Papers and Originals

Ill-health Due to Drugs*

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Drugs administered in the treatment of disease may possess many different pharmacological actions, but they fall roughly into two broad categories.

In the first they provide a substance essential for the health of the body not otherwise available as a result of dietary deficiencies, malabsorption, or the loss of secretion of an organ. Examples are ascorbic acid in scurvy, cyanocobalamin in pernicious anaemia, and the appropriate hormones in myxoedema and Addison's disease. In the first example it is difficult to imagine any ill-health arising from treatment, and in the second the only hazard is that associated with a parenteral injection; excess of the drugs causes no harm. In the third and fourth examples the doses of the drugs must be carefully regulated, as ill effects may arise if the correct amount is not given. In general, when drugs are used as physiological replacements in correct dosage toxic reactions do not occur. However, only a few drugs are employed in this way, and the situation is usually more complex. In a disorder such as diabetes mellitus factors other than a simple deficiency of insulin are commonly at work; beef insulin does not constitute a true replacement therapy, and, accordingly, complications are much more likely to arise as a result of treatment.

In the second category the therapeutic effect is produced by the drug interfering with biological processes either in the patient or in invading organisms. This pharmacological action is essentially a toxic process, which must be strictly limited to the system whose function is to be altered in order to avoid widespread ill effects. This is the basis for the employment of most drugs in therapeutics. Success depends on precision of dosage and a high degree of selectivity in site of action. These are often not attained, and so with potent drugs some undesirable effects are almost inevitable.

The mechanism of development of toxic reactions is frequently complex, and in many instances ill understood. As the variety of undesirable effects from drugs is very great some provisional form or classification must be attempted.

Nature of Undesirable Effects from Drugs

Errors in Dose

An overdose is an obvious way in which harm may be caused. This may be due to a mistake or misunderstanding on the part of doctor, pharmacist, nurse, or patient in prescribing or taking the medicine. Increasing attention has been directed to errors of this sort in hospitals (Fogg, 1965; Vere, 1965), and no doubt they occur at least as often when drugs are taken at home or at work. The slow cumulation of some drugs in the body may not be recognized until some untoward feature appears,

such as haemorrhage during treatment with anticoagulants. This is now a common cause of severe and even fatal reactions (MacDonald and MacKay, 1964).

A suicidal overdose, particularly of barbiturates, is now one of the commonest medical emergencies. In a recent review by Dr. D. I. R. Jones of 60 patients admitted during the years 1962-4 to my clinical unit at Sheffield Royal Infirmary as a result of attempted suicide by drugs, the agent employed had been prescribed by a doctor for the patient in 33 cases (55%). In the other cases the drugs had been bought over the counter (mainly aspirin), stolen from other patients, or the source could not be ascertained.

Delayed Excretion or Metabolism

Defects in the function of the kidneys or liver may increase the retention of a drug in the body. For example, unduly high blood levels of streptomycin may occur in those with diminished renal function, as is often seen in the elderly, who are particularly prone to show toxic effects from this drug. At the other extreme, in the very young the hepatic metabolism of several drugs is defective owing to immaturity of the enzyme systems, particularly glucuronyl transferase. The failure of glucuronidation of chloramphenicol is the probable explanation of the "grey syndrome" in babies, as slow metabolism of the drug results in sustained high blood levels (Hodgman, 1961). An interesting recent development has been the demonstration of inherited deficiencies in enzyme activity which may decrease the rate of metabolism of drugs (F. T. Evans *et al.*, 1953; D. A. P. Evans *et al.*, 1960; Ruddell, 1962; Lehmann *et al.*, 1963). The slow inactivators of suxamethonium and of isoniazid are clearly more liable to experience untoward effects. These studies in pharmacogenetics constitute one of the important growing-points in our understanding of ill-health from drugs (Kalow, 1962; Evans, 1963).

Interaction of Drugs

Interference with metabolism may also be caused by concomitant or recent administration of agents with enzyme-inhibiting properties. This is a prominent feature of the monoamine oxidase inhibitors, which, in addition to delaying the inactivation of such naturally occurring substances as serotonin, adrenaline, and noradrenaline, also affect the metabolism of many drugs, including pethidine, phenothiazines, and amphetamine (Klerman and Cole, 1965). In addition, hypertensive crises may be precipitated by eating varieties of strong or aged cheese and meat extract preparations, probably because of their content of tyramine (*Brit. med. J.*, 1964).

The pharmacological activity of a drug usually depends on the concentration of the fraction that is not bound to plasma protein and is thus free to diffuse. An overdose effect may

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be produced if the level of unbound drug is enhanced by giving another agent at the same time with a higher affinity for the binding proteins. In this way haemorrhage may occur if a patient on treatment with warfarin is given phenylbutazone (Eisen, 1964).

Undesired Effects due to Widespread Pharmacological Action

Some drugs used in the treatment of human disease are remarkably selective in their action. Penicillin, though lethal in low concentrations to certain bacteria, commonly does not disturb the metabolism of human cells even when given in massive doses. At the other extreme, cytotoxic agents used in the treatment of malignant disease are not confined in their action to the neoplastic tissues but are apt to damage normal dividing cells, so that little margin exists between therapeutic and toxic doses. Cortisone and allied steroids are further examples of drugs causing extremely widespread effects far exceeding the desired therapeutic action in a specific case. It is thus not surprising that they may produce unwanted reactions in practically every system of the body. Many drugs, in addition to their desired action at a particular site, have a more general direct irritant effect on susceptible tissues. This may cause difficulty in their administration. Local pain or necrosis after injections and gastro-intestinal inflammation and ulceration may be produced in this way.

Side-effects can often be predicted from the known pharmacological actions of the drug. This kind of problem is well illustrated in the treatment of hypertension. The aim is to block the sympathetic vasomotor nerves. This may now be achieved by a wide variety of different drugs, but none is entirely limited in its site of action to these nerves. Reserpine and methyldopa cause, in addition, effects in the central nervous system of which depression is often the most troublesome. The ganglion-blocking drugs such as pentolinium inhibit the parasympathetic as well as the sympathetic ganglia, thus causing unwanted features such as difficulty in ocular accommodation, dryness of mouth, and constipation. The action of guanethidine is confined to the sympathetic nerves but not to vasomotor nerves alone, with the result that undesirable effects such as diarrhoea and failure of ejaculation are encountered. Nevertheless, drugs such as guanethidine and bethanidine possess considerable advantages over the other agents by virtue of their more restricted site of action, and can be given in doses producing much greater reductions in blood-pressure.

An unsuspected pharmacological action of a drug may first become apparent when it is revealed as an undesirable effect in man. Then it may be reproduced by appropriate experiments in animals. The inhibitory action of thalidomide on developing foetal tissues is an example. All the actions of a drug cannot at present be predicted from its structure, and it is impracticable to test its effect on every biochemical and physiological process that takes place in animals before it is released for human use. Inevitably some unexpected pharmacological actions will continue to come to light when new drugs are employed in man and will restrict or prohibit further clinical use.

The central nervous system has become particularly prominent in recent years as a site of unwanted side-effects of drugs. Occasionally drugs introduced for an action remote from the brain turn out to have unexpected neurological effects. Thus nalidixic acid employed for the treatment of infections of the urinary tract may produce visual disturbances, hallucinations, and confusion (Cahal, 1965). However, the great variety of drugs introduced during recent years for the treatment of mental disorders have been the main source of neurological side-effects. The lack of knowledge regarding the biochemical disturbances underlying psychiatric illness and the production of clinical features such as anxiety and depression makes excep-

tionally difficult the development of drugs with a selective action to correct an abnormality or relieve symptoms. In such a complex system as the brain psychotropic drugs possess a wide range of actions, many of which constitute undesirable side-effects. I have been particularly impressed by the frequency of incoordination of movement and ataxia in patients, especially the elderly, being treated with sedatives and tranquillizers. Often the cause of these features has not been recognized and the sufferers have been subjected to unnecessary detailed neurological investigations. The cure is usually simple and they are most grateful, as fortunately the majority of the side-effects disappear promptly on stopping the administration of the drug. However, an often irreversible neurological disturbance has been reported to follow the prolonged administration of phenothiazines (Hunter, Earl, and Thornicroft, 1964). This is a syndrome of persistent abnormal movements of a grotesque and distressing kind. It is seen particularly in women who have suffered some previous brain damage and have received phenothiazines for a few years. Recently considerable recovery has been reported in one woman after stopping the treatment (Kilpatrick and Whyte, 1965).

Addiction to drugs is becoming an increasing problem. Previously this had commonly been seen only with the narcotic agents, such as morphine, heroin, and pethidine, but now it is realized that it is a feature associated with many drugs possessing a potent action on the central nervous system. The danger of amphetamine in this respect has become apparent, and it is a drug that has little or no therapeutic value (Kiloh and Brandon, 1962). Barbiturates, and particularly combinations of a barbiturate and amphetamine, are also becoming more extensively abused. The distinction between addiction, habituation, and dependence is blurred, but the frequency with which these powerful drugs are regularly sought is a disturbing feature of modern medicine.

Secondary Effects of Drugs

These are most evident in relation to infection by micro-organisms. Glucocorticoids, by interfering with the defence mechanisms, may lead to reactivation of a tuberculous focus or to diffuse spread of a purulent infection which would otherwise be localized. Broad-spectrum antibiotics such as the tetracyclines, by removing susceptible organisms from the alimentary canal, leave the way open to invasion by others, such as monilia or the resistant staphylococcus.

Hypersensitivity Reactions

These constitute some of the most serious toxic effects of drugs, but their nature is ill understood and the term merely cloaks our ignorance. They are erratic in appearance and affect only a few patients, are not directly related to the dose, and are more likely to occur after prolonged or repeated courses of the drug. They include cutaneous eruptions and photosensitivity, bone-marrow aplasias, and certain types of jaundice, and are not readily reproduced in experimental animals. Sensitization may be associated with severe and even fatal anaphylactic reactions to agents like tetanus antitoxin and penicillin.

Psychological Factors

The importance of suggestion in producing beneficial effects is fully recognized. Similarly, harmful effects which are not the result of pharmacological actions may be attributed to drugs. Green ferrous sulphate tablets may produce symptoms not caused by an equal dose of the substance administered in white tablets (Girdwood, 1952), and the psychological factors at work in iron therapy were fully demonstrated by Kerr and Davidson

(1958). In the trial of an antihistamine in the treatment of the common cold the active and dummy tablets produced remarkably similar side-effects (Medical Research Council, 1950). We must be equally critical in claiming both benefit and harm from drugs.

Frequency of Toxic Reactions

The incidence of even major toxic reactions to drugs is not accurately known. Only a fraction are reported, and many probably go unrecognized. It has been estimated that between 5 and 10% of patients admitted to hospital experience some toxic reaction to a drug (Barr, 1955; Schimmel, 1963; Lasagna, 1964). The investigation of MacDonald and MacKay (1964) is of particular interest in showing which drugs are most likely to cause trouble in the United States. Antibiotics, hypnotics, and tranquillizers were the top three classes of drugs causing reactions. These are very widely used agents, and clearly the incidence of reactions to a specific drug is related to the frequency with which it is prescribed and the total amount that is used. McDonald and MacKay (1964) estimated the number of doses dispensed per toxic reaction. On this basis penicillin led, followed by warfarin and imipramine. Among the least toxic drugs were aspirin, phenobarbitone, and digitalis. The high incidence of toxicity due to penicillin undoubtedly reflects the wide exposure of the public to this drug, with resultant sensitization.

Recognition of Ill-health due to Drugs

At the beginning of this century, when our present system of history-taking and clinical examination was firmly established, there was little drug therapy that was capable of altering the natural course of most diseases. Any medication that was prescribed was usually pharmacologically impotent and did not cause much benefit, harm, or diagnostic difficulty. Accordingly the physician in taking a medical history paid scant attention to ascertaining what previous treatment had been given. Since then we have witnessed a therapeutic revolution, and now have at our command numerous potent drugs and have hesitated little in using them. They can influence profoundly the outcome of many diseases, but at the same time may produce clinical features closely resembling naturally occurring disorders and greatly obscure the correct diagnosis. Moreover, the success of further therapy may be jeopardized. Serious post-operative collapse of patients unknowingly treated with corticosteroids and untoward reactions to many substances in those who have received monoamine oxidase inhibitors are well-recognized examples of how this may occur. In these circumstances the immense importance of ascertaining in detail what medicines had been taken by the patient would seem entirely obvious. Yet the tradition of ignoring the possible effect of drugs dies hard.

In two books on clinical methods first published in 1961 and 1964 the necessity of seeking out this information is scarcely mentioned. This is further reflected in the response of the medical student, as it is only too commonly found in his history that there are, for example, details of the toilet facilities but no list of medicines consumed in recent months. Few, however, would disagree that in this country today deplorable sanitary arrangements cause much less morbidity than drug therapy. It cannot be too strongly emphasized that no clinical history is complete without a list of drugs taken during the previous six months. Unfortunately this is rarely achieved. Commonly, inquiries about drugs are made only when suspicion has been aroused, often after the patient has had numerous expensive and uncomfortable investigations of an obscure illness. As so many new drugs are being introduced it is clearly unsatisfactory to wait till this stage. Furthermore, it is only by

making routine inquiries of every patient that new and unsuspected toxic reactions can be revealed.

One of the main reasons for neglecting to record previous drug therapy is undoubtedly the difficulty in finding out precisely what has been taken by the patient. Communications between doctors frequently omit this vital information, the patients usually do not know the names of the drugs that they have consumed, and the container, often produced by the patient in an effort to be helpful, almost invariably carries no useful inscription. Furthermore, both in hospital and in general practice potent drugs are still sometimes given without any entry being made on the patient's record, and when inquiries are subsequently made about a suspected toxic reaction the necessary details cannot be obtained. In such circumstances the only hope is that the prescription can be tracked down through the pharmacist or pricing bureau. This was only too clearly shown in an investigation of infants born with congenital defects due to thalidomide (Speirs, 1962).

Prompt recognition of ill-health due to drugs requires that we are constantly alert to the problem and that the transfer of information about drug therapy is much improved. However, even if more adequate records are kept there are now many circumstances in which patients have to be seen without their notes being readily available. The development of rota systems at night and week-ends, travel from home, emergency admissions to hospitals, and prescription of drugs for the same patient from several different sources all mean that a doctor nowadays often has to attempt to make a diagnosis and arrange appropriate treatment ignorant of what drugs may previously have been given. It has been estimated by a general practitioner that more than a quarter of night and emergency calls are due to drug-induced illness (Kuenessberg, 1965). It is in these circumstances that the importance of having medicine containers inscribed with the name of the contents comes to the fore.

My firm contention is that containers should be fully labelled in this way unless the doctor has specifically ordered that this should not be done. It is very rarely in the patient's interest not to know what drug he has been taking. I am aware of the arguments that have been advanced against the labelling of containers. It has been suggested that if containers were labelled doctors would be less inclined to keep proper records of what they had prescribed, that illicit traffic in drugs would be encouraged, and that drugs would be transferred to the wrong container. Another argument is that it would be better to stamp tablets with a code mark so that they could be identified, but this is technically difficult and cannot be quickly arranged. Furthermore, it would be useless when only an empty box was available. After having heard much discussion on these points and encountered so many difficulties in identifying medicines when drug toxicity is being investigated I am confident that full labelling of containers is an essential and overdue measure (Wilson, 1961).

Reporting of Toxic Reactions

A mechanism for the reporting of suspected toxic reactions to drugs has now been established in this country by the Safety of Drugs Committee. This is a most important measure for ensuring that any harm being caused by a drug is quickly appreciated and an early warning can be given. The success of the measure depends on the co-operation of all doctors who prescribe drugs.

One of the most urgent tasks is to place the toxicity of drugs, particularly the incidence of severe and dangerous reactions, on a sound epidemiological basis. It is, for example, known that chloramphenicol may occasionally cause aplastic anaemia which is fatal in at least half the cases. The incidence of this complication in relation to the number of patients treated with the drug and the amount that has been taken is not known. Yet we can really assess the toxicity of any drug only if this

information is available on a quantitative basis. There are great opportunities for doing this here, as all National Health Service prescriptions are available for examination. With modern computing techniques the number of patients exposed to a drug and the amount prescribed can be ascertained. The adequacy of reporting the toxic reactions lies in the hands of the medical profession.

The accurate recording of toxicity is not entirely a negative process leading to curtailment of use of a drug. The knowledge gained may provide the starting-points for further advances. It is interesting to note how many new drugs have been developed as a result of acute clinical observation of unexpected side-effects. Polyuria observed in a syphilitic patient being treated with an organic arsenical preparation led to mersalyl; an alkaline urine associated with a metabolic acidosis during sulphanilamide therapy started the research that eventually produced chlorothiazide; hypoglycaemia observed as a side-effect of sulphonamide therapy provided the initial stimulus for the development of the oral antidiabetic agents. The tranquillizers stem from the sedation and drowsiness which are often seen as troublesome side-effects during the administration of antihistamines, and the antidepressants from the euphoria observed when tuberculous patients were treated with iproniazid. There is no reason to doubt that clues for further developments in drug therapy will continue to come in this way. Quite apart from this practical advantage there is also every prospect that advances in basic knowledge will continue to occur from the observation of drug toxicity. The contribution to genetic research has already been mentioned, and there are several other exciting prospects.

Preventive Aspects

It must be accepted that when potent drugs are used in the treatment of disease there is always the possibility that some harm may result. No amount of toxicity-testing in animals can eliminate this risk, though it may prevent some of the more toxic compounds coming to clinical trial and may direct the attention of the clinical investigator to possible dangers. It is most important that the limitations of studies in animals should be recognized. Many toxic reactions to drugs observed when they are given to man cannot be reproduced in the experimental animal. A toxic feature seen in an animal may not necessarily occur in man, and it is possible that a potentially valuable drug might be excluded on this account.

The difficulty in prediction of the human toxicity of drugs throws a considerable burden on the clinician. Before any drug is prescribed he should inquire whether the patient has previously been treated with it and experienced any untoward effects. Closely related drugs usually produce similar toxic effects and also cross-sensitization. Thus a reaction to one form of penicillin means that the patient is sensitive to all in the group. Attention should be drawn to the multitude of unrelated proprietary names which may disguise similar or closely related drugs and are certainly not conducive to safety. Unfortunately, a drug is sometimes prescribed under a trade name without realizing that it is closely related to one that has previously caused trouble in the patient. The approved names by their similarity usually indicate drugs in a group, and this is not apparent from proprietary names. A recent example is provided by Ismelin, Envacar, and Vatenzol, which appear quite unrelated but actually refer to closely related antihypertensive drugs having the approved names guanethidine, guanoxan, and guanoclor. There is a strong case for the general use of approved names in the interests of safety and quicker recognition of toxic effects. It was very noticeable how quickly the proprietary names of thalidomide were dropped when its danger was recognized. It should be noted that the authorities concerned have succeeded in the last year or two in making the approved names shorter, more euphonious, and easier to remember.

Prompt recognition of toxic effects ensures that the offending drug is withdrawn and any appropriate treatment started at the earliest opportunity. In general the length of time that a drug is given without realizing that it is producing harm is directly related to the duration and seriousness of subsequent morbidity from the toxic effects.

Some toxic effects of a new drug may not be described until several thousands of patients have received it. This is particularly the case if the effect is novel and unexpected and only becomes apparent either some time after the course of treatment has been completed or after prolonged administration. There is inevitably a greater risk in employing a new drug rather than an established one whose harmful effects have been mainly recognized. Yet the value of a new drug can be ascertained only by extensive use, and no progress would be achieved if we stuck only to the older remedies. It is important that when a doctor is using a relatively untried drug he employs it in circumstances such that the patient is fully safeguarded and the effect, whether beneficial or harmful, can be ascertained. Adequate records must be kept, and the new drug should not be administered along with a multiplicity of other agents.

Harmful Effects and Therapeutic Efficacy of Drugs

The safety of a drug must be assessed in relation to the seriousness of the clinical condition, the efficacy of the drug in curing the illness or in relieving symptoms, and its liability to cause toxic effects. Much attention has recently been directed to the harm that may be caused by drug therapy, and several books and articles have been published on the subject (Meyler and Peck, 1962; Spain, 1963; Lasagna, 1964; Moser, 1964). It is most important that a proper sense of proportion be preserved. Many serious infections which 25 years ago exacted a heavy toll in mortality and morbidity can now be regularly and promptly cured by drugs which may occasionally cause some dangerous toxic effects. In these cases there is no doubt that the overall benefit greatly exceeds the harm. On the other hand, serious toxic effects, even if they occur only rarely, are not acceptable from drugs used for the alleviation of trivial conditions. The evaluation of the relative benefit and risk from a drug depends on proper clinical trials, assessment of toxicity on a quantitative basis, and knowledge of the natural course of the condition under treatment. Only slight benefit and relatively high toxicity may at present be accepted when drugs are employed in an attempt to control leukaemia or metastatic carcinoma. At the other extreme a hypnotic should be entirely reliable and free from any deleterious effects if taken in correct dosage.

It is important to emphasize that the safe use of a drug cannot be ensured by any committee or process of testing, but is a responsibility of all doctors who decide on the treatment of patients. For example, an analgesic may be shown in careful clinical trials to produce occasional serious toxic effects but to have a powerful therapeutic action in severe rheumatoid arthritis which clearly outweighs the disadvantages. On these grounds it would certainly be passed by a committee considering its safety, and would be released for marketing and general prescription. It could then be ordered by a doctor for his patients without any restriction. However, a drug of this type should be used only with considerable discrimination, and, on the evidence, should not be a first choice in the treatment of minor rheumatic disturbances, however great the advertising and other pressures may be.

Conclusion

We live in an age of therapy with potent drugs, and new weapons are coming to hand every year. These changes are to be welcomed; we cannot put back the clock even if we

should wish to do so. The problems now posed by motor-cars and drugs are in many ways similar. We must ensure that the price of advance is not too high and that accidents are reduced to a minimum by foresight and care. Both are examined, licensed, and periodically reviewed. Roads and lines of communication of information are improved. The manufacturers are exhorted to introduce the latest safety devices and tests. However, in the final analysis, most depends on the driver and prescriber.

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Hyaline and Calcified Pleural Plaques as an Index of Exposure to Asbestos

A Study of Radiological and Pathological Features of 100 Cases with a Consideration of Epidemiology

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Benign collagenous pleural thickening is a common finding at necropsy in cases of asbestosis (Gloyne, 1933), and calcification may occur within the thickened serosa (Gloyne, 1938). Focal pleural calcification may be noted radiologically in asbestosis (Hurwitz, 1961; Lawson, 1963), but may also be seen in those who work with asbestos or other silicates without evidence of pulmonary disease (Smith, 1952). There is strong evidence from Finland (Kiviluoto, 1960) that environmental—that is, non-industrial—exposure to asbestos leads to the relatively common finding of focal pleural calcification (calcified pleural plaques) in a community.

This paper is concerned with the association between pleural plaques as seen at necropsy or in routine chest radiographs and exposure to asbestos, and we wish to emphasize the potential epidemiological value of radiology in assessing the prevalence of these lesions in a population.

There were 56 cases in which pleural plaques were found at necropsy, and 50 cases in which pleural calcification was seen on x-ray examination. Six of the patients from the radiological series had the presence of plaques confirmed at necropsy, so that the total number of cases with pleural plaques is 100.

Pathology

Hyaline pleural plaques occur as discrete elevated grey-white areas, usually involving the parietal layer and without associated effusion or adhesions (Fig. 1). The plaques vary greatly in size and shape, and the intervening pleura and unaffected visceral layer show a slight, diffuse thickening (Fig. 1). The cut surface is of a uniform glistening grey colour unless focal

calcification is present, when yellow spots or laminae may also be seen. Focal calcification within plaques is shown in x-ray films of parietal pleura in Figs. 2 and 3. Plaques are usually bilateral, most prominent in the lower halves of the pleurae, and tend to follow the lines of the ribs (Figs. 1, 2, and 3). Although their consistency is that of cartilage, histologically they are composed of laminated hyaline collagen and often show either spotty or massive focal calcification (Fig. 4). There is no suggestion of vascularity or of granulation tissue when examined *post mortem*, although surface fibrin incorporated into a plaque was observed in one case.

We could detect no other histological difference between plaques with some calcification and those with none, and we have used the term "hyaline pleural plaques" to refer to all of them.

Necropsy Prevalence

From 1 January to 31 December 1964 a personal examination of each necropsy at the Bernhard Baron Institute was attempted, and 16 cases with these plaques were found. There was no tuberculosis in the chest in any case, and after histological examination only two cases could be defined as "asbestosis" (pulmonary fibrosis due to asbestos). The total number of necropsies during 1964 was 381.

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