JOURNAL OF Pharmaceutical Sciences

November 1964 volume 53, number 11

Review Article

Toxicity, Untoward Reactions, and Related Considerations in the Medical Use of Plastics

By JOHN AUTIAN

CONTENTS

THE FIFTIES ushered into the medical and related professions a host of devices or items of one type or another composed in part or whole of a plastic material. Nearly a geometric increase in the use of these plastic items has occurred each year. The spectrum of uses today defies any ordinary listing, and it now appears possible that with the correct choice of plastic any desired property can be achieved. For the most part the medical and other ancillary professions have accepted these plastic items with a great deal of confidence—a confidence which perhaps is not entirely justified. Part of this acceptance of plastics for any and all uses stems from a lack of knowledge on the subject of plastics by clinicians, nurses, pharmacists, and hospital administrators. Other segments of the population are also finding that certain polymeric materials and their additives might cause harmful effects to the purchaser, as may be witnessed by recent findings in the United States that a plastic molding toy has caused over 1600 skin irritations.[1] It seems logical then that as more information is accumulated by medical and allied professions on plastics, a greater safety feature will be forthcoming, not only to patients but also to the general public. This review attempts to cover some of the problems encountered in the use of plastics in medicine and is intended to alert those interested in them that consequences—from very minor to extremely serious—may fall upon the user or patient if proper safeguards are not taken. Knowledge of this type can help all segments of the public health professions and their suppliers to produce and use only those items which insure absolute safety for intended use.

In this review the author has attempted to

Received from the Drug-Plastic Research Laboratory, University of Texas, Austin.

[1] From a U. S. Department of Health, Education and Welfare, Food and Drug Administration, News Release, May 17, 1963.

cover the general field (without claiming a complete coverage) of toxicity and untoward reactions which have or may have a direct or indirect effect upon the welfare of the patient.

TOXICITY AND UNTOWARD REACTIONS

General

Toxicity or tissue sensitivity reactions in animals can take place by two distinct routes: (*a*) by direct contact of the plastic material or product with tissue and (*b*) by indirect contact with tissue, such as injection or application of a solution (drug product, nutritional product, blood, etc.) which has had previous contact with a plastic. A number of reports have appeared in the past discussing the toxicity of various polymers and the other ingredients which are utilized to prepare a plastic product (1–8). For the most part these reports have dealt with industrial health problems in relation to the manufacturing of a plastic material. As is well known, many of the chemicals used in the synthesis of a polymer are highly toxic if proper care is not taken to safeguard the health of the worker. However, the discussion presented in this section will deal with the finished plastic material. Texts by Rolf (9) and Wesolowski (10) should be referred to for more detailed and specific information on the use of plastics in medicine and surgery.

Direct Effect on Tissue (Acute)

Pure Plastic (No Additives).—It is a natural biological consequence that any material introduced into tissue will show some degree of reactivity, even if this cannot be truly detected with present means of analysis. Results and conclusions must be viewed as relative and in comparison to a standard state. This "standard state," of course, poses a problem since different investigators may use different standards for comparison. Many of the conflicting reports, or at least differing opinions, dealing with plastics should be examined in the light of what has been said. One other additional factor is relevant, however, in regard to plastics, especially when the same generically named plastic has been used by more than one group with varying results. Since there are no standards for plastics to be used in medical practice, it is very probable that the "same" plastic might not actually be the same, even though the difference may not be apparent by visual observation.

A great body of evidence is readily obtainable to support the claim that a pure plastic material is inert when in contact with normal, healthy, unbroken, or untraumatized tissue such as the skin or mucous membrane (11–13). The use of synthetic yarns in various clothing apparel for a number of years by millions of persons with little incidence to tissue reactivity attests to this statement. Unfortunately, less information is available as to the effect of a pure plastic introduced into tissue of ill or diseased patients.

Early reports of tissue sensitivity, dermatoses, or other untoward reactions ascribed to a pure polymer may be—in the light of present knowledge—traced to the presence of monomers or other low molecular weight polymers rather than to the polymer itself. A good example of this may be seen by referring to the literature in both the dental and ophthalmic professions where acrylic resins were used (and, of course, are used) as prosthetic devices. For one reason or another in these early uses of the acrylic resins, the monomer was not completely polymerized and this caused the tissue response. Contact lenses have caused some difficulty to a small number of patients out of the nearly 5 million wearers. Recently, however, a report pointed out that 14 proved cases of blindness or near-blindness were attributed to contact lenses (14). One suspected cause of blindness is the possibility of a chemical impurity in the plastic migrating onto the surface of the eye.

Patty (15), LaVeen and Barberio (16), and Scales (17) have emphasized the importance of the removal of the monomers before actual medical use. There have been instances of tissue response to other polymeric materials, but most of these can also be traced to factors other than the polymeric material. Harris (12) states that the final polymerized chemical (plastic) is inert to tissue and cites the studies by Schwartz (18), Morris (11), Hine *et al.* (19), Zapp (20), and Calnan *et al.* (21), to support his contention. The reader should note, however, that these reports were based upon experiments on the skin.

Introduction of a pure plastic into the tissue (subcutaneous, intramuscular, intraperitoneal, etc.) has been found in numerous instances to be well tolerated by the host tissue (at least for short periods), but it would be incorrect to assume that tissue sensitivity will not appear. There is difficulty in assessing the results from this type of investigation since the reaction or lack of reaction will depend upon such factors as its particular site of implant, the size of implant, the degree of blood supply, the possible trauma effect of implantation, and the time of tissue contact. It is also possible that even here a reaction might have been caused by a contamination of one form or another rather than by the pure plastic.

Some authors have assumed that tissue re-

activity was due to the pure polymer after short contact with tissue. For example, Harrison *et al.* (22) indicated that Dacron, Ivalon, nylon, Orlon, and Teflon did produce some tissue sensitivity when subcutaneously implanted in dogs. In their study nylon was found to be the least acceptable, while Teflon was the most tolerated plastic in the series. Usher and Wallace (23) found that nylon, Orlon, Dacron, and Teflon were less tolerated in dogs (up to 1 week) than Marlex. Longer periods of contact with tissue (perhaps up to a year) might produce further tissue reactions, depending upon the particular plastic.

Little and Parkhouse (24) investigated a number of plastic materials as to their potential tissue reactivity in guinea pigs and noted that a correlation could be established between crystallite size in the plastic or the size of an added filler to the plastic and the incidence to fibroblast reactions. They employed X-ray diffraction methods to approximate the size of the crystallites or fillers. Results of their study demonstrated that the silicones and low-density and medium-density polyethylene produced little incidence to reactions whereas other types of plastics could elicit responses.

Compounded Plastics (Polymer plus Additives).—The propensity of toxic responses in animals and humans would seem to increase for those plastic materials which require the presence of other ingredients to impart a specific desired property. The evidence to support this previous statement is more difficult to find in the literature since little practical use is made of compounded plastics by surgeons as possible prosthetic devices. In recent years, however, more use is being made of compounded plastics such as polyvinyl chloride for tubings and protective coverings. For example, in-dwelling catheters and other types of catheters which are introduced into a natural body orifice or inserted through a surgical procedure will have contact with tissue which might be susceptible to a leached constituent from the plastic material. Actual clinical reports of this occurrence have been rare in the past, but results from several animal studies do indicate that toxicity of leached constituents is a real possibility. The work of Brewer and Bryant (25) may be cited as an example to demonstrate that even certain commercially available plastic devices used in medical practice can cause tissue sensitivity when implanted in various animal tissues for short periods of time.

Lawrence *et al.* (26) conducted a toxicity study on a number of commercially available plastic administration devices and found that out of 48 samples tested by intramuscular implantation in animals, 25 were found to cause a reaction after 1 week of contact. Most of these devices were tubings of the vinyl type and were packaged in sealed cartons ready for use. This particular investigation indicated that one or more ingredients in the tubings were being released to the tissue. Even though the actual offending agent was not ascertained, it was demonstrated that the plasticizers were not the causative agents in producing tissue reactions. Gas chromatographic techniques suggested that the offending agent was one of the additives incorporated in the plastic in minute quantities. Alcoholic extraction of the "toxic" tubings removed the offending agent from the tubing.

The above authors make a very poignant conclusion in their paper. They state the following:

> The question of course may now be raised that the tubings which are reported in this paper were never intended to be implanted either in animals or humans; consequently, for their intended use, they may be quite safe. Questions of this sort can best be answered by stating that good public health practice would seem to dictate that no plastic item should contain an ingredient which has a potential harmful ingredient that might leach into a solution to be administered to a patient.

Autian *et al.* (27) noted that one type of vinyl urinary bag caused tissue reaction in animals, while a similar type of bag from another manufacturer showed no ill effects.

On a number of occasions in-dwelling catheters have caused problems in patients. Bansmer *et al.* (28) documented a number of complications when catheters were placed into the inferior *vena cava*. Some of the complications were local thrombosis, thrombosis with embolism, suppurative thrombophlebitis with septicemia, and chemical necrosis. Derrick, in animal experiments, concluded that intra-aortic catheters cannot be left for a prolonged period of time without precipitating thrombosis and embolism to vital areas (29). Several reports have also appeared indicating that in-dwelling catheters have been severed and lost in the arm of patients (30). The break in the catheter may have been due to a bending action on the catheter with movements of the arm. Urinary catheters have increased the incidence to bacteriuria in patients (31). The exact reason or reasons for these catheters causing the infection is still unclear.

Direct Effect on Tissue (Chronic)—Cancer

Since no evidence has appeared in humans that a certain plastic material is the causative agent

in the production of tumors, there might be a natural tendency to discount these "inert" materials (plastics) as possible carcinogens. At the moment we must be content to view certain animal experimentations which have demonstrated that long implantations of plastic materials cause responses which would rightly be considered as carcinogenic.

Turner (32) appears to have been one of the first to detect the carcinogenic activity of plastics. In 1941 he reported his findings which showed that implanted Bakelite disks in rats gave rise to sarcomas at the site of implants. In the latter part of the forties, Oppenheimer *et al.* (33) observed that cellophane wrapped around rat kidneys for a period of 24 months gave rise to tumors. This was a chance discovery since these investigators were actually experimenting on hypertension. Further work by the Oppenheimer group reported in 1952 (34) that various types of plastic films caused a certain percentage of sarcomas in rodents tested. Druckrey and Schmahl (35) were able to produce sarcomas in rats at the site of implantation with regenerated cellulose film. These authors noted that the tumors were produced in a strain of rats which had shown no spontaneous disposition to sarcomas during a prior 12-year period.

In 1953, Oppenheimer *et al.* (36) reported the testing of a number of films by implantation in mice and rats. They found the production of malignant tumors when films of regenerated cellulose, pure and impure polyethylene, polyvinyl chloride, Silastic, Teflon, Dacron, polystyrene, and nylon were used. Druckrey and Schmahl (37), in a continuation of their earlier studies, reported that they had produced tumors in rats with a number of polymers, while the team of Laskin *et al.* (38) observed a 25% occurrence of fibrosarcomas in mice after implantation of methyl methacrylate film.

Further work by the Oppenheimer group (39–42), reports by Bering *et al.* (43), Nothdurft (44), Hueper (45–47), Russell *et al.* (48), and Bing (49) clearly show the incidence of sarcomas when various types of plastics are implanted in animals.

An analysis of the previous workers' data and conclusions offers two schools of thought concerning the causative mechanism of polymer cancer. A minority group, particularly Hueper (47) and Druckrey and Schmahl (35, 37), have advanced the hypothesis that a chemical or a physicochemical interaction between the polymer and the tissue is the chief causative factor in the production of tumors, while a much larger group of investigators, *i.e.*, Oppenheimer *et al.* (39), Nothdurft (44), and Russell *et al.* (48) support the physical or nonspecific theory of polymer carcinogenesis.

The chemical theory viewers postulate that such factors as end groups, free radicals, complex formation between the polymer and protein, degradation products of the polymer, and/or the presence of impurities in the plastic might initiate cancer production. On the other hand, those of the physical theory approach point out that many chemically unrelated substances cause cancer, but a specific substance in a number of physical forms, *i.e.*, film, perforated film, powder, size of implants, smoothness of implant, etc., may or may not cause cancer.

The physical theory school would seem to believe that induction of tumors by plastics is indirect and may be due, in a large part, to a general interference with normal cell growth at the interface between the plastic and the tissue. The critical factor, either stated or implied by this group, is the total uninterrupted surface contact. For example, films which have induced tumors will show less tendency to do so when they are perforated, and powders of the polymer show little or no tendency to cause tumors. Horning and Alexander (50) have observed a correlation between the size of the surface area of the implant and tumor production, while a recent report by Oppenheimer *et al.* (51) confirms that powdered plastic materials when implanted do not seem to act as carcinogenic agents.[2]

However, Hueper (47) disagrees with the physical theory group and reinterprets the results of other workers, as well as the results of his own study, to support the chemical or physicochemical thesis as the causative factor in polymer cancer. Therefore, it must be obvious that much more experimental work must be done to define clearly the causative factor which is responsible for the production of tumors when various types of plastics are implanted in animals.

In general, there appears to be a minimum induction period, depending upon the animal, before a tumor will develop from an implanted plastic. Oppenheimer *et al.* (41) noted that if implants are removed from their sheath (pocket or capsule which will form around an implant) within a 6-month period, no tumors will develop in rats. If the implants are kept in place for a longer period than 6 months and then removed, tumors will develop. However, tumor response,

[2] It should be noted that for the same unit weight of plastic, a powder will have more surface area than a film, but the powder will not have an uninterrupted contact with the tissue.

may be eliminated after the 6-month period, if both the implant and the sheath around the implant are removed. This would indicate that once the cells have reached a certain point of alteration, the reaction cannot be reversed even when the causative agent (plastic) is removed. Nothdurft (44) also paid attention to the sheath surrounding the implant as a factor to be considered in tumor production.

What has been noted in animals has, up to the present time, not been seen in man. In fact, Harris (52) points out that from his knowledge of 8000 cases of breast plasty in humans, not one case of cancer was noted due to the plastic implant. Several reports (53, 54) have indicated, however, that tumorlike manifestations in several humans could be traced to the use of aerosol hair products which contained polymeric material, but the evidence cannot be considered conclusive. The experiments performed in animals ranged for a period of several years which in man might mean an equivalent of 15 to 30 years. Since implanted prosthetic devices are of comparatively recent vintage, no sure prediction of either noncarcinogenic or carcinogenic activity can be postulated at this time. The surgeon must weigh the merits of implantation in saving or prolonging life with regard for the possible risk involved.

Indirect Effect on Tissue

Leaching of a Constituent into Solutions.—Another problem is the possibility of one or more ingredients from a plastic device leaching into blood, parenteral products, and other solutions during storage, collection, and administration. These will be referred to as "indirect effect on tissue" since the plastic itself will not have actual contact with tissue. Two questions might be raised here: (*a*) is an ingredient or ingredients being leached into a solution which will then be injected into animals or humans and (*b*) is that ingredient or ingredients toxic to the host?

If the answer to the first question is a definite "No," then there may be little need to seek an answer to the second. At first glance, the previous statement would seem reasonable, but a deeper penetration into the plastic problem will reveal a number of factors which will influence the migration rate of a constituent from the plastic into the solution. Of course, it is assumed here that the plastic is a compounded plastic or has been treated with one or more agents to improve the quality of the device. A plastic device in contact with saline solution may reveal no leaching, but in another solvent system or at another pH there may be significant quantities of the leached constituent in the solution. The problem becomes even more complicated when one considers the variety of parenteral products which could come in contact with a plastic device.

Several years ago, Autian and Brewer reported in a study on a disposable hypodermic needle having a plastic hub that a constituent was being released by certain needles from the plastic hub to a saline solution which on intravenous injection caused the death of mice (55). Further work by Brewer and Bryant (25) on various disposable devices demonstrated that compounded plastic materials may or may not cause a toxic effect when first exposed to several parenteral solvent systems and then injected by different routes into animals.

It is pertinent at this point of the review to mention that very little appears to be known concerning the toxicity of a number of agents which can be formulated into certain types of plastics. Certain countries, for example, the United States, have very stringent regulations on food packaging materials. Physical and biological testing must be performed on these packaging materials before they can be employed as food containers. The biological tests invariably involve long oral feeding tests in groups of animals to ascertain the safety of the substance. Unfortunately, this same information often appears to be used to indicate that the additives approved for food packages will also be safe when they are parts of plastic devices to be used in medicine. Of course, this assumption may be true, but on the other hand strict obedience to this doctrine could present possible harm. Documentation of this statement is not easy in regard to humans, but preliminary animal experiments by Meyers *et al.* (56) on a group of citric acid esters used as plasticizers revealed how false oral testing programs can be when they are extrapolated to parenteral administration. The aforementioned workers studied the behavior response to parenteral administration of these esters in rats, mice, frogs, and rabbits. They noted that all of the esters exhibited a marked effect on the central nervous system. A single dose (depending on the particular ester) killed these animals in a period of several hours. Death was not due to citrate intoxication as may have been anticipated, but due to another mechanism not yet elucidated. The question arises regarding what actions other ingredients used in plastic formulations may have on animals and upon sick persons by routes other than oral if they leach out into a solution.

The work of Autian and his group (57, 58) dramatizes the idea that the particular drug system will influence the rate of release of a constituent from a plastic material, and it should suffice to say that serious concern should be given to drug-plastic interactions as a potential hazard to patients.

Leaching of a Constituent and Other Consequences to Blood.—Clarity, disposability and nonbreakability as well as hemorepellent properties of certain plastics make these polymeric materials useful for devices to collect, store, and administer blood. Logistic advantages (59) also may be gained by the armed forces and civil defense organizations in the replacement of the conventional glass containers by plastic ones. However, problems may arise if the plastic material is not selected with care, properly formulated, and controlled in production and, finally, adequately tested.

It has been well known for a long time that the surface of a vessel can alter the viability of blood. As far back as the turn of the century, Bordet and Gengou (60) noted that clotting time was delayed when the surface of a vessel was coated with petrolatum or paraffin. Later, with the introduction of silicone coatings, the same results were obtained in a more acceptable manner (61). These coatings decreased the adhesive force between the blood and the glass (hemorepellent or nonwettable) and acted to smooth the surface of the vessel. Therefore, the use of plastics for blood appeared to be ideal, since a number of polymeric materials were also extremely hemorepellent.

Much research and development has gone into the present plastic containers used for the storage of blood. Walter (62) introduced the polyvinyl chloride container with the hope that this type of device would delay coagulation and cause less damage to blood. Since that time, various changes have been made in the formulation of the plastic material.

More convincing evidence is now available that the toxic effect imparted by certain containers is actually due to a release of a constituent from the container to the blood and not due to the surface of the container in contact with the blood. One must recognize, as mentioned before, that a plastic material might contain other ingredients to impart certain properties to the plastic. In the case of plastic containers for blood, plasticizers, stabilizers, and other additives are usually added to make possible the construction of the container as a flexible bag. Thus, there is the possibility of one of the additives leaching into the blood and causing the loss of viability. This, in fact, has been found to be the case. Strumia *et al.* (63) showed that certain types of containers (plastic, glass, and silicone-coated glass) might release a constituent which in turn would act as a toxic agent toward the blood cells, no matter if it were stored in plastic, glass, or silicone-coated glass,[3] and that the surface or nonwettability property of the container is not the important factor in blood survival.

Recent reports by Ballinger and Cohn (64) and Wiener (65) on the preservation of whole blood clearly indicate that there is no real proof that a plastic container will afford better protection to blood (erythrocytes) than glass. However, plastics seem to offer certain advantages over glass for prolonged platelet and leukocyte survival (66, 67). Storage of blood products, other than whole blood, in plastic bags have in some instances caused physical changes in the product. The same product stored in glass bottles revealed no changes.

Surface properties become important when blood is passed through a tube or tubing for one reason or another. It would seem logical to assume that less trauma would be imparted to blood when it is passing through a tubing having a smooth internal surface than one having a rough surface. Evidence to this effect has been reported by Stewart and Sturridge (68). Other important factors must also be considered as influencing the survival time of red blood cells, such as the flow rate, time of contact, particular material, and techniques used in circulating the blood through the tubing. All things being equal, however, the internal surface will play a role in helping to preserve or destroy the components of the blood which might be fragile to shock.

Today greater use is being made of extracorporeal devices for the circulation of blood in open heart surgery. The blood in these instances is oxygenated outside the body and then is made to pass into the body again, usually through one or more tubings. These tubings may be plastic and often are of the polyvinyl type which necessitates the addition of other ingredients to make a suitable tubing. That there is the possibility of one or more ingredients leaching into the blood, depending upon the polyvinyl formulation, which may produce a toxic effect, should be recognized.

Meyler *et al.* (69) showed that leaching from a

[3] Glass released small amounts of silica which acted as a toxic agent on blood. The silicone-coated glass also showed in certain instances toxic effects which might be explained on the basis that uninterrupted coatings of the glass probably had not been achieved.

plastic tube into blood can occur. In their study they noted that when they changed from glass tubing to a particular polyvinyl chloride tubing, premature cardiac arrest and ventricular fibrillation occurred on the isolated perfused rat's heart. The important point to be made here is that these authors indicated that some brands of polyvinyl chloride did show this adverse reaction.

Keith *et al.* (70) reported that one batch of plastic tubing enhanced the hemolytic effect on perfused blood. This observation suggested to Hirose and associates (71) that the significant increase in the incidence of renal complications during extracorporeal circulatory bypass in patients in their hospital might be due to the particular plastic and the ethylene oxide method used for sterilization. These investigators noted that ethylene oxide sterilization increased the tendency to hemolysis in blood samples stored in plastics but that the particular plastic would also influence the rate of hemolysis.[4]

There is, therefore, the very serious consequence in extracorporeal circulation in humans that the wrong brand of tubing might release a constituent into the blood and thereby produce one or more untoward reactions.

Another problem has arisen in the use of plastic tubing in heart lung machines. Usually the tubing or tubings are coated with silicone, and if the silicone actually has not been baked on the plastic, which in many cases might be the case, there is the possibility of the blood washing particles of the silicone from the plastic into the circulating blood. A report of this occurring in humans has been given by Lindberg *et al.* (72). In their study 10 patients had died after open heart surgery. On necropsy, clear, refractile emboli were found in the capillaries of the kidney, brain, and heart. The emboli were investigated and found identical to the silicone used in the coating of the tubings. Further work on animals substantiated the human results that silicone coatings can cause embolization and death. Similar results were noted by Helmsworth *et al.* (73), who found silicone emboli in the glomeruli of the kidney of patients and animals. The silicone was traced to the oxygenator pump which had been silicone treated for debubbling.

Here it is important to remember that as new materials are introduced into one or more of the components in various types of extracorporeal apparatus, it is imperative that the material be evaluated biologically to prevent any unnecessary hazard to the patient. Reuse of certain components by specific washing, rinsing, and sterilization should require further evaluation of the component since these treatments may affect the plastic material sufficiently which in turn may produce an untoward effect in the patient. Clearly, more research is needed in this area for better patient protection.

COMPLICATIONS ARISING FROM PLASTIC PROSTHESES

General

The use of synthetic materials as a prosthesis dates back to the year 1890 when Fraenkel repaired a bony defect in the skull by the use of celluloid (74). Since that time and especially within the last 15 years, an array of uses has been found for plastic materials within the body for both physiological and cosmetic needs (10). Many of these surgical procedures with subsequent implantations of the plastic prosthesis have permitted extension of human life or have given certain forms of comfort to the patient. Many problems still need to be studied in detail before an ideal synthetic device becomes possible. The following section attempts to bring some of these problems into focus with past experiences by various investigators.

Vascular Prostheses

The general success of surgical procedures in the replacement of segments of diseased or failing aortas and peripheral arteries with homografts soon made it evident that the supply of these homografts or even heterografts would not fulfill the anticipated needs. Thus, it was quite natural for the surgeon to turn to the various polymeric materials as synthetic vascular replacements.

One need not go too far back into the literature to note that most animal and clinical experiences with synthetic prostheses have occurred within the last 7 or 8 years, even though Deterling (75) refers to Vinylon-N yarn being used as a vessel substitute in dogs in 1951. Since 1957, the two most used plastic materials for synthetic grafts have been Dacron and Teflon; but Ivalon, nylon, Vinylon-N, Orlon, Fortisan, polyethylene, and polypropylene have had some initial success.

Much experience has now been accumulated on Ivalon. It might be of interest to review this material as a synthetic substitute for vessels from its original success to its final demise.

A number of excellent properties such as porosity, compressibility, ease in handling, and ease in molding made this material attractive

[4] It was found that if the ethylene oxide sterilized plastic was kept for 7 days prior to its contact with blood, the gas had no effect on the blood.

as a vessel substitute. Early reports by Shumway *et al.* (76), Ellis and Kirklin (77), Rob *et al.* (78), and Fitch and Denman (79) were extremely encouraging in regard to Ivalon as a vessel replacement; however, Deterling (75), as early as 1956, had some reservations in the use of Ivalon, for he noted that the material could not withstand the pressure in the thoracic aorta unless highly compressed. Creech *et al.* (80), in a report to the Society for Vascular Surgery in 1956, reported some unfavorable results with Ivalon in clinical practice. Rob (81) reversed his earlier impression of the value of Ivalon; in fact, he no longer advocates its use as an arterial replacement. This reversal of opinion also has been enunciated by Fitch *et al.* (82). They now state the following: "The use of Ivalon grafts as arterial conduits in the human patient is unjustified due to the hazards of thrombosis, aneurysmal formation, rupture, and anastomotic disruption." A recent report by Payne and Kirklin (83) on a number of patients having had reconstruction surgery performed on the right ventricular outflow tract with several plastic materials noted that Ivalon was an unsatisfactory material. Further support of the inadequacies of Ivalon is given by Adler and Darby (84), who noted marked changes in physical properties of Ivalon after tissue contact. In the light of present knowledge, it would appear that Ivalon no longer merits a position as a worthy substitute for vessel replacement either in man or other animals.

As early as 1956 an attempt was made to assess actual clinical experiences in the use of synthetic materials as vessel substitutes in humans. This assessment became a preliminary report which has been mentioned previously (80). The report relates the success of aortic replacements with one or more of the synthetic materials (*i.e.*, Ivalon, nylon, Fortisan, Orlon, Dacron, Vinyl-N, and Teflon). Less success was found for synthetic materials when these were used as replacements for peripheral arteries. Critical factors causing the failures of the peripheral vessels were the relatively small diameters of these vessels, the great length, and the crossing of flexion areas.

There appears to be general agreement today that vessels less than 5 mm. in diameter will fail. Most likely these failures will be due to the propensity of thrombi formation. Harrison (85, 86) found this to be the case with nylon, Dacron, Orlon, Ivalon, and Teflon in his studies. Further confirmation of this fact is given by Dale and his group (87, 88), as well as by Cate (89).

Some controversy exists as to the actual causative factor or factors inducing thrombi formation in synthetic vessels. Change in flow rate of blood and turbulence of flow due to the synthetic graft has been believed to be a factor in thrombi formation (90). Szilagyi (91) has viewed thrombi formation in synthetic grafts as possibly due to the nonreactivity of a particular plastic material. The implication here is that arteriogenesis will be delayed and that the intima will not adhere firmly to the synthetic vessel. A recent study of Phillips *et al.* (92) disputes both the turbulent flow and the nonreactivity theories as causative agents; in turn, it postulates that thrombosis formation is a direct consequence of a foreign body—especially if that body is relatively nonporous. They found in their study on Teflon that woven Teflon caused a greater degree of thrombi formation than the knitted material. The knitted Teflon, more porous than the woven form, permitted fibrous tissue to invade the interstices of the fiber, resulting in greater adherence of the fibrin lining in the vessel. Other investigators also have pointed out the importance of porosity in regard to synthetic materials used as vascular substitutes (90, 93–95).

Biogenic conditions will alter physical properties of synthetic materials, even though much still needs to be done to elucidate the actual mechanism underlying such physical changes. It is fairly well established now that polar polymeric compounds such as nylon, Orlon, etc., will show greater changes of properties than the very nonpolar compounds, exemplified by Teflon after long contact with tissue. Tensile strength measurements (for elastic properties) have been conducted for a number of synthetic polymers before and after implantation in tissues. For example, it has been reported that nylon will lose from 20 to 25% of its original tensile strength after 7 to 18 months of tissue contact (80). Other materials also will change significantly, but to varying degrees. This has prompted some to believe that elastic properties might be a critical factor to consider when a decision is made to use a specific synthetic material as a vessel substitute. Present evidence, however, gives little emphasis to tensile strength as a factor in success or failure of grafts (80). A revealing study by Newton *et al.* (96) apparently confirms this fact. In their studies (*in vivo*) they noted that various arterial substitutes showed differing elastic properties within a 6-month period; but after this time period, they all tended to stiffen and reach a constant

elastic value. They concluded that the constant value was due to the formation of scar tissue within the implanted arterial substitute.

As has been mentioned for synthetic materials, a degree of success has been made for grafting of vessels having larger diameters than 5 mm., while, conversely, little success with vessels smaller than 5 mm. A number of investigators recently have observed that homografts have proven more successful postoperatively over synthetic materials when surgical grafts were performed on smaller vessels falling below the inquinal ligament. Irvine *et al.* (97) noted this to be the case in a study of 95 patients who underwent a total of 106 femoropopliteal bypass treatments. Cockett and Maurice (98) in a 9-year observation of direct arterial surgery for claudication and ischaemia of legs, concluded that the synthetic materials were not functioning up to the level of homografts or other surgical techniques not involving synthetic materials.

It should be obvious that for vessels large or small other factors must enter the picture which can give rise to success or failure of synthetic grafts. In this respect it is interesting to note the suggestion of Wesolowski and associates (99), who have contributed a great deal to surgery in techniques and knowledge in regard to vessel and tissue substitutions. These investigators have concluded that the ideal synthetic vascular graft material should meet the following standards: (*a*) no toxicity or no allergenic potential, (*b*) no deterioration of the synthetic fiber upon biological implantation for prolonged periods of time, (*c*) desirable mechanical handling properties of being easily scrunched, crimped, and twisted, (*d*) very low implantation porosity, and (*e*) very high healing porosity or fibroblasting permeability. To achieve the last two requirements (*d* and *e*), Wesolowski *et al.* (99) fashioned compounded prosthetic vascular grafts (a core of resorbable material which has been wrapped with multifilament polymer). These compounded materials were found to be superior (in animals) to the conventional monoplastic material. Similar results with a gelatin-impregnated Dacron prosthesis by Jordan *et al.* (100) also have been reported.

Surgical skill has made it possible to replace faulty or defective cardiac valves in humans. Unfortunately, studies in canines and humans have revealed survival rates not as encouraging as had initially been anticipated. The most serious drawback to the synthetic valves has been the severity of thrombosis formed on the valve. A number of investigators—Frater and Ellis (101), Kolff *et al.* (102), and Muller *et al.* (103)—have observed this serious problem. Gott *et al.* (104) have noted the importance of electrical charge on the plastic (positive charge in comparison to the negative charge on the blood particles) and found that this charge could be reduced or eliminated by coating the valve with colloidal graphite. The coating resulted in producing an extremely smooth surface which apparently dissipated or reduced the positive charge, thereby decreasing the incidence to thrombosis. To date these authors have been able to coat polycarbonate, polyvinyl, and methyl methacrylate; their results appear encouraging. However, final success or failure must wait for long-term studies in both animals and humans.

Subcutaneous Prostheses

Reconstructive surgery on or near the surface of deformatives, either natural or induced by disease, accident, etc., has restored many patients to a normal manner of life. The synthetic materials have been used for this type of surgery for approximately 15 years with various degrees of success. As with other plastic implants, real problems have been encountered which have led to replacement of the original implant or to complete failure after varying periods of time.

Breast plasty has gained some popularity in the past to relieve psychic disturbance caused by actual or imagined hypoplastic breasts. Even though cosmetic acceptance can be achieved by the use of plastic implants behind the breast, the material gradually becomes firm and loses its initial resiliency (105, 106). The implant may also shrink in size or "fall" from its original position, thus creating further psychic disturbance. Hamit (106) lists a number of complications which might result from breast plasty, such as infection, drainage, increasing firmness of the plastic material, disruption of breast function or appearance, development of draining sinuses, and possible carcinogenic activities of the plastic material. Polyvinyl sponge has shown the greatest number of failures up to the present, and it is hoped that newer materials such as silicone rubbers and polyurethanes might prove more satisfactory. Harris (52) appears to be quite satisfied with a special type of polyurethane for breast plasty.

Various other reconstructive procedures on the face and other surface portions of the body have been performed with, in some instances, amazing success. Favorable initial results, however, must be weighed against long-term usage and the possible complications which will be ever

present with a foreign body. It will be interesting to see how plastics such as the dimethyl silicones and the various halogenated carbons will perform over long usage. Encouraging reports on these materials for subcutaneous prostheseis have been given by Brown *et al.* (107).

Synthetic Adhesives

One can see great advantages for adhesive materials which can replace the usual nail, clamp, cast, and other means of closing or holding segments of tissue or bone together. Fruitful progress has been made in this direction in the past 4 years in surgery with the advent of polymeric materials which, when actuated in some fashion, can become a tenacious adhesive for tissue.

In 1958, Manderino and Salvatore (108) were able to restore broken bones by the use of polyurethane material which acted as a very powerful adhesive agent, fixing the break in a very short period of time. Since then considerable use has been made of this material for the same purpose (109–111). To some it is considered as a form of "bone glue," but others are not quite so convinced of this fact (112). Up to the present no definite tissue reactions have been reported (which could be attributed to the polymer), but sufficient time must elapse before a complete evaluation can be made.

A great number of synthetic adhesive materials have been produced in the last decade, but for the most part these had little place in medical practice, since for one or more reasons they were quite noxious to tissue. Then in 1959, Coover and co-workers (113) demonstrated the unusual adhesive properties of alkyl 2-cyanoacrylates, the chief one being that the monomer (as a liquid) polymerizes when spread between two surfaces and pressed. The change from a liquid state to a solid (as the adhesive) takes place with little or no change in volume, enhancing the adhesive quality. Experimental surgical applications, in particular for blood vessel repairs, have been performed by a number of workers using the above-mentioned monomer (114–116). In general, few tissue responses have been noted by most workers, but a word of caution should be noted for these adhesive agents since there appear to be some differences in the compound when purchased from different sources.

Lewers *et al.* (117) have noted that certain of the synthetic adhesives have a distinct toxic effect. For example, in animals they found that both the monomer and the polymer caused death when injected into the liver and peritoneal cavity. Biological mechanism for death still has not been elucidated by these workers, and the possibility of carcinogenic activity is still to be decided. The above workers in their concluding remarks refer to a 1948 paper (118) in which the following sentence was quoted: "Clinical use of cellophane, polythene, or any other plastic carries with it the urgent requirement of knowledge of both the chemical and physical characteristics of the product being used." Lewers *et al.* (117) maintain this statement to be true with the synthetic adhesives.

PLASTICS AND DRUG ACTIVITY

In recent years pharmaceutical scientists have recognized the potential of polymeric materials as vehicles for prolonging the action of medicinal agents. Some success has been achieved in compounding the drug with an insoluble polymeric material which can then be taken by oral ingestion, the drug being released over a prolonged time period as the tablet or pellet travels along the alimentary tract. Similar dosage forms also have been suggested for long-term implantation of certain hormones. Advantages to both the patient and clinician of the above dosage forms are clear (one-time administration instead of multiple-drug administration) if certain unknown complications do not appear. Two hazards, even though they many appear only as remote possibilities, should be considered. The first of these is the release of a greater quantity of the drug than planned due to uncertain biological manifestations on the dosage form. The second is the possible irritating or sensitizing effect the particular plastic might have on the tissue when implantation therapy is employed. It remains to be seen whether these hazards will materialize in the future when more prolonged or sustained dosage forms are used.

Several investigators, in particular Garb (119), Scholtz (120), Sulzberger and Witten (121), and Hall-Smith (122), have noted that plastic films will aid the percutaneous absorption of a number of topical drugs. Such reports have stimulated other clinicians to consider the use of plastic films to decrease the usual concentration of the drug when applied topically. Lack of knowledge of the influence of these polymeric materials on the physical and chemical properties of drugs regarding their rate of penetration and diffusion into the skin may lead to unexpected toxic or untoward reactions. Vickers and Fritsch (123) have documented this fact with several cases where naphazoline was the test drug and Saran the plastic film. These aforementioned authors

give the following warning: "The knowledge of the vast increase in percutaneous absorption due to Saran occlusion might tempt clinicians to try to increase the effectiveness of other topical preparations with possible serious or even disastrous consequences."

DRUG-PLASTIC CONSIDERATIONS

Less recognized as a problem, probably due to the paucity of reports published, is the consequences which might result when a drug or drug product is kept in contact with a plastic material used as a container or administrative device (124–131). These problems may be collectively grouped into five general categories:

(*a*) *Permeation*—Oxygen or other gases permeating the plastic material and causing an incompatibility or, conversely, a volatile constituent in the drug product passing out of the container or device.

(*b*) *Leaching*—One or more ingredients migrating from the plastic into the drug solution.

(*c*) *Sorption* (including adsorption and absorption)—One or more constituents being removed from the drug solution into the plastic by a sorption process.

(*d*) *Chemical Reactivity*—One or more ingredients reacting by covalent bonding with the polymer or one of the additives in the plastic.

(*e*) *Alteration in the Physical Properties of Plastics*—Depending to an extent on one or more of the above or due to environmental effects, the container or device may undergo sufficient changes to no longer function as originally intended.

The above five considerations have been reviewed in some detail in previously published papers (132, 133) and thus will not be discussed any further in this review, except to emphasize that both the manufacturer and the user must share in the responsibility of safeguarding the health of the patient when plastic devices are to function as containers or devices for storing or administering drug products.

NEED FOR STANDARDS

An analysis of what has been reviewed in this paper should note that plastics are not so safe as originally thought. In no manner does this suggest that plastics should be banned or eliminated from medical practice. Such an expression would be ridiculous and certainly is not tenable to the many outstanding advantages to be gained by the use of the synthetic polymeric materials. Rather, a method should be sought which would insure that a particular plastic or plastic device will be safe for intended use. Standards must be created for "medical use" plastics as well as standards for the final plastic device. These standards obviously must include biological, physical, and chemical methods of testing. Finally, these standards must become part of the official compendia to insure legal status.

Autian (58) has published a guide to hospitals in the selection of plastic devices, while The University of Texas Medical Center has undertaken the task of developing its own standards for plastics [see report by Autian and Nicolaides (134)]. Brewer and Bryant were the first in this country to publish biological methods of testing of plastics to be used in medical practice (25). Workers in other countries recognizing the plastics problems have recommended also that stricter controls be maintained on plastics and have suggested a number of testing procedures (135–137). Guess and Autian (138) have presented a tentative protocol for the biological testing of plastic materials. In this country the Pharmaceutical Manufacturers' Association with support from the Society of Plastics Industry has developed a group of biological and physical chemical tests for plastics to be used with drug products.

Much work still remains to be done now and in the future before adequate standards are developed. Certainly, greater emphasis should be given to basic studies on plastics as they are related to medicine. In the past such support from industrial groups interested in plastics has been minimal, but it is hoped that a reversal of this trend will soon be forthcoming. There is also a need for better communication among groups working to manufacture and distribute plastic items to the medical profession. Often one group is not aware of what the other group has done to a plastic item. This point is clearly brought into focus by Bender (139), a consulting engineer, in his excellent article dealing with the trend toward plastics in surgery and medicine.

The plastics problem is such a vital health issue that it no longer can be kept as an "incidental" hazard with the ever-increasing use of plastics in all phases of medical practice. Good public health practice requires as much emphasis on measures to prevent a potential danger from becoming a serious reality as to combat the danger once it has occurred. Perhaps the best example of this in the past years is the pesticide issue brought into shocking public attention by Rachel Carson's "Silent Spring." Even though adverse criticism was given to the author for having overplayed the problem based upon

meager scientific evidence, it was interesting to note that the President's Science Advisory Committee has made a number of recommendations to prevent some of the possible consequences illuminated in the book "Silent Spring" (140). In much the same way, though on a much smaller scale, plastics for medical practice deserve equal attention.

REFERENCES

(1) Harris, D. K., *Brit. J. Ind. Med.*, **10**, 255(1953).
(2) Wilson, R. H., and McCormick, W. E., *Ind. Med. Surg.*, **23**, 479(1954).
(3) *Ibid.*, **24**, 491(1955).
(4) Lieber, E. E., *Brit. Plastics*, **28**, 428(1955).
(5) Rogers, J. C., *A.M.A. Arch. Ind. Health*, **12**, 470 (1955).
(6) Fairhall, L. T., "Industrial Toxicology," 2nd ed., The Williams & Wilkins Co., Baltimore, Md., 1957, pp. 291–292.
(7) Harris, D. K., *Brit. J. Ind. Med.*, **16**, 221(1959).
(8) Wilson, R. H., and McCormick, W. E., *A.M.A. Arch. Ind. Health*, **21**, 536(1960).
(9) Rolf, H., "Kunststoffe in der Medizin," Johann Ambrosius Barth, Leipzig, Germany, 1955.
(10) Wesolowski, S. A., "Evaluation of Tissue and Prosthetic Vascular Grafts," Charles C Thomas, Springfield, Ill., 1962.
(11) Morris, G. E., *Arch. Ind. Hyg. Occupational Med.*, **5**, 37(1952).
(12) Harris, D. K., *Brit. J. Dermatol.*, **72**, 105(1960).
(13) Cranch, A. G., *Ind. Med.*, **15**, 168(1946).
(14) "Eye on Contact Lenses," *Newsweek*, **63**, 70(March 30, 1964).
(15) Patty, F. A., ed., "Industrial Hygiene and Toxicology," Vol. II, Industrial Publishers, Inc., New York, N. Y., 1949, p. 1105.
(16) La Veen, H. H., and Barberio, J. R., *Ann. Surg.*, **129**, 74(1949).
(17) Scales, J. T., *Proc. Roy. Soc. Med.*, **46**, 647(1953).
(18) Schwartz, L., *J. Invest. Dermatol.*, **6**, 239(1945).
(19) Hine, C. H., *et al., A.M.A. Arch. Ind. Health*, **17**, 129 (1958).
(20) Zapp, J. A., *ibid.*, **15**, 324(1957).
(21) Calnan, C. D., Marten, R. H., and Wilson, H. T. H., *Brit. Med. J.*, **2**, 544(1958).
(22) Harrison, J. H., Swanson, D. S., and Lincoln, A. F., *A.M.A. Arch. Surg.*, **74**, 139(1957).
(23) Usher, F. C., and Wallace, S. A., *ibid.*, **76**, 997(1958).
(24) Little, K., and Parkhouse, J., *Lancet*, **1962**, 857.
(25) Brewer, J. H., and Bryant, H. H., THIS JOURNAL, **49**, 652(1960).
(26) Lawrence, W. H., *et al., ibid.*, **52**, 958(1963).
(27) Autian, J., *et al.*, "An Evaluation of Two Urinary Bags as to Their Biological Activity in Animals," presented at the A.A.A.S. Cleveland, Ohio meeting, December 1963.
(28) Bansmer, G., Keith, D., and Tesluck, H., *J. Am. Med. Assoc.*, **167**, 1605(1958).
(29) Derrick, J. R., *Surgery*, **54**, 343(1963).
(30) Taylor, F. W., and Rutherford, C. E., *Arch. Surg.*, **86**, 177(1963).
(31) Cox, C. E., and Hinman, F., Jr., *J. Am. Med. Assoc.*, **178**, 919(1961).
(32) Turner, F. C., *J. Natl. Cancer Inst.*, **2**, 81(1941).
(33) Oppenheimer, B. S., Oppenheimer, E. T., and Stout, A. P., *Proc. Soc. Exptl. Biol. Med.*, **67**, 33(1948).
(34) *Ibid.*, **79**, 366(1952).
(35) Druckrey, H., and Schmahl, D., *Z. Naturforsch.*, **75**, 353(1952).
(36) Oppenheimer, B. S., *et al., Science*, **118**, 305(1953).
(37) Druckrey, H., and Schmahl, D., *Acta Unio Intern. Contra Cancrum*, **10**, 119(1954).
(38) Laskin, D. M., Robinson, I. B., and Weinmann, J. P., *Proc. Soc. Exptl. Biol. Med.*, **87**, 329(1954).
(39) Oppenheimer, B. S., *et al., Cancer Res.*, **15**, 333(1955).
(40) Oppenheimer, B. S., *et al., Acta Unio Intern. Contra Cancrum*, **15**, 659(1959).
(41) Oppenheimer, B. S., *et al., Cancer*, **11**, 204(1958).
(42) Danishefsky, I., *et al., Cancer Res.*, **19**, 1234(1959).
(43) Bering, E. A., *et al., ibid.*, **15**, 300(1955).
(44) Nothdurft, H., *Naturwissenschaften*, **42**, 75(1955).
(45) Hueper, W. C., *A.M.A. Arch. Pathol.*, **67**, 589(1959).
(46) Hueper, W. C., *Am. J. Clin. Pathol.*, **34**, 328(1960).
(47) Hueper, W. C., *Path. Microbiol.*, **24**, 77(1961).
(48) Russell, F. E., *et al., J. Natl. Cancer Inst.*, **23**, 305 (1959).
(49) Bing, J., *Acta Pathol. Microbiol. Scand.*, **105**, 16 (1955).
(50) Horning, E. S., and Alexander, P., *Empire Cancer Campaign*, 35th Annual Report, Part II, pp. 64–65, 1957.
(51) Oppenheimer, E. T., *et al., Cancer Res.*, **21**, 132 (1961).
(52) Harris, H. I., *J. Intern. Coll. Surgeons*, **35**, 630(1961).
(53) Bermann, M., Flance, I. J., and Blumenthal, H. T., *New Engl. J. Med.*, **258**, 471(1958).
(54) Edelston, B. G., *Lancet*, **27**, 112(1959).
(55) Autian, J., and Brewer, J. H., *Am. J. Hosp. Pharm.*, **15**, 313(1958).
(56) Meyers, D. B., Autian, J., and Guess, W. L., "Toxicity of a Series of Citric Acid Esters Used as Plasticizers," presented to the A.PH.A., Miami Beach meeting, May 1963.
(57) Autian, J., *Am. J. Hosp. Pharm.*, **18**, 329(1961).
(58) Autian, J., *Bull. Parenteral Drug Assoc.*, **16**, 24 (1962).
(59) Knudston, K. P., *Am. J. Clin. Pathol.*, **23**, 813(1953).
(60) Bordet, J., and Gengou, O., *Ann. Inst. Pasteur*, **17**, 822(1903).
(61) Jaques, L. B., *et al., Can. Med. Assoc. J.*, **55**, 26 (1946).
(62) Walter, C. W., "Surgical Forum: Clinical Congress 1950," Vol. I, W. B. Saunders, Co., Philadelphia, Pa., 1951, p. 483.
(63) Strumia, M. M., Colwell, L. S., and Dugan, A., *J. Lab. Clin. Med.*, **53**, 106(1959).
(64) Ballinger, W. F., and Cohn, H. E., *Surgery*, **112**, 411 (1961).
(65) Wiener, A. S., *J. Am. Med. Assoc.*, **175**, 644(1961).
(66) Gardner, F. H., Howell, D., and Hirsch, E. O., *J. Lab. Clin. Med.*, **43**, 196(1954).
(67) Klein, E., *et al., Bibliotheca Haematol.*, **7**, 382(1958).
(68) Stewart, J. W., and Sturridge, M. F., *Lancet*, **1959**, 340.
(69) Meyler, F. L., Willebrands, A. F., and Durrer, D., *Circulation Res.*, **8**, 44(1960).
(70) Keith, H. B., *et al., J. Thoracic Cardiovascular Surg.*, **41**, 404(1961).
(71) Hirose, T., Goldstein, R., and Bailey, C. P., *ibid.*, **45**, 245(1963).
(72) Lindberg, D. A. B., *et al., Am. J. Pathol.*, **39**, 129 (1961).
(73) *The Bulletin*, Dow Corning Center for Aid to Medical Research, **5**, 7(1963).
(74) Fraenkel, A., *Wein. Klin. Wochschr.*, **3**, 473(1890); through Stinson, N. E., *Nature*, **185**, 678(1960).
(75) Deterling, R. A., Jr., *Transplant. Bull.*, **3**, 125(1956).
(76) Shumway, N. E., Gliedman, M. L., and Lewis, F. J., *Surg. Gynecol. Obstet.*, **100**, 703(1955).
(77) Ellis, F. H., Jr., and Kirklin, J. W., *Postgrad. Med.*, **20**, 494(1956).
(78) Rob, C. G., Eastcott, H. H. G., and Owen, K., *Brit. J. Surg.*, **43**, 449(1956).
(79) Fitch, E. A., and Denman, F. T., *A.M.A. Arch. Surg.*, **75**, 1027(1957).
(80) Creech, O., Jr., *et al., Surgery*, **41**, 62(1957).
(81) Rob, D., *Transplant. Bull.*, **4**, 51(1957).
(82) Fitch, E. A., Denman, F. R., and Waldron, G. W., *A.M.A. Arch. Surg.*, **81**, 824(1960).
(83) Payne, W. S., and Kirklin, J. W., *Ann. Surg.*, **154**, 53 (1961).
(84) Adler, R. H., and Darby, C., *U. S. Armed Forces Med. J.*, **11**, 1349(1960).
(85) Harrison, J. H., *Am. J. Surg.*, **95**, 3(1958).
(86) Harrison, J. H., *Surg. Gynecol. Obstet.*, **108**, 433 (1959).
(87) Dale, W. A., and Niguidula, F. N., *A.M.A. Arch. Surg.*, **78**, 246(1959).
(88) Dale, W. A., and Mavor, G. E., *Brit. J. Surg.*, **46**, 305(1959).
(89) Cate, W. R., Jr., *Am. Surgeon*, **25**, 523(1959).
(90) Edwards, W. S., and Tapp, J. S., *Surgery*, **38**, 61 (1955).
(91) Szilagyi, D. E., *Surg. Clin. North Am.*, **39**, 1523 (1959).
(92) Phillips, C. E., Jr., DeWeese, J. A., and Campeti, F. L., *A.M.A. Arch. Surg.*, **82**, 38(1961).
(93) Edwards, W. S., *Surg. Forum*, **8**, 446(1957).
(94) Knox, G., and Begg, C. F., *Surgery*, **42**, 922(1957).
(95) Wesolowski, S. A., *et al., ibid.*, **50**, 91(1961).
(96) Newton, W. T., Stokes, J. M., and Butcher, H. R., Jr., *ibid.*, **46**, 579(1959).
(97) Irvine, W. T., Kenyon, J. R., and Stiles, P. J., *Brit. Med. J.*, **1963**, 360.
(98) Cockett, F. B., and Maurice, B. A., *ibid.*, **1963**, 353.
(99) Wesolowski, S. A., *et al., Surgery*, **53**, 45(1963).
(100) Jordan, G. L., Jr., *et al., ibid.*, **53**, 19(1963).
(101) Frater, R. W. M., and Ellis, F. H., Jr., "Prosthetic Valves for Cardiac Surgery," Charles C Thomas, Publisher, Springfield, Ill., 1961, p. 244.
(102) Kolff, W. J., *et al., ibid.*, p. 199.
(103) Muller, W. H., Jr., Littlefield, J. B., and Dammann, J. R., Jr., *ibid.*, p. 493.
(104) Gott, V. L., *et al., Surgery*, **50**, 382(1961).
(105) Kiskadden, W. S., *Plastic Reconstruc. Surg.*, **15**, 79 (1955).
(106) Hamit, H. F., *A.M.A. Arch. Surg.*, **75**, 224(1957).
(107) Brown, J. B., Ohwiler, D. A., and Fryer, M. P., *Ann. Surg.*, **152**, 534(1960).
(108) Manderino, M. P., and Salvatore, J., *Med. Sci.*, **4**, 215(1958).
(109) Salvatore, J. E., and Manderino, M. P., *Ann. Surg.*, **149**, 107(1958).
(110) Manderino, M. P., and Salvatore, J. E., *Am. J. Surg.*, **97**, 442(1959).
(111) Redler, I., Brown, G. G., Jr., and Trekell, W. V., *Southern Med. J.*, **53**, 392(1960).
(112) Macoomb, R. K., Hollenberg, C., and Zingg, W., *Surg. Forum*, **11**, 454(1960).

(113) Coover, H. W., Jr., *et al.*, *Soc. Plastics Eng. J.*, **15**, 413(1959).
(114) Nathan, J. S., *et al.*, *Ann. Surg.*, **152**, 648(1960).
(115) Carton, C. A., *et al.*, *J. Neurosurg.*, **18**, 188(1961).
(116) Bloomfield, S., Barnert, A. H., and Kanter, P., *Am. J. Ophthal.*, **55**, 742(1963).
(117) Lewers, D. T., Just-Viera, J. O., and Yeager, G. H., *Maryland State Med. J.*, **12**, 141(1963).
(118) Yeager, G. H., and Cowley, R. A., *Ann. Surg.*, **128**, 509(1948).
(119) Garb, J., *A.M.A. Arch. Dermatol.*, **81**, 606(1960).
(120) Scholtz, J. R., *ibid.*, **84**, 1029(1961).
(121) Sulzberger, M. B., and Witten, V. H., *ibid.*, **84**, 1027 (1961).
(122) Hall-Smith, S. P., *Brit. Med. J.*, **2**, 1233(1962).
(123) Vickers, C. F. H., and Fritsch, W. D., *A.M.A. Arch. Dermatol.*, **87**, 139(1963).
(124) Autian, J., and Dhorda, C. N., *Am. J. Hosp. Pharm.*, **16**, 176(1959).
(125) Marcus, E., Kim, H. K., and Autian, J., THIS JOURNAL, **48**, 457(1959).
(126) Kim, H. K., and Autian, J., *ibid.*, **49**, 227(1960).
(127) Autian, J., and Shaikh, Z. I., DRUG STANDARDS, **28**, 103(1960).
(128) Guess, W. L., Worrell, L. F., and Autian, J., *Am. J. Hosp. Pharm.*, **19**, 370(1962).
(129) Richards, J. M., and Whittet, T. D., *Chemist Druggist*, **169**, 16(1958).
(130) Denoel, A., and Fagard, J., *J. Pharm. Belg.*, **14**, (11/12), 384(1960).
(131) Fagard, J., *ibid.*, **15**, (3/4), 128(1961).
(132) Autian, J., THIS JOURNAL, **52**, 1(1963).
(133) *Ibid.*, 105(1963).
(134) Nicolaides, M. J., and Autian, J., *Hospitals*, **35**, 63 (1961).
(135) Thomas, J. J., and Lagrange, G., *J. Pharm. Belg.*, **16**, (3/4), 59(1962).
(136) Braun, B., and Kummell, H. J., *Deut. Apotheker-Ztg.*, **103**, 467(1963).
(137) Braun, J., *J. Mondial Pharm.*, **1963**, (No. 3), 151.
(138) Guess, W. L., and Autian, J., "Biological Testing of Plastics to Be Used in Medical Practice," presented at the 6th Pan American Congress of Pharmacy and Biochemistry, Mexico City, December 1963.
(139) Bender, R. J., *Plastics Design Process.*, **3**, 14(1963).
(140) Anon., *Science*, **140**, 878(1963).

Research Articles

Determination of Drug Absorption Rates Without Chemical Assay

By GERHARD LEVY and KAREN E. MILLER*

This study illustrates the possibility of determining absorption rates of certain drugs without using chemical assays. The method is based on the determination of the time of onset of a suitable pharmacologic response under conditions where a constant drug concentration gradient across the absorbing membranes is maintained. While particularly suitable to studies with fish and other aquatic animals, the method may also be applicable to mammals for determining the absorption rate of certain volatile substances or aerosols administered by the pulmonary route and of certain dissolved drugs administered by intestinal perfusion.

ONE OF THE most important considerations in the pharmacologic and toxicologic evaluation of chemotherapeutic agents, pesticides, and other chemicals is their ability to pass across biologic membranes. Absorption studies ordinarily require chemical analysis of blood, urine, intestinal content, tissues, or of the solution from which the drug is being absorbed. At times, this requirement can represent an almost insurmountable barrier because of the lack of a sufficiently sensitive or specific analytical method. Recently, we have developed and tested a mathematical model which describes the relationship between drug absorption rate, drug concentration in the aqueous medium, and time of occurrence of a suitable pharmacologic effect in fish (1). This model is the basis for a novel method for the determination of drug absorption rates without chemical analysis and is described in this report.

Received June 1, 1964, from the Biopharmaceutics Laboratory, School of Pharmacy, State University of New York at Buffalo, Buffalo.
Accepted for publication July 16, 1964.
* Recipient of a 1964 Lunsford Richardson Undergraduate Research Award.

Levy and Gucinski have shown (1) that the time of death (T_L) of fish due to passive absorption of a drug is related to the concentration (C) of that drug in the aqueous medium in the following manner

$$\frac{1}{T_L} = \frac{DA}{L} C \qquad \text{(Eq. 1)}$$

where L is the lethal dose of the drug, D is the absorption rate constant, and A is the area of the absorbing membrane. This relationship is based on the following requirements: (*a*) absorption occurs by passive diffusion and therefore is not a saturable process; (*b*) the drug concentration gradient across the absorbing membranes remains essentially constant during the experiment; (*c*) the permeability characteristics of the membrane do not change with time or drug concentration over the time and concentration range of the experiment; (*d*) drug elimination is negligible during the time of the experiment; and (*e*) the pharmacologic end point (death) occurs without significant delay after a given amount of drug (the lethal dose) has been absorbed.

In essence, the requirement that absorption occur by passive diffusion is fulfilled by most nonphysiologic substances; an essentially constant concentration gradient can be maintained by using sufficiently high drug concentrations and relatively large