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THE PECULIAR SUCCESS OF CHLOROMYCETIN

CONSUMER REPORTS

Two years ago, a California physician journeyed to Washington to tell the Senate Committee on Small Business about the death of his 10-year-old son in 1952. The boy died after his father had given him the drug *Chloromycetin* for a mild urinary infection. As the father explained it, practicing physicians receive from 75 to 80 per cent of their information regarding drugs from drug company salesmen, called detail men, and from advertisements in medical journals. A few days before his son's ailment, the father was visited by a Parke, Davis & Co. detail man, who gave him a supply of *Chloromycetin* and assured him that it was a perfectly safe antibiotic. Yet only three days before that, the father said, the same detail man had been informed by a local pharmacist that *Chloromycetin* had been responsible for the death of a woman in nearby Pasadena.

"He deliberately lied to me that the drug was harmless," the father told the subcommittee.

The weight of medical evidence shows a correlation between the use of *Chloromycetin* and the incidence of aplastic anemia, a frequently fatal condition in which the bone marrow ceases to produce white cells, red cells and platelets (necessary for proper clotting).

There is no known method of determining beforehand a patient's susceptibility to *Chloromycetin* injury. Blood studies done during administration of the drug may suggest bone marrow depression, but even when it is recognized, the condition is often progressive. According to Dr. John M. Adams, of the department of pediatrics at UCLA, "Contrary to the belief of many doctors, *Chloromycetin* has an effect which is harmful in varying degrees to the bone marrow of all persons who take it."

The chances of dying of aplastic anemia as a direct result of taking *Chloromycetin* are fairly remote. A California study estimated the risk at between 1 in 24,200 and 1 in 40,500. Still, those seemingly slender odds should be regarded in the light of two other facts. First, the chances of dying of aplastic anemia, without any contribution from *Chloromycetin*, are less than 1 in 500,000. Second, according to the National Research Council, which investigated *Chloromycetin* for the U.S. Food and Drug Administration, *Chloromycetin* can no longer be considered the drug of choice for any illness except possibly typhoid fever (170 cases reported in the U.S. in 1969). Apart from that rare and not wholly substantiated exception, only in a few life-threatening conditions where other drugs have failed is there any justification for prescribing *Chloromycetin*. Yet it has been prescribed for and is being prescribed for millions.

MEDICAMENTA VERA

Medicamenta Vera (True Medicines) has been the Parke, Davis motto since the company's founding in 1866. In the 1940's, Parke, Davis scientists discovered that certain Venezuelan soil samples contained molds that yielded an antibiotic, chloramphenicol. It was found to be effective in treating various diseases, including typhoid fever and certain rickettsial diseases such as scrub typhus. Shortly thereafter, a Parke, Davis research team learned how to produce chloramphenicol synthetically for less than 10¢ a capsule. That was the first commercial synthesis of an antibiotic drug from soil molds. Parke, Davis rushed construction facilities for manufacturing chloramphenicol. It bestowed the trade name *Chloromycetin* on the drug and was granted a 17-year patent. Soon it had *Chloromycetin* in production at plants in Detroit and Holland, Mich., and in Hounslow, England.

When *Chloromycetin* was introduced on the American market in 1949, it won widespread acceptance for its effectiveness as a broad-spectrum antibiotic. It was also hailed for its apparent lack of adverse side effects. The first year, *Chloromycetin* sales exceeded \$9-million.

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The next year, sales increased to over \$28-million. By 1951, *Chloromycetin* sales reached \$52-million, which helped make Parke, Davis the world's largest pharmaceutical manufacturer.

Beginning in the early 1950's, however, medical authorities became alarmed over reports about the drug. An editorial in the *Journal of the American Medical Association (JAMA)* in June 1952 noted that aplastic anemia "has occurred in patients who have previously received one or more courses of chloramphenicol [*Chloromycetin*] without untoward effect. When the drug was subsequently administered, even in small doses, a severe blood abnormality has appeared. Even deaths have been reported." The editorial warned physicians to be on the alert for reactions following therapy with chloramphenicol. The editor of *JAMA* at that time was Dr. Austin Smith. Today Dr. Smith is president and chairman of the board of Parke, Davis.

In June 1952, after reviewing a number of case histories associating *Chloromycetin* with serious blood disorders, the Food and Drug Administration refused to approve any additional shipments of the drug, pending an investigation by a committee appointed by the National Research Council. The FDA reported in August of that year that the committee had "considered the records of 410 cases of serious blood disorders, of which 177 were definitely known to have been associated with *Chloromycetin*." Half of those blood disorders were reported to have been fatal.

Nevertheless, the FDA decided to permit the continued sale of *Chloromycetin* on grounds that the drug "should continue to be available for careful use by the medical profession in those serious and sometimes fatal diseases in which its use is necessary." In order to prevent the indiscriminate use of *Chloromycetin*, estimated then to have been given to some eight million Americans, the FDA announced that the labeling would be changed to indicate that serious blood disorders had been associated with administration of the drug, and that "*Chloromycetin should not be used indiscriminately or for minor infections.*"

SETBACK AND COMEBACK

Chloromycetin sales dipped sharply following the FDA investigation. In 1952, *Chloromycetin* sales dropped \$5-million. In 1953 and 1954, sales were below the \$25-million mark; the Holland, Mich., plant was closed, and Parke, Davis dropped from first to fifth place in total industry sales.

As time passed, the medical world should have been increasingly alerted to the dangers of *Chloromycetin*. For example, a study report-

ed in *JAMA* in 1959 revealed a five-fold increase in the death rate of premature babies following prophylactic antibiotic therapy in an Alabama hospital. In a four-month period, 160 newborns received such treatment. Twenty-eight died, and all 28 had received *Chloromycetin*. When its use was discontinued, the study revealed, "the neonatal death rate dropped back to and remained at about the level present before the use of chloramphenicol."

But even as the warning signals were being raised by the FDA and independent medical investigators, Parke, Davis was countering with a particular kind of marketing strategy. The company's president at that time, and its former sales manager, was Henry Loynd. In a series of letters to Parke, Davis's 980 detail men, Loynd pointed out that "with so much interest and attention being focused on *Chloromycetin* . . . the subject is doubtless being brought up by almost everyone on whom you call." Loynd went on to tell the detail men in a following letter that *Chloromycetin* had been officially cleared by the FDA "with no restrictions on the number or the range of diseases for which *Chloromycetin* may be administered." That, of course, was directly counter to the FDA's intent in warning against the drug so strongly.

Loynd's letters were followed by instructions from the company's sales director. He suggested that the detail men inform doctors that the FDA investigation had "resulted in the unqualified sanction of continued use of *Chloromycetin* for all conditions in which it had previously been used." However, he cautioned the detail men not to discuss the drug "unless the physician brings up the subject or unless you know that he has ceased prescribing *Chloromycetin*. Your efforts should all be directed in a positive direction designed to provide facts which will induce physicians to use *Chloromycetin* in a wide range of infections in which it is effective."

The marketing strategy was apparently more influential than the intelligence printed in medical journals. *Chloromycetin* sales began to rise. More than four million Americans were treated with the drug in 1959. In 1960, its sales were some \$85-million. That was at a time when *Chloromycetin* was considered the drug of choice only for such rare diseases as typhoid fever and Rocky Mountain spotted fever.

ROUND TWO

The 1960 hearings on the drug industry conducted by Senator Estes Kefauver dealt *Chloromycetin* another setback. There it was revealed that, although Parke, Davis had included the FDA warning for *Chloromycetin* in advertisements carried in medical journals, the

Company had watered down the warning in direct-mail ads to physicians. Testimony from the hearings also indicated that some detail men were employing a somewhat warped sales track, alleging that Chloromycetin was no more dangerous than any other antibiotic and insisting that their information was "based on figures supplied them by their home office." In a letter to Parke, Davis, the FDA noted that it had received complaints from physicians "about your detail men playing down or minimizing the side effects of this drug."

In 1961, Chloromycetin sales declined by more than 20 per cent. In an interview published in a Detroit newspaper, the president of Parke, Davis blamed the Kefauver hearings, which, he said, "caused some very unfavorable publicity, I might say unjustified and some of it ridiculous, which cost us a volume loss on Chloromycetin of about \$15-million." He expressed the hope that the matter would die down.

He also acknowledged that year that Parke, Davis had been or was involved in 25 law suits, some of which had been settled out of court. The first case to come before a jury was pressed on behalf of a woman whose doctor had prescribed Chloromycetin for a sore gum after a tooth extraction and again for a bronchial condition. She contracted aplastic anemia and died. In rendering a judgment against Parke, Davis, the court noted that "there was evidence that the 1952 warning label, the one on the drug at the time prescribed by [the doctor in the case], was ambiguous, inadequate and incomplete and that Parke, Davis was aware thereof." The doctor testified that he had been misled by Parke, Davis detail men and promotional materials.

Some of the suits got quite expensive, not only for the drug company, but for prescribing physicians. In 1962, a verdict of \$215,000 was awarded against Parke, Davis and two doctors following the death of a 7-year-old girl who was given Chloromycetin for a series of minor infections over a three-year period. Here it was argued that Parke, Davis had misled physicians into using the drug indiscriminately, in disregard of the potential toxic effects of the antibiotic, for conditions where drugs of lesser toxicity should have been used.

In 1964, to cite one more instance of substantial reparations, Parke, Davis reached an out-of-court settlement of \$12,600 with a California newspaper publisher. His 19-year-old daughter died after being treated with Chloromycetin, first for a sore throat and later for a mild urinary infection. Three doctors involved paid a total of \$22,400.

But neither unfavorable publicity nor the threat of litigation could dissuade Parke, Davis from encouraging doctors to prescribe Chloromycetin. And, for the second time in nine years, sales bounced back. In 1967, some 3,700,000 Americans received the drug.

As before, some clever promotional devices undoubtedly contributed to the comeback. In 1962, Parke, Davis deleted from "Physicians' Desk Reference," a commercial publication containing drug information provided by the various drug companies and distributed free to physicians, all reference to the hazards of Chloromycetin. Instead, the company inserted a statement advising doctors that they could get information on "dosage, administration, contraindications and precautions" from the package insert, the detail men, or the company. A doctor prescribing Chloromycetin capsules, however, normally would not see the package inserts, since the inserts were sent to the druggist. And Parke, Davis and its detail men had long since made it clear that they would like to see almost unlimited use of the drug.

In 1962, Congress passed the Kefauver-Harris act, which required all prescription drug advertisements to include a statement concerning possible side effects. That didn't faze Parke, Davis. The company obscured the warning for Chloromycetin in a mass of fine print and ran a series of so-called "reminder" ads, which, it insisted, did not come under the terms of the Kefauver-Harris act. An ad would be headlined "When it Counts" and would be followed by the word Chloromycetin and a phrase "Complete information for usage available for physicians upon request." That was all--no warning. Other headlines read "Among the Most Significant Drugs in Use Today" and "A Name You Can Count on When It Counts." Another technique was to include a picture of a bronchoscope in Chloromycetin ads, implying that the drug should be used for respiratory infections.

ROUND THREE

The 1968 Senate hearings, under the chairmanship of Senator Gaylord Nelson, took some of the wind out of that kind of advertising. Medical authorities who testified estimated that Chloromycetin therapy was uncalled for in 90 per cent of the cases in which it had been prescribed. One doctor put the figure at 99 per cent. The committee learned of cases where physicians prescribed Chloromycetin for acne, tonsillitis and minor gum infections. The senators heard of one instance in which a doctor told a woman, who later developed aplastic anemia, to take Chloromycetin whenever she had a cold. Hardly surprising, in view of a study reported in JAMA in 1967, out of 288 cases of aplastic anemia associated with Chloromycetin, 12 per cent of the patients had been treated with the drug for the common cold.

The most immediate effect of the Nelson hearings, and the publicity that attended them, was a sharp decline in Chloromycetin sales. Sales of capsules (by far the most popular form in which the drug

is dispensed) dropped 70 per cent in the first nine months of 1968. Rut Parke, Davis, having been through all this twice before, seemed unconcerned. The company's president, Dr. Smith, advised a group of security analysts not to worry since there would probably be a recovery "after a reasonable period of time."

Dr. Smith apparently knew what he was talking about. The latest FDA figures show a five-fold increase in the certification of *Chloromycetin* capsules in June of this year compared with June of last year, enough to treat from 16,000 to 31,000 people a month. And now that Parke, Davis's patent has run out, two rival companies are making their own chloramphenicol products. McKesson Laboratories calls its drug *Amphicol*; Rachele Laboratories markets its under the trade name of *Mychol*.

The medical literature so abounds with evidence of the dire consequences of taking *Chloromycetin* and similar chloramphenicol products that it's inexcusable for physicians to prescribe those drugs promiscuously. Yet it's clear that some physicians do prescribe them promiscuously and will continue to do so, despite the hottest glare of adverse publicity on the drugs and direct warnings published in medical journals. It's equally clear that the manufacturers are hardly interested in curbing the distribution and demand for a rarely indicated and potentially deadly—but eminently profitable—product.

WHAT TO DO ABOUT IT?

Dr. Raphael Shulman, a member of the FDA's hematology advisory committee, points out that "as long as the drug is available it will be not only used but abused." The 11-man committee reported in March 1969 that its members were generally agreed that the Commissioner of Food and Drugs "should give further consideration to the possible restriction of this drug to hospital use." That seems like a sensible step. Treatment with chloramphenicol is presently advisable for only a few very severe conditions and under certain particular circumstances; you would expect that the few people who could possibly profit by it would already have been hospitalized. Moreover, once the drug is exclusively under hospital control, a physician would be compelled to justify his choice of chloramphenicol to his colleagues; hospitals and the privileges they can confer to (or withdraw from) doctors could bring great pressure to bear.

There remains, however, a larger issue concerning a patient's right to know the risks associated with any drug that his physician prescribes for him. A doctor may not perform surgery without the informed consent of the patient or his next of kin. Drug therapy can

be as dangerous as surgery; witness the sizable number of people hospitalized each year for adverse reactions to prescription drugs. The FDA now requires manufacturers of oral contraceptives to prepare pamphlets for patients explaining in lay language the major side effects and hazards of contraceptive pills. The Commissioner of Food and Drugs has said that this action "may or may not serve as a precedent" for other drugs.

CU believes that it should—that, where appropriate, patients should be informed, in plain, easy-to-read language, of the possible hazards of drugs. Had patients been informed about *Chloromycetin* years ago, many people might have declined *Chloromycetin* therapy for minor ailments and escaped the horrors of aplastic anemia.