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STAINING OF TEETH BY TETRACYCLINE—A CASE OF PRODUCT LIABILITY

JEFFREY J. WALLACH*

The last two decades have seen a tremendous proliferation of drugs for the treatment of an endless variety of disorders “that flesh is heir to.” The use of many of these drugs, however, has been attended by complications. Side effects have ranged from simple gastro-intestinal upsets, such as nausea, vomiting, and diarrhea, to reactions so severe that the consequences have been more serious than the disease the drug was intended to cure. These untoward results have been responsible for evolutionary changes in government supervision of research, development, and marketing of drugs under the Food and Drug Administration in order to better protect the consumer. There have also been changes in the attitudes of the courts, which have not only enabled the plaintiff who was injured by such products to recover for his injury, but have also extended the meaning of “products” from those that are strictly “manufactured” to those that are merely “processed,” such as blood used in transfusions. Theories of both product and tort liability have been extended in drug cases, some of which involved thousands of plaintiffs. Aralen, a drug used for the treatment of arthritis, resulted in blindness in many cases. Similarly, Thalidomide, when used by pregnant women to induce sleep, apparently caused thousands of deformed, limbless babies, and MER/29, used to reduce blood cholesterol (associated with heart disease), caused numerous cases of blindness from cataract formation.

The late 1940’s and 1950’s were marked by the appearance of the new miracle drugs known as antibiotics, developed for the treatment

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1 Perlmutter v. Beth Davis Hosp., 308 N.Y. 100 (1954). This case concerned itself with hepatitis caused by contamination in the blood which was undetectable until after the harm had been done.
of infections. Hitherto virulent, life-threatening, and often fatal infections of the human body yielded to the persuasion of the broad spectrum wonder drugs. This paper deals with one particular group: antibiotics, tetracyclines, and one particular side effect: irreversible, intrinsic tooth staining, frequently accompanied by disfiguring changes in the structure of the teeth. The problem is presented in two parts: the medical-dental picture and the legal picture.

To the best of my knowledge, no cases dealing with this problem have been tried in the courts as yet. The delay is probably due to certain unique features: the injury is not disclosed until about seven years after the administration of the drug; it appears only in children; and the disfigurement is not regarded as serious until the child approaches maturity when esthetics of the teeth becomes more meaningful and the staining is of more consequence. Consider, therefore, that years could conceivably elapse before a genuine concern with the condition arises. For example, a child who took this drug in 1954, when he was about one year old, is now fifteen and first becoming concerned with the appearance of his teeth. Some attorneys, therefore, may have already been consulted on this problem, and it is just a question of time until litigation materializes. This paper will attempt to acquaint attorneys with the particular knowledge necessary to evaluate the merits of this type of forensic problem.

THE MEDICAL-DENTAL PICTURE

Tetracycline was developed between 1946 and 1948 by Lederle Laboratories, and released to the medical professions at about the same time. In October, 1958, a group of researchers and investigators at Harvard were treating children afflicted with cystic fibrosis of the pancreas. Cystic fibrosis is a children's disease with many complications. Besides the lesions of the pancreas, there may be pulmonary complications and other infections requiring continuous treatment with antibiotics over a period of many years. Uninterrupted treatment extending over eight and nine years was reported by these doctors. In those patients who were treated with tetracycline, they noted a staining of the teeth ranging from yellow to brownish gray. The discoloration of

2 Broad-spectrum drugs are those drugs where the use of a single drug to treat many varieties of microbes is effective, as contrasted with an effective range of treatment of only one or two varieties of bacteria.

the teeth was markedly disfiguring and was seen to become darker with age. The stain appeared as a band of color horizontally striping the tooth. This side effect was later noted by others who utilized the unique visible deposition of tetracycline in teeth to facilitate a study of the development of teeth. By examining teeth under a microscope after extraction and preparation, it was possible, by correlating the stained striped areas with the time intervals of serial administration of the drug, to "tag" the stages of development of individual teeth and thereby to plot tooth growth step by step.4

The growth of teeth can be compared with the growth of a tree. After a tree has been felled, one may examine the rings of the stump and equate the size, position, and thickness of each ring with the annual history of the tree. Thin rings, for example, indicate "lean" years caused perhaps by drought or insect infestation which sapped the growing power of the tree. Similarly, injury to the tree caused by fire, physical trauma such as a blow from an axe, or other forces would be indicated by involutions or distortions in the rings formed in that growth period and even in subsequent years, until the injury was healed. A tooth develops in much the same way, except that the tooth is not laid down in concentric rings. It starts growing at the biting edge and then adds layer after layer to its length, until the whole tooth develops through its crown to the final termination at the end of the root. Every significant trauma or serious illness which saps an individual's strength, changes his stress patterns, and interferes with his metabolism, is reflected in the growing tooth: Its development is adversely affected while the body fights the disease, thereby "neglecting" the proper tooth growth. Direct trauma, such as a blow injuring the tooth, will affect growth and development at that point in time. It is possible much later in life to fix the date of trauma, with reasonable certainty, by noting the position of the abnormality on the tooth, and then computing the individual's age at that stage of the tooth development. So the teeth have their "lean" years too. Most of tooth growth takes place deep in the bones of the jaws before the tooth even appears in the mouth, where it finally arrives by the process of eruption. By the time a tooth normally erupts, it has been subjected to all the "slings and arrows of outrageous fortune." In fact, the deciduous teeth start to develop while the child is still in the fetal stage, and the "slings and arrows" even penetrate the mother's womb. In a recent study, thirteen

children were examined whose mothers had been treated with erythromycin (an antibiotic) and/or tetracycline during pregnancy. By correlating fetal growth with the stained areas in the teeth of these children, it was determined that calcification of deciduous teeth begins during the middle of the fourth month of pregnancy and continues to term (the normal end of pregnancy). Mothers who had received tetracycline from the fourth month to term gave birth to children with discolored teeth. Mothers who had received tetracycline prior to the fourth month had children with normal teeth. Mothers who had been treated similarly with erythromycin also had normal children.  

The role of tetracycline in tooth staining was not just deduced by the circumstances, but was induced by particulars revealed in an experiment utilizing the ultra-violet spectrum analysis of material chemically extracted from stained teeth. This elegant technique of preparing the teeth and the spectral analysis of the material extracted is excellently described by the researchers, leaving no doubt as to the culpability of tetracycline. They clearly state that “Tetracycline may now be the commonest cause of enamel hypoplasia in young children.”

It was further determined in this experiment that the amount of tetracycline administered, not the length of time during which it was administered, is the determining factor of the degree of the discoloration. The higher the individual dose the greater the discoloration. If the dose was high enough, yet still within the usual therapeutic levels used in ordinary treatment, there was staining not only in the area of mineralization (the area maturing at that time) but also extending forward to the area of incomplete mineralization (the area about to be matured) and backward to the area most recently mineralized.

The staining itself occurs immediately upon the administration of tetracycline, but of course the longer the drug is administered the more of the tooth that is involved. The immediacy of this side effect has been established by an experiment in which this deposition in the developing teeth of dogs was microscopically observed in a comparison of dogs sacrificed only a day after they had received a single dose of

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tetracycline with those that had received as much as twenty-four weeks exposure.\(^8\)

Pigmentation and faulty enamel in the teeth of children results from the use of the drug by the mother while the child is still prenatal. The consequence is an initial light yellow coloration gradually turning brownish with increasing age. Exposure to light intensifies the coloration.\(^9\) The staining of teeth also extended well into the adult or permanent dentition.\(^10\)

The part of the tooth that can be seen when looking into the mouth is called the clinical crown. This is usually all that can be seen of the tooth by the casual observer. From birth until about the age of eight the child is developing the clinical crown of most of his permanent teeth. Therefore, the first eight years of life are the years that are most crucial in the formation of the crowns. The third molars (wisdom teeth) are susceptible for the longest period, as they continue to undergo crown development until almost the age of fifteen.

The harmful effect of the drug is essentially a cosmetic one; however, there have been reports not only of staining, but also changes in the structure of the teeth (hypoplasia).\(^11\) Indicative of this are the defects in enamel formation, which may be classified as enamel hypoplasia and enamel hypomaturity.\(^12\) Enamel hypoplasia may be defined as a disturbance in enamel matrix formation, whereby the actual growth of the tooth is disturbed. The depth and shape of the deformity depends upon the part of the tooth enamel affected and the duration of the disturbance coupled with the severity of the trauma to the ameloblasts (the enamel-forming cells). Defects of hypoplasia are defects of shape

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\(^10\) Witkop & Wolf, *Hypoplasia and Intrinsic Staining of Enamel Following Tetracycline Therapy*, 185 *J. Am. Med. Ass.* 100 (1963). Children who were between the ages of nine and eleven months old when the drug was administered showed staining of the teeth and hypoplasia of the enamel involving the biting edge of the incisors (front six teeth upper and lower) and biting surfaces of the first molars. Dosage varied from 250-500 mgm per day, or from 20-75 mgm per kilogram per day (about a minimum therapeutic dose). Those with the higher dose had severe hypoplasia. Weyman & Porteus, *Discoloration of Teeth Possibly Due to Tetracyclines*, 113 *Brit. Dent. J.* 51 (1962). Permanent teeth only were affected when the tetracycline had been administered after eleven months of age.

\(^11\) Supra note 7.

\(^12\) Via, *Enamel Defects Induced by Trauma During Tooth Formation*, 25 *Oral Surg.* 49 (1968).
and contour and appear as wavy or pitted surfaces. As opposed to a disturbance in the enamel matrix, enamel hypomaturation is the result of a disturbance in calcification. As such, growth of the tooth is not disturbed, but its quality is abnormal. It is seen as an opacity or discoloration in a section of improperly calcified enamel. With hypomaturation there is no difference in enamel thickness or contour such as that seen in areas of enamel hypoplasia. Combinations of the effects of hypoplasia and hypomaturation may occur in the same tooth as a result of the same etiologic incident. Incidents of surface defects and staining are even more disfiguring than those involving staining alone.

Teeth are classified for the purposes of identification by an internationally accepted method. There are sixteen teeth in each jaw in the adult dentition. They are numbered from the midline of the jaw from one to eight, right and left, upper and lower in the following manner: The teeth in both the upper and lower jaws closest to the midline are called central incisors (designated by the number 1); the teeth immediately adjacent posteriorly are called the lateral incisors (designated by the number 2); next are the cuspids or eye teeth (designated by the number 3); then, a pair of bicuspids (the first of which is designated 4 and the second, 5); then, the first, second, and third molars (designated 6, 7, and 8 respectively). The mouth, as the observer views it, is divided into four quadrants, a vertical line dividing the right and left halves and a horizontal line dividing upper from lower. Thus, the designation \[3_J\] would be the subject's upper right cuspid and the designation \[4_L\] would be the upper left first bicuspid; \[6_J\], the lower left first molar and \[2_J\], the lower right lateral incisor. The following table depicts the ages at which crown growth starts and is completed and when the tooth is erupted into the mouth for each of the teeth in the permanent dentition; it, therefore, represents the years in which the structure and appearance of the crowns may be affected.

Picture, if you will, a great number of boys and girls, of whom there must be thousands by this time, with gray-brown, mouse-colored teeth, with or without pits and other surface defects. Every time they smile or even speak they expose to public view a part of themselves that our society, rightfully or wrongfully, has come to value chiefly for appearance. Mouse-colored brown teeth inhibit the would-be smiler and diminish his personality in the eyes of the beholder. Think of the young adult or mature individual whose entire life has been dulled and hampered because of his grotesque teeth, or the theatrically talented
STAINING OF THE TEETH

BY TETRACYCLINE

DEVELOPMENT AND ERUPTION OF THE CROWN OF THE PERMANENT
TOOTH IN THE HUMAN DENTITION

1969

STAINING OF THE TEETH

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DEVELOPMENT AND ERUPTION OF THE CROWN OF THE PERMANENT
TOOTH IN THE HUMAN DENTITION

1

Age at which Age at which Age at which
crown starts is completely crown is fully
developing developed erupted

Tooth | Age at which crown starts | Age at which crown is completely | Age at which crown is fully 
       | developing               | developed                     | erupted                  

MANDBULAR (LOWER) TEETH

11, 616 | 6 months | 3.75-4.0 yrs. | 6-7 yrs.
2 | 11 months | 4.25 yrs. | 7-8 yrs.
3 | 2 yrs. | 6 yrs. | 7-8 yrs.
4 | 2.5 yrs. | 7 yrs. | 11-12 yrs.
5 | 3.75 yrs. | 7.75 yrs. | 11-12 yrs.
7 | 4 yrs. | 8.25 yrs. | 12 yrs.
8 | 10 yrs. | 14.75 yrs. | 18-21 yrs.

MAXILLARY (UPPER) TEETH

11, 616 | 11 months | 4.5 yrs. | 7-8 yrs.
2 | 20 months | 5.5 yrs. | 8 yrs.
3 | 2 yrs. | 6.5 yrs. | 9.5 yrs.
4 | 3 yrs. | 7.5 yrs. | 10.5-11.5 yrs.
5 | 4 yrs. | 8.5 yrs. | 11 yrs.
7 | 4 yrs. | 8.25 yrs. | 12 yrs.
8 | 9.25 yrs. | 14.75 yrs. | 18-21 yrs.

individual whose career is thwarted, or the salesman whose appeal is
dimmed. Further, not only may the cosmetic value of the teeth be
ruined, but their function and integrity may also be hampered. How
can this condition be prevented? By refraining from the administration
of tetracycline during at least the first eight years of life! Damage done
before birth affects only the teeth that are shed almost entirely by

13 This table was interpolated from data in Nolla, The Development of the Permanent

14 In my own personal dental practice, I have treated two patients age thirteen who
could be archetypes of this type of disfigurement. One of them is also a victim of ram-
pant caries, a condition in which the teeth decay at such a rapid rate that they defeat
all effort at restoration, as they crumble away almost before your eyes. The latter patient
developed from thirty to forty individual cavities in a four month period, and it was
necessary to crown (cap) several of his teeth before he was eleven, since it was impos-
sible to restore them with routine metallic fillings. It is possible that there is a connec-
tion between his lack of resistance to decay and the changes wrought in his tooth struc-
ture by tetracycline. I have noticed when drilling on his teeth that the texture seems much
softer than normal tooth structure. Although this is only one case, it may be reinforced
by further investigation and by comparing the clinical history of other similarly afflicted
patients.
eleven years of age, therefore, prenatal precautions are really not too important. How do we correct the disfigurement that has already been caused? It is impossible to reverse the color change; so, the only course left is to cap all the teeth involved.

Let us confine ourselves to the permanent dentition only. The teeth that are ordinarily exposed to the world in speaking and smiling are usually the incisors and bicuspids. There are six anterior incisors in each jaw and four bicuspids in each jaw—a total of twenty teeth. In some mouths the first molars may also be readily seen, so that these individuals may require four additional crowns. A child's teeth are extremely sensitive to bulk removal of the outer protective layer of enamel. The nerve in the center of the tooth and its accompanying blood vessels shrink as the tooth grows older, and bulk removal may be accomplished when the nerve has matured and shrunken without fatal trauma to the vital structures of the tooth. If the nerve is injured seriously, the tooth "dies" and abscess results, requiring extraction of the tooth or root canal treatment. Crown restorations, requiring removal of large amounts of the outer surface of the tooth should therefore be postponed until the patient is about the age of fifteen. The disfigurement before this age will probably not be too handicapping anyway. The cost of this type of dental work currently averages $125.00 per tooth, or a total of about $2,500.00. Add to this the pain and suffering attendant upon as many as sixty injections of a local anesthetic into the sensitive gums; dental appointments for intensive treatment, numbering from thirty to forty individual appointments spread out over a year at weekly intervals; the humiliation, shame, and discomfort of wearing temporary crowns (which at best are neither pretty nor comfortable); the loss of the use and function of the natural dental apparatus; and the increased care and consideration with which the final porcelain crown restorations must be treated for the rest of the patient's life (since they are not as strong as natural teeth and break more easily, occasionally requiring replacement at additional cost). Now, multiply all that money, and all those troubles and woes by at least three. Now we have a total of $7,500.00 in special damages. This is necessary because the gums continuously shrink throughout life, requiring that the teeth be recapped at least three times. For example, the gums of our young patient will shrink away as he matures, and the necks of the teeth that were originally covered by the gums and are
not covered by the caps will be exposed once again in all their mouse-gray glory. So the whole thing will have to be done again when the patient is about twenty-one years old, and possibly again at thirty-five. The rate of gum shrinkage is more rapid in youth, slows down in the thirties and forties, and speeds up again thereafter. It is even conceivable that the whole process will have to be repeated a fourth time during a lifetime, for the requirement of esthetic teeth certainly does not lessen as life goes on.

THE LEGAL PICTURE

The theory of product liability has undergone explosive changes in recent years, which Dean Prosser calls "the most rapid and altogether spectacular overturn of an established rule in the entire history of the law of torts." Before the 1916 case of *MacPherson v. Buick Motor Co.* was adopted by all jurisdictions, almost half a century had passed. But in just about the eight years since the New Jersey Supreme Court in *Henningson v. Bloomfield Motors* held that a consumer notwithstanding privity and negligence could recover against a manufacturer of a defective product for breach of an implied warranty, more than thirty states have adopted strict liability. It is almost impossible to avoid some notice of peripheral cases dealing with sales, contracts, and liability generally. However, my purpose here is not to write a learned treatise on product liability, but an analysis of its application to the tetracycline tooth staining situation.

The field of drug liability has been examined in a most complete and exhaustive manner by Paul Rheingold, although his article preceded the *Restatement (Second) of Torts*, section 402A, which has been of great influence in the field. For convenience I will use his topics as a checklist, and simply update his effort with more recent cases and articles, leaving the discussion of the historical and philosophical questions to his monumental article.

16 217 N.Y. 382, 111 N.E.2d 1050 (1916).
18 *Supra* note 15, at 805.
From a pharmacological viewpoint we are not concerned in this case with the varieties of reactions (intolerances and allergies) which may occur in individual patients who ingest this drug, nor are we concerned with those effects caused by overdosage, nor change in potency either from synergistic or antagonistic effects of other materials. We are dealing with a specific reaction of the drug common to all who use it. The injury varies only quantitatively with the length of time administered and the size of the dose. Even though therapeutic norms are observed in both time and dose, injury exists in all cases in which teeth are being developed. Even the rule of good medical practice which dictates that the physician in medicating a patient should be alert for adverse reactions does not apply here, for tooth staining is not evident until months or even years after the drug has been used. Now that the side effect is common knowledge the "good practice rule" that applies is that the drug should not be used unless absolutely necessary. Other antibiotics accomplishing the same purpose as tetracycline, without the side effect, are available. It is conceivable that if a choice is available, a practitioner would be liable for using or prescribing a drug which results in harm, if he ignores the consequences of the contraindicated drug.

As is the case with almost all other drugs developed in the United States, tetracycline was developed by one manufacturer who was primarily concerned with its researching, testing, and marketing and who had complete control over these factors, complying at the same time, where applicable, with government supervision under the FDA. The duty rests with the manufacturer to choose his investigators with care and to examine their results.

Ordinarily, initial experimentation involves the use of animals. Rheingold notes that animals are not reliable as to adverse effects, since one species of animal may react differently than another, and
animal reactions may not be conclusive as to reactions in man. However, tetracycline animal research produced conclusive evidence that staining of teeth was an unvarying side effect and should have served to warn the manufacturer to be alert for the same side effect in man. Staining had been observed in dogs and in rats. Both of these are common laboratory animals, and were quite likely used by the manufacturer in his studies. The reports of staining in dogs and rats did not appear until 1963 and 1966, eighteen years after the drug was released, but an examination of the manufacturer's data will disclose whether these animals were used and the side effect disregarded or not noted.

_Adequacy of testing and reports_

As to the clinical use of the drug and its adverse effects on humans there is earlier evidence. In 1958 Schwachman and others, using tetracycline supplied by the manufacturer for their experiments, reported tooth staining. This date is six years before the manufacturers warned the medical profession of the adverse reaction, an apparently unconscionable delay. Rheingold notes that:

[1]t is no longer an uncommon phenomenon for side effects to turn up only after a drug has been marketed and widely used, and then to be of a serious enough nature to justify either its withdrawal from the market or the imposition of stringent restrictions to its use. The question invariably raised in this situation is whether the clinical trials were adequate or shoddily done by the drug houses and their investigators or data fraudulently created either to enhance the efficacy or camouflage adverse reactions.

**FOOD AND DRUG ADMINISTRATION SUPERVISION**

Tetracycline is one of the group of drugs (antibiotics) that is supervised under different rules than those applied to other drugs. Specifically they are certified in batches. Unless one of this group bears a batch number it will be considered misbranded. A drug will also be considered misbranded if adequate warning and directions are not

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21 Supra note 8.
22 Supra note 8.
23 Supra note 7.
24 Supra note 3.
25 Supra note 19, at 958-59.
given where use by children is involved.\(^{27}\) If the question of misbranding can be established, actual violation of the statute may be pleaded in establishing a prima facie case. Rheingold, in considering the question of injury by established drugs, divides injuries into those caused by impure drugs and those caused by pure drugs.

Impure drugs are those drugs sold other than as the manufacturer intended, and containing deleterious impurities. Pure drugs, on the other hand, are those sold as the manufacturer intended, but with the harm arising as a side effect because of some inherent quality, or perhaps, because of some constitutional peculiarity on the part of the user.\(^{28}\)

Tetracycline cases fall into the pure drug category.

Let us examine further the chronology of tetracycline development, and add pertinent data to that already disclosed. Some typical generic names of tetracycline derivatives and their trade names are shown in the following chart.

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline</td>
<td>Terramycin</td>
</tr>
<tr>
<td>Tetracycline Phosphate Complex</td>
<td>Panmycin Phosphate, Sumycin, Tetrax</td>
</tr>
<tr>
<td>Chlortetracycline hydrochloride</td>
<td>Aureomycin hydrochloride</td>
</tr>
<tr>
<td>Demethylchlortetracycline hydrochloride</td>
<td>Declomycin hydrochloride</td>
</tr>
</tbody>
</table>

There are additional derivatives which will be enumerated later, but suffice it to say that the literature indicates that all of them stain teeth. However, it may be necessary to prove the adverse reaction in those that are not specifically mentioned in the literature. Schwachman reported staining with the two most important derivatives, chlortetracycline and oxytetracycline.\(^{29}\) As previously noted, according to Lederle Laboratories, chlortetracycline hydrochloride was the first of the class developed. It was released to the medical profession in 1948, after being developed in the period from 1946 to 1948. It was followed shortly by other releases of tetracycline derivatives from other manufacturers. At the present time there are at least eleven derivatives manufactured under various trade names listed in the *Physician's Desk Reference*


\(^{28}\) *Supra* note 19, at 970.

\(^{29}\) *Supra* note 3.
From the development and release in 1948 until the 1964 issue of PDR there was no warning given by any manufacturer as to the adverse reaction of tooth staining. In 1964, the warning blossomed forth. In each of the manufacturer's product circulars, the warning is worded almost indentically. The following is Pfizer's warning. (The others may vary slightly, but generally only as to the name of the drug.)

**WARNING.** Oxytetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans. However, use of oxytetracycline during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect occurs mostly during the long-term use of the drug, but it has also been observed in usual short-term treatment courses.

The trade names follow with the page numbers in PDR (1967) at which the product circulars and warnings appear:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achromycin (Lederle)</td>
<td>721</td>
</tr>
<tr>
<td>Azotrex (Bristol)</td>
<td>576</td>
</tr>
<tr>
<td>Kesso Tetra Syrup (McKesson)</td>
<td>825</td>
</tr>
<tr>
<td>Mysteclin-F (Squibb)</td>
<td>1113</td>
</tr>
<tr>
<td>Panalba (Upjohn)</td>
<td>1183</td>
</tr>
<tr>
<td>Panmycin (Upjohn)</td>
<td>1183</td>
</tr>
<tr>
<td>Rexamycin (Rexall)</td>
<td>964</td>
</tr>
<tr>
<td>Sumycin (Squibb)</td>
<td>1127</td>
</tr>
<tr>
<td>Tetrachel (Rachelle)</td>
<td>958</td>
</tr>
<tr>
<td>Tetracyn (Roerig)</td>
<td>1015, 1017</td>
</tr>
<tr>
<td>Tetrun (United Labs)</td>
<td>1162</td>
</tr>
</tbody>
</table>

**INJURY CAUSED BY ESTABLISHED DRUGS**

**Full warning of side effects**

The manufacturers did not issue any kind of a warning as to tooth staining until 1964. Cases caused by staining after the warning was finally issued will not arise until about 1971, since the children who first took the drug in 1964 will have to wait at least seven years for their affected teeth to erupt into the mouth in order that the stain be evaluated. These cases will be the ones in which there will be the most difficulty establishing liability. However, there are some theories by which we may still hopefully reach the jury.

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31. Label appearing on oxytetracycline, a drug produced by Pfizer.
The negligence action

In order to establish negligence where there has been adequate warning, it would be necessary to prove that the manufacturer was negligent in distributing the product in the first place, due to the unreasonable risk of harm, regardless of warning.\textsuperscript{32} This theory of negligence relies on "design liability."

There are, however, suggestions in cases and in the views of leading commentators on tort law that if a product is created that is inherently dangerous and it is probable that no amount of warning will prevent it from being used by a substantial number of consumers, the manufacturer would be liable for marketing the ill-designed product.\textsuperscript{33}

It is likely that this rule might be applied where the drug is particularly useful in cases of infection and where a large number of consumers are adversely affected. The case of \textit{Carmen v. Eli Lily & Co.},\textsuperscript{34} however, held that the defendant was not liable, relying on the fact that Lily had warned of the possibility of paralysis though only forty cases of paralysis and two deaths were cited in 100,000 instances of use (.042\% side effects). But tetracycline apparently affects one hundred percent of the users, and the rule of design liability should apply rather than \textit{Carmen}. A case in which the court spoke by way of dictum voices this view. The case involved a hazardous airplane switch and although the judgment was for the defendant, the \textit{dictum} stated that a defendant could be found to have created an unreasonable risk even though it was known and obvious.\textsuperscript{35}

Warranty action

Dealing with a pure product manufactured and distributed as intended by the manufacturer, it would seem easier to maintain an action for warranty than one for negligence, even where the manufacturer has warned of possible harm. Warranty can be said to be an action in strict liability and negligence need not be shown on the part of the defendant. Some stumbling blocks appear in this type of action, two of which, sale and privity, have received some attention from the courts. Some courts have denied the liability by insisting on the proof

\textsuperscript{32} \textit{Supra} note 19, at 982.

\textsuperscript{33} \textit{Supra} note 19, at 982.

\textsuperscript{34} 109 Ind. App. 76, 32 N.E.2d 729 (1941).

\textsuperscript{35} \textit{Goldsmith v. Martin Marietta Corp.}, 211 F. Supp. 91 (D. Md. 1962).
of a technical sale. *Perlmutter v. Beth David Hospital* held that blood received during a transfusion was a service, not a sale. But when the drug was administered by a physician, the opposite result occurred, the court observing that: "Clearly it is the patient and not the doctor who is the ultimate consumer of the vaccine . . . [The] implied warranties . . . run to the benefit of the persons intended to be the consumers."

There are additional new cases that have allowed recovery. In a recent case, the transfusion of blood at the hospital was held to be a sale, and the court said that the discoverability of serum hepatitis in blood was a fact question for the jury even where not discoverable by existing scientific means. The court went on to state: "The modern tendency of the law is to shift the burden from the innocent victim to the community at large and to distribute the losses suffered by the individual among all who benefit."

The *Uniform Commercial Code* may also apply here. It states that there is no intent to "disturb those lines of case growth which have recognized that warranties need not be confined either to sales contracts or to the direct parties to such a contract."

As to privity, the trend of modern case law has been to reject the continued validity of that concept. Rheingold advances this provocative suggestion:

If the argument were to be accepted that adequacy of warning is a negligence theory concept having no role in warranty actions, then even though a full warning would negate negligence on the part of the manufacturer, warranty liability would still be open.

He also goes on to ask:

Could an argument be made on behalf of the patient, who otherwise cannot prevail, that the manufacturer has a duty to warn the patient directly of side effects? That

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30 *Supra* note 1.
38 *Id.* at 609, 6 Cal. Rptr. at 324.
41 *Uniform Commercial Code* § 2-313, comment 2.
43 *Supra* note 19, at 985.
is, can there be a negligent failure to warn when the patient is not informed of the risk he is running in taking the drug? In the usual situation in which an ethical drug is prescribed the patient does not receive from his doctor any warning of side effects or information on the contra-indications which the manufacturer has made; often indeed the patient does not even know what drug was prescribed. Nor is the patient likely to obtain information about the side effects of drugs from sources other than statements from his physician.\textsuperscript{44}

The concept of "informed consent"\textsuperscript{45} comes into consideration here, and also the question of whether the intervening conduct of the doctor serves to relieve the manufacturer from strict liability. A recent case held that the manufacturer was liable to the patient regardless of anything the doctor may or may not have done in the absence of intervening proximate cause.\textsuperscript{46} This may not hold true if there has been an instance of malpractice which may be the proximate cause, although such a set of facts is difficult to conjure up in tetracycline cases in view of the freedom a doctor has to use his own judgment as long as it is within the usually accepted medical standards, as to type of drug, dose, and indications for treatment. In a case where there is malpractice on the part of the doctor, there is no reason why the plaintiff could not join the negligent doctor as a joint tortfeasor.

\textit{Absence of warning or inadequate warning of side effects}

In this category fall all those cases, probably numbering thousands, that occurred as a result of tetracycline administered from 1948 to 1964. No warning was made during those years. Certainly, from the time the first article reporting staining appeared in the medical literature in 1958, the manufacturer should have been alerted to the side effects and then had a duty to warn users of these adverse reactions. The fact that the manufacturer had supplied the tetracycline to these investigators implies that the manufacturer was reviewing the medical literature at least in conjunction with those experiments with which they had such an intimate connection. According to \textit{Yarrow v. Sterling Drug}, if the manufacturer, after reviewing publications which indicate a connection between use of the drug and retinal changes, altered its literature to warn of ocular complications, this is sufficient to support a finding that the drug manufacturer knew or had reason to know that

\textsuperscript{44} \textit{Supra} note 19, at 985.


some persons would be injured by the side effects of the drug. With tetracycline there was a hiatus of six years from report to warning.

Is the publication of warning in the circular which accompanies the drug, or in PDR, enough warning to be adequate? Yarrow says "no"—providing literature explaining the use and warning of side effects was insufficient if the manufacturer's "detail man," who called on the doctor at four to six week intervals, did not personally bring the side effects to the doctor's attention. It is the custom of most large pharmaceutical houses to send detail men out regularly, and this is surely the case with many, if not all, manufacturers of tetracycline.

In a 1967 case, the California Supreme Court held: "Where a drug has not been properly prepared or has been placed on the market and sold without adequate warning, strict liability for resulting injury may be found." Rheingold comments on this point:

The usual practice for a manufacturer who discovers side effects after marketing a drug, after reporting to the FDA, is to send out warnings about the adverse reactions as soon as possible to doctors and dispensaries. It is at least arguable that the failure to adhere to this process of notification constitutes a failure to warn, especially when the causation is fairly certain, the side effects severe, and reasonable means at hand to send out warnings.

**Side effects unknown—Manufacturer's duty to discover**

The theory that a manufacturer should know his own product is a well-settled one. The law imposes a duty on the manufacturer to make tests and conduct proper investigations. The facts in tetracycline prove that the manufacturer did conduct tests. Pfizer, in their product circular, notes, under "Action and Uses for Terramycin," "Terramycin passes through the placenta into the fetal circulation." To make this statement the manufacturer must have made or authorized tests on pregnant animals, and examined the fetuses (and possibly the newborn). The thalidomide cases, which allegedly resulted in deformity to thousands of babies due to the administration of the drug to their mothers while pregnant (and caused the withdrawal of the drug in

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47 Id. at 162.
48 Toole v. Richardson Merrell, Inc., 251 Cal. 2d 689, 60 Cal. Rptr. 398 (1967).
49 Supra note 19, at 995.
51 PDR 755.
1961, three years before the tetracycline warnings appeared) should have demonstrated to those manufacturers the importance of tests on pregnant animals. An examination of the teeth of the new-born would have disclosed the defect easily. Yet this was not done—or, perhaps worse yet, it was done and negligently ignored, or fraudulently concealed.

**STRICT LIABILITY OF THE MANUFACTURER OF DRUGS**

In 1965, a strict liability rule was promulgated by the American Law Institute in the *Restatement (Second) of Torts*, section 402A, which has subsequently been adopted in several jurisdictions. Section 402A provides:

(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm caused thereby to the ultimate consumer, or to his property, if

(a) the seller is engaged in the business of selling such a product, and
(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it was sold.

(2) The rule stated in subsection (1) applies although

(a) the seller has exercised all possible care in the preparation and sale of his product, and
(b) the user or consumer has not bought the product from or entered into any contractual relationship with the seller.

Section 402A is growing in importance and gradually gaining adherents. It clarifies much of the confusion that arises from "warranty" and frees those who adhere to it from the problems inherent in the warranty approach.

One recent case that would seem to bear on a tetracycline set of facts said that contributory negligence is a bar to recovery only if the plaintiff voluntarily assumes the risk of a known defect (relying on comment (n) of 402A). Another case stated that a complaint growing out of a breach of implied warranty by the manufacturer stated a good cause of action even though privity could not be shown. Both of these cases relied heavily on 402A.

These decisions are coming from courts heretofore reluctant to make sharp changes in liability law . . . . While the complaints are couched in terms of implied war-

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52 *Supra* note 19, at 958-59
STAINING OF THE TEETH BY TETRACYCLINE

ranty, the courts are approaching the problem as one in torts as is evidenced by their reliance on the Restatement.55

Strict liability is not absolute liability, but the usual defenses of assumption of the risk and proximate cause do not seem to apply to tetracycline facts. A plaintiff in a strict liability action was defeated for failure to show proximate cause where the plaintiff complained that brown water pouring out of his faucet precipitated a heart attack because he thought that this was the same water that had gone into his morning cup of coffee.56 Proximate cause in tetracycline cases should not present any such problems.

The question of assumption of the risk remains unsettled in recent cases dealing with section 402A, but it should be remembered in the tetracycline cases we are concerned with infant plaintiffs, and therefore, the capacity of the infant to appreciate such a risk (which is in most cases nil) is necessarily placed in issue.

A particular problem that arises with 402A cases concerns itself with comment (k) which deals with “unavoidably unsafe products.” Comment (k) discusses sales of products which “in the present state of human knowledge are incapable of being made safe for their intended use.” In regard to this problem, the Texas Supreme Court concluded that such products:

“properly prepared and accompanied by proper directions and warnings” are not defective or unreasonably dangerous and the seller of such products . . . [again with the qualifications that they are properly prepared and marketed and proper warning is given] is not to be held to strict liability for the unfortunate consequences attending their use.57

This court went on to find the defendant strictly liable “where the facts disclose the drug has not been properly prepared . . . or has been sold without adequate and proper warning, strict liability for resulting injury may be found.”58 In another MER/29 case with the same fact pattern as Toole, the federal court in the Southern District of New York had no trouble finding compensatory damages for the plaintiff, although the punitive damages were denied by the appeal court.59

55 Parker, Horn, King & Trieber, Torts, in 1967 Annual Survey of American Law 211.
57 Supra note 48, at 708, 60 Cal. Rptr. at 412.
58 Supra note 48, at 710, 60 Cal. Rptr. at 412.
59 Roginsky v. Richardson Merrell Inc., 378 F.2d 832 (2d Cir. 1967).
A special problem arises with tetracycline cases. Because of the lapse of time from cause to discovery, proof becomes difficult. None of these cases can come to light until about seven years have elapsed from the time of injury. Even if the plaintiff were alert and started to press his claim at once, he would have to go back seven or eight years to reconstruct the scene completely. He must prove proximate cause. He must prove what the drug was, when it was administered, by whom, and on whose orders. These cases are not like polio vaccine cases, nor like Thalidomide, MER/29 or Aralen where there was only one manufacturer. Here, there is a multiplicity of manufacturers. Pharmacists' records will have to be searched, as will doctors' records, and perhaps, even those of hospitals. Each dose must be pinned down to a specific identifiable product and manufacturer, or all will be lost. There is a possibility that some attorney will be starting with the oldest cases, in point of time of injury, in the near future. The drug came on the market in 1948. A child who was from eleven months to five years old in 1948 when he took the drug will have stains on his permanent incisor teeth, and he would now be from twenty to twenty-five years old. An attorney representing such a client may have to go back twenty years to prove proximate cause. Of course, there are thousands of cases of much more recent origin. The most recent case would involve a child who took the drug eight years ago and has recently erupted a tooth which shows staining. It makes little sense to prosecute such a case at this time since the damages would undoubtedly be relatively slight. A wiser choice is to wait until sufficient permanent teeth have erupted to evaluate the full extent of the damage. This would require that all plaintiffs be at least twelve or thirteen years old. That is the age at which even the second bicuspid has usually erupted into the mouth.

The question of the statute of limitations must be given serious consideration. The attorney will have to determine for himself, under the rules of the forum, whether to sue by legal representative before the statute has tolled, or wait until the disability of infancy has passed and have the plaintiff sue on his own behalf when he is sui juris. According to my computations, the oldest living possible plaintiff with damaged incisors is now about twenty-five years old and the time has run out for him in some if not all jurisdictions.60

An interesting sidelight has arisen because of the multiplicity of plaintiffs in drug cases. Attorneys have banded together to form groups with a common interest. Research common to all and other matters of common interest are pooled, and the information made available to all participants. Such a group was formed to handle the MER/29 cases. The kind of joint discovery accomplished by this sort of group has been attacked with some success in the courts.

The question of punitive damages merits consideration. Even though the damages in a tetracycline case can be extensive, the possibility of recovery in exemplary damages exists. The issues of "reckless" conduct, complicity of corporate officers, and other factors that are essential or nonessential in such an action are considered in detail in the 1967 Annual Survey of American Law. There seems to be a tendency of the courts to protect the corporate defendant from "over kill," as phrased by Judge Friendly in Roginsky v. Richardson Merrell, Inc. citing Toole v. Richardson Merrell, Inc. The decided cases show a regard by the courts for the possibility of catastrophe litigation causing a serious economic harm to the corporate defendants in drug cases. Still, the facts are often of such a compelling nature as to sway the court from its "floodgate" disposition.

An effort has been made to throw some light on a fairly dark and esoteric area, and to correlate a fairly narrow segment of drug liability with the broader field of drug liability generally. It is hoped that this paper has enhanced the knowledge of the attorney both as to drugs and dentistry, and clarified and narrowed the issues and law in this type of case to the benefit of drug manufacturers and plaintiffs alike.

63 Supra note 55.
64 Supra note 59.
65 Supra note 48.