the release of histamine are still very incompletely understood. Much of the recent research on the problem has made use of histamine-releasing substances. These when injected into a normal subject cause symptoms identical with those produced when histamine is injected. In allergic patients, however, these initial symptoms are followed by reactions which closely reproduce the spontaneous symptoms of the individual's disease.

Other Properties

Drugs which act by combining with a histamine receptor will also be likely to have some effect on other physiological receptors. All the antihistamine drugs possess some anti-acetylcholine properties. They act like hyoscyne in causing sedation and inhibiting the vomiting reflex, and they cause side-effects such as dryness of the mouth and constipation. They are also local anaesthetics. The potency of these secondary actions is not proportional to the potency of the antihistaminic action.

The most strongly sedative drugs are diphenhydramine and promethazine ("phenergan"). Sometimes this sedative action is useful, but it is better not to give these drugs to patients who work during the day, and they may be dangerous when taken by drivers or people working with machinery. Moderate sedation is produced by mepyramine, tripelemamine, and bromazine, and the other drugs, though usually free from sedative effects, may induce drowsiness in some individuals. The patients should be warned of this possibility.

Diphenhydramine and promethazine are also highly effective in preventing travel sickness. They are usually given for this purpose in the form of their chlorotheophyllinate salts ("dramamine" and "avomine"). Meclozine is also effective in preventing sickness. Other antihistamine drugs have weaker anti-emetic properties; this action is not related to the antihistaminic activity.

The local anaesthetic action of the drugs is a useful additional property when they are applied to the skin to relieve the itching of urticaria or insect bites. Sensitization reactions, however, are rather frequent, and antihistamine creams are best not used indiscriminately for skin diseases (*British Medical Journal*, 1954).

The antihistamine drugs do not cause addiction. A few cases of agranulocytosis have occurred, but these have been rare considering how frequently the drugs are prescribed. They are dangerous poisons if swallowed by children, producing ataxia and convulsions which may be followed by fatal respiratory depression. The treatment (Craig, 1955) depends chiefly on gastric lavage and artificial respiration.

Administration

All these drugs can be given orally, and this is the usual method of administration for the treatment of allergic symptoms. Since a continuous action is required, the drugs are usually given several times during the day. Some of the drugs have a more prolonged action, and adequate treatment is possible with a single daily dose. The non-sedative drugs chlorcyclizine and diphenylpyraline may be given once daily. Chlorpheniramine is made in double tablets, in which half the dose is in the outer shell and half in a coated inner core for delayed action; they are effective for 8-10 hours. Promethazine also has a long-lasting action. Because of its sedative properties it should be given at night, and on the following day it continues to exert antihistaminic activity after the sedative effect has worn off. Meclozine is also given at night. When avomine and ancolan are taken to prevent travel sickness they should be taken on the night before the journey; dramamine should be taken every four hours.

The administration of the correct dose for each patient, giving relief from symptoms with minimum side-effects, is an important factor in treatment. The dose of any drug required by different individuals varies considerably, and the

amount needed by the same patient may also vary at different times, depending on such factors as the weather (for hay-fever subjects) and emotional stress.

When a rapid action is required an antihistaminic drug may be injected, and those which are suitable for injection are supplied in injectable form. Triprolidine ("actidil") is reported to act more quickly than the other drugs when given orally. Several of the drugs are supplied as creams and ointments, but they should not be applied too freely to the skin. Antazoline ("antistin"), which is the weakest and also the least toxic, is supplied as the phosphate for application to the eye and the nasal mucous membrane.

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THE PHARMACEUTICAL INDUSTRY

BY

R. S. INCH, M.D., M.R.C.P.Ed.

Director, Bayer Products Ltd.

The astonishing expansion of the pharmaceutical industry during the last quarter of a century, and in particular its even more accelerated growth during the past ten years, has, not surprisingly, resulted in certain conflicts. That there should be an undercurrent of disagreement between the industry and dispensing pharmacists is quite understandable, for the latter can claim that the expansion of the industry has resulted in an inevitable loss of prestige (and demonstration of skill), which for so long has been vested in the dispensing chemist. What is not so clear, except when considered in retrospect, is that the pharmaceutical industry should have become involved in a series of clashes with the medical profession and the State. The various aspects of this problem are here reviewed so as to establish, if possible, a better basis for understanding between the various parties involved.

Background to the Problem

The application of a critical approach came to medicine much later than it did to the other sciences. In 1865 Claude Bernard defined the attitude of modern medicine, emphasizing the absolute necessity of an experimental approach. This concept, when associated with the discovery of new synthetic compounds such as chloroform, "salvarsan," and aspirin, gave rise to what we now call pharmacology, a discipline which is so essential to any real advance in treatment. As compounds were synthesized it became necessary to screen them, and these functions were carried on for many years in the academic atmosphere of the university or technical college. In time, however, the complexity as well as the speed with which new compounds were produced necessitated the employment of various industrial techniques, so that more money had to be invested in the equipment of plant to make the compounds.

This transfer of emphasis from the academic to the industrial sphere resulted in the rise of a new class of technologists and scientists working for industry with a definite commercial aim as well as for the advancement of learning. Thus it was from industry that the next great advance, the sulphonamides, originated.

While progress continued in organic chemistry, equally great strides were made in biology. Unfortunately, when the probable therapeutic scope of penicillin was appreciated in 1941 there came coincidentally the realization that we in

this country had not the manufacturing facilities for large-scale production of the life-saving substance. Consequently the initial development work and manufacture had to be carried out in the U.S.A. The lead gained by the United States in pharmaceutical research and development has subsequently been maintained, though during the past few years it has shortened and many other countries have made valuable contributions.

It is now fully recognized that to produce the wide range of modern therapeutic agents a very high standard of technical skill is necessary. The production of these compounds on a commercial scale often necessitates costly and complicated plant; furthermore, the compounds must be manufactured to a uniformly high standard of quality.

The foregoing applies to the manufacture and quality of accepted products, but no mention has yet been made of the place that research must occupy in this already complicated picture. When standard drugs are being manufactured any research that goes on in parallel need only attempt to improve methods of manufacture so that a better quality, at a lower cost if possible, may result. However, when a firm is producing either new permutations of known drugs or totally new compounds, research spreads far wider, so that it covers virtually the whole of medicine and still enlarges its scope to take in many other scientific disciplines. In subsequent sections the various implications that this vast structure imposes are dealt with, and it is hoped that a clearer picture of the pharmaceutical industry may emerge.

Criticisms of the Industry

Criticism is levelled at the pharmaceutical industry from three different sources: (1) medicine, (2) pharmacy, and (3) the State.

Medicine

A legitimate criticism is applicable to a few products such as "tonic" preparations containing drugs which may lead to the masking of serious symptoms or to the indiscriminate use of antibiotics. Another example, not in the therapeutic field, is the tendency of a few manufacturers to exaggerate their claims for a product in an attempt to persuade the less perspicacious physicians that the product is of greater value than is actually the case. A further complaint concerns the weight of advertising that comes through the post, particularly the purely "sales mailings" which make little attempt at being informative. In addition to this some doctors say that they are assailed by an increasing number of representatives from the drug firms extolling their products, sometimes without giving the doctor any real help or information about their true worth or mode of action. Though some of these criticisms are unfortunately true, there is, however, an increasing sense of responsibility in the pharmaceutical industry, and the Association of the British Pharmaceutical Industry does everything possible to promote the standing of the industry as a whole and encourage a high ethical level.

The medical profession in general is largely ignorant about the work of the pharmaceutical industry, and it is unfortunate that medical students are given so little insight into the wider aspects of it. A very brief course of lectures and a visit to one of the factories might enlighten them considerably.

Pharmacy

Some pharmacists complain that the industry is infringing their professional status and cite the decreasing number of extemporaneously prepared prescriptions in support of this. This trend is inevitable, and it is unrealistic of the pharmacist to expect that it should be reversed. The main reason is that the great majority of new compounds have to be made on a large scale under special conditions and cannot be compounded in the retail pharmacy. Furthermore, with an increasing realization of the importance of uniformity, sterility, and quality, doctors are beginning to prefer the safety and predictability associated with a branded product. It is knowledge rather than craftsmanship that is required

to-day to ensure that potent drugs are supplied to the patient as the doctor wishes. Thus the pharmacist who wants to devote his life to compounding should, early in his career, consider entering the pharmaceutical industry, where a wide scope for his qualifications and capabilities exists.

The State

The conflict between the legislature and the industry mainly concerns the question of the cost of pharmaceutical products to the State. In this country probably well over 90% of the pharmaceuticals prescribed are paid for by the National Health Service, and the actual amount spent on drugs has been regularly increasing since the inception of the Service in 1948. But, as may be seen (Fig. 1), the total sum received by the manufacturers of proprietary drugs is less than 4% of the total cost of the N.H.S., while the cost of the hospital services is 57%. In making this comparison the national expenditures on alcoholic drink and tobacco have been included, as they are of considerable comparative interest.

So far as the State is concerned it is unfortunate that the first 10 years of the National Health Service coincided with inflation as well as with a period of quite unprecedented advance in therapeutics. Some officials seem to attribute this increase to extravagance on the part of the doctor or the pharmaceutical industry, rather than to the inevitable reflection of therapeutic advance. Fig. 2 shows the proportion of proprietary drugs supplied in other countries compared with the United Kingdom, and it is significant that in the U.S.A. and Canada, where they are paid for by individuals, there has been no comparable outcry about the rising costs.

In order to try to curb the mounting drug bill some rather makeshift measures have been introduced, such as the insti-

FIG. 1.—Cost of proprietary drugs (black portion of N.H.S. column) compared with other items of expenditure in the United Kingdom. *Hospital services accounted for 57% of N.H.S. costs.

FIG. 2.—Proportion of proprietary drugs prescribed in various countries.

tution of the prescription charge and the organization of local prescribing tribunals where doctors may be called upon to justify what is considered to be extravagant prescribing. Although the prescribing charge may restrain some unnecessary demands on the Service, the prescribing tribunals raise a very different problem. As they are constituted at present they do not seriously limit the freedom of the doctor to prescribe whatever he thinks best, but their existence raises the possibility that at some future date a government may enforce more stringent limitations on what the doctor may prescribe. Should this happen the medical profession would have to consider very seriously some form

of concerted action to prevent the State from interfering with the essential liberty of professional freedom.

A surprising feature of this complex situation is that so little has been said about the quality and general standard of the preparations prescribed. Until recently it has been tacitly assumed that the standard equivalents of proprietary preparations were in fact truly equivalent and as good as the proprietary product in every way. Recently, however, Bagnall and Stock¹ and McClure Browne *et al.*² have shown in impartial surveys that this is not always the case. They have demonstrated that many standard drugs were below the official requirements laid down by the B.P. and B.P.C. and in some cases were much less effective than their proprietary equivalents. These interesting findings have received little comment from official sources, where the policy holds that, whenever possible, practitioners should prescribe the official standard drug rather than its proprietary equivalent. If this opinion was based on comparative prices and if the standard equivalent was always identical as well as cheaper this policy would be justifiable. It is, however, by no means universally valid, and, when this is considered in association with the knowledge that some "standard" preparations are actually substandard, there can be little justification for the sweeping directives of the health authorities to avoid proprietary preparations whenever possible.

Propaganda

The dissemination of information about new drugs presents a peculiarly difficult problem. With the increasing speed at which new remedies are discovered it is obviously essential that doctors in general, and general practitioners in particular, should be advised about them. It is no longer possible, as it was even 50 years ago, to learn *materia medica* as a student and expect to go through professional life drawing on this small treasury of knowledge. Various methods have therefore been evolved in order to keep doctors up to date with therapeutic advances. It is generally agreed that the most valuable channel is through the pages of the reputable medical journals, but many doctors do not avail themselves regularly of this source of knowledge. Consequently, over the years pharmaceutical firms have devised other means of spreading knowledge about their products. The necessity for this is accepted by the great majority of the profession, but criticism is not unnaturally levelled at some of the means employed by certain firms.³

Although advertising in medical journals is a valuable reminder to doctors, this cannot be relied upon as the sole means of approaching the profession. Mailings have therefore to be sent direct to the doctor, and, as is to be expected from a large industry, the methods of individual companies vary greatly. In this respect it should be remembered that an increasing number of other groups, such as insurance brokers and motor manufacturers, have been using this method in recent years.

Some doctors complain about the type and content of the actual advertisements, and it must be admitted that some of the less ethical manufacturers do overstate their claims. This is quite indefensible, but at the same time the righteous indignation of doctors should be tempered somewhat by the knowledge that all of them, even the least qualified, have had at least six years' scientific training, and they should be better able to assess in a critical way the claims made by the pharmaceutical manufacturers than, for example, the general public is able to assess the claims made by manufacturers of soap or toothpaste.

The widespread sending of samples constitutes another problem, and certain groups of drugs likely to be dangerous cannot be sent except on the request of the physician. Sampling, however, has the advantage of allowing the physician to try out a particular remedy, and in this way to assess its value with no cost to himself or the patient.

Finally, as a means of disseminating information, come the pharmaceutical representatives. These men, many of whom are trained pharmacists and all of whom have

received some fundamental training, are in a position to give precise information to the doctor about their firms' products. Although their visits may, if they become too frequent, take up too much of the doctor's time, it seems to be generally agreed that the pharmaceutical representatives of the majority of firms are able to render a valuable service to the doctor by keeping him abreast of recent developments and at times by arranging for him to try out newer preparations on an experimental scale. Of all the methods of propaganda the representative is the most effective, and it is in the interests of the individual representative and the firm that he represents to maintain as high a standard as possible, for it is by him very often that the firm and its products are judged.

It seems likely that unless the pharmaceutical industry becomes State-controlled, which has already occurred in some of the "Iron Curtain" countries with most unfortunate results on therapeutic progress, advertising by the pharmaceutical industry to the doctor must continue. There would appear to be no simple solution, and the medical profession should try to adopt a tolerant attitude to what, at worst, is a relatively minor nuisance.

The Patent Position

Broadly speaking, pharmaceutical manufacturers may be divided into two distinct groups—those who carry out fundamental research, synthesis, and screening of new compounds, and who may spend on this up to a million pounds annually, and those other firms who make standard preparations and whose profits depend on the size of their sales and the economy of their manufacturing processes. These latter firms operate to a varying extent some form of quality control, but they do not take part in any coherent research programme. Consequently, it is in their interest to manufacture as much and as wide a range as possible, and, as they have no research commitments, the selling price of their drugs can be considerably lower.

With this background it should now be fairly simple to consider an example which has occurred not infrequently. As a result of their own researches a firm discovers a new drug which proves to be of considerable value. When it is marketed a selling price is fixed which takes into account the cost of the basic research and development. It is interesting to remember here that the Cohen Committee in its classification made a special category (Category 1) for new compounds considered to be of value and not subject to any price restriction. Furthermore, in recent negotiations between the pharmaceutical industry and the Ministry of Health a three-year period has been granted to the manufacturers of totally new compounds, during which time their prices fixed for the compound would not be subject to any criticism by the Ministry. If, however, the new compound has no patent coverage, it will almost certainly be copied by other firms who, as they have no research costs to cover, will be able to undersell the discoverers of the drug, and the outcome of this might well result in a serious financial loss to the original discoverers. Also, an international respect for patent law means that a country can build up a valuable pharmaceutical export trade with resulting benefit to its economy, as has been happening in Britain during the last few years.

When patent law as applied to the pharmaceutical industry is considered in this way it should be appreciated immediately that it is in fact based on the accepted principles of fair play and is not an aspect of wicked commercial monopoly.

Social and Economic Aspects of Prescribing

The wider economic aspects of prescribing are seldom considered, though recently J. P. Martin⁴ has thrown considerable light on the problem. It is generally appreciated that during the past twenty years there has been a striking fall in both morbidity and mortality figures, and associated with this there is an increase in life expectancy. This has been produced by an all-round improvement in living

conditions as well as by purely medical means, but nobody would deny the important part that the recently discovered drugs have played. As a result there has been a considerable decrease in the number and duration of admissions to hospital. This saving is not fully appreciated, yet the cost per patient per week varies from £24 to £34 for a convalescent to £63 1s. 11d. for an inmate of an acute hospital,⁵ whereas the average cost for a prescription over the same period under consideration is 57.08d.

In spite of these advances further progress is likely to continue, as it is estimated that the loss of man-hours due to sickness at the present time is 75 times greater than that from industrial disputes, and at any one time there are about one million people absent from work on account of illness.⁶ There is every reason to believe that future advances in therapeutics will further this progress, but it must be appreciated that any improvement will almost inevitably result in an increased expenditure on drugs. Consequently it is most important that not only politicians but the general public should realize that the slowly increasing drug bill does not necessarily reflect an increase in the total expenditure on the Health Service. If suitable figures become available at a future date it might be shown that this increasing expenditure has resulted in a striking saving to the community not only in hospital in-patient and out-patient treatment but in decreased absenteeism due to sickness.

At present, patients are required to report to their doctor for sickness certificates. This not only results in an increase in the bureaucratic type of work demanded of a doctor, but, as a visit to the doctor is traditionally associated with "getting some medicine," in many cases it must result in the patient also getting a prescription thought to be suitable to his malady even when this may not be really necessary. There is thus an inevitable increase in prescribing, and in this respect it is interesting that Martin has shown that in areas where prescribing is heavy it is due to an increase in the number of prescriptions issued rather than the high individual cost per prescription.

Finally, as is well known, we are entering a decade in which there will be an ever-increasing proportion of aged wage-earners, and it is becoming more and more important to keep the elderly at gainful employment as long as possible, not only for social but for economic reasons. A great deal of research work is being carried out in the degenerative diseases, and already geriatrics is established as a specialty. The pharmaceutical industry is fully aware of this important and growing section of the population, and it is not unreasonable to hope that before long some new discoveries will be made towards the prevention and treatment of degenerative conditions.

Future of the Industry

It should be clear that the place occupied by the pharmaceutical industry in the future should be an important one. Up to the present its record has been outstanding and its investment in the future by way of research is consistent. In Great Britain it is estimated that some £4m. a year is spent on pharmaceutical research,⁷ though this figure is small when compared with the Swiss pharmaceutical industry, which it is believed spends about £7m., or the American pharmaceutical industry, which spends over £45m., annually.⁸

The benefits accruing to the community from the pharmaceutical industry have not only been confined to individual countries but have affected the export market, so that during the past year Great Britain exported some £39m. of pharmaceutical goods compared with a quite insignificant sum ten years ago.

Because of the splendid prospects of the industry it should attract well-qualified people. Apart from the need for research chemists, physicists, and pharmacists, there is increasing scope for well-qualified doctors, and in particular pharmacologists, to engage in fundamental as

well as clinical research. At a time when serious bottlenecks are occurring in many medical specialties it is strange that there should still be such a great shortage of well-trained pharmacologists and bacteriologists, to name only two special groups. Already the number of specialists employed in the industry has increased enormously, and this in turn has promoted, though somewhat slowly, good public relations among widely different intellectual and social groups. The organic growth of public relations in this way is a gradual process, and the time is already overdue when a wider appreciation of the place occupied by the pharmaceutical industry should be put before the community as a whole. For only when the obstacles caused by lack of information and understanding are removed will the proper atmosphere of co-operation develop that will further the growth in size and status of the pharmaceutical industry.

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SEVENTH INTERNATIONAL CONGRESS OF HAEMATOLOGY ROME, SEPTEMBER 7-13

[FROM A SPECIAL CORRESPONDENT]

The Seventh International Congress of Haematology was held at the Palace of Congresses, Rome, from September 7 to 13, under the auspices of the International Society of Haematology. It was opened by the Italian Minister of Health, and attended by 1,700 delegates from more than 50 countries. The president of the Congress was Professor GIOVANNI DI GUGLIELMO, emeritus professor of medicine at the University of Rome. The subjects discussed included immunohaematology, haemorrhagic diseases, leukaemia, the spleen and the reticulo-endothelial system, anaemia, isotopes in haematology, anticoagulants, haematological genetics, and paediatric haematology. More than 600 papers were given, and in the main lecture hall there was simultaneous translation into English, French, German, Italian, and Spanish.

The first part of this report records some of the more important contributions to the plenary sessions on the first three days. Then follow summaries of symposia on human deoxyribonucleic acid, haematological genetics, and paediatric haematology.

Immunohaematology

In the first plenary session, Dr. J. H. JANDL (Boston) outlined some modern views on the acquired or auto-immune haemolytic anaemias. These anaemias were characterized by the adsorption on to the red-cell envelope of protein substances which diminish the cell's suspension stability. Antigen-antibody complexes could adhere to the cell's surface and caused agglutination either directly or by making the cells susceptible to agglutination by antiglobulin serum. Sensitized red cells were easily filtered by the spleen, but agglutinated red cells were filtered by the liver. Red-cell destruction did not correspond, however, with the amount of protein on the surface. Colonel W. H. CROSBY (Washington, D.C.), discussing therapy, said the haemolytic anaemia did not always need to be treated, as the patient might learn to live with his anaemia; the decision depended on careful diagnosis and observation, as in acute and severe haemolytic crises prompt intervention might be life-saving.

Dr. J. DAUSSET (Paris) discussed antileucocytic auto-immunization, which might be allergic or spontaneous. The