Purity of Drugs

The report by Cohen et al. in this issue of the Journal on the chemistry and toxicology of dichlorohexafluorobutene emphasizes the importance of considering very carefully the potential hazard of impurities present in commercial drugs. The term purity describes the relative degree of contamination which exists for every substance. Every chemist would agree that failure to find a contaminant merely reflects the relative insensitivity of detection techniques used.

The question for the users of drugs is really not "How pure?" but "Is it pure enough?" It is clear from this example and from others that "pure enough" is not necessarily consistent with such concepts of purity as 99.44 per cent or even 99.99 per cent. The important consideration, of course, is the nature of the impurity. The physiological potency of the contaminant and the degree of exposure prevailing during the use of the drug determine whether an impurity present at 1 per cent or 0.1 per cent or 1 p.p.m. or even 1 p.p.b. is too much to be consistent with the safe use of the product. These considerations are recognized implicitly and underlie United States Pharmacopeia specifications limiting the presence of various substances. For example, barium sulfate used routinely in radiography could be a very dangerous drug indeed if any soluble barium compounds were present. This consideration is reflected in the limits and the tests set for phosphates, sulfides, acid soluble substances, etc. Many of the monographs in the Pharmacopeia incorporate specific tests and limits for arsenic and heavy metals which are a reflection of the fact that drug manufacture cannot take place without some contamination by these substances, and that without the limits described these drugs would then carry additional avoidable hazards. In other cases, as for example, benzoic acid, there is a limit on chlorinated compounds. In the case of narcotics, provision is made to insure the absence of related substances. In the case of alkaloids it is necessary to insure the absence of other alkaloids which may have interfering or deleterious side effects. These limitations usually are on the order of p.p.m.

The importance of minute contaminants is further illustrated by the pyrogens, which must be absent from fluids given intravenously. It is obvious to everyone that there must be a tight limit on bichloride of mercury in colomel. The early problems of the antibiotic industry with toxic materials, histamine-like substances, pyrogens, etc., are reflected in the specifications requiring that every batch of penicillin, streptomycin, and the like, be tested to insure the absence of such materials. The suitability of chloroform for pharmaceutical use requires lack of contamination by aldehydes, ketones and phosgene. Diethyl ether must be kept free of traces of peroxides.

Contaminants may be present because of the difficulty of separating substances normally present in the raw material or during manufacture, or as the result of accidental contamination, or decomposition. Vitamin tablets and anti-tubercular drugs, contaminated by the tableting machinery with minute traces of diethylstilbestrol, have caused precocious sexual
development when given to children. Because penicillin is so potent a sensitizer it is extremely important to see that even minute contamination of other drugs with penicillin is avoided.

Foods provide dramatic examples of the physiological effects of extremely minute contamination. Botulinum toxin is the classic example. In recent years contamination of animal diets with the chick edema factor, a chlorinated substance of unknown origin active in parts per billion, and aflatoxin, a mold metabolite showing a similar high degree of activity, have resulted in great losses of economically important animals.

The importance of studying the physiological activity of the other substances present in a drug product, even if only in trace amounts, to insure the safety of the drug, cannot be overemphasized. It is also clear that indictment of a compound for observed deleterious effects should be followed by a study of the impurities present before passing judgment on its safety.

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The d-Tubocurarine Dilemma

To reverse, or not to reverse: that is the question! Since the introduction of d-tubocurarine into clinical anesthesia this question has received opposing answers. In Great Britain the majority of anesthetists have arbitrarily adopted the attitude that the dangers of reversal are far less than those of latent paresis, so that most patients receive at least some anticholinesterase drug at the end of anesthesia. In the United States, however, where admittedly smaller doses are in common use, the emphasis has fallen upon the mortality and morbidity associated with the reversal drugs and also upon reversal being unnecessary when the relaxants have been used sparingly.

It is interesting, therefore, to consider some of the facts that lie behind these two opposing views. First, the degree of muscle paresis produced is of great importance; for example, if a single dose of d-tubocurarine insufficient to paralyse the muscles of respiration is used, then clearly no antidote is required. Secondly, the duration of action of a particular relaxant is probably the most important single factor apart from the actual dose used. In laboratory investigations upon healthy, conscious volunteers a single dose of a relaxant drug can be shown to last for a prescribed number of minutes. These figures usually correspond roughly to the time elapsing between successive doses of relaxant in the operating room. Nevertheless, these additional doses are but a fraction of the original dose required for complete paralysis; they are, in fact, "topping-up" doses, which shows that a large proportion of the original dose injected must persist at the myoneural junction for a period far in excess of that observed in laboratory investigations.

As a general rule, under clinical conditions the duration of action of d-tubocurarine in young adults with a good cardiac output and peripheral blood-flow is relatively short, in the region of 30 to 40 minutes. In other words, it corresponds approximately with the observations made in conscious volunteers. In the old or the seriously ill, however, this no longer holds true; and when no antidote is given to these patients, electromyography shows that some paresis persists for many hours. At present, it is not possible to account for this prolonged activity entirely upon the basis of blood-flow, but there is little doubt that this plays a major role.

Therefore, the problem confronting the anesthesiologist at the end of an anesthetic (in which relaxants have been used) is to determine whether the patient still has some residual paresis or not. In the past, various tests—including deliberately obstructing the patient's airway—have been suggested as rough guides, but all of them require some voluntary effort on the part of the patient, and when he is still unconscious the difficulty of making an accurate assessment is even greater.

It cannot be emphasized too strongly that merely observing the movements of the re-breathing bag is not an adequate assessment