Conclusion

When faced with a patient with persistent and intractable pain, for whom the continued administration of analgesic drugs is for any reason undesirable, the practitioner may do well to consider surgical treatment. This may comprise the severance of nerves or nerve roots or the pain pathways in the central nervous system, or their interruption or destruction by the injection of chemical substances such as procaine, alcohol, and phenol, or by electro-coagulation. If the patient's suffering is likely to be prolonged and the pain intense, and if the cause cannot be eradicated at its source, and addiction to morphine or its derivatives is an undesirable alternative, a good case may be made for employing surgical methods.

I am much indebted to my colleague Mr. Cecil Lewis, F.R.C.S., for the drawings.

Next Refresher Course Article.—"Glandular Fever," by Sir Henry Tidy.

THE CONTROL OF NEW REMEDIES*

BY

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I have chosen "The Control of New Remedies" as the subject of my address because of an uneasy feeling that when new and powerful remedies are evolved the restrictions upon their use in the early stages may often seem unreasonable and even irritating to practitioners eager to give their patients the best treatment possible, and this in spite of the explanatory notices we put in the medical press.

Now, new remedies are of many different kinds and need control for many different reasons, ranging from the really dangerous untried remedy which must be carefully evaluated before doctors are in a position to use it safely to the harmless nostrum which may waste the private resources of the patient or the public resources of the Exchequer or postpone efficient treatment of some fatal disease until it is too late.

I propose to discuss first the control of those remedies usually known as "biologicals," and such control may be divided into three categories: (1) control of importation; (2) control of manufacture for sale; (3) control of distribution.

1. Control of Importation

The Government Departments primarily concerned with this form of control are H.M. Customs and Excise and the Board of Trade, but they depend on the Ministry of Health for expert advice where medical remedies are concerned. This is especially so in the case of those remedies which may be considered "therapeutic substances" within the meaning of the Therapeutic Substances Act of 1925—that is, substances "the purity or potency of which cannot be adequately tested by chemical means." These are the substances usually known as "biologicals," many of which are covered by the generic names of vaccine, toxin, antitoxin, antigen, but which include other substances specifically named in the schedule to the Act, such as insulin, surgical ligatures and sutures, the arsphenobenzene compounds, penicillin, blood products, etc. I will not go into the details of this Act and the necessarily complicated regulations made under it, which came into force in 1927, and which I have administered since 1928, but I would merely ask you to note that, though it provides a most valuable safeguard against the importation of dangerous or useless preparations of such substances, there are many others which, at any rate at first, are not caught by this net, either because they are of a kind to which the Act does not apply or because they are not mentioned, either individually or generically, in the Schedule to the Act. In such cases we have to consider whether the substance should be added to the Schedule if suitable, and whether on medical grounds we can recommend its admission to this country. Such advice is often difficult to give. For example, the antibiotics are being developed in a continuous stream, mostly in the United States, and the issue of each new one is accompanied by glowing claims for its effectiveness in a number of different infections. But we have to determine, in the first place, whether it is worthy of serious attention, and whether it is of sufficient importance to merit all the labour involved in devising a schedule to the Therapeutic Substances Regulations, laying down what tests for potency, toxicity, pyrogenicity, etc., it must pass. Even when we decide we must take it seriously it may still be a long time before satisfactory tests of this kind can be devised to safeguard the patient. In this task, however, the Medical Research Council gives us invaluable aid, though it cannot, of course, be expected to carry out such expensive and laborious investigations in the case of every remedy for which value is claimed.

I would here draw attention to some relevant considerations. First, we are often faced with applications to import a quantity of some new remedy "for research purposes." Obviously our pharmaceutical manufacturers, some of whom maintain research establishments of very high class, should not be hampered in their investigation of new remedies from abroad (on which they may often improve), but it must be remembered that "research" may mean something very far short of scientific investigation, and that the free distribution of new remedies to doctors is a well-established method of "creating a market," the customers in which may not be as discriminating as we would wish. The foreign manufacturers, moreover, well know that the new remedy, on the development of which they have perhaps spent vast sums of money, may be superseded in a short time by a superior rival, so they have got to recoup themselves as quickly as possible.

Of course, dollar expenditure has to be taken into consideration in making decisions (in 1951 we spent over $187,000, or nearly £67,000, on cortisone, and over $582,000, or more than £208,000, on A.C.T.H. and this year we shall be spending more), but fortunately this is an aspect on which the medical side of the Ministry is not expected to tender advice. I must, however, say a word about "free gifts," as this is a question with important medical bearings, and I will take cortisone as best illustrating my points. The importation of free gifts of medical remedies is usually permitted, though H.M. Customs can forbid it if they choose. Many kind persons in the United States, both medical and lay, have sent free gifts of cortisone to doctors here for use in particular cases, or direct to the patients themselves, and you may reasonably ask, "Why not?" Well, there is one very important consideration in such cases, apart from the danger of administration to the patient without proper control—namely, the starting of a treatment which cannot be maintained. I have received many, and often pathetic, appeals for cortisone for the treatment of patients with rheumatoid arthritis who have been greatly benefited by the injection of "free gift cortisone," the supply of which has failed. Usually I have been forced to refuse the request, though I knew that the last state of the patient would be worse than the first, because our limited supplies of cortisone—all that the manufacturers have been able to let us have—must, in fairness to the general body of patients and in order to obtain reliable information about its best method of use, be distributed to the 56 centres now holding it, where there are experienced physicians and adequate laboratory facilities.

And what of applications to import cortisone against dollar payments? Well, there are two cogent objections to allowing such applications. The first is that this means "jumping the queue," and that it would be unfair in prin-

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ciple for patients to obtain a remedy merely because they could pay for it, in preference to others whose needs are as great or perhaps greater. The second objection arises from the fact that in the United States cortisone is obtainable only on prescription—that is, for the treatment of an individual patient in America—so that any cortisone bought by private individuals in this country is obviously "black market."

2. Control of Manufacture for Sale

Let me take as an illustration of this aspect of control the antibiotics. It is well known that, after the demonstration by Fleming of the antibiotic properties of a culture of *Penicillium notatum* in 1928, a long interval elapsed until Florey and Chain at Oxford published their paper on penicillin in 1940. A valuable weapon had been evolved in the fight against infection, and the tremendous significance of such a discovery in the midst of a world war was immediately apparent. But, unfortunately, the pharmaceutical industry of this country was already hard pressed, and materials such as steel, which were essential to large-scale production of penicillin, were earmarked for other essential purposes. In these circumstances we had to turn to our friends (not yet our allies) in the United States, who, with their characteristic energy, quick grasp of the essentials, and genius for large-scale production, proceeded to produce on a tremendous scale this remedy, which played no mean part in winning the war.

Of course, under wartime conditions it was easy to keep a grip on penicillin, and this was true of the immediate post-war period, when production was started in this country but Defence Regulations were still in force. But a time came when a more permanent basis of control was needed—namely, control of manufacture to safeguard the patient from a toxic product or one of low potency; and control of sale and administration by unqualified persons to prevent the development of resistant strains and the masking of infection without curing it. For the first purpose the Therapeutic Substances Act of 1925 was eminently suitable, as penicillin is a substance "the purity or potency of which," as the Act has it, "cannot be adequately tested by chemical means." In 1944 penicillin was therefore added to the Schedule to the Act, and the Seventh Schedule was added to the Therapeutic Substances Regulations, defining what was meant by "penicillin" and the criteria to which it had to conform.

For the second purpose—namely, control of its sale and administration—an entirely new instrument was forged in the form of the Penicillin Act of 1947, which made it an offence for any person other than a duly qualified medical practitioner, a registered dental practitioner, or a registered veterinary surgeon, or a person acting in accordance with the directions of any such practitioner or surgeon, to sell or otherwise supply any substance to which the Act applied, such substances being penicillin in the first instance and then such other antimicrobial organic substances produced by living organisms as might be subsequently prescribed by the Licensing Authorities in England, Scotland, or Northern Ireland. The only antibiotic so far added has been streptomycin, by the Streptomycin Regulations, 1948.

3. Control of Distribution

The control of distribution is of course least difficult in the case of remedies manufactured abroad, as import licences are required, but the method is also applicable under certain conditions to remedies manufactured in this country. The control of "aureomycin" is an example of the first class of case and that of streptomycin of the second class. With regard to streptomycin, a procedure was evolved which we try to apply, with necessary modifications, to other cases. The first stage is that in which little is known of the new substance and the Ministry of Health imports (or, in the case of home manufacture, obtains exclusively by means of a "gentleman's agreement") a limited quantity for use by the Medical Research Council in working out the drug's dangers and uses.

The second stage is when the Medical Research Council advises us at the Ministry that the new remedy has given sufficiently satisfactory results in this preliminary trial to justify wider distribution and more extended trial. We then arrange for the remedy to be made available to certain centres selected for the facilities they possess in the way of clinical staff and laboratories for testing. Sometimes in return for the material we are supplying to the hospitals we ask them to keep certain records, so that experience can be pooled and evaluated to the benefit of all. It was in this way that in the autumn of 1947, soon after a wider distribution of streptomycin had been effected, I formed the Streptomycin Conference of representatives from the various centres which advised on the form these extended trials should take, and, by collecting and analysing the results, obtained some idea of the way in which streptomycin should be used in the treatment of tuberculous meningitis, with or without miliary tuberculosis, and the results which might be expected. It should be noted that this second stage may include, and in most cases has included, arrangements for making the antibiotic concerned available to general practitioners for use in certain specified conditions outside hospital, the conditions specified being those in which the Medical Research Council advises us that the remedy has been shown to be of definite value.

In the third stage the remedy is made available on prescription. This stage should logically be reached when the profession as a whole can be assumed to be sufficiently aware of the potentialities and dangers of the new remedy to use it with discretion, confining it to those conditions in which it may be expected to benefit the patient, and taking such precautions as will safeguard the patient, so far as is possible, from any undesirable side-effects. In practice, however, it is not always possible to wait until this desirable situation has been attained, and in order to make the remedy available for the treatment of patients outside hospital we must accept the prospect of some misuse and waste, a risk with which we are familiar in respect of many remedies which have long been available to the profession.

There might, of course, be a fourth stage, in which the remedy was made available to the public without a doctor's prescription, but the sort of remedies about which I am talking are all too dangerous for self-medication.

It will be realized that the decision when to transfer from one stage to the next is not an easy one to make, and that the considerations governing such a decision vary widely with the remedies concerned. Let me try to illustrate this point. In the case of penicillin, the toxicity was so low (once the product had been satisfactorily purified) that the only *medical* considerations affecting the decision to make it available on prescription were those which, as I have mentioned, led to the establishment of the special control provided by the Penicillin Act—namely, the possible emergence of strains of micro-organisms resistant to the antibiotic and the masking of disease by inadequate dosage. Thus the transition from stage two to stage three was an easy one and would, I think, have been taken without much hesitation even in ordinary circumstances; but time has shown, nevertheless, the reality of both the risks contemplated, and especially that of the emergence of resistant strains of micro-organisms.

Now, in contrast to penicillin, we hesitated long before transferring streptomycin from stage two to stage three, for here we had an antibiotic of marked toxicity, the use of which was fairly often associated wtih vertigo, tinnitus, and permanent deafness, though there is even now some doubt about how much these effects can be attributed to the antibiotic and how much to the disease for which it is given. In any case here was an antibiotic which needed treating with far more respect than penicillin, and when eventually we decided that, in view of the greatly increased scale of manufacture in this country, the extended experience in using it, and the demonstrated usefulness of this antibiotic in various penicillin-resistant infections, we ought to make streptomycin available on prescription, I was not the only person concerned who had serious misgivings.

The Control of Proprietary Remedies

So far I have been concerned with existing controls of new remedies, but it may be helpful to say a word about the so-called "proprietary remedies"—often wrongly referred to as "patent medicines."

The control of proprietary remedies is one of the most difficult and controversial subjects with which I have had to deal at the Ministry of Health, involving as it does such questions as the inevitability and innocuousness of simple self-medication, the freedom of the doctor to prescribe what he thinks best for his patient, the legitimate profits of the manufacturers, who claim that their ordinary "lines" must pay for the research needed to produce their "ethical remedies," and the proper method of determining what remedies are really needed and for what conditions it is justifiable to advertise them. These are questions in which the profession and politicians of all parties are interested, and which have been under active consideration at the Ministry for a very long time.

Now, proprietary remedies can be divided into two main categories—those advertised to the public and those, known as "ethical remedies," which are advertised only direct to the medical profession. Enormous sums of money are spent every year on remedies of the first class by the public in self-medication, and also by the State through prescriptions under the N.H.S.; and on remedies of the second class mostly by the State. I think there is pretty general agreement that a substantial proportion of this expenditure is wasted because the remedies are useless, inappropriately used, or unnecessarily expensive. For this reason many people think that there should be legal control of such remedies (apart from such control as I have already described, which applies entirely to the "ethical" remedies), but when one gets down to considering the appropriate form of control to apply there is a wide difference of opinion.

But first of all let us look rather more closely at the present position. It has been estimated that in 1951 about 229 million prescriptions were dispensed under the N.H.S. at an average cost of 3s. 11½d. per prescription, and of these about 20% by number and 40% by cost were for proprietary preparations. Though valuable new drugs have been developed at great cost by some proprietary firms, other firms, tempted by the facilities for prescribing afforded by the N.H.S., have merely duplicated standard preparations under proprietary names or have formulated medicines of doubtful therapeutic value at high prices. Such duplicate and doubtful medicines appear to constitute a major cause of the increase in the proprietary drug bill and their prescription to be the result of skilful propaganda to the doctors and advertising to the public which, of course, results in pressure on the doctor by the patient. The only existing control of proprietary remedies is that contained in Sections 11, 12, 15, and 16 of the Pharmacy and Medicines Act, 1941. Section 11 requires that every medicine (except one dispensed extemporaneously) shall bear on it a qualitative and quantitative statement of its content. Section 12 restricts the sale of medicines to doctors, dentists, authorized sellers of poisons, and persons who, before the passing of the Act, had served a pharmaceutical apprenticeship and sold drugs in a shop, *but* it is a defence under this Section to prove that medicine sold otherwise than as laid down under this Section was sold under a proprietary designation and was not described by name in the *British Pharmacopoeia* or the *British Pharmaceutical Codex*. Under Section 15 the Pharmaceutical Society has a duty to enforce Section 11, and under Section 16 the Food and Drugs Authorities have power to do so.

Section 11 places no limit on the duplication of proprietary remedies and no check on their therapeutic value. Section 12 allows such remedies to have a widespread sale. They can be prescribed under the N.H.S., and the only factors limiting such prescription are any deterrent effect which the second Interim Report of the Joint Committee on Prescribing (the Cohen Committee) may have had, and any action taken under the N.H.S. Regulations controlling excessive prescribing.

The problem of controlling proprietary remedies is not, of course, a new one. In 1914 a Select Committee of the House of Commons recommended the establishment of a register of remedies, the regulation of "fancy names" for recognized drugs, and the prohibition by a special Court or Commission of the sale of any remedy "in the public interest or on grounds of non-compliance with the law." The report was shelved during the 1914–18 war. In 1920 a Government Bill was introduced, but there was insufficient time to carry it through. In 1931, and again in 1936, private Members' Bills were introduced but made little progress. The possibility of such legislation was reviewed in connexion with the repeal of stamp duties, but the Pharmacy and Medicines Act, 1941, which resulted, was a compromise measure and did not tackle controversial issues.

As I have already pointed out, the advent of the National Health Service has made the position far more serious by the impetus it has given to the unnecessary multiplication of medicines and the intolerable burden thereby placed on the country's finances, so that the finding of a solution is a matter of urgent importance. It is worth noting in this connexion that France has recently taken drastic action to curb the production of unnecessary or valueless proprietary medicines. Following the introduction of legislation, manufacturers have been obliged to register their products and pay a fee for such registration, with the result that the 20,000 marketed proprietary medicines were reduced overnight to 8,000. These 8,000 were then classified therapeutically, and no new preparations were considered for entry on the register unless an expert committee decided that they represented a significant advance on those already available. The brand name of a particular drug has been restricted to the original manufacturer, and the prices of new products have been controlled. A number of other European countries are likely to follow this lead in the near future, and the probable effect of such a change on the British drug trade is obvious.

Effects of New Remedies

In conclusion, just a word about the possible long-term effects of the new remedies which have been and are being evolved at such a phenomenal rate. The resulting situation seems to me another case of the machine running away with us. Heaven forbid that we as medical men should reject or refuse to examine with the greatest care any remedy which may be of benefit to our patients, but we are being forced by circumstances at the present time to use many new remedies because of the immediate benefit they confer, whilst we are still ignorant of their long-term effect, either singly or in combination. For instance, can the sudden and radical changing of the flora of the upper respiratory passages and the alimentary canal by antibiotics like chloramphenicol be regarded with complete equanimity? Again, should we not regard with some apprehension the rapidity with which more and more strains of micro-organisms are being evolved which are resistant to more and more antibiotics, till perhaps we shall eventually reach the stage at which the race between the development of new antibiotics and the acquisition of resistance by the pathogenic organisms is won by the latter? Then what about cortisone and A.C.T.H.? Can it be safely assumed that such powerful hormones, given continuously over a long period as in rheumatoid arthritis, will have no deleterious effect upon other tissues than those whose disturbances have given the indications for such treatment?

And lastly, speaking as an epidemiologist, I find the interference by these hormones with skin reactions, which are such valuable aids in the diagnosis of infection and the estimation of resistance, disturbing to say the least of it.

Certainly we all carry a very heavy responsibility at the present time, and, if the policy of the Ministry of Health seems at times over-cautious, perhaps the memory of what I have recorded here may make our actions appear more reasonable in your eyes.