UNEXPECTED REACTIONS TO MODERN THERAPEUTICS

ANTIBIOTICS

BY LEO SCHINDEL, M.D., (MUNICH)

This book deals with unexpected reactions to antibiotics and describes signs and symptoms due to those reactions. Diseases due to antibiotic resistant bacteria are discussed and the management of them emphasised.

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Jerusalem, Israel

London
WILLIAM HEINEMANN · MEDICAL BOOKS · LTD.
1957

First Published · 1957

Printed in Great Britain by
J. W. Arrowsmith Ltd., Bristol

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Thanks to antibiotics, a million and a half lives were saved in the first fifteen years of the sulphonamide and antibiotic era. These lives represent those persons who might have died if the percentage of mortality from certain infections had continued in the same proportion after 1937—when sulphonamides began to be used in the U.S.A.—as in former years. Of the lives saved from 1938 to 1952, inclusive, 1,000,000 would have died of pneumonia and influenza, 76,000 mothers would have died of puerperal fever, 136,000 of syphilis and 90,000 of appendicitis. . . .

From " The next half-century in Antibiotic Medicine and its impact on the history of the clinical case history." *Antibiotic Medicine and Clinical Therapy* 3, 64, 1956.

FOREWORD

DR. SCHINDEL, the author of this work, was educated at Freiburg and Munich Universities, and early began to specialise in chemical pharmacology and pharmacological research. Starting in Jerusalem in 1935 as a physician, he soon headed the Department of Pharmacology of the TEVA Middle East Pharmaceutical and Chemical Works Ltd., doing research in the fields of bile acid, sterols, liver functions, cardiac glycosides, amoebicides, hypertension, blood dyscrasias.

Interest in recent researches on the actions and reactions of antibiotics brought him to Cornell University and the Pharmacological Department of the University of California, in 1955. The result of his studies is the work here presented. It summarises the latest views on this most important subject.

INTRODUCTION

THERE was until a short time ago but little need to give consideration to toxic reactions connected with the use of medicaments. The practising physician in general accepted as correct the doses which he either learned as a student or from the professional literature. It was understood that an over-dose could kill the patient; however, there was usually a wide margin between therapeutic and lethal dose. In essence this meant that there was practically no such thing as an unexpected reaction to a particular medicament, except in those rare cases in which the patient was hypersensitive to the substance.

The situation today is altogether different. Extremely potent and specific medicaments have been developed by pharmaceutical chemists during the last two decades, medicaments which can cause unexpected and even fatal reactions. Since the introduction of sulphonamides some twenty-five years ago, for example, very numerous reports of unexpected reactions which occurred during treatment have appeared. The same is true for the various antibiotics which have become available during the last decade. It may justifiably be asked whether the risk imposed upon physician and his patient by the use of such therapeutic agents is warranted.

A whole series of related facts are connected up with the introduction of a new therapeutic principle. The compound is either synthesized or isolated from natural sources by the chemist. Next the activity of the compound is tested by the pharmacologist, who in addition examines its toxicity for laboratory animals. After clinical investigation the new drug is released for general use for specific therapeutic indications. The usual reaction to a new medicament is generally excellent during the first few months. Tousseau's famous statement, made some 100 years ago, " Let's hurry, hurry, use the new drug before it stops curing " is just as applicable today as

when it was made. Every new medicament is more effective than those preceding it. Every new medicament receives general acclaim until, after a few short months of increasing use, unexpected and undesirable reactions begin to appear.

The above description is actually applicable to all modern medicaments. It is applicable to sulphonamides, dinitrophenol, trimethadione and thiouracil; it is likewise applicable to antibiotics no matter which of the many available nowadays is chosen as an example—penicillin, streptomycin, chloramphenical, tetracycline, fumagillin, &c. When side-effects become known, the producer of the therapeutic is required to perform check examinations of the substances. It is often found that neither the substance nor its compounding but rather an idiosyncrasy of the patient was responsible for the unexpected side-effect. The final result of such a check is then usually that the physician who prescribed the particular medicament consoles himself that not he, but rather the patient's hypersensitivity, was actually responsible for the undesirable reaction. The patient, on the other hand, is made to understand that his abnormal sensitivity was the decisive factor in producing the unexpected side-effect. Doubtless there are some hypersensitive individuals. However, it would be wrong to assume that hypersensitivity alone is responsible for the side-effects observed with medicaments. For example, the reason for the urinary suppression which occurs after treatment with the sulphonamides is precipitation of the drug in the urinary passage. Such precipitation of the sulphonamides may be prevented by application of proper measures. Appearance of jaundice after chlorpromazine was at first supposed to be due to hypersensitivity, but was subsequently shown to be the result of thrombus formation in the bile-capillaries. Dinitrophenol regularly causes cataracts in hens. This effect has nothing to do with idiosyncrasy, but is rather a specific reaction of the compound. This side-effect has not been observed in humans since it seems that their

metabolic processes are equipped to suppress such effects. Exactly what metabolic processes are involved are at present not known. However, insight into the mechanism of toxic reactions is afforded by examination of an interesting side-effect caused in rats by succinysulphathiazole, namely granulocytopenia and anæmia. These blood changes are regularly caused by the administration of the compound. It is now known that succinylsulphathiazole inhibits growth of intestinal flora responsible for folic acid synthesis, thus causing a folic acid deficiency, which in turn causes the blood changes. When folic acid is given the blood returns to normal.

The examples given above are true cases of toxic reaction, and have nothing to do with hypersensitivity. It is of interest, and indeed of primary importance for the evaluation and effective treatment of side-effects to know what specific side-effects are to be expected from a particular medicament.

Just what is meant by "side-effect?" Under side-effect a reaction is understood, undesirable, unexpected, and annoying, as response to an applied drug principle for which it is not labelled.

Since the side-effects of an applied drug principle can be established by clinical observation, and since the probability of occurrence of such effects can likewise be established by statistical treatment of a great number of observations, it would seem that such side-effects actually form an intrinsic part of the drug's activity. This is, however, not the case, for in a great many cases it is possible to achieve therapeutically positive results and to cause side-effect by using placebos.

The percentage cures achieved through use of placebos cannot, of course, be accurately established. H. K. Beecher was able to show that 35·2 per cent. of 1,082 cases were improved by treatment with placebos.

However, placebos can also cause side-effects, surprising as it may seem. These side-effects are certainly not due to suggestive influence. A number of interesting cases of side-effects

caused by placebos have been reported. Wolf and Pinksy observed toxic effects of placebos such as nausea, tachycardia, excessive sweating, and even such allergic-type skin reactions as itching maculopapular erythema. Epigastric disturbances with diarrhœa were also observed. Angioneurotic œdema of the lips and generalized urticaria have been noted. Occasionally, Beecher mentions dryness of the mouth, nausea, severe headache, difficulty in concentrating, easy tiring, and somnolence. Such side-effects after placebos appeared in from 9–50 per cent. of the patients treated. These facts make it particularly difficult to distinguish between "true" and "false" side-effects. In this connexion it may be in place to quote a passage from an editorial on "The Use of New Drugs" which appeared in the *J.A.M.A.* of 1 September, 1951. "Physicians today have remarkable tools with which to practise medicine. But, as is true of all tools, improper use is attendant with danger. If there is an unusual risk associated with the use of a drug, but the physician is convinced the drug is necessary for, or at least best suited to a patient, he should accept the risk as a challenge by which he cautiously approaches his clinical problem. To indict a drug or all drug therapy because occasional reactions are seen is unfair to patients who might benefit therefrom. However, he cannot afford, for his patient's welfare or his own reputation, to use a drug with which he is not familiar or which he believes is too dangerous for his practice. In the final analysis his decision must rest on his knowledge and experience and on sound judgement."

The author's intention is to present in the following sections a review of the literature concerned with the side-effects of antibiotics. It is hoped that such a compilation of material scattered throughout the literature will make such information more generally available to the medical public.

CONTENTS

CHAPTER I

PENICILLIN

WHEN Fleming in 1928 studied the variant types of staphylococci in his laboratory in St. Mary Hospital, London, he noticed that a contaminating mould of *penicillium notatum* dissolved a culture of bacteria growing on the same medium. This discovery actually ushered in the existence of penicillin. However, it was not until ten years later that Florey and his associates in Oxford were able to carry out systematic research of penicillin-containing culture media and succeeded in isolating penicillin in its pure form. Today, the history of the development of penicillin in all its stages, from the crude yellow amorphous powder to the newest long-acting salts, has become common knowledge.

At present *penicillium chrysogenum* Thom is the principle source for commercial penicillin production. Depending on the structure of the penicillin compounds, there exists penicillin F, G, K and X. In 1946 the Committee on Medical Research reported that the four main natural penicillins differ in their antibacterial potency. The importance of the differences was only realized after observations have been published that the commercial penicillin K preparations were less effective in the treatment of syphilis than other penicillins. Among the crystalline compounds penicillin G salts are actually the only ones still on the market since no natural penicillin offers today significant advantages over penicillin G. Penicillin O, a special salt of penicillin (allyl-mercapto-methyl-penicillin), has attracted some attention among members of the medical profession because of its allegedly reduced antigen property. Similar qualities have been likewise ascribed to 1-ephenamine penicillin G (compenamine) = (N-methyl-1,

2-diphenyl-2-hydroxyethylamine P.G.). In view of the considerations which follow, regarding side-effects, it seems essential to mention compounds characterized by slow resorption or slow elimination: procaine penicillin (beta-diethyl-aminoethyl-4-aminobenzoate of penicillin G acid) and benzathine penicillin G (N : N'dibenzyl-ethylen-diamine dipenicillin G).

These two compounds are probably the compounds with prolonged action most commonly used today. This does not mean, however, that there are no other penicillin salts which have more or less the same qualities of retarded resorption as, for instance, the phenoxymethyl-penicillin which is available as penicillin V.

In 1942, there was only as much penicillin available in the whole world as needed for the successful treatment of one single case. To-day, penicillin production has risen so much that precise details are no longer available. In the U.S.A. alone approximately 324 tons were prescribed in 1951 and already 350 tons in 1952. As to 1953 there are data available in respect of 343 tons which are equivalent in value to 58 million dollars. How much is produced in other countries can hardly be ascertained. Most likely a similar quantity is produced and consumed there. Since penicillin became so readily available, its usage became more and more indiscriminate. It has been proven during recent years that in almost all cases of fever penicillin was prescribed in the first instance. When penicillin did not show the expected results, the whole series of other antibiotics has been tried out. One should not be surprised that at the beginning of the antibiotics era about ten years ago side-effects of penicillin were hardly noticeable. They increased with the growing application of the drug and developed into a real danger. Regarding the first relatively crude, yellow, amorphous penicillin compounds the existing impurities were considered to be responsible for side-effects. When they continued to be observed, however, and remained alike even with the purified crystalline and most modern

penicillin salts and compounds, and that to an ever-growing extent, there exists no doubt any more that the responsibility lies with the penicillin molecule or an intermediate product thereof causing the undesirable and unexpected side-effects. How do these side-effects occur?

Surveying the clinically observed side-effects which occurred in the years 1943–48, E. A. Brown tried to divide the penicillin reactions into three principal types:

1. Reactions caused by local contact. They comprise manifestations appearing on the skin, the mucous membranes or at the site of injections;
2. Reactions expressed as skin allergies like urticaria, erythema and eczema;
3. Generalized systemic reactions, like serum disease, anaphylactic shock effect and cardiovascular and renal disturbances.

In the meantime many more forms of penicillin reactions became known. It is not intended here to go into details of the mechanism of untoward reactions after penicillin medication. Therefore no special emphasis is laid here on the mentioning of allergic mechanisms. There is no doubt, however, that penicillin can act as true antigen. How frequently side-effects may occur is less a question of statistical analysis than of presumptive speculation. Most likely one cannot estimate altogether the occurrence of side-effects quantitatively. Figures mentioned in the literature diverge very largely. But even if one wishes to evaluate the figures mentioned in various publications, they would not constitute accurate proof. The side-effects of penicillin have not been studied systematically. Even material published by several hospitals expresses only the compilation of occasional findings. Hardly any observations have been collected by physicians in private practice. Sometimes individual cases are described. How far the figures differ may be seen from the following data. The available figures refer to the first years

of penicillin therapy and one would be correct to assume that the side-effects increased considerably in the years 1954–55, particularly if one realizes that an ever-growing number of patients became hypersensitive following the more frequent usage of penicillin. Of 10,000 patients treated by E. W. Thomas and associates 2·4 per cent. showed allergic reactions. C. S. Keefer and associates observed that 2·8 per cent. of their 500 patients reacted with side-effects. C. P. Lyons collected material on 209 patients, 5·7 per cent. of whom showed undesired reactions. Sonck reaches up to 16 per cent. of urticarial reactions after penicillin in his survey of literature.

There is an editorial in *The Lancet* of January 1954, indicating that the frequency of all hypersensitive reactions to penicillin varies between 2–8 per cent. of patients under treatment. Meyler mentions in his publication that up to 28 per cent. of patients under treatment show penicillin reactions if they were treated with penicillin already before. He refers to his report in *J.A.M.A.* 1948 in which 300 patients are mentioned of whom 25 per cent. reacted with skin manifestations. These patients had received penicillin already before allergic skin symptoms were observed. Kolodny and Denhoff published their observations regarding 124 patients 16 per cent. of whom showed an immediate and 7 per cent. delayed allergic reaction to penicillin.

It has, of course, often been asked, whether the different forms of penicillin production influence the frequency of side-effects. No satisfactory answer can be derived from the available statistical material. It may, however, be of interest to use comparative values and for this reason the following figures by Lepper shall be mentioned:

1,303 patients showed the following percentage of undesirable reactions:

after administering water-soluble crystalline penicillin between 1·2 per cent. and 7·8 per cent. of side-effects occurred;

after administering penicillin in oil and beeswax: 2·7 per cent.

after administering procaine penicillin in oil: 1·4 per cent.

The same authors collected also a group of patients who had reported allergic reactions in their medical history. This group showed 3·8 per cent. of side-effects after water-soluble crystalline penicillin was administered, while a comparative group without allergic anamneses showed 1·5 per cent. of side-effects after water-soluble crystalline penicillin. It is certain that these published statistics do not fulfil all the necessary conditions in order to establish an evaluation of figures which is comparable and usable. The administered quantities of penicillin were, for example, different for the individual patients; not always has it been stated in which form penicillin was given; sometimes the question remained open at what frequencies and how many injections were given. In any case, the few indications prove beyond doubt how hopeless it is to establish the occurrence of side-effects after penicillin quantitatively, particularly since it is unknown how many people received penicillin altogether. Considering how often penicillin has been administered during recent years it can be assumed with certainty that more and more patients are reacting to this antibiotic with allergic manifestations. Consequently it has been stated again and again that penicillin should be administered with great care and only at specific indications.

The question is asked what are these side-effects or rather the untoward effects in the course of a penicillin therapy?

Allergic Reactions

Changes in the skin and the mucous membranes. The first allergic symptoms can occur very soon after the administration of penicillin, after a few minutes or hours, and become manifest usually in the form of an urticaria. Similar to serum

disease, an allergic reaction can also occur after 7, 8 or 14 days, as described by W. P. Boger. These reactions happen irrespective of the kind of penicillin salts or penicillin compounds given. In regard of procaine penicillin, however, the procaine itself may be the cause for the hypersensitivity.

At the beginning of the penicillin era penicillin ointments, eye-drops or lozenges were quite commonly used. There is no doubt that local application has considerably decreased since 1954.

Contact Dermatitis. It can be seen from publications in the years 1946–50 what side-effects local application may cause. Contact dermatitis has been mentioned by Hopkins and Lawrence. 56 out of 492 patients who received penicillin locally, reacted with a contact dermatitis. Other authors reported the same observations. Berston, R. L., for instance, states that penicillin is a strong dermatological sensitizer causing contact dermatitis in 20 per cent. of all cases treated with penicillin. The most detailed summarizing description of former years was made available by Leon Goldman and his associates. They indicate that medical personnel in particular who are constantly in contact with penicillin often show contact dermatitis. A classical description of their observations at the Gardiner General Hospital in 1943 was given by H. D. Pyle and Herbert Rattner, as follows:

> In November 1943 a penicillin department was established at the Gardiner General Hospital. The head of this department who prepared the solutions himself before he administered them to the patients, noted at the beginning of his activity a slight irritation of his eyelids, conjunctivitis and difficulties in reading. First, glasses were prescribed to remedy his condition. The lid-rim inflammation, however, continued and a dermatitis developed starting at the back of his nose and extending over forehead and temples. Characteristics of an acute contact dermatitis were found. At the beginning, the plastic material of the new optical