of this table is to compare the prices of the U.S. firms which were *not* the inventors with those charged by the firms which did conduct the research and did make the discovery.

TABLE 37.—*Comparison of prices of inventing company in home country and of American licensee in United States*

Product	Inventing company	Home country	Price in home country	U.S. licensee	Price in United States	Price in United States as percent of home country
Chlorpromazine (Thorazine)	Rhone Poulenc	France	$0.51	Smith Kline & French	$3.03	594.1
Prochlorperazine (Compazine)	do	do	.80	do	3.93	491.3
Promazine (Sparine)	do	do	[1].83	American Home Products	3.00	361.4
Reserpine (Serpasil)	CIBA	Switzerland	[2] 1.05	CIBA	4.50	428.6
Prednisone	Syntex	Mexico	[2] 15.07	Schering	17.90	118.8
Insulin [4]	(University)	Canada	.46	Lilly	.84	182.6
Insulin, Protamine Zinc [4]	Nova Terapeutisk	Denmark	.49	do	.99	202.0
Tolbutamide (Orinase)	Hoechst	Germany	1.85	Upjohn	4.17	225.4
Synthetic penicillin (Syncillin)	Beecham	England	7.68	Bristol	18.00	234.4
Griseofulvin (Fulvicin)	Glaxo	do	8.52	Schering	13.00	152.6
Sulfisomidine (Elkosin)	CIBA	Switzerland	[3] 2.00	CIBA	3.30	165.0

[1] Not reported from France; this price in West Germany; $1.32 in Italy.
[2] Not reported from Switzerland; this price in West Germany.
[3] Sold by Sheremex.
[4] 10 cubic centimeters of 40 units per cubic centimeter.

In every instance the price of the U.S. licensee is higher—and usually substantially higher—than that charged by the inventing company in its home country. In the case of chlorpromazine (Thorazine), Smith Kline & French's price in the United States is nearly six times that of the inventing company, Rhone-Poulenc, in France; the American subsidiary of CIBA, Switzerland, charges a price for reserpine which is more than four times CIBA's price in West Germany.[11] Upjohn's price for tolbutamide is more than twice Hoechst's price in Germany. In both the basic form of insulin and the new protamine insulin the U.S. price is about twice that of the country in which they were discovered, Canada and Denmark, respectively; insulin is thus one of the few products which is sold at a substantially higher price in the United States than in Canada. The American licensee, Schering, sells the new antibiotic, griseofulvin, used against fungus infections, for $13; Glaxo, which discovered the drug, sells it in England for $8.52.

There would thus appear to be a rather strong basis for the conclusion that in the drug field patents accomplish their intended purpose of giving the patentholder a private monopoly, which, not surprisingly, is exercised in such a way as to result in considerably higher prices than would prevail in the absence of patent protection.

Chapter 7. Patents and Drug Discoveries

The fact that drug prices tend to be substantially higher in countries which award patents on pharmaceutical products, as compared to those which do not, raises the question of whether the benefits resulting from a policy of awarding patents in this particular industry justify the higher cost. The soundness of the classic justification for a patent policy for industry as a whole or for any individual industry other than drugs is not at issue here, nor is the general desirability of the U.S. patent system under question, either explicitly or implicitly. As noted in the preceding chapter, most countries do not award patents on pharmaceutical products. Because of their unique properties of preventing suffering and preserving life itself, drug products, more frequently than not, have been specifically excluded from the general patent law. And because of these unique properties, it is appropriate to inquire into the question of whether the benefit of the patent grant in this industry justifies the higher price of the product. No final or determinative answer to such a question can be reached with existing information and resources. Any attempt to do so would, among other things, involve such impossible undertakings as attempting to determine the proportion of the higher price under patents that would be offset by new discoveries made possible by the awarding of patents.

This is not to say, however, that no light at all can be shed on the question. It can be approached by a number of methods of analysis, among which is the technique employed in the preceding chapter. In other words, what have been the contributions in the form of new drug discoveries of countries which do not grant patent protection as compared to those which do?

[11] Since no price information is available for Switzerland, the comparison is made with West Germany.

DRUG DISCOVERIES WITH AND WITHOUT PATENTS

At the time of the appearance before the subcommittee of the Pharmaceutical Manufacturers Association, the subcommittee staff prepared and placed in the record a list of important drugs showing their country of origin.[12] No list could, of course, be exhaustive; and often it is difficult accurately to determine origin, since many discoveries appear to occur almost simultaneously from researchers working independently. The attempt of the staff was merely to present a representative listing of important discoveries on which information as to origin could be obtained from available sources.

Subsequently the Pharmaceutical Manufacturers Association submitted its own list prepared by an industry subcommittee.[13] The major difference between the two lists was the fact that PMA included a large number of molecular modifications of the basic drug; and many of these modifications were made in U.S. corporate laboratories.[14] In contrast, the tables prepared by the subcommittee staff sought to list the origins of the basic drug inventions, themselves, which constituted a substantial advance in the healing arts. Table 38 represents a revision of the earlier staff compilations, designed to include additional important drugs supplied by the PMA list as well as corrections in the earlier tables. Inasmuch as most foreign countries did not introduce patent systems until around the middle of the 19th century, the listing excludes products discovered prior to 1875.[15] Under "Foreign discoveries" the items are grouped into two classes: those made in countries without patents and those made in countries with patents.[16] England represents an unusual situation in that it did not award product patents on drugs during the period 1919–49; the discoveries attributed to England are distributed in accordance with these changes in its patent policy. The table also shows in separate columns "U.S. commercial discoveries" (products discovered by drug companies) and "U.S. noncommercial discoveries" (products discovered in universities, private research foundations, governmental bodies, etc.).

[12] Hearings, pt. 19, p. 10943.

[13] Ibid, p. 10840. This list was prepared by an industry committee composed of representatives of Squibb, Wyeth, and Smith Kline & French.

[14] In some drugs PMA listed European discovery and U.S. development, frequently ignoring clinical work in Europe but basing development on the testing in this country required to secure the FDA approval of a new drug application.

[15] Among the products in widespread use today which were discovered prior to 1875 are the following:

Benzoic Acid (Germany)	1832
Chloroform (France)	1831
Cocaine (France) (for anesthetic use)	1868
Codeine (France) (isolation)	1832
Cod Liver Oil (England) (for rickets)	1782
Digitalis (England) (introduced in medicine)	1780
Ergot (England) (used in medicine)	1560
Iodine (France)	1812
Ipecac (Holland) (introduced in Europe)	1648
Potassium Iodide (England) (epilepsy)	1857
Rochelle Salt (France)	1862
Amyl Nitrite (U.S. commercial)	(a)

[a] 1860's.

[16] The antidiabetic drug, Diabinese, is omitted from the listing since its country of origin is currently a matter of dispute; the patent application is in interference, the parties to which are Hoechst of West Germany and Pfizer of the United States.

TABLE 38.—*Listing of drugs according to place of discovery*

Countries without product patents	Countries with product patents			
	Foreign	United States		
		Commercial	Noncommercial	
HORMONES:				
Cortical steroids:				
Desoxycorticosterone (Percorten) (Switzerland) 1939		Cortisone 1948		
Prednisone (Mexico) 1955		Methylprednisolone 1957		
		Triamcinolone 1958		
		Dexamethasone 1958		
Sex hormones:				
Ovarian extract (Switzerland) 1913	Estrogenic substances (Canada) 1943	Norethandrolone (Nilevar) 1956	Estrone (St. Louis University) 1939	
Pregnanediol (England) (isolation) 1927		Norethynodrel (Enovid) 1957		
Androsterone (Switzerland) 1931		Fluoxymesterone (Halotestin) 1957		
Dehydroisoandrosterone (Switzerland) 1934				
Progesterone (Switzerland) 1934				
Testosterone (Switzerland) 1935				
Dienestrol (England) 1938				
Aldosterone (Switzerland and England) 1939				
Methyltestosterone (Switzerland) 1947				
Hydroxyprogesterone caproate (Delalutin) (Germany) 1956				
Norethindrone (Norlutin) (Mexico) 1957				
Other:				
		ACTH 1950	Epinephrine (Johns Hopkins University) 1897	
ANTIDIABETIC DRUGS:				
Protamine zinc insulin (Denmark) 1937	Insulin (Canada) 1922	Phenformin (DBI) 1959		
Isophane insulin (Denmark) 1950				
Tolbutamide (Orinase) (Germany) 1954				
ANTIBIOTICS:				
Penicillin G (England) 1929	Griseofulvin (England) 1954	Chlortetracycline 1948	Procaine penicillin G (Dr. Simon Ruskin) 1945	
Aerosporin (Polymixin B) (England) 1947	Phenoxyethyl penicillin (England) 1959	Oxytetracycline 1949	Chloramphenicol (Yale University) (Dr. Paul Burkholder) 1947	
Spiramycin (France) 1953		Viomycin 1950	Bacitracin (U.S. Army) 1948	
Penicillin V (phenoxymethyl penicillin solid salt) (Austria) 1955		Penicillin O 1950	Streptomycin (Rutgers University) (Dr. S. Waksman) 1948	
Kanamycin (Japan) 1958		Penicillin G benzathine 1951	Tyrothricin (Rockefeller Institute) 1949	
		Erythromycin 1952	Neomycin (Rutgers University) 1951	
		Carbomycin 1953	Fumagillin (New York Botanic	
		Tetracycline 1953		
		Cycloserine 1955		
		Oleandomycin 1956		

TRANQUILIZERS AND CENTRAL NERVOUS SYSTEM DRUGS:

- Barbital (Veronal) (Germany) 1903
- Phenobarbital (Luminal) (Germany) 1912
- Pentobarbital (Nembutal) (Germany) 1930
- Meperidine (Demerol) (Germany) 1939
- Methadone (Germany) (analgesic) 1942
- Mephenesin (England) 1946
- Mephobarbital (Germany) 1935
- Lidocaine (Xylocaine) (Sweden) 1946
- Promethazine (Phenergan) (France) 1947
- Phenylbutazone (Butazolidin) (Switzerland) 1952
- Reserpine (Switzerland) 1953
- Chlorpromazine (Thorazine) (France) 1953
- Promazine (Sparine) (France) 1954
- Mepazine (Pacatal) (Germany) 1954
- Benactyzine (Suavitil) (Denmark) 1954
- Prochlorperazine (Compazine) (France) 1954
- Glutethimide (Doriden) (Switzerland) 1954
- Methylphenidate (Ritalin) (Switzerland) 1958
- Trimeprazine (Temaril) (France) 1958

VACCINES, POLIO:

- Salk vaccine (University of Pittsburgh) 1953
- Sabin vaccine (University of Cincinnati) 1959

GENERAL DRUGS:

- Acetanilid (Germany) 1886
- Acetophenetidin (Phenacetin) (Germany) 1890
- Aminopyrine (Germany) (introduced in medicine) 1896
- Antipyrine (Phenazone) (Germany) (introduced in medicine) 1884
- Arsphenamine (Salvarsan) (Germany) 1909
- Aspirin (Germany) 1898
- Atabrine (Quinacrine) (Germany) 1930
- Colchicine (England) (gout) 1934
- Cyclophosphamide (Cytoxan) (Germany) 1959
- Dextran (Sweden) (plasma extender) 1944
- Dextrose (Germany) (synthesized) 1887
- Dextroamphetamine sulfate (Germany) 1943
- Diethylpropion (Tenerate) (Germany) 1943
- Digilanid (Germany) (introduced in medicine) 1926
- Digitoxin (England) (isolated) 1936
- Diphenylhydantoin (Germany) 1936
- Ergonovine (Germany) 1937
- Ergotamine (Germany) 1920
- Hydroxyzine (Atarax) (Belgium) 1952
- Rauwolfia Serpentina (India) 1953
- Primidone (England) 1954
- Chlorambucil (Leukeran) (England) 1957
- Chloroguanide (England) (antimalarial) 1954
- Cyclopropane (Canada) 1929
- Mechlorethamine (England) 1949
- Meclizine (Belgium) 1951
- Myleran (England) 1953
- Pentolinium Tartrate (England) 1953
- Triiodothyronine (Cytomel) (England) 1952
- Triacetyloleandomycin 1958
- Vancomycin 1958
- Demethylchlortetracycline 1959
- Butabarbital (Butisol) 1937
- Meprobamate 1955
- Perphenazine (Trilafon) 1957
- Phenaglycodol (Ultran) 1957
- Chlorzoxazone 1958
- Phenelzine 1959
- Acetazoleamide (Diamox) 1953
- Aminophylline 1937
- Chlorothiazide (Diuril) 1957
- Chlorpheniramine 1948
- Dextropropoxyphene 1957
- Dicyclomine 1950
- Dimenhydrinate 1949
- Diphenhydramine (Benadryl) 1945
- Ephedrine 1924
- Glutamic acid (mental alertness) 1943
- Hexylresorcinol 1924
- Hydrochlorothiazide 1959
- Inversine 1956
- Isoniazid 1952
- Mercaptopurine 1953
- Nitrofurazone 1946
- Nitrofurantoin 1953
- Prantal 1952
- Probenecid 1950
- Propantheline (Pro-Banthine) 1953
- Garden) 1952
- Nystatin (State of New York) 1954
- Chymotrypsin (Rockefeller Institute) 1955
- Dicumarol (University of Wisconsin) 1941
- Fibrinogen (Harvard) 1947
- Heparin (Johns Hopkins) 1928
- Hyaluronidase (Rockefeller Institute) 1949
- Streptokinase—streptodornase (New York University) 1951
- Trypsin (Rockefeller Institute) 1951

TABLE 38.—*Listing of drugs according to place of discovery*—Continued

Countries without product patents	Countries with product patents		
	Foreign	United States	
		Commercial	Noncommercial
GENERAL DRUGS—Continued			
Hydralazine (Apresoline) (Switzerland) 1950		Pyribenzamine 1946	
Ichthammol (Germany) 1886		Sulfadiazine 1940	
Magnesium Trisilicate (England) 1936		Sulfaguanidine 1941	
Nylidrin (Germany) 1954		Sulfamerazine 1946	
PAS (para-aminosalicylic acid) (Sweden) 1944		Sulfamethoxypyridazine (Kynex) 1957	
Penicillinase (England) 1940		Sulfathalidine 1943	
Petn (Sweden) 1950		Sulfathiazole 1939	
Phenindione (France) 1909		Sulfisoxazole (Gantrisin) 1949	
Phenmetrazine (Preludin) (Switzerland) 1953		Theophylline 1950	
Phenylephrine (Germany) 1934		Thio-tepa 1959	
Pilocarpine (England) (on heart) 1947		Undecylenic acid 1949	
Pituitrin (France) (oxytocic) 1909		Vitamin B-12 1948	
Potassium Bromide (England) 1935			
Primaquine (Germany) 1926			
Privine (Germany) 1941			
Promethazine HCl. (France) 1937			
Sulfadimethoxine (Madribon) (Austria) 1958			
Sulfamethazine (England) 1941			
Sulfanilamide (Germany) 1935			
Sulfapyridine (England) 1938			
Sulfisomidine (Elkosin) (Switzerland) 1944			
Thiocol (Switzerland) 1898			
Tolazoline (Switzerland) 1948			
Urethan (England) 1946			

If the table meets its intended objective of being at least broadly representative of the locus of drug discovery, it can be employed as a useful tool of analysis, particularly if its showings are overwhelmingly on one side or the other of a given issue. On the question of whether more of the foreign discoveries have been made in countries with than without product patents, the evidence is indeed overwhelming. Drugs discovered in foreign countries without product patents outnumber those discovered in countries with such protection in the order of 10 to 1.

On reflection, what is most surprising about this ratio is the relatively small number of drugs discovered in foreign countries which do grant patent protection. Only three products, estrogenic substances, insulin and cyclopropane, are attributed to Canada, which is not only one of the world's important industrial powers but has a long-time history of excellence in medical care. Only two products, hydroxyzine (Atarax) and meclizine, are listed for Belgium, another industrialized country. This is in contrast to 16 for Switzerland. More than one-quarter of the foreign discoveries came from one country, Germany. Indeed, it may come as something of a surprise to note that the following drugs which are among the most widely used in the world were discovered in countries which have never awarded patents on pharmaceutical products.

TABLE 39.—*Examples of foreign discoveries in countries without product patents*

Germany:
- Acetanilid
- Acetophenetidin (Phenacetin)
- Aspirin
- Atabrine (Quinacrine)
- Dipheny hydantoin
- Meperidine (Demerol)
- Methadone
- Pentobarbital (Nembutal)
- Phenobarbital (Luminal)
- Phenylephrine
- Primaquine
- Tolbutamide (Orinase)

Switzerland:
- Androsterone
- Desoxycorticosterone
- Hydralazine (Apresoline)
- Phenmetrazine (Preludin)
- Progesterone
- Reserpine
- Sulfisomidine (Elkosin)
- Testosterone

France:
- Cocaine
- Chlorpromazine (Thorazine)
- Promazine (Sparine)
- Prochlorperazine (Compazine)

Sweden:
- Lidocaine (Xylocaine)
- Para-Aminosalicylic acid (PAS)
- Pentaerythritoltetranitrate (PETN)

Mexico:
- Prednisone
- Norethindrone (Norlutin)

The next question is what has been the record of the United States in comparison with the achievements of foreign countries, particularly those which do not award product patents. Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, has contended that comparisons of drug discoveries in the United States to those in other countries should be limited to the last 20 years. Referring to the original staff compilations, he stated:

> More than half of all the foreign items cited date back before 1939, when the U.S. drug industry was just pioneering modern chemotherapy. A comparison of American drug progress which has been great only in the last 20 years, when stacked up against all the rest of the world for a period reaching back centuries before the American Revolution is regarded by some as intended for only one purpose—to discredit the very real achievements that have

transferred leadership in medical research from Europe to this country in the past generation.[17]

But this merely begs the question. If patents are in fact the key to the unlocking of new drug discoveries, why has it functioned effectively in this country only for the last 20 years? For over a century foreign countries which do not grant patent protection have been making important new drug discoveries. The fact that they were doing so prior to the last 20 years, while the United States, which has granted full patent protection since 1790, was failing to develop an important drug industry of its own, only serves to cast further doubt on the essentiality of patent grants to scientific progress in this industry.

In table 38 the significant discoveries by the U.S. drug industry are shown in the middle column; those which took place in universities, foundations, and other noncommercial sources are listed in the right-hand column. In trying to appraise the importance of patents, the latter pose something of a problem. For some of these products the existence of patent protection undoubtedly contributed to the discovery. This would be true, for example, where the research, though conducted in a university, was financed by a drug company; a case in point might be chloramphenicol. For others, the importance of patents is much less clear. This would be particularly true where the research was financed by solicitation of funds from the public or conducted by Government agencies; an example of the former would be Salk polio vaccine and of the latter bacitracin, which was discovered by Dr. Frank Meleney of Columbia University Hospital working under a grant from the U.S. Army. The number of products in this category, however, is not sufficient to affect any of the major conclusions to be drawn from the table.

U.S. discoveries are outstanding in corticosteroids and antibiotics. In both categories the discoveries in U.S. commercial sources alone outnumber those listed for foreign countries. But even here a few caveats should be noted. During the period since its introduction the most important corticosteroid in terms of sales has been prednisone which, according to the Pharmaceutical Manufacturers Association, was not invented by an American firm. Most of the supremacy of the U.S. firms in the antibiotics field, and much of their income, was based upon the tetracycline family, discovered during 1948–53, as well as chloramphenicol, discovered under a grant from Parke, Davis in 1947. Penicillin V from Austria and Kanamycin from Japan represent more recent contributions from countries which do not grant patent protection. In the other product categories, the U.S. discoveries (even including those from noncommercial sources) are easily surpassed by discoveries in those foreign countries which do not award patents on pharmaceuticals. The conclusion would appear to be warranted that in this industry the mere existence of patent protection is not a guarantee of invention, nor is its absence much of a barrier.

HISTORY OF DISCOVERY IN INDIVIDUAL PRODUCT GROUPS

Another way of appraising the importance of patents to drug discovery is by examining the history of individual product groups. The information presented during the hearings enables this more

[17] Hearings, pt. 19, p. 10836.

detailed approach to be followed for the four product groups examined by the subcommittee—corticosteroids, tranquilizers, oral antidiabetics, and antibiotics.

It is sometimes said that although an American firm did not discover a drug, it nonetheless "developed" it. What this usually means is that it carried out the clinical testing necessary to get the drug approved by the Food and Drug Administration, though often the actual work was done in hospitals at little or no expense to the company itself. Indeed, through grants by the National Institutes of Health, part of the cost of this clinical testing is often borne by the Government. In any event the routine work of determining the reactions of human beings to a drug, while an essential step in determining its usefulness and safety, cannot be compared in terms of conceptual importance to the actual discovery of the drug itself.

Corticosteroids.—In this group of drugs, used in the treatment of rheumatoid arthritis and many other ailments, the first breakthrough was the discovery of the use of cortisone at the Mayo Clinic in Minnesota, aided by financial and other assistance from Merck. One of the discoverers, Dr. Philip S. Hench, of the Mayo Clinic, received the Nobel Prize in 1950 for this work.[18] The substance, being a product of nature, was not patentable.

In the fifties, laboratory experimentation resulted in a new corticosteroid which was given the generic name of prednisone. The Pharmaceutical Manufacturers Association credits the discovery of this product to a small foreign company, Syntex Corp. of Mexico.[19] As of early 1961, however, the product was still involved in an interference proceeding in the U.S. Patent Office; four companies—Syntex, Schering, Pfizer, and Merck—were claiming priority in invention; and the Patent Office had yet to make a determination. Several medical experts appearing before the subcommittee testified that prednisone constituted a distinct therapeutic improvement over the earlier product, cortisone. No such agreement, however, existed with respect to the later molecular modifications which followed in rapid order.[20] These were 6-methylprednisolone (1957), triamcinolone and dexamethasone (1959).

Tranquilizers.—Both of the two most widely used "potent" tranquilizers, chlorpromazine (Thorazine) and prochlorperazine (Compazine), were discovered by the French company Rhone-Poulenc, a point on which the Pharmaceutical Manufacturers Association concurs. In its discovery of the tranquilizing effects of these drugs, known generally as phenothiazines, this company laid the basis for a vast array of slight molecular modifications developed both in this country and abroad, including promethazine (Phenergan), chlorpromazine (Thorazine), promazine (Sparine), perphenazine (Trilafon), prochlorperazine (Compazine), trifluoperazine (Stelazine), and trimepazine (Temaril).

Regarding the many "potent" tranquilizers which have resulted from the intensive efforts to produce a new and supposedly better tranquilizer, Dr. Heinz Lehmann, author of the first publication in the English language on tranquilizers and a member of the Advisory

[18] Hearings, pt. 14, p. 8015.
[19] Hearings, pt. 19, p. 10844. Syntex was subsequently acquired by Allen & Co., a U.S. financial house.
[20] Hearings, pt. 14, pp. 7984–7985.

Committee of the Psychopharmacology Service Center of NIH, testified:

> There hasn't been a very much better one than the very first ones that came out, in the 6 or 7 years of frantic research since then.[21]

The American firm Smith Kline & French received exclusive rights of exploitation of the American market under a patent licensing agreement from the French company.[22] During the hearings, Mr. Walter A. Munns, president of SKF, contended that his company did much of the clinical testing for chlorpromazine (Thorazine) and thus, in fact, was responsible for its commercial development. However, Dr. Lehmann described how the undesirable drowsiness of the antihistamines had been turned into a virtue:

> About 1950 the French anesthetist Laborit commissioned the laboratories of the pharmaceutical manufacturing plant of Rhone-Poulenc to develop a phenothiazine compound with minimal antihistaminic and maximal sedative properties.
>
> * * * * *
>
> So Poulenc Laboratories came up with such a drug and that was chlorpromazine or Thorazine. Laborit used it in anesthesia, and a little later, a year or two later, the French psychiatrists Delay and Denicker at the University of Paris used the same drug in mentally ill people who were very excited, because it had these drowsiness producing properties and they wanted to see what it would do in people who needed to be sedated.
>
> They found it was very effective in very severe mental illness, particularly during the acute stage of excitement.[23]

Later Dr. Fritz Freyhan, psychiatrist and director of research at the Delaware State Hospital, heard about the drug, chlorpromazine, through literature in Europe and tried to find out whether it was available for investigation in this country. He was told by Rhone-Poulenc to get in touch with Smith Kline & French Laboratories, its exclusive licensee in the United States.[24] The drug was first cleared by the Food and Drug Administration for use in nausea and vomiting. When Dr. Freyhan contacted SKF about investigating the tranquilizing effects of chlorpromazine, he reported, "They were delighted that there was interest in this drug." [25]

Meanwhile, Dr. Frank M. Berger, a Czech refugee, had discovered a muscle relaxant, mephenesin, in England and had come to the United States where he was able to patent a closely related product, meprobamate (Miltown, Equanil), as coinventor with another employee of Carter Products, Inc. Under the trade names, Miltown and Equanil, this product is by far the leading seller of the "mild" tranquilizers.

The final tranquilizing drug examined by the subcommittee was reserpine, which is a refinement of the rauwolfia root whose use in India goes back to the days of antiquity.[26] Rauwolfia was employed as a remedy in the treatment of the insane and for insomnia; it was

[21] Hearings, pt. 16, p. 9029.
[22] Ibid., pp. 9024, 9025.
[23] Hearings, pt. 16, p. 9025.
[24] Hearings, pt. 16, p. 9034; pt. 17, p. 9475.
[25] Hearings, pt. 16, p. 9035.
[26] Ibid., pp. 9437 ff.

used for fevers, as an antidote for snakebites and insect bites, for headaches, and a wide variety of other ailments. In 1931 two Indian chemists isolated some of the active ingredients of the crude rauwolfia root; similar work was carried on by two Indian physicians. The Indians did considerable testing of the material and found that it had a hypnotic effect, reduced blood pressure and reduced a mental patient's tendency to violence. They learned that the action of rauwolfia is delayed, and that treatment must cover an extended period of time. They found that the drug promised real usefulness in the treatment of hypertension.

In 1933 an eminent Indian physician presented in Indian chemical and medical journals the evidence that crude rauwolfia had remarkable abilities in producing sedation and lowering blood pressure. Interest spread to the West and by the midthirties, Swiss, Dutch, and French chemists, working independently and with their own funds, were examining rauwolfia and attempting to isolate the various alkaloids. By 1940 experimental work was being done in the United States.

Prior to 1947 research workers in CIBA's laboratories in Switzerland had done some work on the drug but abandoned the project. Then an English Nobel Prize winner, Sir Robert Robinson, asked CIBA for a few grams of ajmaline, one of the ingredients isolated by the Indians. This was supplied, and the CIBA research workers decided to examine the remaining material. By 1950, they had isolated serpentina, which had already been achieved by the Indians; by 1951 they began to examine the brown, muddy fraction that remained. The CIBA work in Switzerland resulted in the development of reserpine, on which it was granted the U.S. patent.

Oral antidiabetics.—The subcommittee examined both tolbutamide (Orinase) and chlorpropamide (Diabinese)—the two leading oral antidiabetic drugs. For the discovery of the first there is no question that credit must go to the Hoechst Co. of Germany. Although extensive pharmacological and some clinical testing of tolbutamide (Orinase) had been performed in Germany, the Upjohn Co., which confirmed the German tests, is listed by the Pharmaceutical Manufacturers Association only as the "developer"; Dr. E. Gifford Upjohn, president of the company, testified that his company had repeated and extended the German tests in a prolonged clinical testing program in order to secure approval by the Food and Drug Administration.

The patent for chlorpropamide (Diabinese), sold by Pfizer, is in an interference proceeding, the parties to which are Hoechst and Pfizer. The Pharmaceutical Manufacturers Association lists Lilly as the discoverer of the product and Pfizer as the "developer." At the outset of the interference proceedings, Lilly was also a party but withdrew, conceding priority to Pfizer. Phenformin, marketed under the trade name of DBI by U.S. Vitamin and Pharmaceutical Corp., belongs to a different chemical family. The product is a molecular modification of the earlier biguanides, which were subjected to intensive examination by scientists prior to the discovery of insulin in 1920.[27] Further work was discouraged by their toxicity, and the project was dropped after the appearance of insulin. The market for DBI has also been limited for the same reason.

Antibiotics.—Any examination of the origin of antibiotics must go back to the discovery of penicillin in 1929 by Sir Alexander Fleming

[27] The PMA list ascribes the discovery of phenformin to U.S. Vitamin Corp.

and to the early investigative work carried on at Oxford University and English hospitals a few years later. It was in England that the remarkable therapeutic properties of the drug were first recognized. It was not until 1941 that a small group of English physicians arrived in this country and talked, among others, with officials of the Office of Scientific Research and Development. The immediate problem was commercial production in quantities adequate for the war effort. To this end the U.S. Government agency contributed large funds and enlisted the efforts of drug manufacturers, universities, and Government research groups.

For some time it has been recognized that the significant contributions which formed the basis of commercial production had emanated from two universities and the Northern Regional Research Laboratory of the U.S. Department of Agriculture in Peoria, Ill.[28] In conformity with the patent policy of that agency, patents on these developments were dedicated to the public and thus made available to the 20-odd companies which had been financially aided by the U.S. Government to enter into production.

The next developments in the field of antibiotics were the discovery of streptomycin at Rutgers University with the assistance of Merck and of chloramphenicol (Chloromycetin) at Yale University, the latter with the aid of Parke, Davis. As the recognition grew that nature provided a multitude of molds, the efforts of the private companies in screening them were intensified, and within a short time a number of new antibiotics appeared on the market. These included particularly the tetracycline family—chlortetracycline (Aureomycin) oxytetracycline (Terramycin) and tetracycline. All came from the laboratories of the large U.S. drug companies and their importance cannot be minimized. It is only fair to state, however, that their appearance was made possible, first, by the basic discoveries of the British and later by the creative solution of the Government scientists at Peoria Laboratory of problems of large-scale production. The discovery of new molds in nature was undoubtedly time-consuming and costly to the companies in terms of laboratory and clinical testing, but it hardly falls in the same creative category as the earlier work.[29]

The newer penicillins are of particular interest. Benzathine penicillin was the first to appear. In 1952 four companies, Wyeth, Lilly, Pfizer, and Bristol, each of whom had substituted benzathine for procaine in the penicillin compound, were involved in an interference in the U.S. Patent Office respecting priority of discovery. Subsequently the three latter companies conceded priority to Wyeth in return for a license to market the product under their own trade name only.[30] Here is an instance where discovery clearly lay in an American source, with several companies hitting upon it almost simultaneously.

The situation is different in the case of phenoxymethyl penicillin, commonly known as penicillin V. As early as 1951 Lilly secured a patent of unusual breadth which, it turned out, embraced this product among many others; at the time Lilly apparently did not recognize

[28] Cf. Federal Trade Commission, "Economic Report on Antibiotics Manufacture," 1958, Appendix A.

[29] Two other areas in the antibiotic field should be briefly noted. PMA lists "antifungal antibiotics" in a separate grouping. Two products are shown—nystatin discovered by an employee of the New York State Department of Health, and griseofulvin which came out of the research laboratories of Imperial Chemical Industries, England.

[30] PMA lists benzathine penicillin as a discovery of Wyeth, subsidiary of American Home Products.

that it had any unusual therapeutic advantages and commercial value. It was not until the Austrian company Biochemie in 1953 filed a patent application on a solid, crystalline phenoxymethyl penicillin acid salt that Lilly learned of its possibilities. It immediately entered into a cross-licensing patent agreement with Biochemie under which Lilly secured use of the Austrian development.[31] Actual marketing of the product by Lilly began in 1955, 6 years after the issuance of the first Lilly patent.

Finally, consideration should be given to the new so-called synthetic penicillin. Actually this label is misleading since phenoxyethyl penicillin (Syncillin, Maxipen, Chemipen) is a homolog of phenoxymethyl penicillin (penicillin V). Both contain the same essential ring structure which is common in all the penicillins and which is produced by microbic fermentation. This latest penicillin development originated in Beecham Laboratories, England. A copy of the licensing agreement under which Bristol markets the product under the Bristol trademark is contained in the subcommittee record.[32]

An independent evaluation of the contributions of the U.S. drug industry versus those of foreign countries (most of which, as has been seen, do not award patents on drug products) was offered before the subcommittee by Dr. Frederick H. Meyers, professor of pharmacology, University of California. Giving credit to the American drug industry for the hydrazides (important in the treatment of tuberculosis), the corticosteroids, the newer diuretics, and the screening and development of important antibiotics, Dr. Meyers nonetheless held that "our industry has usually followed and often after a clear lag":

> The drug business makes many references to the patients benefited by the revolution in therapy of the past 25 years. The progress is real but how should we distribute our gratitude?
>
> Without going back too many years and penalizing our relatively young industry, let me provide some examples. Nonindustrial American investigators provided the anticoagulants, anterior pituitary hormones and, with help from the British, the antithyroid drugs.
>
> Most of the progress has come from European and British researchers both industrial and independent. The antihistamines, synthetic morphine substitutes, the only recently introduced local anaesthetic that has any real advantage, new antimalarials (in spite of our own screening program), synthetic estrogens, insecticides and others. The most potent treatment for hypertension, the ganglion blocking agents, is British in origin.
>
> Reserpine, the most common treatment for hypertension, was brought to the attention of the British and Swiss by two Indian cardiologists. The first phenothiazine tranquilizers were synthesized in France and their significance, that is the idea of the tranquilizing drug effect, was developed by a French Army surgeon and by French psychiatrists.
>
> Oral insulin substitutes were French in origin really, although best exploited by the German drug trade. Penicillin is acknowledged to be a British discovery but it is not

[31] Hearings, pt. 26, p. 16348.
[32] Ibid., pt. 26, p. 16756.

so freely acknowledged that in the wartime developmental phase, the significant technological advance was made in a Department of Agriculture Laboratory and that American industry ventured no capital.

The War Production Board ventured the capital. What has the American industry to its credit? Following the ideas of Dubos and Waksman, it screened a tremendous number of soil samples and has contributed many antibiotics beyond streptomycin.

That is, once the basic work was done, the assets of the industry are such that they could throw a tremendous effort into this, and one must acknowledge that they have contributed antibiotics more useful or newer than streptomycin.

The hydrazides that are so important in the treatment of tuberculosis are American. You have already heard opinions as to how credit for the corticosteroids should be apportioned. I hesitate to reopen that discussion.

I personally would have felt that the Diuril type of diuretic, in effect an orally active replacement for the mercury diuretics that had to be injected, is a great credit to the industry.

Mr. Connor who appeared before you earlier, says in Drug and Cosmetic Industry that a discovery by Dr. Shartz of Boston "set off a race between several pharmaceutical companies to see which one could reach the goal line first."

He seems to feel there was a certain inevitability in the development of this product of his. Actually I think he misunderstands the significance of the research and I tend to insist that he take some credit for it.[33]

BASIC RESEARCH VERSUS PRODUCT DEVELOPMENT

What is perhaps most disturbing about the record of inventiveness of the U.S. drug companies is the relative paucity of significant drug discoveries since around the midfifties. Most of the contributions for which the American drug industry is most noted took place in the late forties or early fifties. Among the hormones, newer corticosteroids have, of course, made their appearance, but cortisone was discovered in 1948 and ACTH 2 years later. Whether the newest steroids represent real improvements over the earlier steroids is very much in question.[34] Since the discovery of tetracycline in 1955, no important antibiotic of American origin has made its appearance, the most widely used of the more recent antibiotics, oleandomycin, accounted in 1959 for only 5.4 percent of the sales to the U.S. drug trade of all broad spectrum antibiotics and only 0.4 percent of sales to hospitals. The leading seller among the oral antidiabetic drugs is of German origin. Among the tranquilizers, the U.S. contributions since the introduction in 1955 of meprobamate have largely consisted of further types of phenothiazine derivatives, none of which has achieved widespread usage. Of the 42 general drugs shown on table 38 as having been discovered by U.S. drug companies, only 6 have made their appearance since 1955.

[33] Hearings, pt. 18, pp. 10393-10394.
[34] See ch. 12, p. 202.

Why has the record of the American drug companies not been more productive in recent years? At least one possible explanation was advanced before the subcommittee by two physicians, Dr. A. Dale Console and Dr. Haskell J. Weinstein, both of whom had formerly been medical directors of large drug companies and were therefore in a position to have learned something at first hand about the nature of research conducted by the industry.[35]

According to Dr. Console, formerly medical director of Squibb, the basic trouble is that too much of the research is misdirected; which, however, is commercially possible because the companies are able to "market so many of their failures."

> While the industry spokesmen would have us believe that all research is on wonder drugs or better medicinal products this is no more true than the euphemism of postgraduate medical education. They stress that there are many failures for each successful drug. This is true since it is the very essence of research. The problem arises out of the fact that they market so many of their failures. Between these failures which are presented as new drugs and the useless modifications of old drugs, the addition of zinc to vitamins is a good example, most of the research results in a treadmill which moves at a rapid pace but goes nowhere. Since so much depends on novelty drugs change like women's hemlines and rapid obsolescence is simply a sign of motion, not progress as the apologists would have us believe.
>
> * * * * *
>
> I doubt that there are many other industries in which research is so free of risks. Most must depend on selling only their successes. If an automobile does not have a motor no amount of advertising can make it appear to have one. On the other hand, with a little luck, proper timing, and a good promotion program a bag of asafetida with a unique chemical side chain can be made to look like a wonder drug. The illusion may not last, but it frequently lasts long enough. By the time the doctor learns what the company knew at the beginning it has two new products to take the place of the old one. This, too, is well recognized and in some companies calls for casuistry of a high order. In others, it is simply called a business decision.[36]

Dr. Console maintained that the devising and marketing of drugs which have very little value inevitably operates to limit the research talent, time, and resources available for work in areas that might yield significant discoveries:

> Senator KEFAUVER. You stated that there are four kinds of drugs—effective drugs prescribed only for patients who need them, those prescribed for patients who do not need them, drugs from which a patient derives no benefit or no more benefit than would be derived from an inexpensive substitute, and drugs which have a greater potential for harm than good. You state that in your opinion more money was spent on the

[35] For description of the background of Drs. Console and Weinstein, see ch. 9, p. 156 and 10, p. 174.
[36] Hearings, pt. 18, p. 10372.

promotion and development of the latter three classifications than the first classification; is that correct?

* * * * * * *

Dr. CONSOLE. I think if we could eliminate only a part of the drugs in the last three categories, the cost of drugs would be greatly lowered, even if it meant increasing the price of drugs that are effective and are prescribed properly. So much of it—the waste—goes into these other areas, and, in addition, the effort that goes into creating these atrocities is such that good research is very frequently postponed because laboratory personnel and equipment and facilities are limited.

When a "crash program" comes along in which some product is being pushed in order to get it out before a competitor gets it out, it is not unusual for a worthwhile research program to be postponed so that the people can be taken off it to be put on the "crash program." Very frequently some of these programs are never picked up again. So that I think that good research is actually hampered by this type of thing.

Senator KEFAUVER. Is there much of this type of research that you are talking about that really produces nothing worthwhile and is not intended to?

Dr. CONSOLE. I think the majority of it is in that category. I think more than half is in that category, and I should point out that with many of these products, it is clear while they are on the drawing board that they promise no utility; they promise sales. It is not a question of pursuing them because something may come of it. It is quite clear that there is no point in pursuing this: that you won't end up with a product that has any real value, but it is pursued simply because there is profit in it.[37]

As an example of the type of work which diverts resources from more important undertakings, Dr. Console cited the efforts made to prove that the addition of what is known as "intrinsic factor" to vitamin B^{12} enhances its value for people who do not suffer from pernicious anemia:

Offhand I think of intrinsic factor, which in patients with pernicious anemia can be extremely valuable, at least when it first was discovered it looked like it could be used in order to eliminate injections of vitamin B^{12} and it could be given by mouth if intrinsic factor were given along with it. Now there are so few patients in the country with pernicious anemia that a company would hardly make very much profit if it sold intrinsic factor for this purpose alone.

Therefore, attempts are made to indicate that it also increases the absorption of vitamin B^{12} in patients without pernicious anemia. I have not followed the final outcome of intrinsic factor, but certainly during the time that I was involved in it, there was absolutely no evidence that it increased the absorption of vitamin B^{12} in patients without pernicious anemia. Still the promotion tried to get across the idea that anyone who took a vitamin pill that contained vitamin B^{12} would be better off it his pill contained intrinsic.

[37] Hearings, pt. 18, 10379.

factor. This spreads the use of the drug to a much broader area.[38]

Pointing out that much of the research conducted by the drug companies is not really research in the sense in which the term is usually understood, Dr. Weinstein, formerly acting medical director of the J. B. Roerig Division of Pfizer, recommended that the drug companies "* * * be required to clearly identify expenditures for research as those which are devoted to basic studies," adding that this should "markedly decrease the justification for some of the very high prices." [39] Deploring the waste of talent of well-trained capable scientists employed by the drug companies he stated:

> As a corollary to this point it should be mentioned that a great many extremely fine scientists are employed by those manufacturers. Their talents should not be expended on patent-bypassing chemical manipulations, on ridiculous mixtures of drugs, or inconsequential additives to established drugs. Since the number of well-trained capable scientists is severely limited, their potential should not be wasted. The long-term benefits of the appropriate utilization of the abilities of these skilled individuals would be immeasurably greater.[40]

As specific examples of products which have limited usefulness but whose development and promotion has nonetheless absorbed the talents of the drug company scientists, Dr. Weinstein cited the corticosteroids following prednisone, the phenothiazine derivatives following Thorazine and Compazine, new reserpine derivatives, certain combination drugs such as those which combine antibiotics with steroids, and "the battle of the additives" among tetracycline manufacturers; concerning the last he stated:

> * * * the two best known examples are probably the products that Pfizer puts out, which are the tetracyclines, with glucosamine.
>
> * * * * * * *
>
> Glucosamine is a naturally occurring substance which occurs in the blood. And this has been added to the tetracyclines, with the hope that this would increase the absorption of the tetracyclines. This is the only thing hoped for. There is nothing in the combination to change the effect of the drug itself, the tetracycline itself. And the efforts that went into trying to prove this, and this is certainly far from proven at the present time, have been really quite extensive and quite fantastic. The consensus in the medical literature is that these additives add nothing to these antibiotics. They are merely an extra piece of luggage that is carried around. The other example of the same sort of thing is the Achromycin V products, with citric acid, that Lederle puts out. The intensity with which these have been promoted, as though they were something really special, is quite fantastic. That promotion has died down at the present time. But in the last year and the year before that par-

[38] Hearings, pt. 18, p. 10379.
[39] Hearings, pt. 18, p. 10254.
[40] Hearings, pt. 18, p. 10254.

ticularly, there was rarely a day's mail arriving without at least one piece from each of the companies on this subject.[41]

Dr. Weinstein objected to dignifying the concoction of drugs of little value with the word "research":

> A major justification for the high prices of many prescription drugs has been the very well publicized vast expenditures of funds and energy by the pharmaceutical manufacturers for what has been labeled "research." This activity has been emphasized to the public and to the medical profession by rather grandiose, self-servicing slogans as "Science for the World's Well-Being," and "Research in the Service of Medicine." No clear-cut definition has been given by the representatives of the pharmaceutical industry of just what is included in their definition of research.
>
> There can be no question that some very wonderful, exciting, extremely important, and productive research has been and is being done within the pharmaceutical industry. However, I do not think that it would detract in anyway from these fine and worthwhile activities to point out that much that is called research in the pharmaceutical industry has little relationship to what most people engaged in academic and research activities would consider to be scientific research.[42]

According to Dr. Frederick H. Meyers, of the University of California, the principal reason why drug companies devote most of their scientific resources to what he regarded as relatively unimportant work is their desire to obtain a patentable derivative of a basic drug which is either not patented or on which the patent is held by others:

> The question is what then is the goal of this admittedly large-scale laboratory effort of our industry? Partly to exploit and market these foreign and nonindustrial advances and compounds that I have mentioned. Mostly, however, to modify the original drugs, the drugs based on the real research as it were, mostly to modify the original drugs just enough to get a patentable derivative, but not to change it enough to lose the original effect.[43]

In point of fact this is exactly what Mr. John McKeen, president of Chas. Pfizer & Co., described as "the avenue of approach being most extensively explored by certain antibiotic houses today." Over 10 years ago in a speech before security analysts, he said:

> * * * it is apparent that neither penicillin nor streptomycin furnishes any real indication of the outlook for the antibiotic industry. From a profit point of view, and that is what I believe you gentlemen are primarily interested in, the only realistic solution of this problem lies in the development of new and exclusive antibiotic specialties. This as I have previously indicated is an exceedingly costly and vigorous alternative; nonetheless, it is the avenue of approach

[41] Hearings, pt. 18, p. 10257.
[42] Hearings, pt. 18, p. 10243.
[43] Hearings, pt. 18, p. 10394.

being most extensively explored by certain antibiotic houses today. This is the approach being followed by Pfizer.[44]

If the drug industry subordinates basic research to minor modifications which hold greater assurance of commercial success, it is merely following the pattern of American industry generally. The difference, however, is that no other industry approaches drugs in stressing its research activity as the rationale for extraordinary profitmaking.

Referring to the economy as a whole, Mr. David Novick, chief, cost analysis department, the Rand Corp., testified that there are four different types of functions carried on under the general heading of research and development. His classification, together with his estimates of the proportion spent on each of the four types of the reported $10 billion total expenditure on research and development in 1959 are as follows:[45]

Research and development: Steps, activities, and promises for the future

Activity	Promise
Step I. "Brave New World": Basic research, experimental research, basic development. $100,000,000	Understanding of universe and organization of knowledge about it to— (a) Permit major changes in ways of looking at phenomena and activities; (b) Create new devices and methods for accomplishing scientific objectives; and (c) Identify phenomena and activities which permit revolutionary changes in existing products, methods, and approaches. Its promise is great but not identified as to specific purposes and the possibility of fulfillment is highly uncertain.
Step II. Possible use of new discovery: Applied research, advanced development, basic evaluation, basic testing. $300,000,000	Singling out or identifying specific potentials or applications with a view to developing devices or methods for utilizing the new general knowledge obtained in step I. Scientific application or usefulness is identified but the economy, efficiency and acceptability of the proposals remain uncertain. Promise is for great new things.
Step III. Application of new knowledge: Product development, product testing, product evaluation, pilot production. $2,600,000,000	Specific devices or methods appear as likely solutions but must be brought reasonably close to final application to determine effectiveness, economy, and acceptibility. Do-ability has been established and major advances are promised.
Step IV. Improved application: Product application, application research, applied testing, applied evaluation. $7,000,000,000	New uses and application or modifications of existing uses or applications are sought for existing methods, products or components; may result in substantial benefits to users or producers. Some success is reasonably assured since it is evolutionary rather than revolutionary.

For the economy as a whole, Novick estimates that 70 percent of the total amount spent on research and development goes for the last step, while only 1 percent goes for basic research. That the American record in scientific achievement has been as good as it is Novick attributes in large part to the immigration of European scientists.

> Probably most important in establishing the low level of activity in step I is the fact that we, in the United States, have been more interested in application or experimentation than in pure research. Most of our science has been imported, chiefly from Europe, either as principles or scientists who developed their ideas in this country. The bulge in our scientific discoveries in the last 25 years is probably more the result of European scientists coming to this country to

[44] "Antibiotics and Pfizer & Co." Armed Forces Chemical Journal, vol. III, No. 8, April 1950, pp. 37–38.
[45] Hearings, pt. 18, p. 10512.

escape fascism, communism, and nazism than any real expansion in our indigenous capability. Einstein, Fermi, von Neumann, and Teller are a few of the scientists whose U.S. contributions are transplants from Europe. There is no assurance that we have yet developed the essential "climate" for basic research in this country.[46]

In the field of medicine this country has shared in the benefits of this inflow of talent. Table 40 is a listing of 30 Nobel Prize winners in medicine and physiology from 1945 to 1959.[47] At the time of the award 18 of the winners were of American nationality, although 7 had been born in another country. The table also brings out the interesting fact that in only one year was the award granted for research conducted in a drug company; this was the award in 1948 to Dr. Paul Mueller for his work in discovering the insect-killing properties of DDT carried on in the Swiss drug company, J. R. Geigy.

TABLE 40.—*Nobel prize winners in medicine and physiology, 1945–1959*

Year	Winner and nationality (at time of award)	Nation of birth (where citizenship changed)	Reason for awarding prize	Research done at (or place where working on award date)
1945	Sir Alexander Fleming (British), Sir Howard Florey (British), Ernst Boris Chain (German).		Discovery of penicillin	London University.
1946	Herman Muller (American).		Discovery regarding hereditary changes or mutations produced by X-rays striking the gones and chromosomes of living cells.	Indiana University.
1947	Carl and Gerty Cori (American),	Czechoslovakia.	Discovery of the process in the catalytic metabolism of the glycogen, or animal starch.	Washington University (St. Louis).
	Bernardo Houssay (Argentine).		Discovery of the significance of the hormone produced by the pituitary gland.	Institute of Biology and Experimental Medicine (Buenos Aires).
1948	Paul Mueller (Swiss)		Discovery of the insect killing properties of DDT.	J. R. Geigy, A. G. Basle, Switzerland.
1949	Walter Hess (Swiss)		Discovery of how certain parts of the brain control organs of the body.	Zurich University's Physiological Institute.
	Antonio Moniz (Portuguese).		Discovery of a surgical technique that opened up new possibilities in the treatment of mental illnesses.	University of Lisbon.
1950	Philip Hench (American), Edward Kendall (American), Tadeus Reichstein (Swiss).		Work in cortisone and ACTH, hormones which relieve arthritis.	Mayo Clinic (Hench) University of Minnesota and Mayo Foundation (Kendall), Basle University (Reichstein).
1951	Max Theiler (American)	South Africa	Development of "17-D" vaccine against yellow fever.	Rockefeller Foundation (Public Health Division)
1952	Selman Waksman (American).	Ukraine	Discovery of streptomycin	Rutgers University (Institute of Microbiology).
1953	Fritz Lipmann (American).	Germany	Discovery of coenzyme A and its significance in the intermediary metabolism.	Harvard University and Massachusetts General Hospital.
	Hans Krebs (British)	do	Discovery of citric acid cycle.	Sheffield University, Sheffield, England.
1954	John Enders (American), Thomas Weller (American), Frederick Robbins (American).		Cultivation of the polio virus, free from harmful tissue components, in the test tube.	Harvard University (Enders), Harvard University (Weller), Western Reserve Medical School (Robbins).

[46] Hearings, pt. 18, 10513.
[47] Hearings, pt. 19, pp. 10950–51.

Nobel prize winners in medicine and physiology, 1945–1959—Continued

Year	Winner and nationality (at time of award)	Nation of birth (where citizenship changed)	Reason for awarding prize	Research done at (or place where working on award date)
1955	Hugo Theorell (Swedish)		Isolation of yellow enzyme and the splitting of it into its constituent parts (20 years previous), and additionally, the isolation of a whole series of enzymes over the years, with demonstration of their functioning.	Biochemistry department of the Nobel Medical Institute.
1956	Dickinson Richards (American), Andre Cournand (American).	France (Cournand)	Heart catheterization and research carried out by its means.	Columbia College of Physicians and Surgeons and Bellevue Hospital.
	Werner Forsemann (German).		(Same as above)	Germany.
1957	Daniel Bovet (Italian)	Switzerland	Discovery relating to synthetic compounds that inhibit the action of certain body substances and especially their action on the vascular system and the skeletal muscles.	Superior Institute of Health, Rome, Italy.
1958	George Beadle (American), Edward Tatum (American), Joshua Lederberg (American).		Experiments with bread molds showed that genes transmit hereditary characteristics by continuous chemical reactions. Discovery concerning genetic recombination and the organization of the genetic material of bacteria.	California Institute of Technology (Beadle), Rockefeller Institute (Tatum), University of Wisconsin (Lederberg).
1959	Svero Ochoa (American), Arthur Kornberg (American).	Spain (Ochoa)	Research on basic chemistry of life and heredity, and discovery of enzymes for artificially producing some of the key substances of life, nucleic acids.	New York University, (Ochoa), Stanford University (Kornberg).

Using penicillin to illustrate the application of his classification to the drug industry, Mr. Novick stated that the discovery in 1928 of the effect of the mold on bacteria by Sir Arthur Fleming "* * * provided an observation which promised a better understanding of a part of the universe. The promise was great but not yet identified as to specific purpose. The possibility of fulfillment was highly uncertain. This might truly be described as step I." The work of the Oxford scientists, particularly Florey and Chain, was conceived of "as an academic study with possibilities of wide theoretical interest, both chemical and biological"; according to Novick this was both step I and step II in character. When the value of penicillin in the treatment of septic wounds was discovered, the Oxford scientists intensified their efforts to improve the method of production. Next, the U.S. Office of Scientific Research and Development in this country and the General Penicillin Committee in Great Britain "took the program from the research laboratories and transferred it into full-scale production, development, tests, and evaluation." It was not until this stage, classified by Mr. Novick as step III, that the drug companies became involved in the project, without, incidentally, any risk of their own capital. The subsequent work of improving the method of production, seeking strains with higher yields and better therapeutic properties, etc., falls into step IV.[48]

[48] Hearings, pt. 18, pp. 10515–10517. For a fuller description of the history of penicillin see Federal Trade Commission, "Economic Report on Antibiotics Manufacture," 1958, appendix.

Indeed, virtually all of the research and development work on antibiotics carried on by the drug companies has been of the step IV nature. The screening of molds to find new antibiotics is an undertaking which for some years has been wholly justifiable from a strictly business point of view because (*a*) the principle that certain molds attack bacteria had already been established and (*b*) an economical method of production suitable to practically any antibiotic, the deep-vat fermentation process, had already been developed. Likewise, the molecule manipulation, the devising of slight variations of existing drugs, the concoction of most combination drugs, is step IV in character. Speaking of the nature of step IV work in general, Novick states:

> There is at that point a reasonable assurance of success since the changes sought are small-order variations in proven methods, devices, and approaches. Because a substantial body of information is available, very large numbers of people can be employed at this point. Finally, making changes and improvements of this kind is the essence of day-to-day business or professional activity.[49]

Work of the step IV character can be conducted, however, only when the preceding steps have been successfully carried out. It is not just that they are desirable; they are essential prerequisites. It is therefore at least a reasonable possibility that the disappointing record of the U.S. drug industry during the past 5 years in creating important new drugs is due to an excessive preoccupation with step IV activities at the expense of what must come before.

Of course it may be pointed out that the pace of the drug industry since World War II in the United States has certainly kept abreast, if not exceeded, that of countries which do not grant patents on pharmaceuticals. But if this were not so, it would be most unusual. The effect of World War II on the American drug industry was that of a great stimulus, much of it financed by the Government.[50] The effect on the drug industry of Germany, the historical fountainhead of drug discovery, was exactly the reverse. The research staffs of the great German drug companies were dispersed and destroyed. Their records, including all of their secret know-how, were thrown open; representatives of the American drug companies searched their files for anything of possible value. Moreover, one of the two principal German firms had the misfortune of entering into a restrictive contract with an American firm primarily engaged in another industry which ventured into the drug field only to withdraw in a few years. The same German firm has devoted a considerable portion of the scientific staff which it has gradually been rebuilding into fundamental research on cancer, endeavoring among other things to discover the metabolism of cancer as well as some compound which would inhibit its growth; this research, while valuable to the scientific community, has not yielded any product of commercial value. Despite the handicaps under which the industry has labored, five of the drugs shown on table 38 developed since 1945 came from West Germany. Moreover, the leading German companies have developed a number of new drugs which are not yet marketed in the United

[49] Hearings, pt. 18, p. 10518.
[50] Cf., e.g., Federal Trade Commission, "Economic Report on Antibiotics Manufacture," 1958, pp. 46–55.

States, among which is a pancreatic inhibitor (i.e., a drug which reduces the sometimes fatal excessive secretion of the pancreatic glands), a new drug which is effective against fungi, a new antibiotic which they feel is an improvement, and further modifications of tetracycline.

The Italian drug industry has also developed a number of possibly significant new drugs, most of which are not available in the United States. Among these are several new antibiotics, new anticholesterol drugs, new antifungus drugs, new ergot derivatives useful in easing childbirth, a new form of injectible chloramphenicol, and a synthetic chemical which gives some promise of being effective against two strains of influenza. The significance of the last lies in the fact that influenza is a virus, against which neither antibiotics nor any other drug is effective. This new drug is now being tested in over 100 hospitals in Italy; it is claimed to reduce the average length of illness by more than half; and a leading American firm has already secured distribution rights in the United States.

It should be recognized that some of these developments are only in the nature of possibilities for the future. The Italian drug industry is largely a creation of very recent years. That it did not contribute significant new discoveries prior to World War II is no more significant than the absence of scientific achievements in other Italian industries which were also virtually nonexistent but which, incidentally, were the beneficiaries of product patent protection.

In a recent article [51] Mr. Paul de Haen, a leading authority on drug development and consultant to the drug industry, described the rapid expansion now taking place in the research facilities of European drug manufacturers. That patents are not an essential prerequisite to research is supported by the fact that the examples he happens to give are all in countries which do not grant patents on pharmaceutical products:

> Farbenfabriken Bayer is putting up a 33-story story office building; Farbwerke Hoechst has just completed a 300-foot private bridge over the River Main and opened up a large tract of land to be used for research facilities, pilot plants, and manufacturing purposes. The interesting feature of this setup is that each new research building will have adjacent to it a pilot plant of substantial size suited to each special type of research—pharmaceutical, chemical, dyestuffs, plastics, petrochemical. Philips-Duphar in Holland is doubling its research building and is extending its plant for the commercial production of radioactive pharmaceuticals and chemicals, similar to the facilities available in this country at Abbott Laboratories and E. R. Squibb & Sons. The research staff of another Dutch manufacturer, Brocades-Stheeman & Pharmacia, moved last year into a sizable new and well-equipped research building. C. H. Boehringer & Sohn, Ingelheim, Germany, has put up modern structures which overshadow the old one-story buildings, and several new buildings are in various stages of completion. Room for expansion is contemplated everywhere.

[51] Paul de Haen, "European Pharmaceutical Research," Drug & Cosmetic Industry, January 1961.

Mr. de Haen then goes on to note some differences in the way research is carried on in European as contrasted to American drug firms:

> Europeans have learned by tradition to get along with less personnel, especially less university-trained personnel. I have been told that, after the war, United States and British industrialists could not understand how so important a drug as the antimalarial quinacrine could have been developed by researchers operating in three small rooms, since in the United States several hundred scientists were employed to test all possible variations of the basic formula and, in the end, came up with the same compound.
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> The general approach to research in Europe seems to incline more toward intuition and feeling for a new lead to new chemical possibilities than to routine elaboration of already known facts, as is often the case in the United States.
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> It is significant that a director of one of the largest pharmaceutical research institutes in Europe still has the time and inclination to put on the white coat and direct his laboratory assistant in carrying out chemical experimental work that he hopes will prove fertile. To reflect and dream, this seems to be one of the prime objectives of the European pharmaceutical researcher. There is evidence that this method is bearing fruit.
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> Some [European] firms seek deliberate confirmation of their pharmacologic studies by independent outside workers associated with universities. This praiseworthy custom is not always followed today by commercial laboratories in this country.
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> It is my impression that the medical departments of pharmaceutical firms in Europe have always had a substantial influence on the clinical evaluation of new products, on the decision as to which preparation to market as well as on how to promote it.
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> * * * * * *
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> Development research seeking new product formulations has not as yet been given the share in research expenditure in Europe that it has received in this country. Whether this will change in the future it is difficult to say. Those manufacturers who have constant contact with American firms may realize the financial benefits to be derived from improvements in formulations, such as tableting, coating, capsulating, suspensions, the preparation of stable solutions, and others.

In 1960 the trade press of the U.S. drug industry began to refer to the last few years as constituting a "research gap," commenting that the flow of important new drug discoveries has for some inexplicable reason diminished. Failing to come up with attractive new drugs, some companies are now resurrecting old products which they have

long neglected in their promotional efforts. An example is Pfizer's current promotional drive for Terramycin, originally introduced by the company in 1950. According to a trade source:

> Pfizer has been engaging in an interesting marketing project—heavy promotion for its Terramycin wide-spectrum antibiotic. Sales dropped off sharply with the introduction of the tetracyclines, and Pfizer's push for Terramycin is being watched to see what can be done to bring an "older" drug back.[52]

Although the trade sources do not delve into the causes of this "research gap," among the possibilities must be included insufficient attention to basic research as well as to the earlier stages of improvement and development. The importance of the latter lies in the fact that time can be saved after a fundamental discovery at the step I stage by allocating greater resources to these immediately succeeding stages. Referring to the penicillin example, Novick stated:

> The small improvements which characterize step IV and the long cycle which started in 1928 with Fleming's discovery and ended in 1945 with the availability of commercially produced penicillin may be both byproducts of the failure to provide more adequate support at steps I and II.[53]

There is a very real question whether the granting of patents by putting a premium as it does on immediate results (or step IV type of work) actually diverts resources and talent which would otherwise be placed on basic research and the other earlier steps of the research and development process. Neither the recent record of the U.S. industry in drug discoveries nor the way in which it has been utilizing its scientific personnel would constitute a clear refutation of that possibility.

From this discussion it should be apparent that equally important to the quantity of resources directed toward research and development is the manner in which it is directed. In the subcommittee hearings the drug industry tended to stress the question of quantity. Thus, Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, attacked the subcommittee's figures on research expenditures as too low. The subcommittee showed weighted average expenditures on research by 20 drug companies of 6.4 percent of drug sales and other receipts in 1958. Dr. Smith and his associate, Dr. Bambach, claimed a higher relative expenditure for the industry, 9.5 percent.[54] Aside from technical objections to his statistical procedure, the difference in the estimates may be quite irrelevant in the light of the testimony of Console, Weinstein, and Novick. When resources are directed at the wrong objective, it is not particularly useful to measure their extent.

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[52] FDC Reports, "The Pink Sheet," Feb. 20, 1961, p. 26.

[53] Hearings, pt. 18, p. 10518.

[54] Discussion brought out the fact that Dr. Bambach had used a broad definition of "research and development," perhaps broader than some of the drug manufacturers themselves would have thought of. He also estimates expenditures for companies which did not respond to his questionnaire. Thus, the numerator, expenditures on research and development, was considerably higher for the PMA than for the companies replying to the subcommittee. On the other hand the denominator used by PMA was considerably smaller. Dr. Bambach pointed out that veterinary sales, and exports, were eliminated. Hence with a larger numerator and a smaller denominator, PMA obtained a larger percentage figure than did the subcommittee. Also, the original information had been returned to the companies or destroyed, hence was not available for comparison with reports of the same companies to the subcommittee (hearings, pt. 19, pp. 10957, 10958, 10771).

Chapter 8. Patents and the Restriction of Competition

Patents by their very nature restrict competition. The existence of a patent system reflects an explicit or at least implicit decision that the gain resulting therefrom through the promotion of inventiveness more than outweighs the loss resulting from the elimination of competition. For the period covered by the grant the patent holder is a monopolist, immunized from the normal forces of competition. He can, if he so elects, charge whatever price he desires and prevent others from selling his product or using his process.

There are, however, certain recognized legal limitations under the Sherman Act on the extent to which the patent holder may go in using his patent to control the market. Thus, if he licenses others, he may not as a condition to receiving the license require them to observe his prices. He may assign territories in which his various licensees are permitted to sell, but if there is a reciprocal arrangement among several competing patent holders, implemented by cross-licenses, such that competition among them is effectively eliminated, the Sherman Act may be violated; the most well known cases of this type relate to international cartel agreements. Between the simple single-company patent monopoly and those uses, or more properly "abuses" of patents which have been struck down by the courts, there is a "grey" area in which patents are used to eliminate competition in ways undoubtedly not contemplated by our Founding Fathers but which have not been specifically held to be illegal by the courts. The drug industry would appear to be unexcelled in its ability to devise new and ingenious methods of using patents (or even applications therefor) which fall within this "grey" area.

It should be remembered that nowhere in the Constitution is the world "patent" used; it merely provides:

> The Congress shall have power * * * To promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive rights to their respective writings and discoveries (Art. I, Sec. 8: Powers of Congress).

The "exclusive right" referred to is left to be defined by Congress, and is subject to redefinition by Congress. Indeed, at the time of the writing of the Constitution, there was considerable doubt of the desirability of granting exclusive rights under patents. A number of early inventors of eminence refused to take out patents. Benjamin Franklin said of one of his early inventions of the stove:

> Gov'r Thomas was so pleas'd with the construction of this stove, as described in [a pamphlet] that he offered to give me a patent for the sole vending of them for a term of years; but I declined it from a principle which has ever weighed with me on such occasions, viz., That, as we enjoy great advantages from the inventions of others, we should be glad of an opportunity to serve others by any inventions of ours; and this we should do freely and generously.[55]

[55] Writings of Benjamin Franklin, p. 370, Albert H. Smith, ed. 1907.

Thomas Jefferson, at the time of his invention of a hempbreak, took positive steps to prevent the issuance of a patent.[56] In fact, Jefferson at one time expressed grave doubts of the basic premise on which patents are granted, stating:

> Society may give an exclusive right to the profits arising from them [inventions], as an encouragement to man to pursue ideas which may produce utility, but this may or may not be done, according to the will and convenience of the society, without claim or complaint from anybody. Accordingly, it is a fact, as far as I am informed, that England was, until we copied her, the only country on earth, which ever, by a general law, gave a legal right to the exclusive use of an idea. In some other countries it is sometimes done, in a great case, and by a special and personal act, but, generally speaking, other nations have thought that these monopolies produce more embarrassment than advantage to society; and it may be observed that the nations which refuse monopolies of invention, are as fruitful as England in new and useful devices.[57]

In industry generally the views expressed by Jefferson and Franklin with respect to patent monopolies appeared to fade rapidly, but for a time they continued to prevail in the drug industry, reflecting a recognition of the peculiar and unique relationship of this industry to the public health. In 1854 when Dr. E. R. Squibb, founder of E. R. Squibb & Sons, managed to distill for the first time pure ether of uniform strength, he declined to take out patents. Instead he published his discovery in the September 1856 issue of the American Journal of Pharmacy. The essential difference between most other countries and the United States on this matter is that the views held by Dr. Squibb have continued to prevail abroad but have long since been abandoned here.

Conditions have also changed in another important respect. The beneficiary of the patent grant has become increasingly the corporation, not the individual inventor. At the time the Constitution was written, the inventor was a solo worker making his experiments in the garret or toolshed; the purpose of the patent grant was to make it possible for this individual inventor to gain some financial reward from his creative effort.

Today in the drug industry—as in many other industries—the inventor who works in the large corporate laboratory is an employee of that corporation; at the time of his employment he agrees in writing to assign all of his future inventions to his employer. Thus, at the very outset, his work becomes a pawn in the business struggle; and the nature and quality of his work—including the lines of inquiry he may follow—are largely dictated by the expectation of businessmen, untrained in science, as to what areas appear to hold the greatest promise of commercial gain. If he does fulfill the aspiration of his employer and hits upon a highly marketable product, known in the trade as a "hot" drug, it is the corporation and its stockholders who are the beneficiaries; his reward may be comparatively negligible or

[56] He wrote a friend: "something of this kind has been so long wanted by cultivators of hemp, that as soon as I can speak of its effect with certainty, I shall probably describe it anonymously in the public papers in order to forestal the prevention of its use by some interloping patentee." "Writings of Thomas Jefferson," p. 506, H. A. Washington, ed. 1854.

[57] "Writings of Thomas Jefferson," pp. 180–181, H. A. Washington, ed. 1854.

nonexistent. Virtually all of the products examined by the subcommittee were those where patent control lay in the hands of drug manufacturing companies. In only one instance was a sizable financial reward received by the inventor. This was the case of Dr. Frank M. Berger, the co-inventor of meprobamate, who in the 3-year period from 1957 through 1959, reported receiving from Carter over $800,000, most of which represented his agreed percentage on sales.[58]

Another individual inventor did not fare so well. This was Dr. Simon L. Ruskin, a private physician, who secured the dominant patent on procaine penicillin following years of delays in the Patent Office, after he had been eliminated from an interference "by any means" upon motion by the companies.[59] Two of these, Lilly and Pfizer, agreed to split the royalties received from the licensees[60] of Lilly, which acquired a subservient patent. After fighting from 1945 to 1957, Ruskin turned over complete title to his patents to Union Carbide, which immediately settled all litigation. Eli Lilly & Co., which had been in the center of the extensive litigation, agreed to pay Union Carbide a total of $90,000 in payment for all claims and damages and to take a license under the Ruskin patent, with rights to grant sublicenses to all of Lilly's licensees.[61] Pfizer agreed to share with Lilly all royalty payments made by Lilly to Union Carbide under the settlement agreement.[62]

The extent to which the patent has been transformed in the drug industry from a reward to the individual inventor into an instrument of market control can be seen through a delineation of various ways in which patents have been used to limit competition. In some cases the exclusion of competition is total; the company owning the patent retains a complete monopoly in the U.S. market. In others it licenses one other firm, establishing a "duopoly." In still others several large firms become licensees, creating an "oligopoly." The latter frequently arises when the firms involved have been simultaneously working on the same development and have all filed patent applications, with the result that the U.S. Patent Office has declared an "interference" to determine priority of invention. In the drug industry this issue is often settled privately, with the company securing the patent agreeing to license only the firms involved in the interference. Patents may be used as a basis for the establishment

[58] According to testimony by Dr. Berger and H. H. Hoyt, president of Carter, Dr. Berger's compensation for the 3 years from 1957 through 1959 including salary, executive compensation, and income from the meprobamate patent rose from $166,500 in 1957 to $424,000 in 1959. Apparently, Dr. Berger's incomes in 1955 and 1956 were also sizable—so much so that in 1956, for tax purposes, he converted much of his income into the category of capital gains, thus substantially reducing his tax liability. Berger's method for taking advantage of the change in the tax laws was to attempt a retraction of the assignments of 1950 and 1953 of his patent applications, the terms of his employment agreement of 1951 and employment contract of 1953. The agreement of 1951 had assigned to Carter all inventions made or conceived during the terms of his employment. Despite the fact that Carter was granting both domestic and foreign patent licenses on meprobamate in reliance upon the assignments, the same property rights were again conveyed by a purchase agreement between Carter and Berger which was completed on September 1, 1956. (Hearings, pt. 17, pp. 10195–6.)

[59] Hearings, pt. 26, p. 16368, excerpts from agreement of Mar. 22, 1950, between Eli Lilly & Co., Bristol Laboratories, and Merck & Co., Inc.:

"Whereas Chas. Pfizer & Co., Inc., of Brooklyn, New York is a party to said interference on an application serial No. 758,230, filed June 30, 1947, but has exchanged information with Lilly respecting invention dates, reduction to practice and evidence in support thereof pursuant to the terms of a separate agreement dated February 27, 1948 between Lilly and Pfizer, * * *

"Now therefore, in consideration of the premises and in consideration of the mutual promises and covenants herein contained the parties do hereby stipulate and agree as follows:

"1. The provisions hereinafter set forth in this agreement involving United States patent applications and patents shall become effective when and if Ruskin is finally eliminated from said interference by any means * * *."

[60] Hearings, pt. 26, pp. 16357ff.

[61] Hearings, pt. 26, pp. 16399ff.

[62] Hearings, pt. 26, pp. 16357ff.

of international cartels, and have been so employed in this industry. Effective control of the market also has been obtained by the ingenious use of patent applications. These and other uses of the patent mechanism to suppress competition will be discussed in the remainder of this chapter.

MONOPOLY

The simplest form of market control through patents is the preemption of the entire market by the patent owner. If no other seller is licensed, the patent owner is free to charge what the traffic will bear without hindrance from the antitrust laws or any other statute. The classic and pervasive paradox of the antitrust laws is also applicable to the area of patents. The greater the departure from concentration per se as the basis of market control and the greater the reliance upon less effective and enduring arrangements, such as contracts and agreements, the greater the applicability of the antitrust laws. Where the market is shared by several licensees, the patent holder may endeavor to secure observance to his price structure and thus possibly run afoul of the antitrust laws. But where he licenses no one, keeping the entire market for himself, the danger of antitrust action is virtually removed and the buyers must pay whatever price he elects to charge for at least 17 years.

The phrase "at least" is used intentionally. It is true that the law limits the exclusivity of the grant to 17 years, and under the simpler economic conditions of an earlier day, when the inventor was the individualistic tinkerer in his workshop, this statutory limitation was probably effective. But under modern conditions, where the large corporate laboratory is the center of activity, patent dominion in a particular area can often be extended for far longer periods. This can be achieved through judicious spacing of improvement patents over the years or by making slight changes in the drug's molecular structure, allegedly increasing its potency, efficacy, or safety, while at the same time stressing the side-effects of its earlier versions. In insulin the basic patent held by the University of Toronto expired 20 years ago; but through a series of improvement patents and licensing arrangements with Danish firms on newer types of insulin, the international structure of patent control still remains. In this country where Lilly was the first—and for a time the sole—licensee, its market position on insulin has been unassailable for 40 years.

Perhaps the outstanding examples of the single-company patent monopoly are the early broad-spectrum antibiotics introduced around the turn of the last decade. Because of its prior discovery in England, no product patent could be secured on penicillin in the United States. Another stumbling block was the objection that a product yielded by a mold, being a product of nature, was per se unpatentable. However, when Dr. Waksman at Rutgers discovered streptomycin in the mid-forties, a patent was sought on the ground that, even if a product of nature, it was only transitory in nature, had never been isolated, and the therapeutic use was unknown. The acceptance of this view by the U.S. Patent Office was of far-reaching consequence since it opened the way to the issuance of patents for each new mold product as it was discovered.

In 1948 American Cyanamid introduced the first broad spectrum antibiotic in the U.S. market. This was chlortetracycline (Aureo-

mycin). From the outset the American Cyanamid policy was to license no other companies, maintaining for itself a complete monopoly on this product. This course was also followed for the other early broad spectrums—Parke, Davis in the case of chloramphenicol (Chloromycetin) and Pfizer for oxytetracycline (Terramycin). To this day each of the companies has continued in its steadfast refusal to license others. Incidentally, it will be recalled that from 1951 until the time of the subcommittee's hearings on antibiotics in September 1960, the price for each of these three products had remained identical and unchanged.

The case of chloramphenicol is of particular interest. Of all the broad-spectrum antibiotics, this is the only one which is synthesized chemically, although it was originally produced by fermentation. The others, including tetracycline, are the result of the activity of microorganisms grown in suitable culture media. Shortly after the U.S. Government attempted to interest the drug manufacturers in the commercial production of penicillin, the four large companies in the Midwest, Lilly, Upjohn, Abbott, and Parke, Davis, entered in 1943 into the so-called Midwestern Agreement which was renewed annually. This agreement provided that these companies would cross-license each other royalty free under any patents secured:

> relating to the manufacture, production, or synthesis of penicillin or any derivative thereof or improvement therein * * *[63]

Parke, Davis' first patent application for chloramphenicol was made in March 1948. Later in that year it withdrew from the Midwestern Agreement. In consequence, when the patent was issued in 1948, Parke, Davis was able to exercise its full monopoly rights; at no time from then to the present has it licensed any other company to manufacture[64] or sell the product in the United States.

The broad spectrums concern developments made by American firms. Insofar as the U.S. market is concerned, exactly the same situation can exist where a foreign company originates the development and grants an exclusive license to an American company for sale in this country. In the case of the two most important tranquilizers currently used for severe mental illness, chlorpromazine (Thorazine) and prochlorperazine (Compazine), Smith Kline & French is the exclusive U.S. licensee of the patentee, Rhone-Poulenc of France.[65] Under the licensing agreements, the royalty charges vary from 4 to 10 percent, increasing with total volume of annual sales.[66] Recognition of the monopoly element in these royalty fees is reflected in a provision that if a competitor enters the U.S. market selling substantial quantities of these products, SKF shall be entitled to a reduction in the royalty charge. The term "substantial quantities" is curiously defined in the contract; the condition exists if the products may be obtained in the normal course of business in five retail outlets in each of the following cities: New York, Philadelphia, Chicago, San Francisco.[67] Up to the present SKF has not had recourse to relief under

[63] Agreement may be found in files of subcommittee.
[64] Parke, Davis had chloramphenicol produced solely for its account by Monsanto Chemical Co., 1949–53. Cf. FTC Economic Report on Antibiotics Manufacture, pp. 59, 74–75.
[65] See agreements for Thorazine (listed as R.P. 4560) dated 1952, pt. 17, p. 9474, and Compazine (listed as R.P. 6140), ibid., p. 9484.
[66] Ibid., p. 9484.
[67] Ibid., pp. 9474, 9482, 9485.

this provision. Testimony during the hearings showed that 39 percent of SKF's total sales volume derived from Thorazine and Compazine; and Walter A. Munns, president of the company, testified that 70 percent of this business represented sales to State and Federal mental hospitals.[68] The profits enjoyed by this company since its introduction of these tranquilizers are discussed in chapter 3.

Another example is the new oral antidiabetic drug, tolbutamide, sold in the United States only by Upjohn which markets it under the brand name, Orinase. Under the licensing agreement of 1956 between Hoechst and Upjohn, the latter received an exclusive, nontransferable license to make, use, and sell in the United States of America, its territories and possessions.[69] Thus, even Hoechst, the originator of the product, is barred from entrance to this market. It is of interest that this exclusivity continues "until the expiration of the last to expire of any patents included at any time within the license patent rights, *including improvement patents.*[70]

DUOPOLY

The patent holder may find it advantageous to license one other firm for a variety of reasons, including virtually simultaneous discovery, a quid pro quo arrangement under which the patent owner is the recipient of a license on a different drug, or the desire to profit from sales made by a firm with a larger distribution organization. The last consideration is illustrated by the interesting case example of meprobamate. Early in the 1940's, Dr. Frank M. Berger was working on muscle relaxants for British Drug Houses in England and there discovered mephenesin. Because of the statutory absence of patent protection on drug products in England at that time, he could not secure a product patent. In 1947 Dr. Berger emigrated to the United States; in 1949 he became director of research for Carter Products; and in the following year a patent application was filed on meprobamate, assigned to Carter Products.[71] In 1953 an arrangement was made for Berger to receive a share in the profits derived from the sale of drugs developed by him. The patent was issued on November 22, 1955, and will run until 1972.[72]

Since Carter lacked the facilities to produce meprobamate, it arranged with several chemical companies to supply the bulk finished product.[73] Not only were these companies required to sell exclusively to Carter; the contract required that any "inventions or improvements in the product" made by the supplying companies must be turned over to Carter on a royalty free basis.[74] In 1955 this mild tranquilizer was introduced on the market by Carter under the trade name "Miltown." Sales exceeded their wildest expectations; it was evident that the company had hit upon a winner.

While a leading seller of over-the-counter drugs (Carter's Little Pills), it lacked the large force of detail men believed necessary

[68] Hearings, pt. 16, pp. 8927-8928.
[69] Hearings, pt. 20, p. 11269.
[70] Ibid, p. 11278 (emphasis added).
[67] Hearings, pt. 16, p. 9198.
[68] Hearings, pt. 16, p. 9108.
[71] Hearings, pt. 17, pp. 10170-1.
[72] Hearings, pt. 17, p. 9635.
[73] Hearings, pt. 17, 9656-9657.
[74] Hearings, pt. 17, p. 9661. One of the supplying companies, Abbott Laboratories, is itself a major drug company, with a large distribution organization; Abbott has a process patent on meprobamate; nonetheless it too is barred from marketing meprobamate.

for the full promotion of an ethical drug. On December 5, 1955—hardly 2 weeks after the issuance of the meprobamate patent—Carter entered into a licensing agreement with American Home Products Corp.[75] The latter secured the right to sell, but not to manufacture, meprobamate in the United States and most of the countries of the world. This right was limited to meprobamate as a single drug and not in combination with other drugs. Subsequently combinations were permitted, however, with other drugs where American Home held the exclusive rights on their exploitation. Thus meprobamate would be combined with other products which constituted patent monopolies in their own right. American Home agreed that it would purchase its bulk supplies of finished meprobamate powder only from Carter. To close all possible loopholes of competition by outsiders, American Home also agreed that it would make no sales in bulk powder to any other companies. Under these arrangements American Home proceeded to bring on the market "Equanil" whose sales quickly exceeded those of Miltown in the United States. As has been noted, Carter under this arrangement was collecting not only royalties on Equanil but was making substantial profits on the sale of bulk powder to its licensee.[76]

Thus the pattern of domestic marketing was set, with a rigid control constructed around licensing agreements under the patent grant. The price charged by American Home Products for Equanil and by Carter for Miltown is identical—$3.25 for 50 400-milligram tablets. As time passed new agreements were worked out with Cyanamid, Merck, and Wyeth for combinations of meprobamate with other drug products, such combinations being permitted only in conformity with Carter's policy that the other product had to be exclusively controlled by the licensee.[77]

Carter also established a duopoly of sorts on sales in foreign markets. Again, the motivation was its lack of an established distribution organization. Since most foreign countries do not grant patents on pharmaceuticals, Carter could not hope to keep control over the entire supply of the product in the hands of just two companies. On a "hot" item such as meprobamate other firms could be expected to enter the market, which in fact has happened. But Carter did have a valuable property in the tradename, Miltown. Hence, it entered into a contract with American Cyanamid under which the latter was given the exclusive right to sell the product abroad under the brand name Miltown (in Germany Miltaun). Like American Home Products, it also was required to obtain its supply from Carter. Inasmuch as American Home Products was selling the product abroad as well as at home under its brand name, Equanil, this arrangement had the effect, insofar as tradenames are concerned, of extending into foreign markets the duopoly established in the United States, with American Cyanamid replacing Carter as the marketer of Miltown.

It is interesting to note that in foreign markets there is substantial similarity in the prices charged by American Home for Equanil and by American Cyanamid for Miltown. Of the 10 countries for which price information is available, the prices of the two items were exactly the same in three while in three additional countries the difference was less than 5 percent.

[75] Hearings, pt. 17, 9637.
[76] For a discussion of these profits, see Hearings, pt. 16, pp. 9153–9157.
[77] Hearings pt. 16, pp. 9202–9203.

OLIGOPOLY

In the drug industry, oligopoly—the control by the few—often results when several large companies accommodate themselves to their respective claims concerning an invention which each happened to make at about the same time but for which only one, of course, can obtain a patent. As an alternative to letting the Patent Office perform one of the functions for which it was established, namely that of determining priority, the companies may themselves decide which should receive the patent. The others thereupon withdraw their applications, in exchange for which they are licensed by the company receiving the award. This process of intercompany agreement on priority is quaintly referred to in the trade as "arbitration," although there is present no outside arbitrator nor indeed any individual other than representatives of the companies involved.

The most important and well-known example of the emergence of oligopoly from this process of mutual accommodation is the important antibiotic, tetracycline—manufactured by three of the leading drug companies and sold by five.

The moves and countermoves of the companies were of an almost incredible complexity. Accord was difficult to come by since the companies involved correctly anticipated that the stakes were extremely high. Moreover, it was touch-and-go whether the product was even patentable. To the intense distress of the companies, it developed that some quantities of tetracycline are obtained in the production of chlortetracycline—a fact which might well make the product unpatentable. The problem was further aggravated by laboratory and clinical tests which appeared to indicate that tetracycline is superior to its patented predecessors—chlortetracycline and oxytetracycline. Under these circumstances the prospects of a repetition in the broad spectrums of what was so widely deplored in penicillin—free competition, falling prices and shrinking profit margins—appeared very real indeed.

It was against this background that the companies made their legal maneuvers with the twofold objective in mind—to assure the issuance of a patent and to secure the patent for themselves. The first step was the filing of a patent application by Pfizer in September 1952. This was followed by a similar application by American Cyanamid in March 1953; and one by a small company, Heyden Chemical Co., in 1953.

Shortly thereafter this number was reduced to two. Less than 6 weeks after Heyden announced that it had filed an application for tetracycline, its antibiotics division was purchased by Cyanamid. Cyanamid paid $600,000 in excess of the book value of the assets of the Heyden antibiotics division—at a time when the industry was suffering from excess capacity in antibiotics production, when selling prices for penicillin and streptomycin were extremely low, and profits on this business were falling.

On January 11, 1954, Pfizer and Cyanamid entered into an agreement. They agreed to make a private determination of priority in the invention, to the end that the loser would withdraw and thus end the interference. It was stipulated that the winning party was to license the other.[78]

[78] U.S. Patent Office Interference File 86861.

In the meantime, Bristol had also filed a patent application on a commercial form of tetracycline; namely, tetracycline hydrochloride. Public announcement of this fact was made on November 5, 1953. The Patent Office then declared another interference on tetracycline hydrochloride on March 2, 1954, involving Pfizer, Cyanamid, and Bristol as the parties. By this time Cyanamid had already filed formal concession in the earlier interference, yielding priority to Pfizer. Bristol then approached Pfizer for a license, but was turned down.

Almost immediately—on April 30, 1954—Bristol entered the market with its own tetracycline. A number of companies—including Upjohn, Squibb, Smith Kline & French, and Parke, Davis—sought to purchase the bulk material from Bristol. Of these, Upjohn and Squibb were selected by Bristol to sell its tetracycline production in addition to itself.

Although, under the earlier private agreement between Cyanamid and Pfizer, it was Pfizer who was to get the tetracycline patent, the latter could not act since no patent had yet been issued. Cyanamid then moved into the breach; on September 29, 1954, it instituted action against Bristol on the ground that Bristol's manufacture of tetracycline infringed Cyanamid's Aureomycin patent. This turned out to be strategically sound, for a month later, on October 14, 1954, the examiner in the Patent Office dissolved the second interference. He stated that since tetracycline had been produced in the manufacture of Aureomycin, the product was old, had been sold in the market, and was therefore unpatentable. Had this decision stood, what has turned out to be the country's largest-selling broad-spectrum antibiotic would have been marketed as an unpatented drug.

Pfizer, however, persisted in its submission of affidavits to overcome the rejection by the patent examiner, who asked if tetracycline could be shown to be present in Aureomycin "in clearly identifiable form." Pfizer scientists conducted tests purporting to prove that Aureomycin fermentation broth did not contain tetracycline. Using what Pfizer itself described as "low potency" broth and "commercial" tests, a negative result was secured, although the use of known sensitive tests would have shown the presence of identifiable tetracycline in the broth. In an affidavit submitted to the Patent Office, the Pfizer scientist swore that "in fact there was no indication whatever of the presence of tetracycline." This led the patent examiner to grant the patent to Pfizer.[79] On the same day separate infringement actions were instituted by the patentee against Bristol, Upjohn, and Squibb.

This set the scene for the end of the matter. On January 13, 1955, Cyanamid's infringement action against Bristol was settled with a license by Cyanamid for use of its Aureomycin patent in the manufacture of tetracycline. In return, Bristol agreed to pay royalties to Cyanamid on all of its sales of tetracycline. A month later on February 25, 1955, Bristol formally moved to abandon its patent application still pending in the Patent Office, on the ground that the product claims were unpatentable. This left only the Pfizer infringement suits to be disposed of. For another year, litigation continued. Pfizer pressed its action. Bristol, Upjohn, and Squibb counterclaimed with charges of lack of invention, prior use, and misrepresentation of the facts in the Patent Office.

[79] File, U.S. Patent No. 2,699,054. The validity of this assertion is a central point at issue in the FTC case, docket 7211, In the Matter of American Cyanamid et al.

Then suddenly the controversy was stilled. In March 1956 the six lawsuits then pending were privately settled in a series of agreements among the companies. Squibb and Upjohn were licensed by Pfizer merely to sell, but not to manufacture, tetracycline. In addition to paying a lump sum for infringement, Bristol received a license from Pfizer for the manufacture and sale of tetracycline with the payment of royalties. In turn Pfizer was granted access to any Bristol patents in this field; if it exercised this option, Pfizer was obligated to pay royalties to Bristol.

With the consummation of these arrangements, the orderly and controlled marketing of tetracycline was an inevitable and expected result. At the present time there are five marketers of this product in the United States—Cyanamid, Pfizer, Bristol, Squibb, and Upjohn. Each of the three manufacturers produces roughly a third of total production; though the costs of the producers are, as has been shown, very different from those of the bulk buyers (Squibb and Upjohn), all five have consistently sold at identical prices, and until just before the subcommittee held its hearings on antibiotics in September 1960, at which time a 15 percent reduction was made, the price of tetracycline had remained unchanged since its introduction in 1955.

PATENTS AS THE BASE FOR INTERNATIONAL CARTELS

Patents are also of vital importance in the formation of cartels for the international control of drug prices. In each of the major drug fields examined by the subcommittee, the use of patents to restrict competition in international trade was spelled out in great detail in patent agreements among the world's major drug companies. Even in the domestic licensing agreements, restrictive provisions of highly doubtful validity were found. A typical limitation, for example, is that the licensee can market in final packaged form only; this, of course, is designed to prevent the smaller companies from securing access to the product in bulk form.[80]

This, as well as more far-reaching restrictions, has been written into the patent-licensing agreements with foreign firms. In cortical steroids, tranquilizers, antidiabetic drugs, and the broad spectrum antibiotics, the licensing contracts contain such provisions.[81] Typical license agreements may be found in the appendixes of the hearings. In general the pattern is the same. The patentee—or sometimes merely the applicant for a patent which has not as yet been issued—grants to a single company in each of a related group of countries the exclusive right to sell in that market. Where the foreign companies are large and economically powerful, the license usually covers the right to make and sell; if the licensee lacks the requisite bargaining power, it may secure the right to sell, and the contract specifically provides that the product in bulk form is to be purchased from the licensor.[82] A geographical limitation upon the marketing area of the licensee is usually imposed, which is often buttressed by a specific provision that he will not engage in export of the product. The

[80] Prior to 1950 many of the established drug companies relied upon volume and bulk sales for what would be regarded today as moderate profits. In recent years there has been a growing tendency among these old-line companies—and predominantly among the newer entries into the field—to limit sales to final packaged form only.

[81] For examples, see hearings, pts. 15, 17, etc.

[82] Examples of the latter are the Merck international agreements on dexamethasone, hearings, pt. 15, pp. 8510–8637; Carter's first agreements, both domestic and foreign, relating to meprobamate, hearings, pt. 17, pp. 9637 ff.

geographical confines of his marketing territory are rigidly imposed for companies in the highly industrialized countries, such as the United States and the individual countries of Europe. Usually the British Commonwealth is regarded as a single unit for exploitation by the British licensee. In less industrialized countries, the various areas may be parceled out in a variety of ways; often because of the limited markets, they are open to those licensees who can meet the local regulations of these countries.[83]

An interesting example is found in the case of Chloromycetin. In this country Parke, Davis holds product patent No. 2,483,885, issued in October 1949. The patent will not expire until 1966. Parke, Davis has from the first consistently refused to license any other American company and has maintained a total monopoly in the U.S. market on this drug. It has, however, faced a different situation in many countries abroad where product patents are not permitted. Chloramphenicol, the generic name for Chloromycetin, is the only antibiotic made entirely by chemical methods; almost immediately several European companies were able to make the product, in some instances with the development of their own processes. The high profits enjoyed by Parke, Davis on its sales invited the entrance of outsiders who found they could sell at prices lower than the American company and still make a handsome profit on sales abroad.

Parke, Davis adopted a threefold strategy to rid the market of these outsiders. Complaints were filed with the U.S. State Department, and our embassies abroad made formal protest to foreign governments on the sales of chloramphenicol by their nationals. Moreover, upon the prodding of American companies, including particularly Parke, Davis, the State Department urged other governments to reverse their historical position and revise their patent laws to permit the issuance of patents in the field of drugs. Simultaneously, a number of infringement suits were brought against foreign companies in those countries which do grant patent protection.

Next, Parke, Davis took steps to bring foreign marketers under its control with patent licensing agreements containing severely restrictive provisions. Of the 10 foreign licensing agreements submitted by Parke, Davis in response to the subcommittee's request, all but one company—a Japanese firm—had been engaged in chloramphenicol sales prior to the agreement with Parke, Davis, and several were currently defending themselves from infringement actions by the American company.[84]

The nature of the restrictive provisions in the agreements are of particular interest. All of them, of course, are still in effect; for most, their terms run to 1967 or later.[85] An example is the agreement with Laboratoire Français de Chimiothérapie, dated January 25, 1950, which limits the sales of this company to France and French territories. Not only does the licensee agree neither to buy nor sell outside of this territory, it covenants to use all means, including litigation, to prevent reselling of its chloramphenicol outside of this territory. Indeed the

[83] Many of the less industrialized countries, in an effort to develop local manufacturing facilities, require that drug products be manufactured locally. In most countries this, in practice, has meant the establishment of tableting and packaging plants using finished bulk material imported from the home plants of United States and European countries. This has the effect of excluding companies who, for one reason or another, have not established tableting and packaging plants.

[84] The Sankyo Co. of Japan was merged with Parke, Davis in November 1960 to form Sankyo-Parke Davis Co.

[85] For full text of these agreements, see hearings, pt. 26, pp. 16031 ff.

licensee agrees that it will *"refrain from shipping in any parts of the territory quantities of chloramphenicol notoriously above its needs."* [86] This remarkable provision, which is found in contracts between Parke, Davis and other licensees, is intended to remove the possibility of any "uncontrolled" supply entering any market. There is the usual provision permitting the licensee to sell in finished form only. The parties also agree that neither will contest the validity of each other's patents. The French company is required to make available to Parke, Davis its present and future technological advances in the field; and Parke, Davis is free to use any of these French processes outside of the territory allocated to Chimiothérapie.[87]

Five of the ten foreign companies licensed by Parke, Davis under its Chloromycetin patents are Italian. All had been marketing chloramphenicol prior to the agreements. All were involved in infringement suits brought by Parke, Davis in those countries where they were selling which gave patent protection on drugs. The contracts indicate, however, that these companies developed manufacturing processes of their own.

A typical example is the contract between Parke, Davis and Lepetit, a large Italian company. Prior to the consummation of the agreement, dated January 1, 1953, Lepetit had also been involved in infringement actions brought by Parke, Davis. The preamble of the license agreement states that Lepetit has done "extensive independent research" in chloramphenicol; and Parke, Davis is licensed under Lepetit's patents to use these developments.[88]

The Italian company's marketing territory is written in terms of exclusion; it may sell everywhere except in the United States, the United Kingdom, France, West Germany, Canada, Japan, etc. That is, it may sell in Italy and most of the semi-industrialized countries of the world where the market is limited and exclusive grants by Parke, Davis have not been made. Lepetit agrees that it will make no further sales to distributors outside of its allotted territory; and in the future will notify Parke, Davis of any sales of chloramphenicol by outsiders. All infringement litigation pending between the two companies in Israel, Greece, and Japan is resolved with consent judgments in favor of Parke, Davis. Apparently the quality of Lepetit's product is not questioned by Parke, Davis, the contract also providing that both will sell chloramphenicol in bulk form to each other as the need arises. Bulk sales by Lepetit are not specifically prohibited; but

[86] Emphasis added.

[87] The contract with Bayer of Germany, dated Sept. 21, 1951, follows the same lines. In this case the licensee's territory is West Germany. Bayer agrees that it will not ship anywhere in West Germany amounts of chloramphenicol "obviously in excess of the needs thereof."

[88] On the same day the agreement on chloramphenicol was reached, Parke, Davis and Lepetit also entered into an agreement providing for an exchange of future drug products which either company may discover. In view of the criticism of Italian companies for "coattail riding" on drug developments, the preamble is worth quoting in full:

"Whereas Lepitit has similarly been engaged in the manufacture of pharmaceutical products for the alleviation and treatment of human diseases for a comparable period (more than 80 years) and is likewise well known in Italy and other portions of the world for its activities in said field; and

"Whereas both Parke and Lepetit have for many years carried on intensive research activities looking toward the discovery, invention, preparation, and development of new, improved, and valuable products intended for the treatment of such diseases, and * * * (Cf. hearings, pt. 26, p. 16131).

this contingency is taken care of by a provision that the Italian company is obligated to pay royalties based on sales in finished form.[89]

Effective worldwide control of chloramphenicol by Parke, Davis has resulted from this structure of patent licensing agreements. To be sure, it lacks the perfection of a one-company monopoly of production and sale throughout the world—the goal toward which Parke, Davis first directed its efforts. But as a device for subduing splinter groups—particularly the activities of the Italian companies—and avoiding price competition in European markets and elsewhere, it has been strikingly successful. As the price information obtained by the State Department reveals,[90] there is nothing like the widespread variations in the prices of chloramphenicol as among different countries which are to be found in other drug products where the scheme of control over European producers has been less effective.[91]

PATENT APPLICATIONS USED AS PATENT GRANTS

Although a marked difference would appear to exist between a patent application and an issued patent, the drug companies on occasion seem to regard this as a distinction without a difference. In a number of instances examined by the subcommittee, the structure of market control was built up not on the patent itself but on the patent application. This happens when several companies are involved in an interference action which the companies have not been able to settle by "arbitration" among themselves.

Senator Kefauver expressed considerable perplexity on this subject: How could licensing arrangements be negotiated when the Patent Office had not granted a patent? Witnesses conceded that until the patent was issued, any company was free to enter into the manufacture of the product unless process patents existed covering essential methods of production. At the same time, however, the mere fact that an interference existed in the Patent Office acts as a powerful deterrent to outsiders; substantial investments which might be required to produce and sell a product would be money wasted if the patent was finally issued and the concern was then refused a license by the patent holder. For this reason companies wishing to manufacture move early to secure licenses under patent applications; and the structure of market control becomes frozen long before the patent grant is issued by the Patent Office.

The use of patent applications as a device for monopolistic control is epitomized in the subcommittee's hearings on cortical steroids. The record contains copies of the agreements on prednisone entered into

[89] In addition, Farmitalia, Italy's largest drug company, as well as three other smaller Italian companies, were brought under licensing contracts by Parke, Davis in 1955. In each case, a condition is that pending infringement suits brought by Parke, Davis are resolved in favor of the American company. In return for a license from Parke, Davis to make and sell in Italy and several semi-industrialized countries, Farmitalia acknowledges the validity of the American company's patents and turns over its own processes for Parke, Davis' use. The contract provides that all pending litigation between the two companies, respecting Farmitalia's distributors in England, Greece, and other countries, shall be ended with a consent judgment in favor of Parke, Davis. Farmitalia agrees not only to police infringement activities of others in its marketing area and inform Parke, Davis; it covenants that it will market in finished form only. The single exception is the British firm, Allen & Hanburys, to whom it may sell in bulk, unfinished or finished form.

In the case of Zambon, a settlement of the litigation is arranged by payment in kind; the Italian company agrees to supply Parke, Davis with a certain amount of chloramphenicol of U.S. quality. The contract with Istituto Sieroterapico provides that the Italian company may "make and sell under licensee's label in such finished forms as may be suitable for pharmaceutical or medical use without further processing or repackaging." A similar provision is included in the Carlo Erba contract. All three of these companies are licensed to sell in Italy and many of the semi-industrialized countries of the world.

[90] Hearings, pt. 24, p. 14084.

[91] Cf., for example, price table on meprobamate, hearings, pt. 16, p. 9222; reserpine, pt. 16, p. 9433; tolbutamide, pt. 20, p. 11061; chlorpromazine and prochlorperazine, pt. 16, p. 8956.

by Schering with five of the country's large drug companies—Merck, Upjohn, Pfizer, Parke, Davis and CIBA.[92] All of these agreements, covering the period from 1955 through 1958, involved only patent applications; indeed, up to early 1961 the interference proceeding has not been settled and the Patent Office has not issued a patent. During the hearings, Francis Brown, president of Schering, admitted that any nonlicensee was free to engage in manufacture of prednisone until the patent was issued; he indicated clearly, however, that were his company to get the patent, unlicensed production would be stopped.[93] Later, the subcommittee summoned as a witness an official of a small company currently manufacturing prednisone. Dr. Philip Berke,[94] vice president of Formet Laboratories, testified that, if and when a patent is issued, he has little expectation of being able to continue manufacture.[95]

When asked why his firm had agreed to pay an "interim royalty" of 3 percent on net sales to Schering when no patent had been issued, Mr. John Connor, president of Merck, replied that his company had strenuously objected to such payment and agreed only after Schering had made it clear that, in the event Schering won in the interference proceeding—as was widely expected in the industry—Merck could expect hard going if it then applied to Schering for a license.

The Schering licensing agreement on prednisone is of particular interest because, on the basis of patent applications, it establishes marketing restrictions designed to prevent small companies from marketing this drug. In four of the five licenses granted by Schering, the licensee is obligated to sell in specialty form only.[96] That is, the licensee may make no bulk sales of the product to nonlicensed companies for tableting, packaging, and marketing by them.[97] Only one contract—that with Upjohn—omitted this provision; on questioning, Dr. E. Gifford Upjohn, president of the Upjohn Co., stated that his company had sold in bulk only to one company—Schering Corp. itself. As has been shown in part II of this report, all five of these companies sell prednisone at identical prices.

The use of this type of market restriction throughout the drug industry not only where patents have been issued but even where they have only been applied for is a type of practice which most closely approaches illegality under the Sherman Act.

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[92] Hearings, pt. 15, pp. 8364–8383.

[93] Hearings, pt. 14, p. 7929.

[94] Hearings, pt. 14, p. 8057.

[95] Subsequent to the steroid hearings, and during those on the antidiabetic drugs, Upjohn submitted a memorandum in support of the legal arguments that license agreements based upon patent applications are valid. The basic defense was that such licenses covered the transmission of know-how by the licensor to the licensee. Upjohn's license from Hoechst on Orinase was based upon patent applications rather than an issued patent. Orinase would appear to be a good product on which to make this defense since Hoechst's know-how and clinical testing data on this revolutionary new development were undoubtedly of considerable benefit to Upjohn both in starting manufacture and in preparing for clearance of the new drug through FDA (hearings, pt. 20, p. 11283).

In prednisone, however, several of the licensees of Schering are parties to the interference proceeding, so presumably know-how in manufacture is not an entire mystery to them.

[96] The Schering-Merck license provides: "* * * all such licenses being expressly understood to authorize the sale in specialty form only of licensed compounds as such or in combinations, mixtures, formulations, solutions, etc." (hearings, pt. 15, p. 8365). Similar restrictions are to be found in the Parke, Davis, Pfizer, and CIBA contracts.

[97] When Francis Brown, president of Schering, was asked about the intent of this provision, he replied: "The license as I understand it provides that it must be sold in specialty form only, but this is a provision which cannot be enforced until the patent issues, because until the patent issues, there is no right to restrict anyone's freedom of action. Any one of these companies could have sold this compound without obtaining, without entering into this cross-license arrangement just as we could have. But then there would have been hanging over the situation the uncertainty which might have well restrained any one of us from putting as much in the development of these compounds as we did" (hearings, pt. 14, pp. 7929–7930).

PRIVATE SETTLEMENT OF INTERFERENCES

The U.S. Patent Office is empowered by statute to determine who shall be awarded a patent. Application is made for a patent on the ground of novelty and usefulness of an alleged invention; the function of the Patent Office is to decide whether there is sufficient novelty and usefulness in the claims to warrant the issuance of a patent.

If applications are filed by different parties, all laying claim to the same alleged invention, determination must be made as to which is the "true" inventor. In this case the Patent Office declares an "interference" which in essence is an administrative hearing on the claims of the various parties. However, unlike the ordinary hearing of a trial examiner in an administrative agency such as the Federal Trade Commission, the hearings of the patent examiner are entirely secret, except among the competing inventors. The names of the applicants are not released by the Patent Office; the patent applications, and supporting documents, are secret; and the record of the proceedings is not disclosed for public scrutiny.[98] The final award of the patent to one of the contesting parties is the single public document in the entire proceedings.

The problem of determining who, among the various contestants, is the "true" inventor is admittedly complex. Over the years the issue has become focused on the question of which of the applicants first conceived the idea that finally culminated in the invention under examination. Thus, in essence, the conflict becomes a battle of laboratory notebooks—scribbled accounts of experimental work in faded ink on yellowed pages.

The practices of the Patent Office were established in the early days of our Republic when applications were made and processed by the individual inventor. The presumption existed that, with the issuance of the patent, the inventor would proceed to commercial exploitation of his invention or market it to others. Today many of the important patent applications received by the Patent Office are the property of large corporations, and the pressing of their claims is in the hands of skilled attorneys who are specialists in the lore of Patent Office procedure. The application must still be made in the name of the individual inventor; but in many cases he has already made formal assignment to his corporate employer in accordance with the contract of his employment. Assignment of the application is generally recorded in the Patent Office shortly before the patent is issued.[99]

The participation of a number of large corporations in an interference proceeding brings heavy financial resources to the legal struggle. Countermove follows countermove; if the invention is

[98] Even a congressional subcommittee may not secure access to these data except under the exercise of discretion by the Commissioner of Patents when necessary to carry out the provisions of any act of Congress (35 U.S.C. 122). In connection with its investigation of prednisone and the antidiabetic drugs, this subcommittee requested the Patent Commissioner to supply copies of the patent applications of the parties and supporting submissions. This information was refused by the Patent Commissioner on the ground of secrecy; he stated that approach should be made to the various parties whose names he did supply; if information were denied by these various sources, he said he would take the matter under further advisement. All of the drug companies complied with the subcommittee's request for information with the exception of foreign applicants. In the case of Orinase, it was discovered that Upjohn was acting on behalf of Hoechst in the interference; request was then made to Upjohn for the Hoechst data but it was denied on the ground of the privileged relationship between lawyer and client.

[99] Ownership of patent applications is easily identified by the initiated. The name of the applicant is recognized as an employee of the research staff of the company, and the appearance of the company's patent attorney to handle the case identifies the real party of interest.

regarded as significant, every legal device that can be invoked by ingenious and imaginative legal talent is brought into play. The evidentiary material relating to the "conception of the idea" is essential.

Making the date of the germination of the idea a central issue in its proceedings invites serious problems for the Patent Office. During the early period of his work, the inventor is often groping for his idea; he may follow one tangent only to discard it for something that he thinks better. If he is a solo inventor, he may have little patience with notetaking; he is more concerned with reaching solutions to his problems. Thus he is at a marked disadvantage as against the research scientist in the large corporate laboratory where heavy emphasis is placed upon documentary material to be used later for effective patent applications.

There is another important factor. When companies are working on the last stage of research and development, it is almost inevitable that the general nature of the improvement on new adaptation which will yield a profitable product is "in the air," with the result that several companies are working on it at the same time. Hence, the administrative determination of who had the original idea is not an easy matter. And it is not surprising that, even with the best intentions by officials in the Patent Office, the decisionmaking process in a hotly fought interference proceediug is regarded by all the participants as a hazardous gamble.

As a result, there has come to be widely employed the device of the private settlement of interference actions. The various parties to the interfcrence enter into an agreement—usually written—that their attorneys will meet privately for an examination of all the evidence respecting priority; they will, if it is at all possible, reach an agreement as to which, among them, is entitled to receipt of the patent. Once this is done, all of the others immediately withdraw their applications, and the interference proceeding is automatically ended. The single remaining applicant energetically pushes forward his claims for a patent; and the Patent Office processes the unopposed application to its logical conclusion. The patent issues, and all the companies involved in the interference become licensees.

The usefulness of the private settlement in interference procedures to the Patent Office is very real. It constitutes an easy way of reaching a settlement of a complex problem with a minimum of time expended by the agency's overburdened staff. If a multiparty interference proceeding has been set up, only to be closed out by all but one of the parties withdrawing their applications, it is no secret in the Patent Office that a private settlement has been reached. The nature of the private settlement is not part of the record, and the details of the final agreement are not known in the Patent Office. But the case is closed, and the patent examiner is now free to go on to other pressing matters, of which there is never any shortage.

To the companies the private settlement has even greater advantages. It is more expeditious and less costly than a prolonged legal controversy in the Patent Office; it eliminates allegations by probable losers that the product was not patentable in the first place; it leaves everybody directly involved reasonably satisfied. The important thing is to get the protection from competition inherent in the

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patent grant. Although an outright monopoly would of course be preferable to each participant, the next best solution is oligopoly.

Great as are the benefits to the Patent Office and to industry, it is not clear that the private settlement procedure also benefits the consumer. What is involved here is the abdication by the Patent Office of its important statutory function of determining who is entitled to the award of a Government grant of monopoly for 17 years—an abdication which has taken place without any sanction or approval by Congress. The Patent Office—like an administrative agency—is established to protect the public interest in its particular domain. It is supposed to examine all of the evidence, hear all of the testimony of the parties, weigh all the issues carefully. The device of the private settlement with administrative sanction takes away all of the safeguards for the public, and converts the Patent Office into a rubber stamp, approving a decision arrived at in secret by the parties who have most to benefit from the governmental grant. The use of the procedure has now become so widespread that its lack of any statutory basis represents an appropriate matter of congressional interest.

PART IV

ADVERTISING AND PROMOTION OF DRUGS

There is a marked difference in the advertising and promotion of proprietary and ethical drugs. Proprietary drugs—those sold over the drugstore counter—are like most other products in that sales pressures are exerted upon the final consumer who is subjected to an intensive barrage of advertisements for brand name products in newspapers, magazines, radio, and television. In the case of ethical drugs—those sold under prescription—the brunt of promotional effort is directed to the prescribing physician. Since his prescription dictates the particular drug to be used, usually by brand name, the physician is the focal center of advertising and promotional pressures. And since what is involved is the health of their patients, advertising of drugs which in any way misleads the physicians has a potential for harm not present in any other industry. In the words of Dr. Harry F. Dowling,[1] head of the department of medicine, College of Medicine, University of Illinois:

> One especial source of confusion for the practicing physician is printed advertising that comes to him by direct mail or in medical journals. In this present era when truly new drugs are appearing with rapidity and causing revolutionary changes in the practice of medicine, the physician needs facts most of all. Because misinformation and mistakes about drugs can affect health and life, advertising of drugs cannot be allowed to fall to the level of other advertising.
>
> Advertising of drugs should be informative. Above all, it should not be misleading. Misleading advertising by one company not only causes doctors to make mistakes in using their drugs; it also affects other pharmaceutical companies adversely (1) because it destroys the confidence of the physician in the industry as a whole, and (2) because competitive advertisements may tempt another company to make its own advertising a little more blatant, a little more suggestive than it would otherwise be, thus making this competing company's advertising misleading also.[2]

Dr. Maxwell Finland,[3] associate professor of medicine, Harvard Medical School, informed the subcommittee:

> There can be no doubt that the representatives of the pharmaceutical companies have a great deal of influence on

[1] Harry F. Dowling, born 1904 Washington, D.C., certified internal medicine, 1940. M.D., George Washington 1931; intern Baltimore City Hospital, 1931–32; assistant in medicine, Johns Hopkins, 1932–33; fellow in medicine, Harvard, 1933–34; clinical instructor to professor of medicine, George Washington University, 1934–50; Chief, Medical Division, Gallinger Municipal Hospital, 1940–50; professor and head department preventive medicine, 1950–51, professor and head department medicine, 1951, both at University of Illinois. Associations: AMA, ADP(F), ASCI, etc.

[2] Hearings, pt. 24, p. 14172.

[3] Maxwell Finland, born 1902 Russia, certified internal medicine, 1937. M.D., Harvard 1926; intern Boston City Hospital; Associate professor medicine, Harvard; associate director, Thorndike Memorial Laboratory; physician-in-chief, Fourth Medical Service, Boston City Hospital. Associations: AMA, ASCI, ACP(F), etc.

> the prescription of drugs. And I think also that there cannot be any doubt that the quality of information that is given by different drug houses varies with the quality of the personnel in that drug house, and also with the integrity of the individuals in these drug houses.[4]

During the subcommittee's hearings on ethical drugs, a number of medical experts testified at length with respect to the excessive promotional practices currently directed to physicians.

In general promotion takes four separate forms. They are described by Dr. William Bean,[5] School of Medicine, Iowa State University, as follows:

> What are the ways of promoting the sales of drugs, new and old? Four major avenues are (1) visits by detail men, (2) mailing of brochures and samples, (3) advertising in medical journals, and "throw away" journals which have no subscription cost, and (4) the exhibits at medical meetings. None of these is bad in and of itself, but certain abuses and corruptions may occur. Some of the dangers and damages are self-evident.[6]

Another physician, Dr. Dale Console,[7] former medical director of E. R. Squibb & Sons and presently in private practice, referred to

> * * * the triphammer effect of weekly mailings, the regular visits of the detail man, the two-page spreads, and the ads which appear six times in the same journal, not to mention the added inducement of the free cocktail party and the golf outing complete with three golf balls stamped with the name of the doctor and the company in contrasting colors.[8]

Chapter 9. Magnitude of Promotion Expense

Expenditures for promotion of ethical drugs have been rising at a rapid pace. According to Advertising Age, advertising expenditure in medical journals and direct mail alone rose by 219 percent between the years 1953 and 1958.[9]

The subcommittee secured information from the 22 largest drug manufacturers on their promotion expenses for all types of drugs for the year 1958.[10] In addition to their expenditures for direct

[4] Hearings, pt. 24, p. 13944.

[5] William Bennett Bean, born 1909, Manila, Philippine Islands; certified internal medicine, 1947; M.D., 1935, University of Virginia; intern medical, 1935–36 Johns Hopkins Hospital; assistant resident physician, 1936–37, Boston City Hospital; senior medical resident, 1937–38, assistant visiting physician, 1941–46, outpatient clinic, 1947, visiting physician, 1947, Cincinnati General Hospital; fellow in nutrition, 1938–40, University of Cincinnati; assistant visiting physician, 1940–42, Hillman Hospital; consultant internal medicine, Surgeon General, U.S. Army; teaching fellow, 1936–37 Thorndike Memorial Laboratory, Boston; teaching fellow in medicine, 1936–37, Harvard; instructor in medicine, 1938–40, assistant professor of medicine, 1940–46, associate professor of medicine, 1947–48, University of Cincinnati; professor and chairman, department of internal medicine, 1948, University of Iowa; physician in chief, 1948, University Hospitals, Iowa. Associations: AHA, AMA, ACP, ASCI, etc.; fellow vice president, and chairman of the medical section, 1958 World Medical Association; specialist cirrhosis of liver nutrition and heart disease. Chairman, board of regents, National Library of Medicine, Bethesda, Md.

[6] Hearings, pt. 18, p. 10336.

[7] Dr. A. Dale Console, born 1914, New York City; certified surgery, 1949; M.D., 1941, Cornell; intern, 1941–42, assistant resident surgeon, 1942–45; resident surgeon, 1945–46; resident neurological surgeon, 1946–48; assistant attending surgeon, 1946–57, New York Hospital; resident research fellow, 1957, Pennsylvania Hospital; assistant professor, clinical surgery, 1946–57, Cornell; associations: American Federation Clinical Research; Society University Surgeons; address: Princeton, N.J.

[8] Hearings, pt. 18, p. 10375.

[9] Advertising Age, Feb. 1, 1960.

[10] Because of the complexity and conglomerate character of the operations of several of the companies marketing drugs, they were asked to segregate their total drug activities from other branches of their business. No attempt was made to separate their proprietary operations from ethical drugs because of the difficult accounting problems involved. Virtually all of the large drug companies are engaged in the manufacture and sale of both proprietaries and ethical drugs.

mail and advertising in medical journals, these companies were asked to supply data for all other promotion expenses including costs of detail men, samples and the like. The total reported by these 22 companies for all promotion in 1958 amounted to some $580 million.

It should be emphasized that this sum represents promotion expenditures for only the 22 companies examined by the subcommittee; it does not reflect the total for the entire drug manufacturing industry. Although it is true that, in general, the smaller drug companies incur nothing like the promotion expenses of their larger competitors, many of them incur some expense for detailing. In addition, virtually all who attempt to market some trademarked specialties engage in journal advertising, direct mail, and the supplying of free samples to physicians. One of the physicians testifying before the subcommittee kept a record of circulars and samples received at his office for a single month; the flow averaged 10.5 pieces per day with some 60 pharmaceutical houses represented.[11] Taking into account the entire industry, the subcommittee staff has estimated the current promotion expenses for the entire industry at around $750 million.

It is of interest to contrast this figure of $750 million for advertising with the total budget for this country's medical schools. In 1957 total funds available to all medical schools in the United States for their educational programs were only a little more than one-fourth of this figure, $200 million.[12]

The data submitted by the 22 largest drug companies to the subcommittee show that approximately 24 percent of drug receipts of these companies is expended for promotion. On the average, selling expense constituted the single largest item for all of these companies, often exceeding the cost of goods sold.[13] The latter category averaged only slightly above selling expenses, with a figure of 32 percent. In comparison, research and development accounted for 6 percent; general and administrative, 11 percent; taxes, 13 percent; and net profit after taxes, 13 percent.

The companies were asked to supply a breakdown of the selling and promotion expenses on the basis of the particular method of promotion used. Because of the variety of methods of cost allocation used by the 22 companies, the figures can, at best, be considered only as approximate. They are, however, suggestive and provide some light on the manner in which this huge sum is divided among the various avenues of promotion. Twenty of the companies supplied separate figures for Salesmen's and Detailmen's Compensation and Expenses. This accounted for $200 million out of the total of $577 million. Another item entitled "Other Selling Expenses"—expenses ancillary to the first—totaled $130 million.[14] Thus these two selling expenses combined for the 22 companies represented an expenditure of $330 million for 1958.

The remaining sum, roughly $250 million, was classified under "Advertising and promotion." The initial request of the subcommittee to break this item down further into expenditures for samples,

[11] Hearings, pt. 18, pp. 10453-10454.

[12] Dr. Charles D. May, "Selling Drugs by 'Educating' Physicians," Journal of Medical Education, Jan. 15, 1961.

[13] In the parlance of the drug industry, cost of goods sold includes the cost of labor, materials, supplies, factory overhead and depreciation of plant investment. It does not include selling expenses, advertising, research, and general and administrative expenses, and taxes (other than direct property taxes allocable to production of the product in question).

[14] Two of the companies supplied a single figure for the items combined on the ground that their accounting procedures made a breakdown impossible.

direct mail, journal advertising and the like was not fully complied with; some of the companies insisted these data could not be supplied from the accounting procedures they employed. The problem was aggravated by the fact that the drug company's books will show how much was paid to an advertising agency but may not show how much was spent by the advertising agency on advertisements appearing in medical journals as contrasted to direct mail ads. A further difficulty in allocation arises when the same advertisement is used in both media, as is not infrequently the case. Therefore the effort to distribute this total among the various media of advertising was abandoned. All that can be said is that the 22 largest drug companies, in addition to $330 million spent on salesmen and detailmen's compensation and expenses and ancillary items, spent a quarter of a billion dollars on advertisements in medical journals, direct mail ads, samples and miscellaneous items.

Some further indication of the significance of selling expenses in the prices charged by pharmaceutical manufacturers is revealed in the number of detailmen employed. The detailman—a euphemism in the industry for salesman—represents one of the most expensive modes of selling employed anywhere; his function is to make the rounds regularly of the physicians in his assigned area and extoll—subtly or blatantly—the wares of his employer.[15] Officials of the large drug companies appearing before the subcommittee were reluctant to give any estimate of the cost of detailmen per individual visit to their customers; but an official of a smaller company quoted the advertising director of Smith Kline & French as an authority for an estimated cost of between $9 and $10 for every physician visit.[16] With a total of about 150,000 physicians in the United States, this comes to a cost of roughly $1.5 million for a single detail call upon every doctor in the country.

Some drug company officials appearing before the subcommittee were specifically interrogated on the subject of the number of detailmen employed. In the case of the Upjohn Co., for example, the number of detailmen employed was 1,030 as against a total force of 5,700.[17] That is, roughly, one out of every six employees for Upjohn engages in detailing to physicians. For Smith Kline & French, which conducts an extensive wholesaling operation, the ratio was somewhat lower, detailmen numbering 400 out of a total of 3,000, or about 1 in 8.[18] In the case of CIBA, the figure was 300 out of 1,500, or 1 in 5.[19] The president of Parke, Davis stated that they had 1,540 detailmen out of a total of 10,980, or 1 in 7.[20] It is difficult to think of any other manufacturing enterprise in the country where the sales staff would constitute such a large proportion of total employees.

[15] Herman W. Leitzow, vice president, Schering Corp., makes the point in this fashion:
"So, you see, we believe in the preeminent importance of detailing. We believe that our trained, highly professional sales representative is the most capable medium we have of persuading the physician to prescribe our products and the pharmacist to stock them. Being experts in professional relations, they instinctively act so as to please the physician." (Proceedings of Program, Midyear Conference, American College of Apothecaries.) (Quoted by Seymour Blackman, hearings, pt. 14, p. 8219.)

[16] Seymour Blackman of Premo Pharmaceutical Laboratories, Inc., quoted from a speech of Tobias Wagner, advertising director of Smith, Kline, & French before the National Pharmaceutical Forum:
The well-trained detailman can do what medical ads and direct mail cannot do. The pharmaceutical company spends between $9 and $10 for every physician visit. (Hearings, p. 8218.)
A slightly lower figure—between $7 and $8 per call—was suggested by one of the physicians appearing before the subcommittee. (Hearings, pt. 18, p. 10456.)

[17] Hearings, pt. 14, p. 8322.

[18] Hearings, pt. 16, p. 8980.

[19] Ibid., pt. 16, p. 9415.

[20] Ibid., pt. 24, p. 13958.

As might be expected, there was considerable unanimity on salaries paid to detailmen by the various companies. A Merck official stated that their detailmen received, on the average, about $7,500 yearly;[21] the Upjohn figure was $8,000;[22] Lederle's was between $7,200 and $8,400.[23] The Smith Kline & French figure was relatively low, around $6,250 annually.[24]

Detailmen, like salesmen generally, have their expenses paid in addition to receiving salaries. From the fragmentary evidence available to the subcommittee, it would appear that the expense of maintaining detailmen by the various companies is roughly in the same neighborhood as their yearly salaries. Merck, for example, reported that total "Salesmen's and detailmen's compensation and expenses" were $11,528,000; dividing this figure by the 730 detailmen reported, the result is a cost of a little over $15,000 per detailman. The same procedure yields a cost of $14,000 per detailman for Upjohn, $16,000 for Lederle, $20,000 for SKF, $12,000 for CIBA.

A different way of appraising the magnitude of the selling effort is through the testimony of physicians appearing before the subcommittee. Dismayed by the vast amount of direct mail advertising from drug manufacturers which arrived at his office, one of these physicians made a statistical study of the subject. In reporting on this project, Dr. James E. Bowes,[25] a physician in private practice in Salt Lake City, informed the subcommittee:

> It is my feeling that the drug manufacturers have been misled somehow into distorted promotional methods that border on tbe unprofessional.
>
> I have no complaint with their margin of profit. But, such waste of "throwaway" drugs and circulars as I shall mention today are a major factor in needlessly increasing the drug firms' total cost of operation.
>
> Therefore, I submit this thesis: If direct promotion to doctors were eliminated, final drug prices could be greatly lowered.
>
> It seemed to me one day that I was spending quite a large part of my mornings looking at circulars sent by drug firms. As I devoted more and more time to this rather unprofitable and often repetitious reading, I thought I'd start keeping track of just how much mail of this type came into my office daily. So for 2 calendar months I weighed every piece of mail on a postal scale, noting the company, the bulk rate paid, and the corresponding third-class rate that you or I would have to pay if we were doing the mailing. I noted the drug samples received and calculated the wholesale cost of each pill, powder, and liquid they contained. The results soon began to look fantastic.

[21] Ibid., pt. 14, p. 8133.
[22] Ibid., pt. 14, p. 8322.
[23] Ibid., pt. 24, p. 13710.
[24] Ibid., pt. 16, p. 8980.
[25] Dr. James E. Bowes—Graduate, Georgetown University, 1944. Graduate, New York Medical College, 1949. Interned, New York City, 1950. Specialized training in obstetrics and gynecology, Cleveland, 1951–52. Specialized training in obstetrics and gynecology, Philadelphia, 1953. Graduate work, obstetrics and gynecology, University of Pennsylvania, 1954. Obstetrical practice, U.S. Army Hospital, Fort Hood, Tex., 1955–56. Private practice, Salt Lake City, Utah, 1957–60. Conducted mass polio immunization campaign, Salt Lake City, 1957. Medical society memberships: AMA; American College of Obstetrics, Gynecology; American Society for the Study of Sterility; Utah State Medical Society.

It would take 2 railroad mail cars, 110 large mailtrucks, and 800 postmen to deliver the daily load of drug circulars and samples to doctors if mailed to 1 single city. Then after being delivered, it would take over 25 trash trucks to haul it away, to be burned on a dump pile whose blaze would be seen for 50 miles around.[26]

The average daily weight of my particular circular and sample pile was 1.06 pounds, making the total for all the physicians nearly 80 tons per day. Doctors also received 69 tons of journals and periodicals daily as well as 24 tons of ordinary mail * * *.

Simple addition of the 80 tons of circular and sample mail delivered daily results in 24,247 tons per year. What purpose does it accomplish for the drug manufacturer or for the doctor? Does a doctor, who has a professional education, require so much repetition to get across to him the idea of a new drug, or push an old one? And do the drug firms have the right to take up so much of a doctor's time or his tax money—and that of other taxpayers—by burdening the post office to deliver circulars at a reduced rate?

* * * * * * *

But can the average doctor take 1 hour out daily for reading all the drug literature? I decided to find out just how other doctors in the community viewed this office nuisance.

In phone contacts with a hundred doctors' secretaries I found that 54 percent of them immediately dumped most circulars into the wastebasket, excepting only those which dealt with new drugs. They let only the first-class mail go through to the doctors' desks, in this way avoiding repeated advertisements. The remaining 46 percent reported that the doctors sorted all of their own mail. One busy specialist should receive special praise from the drug companies. He dictates important points from the circulars over his tape recorder for the secretary to type.

Doctors in two of the large medical clinics in town had an equally drastic policy. Their mailroom clerk was instructed to throw out all circulars and store the samples in a separate room for the doctors' leisured perusal. One clinic tried to have the post office burn all their circulars before delivery to save wear and tear on the postmen. This idea had to be shelved because "the mail must go through."

[26] Hearings, pt. 18, p. 10453. Dr. Bowes added more details concerning the makeup of his collection:
All told nearly 60 pharmaceutical houses were represented in the grand total of circulars and samples that began to pile up in my office in both the 1957 and 1959 survey. In a single day these varied from 1 to 28 pieces with a daily average of 10.5. (The average in 1957 was 9.1 pieces as shown in table 1.) This meant that the estimated 150,000 doctors all over the country were receiving daily over 1.5 million pieces of mail. The Salt Lake City post office can handle only 1 million pieces of mail per day. There are more than 150,000 doctors but this is the approximate number on the drug houses' mailing lists.
The Wallace Co. alone sent 17 pieces of mail during 1 month to my office. Lederle, Abbott, Mead Johnson, Smith Kline & French, Pfizer, and A. H. Robins followed closely with heavy volume (p. 10453).
And the comment:
The circulars are interesting to read for the new doctor and a considerable amount of money and talent is put into them. The samples are sometimes useful for indigent patients or even the doctor's family. But the average doctor can't take the time to seek out the indigent for his drug samples. Most physicians and clinics keep the samples the drug houses supply because it would be wasteful to throw them away. In my survey 47 pieces of mail out of 264 delivered for the 1 month contained samples. This is an increase of 14 percent over those received in 1957. Ten out of eleven times Smith Kline & French sent samples combined with circulars (p. 10455).

Hospital physicians often instruct their mail clerks to discard all circulars that are delivered. At one university hospital there are several huge wastebaskets at the foot of the mail slots for quick disposal of all third-class mail.[27]

* * * * *

Apart from the actual cost of designing and printing the circulars, what is the daily postal tab for the drug firms? The circulars and samples sent to my office for 1 month cost the drug firms $6.85 in postage for the month, an average of 28 cents per day. But if you or I send the same number of pieces through the mails at third-class rate we would have to pay $9.95 for the month, or 40 cents daily.[28]

* * * * *

If estimated out, this bulk rate comes to for the 150,000 doctors, over $41,000 daily or slightly over $1 million postage a month for all physicians, and over $12½ million per year postage for the circulars and samples.

* * * * *

The $12 million paid by the drug manufacturers merely for bulk rate postage on the circulars and samples would build three large hospitals per year. Probably 50 hospitals could be added to this figure if we had the amount of money

[27] Hearings, pt. 18, pp. 10454–10455. Dr. Bowes added:

"Ask any postman what his biggest burden is and he will answer 'the circulars,' or as he calls them, 'the flats.' Postal officials say it takes a new postman some time before he becomes calloused to seeing the doctor's secretary dumping the circulars into the trash can before his very eyes.

"Is this just another one of our wasteful American habits? Or is more involved than an overflowing trash basket after the mailman leaves his load? What is the pharmaceutical house really accomplishing? Is there a loss of money involved to the firm as well as to the taxpayer?" (P. 10455.)

On an earlier day of the hearings (see p. 10336) Dr. Bean inserted in the record a verse "somewhat changed" from one that appeared in the British Medical Journal called Lancet:

"The mail man homeward plods his weary way,
His letter pouch divested of his load,
Perhaps he ought to get a raise in pay
With all those doctors on his daily road.
Brochures and photographs ensnare the eye,
Samples the children swallow up, he hoped;
Blotters well used could suck the ocean dry,
Though most go straight into the trash, unopened.
Each month new scenery assails the eye,
A newer hormone from a higher Alp
Claims magic cures for those about to die,
As Pocahontas once saved John Smith's scalp.
Full many an ad is born to blush unread,
Providing tinder for some bonfire's glow,
Full many an alpine scene resides instead,
Where dark unfathomed oceans melt its snow."

[28] Dr. Bowes explained:

"The drug circulars require much less postage than a private citizen is charged for the same item. Drug firms can mail it bulk rate at a minimum charge of 2 cents per piece for the 1st 2 ounces plus 1 cent per additional ounce, compared to our 3d-class mailing at 3 cents for the 1st 2 ounces and 1½ cents each additional ounce. Even after the proposed increase to 2½ cents per piece for circulars in July 1960, it will still not meet the handling cost to the post office" (p. 10455).

that the pharmaceutical houses throw into the doctors' wastebaskets.[29]

* * * * *

Many of the smaller firms cannot possibly compete with the few larger companies in multimillion-dollar promotional campaigns directed at doctors.

An example of a big promotional idea was that of Smith, Kline & French who in October 1957 sent this assorted sample package of drugs to my office and, it is assumed, to all 150,000 doctors' offices throughout the country, and as shown here in the statement, the wholesale cost of these drugs amounts to $18.99. The postage alone, 4 pounds, amounted to $1.05. When estimated for all 150,000 doctors, it comes to the wholesale cost of the drug, $2,248,500, and the postage at $157,000, making a total for that one promotional campaign of slightly over $3 million. The comments of $9 million for research, previously made, is nothing compared to this.

* * * * *

At this very moment I would estimate that there are 2,025 tons of drug samples in the backrooms of doctors' offices throughout our country valued at $30 million. This means,

[29] Hearings, vol. 18, p. 10456. His table and explanation follow: Comparatively for the 3d-class rate, it comes out to a total, if the ordinary taxpayer had to pay for this postage, of slightly over $18 million a year. Thus, showing the differences between the bulk rate, actually what the drug firm is allowed to pay and the 3d-class rate that the ordinary taxpayers are allowed to pay in 1957 before that postal increase rate, the yearly difference was over $2½ million.

In December 1959, based on that month, the annual difference between bulk rate and the 3d-class rate, the annual difference is $5½ million.

	1959			
	Bulk rate (actual rate used by drug companies)		3d class mail rate (for comparison)	
	1 office	150,000 medical doctors	1 office	150,000 medical doctors
Daily	$0.28	$41,670	$0.40	$59,670
Monthly	8.85	1,026,000	9.95	1,491,750
Yearly	84.73	12,709,350	121.53	18,229,500

DIFFERENCES BETWEEN BULK RATE AND 3D-CLASS RATE

	1957	1959
Daily	$9,000	$13,000
Monthly	138,000	465,000
Yearly	2,700,000	5,520,150

Quite a difference—$5½ million—and of course the only one to make up the difference is the Government, alias you and I, in our role of taxpayer. This also means that each of us 150,000 doctors pays this difference of $36 yearly out of our own pocket for the privilege of being snowed under with circulars and samples. (See table 2.)

That $5½ million would finance many a research project in our medical schools.

in terms of each doctor, 27 pounds or $200 worth of medicines, wholesale cost not being used.[30]

* * * * * *

The total cost of all of this postage, drug samples, printing, and packages amounted to $210 million a year. This is greater than the $194 million annual price tag for research and slightly more than 10 percent of the reported $2 billion annual gross sales on prescription drugs. Therefore, if this promotional phase were discontinued it could readily result in an overall reduction in the cost of drugs to the patient by at least 10 percent.

No attempt has been made to estimate in this statement the cost of promoting drugs at the many medical conventions throughout the country nor of the tremendous expenditures paid for medical journal advertising.[31]

That Dr. Bowes is not alone in his finding is confirmed by a study entitled "Attitudes of U.S. Physicians Toward the American Pharmaceutical Industry" made for the American Medical Association in 1959.[32] Of the physicians interrogated, 62 percent reported that half or more of the vast amount of direct mail received at their offices

[30] Hearings, pt. 18, pp. 10457–10458. He added:

"During the month of December 1959, seven detailmen visited my office and left 65 drug samples (table 3) valued at $48.07, an average of $6.87 in samples from each man in 1 month. My office is not in a medical center neighborhood, so I probably don't get as many visits from detailmen as do my colleagues in office buildings * * * the detailmen, therefore, leave $576.84 worth of drugs at my office in 1 year, or a possible $86,526,000 worth from the detailmen in 150,000 medical doctors' offices per year. It has been a puzzle to me how a registered pharmacist is restricted in giving drug samples to doctors, friends, and relatives and yet a drug detailman can so freely give samples away to doctors and office assistants without any authority to dispense drugs.

* * * * * * *

"As proof of these facts, I recently solicited the offices of 22 of my fellow doctors in Salt Lake City for their throwaway drug samples that they could not possibly find use for. I collected over 600 pounds of drug samples. The wholesale value of them was $4,400. This amount represented an accumulation of samples over not more than a 6-month period. Thus, the $30 million estimate could further be stated as $60 million worth of drug samples going to waste per year.

"As a constructive solution to making use of the pile of drug samples collected from my colleagues' offices, I began a project of 'medicines abroad.' So far, we have provided and shipped drugs to—

	Pounds	Wholesale cost of drug
West Side Clinic (charity indigent clinic)	43	$235.32
Mission hospital in Tanganyika, Africa	100	770.66
Mission hospital in Philippines	154	961.60
Home for the aged in Salt Lake City	3	30.70

"We are now preparing shipments to India and Sumatra and it is hoped that we might enlarge this program to include many other indigent countries of the world."

[31] Ibid, p. 10464. Later, Dr. Bowes referred again to the question of promotion of drugs at medical conventions:

"Dr. Bowes. May I, Mr. Chairman, read something very quickly here that might be apropos of what has been stated yesterday?

"Here is a program from a medical convention that I just returned from, a national organization, and I would like to read this general information.

"The heading is: 'Cocktail Party': The official cocktail party of the American Society, of so and so, will be held on Friday, Apr. 1, 1960, from 6 to 8 p.m. in the ballroom. All members, guests, exhibitors, and the wives are invited. An individual ticket of admission complimentary for each person must be obtained in advance at the registration desk. The party is being provided as in the past 4 years through the courtesy of the E. R. Squibb & Sons to whom the society is greatly indebted for generously supplying continued support for this important function.

"And another heading quickly sir: 'Scientific and Technical Exhibits': The exhibits are located in the foyer through which the participants pass to reach scientific sections of the roof garden. Technical exhibits, the list of exhibitors is given elsewhere in the program, those attending the 1960 annual meeting are urged to visit and register with these carefully selected exhibitors, whose financial contributions constitute invaluable support for the annual meeting of the society" (p. 10473).

[32] Study conducted by Ben Gaffin & Associates, Inc., Chicago, Ill. The preface states the report is "based on personal interviews with a representative national cross section of 1,011 practicing physicians. The sample was scientifically designed so that the findings as here shown are true within 1 or 2 percent for the total body of practicing U.S. physicians. The interviews were made during December 1957 and January 1958."

advertised types of products which they would not have occasion to use in their medical practice. Approximately 66 percent of these physicians reported that, of the direct mail received in the 7 days previous to their answering the question, they had read less than half. When asked why they had not read this mail, replies were coded as follows:[33]

	Percent
No time; waste of time; too busy	34
Not related to my specialty; not applicable to me	25
Repetition, duplication of previous mailings	20
Already familiar with company's products through detailing, medical journals	9
Just not interested in it	7
Too large a volume of mail	7

When directly asked, "What could be done to make direct mail more useful to you?" replies were as follows:[34]

	Percent
Less of it; less frequent	26
Control it; send only what is applicable to doctor's practice and interest	16
More concise, to the point; condensed	15
Stop repetition, duplication of mailings	11
More factual documented	8
Eliminate it; stop it entirely	7

In answer to a related question "In what ways do you think advertising to doctors should be different?" (from advertising to laymen), replies were as follows:[35]

	Percent
Factual; scientific, more informative; accurate	35
On a higher intelligence level for more informed audience; it can tell values and faults	10
Honest, less exaggerated	8
Give complete, clear research statistics and data	7
More dignified; less emotion; no cartoons, sensationalism	6

Speaking of the tremendous flood of direct mail to physicians, Dr. Solomon Garb,[36] associate professor of pharmacology, Albany Medical College, Albany, N.Y., remarked:

> Spokesmen for the drug industry often claim that these excessive mailings are needed to acquaint doctors with the newest drugs. However, the most heavily advertised drugs aren't new. The one that required 71 mailings per doctor was 3 years old. The second most advertised drug was 2 years old, the third most advertised drug was 5 years old. No. 4 was a full 12 years old. No. 5 was actually new. No. 6 was 8 years old.[37]

[33] Op. cit., p. 25.
[34] Ibid, p. 26.
[35] Op. cit., p. 29.
[36] Dr. Solomon Garb, associate professor pharmacology, Albany Medical College, Albany, N.Y.; born Brooklyn, 1920; A. B., Cornell 1940; M.D. 1943; New York Heart Association research fellow 1949–51; assistant professor Clinical Pharmacology Medical College, Cornell 1952; American Heart Association research fellow 1952–54; Medical Corps, 1944–46, captain. Society Pharmacology: Physiology and Pharmacology of Heart Muscle; chemotherapeutic agents; treatment of hypertension.
Garb, Solomon, "Essentials of Therapeutic Nutrition." New York, Springer 1958, 147 pages. "Laboratory Tests in Common Use." New York. Springer, 1st ed., 1956. 160 pages, 2d ed., 1959. 1958 pages. Chapter "Cations" in Drill's Textbook of Pharmacology; associate, American College of Physicians.
[37] Hearings, pt. 18, p. 10500.

CHAPTER 10. PHYSICIANS' CRITICISMS OF PROMOTIONAL PRACTICES

Various facets of the promotional practices currently employed by the drug manufacturers were questioned by medical experts before the subcommittee. Because of the complex character of the problems involved, their remarks are not capable of easy summary. For this reason the principal objections cited before the subcommittee are illustrated with typical extracts from the testimony of the physicians themselves. An attempt has been made to group their remarks under major headings for easy reference, and, in the interest of economy of space, effort was made to select the most concise exposition of their points of view.

Types of misleading advertising.—The medical experts appearing before the subcommittee were doubtful of the reliability of much of the printed advertising material. For 3 years the Albany Medical College has included in its course work for second year medical students an evaluation of drug advertising. Dr. Garb stated:

> We believed such a project was needed to enable the physician to cope with the flood of excessive and misleading advertising to which he is subjected, day by day, for his entire professional lifetime. The experience of the first year of this project was reported in the New England Journal of Medicine, July 17, 1958. Since then, many medical educators have expressed interest in our project, and faculty members from 20 American and 5 foreign schools have asked for and received our teaching materials, with a view toward adopting them to their own curriculums.
>
> * * * * * * *
>
> In all 3 years, it was found that the majority of the mailed ads were unreliable, to the extent that a physician trusting them could be seriously misled.
>
> On the other hand, we did find that the ads and policies of a substantial number of pharmaceutical companies were thoroughly reliable and honest.[38]

Dr. Garb presented a classification of the types of abuses in drug advertising. The first listed is the ad, not untruthful in itself, which is misleading in its result. He said:

> The first abuse involves misleading ads. It is not always easy to spot these. There are no untruths.
>
> The statements on the ads themselves taken alone are truthful. Instead the truth is presented in such a way as to mislead the reader. I do not claim that it is done so deliberately, but the effect is to mislead the reader. For example, I have here an ad for a product known as nitroglyn. This ad states "It is generally accepted that glyceryltrinitrate (nitroglycerine) is the most effective medication for patients with coronary insufficiency" and there is a quotation of an article in the Journal of the American Medical Association.
>
> * * * * * * *

[38] Hearings, pt. 18, p. 10483.

Dr. GARB. It is not an exact quotation but this statement from the JAMA article is placed in juxtaposition to this statement "Prevent angina attacks with nitroglyn sustained action nitroglycerin" so that one would think that that article in effect endorsed this product.

Now here is the journal in question.[39] Let's look at the article on page 448. * * *

"The drug of choice is glyceryltrinitate (nitroglycerine) given sublingually."

Now those last two words change the whole picture. Nitroglyn cannot be given sublingually. It is a "long-acting" nitroglycerine preparation, and the authors of the JAMA article state also on page 448, here, the next paragraph:

"Of the long-acting nitrites, pentaerythritol tetranitrate appears to be the most effective."

* * * * *

Sublingually means placed under the tongue and kept there. Nitroglycerine is absorbed by the mucous membrane under the tongue. Nitroglycerine pills taken sublingually are not swallowed. They are placed under the tongue. The blood vessels in the mucous membrane under the tongue absorb the material and take it directly into the circulation without going through the liver. If the material is swallowed, it has to go through the portal circulation to the liver and the liver metabolizes the nitroglycerine to a large extent. The sublingual route is the usual route for nitroglycerine.

Senator HART. And this action is not possible with the drug called nitroglyn?

Dr. GARB. No, sir. It is a long-acting material. It is made to be swallowed. If you kept it under your tongue you could keep it there, I don't know, hours, days perhaps. It is made to be swallowed and it breaks down gradually in the stomach and small intestine, releasing small amounts of nitroglycerin. Now, I do not claim that the drug is or is not effective. This is not the point at all. I simply claim that the way they have used this reference is misleading.[40]

Another type of abuse he cited was of the ad which emphasizes the minority view of a favorable verdict on a particular drug, and totally ignores the great weight of evidence leading to an opposite opinion. He stated:

Now there is another category. This is not a misleading ad at all. This ad is substantially truthful. Nevertheless it is objectionable because by virtue of swamping the physician with one point of view based on a mimimum of evidence, it is possible to divert him or at least to override all the other points of view.

I think I can make this point very clearly with this ad. This is an ad which was received in the mail for a drug known as Achrocidin and the legend here is: "It started as a cold." This is part of a larger series of ads. I have here examples

[39] "Current Status of Therapy in Coronary Artery Disease," by Dr. Lawrence B. Ellis and Dr. Ernest W. Hancock. Journal of the American Medical Association, volume 163, No. 6, February 9, 1957, page 445.
[40] Hearings, pt. 13, pp. 10483–10486.

of the same ad from one medical journal, from another medical journal. This ad has been running for over a year. And it refers to the complications of the cold. Now nothing is said that one can take issue with directly. However, I think it clear from the context, from the picture and from the statement "to prevent the sequelae of URI," upper respiratory infection, "and relieve the symptom complex," the statement:

"Otitis, tonsillitis, adenitis, sinusitis, pneumonitis, or bronchitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection. To protect and relieve the 'cold' patient * * * Achrocidin."

Achrocidin contains an antibiotic. I think it clear that the intent of this piece of literature is to convince the physician that he should treat his patients with colds with Achrocidin to prevent the sequelae, to prevent any bacterial complications of a cold. Now the reference which is given is based on an estimate by Van Volkenburgh and Frost, American Journal of Hygiene for 1933, more than a quarter of a century ago before antibiotics were developed.

This puzzled me. Why was it a firm could not find a more recent reference?[41]

* * * * *

My point is that there is one article which implies that this drug may be worthwhile. That one article is quoted in the ad in the brochure. There may be 20 articles by far more distinguished scientists which say the drug should not be used. Those articles are not mentioned.[42]

In a third type of abuse the experience with a single patient becomes the subject of an ad; and an inundation of advertising material covers, in fact, only a handful of individual patients:

In this type, the doctor is swamped with advertising mail for a single product. Here are eight ads received by me in a short time. Six of the eight refer to experience with a single patient. In a comparative study of drugs, a physician will often study 50 to 100 patients or more before summarizing the data and reporting it. Here, a single patient is made a subject of an ad. Presumably, this series of ads went to all doctors in the country. This means that a group of 21 patients, with no controls, was made the excuse for a mailing campaign in which close to 1½ million pieces of mail were sent.[43]

Dr. Console's approach to the same problem was somewhat more caustic; he also presented a classification of types of misleading advertising, drawing a distinction between the naive and sophisticated approaches in the handling of medical advertising. Of the former, he stated:

* * * To help drive this valuable lesson home in one promotional program a free clinical thermometer was sent to

[41] Hearings, pt. 18, pp. 10487-10488.
[42] Hearings, pt. 18, pp. 10490-10491.
[43] Ibid., p. 10496.

physicians. The invitation is delightfully tempting. Too many physicians, pressed for time, would like to believe that medicine can be practiced with a thermometer and a bottle of pills. The authority of the written word driven home by repetition is often enough to tip the balance. The exercise of judgment takes far more time and uses less drug. If this is education, then we should also include lessons on how to smoke an opium pipe.

This approach is used only by the more naive since it does antagonize some physicians. It hardly does justice to the ingenuity of the more experienced drug house.[44]

For the more sophisticated approach, he gave as an example the promotion of tranquilizers, a type of promotion which, he stated, with minor variations has equal applicability to many other drugs:

Either in the course of legitimate investigation or in the search for a new promotion device it is found that a drug which is claimed to be effective in relieving anxiety, produces, in rats, specific objectively measurable changes in a particular area of the brain. Now this is an interesting truly scientific finding but in the present state of our knowledge its significance is unknown. To the promotion people this lack of significance is unimportant since it is both intriguing and impressive. It is presented in an advertisement or a brochure complete with accurate anatomical illustrations of the brain beautifully executed in vivid colors. This is coupled with the claim that the drug relieves anxiety. The usual response of the average practitioner who is not, and is not expected to be, an expert in neurophysiology is to associate the two and to assume that they support each other. To the expert, however, any attempt to relate the claim and the finding is absurd since there is no known relationship between human anxiety and this finding. It is no more absurd to relate the claim to this finding than to the finding that the drug when given to cats, makes their tails curl up and form a square knot. The latter is obvious, the former is not. Because it is not, the impressive but irrelevant fact is carefully presented in vivid form. The clarifying facts are equally carefully omitted. The desired effect is achieved by encouraging false associations and the frequency with which this approach is used is adequate evidence of its success. This, too, is called education.[45]

Another example of more sophisticated promotion practices he defined as the "confusion technique."

* * * When the novelty of more potent vitamin pills began to wear thin, someone conceived of adding minerals and trace elements. Among these is zinc and since I am not an expert on zinc it may not be significant that I know of no evidence of zinc deficiency in man. If, however, one searches the literature long enough he will find that when chickens are deprived of zinc they cannot form a hard shell on the eggs they lay. When this curious fact is added to

[44] Hearings, pt. 18, p. 10370.
[45] Hearings, pt. 18, p. 10370.

> others similarly curious and mixed with some which are significant one ends up with an impressive array of "evidence" for the rationale of the product being advertised and apparent reasons why the doctor should prescribe this mixture of vital ingredients. Now let us look at only one of the facts which are carefully omitted. No mention is made of the fact that the zinc deficiency can only be produced by extremely careful and expensive purification of the diet. Every trace of zinc must be eliminated and if the chickens get only an occasional meal by random pecking in the barnyard they obtain enough zinc to destroy the effect. In short, the deficiency is a laboratory artifact and has no counterpart outside the laboratory. Or stated differently, if one is to draw logical conclusions the zinc makes the vitamin pills invaluable for laboratory chickens provided, of course, that one is willing to go to the expense of purifying their diet.
>
> Here the physician is bludgeoned with a barrage of irrelevant facts he has neither the time, the inclination, nor frequently the expert knowledge to examine critically. Multiply this by a dozen detail men each selling a dozen products and backed by a dozen wizards in the home office who hold a dozen conferences trying to determine the best way to make nothing appear like a pot of gold. This, too, is called postgraduate medical education.[46]

The use of useless drugs.—Several witnesses noted the possibility of conflict inherent in the fact that the drug company's primary responsibility is to its stockholders while that of the physician is to his patient. The crux of the problem appears to lie in the differing approach to drugs of the drug manufacturers and the medical profession. Dr. Bean put it this way:

> What is the organizational structure in which physicians and a manufacturer of drugs, untrained in medical problems, may find themselves at odds? I am not concerned with the many fine pharmaceutical companies which exercise scrupulous caution in releasing new drugs. The problem is with companies whose sole concern is business. The stockholders' appropriate interest is in income. The richest earnings occur when a new variety or variation of a drug is marketed before competing drugs can be discovered, improvised, named, and released. This bonanza time may last only a few months. Unless there are large earnings, the quick kill with the quick pill, the investment does not pay off. Commercial secrets must be kept dark, less a competitor get the jump. Under this system it is impracticable to do tests extending over a long period of months or years to establish the range of usefulness and potential dangers from toxicity. Such tests usually have to be done in hospitals and often in medical schools, where secrecy in science cannot be tolerated. Thus, after extensive laboratory tests on toxicity and pharmacologic properties, but sometime with a minimum of clinical trial, a drug may be marketed.[47]

[46] Hearings, pt. 18, pp. 10370–10371.
[47] Hearings, pt. 18, p. 10335.

If new drugs do not emerge from the research laboratories fast enough, then there must be forced—for marketing purposes—a semblance of the reality. Dr. Louis Lasagna,[48] head of the division of clinical pharmacy, Johns Hopkins, stated:

> The problem of "built in obsolescence" of drugs, which has been referred to repeatedly, is I think tied in not only to the appearance of new and better substitutes, but to the miserable quality of drugs that are issued each year.
>
> The advertising agencies are being asked to sell to the medical profession a whole bushel basketful of sows' ears for silk purses each year. It is no wonder that there are advertising excesses, and that there are so-called product failures and that obsolescence sets in.
>
> This plethora of poor compounds, and of new mixtures of old agents that appears each year confuses physicians.
>
> It raises the cost of drugs, I would think, and may harm patients either through keeping them from adequate therapy or by causing them serious side effects.[49]

Of slight molecular modifications on existent drugs, he observed:

> Another point that might be made here is that the history of pharmacology indicates that minor modifications of an original drug do not often provide major therapeutic advantages. I think one can come up with differences in side effects, but major qualitative therapeutic advantages by such modifications are rare.[50]

Dr. Console classified drugs roughly in four categories as follows:

> 1. Effective drugs prescribed only for patients who need them.
>
> 2. Effective drugs prescribed for patients who do not need them.
>
> 3. Drugs from which all patients derive either no benefit or no more benefit than would be derived from an inexpensive substitute.
>
> 4. Drugs which have a greater potential for harm than for good.[51]

He continued:

> These are all products of the pharmaceutical industry and it should be clear that the cost of drugs cannot be measured by price alone. * * *
>
> The incidence of disease cannot be manipulated and so increased sales volume must depend at least in part on the use of drugs unrelated to their real utility or need, or in other words, improperly prescribed. Human frailty can be manip-

[48] Dr. Louis Lasagna, Johns Hopkins University School of Medicine. Graduated from the College of Physicians and Surgeons of Columbia University in 1947. Internship and residency training in internal medicine for 3 years in the New York City area. In 1950 joined the department of Pharmacology in Experimental Therapeutics at Johns Hopkins. In 1952 was assigned by the U.S. Army to a clinical pharmacological research project at the Massachusetts General Hospital. In 1954 rejoined the Johns Hopkins Medical School as a member of the Departments of Medicine and Pharmacology, and is head of the Division of Clinical Pharmacology.

Currently associate professor in these departments. Also a consultant to the National Cancer Institute and National Institute of Mental Health. Coeditor of the Journal of Chronic Diseases. Associate editor of the Journal of Pharmacology and Experimental Therapeutics.

[49] Hearings, pt. 14, p. 8140.

[50] Idem.

[51] Hearings, pt. 18, p. 10368.

ulated and exploited and this is fertile ground for anyone who wishes to increase profit.

The enormous sales of so-called tranquilizers are only a small part of the crop reaped from this ground. The pharmaceutical industry is unique in that it can make exploitation appear a noble purpose.

It is the organized, carefully planned, and skillful execution of this exploitation which constitutes one of the costs of drugs which must be measured not only in dollars but in terms of the inroads the industry has made into the entire structure of medicine and medical care.[52]

Difficulties in drug evaluations.—The subcommittee included among its medical witnesses both general practitioners and specialists in various fields. Several of the specialists stated that, even in their areas of specialty, it was an almost impossible task to keep abreast of developments because of the heavy volume of medical literature both in this country and abroad. All of them voiced concern at the inadequate information supplied general practitioners from drug company advertising. The problem, they thought, was particularly serious because many of the new drugs are prescribed by general practitioners rather than specialists; and it was of the utmost importance that the fullest knowledge should be available.

Dr. Fritz Freyhan,[53] director of research, Delaware State Hospital, expressed the problem in these terms:

The main problem here which needs to be discussed involves the amount of information which is given to those physicians who are not really specialists in the field of psychiatry.

While it may, even for psychiatrists, be difficult to keep up with the literature, psychiatric drugs are now prescribed for many reasons by every doctor; the family physician, the obstetrician, the pediatrician, and so on. The physician who is not a psychiatrist depends that much more on the accuracy of information which comes from the promotional literature.

These physicians are less apt to read the articles in the specialists' journals. They might read the American Journal of Medicine, which will bring a certain number of psychopharmacological articles, but they will rarely read journals devoted solely to psychiatry.

I think one has to keep in mind that prescription of these drugs is no longer the province of the psychiatrist. But the

[52] Hearings, pt. 18, p. 10369.—Dr. Bean, in looking back upon the parade of new products introduced with such fanfare, had this to say:

"Now another side of the picture is seen in the ultimate fate of many a drug acclaimed as the latest and best cure. Promotion brings enthusiastic use. Then, too often, come gradual disappointment, delayed or bizarre reactions, disillusion, rejection and oblivion, or final acceptance suitable to the observed level of performance. No one has worked on the necrology of last year's sure cures, whose costly colored advertising brochures gather dust. What, in short, is the 5-year survival rate of new drugs? Where are the cures of yesteryear? A study of abandoned drugs may seem a little foolish when so many new ones are arriving daily. But each failure is costly and wasteful—in time, money, hope, and perhaps in health. (Ibid., p. 10335.)

[53] Fritz Adolph Freyhan: Born in Berlin, Germany, 1912. M.D. University of Berlin, 1937. Interne Sydenham Hospital, New York City 1938–40; advanced training in clinical pathology 1938–39, rotating internship 1939–40. Now clinical director and director of research, Delaware State Hospital in Farmhurst, where was resident physician 1940–42 and assistant director 1942–45; director, department of psychiatry and neurology, Delaware Hospital, Wilmington, assistant professor of psychiatry University of Pennsylvania. Licensed in State of Delaware. Certified American Board of Psychiatry and Neurosurgery. Member American Medical Association, American Psychiatric Association, Association for Research in Nervous and Mental Diseases, and American Psychopathological Association.

actions of these drugs presuppose a great deal of understanding of psychiatric illness, of the symptoms of various disorders, of the various methods to treat mentally ill patients.

Therefore, when it comes to promotion, it is not simply a question of what the psychiatrist should know. One of the most essential problems is how comprehensive information can be made available to the multitude of physicians who prescribe these drugs for the patients whom they see in everyday practice.[54]

As a specific example, he cited the case of the mild tranquilizer, Miltown:

The general practitioner, the specialist in another field, does not read these articles, and he may be altogether dependent on a page such as this on Miltown which says, "For the tense and nervous patient, relief comes fast and comfortably." Then these advertisements simply say what this drug does not do, but they will never mention what complications have also been observed. Even if these complications have only been observed in a relatively small number of patients, the physician must still know this since it may occur in the particular patient whom he treats.

The danger then, I would say, is that if you get a number of witnesses, they may say that they can't find too much fault with the sentence "Relief comes fast and comfortably" and they will provide evidence to this effect. But the advertisements do not say anything about the undesirable reactions which have also been observed in the literature. Therefore, I think they are misleading.

Senator KEFAUVER. The undesirable reactions you think should be listed if that is going to the general practitioner: What are they?

Dr. FREYHAN. Well, there is, first of all, the observation that in a certain number of patients, and I am not prepared to say what percentage this would be, addiction has been observed and has been reported in a number of very authoritative articles.[55]

Dr. Heinz Lehmann,[56] clinical director, Verdun Protestant Hospital, Montreal, Canada, took much the same view as Dr. Freyhan:

Like most psychiatrists, I feel that one is subjected to a great assault of unwarranted and undocumented and sometimes very unprofessional advertising literature. A good ad, if it really would help the physician to inform him as it should about new drugs, would simply state clearly and in scientific and technical language, not in blown-up dramatic language, it would state in scientific and technical language the indications for the use of the product. It should make brief reference to the class of drugs, chemical to which it belongs or to the general mechanisms, physiological mechanisms by

[54] Hearings, pt. 16, pp. 9037-9038.
[55] Hearings, pt. 16, pp. 9057-9058.
[56] Heinz Edgar Lehmann, born in Germany 1911; M.D., University of Berlin 1935. Intern Martin Luther Hospital and Jewishpolyclinic Berlin 1935-35. Residency in psychiatry Verdun Protestant Hospital, Montreal 1937-41. Since 1941 clinical director, Verdun Protestant Hospital; since 1951 assistant professor psychiatry, McGill University. Licensed, Province of Quebec. Fellow, American Psychiatric Association.

which it acts if these are known, and it should point to well-established advantages of the particular drug if they exist, and should also point out the caution and precautions and side effects that apply to that particular drug.[57]

Role of medical director.—Virtually all of the large companies maintain medical directors who, it appears, have varying degrees of responsibility for the content of the promotional material going to physicians. In no company does it appear that the medical director has final authority; and the testimony heard by the subcommittee shows that too often he is bypassed or overruled by the advertising staff. Dr. Console, himself a former medical director of one of the companies, had this to say in an exchange with the chairman:

> Senator KEFAUVER. In connection with what is put out, I know there are variations for different drug companies, and some may give their medical directors more authority in this regard. But in your opinion should the medical director have the final word on what is going to be said about medical qualities and side effects of drugs put on the market?
>
> Dr. CONSOLE. Yes; the medical director generally has a rather large staff behind him. He has at his command an enormous number of consultants. He generally has a better than speaking acquaintance with the authorities in most fields. It is simply a matter of picking up the telephone and asking any of these people what they think about something, or holding a conference with them and getting their opinions.
>
> So that when the medical director expresses an opinion regarding the ethical nature or the scientific validity of any advertising, he is not merely expressing his opinion. That is gathered from many sources, which I think can be accepted as being reliable, because most of these people are relatively unbiased. They have no ax to grind.
>
> Senator KEFAUVER. You are referring to medical directors. Then what happens in many instances when a conflict arises between the promotion and advertising department and the medical director? Who has the authority?
>
> Dr. CONSOLE. This varies from company to company. It would be awfully hard for me to give you any answer that would hold for all companies. In some companies the medical director is more or less a screen, and by that I mean a smokescreen.
>
> He merely throws a cloak of respectability over what are really business decisions. In other companies on some products he has the final word. Usually if the investment in a product has been large, and if it has great potential for sales, and particularly if the underground indicates that another company is going to market it, the medical director will be overruled. He has one vote.
>
> Senator KEFAUVER. Article 6 of the present statement of principles of ethical drug promotion of the PMA board of directors, passed on May 24, 1958, as we have it here, states: "All medical claims and assertions contained in promotional communications should have medical review prior to their release."

[57] Hearings, pp. 9033-9034.

> So that your statement is correct. It is not a veto power; it is a review.[58]

A similar exchange occurred between Senator Kefauver and Dr. Bean:

> Senator KEFAUVER. Do you feel that the medical directors of these drug companies should have the last word on when clinical testing has been sufficient, whether the advertising is proper and factual, rather than to have the desire for sales and advertising dictate these matters?
>
> Dr. BEAN. I think that a professional opinion on both toxicity and efficacy of drugs should be in the hands of scientifically trained medical people, and that if they believe that a drug is dangerous or inactive they should at least have veto power in preventing its being launched or promoted.[59]

Overemphasis of brand names.—In the drug manufacturing industry, where price competition is virtually nonexistent among the large companies, intensive advertising pressures are directed to brand names. Dr. H. J. Weinstein,[60] former medical director of a division of Pfizer, put it very bluntly:

> The entire promotion and advertising program has been directed at the physician in recognition of his special role. He has been taught, one might almost say brainwashed, to think of the trademark name of the drug at all times. Even new disease states have been invented to encourage the use of some drugs. He has been exposed to remarkably little information concerning the efficacy of the drugs he is asked to prescribe. He is given practically no information as to the cost of the drugs to his patients. Instead, he is seduced with gimmicks of all sorts in an attempt to make him loyal to a particular company or a particular drug, with relatively little attention being paid to the specific merits of the drug in question.[61]

The problem is magnified by the current practice of developing slight molecular modifications on existing drugs, and marketing them under brand names. Dr. Dowling used erythromycin to illustrate the situation in antibiotics. He stated:

> I believe that most of the competition among pharmaceutical companies is in the wrong area today. Under the present system, a successful pharmaceutical company works at a frenetic pace to produce slight modifications of existing drugs in order to keep abreast of its competitors. Let us take a concrete example—the development of erythromycin and its analogs.

[58] Hearings, pt. 18, p. 10378.
[59] Hearings, pt. 18, p. 10348.
[60] Dr. Haskell J. Weinstein: "I am a native of the State of Washington and have had most of my education in Seattle, Wash. I attended the University of Washington, where I received a B.S. degree in 1949, following military service, and my M.D. degree in 1953. Subsequently, I had postgraduate training at the Teaching Hospital there, in internal medicine, and had further fellowship training in infectious diseases. I worked in a tuberculosis hospital and chest hospital in Seattle until the first part of 1959, at which time I joined Charles Pfizer & Co., in the clinical research division, and remained in that division until the middle of September of 1959, at which time I moved over to the J. B. Roerig Co. as acting medical director, and remained there until the 18th of December, when I left the company.
"At the present time I am the director of the Chest Hospital of the City of Hope National Medical Center, in Duarte, Calif."
[61] Hearings, pt. 18, p. 10245.

I have chosen this example because the erythromycin groups of drugs, unlike some other groups, were produced entirely within the drug industry and by several different companies. Although other examples could be cited, erythromycin and its analogs serve our purpose best because they act against a definite group of microorganisms and because there is general agreement that they act alike.

Erythromycin was discovered by Eli Lilly & Co., was found to be effective against infections caused by staphylococci and other cocci, and was first marketed in 1952.

It represented an important discovery because erythromycin was different from all of the antibiotics known at the time.

In 1953, Charles Pfizer & Co. introduced an analog, carbomycin, which affected the same bacteria as erythromycin. This was marketed and advertised, although it was soon found that it was not as effective in human disease as it had been in the test tube. Finally, in recent months, it was withdrawn from the market.

Some time later, another analog was discovered in Europe and called spiramycin. My colleagues, and I, among others, tested it in the laboratory and could not see that it had any advantage over erythromycin. We advised the company that sent it to us not to introduce it to the American market, since another erythromycin-like drug would add nothing and would only serve to confuse the physician. It should be recorded to the credit of the company we counseled that it did not purchase spiramycin nor did any of the other companies to whom I understand it was offered, so that today it is not marketed in America, although it is sold in Europe.

Unfortunately, the same cannot be said for other analogs of erythromycin. In 1956, Charles Pfizer & Co. introduced oleandomycin, which has essentially the same effectiveness as erythromycin. A year later the same company produced a modification of oleandomycin, triacetyloleandomycin. This was heralded as an important drug because the same oral dose that was used for oleandomycin produced somewhat higher concentrations of the drug in the blood.

To counter this competing drug, Eli Lilly & Co., which had developed the original erythromycin, introduced in 1958 the propronyl salt of erythromycin which is said to produce higher antibacterial activity in the blood than triacetyloleandomycin.[62]

Speaking of this last type of claim, Dr. Dowling remarked:

> All of these attempts to produce higher blood concentrations are of doubtful benefit, since a slightly higher dose of the original drug would achieve the same results. The increased cost of the higher dose would be more than offset by the savings in not developing and promoting the analog. If very high blood concentrations are needed, they may be obtained with intravenous preparations of these drugs.

[62] Hearings, pt. 24, pp. 14167–14168.

Now, I am not claiming that producing and marketing these modifications is reprehensible or morally wrong. I am merely saying that the promotion of so many drugs that are essentially the same is confusing to the physician—and the confusion is compounded when each drug is marketed under several different trade names.

Furthermore, the money spent on discovering, developing and promoting these drugs is largely wasted. This money could be better spent in looking for truly new drugs.[63]

Dr. Frederick H. Meyers,[64] associate professor of pharmacology, University of California, after remarking that when "manufacturers try for a share of the market," they do not "choose to use price competition," went on to say:

* * * instead of price competition, the manufacturers will use any method that will establish their trade name in the mind of the physician. They are no longer advertising the drug group. They are no longer striving, to use the terms of the previous witnesses, to educate the physician, except that they are educating him to choose their preparation, their trade name from among these roughly equivalent or almost identical products.

Now these other methods include expensive and shifty advertisements in many forms. I say "shifty" in the sense that they conform to the minimum standard of the medium being used at the time.

If a medical journal has a certain standard, they will meet it, their detail men, their salesmen who are subject to no such discipline, will slide down a few notches, for example. It is expensive because the physician resistance must be overcome at any cost. If he tells his secretary, as many of us do, to throw out all the second class mail, it will be mailed first class with the medical director's name and home address in the corner.

When this fails, they will be sent airmail. They will be mailed from other countries. Any device, regardless of its expense, will be used to overcome the physician's resistance. * * *

To me they talk about seeding. When they are ready to release a new compound, they don't say we will get a clinical investigation at every medical center in the country.

They say, "We are going to get the seeding from coast to coast and on this one."

Senator KEFAUVER. What does the word "seeding" mean?

Dr. MEYERS. Much of what passes as clinical investigation from an accounting and advertising point of view is really an effort to get the drug used in a medical center before general release, to get a physician of some influence to use the drug as part of a clinical trial, often with perfectly good

[63] Hearings, pt. 24, pp. 14167-14168.

[64] Frederick H. Meyers, M.D., University of California 1949; assistant professor pharmacology, University of Tennessee, 1951-53; associate professor pharmacology and assistant clinical professor medicine, University of California, 1953 to present. Associations: American Pharmacological Society, Society for Experimental Biology and Medicine, American Therapeutic Society.

motives, but to establish the name and ability, if any, of the drug before its general release.

This I regard as a form of advertising, because I do not think it is a sincere effort to accomplish a clinical evaluation of the drug.[65]

Dr. Chauncey D. Leake,[66] professor of pharmacology at Ohio State University, likened the advertising of brand names for drugs to similar programs for popular brands of cigarettes:

Senator CARROLL. Then it is a part, is it not, of an advertising scheme or program to convince them that drug A is more effective than drug B, although they both achieve the same end?

Dr. LEAKE. Yes, but it is a little bit like the cigarette advertising, and I think you are aware of that.

It gets rather narrow, because sometimes there is very little to choose.[67]

In the same vein Dr. Bean stated:

What I object to is that each person naturally says his brand is good, even if it is of the same thing. I have no objection to competition as such, but when claims are made in comparison with different brands of the same chemical, it becomes something that may get out of hand.[68]

An almost inevitable effect of the emphasis on brand names is that the generic name is often obliterated from the mind of the practicing physician. According to Dr. Weinstein:

The doctor unfortunately has been so snowed under with all sorts of efforts to make him remember only the trademark name with practically no attention given to the generic name in the slightest, that being a normal human being he reacts automatically to the trademark name. And so when he prescribes he writes that which is the first thing that comes to his mind in a particular condition. He is tying his own hands, he is tying the pharmacist's hands, and he essentially is tying the patient's hands.

Senator HRUSKA. Well, now, if he has difficulty with the avalanche of trademarks and has difficulty mastering their component elements and so on, trademark products, how much more difficult would it be to try to master the detail by generic name which sometimes goes into dozens of words?

Dr. WEINSTEIN. No, I don't think this latter part is necessarily true.

Senator HRUSKA. Not necessarily, but often true. We had a chart here——

Dr. WEINSTEIN. You see, sir, this is artificial. The generic name is not the chemical name. The generic name

[65] Hearings, pt. 18, p. 10398.

[66] Chauncey D. Leake, born, New Jersey, 1896; Ph. D. Wisconsin, 1923; instructor to associate professor pharmacology and physiology, Wisconsin, 1920–28; professor, lecturer, medical history and librarian, medical school, University of California, 1928–42; vice president, Medical Branch, University of Texas, 1942–55; professor of pharmacology and assistant dean, College of Medicine, Ohio State University, 1955. Associations: American Society of Pharmacology and Experimental Therapeutics (president), American Association for Advancement of Science (president), American Association for the History of Medicine (vice president), etc.

[67] Hearings, pt. 18, p. 10429.

[68] Ibid., p. 10341.

is supposed to be a shorthand name for the drug. If your shorthand is not very effective, you are going to have a very long name. But you can make it shorter. But to go back to the problem you are talking about, take a well-known drug such as hydrochlorthiazide, which is marketed under the names of Hydrodiuril and Esidrix, and I think there are two or three other companies manufacturing it, under the trademark names. Hydrochlorthiazide is not terribly difficult to remember, but the advertising has it in extremely minute letters. And no effort is made to get the doctor to remember hydrochlorthiazide. The effort is made to make him remember Hydrodiuril or Esidrix, or one of the others.

Senator HRUSKA. That effort is by the detailmen to whom you refer?

Dr. WEINSTEIN. By the detailmen, and by advertising; yes, sir.[69]

The success of this approach is attested by Dr. Leake who was concerned about the monopoly aspects of the problem. He said:

> It is unfortunate that the trade name of a drug is a matter of perpetual ownership. If the trade name is short and easy to be remembered, and is carefully plugged during the time the patent is in effect, the trade name will stick in the minds of physicians and other users, and result in a continued monopoly on the drug even after the patents have expired and even after the price presumably could come to competitive levels.[70]

In fact, so great has been the manufacturers' compulsion for new brand name products that on occasion there are developed combinations whose therapeutic usefulness has been sharply questioned. An instance of this type of product is Deprol, sold by Wallace Laboratories, a subsidiary of Carter Products, Dr. Lehmann stated:

> It is a combination of Miltown again, which is one of the components, and the other component is Benactyzine, which is another one of the minor, or less potent, tranquilizers which hasn't found much of a market because it produces not much freedom from anxiety but sometimes causes more anxiety.
>
> In other words, it produces very unpleasant side effects in many cases. So what has been done is to combine these two, one effective and one not so effective, minor tranquilizers, and ascribe to them a new effect; namely, one of being effective in depressions. And that was done on the basis of one article which was published, and when the promotion campaign was started, the article had not even appeared in print yet although the work had been done. There is not much to substantiate the first early claims of its efficacy in depressions.[71]

Referring to a piece of direct promotional material, Dr. Freyhan stated:

> The letter starts, "Dear Doctor," which is followed by a number of statements, again raises the impression that this is

[69] Hearings, pt. 18, p. 10269.
[70] Ibid., p. 10435.
[71] Hearings, pt. 16, p. 9065.

a most effective drug to be used in the treatments of depressions.

It says: "Also, it is good in emotional fatigue and nervous exhaustion."

Then: "It acts fast to relieve tiredness, lethargy, apathy, listlessness associated with emotional fatigue. It doesn't overstimulate your patient. Thus, Deprol restores normal interest and vitality before the condition deepens."

Then it goes on. Now, the trouble with this is that neither of the two component parts which Dr. Lehmann already identified and commented on can have any conceivable effect on the conditions here stated.

Miltown certainly isn't relieving tiredness or lethargy since it is well known to have an effect which is in the nature of a sedative. As far as the other component is concerned, which had been marketed as Suavitil a number of years ago, and I do not think it is of much use today, again that is a compound which induces such symptoms as a dry mouth and sometimes blurred vision.

* * * * *

The very intensive Deprol promotion campaign which reaches my desk at least two or three times a week really makes me feel quite concerned about what may happen to depressed patients who are treated by the general practitioner.[72]

Dr. Maxwell Finland was critical of the numerous mixtures of antibiotics which are now marketed, each under a separate trade name. After stating that there were limited situations where antibiotic combinations had beneficial effects, he stated:

There are now, however, perhaps more than 100 mixtures of drugs that are being marketed by drug manufacturers and it is doubtful that any of these particular combinations can be justified.

The most striking real or potential disadvantages and objections to the use of these fixed combinations may be summarized as follows:

1. They encourage "shotgun therapy," which in turn discourages the proper study and observation of the patient. Dr. Ernest Jawetz of the University of California, an outstanding authority in this field, stated it thus:

"Due to their implied promise of 'broad spectrum' and 'greater efficiency,' they engender a false sense of security, discourage specific etiologic diagnosis and encourage inadequate antibiotic dosage."

2. These fixed combinations may fail to provide optimum treatment in the relative amounts contained in the commercial mixtures for any single known disease.

3. They contain constituents of which at least one has a tendency to give rise rapidly to increased resistance, particularly of staphylococci. Moreover, organisms resistant to one or the other, or both, are already prevalent

[72] Hearings, pt. 16, pp. 9065-9066.

wherever these agents are popularized or where antibiotics in general are widely used.

Thus, they cannot serve to protect against the development of resistance in the manner that I have indicated.

4. The general use of multiple antibiotics gives rise to an increase in the occurrence and spead of certain resistant organisms that are normally not pathogenic, but which may increase in virulence by virtue of the increase in their numbers and perhaps by the removal of their normal competitors.

5. One or another of the constituents may be particularly useful in certain serious specific infections and should best be reserved for use in circumstances in which it may be specifically indicated. This advantage is generally lost when that agent is used widely and especially in these mixtures.

6. When one or another constituent is especially indicated in a given condition, it is not possible to adjust the dose of the useful one to provide optimum treatment without needlessly increasing the dose of the other.

7. It is incorrect and misleading to speak of a synergistic drug pair as has been done in promoting some of these combinations. This implies a greater activity from the pair of drugs than could be achieved by either component of the combination.

Such greater activity or "synergism" is a highly specialized property related to individual strains of bacteria and is recognizable only after special tests. Thus, a so-called synergistic drug combination can only be tailormade to an individual strain of bacterium after such tests.

8. Because of proprietary interests in certain antibiotics, particularly some with inferior properties as compared to others that are available for the same purpose, some manufacturers have been promoting the sale of their products in combinations with other useful ones, and other manufacturers unfortunately have seen fit to follow suit, and have been combining pairs of antibiotics each of which is useful by itself.

9. Since none of the available combinations has clearly shown any advantage over the proper use of the more effective constituent alone, the patient is unnecessarily exposed to the risk of toxic reactions to the other component of the mixture.

As a teacher and one who has worked hard in this field, I am naturally discouraged and disturbed that these combinations continue to be prescribed by physicians in spite of repeated expositions of their potential and actual dangers by most of the leading workers in this field, at least those in this country.[73]

Drug companies and medical journals.—According to some of the witnesses, there are medical journals deriving much of their income from advertising, which have not been unaffected by the constant and intense effort to promote particular brand names. Dr. Lehmann drew a distinction between some medical journals "notorious" for

[73] Hearings, pt. 24, pp. 13927-13928.

their subservience to the drug industry and those with high editorial standards:

> How misleading or accurate or informative or ethical an ad, a pharmaceutical advertisement is, or will be, will depend greatly if not mainly on the editorial policy of the journal, for one thing, because if an editorial policy would be rather tight in a journal, as we have seen in these different journals then certain ads would not be allowed to appear. And if, for instance, ads would be scrutinized as carefully as manuscripts of papers are—we do know that there are certain medical journals which are known to be almost notorious to be very easy to get into, because the editorial policy is not very tight, and their articles do not carry particular value. Other articles, if they appear in certain other journals, are of greater value simply because they appeared in a journal with better editorial policy.
>
> If the same would be true for ads, if one could judge the journal by the kind of pharmaceutical ad that they allow, we could probably get ahead quite a bit.
>
> May I give one example, I cut two ads out about a certain drug, an antidepressant, Niamid, of two different journals, but both advertised in the same month.
>
> In one journal which is a rather responsible one, Mental Hospitals, there are various statements made: "Side effects are infrequent and mild and often eliminated by reduction in dosage."
>
> Then it goes on to state about dosage. But then there is one heading "Precautions" and it says:
>
> "Niamid has not been reported to cause jaundice. However, in patients with a history of liver disease the possibility of hepatic reactions should be kept in mind."
>
> That is a very valuable warning. But the same firm advertising the same month with the same picture and otherwise quite an identical advertisement in another journal simply says in the other journal:
>
> "A high degree of safety already proved in several thousand patients. Niamid has not been reported to cause jaundice or glandular symptoms.
>
> "Visual disturbances and hypotensive effects have rarely been noted."
>
> It states only negative things and makes no allowance for the category of precautions as in the other. The conclusion then is that if a journal has a better editorial policy the ad will be better.[74]

Senator Hart later inquired where primary responsibility for this situation lay and Dr. Lehmann replied:

> As far as the manufacturer is concerned, I would feel as a psychiatrist that their motivation is one of selling, and therefore I would not have too much confidence in their policing themselves, unless they are being helped, because even in a manufacturing firm's promotion I think there is a split between the research department showing more re-

[74] Hearings, 16, pp. 9076-9077.

sponsibility and the promotion department only interested in promoting.[75]

With his experience in the medical department of one of the country's largest drug companies, Dr. Weinstein could be more specific. He stated:

> It may be of interest to the committee to know that a substantial number of the so-called medical scientific papers that are published on behalf of these drugs are written within the confines of the pharmaceutical houses concerned. Frequently the physician involved merely makes the observations and his data, which sometimes are sketchy and uncritical, are submitted to a medical writer employed by the company. The writer prepares the article which is returned to the physician who makes the overt effort to submit it for publication. The article is frequently sent to one of the journals which looks to the pharmaceutical company for advertising and rarely is publication refused. The particular journal is of little interest inasmuch as the primary concern is to have the article published any place in order to make reprints available. There is a rather remarkable attitude prevalent that if a paper is published then its contents become authoritative, even though before publication the same contents may have been considered nonsense.[76]
>
> * * * * * *
>
> Of further interest may be the existence of a journal, recently founded, called Current Therapeutic Research, which appears to be devoted entirely to pharmaceutical promotion. It accepts no advertising as such. However, there is a fee per page for any article published and publication is very prompt. The publisher's major source of income presumably is the lucrative reprint market.[77]

Dr. Console, also formerly connected with a drug manufacturer, denounced publication in scientific journals of allegedly scientific studies by doctors, which he held amount in many cases to no more than testimonials of no scientific validity. He described the practice as follows:

> Let me emphasize that no drug study is foolproof, but that the scientific validity of any study can be immeasurably increased by proper experimental design. A drug trial which makes no allowance for placebo effect, and which fails to make accurate comparison with an untreated group is suspect, and the vast majority of reports on such studies are simple testimonials, not scientific evidence. A testimonial written by a doctor, even when it is given the additional cloak of respectability afforded by publication in a scientific journal, is still a testimonial.
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> * * * * * *

[75] Hearings, pt. 18, p. 10501.

[76] Dr. Weinstein added: "I was involved in a situation which will, I believe, describe the relations between the pharmaceutical house and the publisher quite adequately.

"I was assigned the task of writing a paper on a new formulation of a broad spectrum antibiotic. I was informed that this paper had been accepted for publication and the 100,000-plus reprints were ordered before I finished the writing assignment. The paper, of course, was published exactly on schedule, which incidentally was within a few days of the introduction of the product on the market.

"In contrast, scientific papers I have written have waited many months for publication."

[77] Hearings, pt. 18, pp. 10244–10245.