Before a New Drug Comes to the Market

A. D. PISHAWIKAR*

IN last decade scores of new drugs have appeared on the market. This may lead one to think that putting a new drug on the market is an easy task. Few people realize that years of painstaking research and clinical trials are necessary before a drug could be announced as an effective remedy against a particular disease, and that thousands of chemicals have to be discarded before one single drug could be put on the market as useful one. Taking the example of sulpha drugs for illustration, after Domagk found that prontocil was an effective anti-infective in mice, it was a result of a long research programme which revealed that it was the sulphonamide nucleus of the dye which was the active part of it and it was a tedious work after that which gave us sulphapyridine popularly known as MB693. It was the 693rd compound belonging to the Sulpha-series synthesized by the May and Baker research workers. Antibiotics again support the same thesis. Although the discovery of Penicillin could be considered as by accident, discovery of each of the other antibiotics took years of painstaking investigations sometimes incurring expenditure in terms of millions of dollars.

The actual procedure followed may differ with objectives in view. For example the preliminary investigation for finding a new antiinfective drug starts with preparing and testing a large number of compounds analogous to those known to possess some activity. The preliminary tests are *in vitro* tests against a number of pathogenic fungi and bacteria. Whereas for a antihistaminic drug direct experiments on animals are necessary.

Taking the case of an antiinfective drug it is necessary to find out whether it is active against a wide range pathogenic organisms (fungi and bacteria) or against a limited member of organisms. Penicillin for example is active against gram-positive organisms whereas chloromycetin is active against only a limited number of gram-negative bacteria. Taking the case of the anti-fungal substances, none of them is active against all the varied infections and attempts of research workers have been always to find out substances with wider range of activity.

One of the first experimental measures in determining the usefulness or otherwise of the substance is the estimation of acute toxicity. The effect of single or multiple doses, administered over a period of 24 hours to a set of experimental animals is observed. The animals used for this purpose include mice, rats, rabbits, guena pigs etc. One of the improtant determination carried out in this respect is of LD_{50}. It is the minimum amount of the substance that when administered to a set of experimental animals belonging to the same species brings about fifty per cent deaths. The figures are generally expressed as mgs. or gms. per kelogram of the body weight of the animals. The test is carried out on a large number of animals belonging on an average to the same age group etc. Further this test is carried out on different species of animals. In case there is considerable variation in LD_{50} for the various species, humans are considered at least as sensitive as the species which has been found to be most sensitive to the substance under test. Another test carried out in this connection is the protection test. A number of animals are infested with infection against which the drug is being tested and the minimum amount of the drug in gms. or mgs. per kg. of

*Demonstrator in Pharmaceutical Chemistry.

body weight of the animals necessary to protect them from the infection is found out. The difference between the two doses found out by these two methods represents the 'margin of safety' available for that particular drug. The example of diamino-diphenyl-sulphone (DDS) is very illustrative. For this antileprotic drug the margin between the curative dose and the one that causes toxic symptoms is very little, and evidently it has to be administered carefully under expert supervision. One can imagine the importance of protection test which actually tests the activity of the drug, when he sees the case of oxyphenarsine hydrochloride, which was discarded originally as useless by Elherich due to its high toxicity, but was put in as a useful one when it was found to be active at comparatively low concentrations.

Finding out mechanism and site of action are the next important steps towards the final evaluation of the substance. Without these many of the drugs today in use would have been thrown as useless. Sulphaguanidine for example does not show the normal activity of sulpha drugs, but it is extremely useful against intestinal infections. It is the study of the site of action that has revealed this.

In the aforesaid tests the effect of only a single does is considered. It is necessary to study the effects of prolonged administration i.e. chronic toxicity. Depending on the use of the substance for a chronic disease or otherwise the duration of the test ranges from three months to one year. The experimental animals are administered regular dosages as in the case of human beings. Effective minimum dosages as well high dosages which will definitely cause toxic symptoms are administered and observations are made with regard to any untoward effects such as ulcerations, cumulitive poisioning, shock symptoms etc. Development of resistant strains if any is also noted down at this stage. It must made clear that this necessarily does not prove that there will not be any development of resistant strains. Streptomycin, the wonder cure for tuberculosis was found to develop resistant strains years after it was put in the market, though the later work has revealed that the development of resistant strains is much reduced if Streptomycin is administered with para-aminosalicylic acid and this is the way it is used today. Same could be said of the untoward effects. Since we have to depend heavily on laboratory experiments, untoward effects are sometimes not observed. Penicillin supposed to be the least toxic and safest of all the antibiotics was found to create shock conditions in some patients, long time after it was put in the market. It is clear that it is extremely difficult to say everything about a drug right in the beginning.

Pathological studies of the substance under consideration form an important part of the investigation. After administration of the substance to the animal, autopsy is carried out. Various animal organs such liver, kidney etc. are separated from the adjoining tissues and examination is carried out to find the effect of the drug on those particular parts. Sometimes it is the pathologists report that decides the usefulness and hazards of the drug. It was such experimentation that revealed the dangers of taking sulphadrugs as such. The examination of urinary bladder showed the formation of crystals due to insolubility of sulphadrugs in acidic medium. This is what has led to use of alkalibicarbonates with sulphadrugs.

Additional studies such as mode of excretion, finding out of an antidote in case of poisioning due to overdoses, effect of creation of depot of the drug in the body etc. also form part of laboratory studies. Results of these investigations are tabulated and it is only after that the recommendations are made with regard to studies in human beings and it

is only then and then alone that the cilincal trials are undertaken. Still the drug may show quite different results than what has been observed in the lower animals. Alternatively the drug may not prove to be superior to already in common use or somebody else in the mean time may find out another drug which is slightly superior and the efforts and money put in might be wasted. When somebody crosses all these hurdles sucessfully a new drug comes to the market.