PROBLEMS IN THE MANAGEMENT OF URINARY TRACT INFECTIONS

- CLINICAL, EPIDEMIOLOGICAL AND LABORATORY STUDIES -

BY

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PREFACE

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These colleagues have provided help and encouragement in the various investigations listed. However, except where noted, I have personally undertaken all aspects of the collection of the data and its subsequent processing, analysis and interpretation.

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PUBLICATIONS

Some of the material described in this thesis has been published in the medical literature:

Screening for bacteriuria in pregnancy.

Lawson, D.H., Miller, A.W.F.

Lancet (1971) 1 9.

Extended therapy in patients with established urinary tract infection.

Lawson, D.H., Gleadle, R.I., Linton, A.L.

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Extended therapy with a trimethoprim-sulphonamide for the treatment of established urinary tract infection.

Gavras, H., Lawson, D.H., Linton, A.L.

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Tetracycline and drug-attributed rises in blood urea nitrogen.

A report from the Boston Collaborative Drug Surveillance Program

Journal of the American Medical Association (1972) 220 377.

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Linton, A.L., Lawson, D.H., Eakin, J., McVarish, J.

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Nephrotoxicity of cephaloridine

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Lawson, D.H., Macadam, R.F., Hartz, S., Singh, H., Gavras, H., Turnbull, D., Linton, A.L.

Journal of Infectious Diseases (1972) in press.

Urinary Tract Symptomatology in General Practice

Lawson, D.H., Clarke, A., McFarlane, D., McAllister, T., Linton, A.L.

Journal of the Royal College of General Practitioners (1972) in press.

In addition, I have presented parts of the data to several scientific societies:

Screening for bacteriuria: theory and practise (by invitation)

Lawson, D.H.

Seminar: Department of Epidemiology, Columbia University, New York, U.S.A. 1972.

Analgesic consumption and renal function

Lawson, D.H.

Seminar: Department of Epidemiology, Columbia University, New York, U.S.A. 1972. (by invitation)

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U.S./Scottish Societies for Study of Infectious Diseases, Joint Meeting in Edinburgh, 1970.

Scottish Society for Experimental Medicine, Aberdeen 1970.

Royal College of Physicians of Canada, Ottawa 1971.

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Lawson, D.H., Linton, A.L.

Symposium Internacionale Sobre Antibiotics y Medicina Hospitalaria, Madrid, Spain 1968.

INTRODUCTION

Urinary tract infections are a common cause of morbidity in the community. They are a frequent source of symptoms leading to consultations with general practitioners and may often result in hospitalisation of the individual concerned. They may occur in all age groups and are particularly prevalent in the young adult female.

The renewed interest in urinary tract infections observed in the last decade has been due in part to the development of quantitative bacteriological techniques for examining urine specimens (Kass 1956) and in part to the development of regular dialysis therapy and renal transplantation.

With this increased interest has come the realisation that the relationship between symptomatic urinary tract infection on the one hand and chronic pyelonephritis on the other is considerably more complicated than was originally thought. In particular the studies of Kimmelstiel et al (1961) and of Angell et al (1968) indicate that a history of recurrent symptomatic urinary tract infection is relatively uncommon in patients with non-obstructive chronic pyelonephritis. Moreover, Leonard and his colleagues (1969) showed that bacteriuria was a common accompaniment of renal disorders irrespective of the aetiology. Thus the interrelationships between clinically apparent urinary tract infection, bacteriuria and impaired renal function are far from clear-cut and are currently receiving considerable attention.

Although patients with symptomatic urinary tract infections may rarely go on to develop frank renal failure, once renal failure from any cause has occurred, urinary tract infections are common (Montgomerie et al 1968). Thus to treat adequately all patients with urinary tract infection, requires an extensive knowledge both of the effects of antimicrobial agents on the kidney and of the effects of renal impairment on the body handling of these drugs.

Recently it has been suggested that there is a relationship between long-term analgesic use and the development of renal impairment (for extensive reviews of this topic see Shelley 1967; Abel 1971). The nature of this relationship is currently under investigation; however, it is possible either that analgesics are taken to relieve symptoms of an underlying chronic pyelonephritis or that these drugs may predispose each individual consuming them to chronic renal failure as a result of a direct nephrotoxic action or finally that there is a group of individuals with an enhanced susceptibility to renal damage caused by analgesic preparations.

Thus the management of patients with urinary tract infection can be considered under various headings:

(a) Prevention if possible, particularly in a selected population (e.g., pregnant patients).

(b) Management of the acute symptomatic episode when this occurs.

(c) Management of recurrent attacks in patients who have previously responded to therapy.

(d) Management of patients with moderate or severe renal failure complicated by, or associated with, urinary tract infection.

(e) Assessment of the general and nephrotoxic adverse effects of antibiotic therapy required by these patients.

(f) The investigation of possible complicating factors in relation to the episode of urinary tract infection.

The purpose of this thesis is to investigate certain aspects of the management of patients with urinary tract infections. The investigations undertaken were:

1. An epidemiologic survey of the benefits of routinely screening all pregnant patients for the presence of asymptomatic bacteriuria in the first trimester of pregnancy (Chapters 1 and 2).

2. A series of investigations into the efficacy of antibacterial therapy in the treatment of ambulatory patients with urinary tract infection (Chapters 3 and 4).

3. A search for possible relationships between recurrent urinary tract infection and latent diabetes mellitus (Chapter 5) and between prolonged analgesic consumption and impaired renal function (Chapter 6).

4. An assessment of the frequency of adverse reactions attributed by physicians to twenty commonly prescribed antibacterial agents (Chapter 7).

5. A study of the frequency with which tetracycline is associated with clinically significant rises in blood urea nitrogen levels (Chapter 8).

6. A series of investigations into the nephrotoxicity of a number of antibiotics in animals (Chapters 9 and 10).

7. A study of the pharmacokinetics of several antibiotics in patients with impaired renal function, together with a review of the current bibliography concerning antibacterial therapy in patients with impaired renal function (Chapters 11 and 12).

The major part of the work for this thesis was performed in Glasgow. However, the data discussed in Chapters 6, 7 and 8, were obtained and analysed during a visit to the Boston Collaborative Drug Surveillance Program of the Department of Medicine, Boston University, Massachusetts, U.S.A. In order to simplify the description of the methods used in these chapters, a detailed review of the aims, methods and techniques of this program follows.

BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM

The Boston Collaborative Drug Surveillance Program (B.C.D.S.P.) is the largest drug monitoring scheme in operation. Since 1966, it has monitored over 10,000 patients admitted to the medical wards of nine hospitals in three countries. A detailed description of the aims and methods of the program has been given by Jick et al (1970) and will be only briefly mentioned here.

The main aims of this program are:

1. To quantitate clinical drug usage.
2. Evaluate known or suspected drug effects.
3. Detect unsuspected drug effects.
4. Characterise groups of patients at particular risk of developing adverse drug reactions.

In order to fulfil these aims, nurse monitors are employed and, after training, are assigned to medical wards where they record data on consecutive admissions. The data recorded include routine demographic information, e.g., age, sex, race, height, weight, parity, marital status, etc., together with the results of certain laboratory tests, e.g., blood urea nitrogen (BUN) level on admission, serum protein, haptoglobin titre, and a detailed genetic grouping.

All drug starting and stopping dates are recorded on special forms by the monitor who also obtains, by interview with the attending physician,

the reasons for starting and stopping the drugs. At this time, the physician is also asked whether any adverse drug effects developed during therapy. Finally, his opinion on the efficacy of the drug is solicited. If an adverse event is reported, a more detailed review of the circumstances is undertaken and a judgment is made concerning the existence of a connection between the drug and the adverse reaction (-- in terms of "definite," "probable," "doubtful" or "don't know"). At the time of discharge, the physician is again interviewed to obtain information on the o-currence of certain adverse events, irrespective of whether or not they have been attributed to a specific drug. The data are then reviewed for accuracy and entered onto computer files. At regular intervals these are brought up to date and subjected to a variety of routine analyses. Detailed analyses can be undertaken depending on the nature of the problem under study.

For a more detailed reivew of the nature of the program and the type of information which can be obtained, see Jick et al (1970) and Lawson et al (1972).

While such a system can be readily used to quantify both clinical drug usage and known or suspected adverse reactions to drugs, the detection of previously unsuspected "reactions" or "events" presents considerable problems. Undoubtedly the most satisfactory method for accomplishing the latter aim would be to adopt the approach advocated by Finney (1965). In essence, this consists of collecting information on all "events" occurring in an individual patient during his stay in

hospital, together with data on diagnosis, drug exposure, routine demographic data and so on. Finally when the time comes to analyse the results, it is likely that a large number of "events" will be found to be related temporally with drug exposure and hence to be possibly "drug-related." However, this type of system, while admirable in theory, would be likely to produce "significant" results only after an enormous amount of data had been collected. In addition, the handling of such data would be difficult and extremely costly. As yet, no one has embarked on such a project in large scale, although the program organised by the Kaiser-Permanente Foundation in California has in part adhered to this scheme (Friedman et al 1971).

While this method is likely to be more conclusive and to receive more widespread acceptance in the medical community, its costs are likely to be prohibitively greater than the alternative approach adopted by the Boston Collaborative Drug Surveillance Program. Furthermore, the latter program has been in progress for six years and has already accumulated vast quantities of data. For these reasons the approach of this group to the detection of unsuspected events is of interest.

Detection of Unsuspected Adverse Effects of a Drug. In the data collected by the B.C.D.S.P., only events deemed to be drug-related are recorded. Thus if a patient develops an arrhythmia following a myocardial infarction, that event "arrhythmia" will only be recorded within the data if the attending physician felt that it was drug-related, as would happen, for example, if the arrhythmia was thought to be the result of digitalisation.

To look for unsuspected events then one has to look within that set of events deemed to be drug-attributed. For example, if drug X was recently released on to the market and if, unknown to manufacturers or to physicians, this drug was a potent cause of arrhythmias, this would be detected in the data by looking at the frequency of exposure to drug X in patients who developed digoxin-attributed arrhythmias and comparing this to the frequency of exposure to drug X in patients who did not develop drug-attributed arrhythmias. If a significantly greater proportion of patients in the digoxin-attributed arrhythmia group had received drug X as compared to those who did not have digoxin-attributed arrhythmia, then it could be concluded that either drug X alone or drug X in combination with digoxin may be the cause of the arrhythmias.

An example of the type of unsuspected drug reaction uncovered by this technique is the relation between ethacrynic acid given intravenously and the development of clinically significant gastro-intestinal bleeding (Slone et al 1969). Thus with economy of effort and minimised cost, unsuspected events may be detected by using a monitoring scheme based primarily on recording suspected events. This technique, however, has drawbacks, firstly due to the considerable difficulties involved in interpretation of the data, and secondly, due to the imprecise nature of the conclusions, that is, the difficulty of separating a primary unsuspected effect from that of an unsuspected interaction. It is likely that this distinction will not be made successfully with any regularity

by the B.C.D.S.P., but rather the initial results will require to be further rested in prospective trials.

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CHAPTER 1

SCREENING FOR BACTERIURIA IN PREGNANCY:

A PILOT STUDY

Asymptomatic bacteriuria in pregnancy has been widely studied since the observation by Kass (1959) that a large proportion of patients with bacteriuria in early pregnancy develop symptoms of acute urinary tract infection (U.T.I.) later in the pregnancy. In subsequent publications, he recorded a high prevalence of prematurity and foetal loss in bacteriuric patients and suggested that these complications could be reduced by treating the bacteriuria early in pregnancy (Kass, 1960, 1962; Norden and Kass 1968).

Little (1965) supported Kass in regarding urinary tract infection in pregnancy as a preventible disease indicating that detection and treatment of asymptomatic bacteriuria in early pregnancy leads to a drastic reduction in the subsequent incidence of this complication.

Kincaid-Smith and Bullen (1965) reported an increased frequency of acute pyelonephritis, prematurity, pre-eclampsia and perinatal loss in a series of 240 bacteriuric patients. Successful treatment of a group of these bacteriuric individuals reduced the incidence of acute urinary tract infection but not of the other complications of pregnancy. However, even urinary tract infection in pregnancy was not eradicated by treatment. These workers indicated that underlying renal disease was the cause both of the bacteriuria and of the increased incidence of prematurity, foetal loss and pre-eclampsia. As evidence for this they recorded a prevalence of radiological abnormalities of 51.4% in 148 bacteriuric patients, the majority of the radiographs being taken within six weeks of the end of pregnancy.

Other workers have remained unconvinced of the magnitude of the link between asymptomatic bacteriuria in early pregnancy and the subsequent appearance of these complications (Pinkerton et al 1965; Dixon and Brant 1967). In particular, Dixon and Brant noted that, in their series of 1309 patients, only 31.8% of those developing an acute urinary tract infection had bacteriuria on first screening.

In a recent extensive review of the topic, Whalley (1967) tabulated the results available to that date. The frequency of urinary tract infection in bacteriuric individuals varied from 45% to 63% and similarly the frequency in non-bacteriurics varied from 0 to 14%. Of particular interest was the wide variation in the frequency of this complication in non-bacteriuric individuals -- due, no doubt, at least in part to differences in the criteria used to assign an individual to such a group.

Kass (1962) considered significant bacteriuria to be present when over 10^5 organisms per ml of urine were present in at least two consecutive clean-catch mid-stream specimens of urine, and indicated that the reliability of the test increased with increasing numbers of samples taken. Unfortunately, the collection of so many specimens at a busy ante-natal clinic and the subsequent bacterial counting impose considerable burdens on both clinical and laboratory staff. For this reason, it was decided to carry out a preliminary survey of possible benefits to be obtained by routinely screening all pregnant patients appearing at the ante-natal clinics of the Queen Mother's Hospital in Glasgow. This survey was commenced in 1967.

PATIENTS AND METHODS

Patients admitted to the survey were all attending hospital for their first visit to the ante-natal clinic in that pregnancy. All were questioned regarding their age, parity, previous medical history including hypertensive episodes during pregnancy and any incident of urethral catheterisation. All were examined for pre-existing disease such as diabetes and, in addition, a record was made of their blood pressure. Patients with blood pressures exceeding 140/80 mm. of mercury after five minutes' rest were said to be hypertensive.

Following the history, a sample of urine was obtained by a standard technique. The vulva was cleaned with sterile water and a clean-catch mid-stream specimen was collected in a sterile honey-pot. This sample was divided into two and the aliquot to be cultured was stored at $4^{o}C$ until plating, which took place within three hours of collection. A modified Addis count (McGeachie and Kennedy 1963) was performed on the other sample of urine. The collection of all specimens was under the direct supervision of one nurse throughout the study.

A standard loop of urine was spread on nutrient agar and on MacConkey's agar and incubated overnight at $37^{o}C$. Specimens containing more than 10^5 organisms per ml were regarded as positive and colony counts were performed on specimens containing organisms in concentrations less than 10^5 per ml of urine. The antibiotic sensitivity of the organisms was determined using Oxoid Multodiscs.

The patients were divided into three groups on the basis of the findings on urine culture:

Group A - "Bacteriurics" - patients whose urine culture yielded bacteria in concentrations exceeding 10^5 organisms per ml.

Group B - "Doubtfuls" - patients whose urine culture yielded bacteria in concentrations between 10^4 and 10^5 organisms per ml.

Group C - "Non-bacteriurics" - patients whose urine culture yielded bacteria in concentrations of less than 10^4 organisms per ml.

All patients were followed in a routine manner, being treated by the obstetricians who were unaware of the results of the patients' urine culture. Patients were instructed where possible to return to the clinic should symptoms referable to the urinary tract develop.

After parturition, all patients were seen and all their records examined by Dr. A.W.F. Miller. A detailed history was taken of all complications arising during pregnancy, of the presence of symptoms of urinary tract infection (frequency, nocturia, pyrexia and loin pain) and of any foetal abnormalities which occurred. The resulting data was then transferred to punch-cards and detailed analyses carried out.

RESULTS

A total of 1160 patients were studied. Of these 54 (4.6%) had asymptomatic bacteriuria on screening and a further 89 (7.7%) had bacterial counts in the doubtful range. The remaining 1017 patients were non-bacteriuric.

Urinary tract infection (U.T.I.). The frequency of U.T.I. in the comparison groups is shown in Table 1.1. When this complication was defined clinically as the occurrence of frequency, dysuria, loin pain and pyrexia, 27.7% of Group A, 10.1% of Group B, and 6.9% of Group C developed U.T.I. If the definition was further restricted to include only those patients with such symptoms who also had bacteriuria detected at that time (i.e. over 10^5 organisms per ml of urine) there were 47 such individuals -- 16.6% of Group A, 6.7% of Group B, and 3.1% of Group C.

The relationship between the initial screening test and the subsequent development of urinary tract infection is emphasised in Table 1.2. The sensitivity of the screening test in predicting U.T.I. was 15.9% when this complication was defined clinically, and 19.1% when it was restricted to those cases with clinical and bacteriological evidence of infection. In addition, under these conditions the specificity of the test was 95.4% and 91.3%, respectively. [The sensitivity of the test was calculated as the percentage of patients with U.T.I. who had an initially positive screening test and the specificity as the percentage of patients without U.T.I. who had an initially negative screening test.]

Bacterial counts and hypertension. There were no significant differences between Groups A, B, and C, with respect to the history of previous hypertension or pre-eclampsia (Table 1.3). Elevation of blood pressure at the first clinic visit was commoner in Group A patients (15 of 54 = 27.8%) than in the other groups (16 of 89 = 18% and 162 of 1017 = 15.9%, respectively). However, the results fall short of statistical significance ($\chi^2_1 = 3.43$, $p > 0.05$ when comparing frequency in Group A with that of Group C). Similarly, hypertensive disorders of late pregnancy were commoner in patients in Group A (20.4%) than in the other Groups (15.7% and 11.1%, respectively), although again the results are not statistically significant.

Addis count and hypertension. Modified Addis counts were available for 966 patients (83%). The distribution of patients with recorded counts was similar in Groups A, B and C (46 of 54 = 85%; 74 of 89 = 83%; and 846 of 1017 = 83%, respectively).

Of the 966 patients, 90 (9.3%) had positive Addis counts (as defined by McGeachie and Kennedy 1963). The proportion of patients with positive counts was greatest in Group A (28 of 46 = 61%) and lower in Group B (16 of 74 = 22%) and Group C (46 of 846 = 5.5%).

The frequency of recorded hypertension at the first clinic visit was similar in those with a positive Addis count and those without (15.5% and 16.0%, respectively). However, a past history of hypertensive disorders of pregnancy was significantly commoner ($\chi^2_1 = 3.92$, $p < 0.05$) amongst those presenting with a positive Addis count (15 of 90 = 16.6%) than amongst those with a negative count (87 of 876 = 10%). Similarly, hypertensive

disorders occurred more frequently during the pregnancy in those with initially positive counts (20 of 90 = 22%) than in those with initially negative counts (119 of 876 = 13.7%) -- $\chi^2_1 = 4.94$, $p < 0.05$ -- Table 1.4.

Other complications. Premature labour, stillbirth, abortion, foetal abnormalities and maternal anaemia were rare in the present series and were not related to bacteriuria or to abnormal Addis counts.

Bacteriuria and previous catheterisation. Of the 1160 patients studied, 434 (37%) gave a history of urethral catheterisation. Of these 305 (70%) had been catheterised once, 81 (19%) twice and 48 (11%) more than twice. The distribution of the cases by initial bacterial counts was similar to control subjects who had not been catheterised (Table 1.5).

DISCUSSION

The results of the present survey are in substantial agreement with many of the previously published series (for review see Whalley 1967). Using a single specimen of urine for test purposes, the prevalence of bacteriuria in the studied population was 4.6%, and some 27.7% of these patients went on to develop urinary tract infection during the pregnancy. One disadvantage of using the single test for screening purposes was that the number of patients whose test yielded doubtful results was greater than would have been the case had multiple samples of urine been tested. However, this disadvantage was outweighed by the convenience and reduction in work load involved.

Nevertheless in one important area the pilot study results disagree with many previously published data. The current data show that some 3.1% to 6.9% of patients with initially negative screening tests developed urinary tract infection during pregnancy. This figure is considerably higher than that reported by Kass (1959), Little (1966), and Kincaid-Smith and Bullen (1965). However, the magnitude of this proportion is critical when assessing the value of routine screening for bacteriuria in the prevention of urinary tract infection in later pregnancy. The reasons for this will be explored in greater depth in Chapter 2. For the present, it should be emphasised that the discrepancy between the results found in the present survey and those of many previous workers is not due to the nature of the screening test employed, since the relevant patients all had negative screening tests on their first visit. The most likely cause for the observed discrepancy is that most workers in the field have failed to follow-up *all* patients who had an initially negative screening test. The commonest study plan has been to investigate all patients with proven bacteriuria together with an approximately equal number of "controls." (For example see Kincaid-Smith and Bullen 1965; McFadyen and Eykyn 1971) This plan is unsatisfactory since the proportion of controls expected to develop urinary tract infection is so small (0-6%) that with a total control group of 100 to 300 individuals, the accuracy of the observed proportion is low. That is, the 95% confidence limits around the observed frequency reported by these workers are very large. To reduce the size of these confidence limits many more "controls" than "cases" are required.

One of the critical factors in assessing the value of a screening test for bacteriuria of pregnancy is the sensitivity of the test in predicting the development of urinary tract infection. The sensitivity of the test used in this study was 15.9% to 19.1% depending upon the criteria used to define urinary tract infection. Comparable figures from some other series are 31.8% (Dixon and Brant 1967) 44% (Pinkerton et al 1965), 59% (Kincaid-Smith and Bullen 1965) and 67% (Little 1965). Thus at first sight there are wide discrepancies in the sensitivity of these tests for predicting urinary tract infection. This is partly explained by differences in definitions of bacteriuria and urinary tract infection, partly by the use of insufficiently large control groups and partly by using different follow-up techniques for "cases" (bacteriuric patients) and "controls" (non-bacteriurics). When these differences are taken into account it would appear that the sensitivity of this screening test is likely to lie between 15% and 35%, rather than 50% to 75%. Thus the conclusion reached by Beard and Roberts (1968) that acute pyelonephritis is unlikely to be eliminated as a disease of pregnancy by the detection and treatment of bacteriuria in early pregnancy, seems amply justified. For this reason, the pilot study was concluded after the 1160th patient had been investigated.

Certain other aspects of the study deserve mention. Kass (1962), Stuart et al (1965) and Kincaid-Smith and Bullen (1965) reported a higher prevalence of hypertension in bacteriuric patients than in controls. Others have failed to confirm this (Little 1966; Dixon and Brant 1967)

and the present study provides equivocal results. However this study revealed a positive association between hypertensive disorders of pregnancy and an abnormal modified Addis count. This finding supports that of Cross and Leather (1965) who recorded a high frequency of abnormal urinary white-cell excretion rates in 31 patients with hypertension in pregnancy. Since there is a correlation between urinary white-cell excretion rates and bacteriuria of pregnancy (Little 1966) the present observation may account for some of the variability in the observed results of other workers who have searched for a relationship between hypertension and bacteriuria while frequently omitting mention of the urinary white-cell excretion rate.

The present data provide evidence against the value of using a single, carefully collected mid-stream specimen of urine as an indicator of patients at high risk of developing urinary tract infection in pregnancy, and thereby hoping to eradicate this condition as a disease of pregnancy by prophylactic therapy of all those with a positive screening test.

Laboratory resources could be better employed following those patients who develop urinary tract infection in pregnancy once this infection has been successfully treated, since it is known that these patients are prone to sustain recurrences of infection during the pregnancy (Little and deWardener 1966).

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CHAPTER 2

SCREENING FOR BACTERIURIA:

A CRITICAL REAPPRAISAL

In the past ten years, a considerable amount of time and effort has been spent investigating both the frequency of occurrence and the outcome of asymptomatic bacteriuria in pregnancy. This topic has been reviewed on many occasions, notably by Whalley (1967) and by Beard and Roberts (1968). Initial reports suggested that the detection and treatment of asymptomatic bacteriuria could lead to the virtual eradication of urinary tract infection in pregnancy (Kass 1960; Little 1965). This claim has been challenged by several groups who have noted that less than 50% of patients developing urinary tract infection in pregnancy are detected by the initial screening procedure. (Pinkerton et al 1965; Dixon and Brant 1967; Lawson and Miller 1971). The main arguments against routinely screening all pregnant patients for asymptomatic bacteriuria revolve around the practical problems of collecting and analysing the large numbers of specimens obtained and around the value of the resulting data.

It is therefore apparent that some reassessment of the procedure is necessary before its use becomes widespread. In order to do so the answers to several questions must be considered: Firstly, how accurate are the tests used to detect bacteriuria in pregnant patients? Secondly, with what frequency do positive tests for bacteriuria occur in pregnancy? Thirdly, what proportion of patients with untreated bacteria go on to develop complications in that pregnancy; and fourthly, what proportion of patients without bacteriuria go on to develop the same complications? Knowing the answers to these questions leads to a further group of questions. For example: How "expensive" is the test in terms of time, personnel and materials involved? How serious is the main complication (urinary tract

infection) both in terms of maternal and fetal outcome? How difficult is the complication to treat successfully once it has arisen, and finally, is bacteriuria an indication of basic underlying renal disease? The answers to most of these questions are well known but are worth reconsidering here.

Accuracy of Screening Tests. Kass (1962) clearly demonstrated that the accuracy of determining the presence or absence of bacteriuria in a given patient depends upon the method of collecting the urine sample and the particular tests applied to it. Under ideal collection circumstances, with rapid and efficient bacteriological services, if the results of two consecutive specimens are in agreement, the accuracy of the screening test is 96%. That is to say, when a patient has bacteriuria the test will be positive 96 out of 100 times. With less stringent methods of collection and processing of the samples, the accuracy of the test may fall to 80% or less--particularly if the results are based only on a single sample of urine (Norden and Kass 1968). Chemical tests are considerably less accurate. Williams et al (1965) stated that the T.T.C. test was 87% accurate, however this was when it was compared to the conventional test. Thus if a single routine culture procedure is 80% reliable in detecting bacteriuria, the T.T.C. Test is 0.8 x 0.87 = approximately 0.70 or 70% reliable and as will be shown later, this is insufficient to be of value as a test for predicting the development of urinary tract infection in later pregnancy.

Bacteriuria and Urinary Tract Infection. Using the standard microbiological methods the frequency of a positive test for bacteriuria in the pregnant population in the first trimester of pregnancy varies in most series, between 3.6% and 7% (Beard and Roberts 1968). The frequency with which untreated bacteriuric patients develop urinary tract infection varies from 20% to 30%. However, the important fact when considering the accuracy of screening tests in predicting urinary tract infection in pregnancy is the frequency with which patients without demonstrable bacteriuria in the first trimester of pregnancy subsequently develop urinary tract infection. This frequency varies widely according to the series consulted (see Whalley 1967) and obviously depends upon differences in techniques, definitions of bacteriuria and urinary tract infection between the series, figures varying from 0 to 14% being reported.

Relationships between Screening Tests, Bacteriuria and Urinary Tract Infection. Knowing the accuracy of a screening test and the frequency of bacteriuria in a population, it is a simple matter to produce tables showing the distribution of cases of bacteriuria according to the results of the screening test. This can be done by multiplying together the probabilities of the two events (positive screeningtest and bacteriuria) happening on their own. Furthermore, knowing the rate at which patients with and patients without bacteriuria independently develop any complication of pregnancy, the numbers in each group can readily be calculated. An example of such a calculation is shown in Figure 2.1. The numbers in this figure are those expected, following the screening of 1,000 consecutive pregnant patients.

The screening test used, has a reliability of 95% and the frequency of positive tests in the populace under survey is 4.6%. The basis of the calculation for the development of urinary tract infection depends upon the assumption that 25% of untreated bacteriuric patients go on to develop urinary tract infection, whereas only 1% of nonbacteriuric patients do so (Savage et al 1967). It can be seen that the overall proportion of patients developing urinary tract infection is 3.2% of the population at risk (31.8 out of 1,000 patients). Further consideration of this table shows that if all patients with a positive screening test are treated, and assuming that all treated patients will not develop urinary tract infection in pregnancy, the reduction in numbers of patients developing urinary tract infection will be only one third (31.8 to 20.9). In practice even this reduction will not be attained since it is widely recognised that a proportion of patients with treated asymptomatic bacteriuria will nevertheless develop urinary tract infection during pregnancy (Sleigh et al 1964; Condie et al 1968). Furthermore, since three quarters of the patients with a positive screening test will not go on to develop urinary tract infection, they will have been exposed needlessly to the dangers of antibacterial therapy and in some instances, to the emergence of bacterial strains resistant to the therapeutic agent used (Williams and Smith 1970).

Tables similar to Figure 2.1 can be produced for a wide variety of variables. For example, the accuracy of the screening test may vary from 80% to 97.5%, the frequency of bacteriuria in the populace from 3.6% to 8%, and the occurrence of urinary tract infection in bacteriuric and non-bacteriuric patients may also vary widely. The results of several such calculations are shown in summary form in Tables 2.1 and 2.2.

The terms "sensitivity" and "specificity" used in these tables require careful definition. The sensitivity of a screening test in, for example, predicting urinary tract infection is obtained by calculating that percentage of all patients developing urinary tract infection, who had an initially positive screening test. Likewise, the specificity of a screening test in predicting urinary tract infection is obtained by calculating that percentage of patients not deveveloping urinary tract infection who had an initially negative screening test. A more detailed account of these terms and their applicability is given by Cochrane and Holland (1971) who observed that "sensitivity is inversely related to specificity, that is, few false positives = many false negatives." The reverse also holds true and this is particularly germane to the present issue, since the specificity of the screening test is high (Tables 2.1 and 2.2).

The relationship between the accuracy of the screening test and the prediction of subsequent urinary tract infection in pregnancy is shown in Figure 2.2, where it can be seen that the sensitivity increases as the accuracy of the test increases. This figure also emphasises that for a given degree of test accuracy, the sensitivity of the test increases as the proportion of persons with a negative screening test who develop urinary tract infection decreases. However, even under the most ideal conditions, the test sensitivity is only 54%--that is, out of every one hundred patients developing urinary tract infection, only 54 will have been predicted by the screening test, and of those, only three quarters (40 to 41 patients) are likely to have the infection prevented by treatment of the patient at the time of the initial screen (Condie et al 1968).

Given such figures, it is obvious that unless the condition under investigation is a serious one, this procedure does not justify the effort involved in its execution. In the case of urinary tract infection in pregnancy the condition is virtually always amenable to appropriate therapy and appears to be for all practical purposes without risk to the mother or child. In a survey of the annual reports of several maternity units in the west of Scotland over a period of five years, no reference to pyelonephritis or urinary tract infection in pregnancy was made--evidence that in practical terms this condition appears to be a benign one, at least during the course of the pregnancy.

Bacteriuria and Radiological Abnormalities. Although the above-stated calculations have been orientated to a consideration of urinary tract infection in pregnancy, it has been suggested that asymptomatic bacteriuria is an indication of basic underlying renal disease (Monzon et al 1963; Low et al 1964). Kincaid-Smith and Bullen (1965) demonstrated a 30% prevalence of major abnormalities of the intravenous pyelogram of bacteriuric patients some six weeks post-partum and suggested that, for this reason alone, screening for bacteriuria is indicated. This policy has been supported by Pinkerton et al (1971). However, the same arguments which apply to the prediction of urinary tract infection by the screening test must also apply to this indication with the additional constraints, firstly, that in none of the reported surveys has a control study been undertaken, and secondly, that the investigation of any underlying renal disease cannot be carried out until after completion of the pregnancy.

The situation has arisen that, on the basis of uncontrolled observations on the frequency of radiological changes in pregnant patients with bacteriuria, screening for bacteriuria is being advocated for all pregnant patients. This could only be justified after control studies are made. If the finding is shown to be real (i.e. if less than, say, 0.2% of non-bacteriuric women have major radiological abnormalities on intravenous pyelography) it has further to be shown that treatment of the bacteriuria is of value to the patient. Finally, were this the case, the question would then arise as to the reason for excluding persons not choosing to become pregnant, since the renal changes shown in bacteriuric patients are widely held to pre-date the pregnancy (Beard and Roberts 1968; Kincaid-Smith and Bullen 1965; Sidaway 1968).

In the best study of radiological changes in patients with bacteriuria yet reported, Gower et al (1968) noted a frequency of major radiological abnormalities in a series of 164 patients of only 11.6% and recorded that treatment of the bacteriuria during pregnancy appeared to have no effect upon the subsequent occurrence of radiological changes.

Long-term Follow-up of Bacteriurics. In the longest follow-up of patients with bacteriuria in pregnancy yet reported, Zinner and Kass (1971) observed that 38% (51 out of 134) of patients with bacteriuria during pregnancy were also bacteriuric when examined 14 years later, *regardless of treatment at the time of pregnancy.* The frequency of pyelographic changes of pyelonephritis in the previously bacteriuric patients was 29% (12 out of 41).

The only evidence of impaired renal function in this group of patients was a significantly lower mean urine osmolality in those who were bacteriuric at follow-up when compared to those who were not.

CONCLUSIONS

Beard and Roberts (1968) concluded that screening was justified on the grounds that it could lead to the prevention of about two thirds of the cases of acute pyelonephritis in pregnancy, that it could alert the obstetrician to the presence of surgically remediable renal lesions and finally, that it could identify those patients at risk from developing chronic pyelonephritis. The evidence presented here suggests that in the case of acute pyelonephritis of pregnancy the proportion of cases prevented will be considerably less than 66%. The evidence for a high proportion of patients with surgically remediable lesions being detected by the procedure has yet to be conclusively produced. Finally, as yet no one has demonstrated that patients with persistent bacteriuria go on to develop chronic pyelonephritis or even have significant deterioration in renal function. For these reasons, it seems that the case for routine screening of all pregnant patients for the presence of bacteriuria is not proven. Before costly, large scale epidemiologic surveys of pregnant women are undertaken, a test which has both a specificity and a sensitivity of over 90% is required.

Pending such a test it would seem reasonable to investigate those patients generally thought to constitute a "high risk" group, for example: firstly, those with previous histories of urinary tract infection in pregnancy; secondly, those with co-existing disease, e.g. diabetes; and thirdly, those with known renal abnormalities.

Finally, where any patient develops urinary tract infection during pregnancy, it would seem advisable to investigate such a patient after completion of pregnancy. Should persistent bacteriuria be detected, then intravenous pyelography and other urological examinations may be indicated some months later. However, it should be emphasised that the connection between symptomatic urinary tract infection and chronic, non-obstructive pyelonephritis, is as yet a tenuous one, since there are considerable difficulties in correctly diagnosing the latter condition (Heptinstall 1967). In a recent survey of 173 patients considered for regular dialysis therapy, Schecter et al (1971) stated that they were "unable to find a single case of unequivocal non-obstructive chronic pyelonephritis (excluding patients with uretero-vesical reflex) which progressed to end-stage renal failure in young or middle-aged patients." Thus they provide more evidence in support of the findings of Kimmelstiel et al (1961), who recorded only five cases of uraemic non-obstructive chronic pyelonephritis in a study of over 3,300 autopsies. In the survey cited above, Schecter et al concluded that their findings "suggested but did not prove that mass screening programs for the detection of asymptomatic bacteriuria may have little impact on the reduction of end-stage renal

disease in the young and middle-aged population." Taken in association with these findings, the results of the calculations presented here, strongly question the value of screening for bacteriuria in pregnancy.

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CHAPTER 3

URINARY TRACT SYMPTOMATOLOGY IN GENERAL PRACTICE

Considerable controversy exists as to the nature and outcome of the lesion in patients with acute urinary tract symptomatology. Several clinical studies have been undertaken to elucidate this problem, notably those of Fry et al (1962), Mond et al (1965) and Steensberg et al (1969). However, the issue remains in doubt.

Angell et al (1968) observed that many patients found at autopsy to have "active non-obstructive chronic pyelonephritis" had denied previous symptoms of urinary tract infection during life. It may be therefore that the current view of *all* cases of urinary tract infection as potentially serious conditions which might become established and later present as chronic pyelonephritis is incorrect (Editorial, Lancet 1968).

Waters (1969a) has advocated a detailed cohort study of such patients as one way to solve the problem. However, such a study will, of necessity, be a long-term undertaking. To assess the practical problems likely to be encountered in such a large study, a small pilot survey of two group practices in the Glasgow area was carried out. The present report deals with the findings on initial examination together with the results of a follow-up analysis on a group of patients admitted in the initial phase of the study.

PATIENTS AND METHODS

Patients selected for the survey were those who complained directly or on questioning of symptoms which led their practitioners to diagnose the presence of "urinary tract infection" (U.T.I.). Female patients

between the ages of 15 and 55 years were investigated from both practices and a separate group aged over 55 years were included from one. All pregnant patients, patients with diabetes mellitus and all males were excluded from the survey.

Following admission by the practitioner, each patient was interviewed by a trained nurse who collected certain demographic data on a standard form (Figure 3.1) and thereafter obtained a specimen of urine by a standard technique. The vulva was cleansed with sterile water and a clean-catch, mid-stream specimen of urine collected directly into a sterile honey-pot. Where the patient was unable to produce a specimen, she was instructed to return within a short period when a further attempt was made to collect the specimen. When a sample was obtained, it was divided into two, and placed in a refrigerated container in which it was transported to the laboratory within four hours.

At the outset of the trial a further sample collected at the beginning of micturition was studied, but this was subsequently discontinued.

When a satisfactory sample was obtained, the patient was then allocated randomly to one of three treatment groups, supplied by the nurse with the appropriate tablets and instructed in their use. The treatment groups were:

1. Sulphadimidine 1 g six-hourly for seven days.
2. Ampicillin 500 mg six hourly for seven days.

3. Sulphadimidine 1 g six-hourly for four days, after which the therapy could be changed, if necessary, to the drug indicated by the bacterial sensitivities reported to the practitioner. Where the patient was symptom-free the sulphadimidine was continued to a total of seven days.

Patients were given a full course of treatment even if the urine culture was sterile and irrespective of the sensitivity pattern of the organisms discovered except where indicated for those patients in Group 3.

All patients were seen again at 14 days after admission to the survey and a repeat sample obtained. They were instructed to return to the clinic if symptoms recurred and a group were reviewed at a period of one year after therapy commenced. All patients who failed to respond to therapy or who developed more than two recurrences within 18 months of admission to the study were referred to hospital for detailed investigation.

Urine Samples. One specimen was taken for culture in the laboratory where one of two technicians plated the samples using the technique described by McGeachie and Kennedy (1963) and also tested the sensitivities of the organisms to various antibacterial drugs using a U2 Oxoid Multodisc.

The second sample was centrifuged and a modified Addis count performed using the method of McGeachie and Kennedy (1963).

On the basis of the laboratory findings patients were allocated to one of four groups:

(A) Urine culture > 10^5 organisms/ml; Addis count > 10 white cells per counted field.

(B) Urine culture > 10^5 organisms/ml; Addis count < 10 white cells per counted field.

(C) Urine culture < 10^5 organisms/ml; Addis count > 10 white cells per counted field.

(D) Urine culture < 10^5 organisms/ml; Addis count < 10 white cells per counted field.

No attempt was made to estimate blood urea or serum creatinine levels, or to perform intravenous pyelography since it was felt that such procedures could lead to a substantial number of patients failing to return for follow-up examinations.

Patients were admitted to the study during an 18-month period commencing 1st October 1967 and a random sample was interviewed one year after admission.

RESULTS

A total of 343 patients were admitted to the survey. Of these, 201 were from practice R and 142 from practice S. The mean age of the 134 patients agend 15-55 years from practice R was 34.7 (SEM 0.6) years, that of the 67 patients aged over 55 years was 65.0 (SEM 0.4) years, and that of the 142 patients from practice S was 34.5 (SEM 0.6) years. Of the 343 patients, 79% were married, 15% single and 6% widowed. A total of 53.3% had one child or less, 27.6% had 2-3 children, and 19.1% had four or more children.

Urine analyses. The findings on initial examination of the urine are shown in Table 3.1, together with the therapy group to which the patients were allocated. There were no significant differences between the practices with respect to the findings on initial urine examination, nor was there an association between the number of children and the findings on urine examination.

Symptoms. The symptoms recorded on presentation are shown in Table 3.2. There were no significant differences between any of the groups with respect to these symptoms considered individually. In addition when combinations of two symptoms were considered together (loin pain and pyrexia; stress and nocturia; loin pain and dysuria) no significant differences were observed. In particular, patients in Group A could not be differentiated from the others by consideration of symptoms alone.

Social and past histories. Patients were compared with respect to social status, parity and a history of previous urinary tract symptomatology. There was no evidence that any of these factors considered alone played a significant role in determining the urinary findings on presentation. Previous symptoms of U.T.I. occurred in 49.3, 57.5, 47.7 and 43.1% of patients in Groups A to D, respectively.

Bacteriological findings. Bacteria isolated in concentrations of over 10^5 organisms per ml of urine are shown in Table 3.3, together with a comparison of organisms isolated from the two practices. There were no significant differences between the practices with respect to the types of organisms isolated ($\chi^2_5 = 4.1$, $p > 0.1$). Micrococci were isolated in 12% of cases (14 out of 118 positive cultures).

Urine microscopy. Patients were assigned to Groups A to D on the basis of a modified Addis count performed on a *mid-stream* specimen of urine together with the bacterial count. In addition, in 75 patients the results of the mid-stream specimen Addis count were compared with an early-stream specimen Addis count. This comparison revealed that, apart from a greater proportion of squames in the latter group, there were no significant differences between the two samples (Table 3.4). This procedure was therefore abandoned.

Effect of therapy. (Table 3.5) At the return visit 14 days after admission to the survey, 296 patients were interviewed (86.8%). The remaining patients were either lost to follow-up (33 patients) or were unable to attend for other reasons (14 patients). Of the 296, 50 (16.8%) either had persistent symptoms (37 patients) or persistent urinary abnormalities (32 patients). The distribution of patients with abnormal urine was 28% Group A; 16% Group B; 20% Group C and 36% Group D. Comparable figures for the entire series were 21%, 14%, 13%, and 52%, respectively. When these patients were given a course of therapy appropriate to the infecting organism, all responded satisfactorily.

The initial therapy was therefore successful in 246 patients (83.2%) The three treatment regimes appeared equally effective in relieving symptoms and in rendering the urine free of abnormalities. In particular, only nine patients (15%) of those allocated to treatment Group 3 were changed to another drug after four days (two received ampicillin and seven nitrofurantoin).

Reported recurrences. *(Table 3.6)* Of the original 343 patients, 310 (90%) were available for follow-up during the 18 months of the study currently under evaluation. The mean follow-up period was 11 months. The overall recurrence rate amongst these patients was 11.3% (35 individuals). Recurrences were reported significantly more often from patients in Group A than from those in the other groups ($\chi^2_1 = 8.46$, $p < 0.01$). There were no significant differences between Groups B, C and D in this respect, nor were there differences between patients in the two practices.

Recurrences on questioning. A group of 137 patients were reviewed at one year after admission to the survey. At the time of interview, seventeen patients (12.4%) had reported recurrence of symptoms to their practitioner. On questioning 38 patients admitted recurrences (27.7%)-- a significantly greater number than spontaneously reported them ($\chi^2_1 = 6.70$, $p < 0.05$). Further analysis of this group revealed that patients between the ages of 15 and 55 years reported about one third of the recurrences (eight out of 25 = 32%) and those over 55 years about two-thirds (nine out of 13 = 69%).

Of the 38 patients with recurrences, 21 (55%) had experienced epi·sodes of U.T.I. in the past whereas of the 99 without recurrences, nineteen (19.2%) had such episodes -- $\chi^2_1 = 16.6$, $p < 0.001$.

Analgesic consumption. The regular consumption of analgesic preparations was common; 15.3% (21 out of 137) of patients admitted regular consumption of over 10 analgesic tablets or powders per week and 8.7% (12 out of 137)

of patients gave histories of consuming analgesics in excess of 1 kg of salicylates or phenacetin or codeine in their life-time. The drugs most commonly taken were aspirin (in various proprietary preparations), Askit powders, compound codeine tablets and paracetamol. Of the 21 regular analgesic consumers, 14 had no abnormality in the initial urine sample, and the remainder had abnormal Addis counts and infected urine.

Referral to hospital. Only eight of the 343 patients in the study were referred to hospital (2.7%). Details of these patients are appended (Case Reports 3i - 3viii). Of the eight patients, three had persistent frank U.T.I. (Group A), two had persistently negative urine examination (Group D) and the remaining patients had chronic cystitis (1 patient), malabsorption syndrome (1 patient), systemic lupus erythematosus (1 patient).

Comparison of practices. The observed incidence of urinary tract symptoms was over twice as great in one practice than in the other--a finding which was consistent at all ages other than the 20 to 29 year old group, where the difference was not so marked (Table 3.7).

When incidence rates were calculated per 1000 patients at risk per annum, the differences between the two practices become quite apparent, the overall incidence rate being 35.1 per 1000 patients per annum in practice R and 76.2 per 1000 patients per annum in practice S (Table 3.8).

Because of this disparity in the incidence rates between the practices several other (potentially confounding) factors were investigated. In particular the social grading of the patients in the two practices was

investigated and found to be similar to each other (Table 3.9). Moreover, when this social grading was compared with that of the general female population of Glasgow city in 1961 (the most recent full census figures available) there was a tendency for the patients to aggregate in the lower social grades.

DISCUSSION

Pyelonephritis is a term which has come to be applied loosely to a wide variety of apparently different conditions (Jackson et al 1962) and so much confusion has been caused by failure to define the exact terms used when describing patients with urinary tract symptomatology (Editorial Lancet 1968). For this reason, no rigid definitions have been applied to patients in this study.

In British general practice some 12 to 13 consultations per 1,000 concern patients with urinary tract symptoms and bacteriuria (Fry et al 1962; Milne et al 1969). In Denmark some 34 consultations per 1,000 concern patients with urninary tract symptoms alone, irrespective of the presence or absence of bacteriuria (Steensberg et al 1969). In the present study 33 patients per 1,000 consulted their practitioners on account of urinary tract symptoms from one practice and 82 per 1,000 from the other. This highly significant difference ($p < 0.001$) between the two practices could be due to:

(a) failure to report about half of the cases in practice R - an unlikely event.

(b) overenthusiastic reporting of cases from practice S - an equally unlikely event since under those circumstances a preference for certain symptoms should have been observed from this group.

(c) a true difference between the practices. Several possible differences were considered and two seem likely to be significant. Practice R serves an area of considerably higher social status than practice S, yet the social grading of patients was similar in the two groups of patients considered here. Unfortunately, the exact social grading of patients in both practices was not available, however, it is the impression of both practitioners and myself that the social grading of patients in this study was similar to the overall grading of practice S and distinctly lower than that of practice R. While this data is merely "impressionistic" it raises the possibility of either a higher prevalence of U.T.I. in the lower social classes or a greater tendency to report such symptoms by these groups. Finally, the physicians in practice R were all male and those in practice S all female, a possible source of variability in the proportion of symptomatic patients who were willing to discuss their symptoms with their practitioners.

Although the prevalence of urinary tract symptomatology is higher than that previously reported in Britain, Waters et al (1970) recorded that 48% of an asymptomatic group of females drawn randomly from a general population, gave a history of dysuria. In this study some 22% of those interviewed had experienced dysuria in the year preceeding the

survey (Waters 1969b). Other workers have suggested that only some 40% of patients with urinary tract symptoms actually consult their practitioners about them (Danish National Morbidity Survey 1960). It would therefore seem that previous general practitioner surveys have underestimated the size of the problem of urinary tract symptomatology usually be excluding from analysis (or analysing separately) the 30-50% of patients who do not have bacteriuria at the time of the symptoms (Fry et al 1962; Gallacher et al 1965).

The present study confirms the findings of Mond et al (1965) and Steensberg et al (1969) that the analysis of presenting symptoms does not help to select those with bacteriuria from those without. However, the use of a modified Addis count together with a bacterial count has proven of value in detecting patients with the highest risk of recurrences. This may be of help if the data presented by Little and deWardener (1966) is considered. These workers suggested that all patients with a history of acute loin pain, pyrexia and infected urine should be examined at short (undefined) intervals to detect and treat recurrences early. However, the majority of patients with recurrences in the present study were apyrexial on presentation and most of those who were pyrexial did not have recurrences during the study.

Moore et al (1965) claimed to be able to differentiate patients with lower urethral disease from those with infection occurring at or above the bladder, by means of a differential urethro-vesical count. Using a modification of their technique, the present investigation failed to lend support to this observation.

Organisms other than *E. coli* can cause U.T.I. (Mitchell 1964; Stamey et al 1965; Kincaid-Smith 1965; McGeachie 1966; McFayden and Eykyn 1968; Mabeck 1969; McAllister et al 1971). In the present study 64% of bacteria isolated from the urines were *E. coli*, the remainder being staph albus, proteus mirabilis and micrococci. This data confirms the observation by Mabeck (1969) of a high prevalence of staphylococcal U.T.I.

The proportion of patients with micrococci in high concentrations (12%) is an index of the inherent error of accepting the result of a single mid-stream specimen before treatment. It is likely that these are "false-positives" which would have been sterile on culturing a second specimen, however it is impractical for a practitioner to repeat cultures before commencing therapy and so such patients have been classified in Groups A-B in this study.

The clinical effectiveness of sulphadimidine was striking. This drug was as effective as ampicillin in therapy of such patients. Sixteen patients received sulphadimidine despite a later bacteriology report of sulphadimidine resistance. Only four of these patients had recurrences on questioning--a rate similar to the overall rate in the study. This supports the observation of Harper and Cowston (1945) that sulphonamide sensitivities are of little value unless steps are taken to avoid antagonists in the medium and the true mean inhibitory concentration of drug to the organism is reported.

This study confirms the observations by Brocklehurst et al (1968) and McMillan and Linton (1968) that the prevalence of U.T.I. is approximately constant in the over 55-year olds. The condition did not appear more difficult to treat initially in these patients, but the recurrence rate was higher than in the younger age groups.

The prevalence of analgesic abuse in the present patients is high. McMillan et al (1968) reported that 14.2% of patients attending a renal clinic with chronic pyelonephritis abused analgesics and Murray et al (1970) observed that 8.8% of a group of psychiatric patients did so. However, until the true prevalence of analgesic consumption in the community from which these patients were drawn is known, the relevance of these figures must remain in doubt. Nevertheless, it would seem prudent to question all patients with urinary tract symptoms regarding their consumption of analgesics since there is some evidence that these drugs may be associated with impaired renal function which can be readily halted if analgesic intake ceases (Bell et al 1969; Murray et al 1971).

These data suggest that it is reasonable to perform routine bacteriology and Addis counts on all patients with symptoms of U.T.I. presenting to a general practitioner in order to select a group at particular risk of developing recurrences after therapy. This, however, is the only indication for these examinations since some 90% respond adequately to the initial therapy and of those who do not, the majority continue to have symptoms of U.T.I. Thus the taking of an initial M.S.U. and Addis count from patients with urinary tract symptomatology has value mainly in predicting recurrence rates and will not materially affect the outcome of the presenting episode.

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CHAPTER 4

EXTENDED THERAPY IN THE TREATMENT OF ESTABLISHED URINARY TRACT INFECTION

In the past decade increasing interest has been shown in the management of urinary tract infections. Despite this, controversy still exists as to the value of prolonged therapy in preventing occurrence of these infections once they become established. Orsten (1962) reported a beneficial effect with long-term therapy as did Murdoch et al (1968), but others notably Turck et al (1962), Campanacci et al (1963), Little and deWardener (1966) and Bengtsson et al (1967) have failed to confirm this finding.

The present investigation was undertaken to assess the benefits of a three-month course of therapy given to patients with established urinary tract infection. Treatment was undertaken as an outpatient and the patients were given a three-month course of the antibacterial agent to which the organism responsible for the urinary tract infection was sensitive. Patients who failed to respond to therapy or whose infection returned after treatment were treated with a further three-month course of the trimethoprim-sulphonamide combination "Septrin" (Burroughs-Wellcome). This combination is known to attain both therapeutic tissue levels and a high urine concentration. It is effective against all gram-negative organisms occurring in the urine except pseudomonads (Darrell et al 1968; Bushby 1969). The minimum inhibitory concentration of the drug is considerably lower than that of sulphonamides alone and the effect is bactericidal rather than bacteriostatic.

PATIENTS AND METHODS

All patients were referred to the Renal Clinic by their practitioners because of recurrent urinary tract symptoms which had either failed to respond to short courses of antibiotics or relapsed after therapy was stopped. Mid-stream speimens of urine were collected from the patients weekly for three weeks, using the method cited by Kincaid-Smith and Fairley (1967). A quantitative bacterial count with a modified Addis count (McGeachie and Kennedy 1963) was performed on each specimen. The patient was said to have a urinary tract infection if on each of the three visits the same bacteriae were present in concentrations exceeding 10^5 organisms per ml of urine and the modified Addis count was positive. At the same time the in-vitro drug sensitivity of each organism was obtained using a standard disc technique.

Blood urea estimations were carried out on all patients and an intravenous pyelogram (I.V.P.) was performed where no contra-indications were present. The latter investigation was undertaken after the acute infection had settled.

All patients were given a three-month course of the antibacterial agent indicated by the sensitivity tests. The drugs used were sulphadimidine, nitrofurantoin, nalidixic acid and ampicillin.

If the patient failed to respond to the first drug given or if infection returned after stopping treatment, the therapy was recorded as a failure and the patient was reassessed prior to entering into the second part of the investigation.

In the first stage of the investigation no attempt was made to check regularly that the patients were in fact taking the prescribed drugs. During the second stage, that is if a patient failed to respond to the initial three months of therapy or if the infection returned, the discrepancy count method of Porter (1969) was adopted as a simple check on consumption of tablets.

Patients proceeding to the second part of the investigation were given a three-month course of the trimethoprim-sulphamethoxazole combination (Septrin--Burroughs Wellcome) in a dose of two tablets twice daily. (One tablet contains 80 mg trimethoprim and 400 mg sulphamethoxazole).

All patients were followed at regular intervals during therapy and for a prolonged period after therapy ceased.

RESULTS

Initial therapy. A total of 66 patients were studied for periods ranging from 12 to 72 months (mean follow-up - 26 months). The mean age of the patients was 46 years (range 17 to 79 years), and the female to male ratio was 4.5:1. The mean age of males was 45 years and of females 47 years. Patients were seen on average once every eight weeks.

On the basis of presenting I.V.P. and blood urea estimations they were divided into four groups:

(A) Normal I.V.P. and blood urea below 40 mg/100 ml - 27 patients

(B) Abnormal I.V.P. and blood urea below 40 mg/100 ml - 12 patients

(C) Abnormal I.V.P. and blood urea above 40 mg/100 ml - 15 patients (no history of excessive analgesic intake)

(D) Abnormal I.V.P. and blood urea above 40 mg/100 ml - 12 patients (history of excessive analgesic intake)

Groups C and D included three and two individuals, respectively, whose renal function did not permit intravenous pyelography. Excessive analgesic intake was defined arbitrarily as the ingestion of more than one kilogram salicylates or phenacetin in a life time (MacMillan et al 1968). The abnormalities noted on I.V.P. included calyceal clubbing - 28 patients, cortical scarring - 36 patients, dilated pelvic-calyceal system - 3 patients, and urinary calculi - 6 patients.

The reason for referral to the renal clinic is shown in Table 4.1 -- fifty-eight patients had recurrent urinary tract infections and the remaining eight were found to have recurrent infection although they had been referred because of other conditions. Nineteen patients had mixed infections, the most common organism being Escherichia coli (Table 4.2).

The overall effect of therapy is shown in Table 4.3. Three months after stopping therapy, 18 patients (27%) had infected urine and by six months after stopping therapy 25 patients (38%) had had further significant

bacteriuria. By 24 months, 37 patients (56%) had developed bacteriuria once again. Only one third of the patients followed up for 30 months had sterile urine throughout this period.

When the results were analysed by groups, the recurrence rate at twenty-four months in patients with normal I.V.P.s (Group A) was significantly lower -- 11 out of 27 patients = 41% -- than in patients with abnormal I.V.P.s (Groups B, C, D) -- 26 out of 39 patients = 66% -- ($\chi^2_1 = 4.33$, $p < 0.05$). The recurrence rates in Groups B, C, and D did not differ significantly one from the other, however, there was a tendency for patients in Groups B and D to fare better than those in Group C. Further studies will be required to adequately quantitate this difference between the groups.

Effect of trimethoprim-sulphisoxazole mixture. A total of 32 patients were admitted to this phase of the study - three males and 29 females. Their mean age was 44 years (range 17 to 78 years). The causative organisms were Escherichia coli 26 cases, proteus spp. in four cases and klebseillae in two cases. Two patients defaulted from the study, the remainder were seen monthly for six months after completion of therapy.

On the basis of the I.V.P., patients were divided into two groups:

Group E - normal I.V.P. - 15 patients

Group F - abnormal I.V.P. - 15 patients

(Table 4.4)

The abnormalities noted on I.V.P. were clubbed calyces - 10 patients (including eight with cortical scarring); renal calculi - 2 patients; hydronephrosis - 2 patients; and previous nephrectomy - 1 patient. Of the fifteen patients in Group E all had blood urea levels below 40 mg/100 ml and of the 15 in Group F, 12 had blood urea levels above 50 mg/100 ml.

Treatment had to be discontinued in the first week of the trial in eight patients out of the 30 studied -- 26.6% (95% confidence limits 10.8 - 42.4%). In four patients this was due to skin sensitivity and in four to severe gastrointestinal upset.

Six months after completing the three-month course of therapy, nine patients out of the remaining 22 (41%) had experienced a further episode of symptomatic urinary tract infection in association with bacteriuria. There was no evidence of a significant difference in recurrence rates between Groups E and F. Finally, the overall recurrence rate of 41% was similar to that found at the same time interval after therapy in the initial study (38%).

DISCUSSION

There is widespread pessimism about the results of prolonged anti-bacterial therapy in patients with urinary tract infection. Kennedy et al (1969) studying a group of female patients found to have urinary tract infection in hospital reported a recurrence rate of 53% at six months in 28 patients who had received short courses of appropriate therapy (five to ten days). Half of their patients were asymptomatic at the time of

initial therapy. Only three of their patients had elevated blood urea levels and the failure rate observed is somewhat higher than that noted in patients in Group A of the present study (the most comparable group).

Petersdorf and Turck (1967) reported a 75% failure rate in 48 patients who were known to suffer from chronic bacteriuria and who were given one to two week courses of ampicillin. This rate is considerably higher than that reported either in the present study or by Kennedy et al (1969).

Murdoch and his co-workers (1968) reported a 35% failure rate in forty-six patients who had previously failed to respond to short-term therapy. This group of patients is comparable to the present series and the recurrence rate is similar to that reported in Group A. Murdoch gave his patients 500 mg ampicillin nightly for one to two years and failure of therapy occurred in all cases during the time when the patients were presumed to be taking the antibacterial agent.

In a recent trial of a single daily dose of nitrofurantoin given at night to a group of patients with recurrent urinary tract infection, Bailey et al (1971) reported a significant reduction in the frequency of recurrences in the treated group when compared to control subjects. This study was reported after completion of the present investigation and its results apply only to patients with normal renal function since nitrofurantoin should be avoided in patients with even mild renal impairment.

Gower (1968) studied 81 patients with chronic renal infection and found the bacteriological relapse rate to be constant irrespectice of the length of therapy, whereas there was evidence of symptomatic improvement during continuous treatment. In addition, he found no evidence of progressive

impairment of renal function with succeeding episodes of infection.

Turck et al (1967) suggested that patients with recurrent urinary tract infections be grouped into those with relapsing infections (probably due to renal involvement) and those with reinfections (probably only bladder involvement). They felt that the former might respond to long-term therapy whereas the latter rarely does. This work has subsequently been confirmed by several independent groups of investigators. However, to discover if a patient is suffering from relapse or reinfection requires careful urine examination including full serological identification of the infecting organism. This is a time consuming task not suitable for use in a district hospital or laboratory. Moreover, it requires the patient to attend clinics regularly for periods of up to two to three months before a definite decision can be made regarding the nature of the recurrence (Turck and Petersdorf 1968).

Although no sero-typing could be undertaken in the present study, it is possible that the response to a three-month course of treatment is, in itself, a diagnostic as well as a therapeutic procedure. If this is so it may prove to be more economical to select patients who should be closely investigated by using their response to three-months therapy as a diagnostic criterion rather than deny such patients therapy during the initial three-month period.

Bengtsson (1967) reported that patients who have renal disease as a result of analgesic abuse tend to fare badly when suffering from superimposed urinary tract infections. In her series most patients had experienced

episodes of renal papillary necrosis. In the present study, there was no evidence of a difference between patients with impaired renal function with or without a history of excessive analgesic intake (Groups D and C, respectively).

To date several investigations into the effect of trimethoprim-sulphonamide combinations on urinary tract infection have been reported (Gruneberg and Kolbe 1969; Reeves et al 1969; Allison et al 1969; O'Grady et al 1969). However in the majority of cases, the follow-up period has been short (six weeks or less). Such a brief period is unsatisfactory as an indicator of the efficacy of a new drug in the treatment of established urinary tract infection since it has been shown frequently that almost any antibacterial agent to which the causative organism is sensitive will result in an initial period of relief of symptoms and sterilisation of urine. The results of the present investigation into the long-term efficacy of this combination are disappointing. One quarter of the patients had to stop the drug because of unwanted side effects, all of which developed in the first week of therapy. This is a considerably higher frequency than expected from previous studies (Allison et al 1969; Czonka and Knight 1967; Drew et al 1967) and it may not reflect the true rate, being rather a chance finding since the 95% confidence limits around the observed frequency varied from 10% to 42%. The recurrence rate in those who completed therapy was not significantly different from that observed to occur with other antibacterial agents.

Despite previously reported cases of leucopenia and thrombocytopenia after administration of trimethoprim in doses of 500 mg to 1500 mg per day (Drew et al 1967; Sourander and Werner 1967) no such adverse reactions were observed in the present study where the trimethoprim dosage was 320 mg per day. Similar negative findings have been reported by Allison et al (1969).

The present study of a large group of patients suffering from recurrent urinary tract infection which was refractory to previous short courses of antibacterial therapy indicates that the recurrence rate after a three month course of therapy with the indicated antibacterial agent is 38% at six months, and 61% at two years. This recurrence rate is somewhat lower than reported from other centres but the comparability of these series in terms of the type of patient included, the degree of renal damage involved, and many other factors is difficult to assess. The response to a three month-course of therapy was significantly better in those patients with normal intravenous pyelograms than in patients with abnormal pyelograms (most of whom also had elevated blood urea levels).

There was no evidence of a significantly better response to therapy with a trimethoprim-sulphonamide mixture than with ampicillin, sulphonamide or nitrofurantoin. The observed adverse reaction rate to the trimethoprim sulphonamide mixture was high-26.6%-although the 95% conficence limits of this observation were wide (10% to 42%).

In patients who do not experience adverse reactions to the drug, this mixture may have some advantages over conventional antibacterial therapy on the grounds of cost and convenience (twice daily administration). These advantages however may be outweighed by the fact that in renal failure the renal handling of the two constituents of this mixture are different (for detailed discussion see Chapter 12).

Finally, these results indicate the need for a large (and therefore multicentre) study into the effect of various treatment schedules in patients with recurrent urinary tract infection. All of the studies reported to date involve relatively small numbers of patients (usually less than 100) and therefore are of insufficient size to fully assess the effect of such variables as patient age, renal structural and functional abnormalities and previous history of childhood or pregnancy bacteriuria upon the outcome of treatment. In addition, because of interstudy variability in inclusion material, comparability of results has not been attained. In view of the impressive results claimed for a nightly tablet of nitrofurantoin (Bailey et al 1971), such a multicentre study might compare the effects of nightly nitrofurantoin, nalidixic acid, and sulphadimidine, with short and long-term courses of standard antimicrobial therapy and with, if possible, a placebo control group. Pending the results of such a trial, the present evidence suggest that patients with established urinary tract infection should be given 50 mg nitrofurantoin nightly if renal function is normal (as judged by blood urea levels below 40 mg/100 ml) and a three-month course of continuous sulphadimidine or other suitable antibacterial agent if renal function is abnormal.

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CHAPTER 5

GLUCOSE TOLERANCE IN PATIENTS WITH ESTABLISHED URINARY TRACT INFECTION

Urinary tract infection is a common condition in the community. Some 30 to 40 per 1,000 consultations with general practitioners are a result of symptoms due to this condition (see Chapter 3). Nevertheless its true prevalence is unknown, although it is commoner in women of childbearing age than in any other group.

Urinary tract infection is a frequent and often severe complication of diabetes mellitus. While it has been stated that such infections are more common in diabetics than in non-diabetics (Sharkey and Root 1935; Kass 1960), this may be a reflection of the increased frequency of catheterisation, of hospitalisation, or of physician awareness rather than a true increase in its prevalence in diabetics. Both Huvos and Rocha (1959) and Rengarts (1960) recorded similar rates of bacteriuria among hospitalised diabetic and non-diabetic patients. Moreover, Oseasohn et al (1962) found a low prevalence of bacteriuria in a group of post-partum diabetics. Nevertheless, the true frequency of bacteriuria and of urinary tract infection in the diabetic population at large is unknown.

Diabetes mellitus itself is a common condition. Several large population surveys have reported a prevalence of known diabetics in the community of 0.64% and of undiagnosed diabetics of 0.69%, giving a combined prevalence of 1.33% (Pyke 1968).

Thus, both diabetes and urinary tract infection frequently occur in the community. Unfortunately the exact relationship between them is ill-defined.

The present investigation was conducted to test the hypothesis that latent diabetes mellitus is commonly associated with recurrent urinary tract infection occurring in the absence of other "risk" factors such as analgesic consumption, obstruction to the urinary tract or vesico-ureteric reflex.

PATIENTS AND METHODS

A group of female patients referred to the Renal Clinic, Western Infirmary Glasgow, by their general practitioners for the investigation and treatment of recurrent episodes of urinary tract infection, were studied. All patients had evidence of urinary tract infection on or shortly after their first visit to the Clinic. Following investigation of the infection all responded to appropriate therapy and at the time of the present investigation were free of symptoms, had sterile urine, and were not taking regular antibacterial therapy. No patients were pregnant at the time of the study.

After an overnight fast, the patients were seen at the hospital and a standard glucose tolerance test was performed. A sample of venous blood was drawn on arrival to estimate fasting blood glucose level and thereafter the patients were given 100 grams glucose diluted with 400 ml water. Blood samples were taken for glucose estimations at 0, 30, 60, 90, 120 and 180 minutes after ingestion of the glucose. In addition, prior to the administration of the glucose, the patients were asked to provide a specimen of urine which was tested for glucose using both the Clinistix and Clinitest reactions (Ames Company). Further samples of

urine were obtained at 60, 120 and 240 minutes, respectively.

Blood glucose estimations were performed on venous blood samples to which had been added a small amount of sodium flouride. Samples were assayed on an Auto Analyzer using the Hoffmann ferricyanide method (Hoffmann 1937). Estimations of blood urea, serum creatinine and packed cell volume using the microhaematocrit method were made on further aliquots of the initial blood sample.

All patients were informed of the reason for the test and their consent obtained.

After the glucose tolerance test was completed and the results available for study, patients were questioned regarding the presence or absence of a family history of diabetes mellitus.

RESULTS

Glucose tolerance tests were performed on 15 patients. The average age of the patients was 33.4 years (range 16 to 53 years); all were female; mean presenting blood urea levels (±S.E.) were 24 ± 1.5 mg/100 ml; mean presenting serum creatinine levels were 0.8 ± 0.05 mg/100 ml and the mean packed cell volume was 35 ± 0.5%. All patients had sterile urine at the time of the investigation and were taking neither antibacterial therapy nor any analgesic preparations which might interfere with the Clinitest reaction.

Of the 15 patients, three (20%) had abnormalities detectable on intravenous pyelography (I.V.P.)--one had cortical scarring and all three had evidence of calyceal clubbing.

The results of the glucose tolerance test are shown in Table 5.1 and Figure 5.1. In no case was there evidence of an abnormality in glucose handling. In particular, all patients had fasting blood sugar levels within normal limits and no patient showed evidence of either "diabetic" or "lag" curves. Glycosuria was not demonstrated in any patient.

No patient in this study had a family history of diabetes mellitus which was sufficient in severity to require therapy. However, one patient (a 34-year old mother of two children) reported that her maternal grandfather and her mother's sister had both been said to have glycosuria by their general practitioners.

DISCUSSION

In fifteen patients with recurrent urinary tract infection, no case of latent or asymptomatic diabetes mellitus was detected using the standard glucose tolerance test. This result was not entirely unsuspected, since Monod (1942) showed that the growth rate of coliform bacilli in synthetic media is dependent on glucose concentrations only up to 25 mg/litre, while Fine (1965) recorded that the glucose concentration in the urine of normal subjects is well above this, being over 60 mg/litre. Moreover, Asscher et al (1968) reported that increasing the concentration of glucose in the

urine from 28 mg/l to 1 g/l made a relatively small contribution to the total numbers of viable organisms growing in a culture medium of human urine. Thus even the presence of extremely high concentrations of glucose in the urine makes a minimal contribution to the number of organisms present in the urine once this becomes infected.

However, factors other than glycosuria may affect the prevalence of bacteriuria in diabetic patients. Hyperglycaemia can cause a reduction in leucocyte mobility (Brayton et al 1970) and leucocyte function itself may be impaired under those circumstances (Thornton 1971). These factors may separately or in combination lead to a reduction in host antibacterial defenses and so an increase in the prevalence of all infections including bacteriuria.

Nevertheless, the data presented provide no evidence that patients with recurrent urinary tract infection frequently suffer from latent diabetes mellitus.

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CHAPTER 6

ANALGESIC CONSUMPTION AND RENAL DISEASE

During the past twenty years, a large volume of literature has accumulated on the relationship between long-term analgesic consumption and impaired renal function. The topic has been the subject of two extensive review articles (Shelley 1967; Abel 1971), and has aroused considerable public interest and controversy. A critical question, as yet unanswered, concerns whether continuous analgesic ingestion per se leads to a progressive deterioration of renal function in all patients.

Unfortunately, most of the published studies on this subject have lacked suitable controls, and therefore their interpretation is open to question. Where adequately controlled observations on hospitalised patients have been carried out, the existence of a cause and effect relationship has remained in some doubt (Sorensen 1966; Gault et al 1968).

The present report describes a further investigation into the possible association between regular analgesic consumption and impaired renal function, using data collected by the Boston Collaborative Drug Surveillance Program (BCDSP).

METHODS

The BCDSP uses nurse monitors who are provided with standardised self-coding data sheets and are assigned to medical wards where they record data on consecutive admissions. The data include patient characteristics, discharge diagnoses, details of all drugs administered

in hospital, and certain routine laboratory tests such as admission blood urea nitrogen (BUN) levels and urinalysis (Jick et al 1970). For the last three years of the study, a history of all medications taken in the three months prior to admission to hospital has been obtained routinely. For each drug taken by the patient during this time, a record is made of the frequency and duration of its consumption.

A medication history was obtained from 7,017 patients. Of these, 331 (4.7%) were excluded because of unknown BUN levels on admission and a further 279 (4.0%) because of an unknown frequency or duration of analgesic consumption. The remaining patients were divided into four groups:--Figure 6.1

Group A - Daily oral analgesic consumers.

Group B - Occasional (less than daily) analgesic consumers.

Group C - Patients taking drugs other than analgesics.

Group D - Patients who denied taking any medication.

For each of these groups, frequency distributions were obtained for age, sex, survival, first discharge diagnosis, blood urea nitrogen levels on admission, presence of proteinuria, and abnormalities of the urine cell counts.

Finally, the records of all patients admitted to hospital because of an adverse drug reaction were scanned to determine the frequency with which analgesic preparations had been implicated in the development of impaired renal function.

RESULTS

Patient Characteristics.

A total of 6,407 patients were reviewed. Their average age was 53 years, 36% were female, and 6.2% died while in the study. Four hundred and sixty-one patients (7.2%) were daily analgesic users (Group A); 2,438 (38%) were occasional analgesic users (Group B); 3,215 (50.2%) used drugs other than analgesics (Group C); and 292 (4.6%) had taken no medications (Group D). The first recorded discharge diagnoses of these patients are shown in Table 6.1. Details of the ten commonest types of analgesics consumed are shown in Table 6.2.

Frequency of Analgesic Use.

(1) Relationship to Diagnosis (Table 6.3): A primary diagnosis of renal disease was given in 234 out of the 6,407 patients (3.7%). The frequency of renal disease was 4.5% in daily analgeisc users, 3.8% in occasional analgesic users, 3.4% in users of other drugs, and 3.8% in patients taking no drugs. The frequency of renal disease in daily analgesic users was not significantly greater than that in occasional analgesic users ($\chi^2_1 = 0.44$; $p > 0.5$) or in non-users ($\chi^2_1 = 1.14$; $p > 0.2$).

(2) Relationship to Renal Function: *Admission BUN levels* (Table 6.4). The unadjusted mean admission BUN levels in Groups A to D were similar (19.3, 19.5, 23.4, and 18.8 mg/100 ml, respectively). Stratification by age, sex, and survival was carried out since there were small differences between the groups with respect to each of these factors. In addition, the data were stratified by discharge diagnosis, since there was a greater

proportion of patients with musculo-skeletal disorders among the daily users of analgesics (11.5%) than among the other groups (2.8%, 1.9%, and 1.4%, respectively). Within each stratum there were no significant differences in mean BUN levels between the four groups.

Urine analysis. A record of urine protein concentration was available for 6,052 patients (95%). Proteinuria was detected in 29.4% of those in Group A, 32.1% in Group B, 34.4% in Group C, and 41.1% in Group D. Heavy proteinuria (3-4+ albustix) was noted in 4.3%, 4.6%, and 7.6% of these groups, respectively (Table 6.5).

A record of the findings on microscopic examination of urine was available for 5,986 patients (92.5%). White cells were reported in 21.1%, 16.7%, 21.4%, and 26.6% of Groups A to D, respectively. Red cells and/or casts were recorded in 3%, 3.7%, 4.1% and 4.8% of the Groups (Table 6.6). Thus, there were no statistically significant differences between the four groups with respect to either urine protein concentration or the findings on microscopic examination of the urine.

Duration of Analgesic Use.

(1) Daily Consumers: Of the 461 daily analgesic consumers, 259 (56.2%) admitted taking them for up to one year, 100 (21.7%) for periods of one to six years, and 102 (22.1%) for periods in excess of six years. These three groups were compared with respect to admission BUN levels and results of the urine analyses.

Admission BUN level. The unadjusted mean admission BUN levels in the three groups were 18.9, 19.3, and 20.2 mg/100 ml, respectively (Table 6.7).

Since there were differences between these groups with respect to age and sex, the data were stratified by these factors. In each stratum the mean BUN levels for the three groups were similar.

Urine analysis. A record of urine protein concentration was available for 438 patients (95%). Proteinuria was detected in 28.5%, 28.7% and 32.6% and heavy proteinuria was reported in 4.8%, 3.2%, and 4.2% of the groups, respectively (Table 6.8). Thus, there were no significant differences by duration of daily analgesic consumption with respect to urine protein concentration.

A record of the findings on microscopic examination of urine was available for 432 patients (93.5%). White cells were reported in 16.2%, 21.1%, and 33.7% of these groups, respectively (Table 6.9). Since there were differences between the groups with respect to age and sex, the data were stratified by these factors. The proportions of patients with white cells reported in their urine were similar in each stratum except in the case of females over the age of 60 years, in whom the proportions increased with increasing duration of analgesic use ($\chi^2_2 = 22.8$; $p < 0.01$) (Table 6.10). Red cells and/or casts were reported in 2.8%, 4.4% and 2.1% of these groups, respectively. Thus, there were no statistically significant differences between the three groups with respect to urine protein concentration or the findings on microscopic examination of the urine except in the case of the urine white cell concentrations in females over the age of 60 years.

(2) Occasional Consumers: Of the 2,438 occasional analgesic consumers, 386 (15.8%) admitted taking them for up to one year, 315 (12.9%) for periods of one to six years, and 1,737 (71.3%) for periods in excess of six years. These three groups were compared with respect to admission BUN levels and results of urine analysis.

Admission BUN level. The unadjusted mean admission BUN levels in these three groups were 20.4, 20.2, and 19.2 mg/100 ml respectively (Table 6.11). Since there were differences between these groups with respect to age and sex, the data were stratified by these factors. In each stratum the mean BUN levels for the three groups were similar.

Urine analysis. A record of urine protein concentration was available for 2,317 patients (95%). Proteinuria was detected in 32.1%, 30.4%, and 32.4%, and heavy proteinuria was reported in 5.7%, 4.4%, and 4.4%, respectively (Table 6.12).

A record of the findings on microscopic examination of urine was available for 2,288 patients (94%). White cells were reported in 14.8%, 12.9%, and 17.7% of these groups respectively. Red cells and/or casts were reported in 3.6%, 4.6%, and 3.6% of these groups, respectively (Table 6.13). Thus, there were no significant differences by duration of occasional analgesic consumption with respect to urine protein concentration, or the findings on microscopic examination of the urine.

Effect of Missing Values.

From the original 7,017 patients, 331 were excluded because of unknown BUN levels on admission (4.7%) and 279 were excluded because of

unknown frequency or duration of analgesic consumption (4.0%). Thus, 8.7% of the original population were excluded from detailed analyses (Figure 6.1). To insure that the final conclusions of the investigation could not be influenced by these exclusions, the distribution of patients with unknown BUN values with respect to medication history was obtained and compared with that of the remaining patients (Table 6.14). There were no significant differences between these groups with respect to medication history.

In addition, the mean BUN level of patients excluded because of unknown details of analgesic consumption (20.7 ± 1.2 mg/100 ml) was compared to that of the remaining patients (19.5 ± 0.4 mg/100 ml). The BUN values from these two groups did not differ significantly ($p > 0.2$).

Admission due to Adverse Drug Reactions.

Of the 11,526 patients admitted to the monitored hospitals, 829 (7.2%) were admitted because of a suspected adverse drug reaction. In eight patients (0.07%) the admission was a result of renal disease attributed by the attending physicans to analgesic preparations. Of these eight patients, six had consumed preparations containing mixtures of aspirin and phenacetin, and two had taken aspirin-containing preparations. The mean age of these patients was 52 years, their mean admission BUN level was 98 mg/100 ml, and mean presenting hematocrit was 27%. Details of each individual are given in Table 6.15.

DISCUSSION

Data on 6,407 consecutive medical patients admitted to hospital have been analysed to assess the relationship between regular analgesic ingestion and impaired renal function. A history of daily oral analgesic use was given by 461 patients (7.2%).

The present data indicate that the frequency of renal damage as measured by a discharge diagnosis of renal disease, elevated presenting blood urea nitrogen levels, the presence of proteinuria, or abnormalities in the microscopic examination of the urine was not significantly higher among regular analgesic consumers, when compared with occasional analgesic consumers or patients who denied analgesic consumption. Furthermore, there was no evidence of a relationship between increasing duration of analgesic consumption and these indices of renal disease, except in the case of females over the age of 60 years. In such patients, there was a relationship between increasing duration of daily analgesic consumption and the demonstration of white cells in the urine. However, in view of the large number of comparisons made in the present analysis, it is possible that this finding -- the only positive one in the present investigation -- could have occurred by chance. Moreover, even if it did not, the possibility remains that the analgesics were taken by these patients for minor symptoms related to their urinary tract. The data provide no evidence of a causal association between analgesic consumption and the subsequent development of impaired renal function.

While the data did not show a difference in the frequency of renal damage in patients taking salicylate-containing analgesics and those taking phenacetin-containing analgesics, the number of patients in the latter group was small, and therefore, it remains possible that such a difference could exist.

The result of the present study is consistent with data obtained by Sorensen (1966) who examined over 2,000 consecutive patients seen in a variety of hospitals in Copenhagen, and failed to show a difference in creatinine clearance between consumers and non-consumers of analgesic preparations.

By contrast, Dubach et al (1968) in a preliminary review of a large, prospective study of Swiss watch workers, reported that a history of urinary tract illness was more frequent in females who consumed analgesics regularly than in those who consumed them occasionally or not at all. They further showed that females with metabolites of phenacetin in their urine at the time of the study had a greater prevalence of bacteriuria, hematuria, proteinuria, and elevated serum creatinine levels than those who were free of such metabolites. No such relationships were observed in males, raising the possibility that the analgesics were taken to relieve mild symptoms of urinary tract disorders rather than producing them. Although the data reported by Dubach et al were of a cross-sectional nature, this study continues and it is likely that these workers will be able to report upon the incidence of renal impairment and urinary tract illness both among analgesic consumers and among controls in the future.

Possible explanations for the different results found by many other workers (see review by Abel) are firstly, a failure to take into account the effects of age on any postulated association between prolonged analgesic intake and impairment of renal function; secondly, absence of a control population not consuming analgesics; and thirdly, differences in the types of analgesics available as over-the-counter preparations.

A further possibility which could account for a relationship between analgesic consumption and renal disease is that there is a small group of patients at particular risk of developing renal impairment following exposure to oral analgesics. In support of this, Prescott (1965) observed that only a fraction of normal adults showed evidence of nephrotoxicity as determined by renal tubular cell excretion following acute administration of phenacetin. The present data do not provide evidence for or against this hypothesis, and indeed, are consistent with the possibility that a small proportion of long-term analgesic consumers develop impaired renal function as a result of this habit. In fact, in the monitored wards eight patients (0.07% of admissions) had renal disease attributed by the attending physicians to long-term analgesic use.

In conclusion, whatever the true relationship between analgesic consumption and renal impairment may be, this study of a large series of hospitalised patients provides no evidence of gradual deterioration in renal function with increasing duration of analgesic consumption.

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CHAPTER 7

ADVERSE REACTION RATES TO

COMMONLY ADMINISTERED ANTIBIOTICS

INTRODUCTION

As already described (pp5-9), the Boston Collaborative Drug Surveillance Program (BCDSP) prospectively collects data on drug exposure, adverse reactions, drug efficacy, etc., on consecutive admissions to medical wards in three countries. The participating hospitals are Massachusetts General Hospital, Boston Veterans Administration Hospital, Boston City Hospital, Peter Bent Brigham Hospital, and Lemuel Shattuck Hospital in Boston, Massachusetts; the Roger Williams Hospital at Brown University, Providence, Rhode Island; St. Joseph's and Westminster Hospitals in London, Ontario, Canada; and Hadassah Hospital in Jerusalem, Israel.

The data are collected by nurse monitors who review all patients admitted to their wards in the above hospitals. Following review and editing procedures, the data are then placed on magnetic tape files for random access at a later date.

For the present purpose, data pertaining to a group of antibiotics were reviewed to give information on the relative frequencies with which each drug was administered in the monitored wards, the rates of adverse reactions occurring in patients receiving these antibiotics, and the frequencies of life-threatening adverse reactions to each antibiotic.

METHODS

The computer was programmed to give details of patients exposed to each antibiotic prescribed, the number who develop adverse reactions attributed by attending physicians to these antibiotics, the hospital number

of each patient developing a reaction, and the proportion who developed life-threatening adverse reactions. Thereafter, additional information was obtained by scrutinizing the patient's abbreviated record stored on microfilm in Boston or, when necessary, the full hospital record of a particular patient was obtained from the participating hospital.

RESULTS

Details of the number of patients exposed to the twenty antibacterial agents used most frequently in the monitored hospitals are given in Table 7.1, together with the frequency of adverse reactions to each drug and a note of the type of reaction encountered (Tables 7.1, 7.2).

Penicillins: Over 1,700 drug orders for the penicillins have been monitored, 590 patients receiving aqueous penicillin, 592 receiving procaine penicillin, 299 receiving penicillin G (ordered in this form rather than aqueous penicillin), and 237 receiving penicillin V. The adverse reaction rates to these preparations are low ranging from 2.9 - 4.6% of patients exposed. Life-threatening adverse reactions occurred only rarely with these drugs. The major adverse events attributed to the penicillins are allergic reactions (skin rashes, urticaria, and pruritus) and complications of injection (usually, pain or haematomata). In addition, two patients receiving high doses of penicillin G for the treatment of septicaemia and peritonitis developed convulsions (Case Reports 7i and 7ii). Finally, one patient with pneumococcal pneumonia and congestive cardiac failure developed hyperkalemia following therapy with penicillin (Case Report 7iii).

Semisynthetic Penicillins: The most commonly administered antibiotic in this large series of patients is ampicillin which was given to 1,322 of the 10,209 monitored patients (13%). The adverse reaction rate observed with this drug was 11.1% -- the predominant reaction being skin rash which accounted for 58% (85/147) of all observed reactions attributed to ampicillin. The major number of remaining reactions were either nausea and diarrhea (45 patients) or superinfection (12 patients).

The other commonly used semisynthetic penicillin is oxacillin which was given to 228 patients. The observed adverse reaction rate was 6.6%. The major adverse reactions occurring were convulsions which developed in two patients, one of whom also received penicillin G (Case Reports 7iv and 7v).

Cephalosporins: The preeminent cephalosporin in the United States is cephalothin. Cephaloridine is rarely used and was only given to 69 patients in the present series of whom 60 were treated in Israel (Hadassah Hospital, Jerusalem).

Of the 530 patients who received cephalothin, 64 (12.1%) developed an adverse reaction and of those half (32 patients) complained of injection complications (pain at injection site, haematomata, and/or transient phlebitis). In addition to skin rashes observed in ten patients, two others developed jaundice attributed to the drug and eight sustained clinically significant superinfections. Three patients developed impaired renal function following administration of cephalothin, usually in combination with other nephrotoxic drugs (2 received kanamycin and 1 received polymixin B).

Aminoglycosides: Over 630 drug orders were made for streptomycin, kanamycin, and gentamycin -- the aminoglycosides given parenterally for the treatment of infection, and over 500 drug orders were made for neomycin and paromomycin -- the aminoglycosides given orally to sterilize the bowel (usually in patients with cirrhosis).

a) Streptomycin group. Observed adverse reaction rates varied from 3.6% for streptomycin to 14.3% for kanamycin. In particular, the low rate observed with streptomycin is noteworthy. Two patients developed psychosis while taking this drug along with isoniazid for the treatment of tuberculosis. (It is, however, likely that the isoniazid was responsible for this adverse event rather than the streptomycin.) Tinnitus and deafness were observed in eight patients receiving drugs in this group.

Observed rises in blood urea nitrogen were attributed to kanamycin on 17 occasions -- 50% of all adverse reactions to this drug (See Chapter 8). In addition, four patients developed a rise in BUN attributed to gentamycin (again, one half of all adverse reactions reported by the attending physicians as being related to this drug).

b) Neomycin group. Neomycin and paromomycin were given predominantly to patients with severe cirrhosis. The adverse reaction rate to neomycin was high (13.9%) -- the major reactions being related to the alimentary tract. It is, however, interesting to note that in eight patients clinically significant rises in blood urea nitrogen

were attributed to this drug. The adverse reaction rate for paromomycin was lower (8.4%) as were the numbers exposed to this drug.

Polymixins: Polymixin B and Polymixin E (Colistin) are used interchangeably in the monitored wards. The former was given to 63 patients and the latter to 65 patients. Since the adverse reaction rates to each drug were similar, the numbers were added giving an overall adverse reaction rate of 16.4%. The predominant events attributed to these drugs were rise in BUN (9 patients) and paraesthesiae (7 patients).

Chloramphenicol: This drug was given to 224 patients in the monitored series. The observed adverse reaction rate was 9.8%. The commonest adverse reactions were bone marrow depression (7 patients) and alimentary upsets (7 patients). One individual developed jaundice shortly after commencing the drug, which was felt to be responsible for the jaundice by the attending physician.

Tetracycline: Next to ampicillin, this is the most commonly prescribed antibiotic in the monitored wards. The adverse reaction rate is relatively low at 6.4%. The major events attributed to this drug were alimentary upsets (nausea, vomiting, and diarrhea). In addition, seven patients developed a rise in BUN attributed to tetracycline (See Chapter 8) and one patient developed hypoprothrombinaemia when started on tetracycline during a period of long-term (stabilized) warfarin therapy.

Erythromycin: This drug was given to 253 patients of whom 24 (9.5%) developed an adverse reaction -- the major one being diarrhea (16 patients).

Isoniazid: This, the most active tuberculostatic drug, was given to 361 patients in the series and was implicated in the development of adverse events in 16 patients (4.4%). Although this frequency seems low when compared to other drugs in the group, many patients were admitted to hospital while taking the drug, hence it can be assumed that the "true" adverse reaction rate is higher than that observed. In support of this, the majority of the observed adverse reactions (10/16 - 62%) were severe events which are commonly linked to prolonged high-dosage therapy. Psychosis and severe depression was observed in six patients, jaundice in three, and a widespread vasculitis in one individual.

Sulphonamides: Sulphisoxazole is the member of this group used most frequently in the monitored wards (298 patients). Adverse events were recorded in 5.4% of patients, the majority being alimentary upsets. Of particular interest and importance is the development of petechial haemorrhages in three patients, none of whom had thrombocytopenia. In all three cases the lesion gradually recovered on the withdrawal of the sulphonamide.

Urinary Antiseptics: These drugs were given to 133 patients. Adverse reaction rates were 12% for nitrofurantoin (skin rashes, nausea, and vomiting) and 4% for nalidixic acid (nausea).

DISCUSSION

The results presented above give adverse reaction rates for the 20 most commonly used antibacterial agents in a group of over 10,000 consecutive admissions to medical wards in the monitored hospitals. Three aspects of this study are of particular relevance to the management of urinary tract infection.

Firstly, the adverse reaction rates to those drugs most commonly used to treat urinary tract infection - sulphonamides, nitrofurantoin, nalidixic acid, ampicillin and tetracycline are of major interest. The reported reaction rates varied from 4% with nalidixic acid (but note small numbers of patients exposed to this drug) to 11.1% with ampicillin. Although the drug of choice for a particular patient will depend upon many factors including the sensitivities of the infecting organism, the data presented will provide additional aid in coming to a final decision. In particular the reports of rise in BUN levels after tetracycline administration should, taken in conjunction with its bacteriostatic rather than bacteriocidal properties argue convincingly against its use in patients with even mild renal impairment (see Chapter 8). Moreover, the high frequency of rash among ampicillin recipients will be a factor against this drug's use when alternative, less toxic drugs are available.

Secondly, the frequency with which rise in BUN was attributed to an antibiotic is of considerable importance and will be separately analysed (Chapter 8). Despite the absence of full data on sequential serum creatinine levels, creatinine clearances etc., it must be considered likely that a high proportion of patients in the present study with drug-attributed rise in BUN levels do in fact have considerable

renal impairment. Drugs reported to cause this complication (the amino-glycosides, tetracycline and cephalothin) should be carefully evaluated before being given to patients with urinary tract infection, particularly those with pre-existing impairment of renal function.

Other potential causes of significant deterioration in renal function in patients with borderline or actual renal impairment, are factors such as severe vomiting or diarrhoea. Drugs most frequently implicated in such complications were neomycin (10.7% of exposures), erythromycin (6.3%), and ampicillin, chloramphenicol and tetracycline (3.1% to 3.4% each). Although these observed rates refer only to the present series of monitored patients and are unadjusted for factors such as age, sex and admission diagnosis, they can be taken as giving some idea of the relative frequencies of such events in other populations receiving these drugs.

Thirdly, since patients with poor renal function due to chronic pyelonephritis may develop other types of infection (for example pneumonia, septicaemia, etc.), knowledge of the probability of a given adverse reaction is of considerable importance. In particular, the development of convulsions and hyperkalaemia following penicillin therapy is of major importance and has previously been recorded by other investigators (Weinstein et al 1964; New and Wells 1965).

One surprising finding is the relative rarity of clinically significant super-infection attributed to antibiotics. Such a complication has been reported to occur in about 2.5% of courses of antibiotic therapy, whereas the figure observed in the present programme is 0.6% to 0.7%. For a detailed

review of the factors which contribute to this complication see Weinstein et al (1954). These authors observed a superinfection rate of 2.19% in 3,095 patients given chemotherapy, and emphasised that the major predisposing factors were age (patients aged less than three years had a three to four fold increase in frequency of superinfection) and infections of the ear, particularly the middle ear. If such patients are excluded from the data, the prevalence of superinfection falls by a factor of three to four, coming closer to that reported in the present study.

Louria and Brayton (1963) reporting on the frequency of superinfection following penicillin therapy noted that the rate of this complication was proportional to the dose of antibiotic received. There was, however, no evidence of this in the group of patients with clinically significant superinfection in the present study. Finally, these authors noted that only a fraction of the bacteriologically detected cases were clinically apparent (the proportion being close to one third).

In conclusion, it must be emphasised that the data presented in this chapter are essentially uncontrolled data based on the opinions of the various attending physicians in charge of the monitored patients. It is likely that a (small) proportion of patients in the study may have developed, for example, diarrhoea which was attributed to ampicillin, yet the true cause was not the drug, but some other factor. Thus the observed adverse reaction rates may be somewhat higher than the "true" rates, because of the occurrence of events wrongly attributed to the drugs. Likewise, some events may have escaped the attention of the attending physician and hence will not appear

in the present data. An example of this type of event would be a transient abnormality of liver function tests which was disregarded, unnoticed, or misinterpreted. For a discussion of the need for controls in drug monitoring programmes see Reidenberg and Lowenthal (1968). Despite this limitation, it is likely that the rates observed in this study are close to the "true"rates. Moreover since any errors are likely to be randomly distributed among the various drugs, no systematic bias results from the absence of suitable control data.

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CHAPTER 8

TETRACYCLINE AND DRUG-ATTRIBUTED RISE IN BLOOD UREA NITROGEN LEVELS

A routine computer scanning of the data derived from 10,209 consecutive admissions to medical wards monitored by the Boston Collaborative Drug Surveillance Program revealed that there was a strong association ($p < 0.0001$) between the adverse event "rise in blood urea nitrogen (BUN)" which had been attributed to any drug, and the administration of tetracycline. Whereas 25 of the 147 patients in whom such a rise in BUN was reported received tetracycline, the drug itself was only implicated in seven instances. This prompted a detailed evaluation of the relationship between tetracycline and reported rises in BUN.

METHODS

For the evaluation of this relationship, data from the first monitored admission of any patient was considered except where a rise in BUN was only reported on a subsequent admission in which case data from only the later admission were used.

Patients receiving known nephrotoxic antibiotics were excluded from the analysis since any relationship between tetracycline and rise in BUN in such patients would probably be obscured by the other antibiotic. The drugs excluded were amphotericin, polymixin B, colistin, kanamycin, gentamycin, neomycin and paromomycin. A total of 780 patients received these drugs, of whom 58 (7.4%) had a recorded rise in BUN. (Included in this group of 58 patients were four recipients of tetracycline.)

The analysis was further confined to diuretic recipients, since the vast majority of the remaining cases of reported rise in BUN (82/89 = 92%) also received diuretics. The diuretics regularly administered in the surveillance wards include chlorothiazide, hydrochlorothiazide, bendroflumethiazide, trichlormethiazide, chlorthalidone, mercaptomerin, mersalyl, frusemide, triamterene and ethacrynic acid. Since these drugs were usually given in combination and since the number of patients with a rise in BUN was small for each specific drug, the diuretics were considered together in further analyses.

Finally, all patients for whom the admission BUN level was not recorded were excluded from the analysis (202 patients out of 2,158 - 9.3%).

The remaining patients who were investigated further, were divided into three comparison groups:

Group T - patients receiving tetracycline

Group A - patients receiving any remaining antibiotic other than tetracycline

Group N - patients who received no antibiotic

The homogeneity of Group A was verified. All antibiotics in this group had similar frequencies of observed rises in BUN.

Factors explored as possibly providing an explanation of the observed association between tetracycline and rise in BUN included age, sex, admission BUN, survival, first discharge diagnosis in terms of the categories of cardiovascular, respiratory, hepatic, neoplastic and other conditions,

and referring hospital. Frequency distributions of these variables were obtained for each of the three comparison groups and also for patients with and without a reported rise in BUN.

RESULTS

1. Screening Procedure

Data from 10,209 patients were analysed. A recorded rise in BUN attributed to any drug was noted in 147 (1.4%) of patients. Drugs given to patients who developed a rise in BUN, with a greater than expected frequency when compared to patients who did not have a recorded rise in BUN, are shown in Table 8.1.

2. Detailed Analysis

These were confined to patients who received diuretics and who did not receive nephrotoxic antibiotics (as defined in Methods). There were 1,957 such patients. Their average age was 61 years; 60% were male; 10.7% died while in the monitored wards; and 36.9% had an admission BUN greater than 25 mg/100 ml. The first recorded discharge diagnosis was of cardiovascular disease in 957 patients; respiratory disease in 254 patients; hepatic disease in 166 patients; neoplastic disease in 163 patients; and other conditions in 417 patients. The relationship of discharge diagnosis to treatment group is shown in Table 8.2.

Validity of Comparisons. The numbers of patients in groups T, A, and N were 204, 596, and 1,137, respectively. The distributions of these groups by age and sex were similar and therefore these were not controlled in further analyses. In addition, the distribution of patients with rise in BUN and those without were similar with respect to hospital, survival and discharge

diagnosis and so were not controlled further. However, there were differences between the comparison groups with regard to admission BUN (Table 8.3) and this factor was taken into account in evaluation of the relationship between tetracycline-diuretic receipt and recorded rise in BUN.

Tetracycline and Rise in BUN (Table 8.4; Figure 8.1). The observed, unadjusted frequency of drug-attributed rise in BUN among diuretic recipients was 9.8% for Group T, 3.5% for Group A, and 3.4% for Group N. These frequencies are not fully comparable in view of the difference between groups in terms of admission BUN. The subjects were thus stratified by admission BUN. There was a higher frequency of recorded rise in BUN in the tetracycline group in each stratum. Using the Mantel Haenszel technique (Mantel and Haenszel 1959) the differences between Group T and A, and separately between Groups T and N were found to be significant at p values of less than 0.001 and 0.0005, respectively. The pooled estimates of relative risk were 3.0 (99% confidence limits 1.2 - 7.3) and 2.8 (99% confidence limits 1.3 - 6.1), respectively.

The mean admission BUN level in patients in groups T, A, and N who had a reported rise in BUN was 34, 41, and 31 mg/100 ml, respectively, and in those with no reported rise in BUN was 27, 32, and 26 mg/100 ml respectively (Table 8.3). The mean rise in patients with a recorded rise in BUN was 28 mg/100 ml (range 6 - 77 mg/100 ml). The mean rises in groups T, A, and N were 34, 33, and 22 mg/100 ml, respectively (Table 8.5). In five of the 20 patients in group T serial creatinine levels were available and of these, four had a rise in creatinine recorded at the time of the rise in BUN (Case Reports 8i, 8ii).

Dose, Route and Time Relationships. There were no differences in the mean daily dose and route of administration of tetracycline between patients with reported rises in BUN and those without.

In 18 of the 20 cases of rise in BUN in association with tetracycline-diuretic exposure, tetracycline was administered within one week prior to the reported rise. In the remaining two instances, one patient received tetracycline eight weeks before and the other three weeks after the detected rise in BUN. These latter cases were not excluded from the analysis since it is likely that similar cases were to be found in the two comparison groups (A and N). In these groups, however, the fact that many drugs were involved in the rises in BUN, provided considerable difficulties in determining which one should be reviewed for the purpose of exclusions.

Diagnoses. Of the 18 patients who received tetracycline and diuretics prior to the reported rise in BUN, 11 received the drug for treatment of respiratory infections and 7 for urinary tract infections. The major discharge diagnosis in these patients was congestive cardiac failure - seven patients, chronic bronchitis - five patients, cirrhosis (alcoholic) - three patients, neoplasm (colon) - one patient, gastric ulcer - one patient, diabetes mellitus - one patient.

DISCUSSION

Although several authors have drawn attention to the development of a rise in BUN following tetracycline therapy (Shils 1962, 1963; Lew and French 1966; Roth et al 1967; Perkash et al 1969; George and Evans 1971) this adverse event is not yet sufficiently well recognised (Eastwood et al 1970; Edwards et al 1970).

Shils (1962) treated patients with this drug under standardised conditions in a metabolic ward and concluded that it causes a negative nitrogen balance which he attributed to an inhibition of protein synthesis. Subsequently, he emphasized that this side-effect may be clinically more important in patients with renal failure, presumably because of a failure on the part of the kidney to handle the additional load of urea (Shils 1963). More recently, Korkeila (1971) has suggested that the tetracyclines should be avoided in patients receiving parenteral nutrition since the antianabolic effect of tetracycline interferes with effective use of the administered protein leading to further elevation of BUN levels. Whereas several of the above authors have concluded that the rise in BUN associated with tetracycline could be explained on the basis of an antianabolic effect alone, it has been noted that an additional toxic effect on the kidney could not be ruled out. (Shils 1963; Lew and French 1966; George and Evans 1971; Polec et al 1971) Of additional interest, Kuzucu (1970) has reported the development of renal failure in five patients given tetracycline and methoxyflurane concurrently. This drug is an anaesthetic agent which has been shown to have a marked diuretic effect in some individuals (Crandell and MacDonald 1968).

Finally, in contrast to the above reports, tetracycline which has been improperly stored may form degradation products which themselves are strongly nephrotoxic, producing a marked lesion in the renal tubules (Gross 1963; Benitz and Diermeier 1964).

The present study of a large series of hospitalised medical patients is the first systematic evaluation and verification of the existence of an association between tetracycline therapy and clinically important rises in BUN level. When this drug was given in association with diuretics, the recorded freqeuncy of this event was threefold relative to patients receiving diuretics without tetracycline. The statistical significance of the difference between tetracycline recipients and those in the comparison groups was high and the association remained strong even when taking into account various patient characteristics by stratifying the results.

Although there was no apparent relationship between the rise in BUN and dose or route of administration of tetracycline, the time relationship between tetracycline exposure and rise in BUN is striking, in that 18 of the 20 patients received tetracycline within one week prior to the record of the rise.

While the evidence thus points to a causal relationship between the tetracycline therapy and the recorded rise in BUN, there remains the possibility that it results from physician bias. Had there been no prior suspicion of this association, this would pose no problems. However, as already indicated, there is within the literature evidence pointing to this

possibility and in five cases in the present study, tetracycline itself was implicated, along with diuretics, as a cause of the rise in BUN. Thus the observed association could at least in part be attributed to physican bias. However, on clinical grounds, it seems unlikely that such bias could fully explain the large differences observed between tetracycline recipients and those in comparison groups, particularly when the analyses were confined to diuretic recipients.

Because of the nature of the system of data collection, the observed frequencies of rise in BUN in the three comparison groups are likely to be underestimates of the true frequencies since only those rises detected and deemed to be drug-related are recorded.

The mean rise in BUN in the current series was considerable (28 mg/100 ml) and of obvious clinical importance. It was frequently associated with overt symptoms such as nausea and vomiting, and in all cases prompted discontinuation of the suspicious drug(s) by the attending physician. It is likely, however, that the magnitude of this rise is an overestimate of that which would be found in a prospective survey of a group of tetracycline recipients since it can be assumed that a greater proportion of large as opposed to small rises were detected by the monitoring system.

Patients in the tetracycline-diuretic group who developed a rise in BUN had admission levels of BUN which were higher than those who did not, suggesting that those with pre-existing renal impairment are more prone to develop this complication.

Little information is available from the monitoring system on the tendency of tetracycline to produce uremia in the absence of diuretics, because a search for this event is generally prompted by diuretic treatment. In addition, the data from this study do not allow for speculation as to the etiology of the tetracycline-associated rise in BUN, particularly as the finding relates to patients who received other drugs (i.e., diuretics) which act on the kidney. However, the finding of a coincidental rise in creatinine levels in four of five cases in the tetracycline group where this information was available, suggests that at least in those cases deterioration in renal function was a factor in the observed rise. Moreover since the point of entry to the study was a drug-attributed rise in BUN, such factors as high protein intake and gastro-intestinal haemorrhage are automatically excluded. Of the remaining possible causes of elevation in BUN levels (Dossetor 1966), dehydration and renal impairment are the two major possibilities. Although the necessary details were not recorded in many instances, it is likely that deterioration in renal function was the major cause of the rise in BUN levels in 14 of the 18 patients in whom tetracycline therapy preceded the rise.

In conclusion, the data presented provide evidence that tetracycline therapy in patients with conditions which require diuretic therapy, is associated with an enhanced risk of developing clinically significant uremia, particularly in patients with an initially elevated BUN level. It therefore seems advisable to avoid tetracycline in these patients when alternative antibiotics can be administered.

STATISTICAL ANALYSES

The comparison of the frequency of recorded rises in BUN within two subsets of groups T and A (those with presenting BUN levels below and above 25 mg/100 ml) is made by computing the pooled χ^2 value with one degree of freedom. Thus, using the terminology --

a_1	b_1	$a_1 + b_1$
c_1	d_1	$c_1 + d_1$
$a_1 + c_1$	$b_1 + d_1$	n_1

the expected value for $a_1 (Ea_1) = \frac{(a_1 + c_1)(a_1 + b_1)}{n_1}$

the variance of a_1 $(Va_1) = \frac{(a_1 + c_1)(b_1 + d_1)(a_1 + b_1)(c_1 + d_1)}{n_1^2(n_1 - 1)}$

and $\chi_1^2 = \frac{[|a_1d_1 - b_1c_1| - \frac{n_1}{2}] (n_1 - 1)}{(a_1 + c_1)(b_1 + d_1)(a_1 + b_1)(c_1 + d_1)}$

$$= \frac{[|\Sigma a_1 - \Sigma E(a_1)| - 1/2]^2}{\Sigma V(a_1)}$$

$$= \frac{[|20 - 10.53| - 1/2]^2}{7.35}$$ when comparing groups T and A

$$= 10.954$$

giving $p < 0.001$

Similarly, when comparing groups T and N

$$\chi_1^2 = \frac{[|20 - 9.69| - 1/2]^2}{7.59}$$

$$= 12.67$$

giving $p < 0.0004$

In calculating the pooled estimates of relative risk from two fourfold tables, the formula used was

$$\text{Pooled estimate of relative risk} = \frac{\frac{a_1 d_1}{n_1} + \frac{a_2 d_2}{n_2}}{\frac{b_1 c_1}{n_1} + \frac{b_2 c_2}{n_2}}$$

and so in comparing groups T and A

$$\text{Pooled estimates of relative risk} = \frac{\frac{8 \times 328}{445} + \frac{12 \times 247}{355}}{\frac{5 \times 104}{445} + \frac{80 \times 16}{355}}$$

$$= 2.98$$

and similarly in comparing groups T and N

$$\text{Pooled estimates of relative risk} = \frac{\frac{8 \times 770}{902} + \frac{12 \times 348}{459}}{\frac{104 \times 20}{902} + \frac{80 \times 19}{459}}$$

$$= 2.84$$

To apply the 99% confidence limits around the pooled estimates of relative risk, the formula used was --

$$99\%\ \text{confidence limits} = \text{pooled estimate of relative risk} \pm [2.58 \times \text{standard error of the mean}]$$

The resulting confidence limits are not symmetrical about the relative risk since the standard error is of a logarithmic type. For a detailed discussion of the statistics involved in this chapter, see Armitage (1971).

APPENDIX

In the course of investigating the relationship between tetracycline and recorded rise in BUN, patients receiving nephrotoxic drugs were excluded from the analyses since these would tend to obscure the effect of tetracycline. However, in view of the suggestion that diuretics may enhance the nephrotoxicity of various antibiotics (see Chapter 9), these data were further explored to assess the relationship between nephrotoxic drugs, diuretic administration and recorded rises in BUN.

For the purpose of this analysis the data were stratified by diuretic usage, the diuretic drugs being those enumerated in METHODS. Whereas in general tetracycline administration does not lead to a regular search for elevation in BUN levels, such a search is likely to occur, following the administration of nephrotoxic antibiotics. Thus while it is not possible to compare the frequency of rise in BUN amongst tetracycline recipients who did not receive diuretics with those who did, such a comparison is valid in the case of recipients of nephrotoxic antibiotics.

A total of 780 patients received nephrotoxic drugs (METHODS) of whom 733 (94%) had a recorded admission BUN level available. The analyses were therefore restricted to these 733 individuals of whom 57 (7.8%) had a recorded rise in BUN. The frequency of recorded rises in BUN for each antibiotic in the group is given in Table 8.6,together with this data analysed by diuretic usage. In this table a patient is counted more than once if he or she received more than one of these antibiotics. In all cases the proportion of diuretic recipients who developed a rise in BUN was greater than the proportion of non-recipients who developed a rise.

Since neomycin and paromomycin are given in the monitored wards

predominantly for the therapy of severe hepatic disease, a condition which is not infrequently associated with renal failure (Sherlock 1968), further analyses were confined to patients receiving only kanamycin, gentamycin, polymixin, colistin, and/or amphotericin. There were 327 such patients of whom 9.8% developed a rise in BUN (Table 8.7). The frequency of recorded rise in BUN was greater amongst diuretic recipients (16/110 = 14.5%) than amongst non-recipients (16/217 = 7.4%) although this difference does not reach the conventional levels of statistical significance ($\chi^2 = 3.48$ $p = 0.06$).

In addition direct comparison of diuretic users with non-users within this set of antibiotic recipients is not valid without taking into account other variables such as age, sex, hospital and survival. A review of the data revealed that the distribution of these comparison groups by hospital and by sex were similar and hence these variables could be disregarded in further analyses. However, both age and survival were positive confounding factors - that is diuretic users were both somewhat older, had a poorer prognosis in terms of survival and had a higher proportion of recorded rises in BUN than did the non-users. While the effect of these variables on the final result could be taken into account using the Mantel-Haenszel proceedure as described previously, this was not done since the association was insufficiently strong to warrant further pursuit.

It is concluded that, on the evidence available at present, the clinical relevance of a potential interaction between nephrotoxic antibiotics and diuretics has not been proven within the data of the Boston Collaborative Drug Surveillance Program. The evidence, however, is suggestive of such an effect, and it is likely that, with accumulation of more data, this interaction may be demonstrated in the future.

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CHAPTER 9

Effect of Frusemide on Antibiotic-induced Renal Damage

In a recent study of factors involved in the pathogenesis of acute renal failure in man, it was noted that of forty consecutive patients treated for this condition in a renal unit, seventeen had received cephaloridine in the few days preceding the onset of the condition (Lawson et al 1970). Other antibiotics had been given much less frequently (five had received tetracycline, three ampicillin, and one kanamycin). In addition, fifteen of these seventeen patients had also been given diuretics concurrently with the antibiotic, an observation which raised the possibility of an interaction between these drugs leading to the development of acute renal damage. The present study was designed to investigate the possibility that the administration of antibiotics and diuretics to patients with mild transitory renal impairment after surgery, dehydration or trauma, might result in frank acute renal failure.

This report describes a series of animal experiments in which transitory renal impairment was induced with glycerol, and the effect of various combinations of antibiotics and a diuretic on renal function and histology was studied.

METHODS

Female rats aged between eight and 12 weeks and weighing between 100 and 350 grams were used for the experiments. All received a commercial diet free of antibiotics and were given unlimited access to fluids during

the course of the experiment. Groups of animals were lightly anaesthetised using chloroform. Normal saline, glycerol B. P. diluted with normal saline, antibiotics or frusemide were injected subcutaneously either singly or in various combinations. Where appropriate, blood was taken at 90 minutes for assay of serum antibiotic levels. This was obtained from a ventricle after a brief chloroform anaesthetic.

The animals were sacrifised at 48 hours and blood was taken for urea estimation. The kidneys were removed and submitted for pathological examination under code. The tissues were fixed in 10% formol-saline, embedded in paraffin and sections stained with haematoxylin and eosin. Each kidney was assigned to one of three histopathological sub-groups:

1. Normal kidneys. (Figure 9.1)

2. Focal proximal tubular necrosis, in which there was evidence of patchy areas of proximal tubular cell necrosis and regeneration, with mitotic activity occurring in more than five separate areas of one cut surface of the kidney. (Figure 9.2)

3. Diffuse proximal tubular necrosis, in which the lesions were more widespread and more severe than in Category 2. (Figure 9.3)

Serum concentrations of antibiotic were determined by a diffusion technique with serial dilutions of serum where necessary (Humphrey and

Lightbown 1952). Assays of cephaloridine, cephalothin, and kanamycin were performed using bacillus subtilis as test organism and those of colistin using a sensitive strain of bordetella bronchiseptica.

The experiments were carried out on a single strain of rat except where noted.

RESULTS

Control animals injected with normal saline in volumes of one ml and 4 ml showed no evidence of renal damage 48 hours after the injection. Similarly, frusemide in doses of 50 and 150 mg/kg produced no changes in renal histology, or elevation of the blood urea above 40 mg/100 ml. By trial and error, a dose of glycerol (2 ml/kg) was obtained which consistently produced patchy focal acute tubular damage in about 50% of the animals studied. When a group of eight animals was given glycerol 2 ml/kg in combination with frusemide 50 mg/kg the effect was similar to that observed with glycerol alone.

Nephrotoxicity of cephaloridine alone. Table 9.1 shows the effect of various doses of cephaloridine on renal histology and function. With cephaloridine doses ranging from 250 mg/kg to 1 g/kg, mean blood urea levels in these groups did not differ, although there was a positive association between the dose of drug given and the number of rats sustaining focal acute tubular necrosis (regression coefficient 0.33 ± 0.09: $p < 0.01$)--Snedecor and Cochrane (1967).

Nephrotoxicity of cephaloridine with frusemide or glycerol. Groups of rats given cephaloridine in a dose of 500 mg/kg plus frusemide 50 mg/kg did not exhibit increased nephrotoxicity when compared with rats given cephaloridine alone. Coincidental administration of cephaloridine (500 mg/kg) and glycerol (2 ml/kg) did not produce significant elevation of blood urea levels at 48 hours, nor did the combination lead to more severe pathological changes than those observed with glycerol alone. Thus there was no evidence of an interaction between cephaloridine and either frusemide or glycerol alone. Mean blood levels of cephaloridine at 90 minutes after injection in these animals were similar to those observed in animals given cephaloridine (500 mg/kg) alone.

Nephrotoxicity of cephaloridine, glycerol and frusemide. The effect of administering various doses of cephaloridine to animals also receiving glycerol (2 ml/kg) and frusemide (50 mg/kg) is shown in Table 9.2. This experiment was performed on two different strains of rat. In both strains the proportion of animals sustaining renal damage (irrespective of severity) was positively associated with the dose of cephaloridine injected--in the case of strain A the regression coefficient was 0.18 ± 0.04 ($p < 0.001$), and with strain B, the regression coefficient was 0.27 ± 0.05 ($p < 0.0001$). There were no statistically significant differences between these two slopes ($p > 0.05$) or between these slopes and the previously observed regression lines for cephaloridine alone ($p > 0.05$).

Nephrotoxicity of cephalothin. The effect of substituting cephalothin for cephaloridine is shown in Table 9.3. These experiments were performed on animals of strain B. Cephalothin alone produced minor pathological changes but no elevation of blood urea in a group of rats given the drug in a dose of 1500 mg/kg. However, the addition of glycerol (2 ml/kg) and frusemide (50 mg/kg) produced marked elevation of blood urea in groups of animals given cephalothin in doses of 500 mg, 1,000 mg and 1,500 mg/kg. The proportions of animals showing histological evidence of renal damage was positively associated with cephalothin dosage (regression coefficient 0.42 ± 0.09: $p < 0.001$). When this coefficient was compared with that calculated from the data on rats in strain B who received cephaloridine with glycerol and frusemide (0.27 ± 0.05) there was no statistically significant difference between the coefficients ($p > 0.2$). Rats receiving cephalothin in a dose of 1 g/kg together with frusemide and glycerol sustained extensive tubular necrosis at mean serum cephalothin levels of 113 µg/ml (range 73 - 132 µg/ml), close to that obtained in routine clinical practice.

Nephrotoxicity of colistin sulphomethate. The results of a similar study using colistin sulphomethate as the antibiotic are shown in Table 9.4. In a dose of 8 mg/kg this drug did not produce biochemical or histological evidence of nephrotoxicity, either alone or in combination with glycerol and frusemide. However, when colistin was given in a dose of 24 mg/kg, with glycerol and frusemide, the majority of animals developed extensive tubular necrosis. Since this occurred at dosage and serum antibiotic levels which were considerably higher than those attained in clinical practice, further experiments were not undertaken with this drug.

Nephrotoxicity of kanamycin. A study of the nephrotoxic effects of kanamycin alone and in combination with glycerol and frusemide again revealed increased damage when the drugs were given in combination (Table 9.5). However, the dose of kanamycin required to show this effect and the resulting serum kanamycin levels were much higher than those normally attained in practice.

DISCUSSION

Antibiotics and diuretics are regularly given together to patients who may at the time be suffering from renal impairment of either a temporary or a permanent nature. The clinical observation that a greater than expected number of patients suffering from acute renal failure after surgery or trauma had been exposed both to cephaloridine and diuretics led to the design of this experiment (Lawson et al 1970).

In an attempt to mimic the clinical situation of patients who had suffered mild transient renal impairment, small doses of glycerol were given to rats. The dose used was determined by trial and error and was enough to produce only mild and reversible pathological changes in the rat's kidneys. The cause of glycerol-induced acute renal failure was initially thought to be intravascular haemolysis (Carroll et al 1965; Oken et al 1966), but subsequently Thiel et al (1970) showed that saline loaded animals given glycerol do not develop acute renal failure despite having severe intramuscular haemolysis. In addition, Hayes et al (1970) showed that prior injection of glycerol protects animals against acute

renal failure produced by a second injection of glycerol, a finding which is not compatible with intravascular haemolysis as a primary cause of renal failure. One possible explanation of these findings is that glycerol induces acute renal failure via the renin/anginotension system. Since Brown et al (1970) have implicated renin release as a possible factor in the development of acute renal failure in humans, it seemed appropriate to use glycerol-induced tubular damage as a model of the clinical situation in the present studies.

Cephaloridine is known to be nephrotoxic in animals and man (Atkinson et al 1966; Perkins et al 1968; Foord 1969). In rats one gram to 1.4 grams per kilogram body weight will produce proximal tubular necrosis in over half of the animals examined 48 hours after the injection (Currie 1967). Similar results were obtained in the present investigation. Tuano et al (1966) suggested that cephaloridine nephrotoxicity was a dose related condition, and Foord (1969) supported this view, stating that renal damage was rare in humans if the blood levels of antibiotic were maintained below 100 µg/ml. In rats, Dodds and Foord (1970) noted that frusemide had an enhancing effect upon the degree of renal damage caused by cephaloridine but the doses these workers used were similar to those required to produce renal damage in over half the rats injected with this substance alone (LD_{50} = 1 - 1.4 g/kg). In the present experiments, significant renal damage was produced in rats given glycerol and frusemide together with a cephaloridine dose varying from one-twelfth to one-third of the known nephrotoxic dose for rats. The extent of damage inflicted when cephaloridine was given in a dose of 500 mg/kg was severe, as

indicated by the extensive histological changes and the markedly elevated blood urea levels 48 hours after the challenge.

Cephalothin is thought to be less nephrotoxic than cephaloridine when given to animals in identical circumstances (Perkins et al 1968). However, Thoburn and Fekety (1970) have reported cases of deterioration in renal function following treatment with cephalothin in combination with other potentially nephrotoxic antibiotics. The present experiments reveal that cephalothin, like cephaloridine, exhibits enhanced nephrotoxicity in rats when combined with glycerol and frusemide. Although the dose of cephalothin required to produce extensive acute tubular necrosis was higher than with cephaloridine the damage was apparent at serum levels of cephalothin close to those obtained in routine therapeutics.

Colistin is a polypeptide antibiotic largely excreted in the urine and has a considerably prolonged half-life in patients with renal failure (Goodwin and Friedman 1968). It has been reported to cause a major but transitory fall in glomerular filtration rate which may revert to normal on stopping the drug (Brumfitt et al 1966, Price and Graham 1970). Vinnicombe and Stamey (1969) failed to demonstrate a nephrotoxic effect of colistin given intravenously to dogs. Although in the present experiment colistin was associated with increased nephrotoxicity in rats when combined with glycerol and frusemide, this occurred at serum levels many times greater than those achieved clinically.

Similarly, with kanamycin, an antibiotic known to be ototoxic and nephrotoxic, enhanced nephrotoxicity was demonstrated when it was combined with frusemide, but only at serum kanamycin levels approximately four times higher than the recommended maximum in humans.

The present experiments indicate that in the rat suffering from transitory renal impairment caused by the injection of glycerol, the nephrotoxicity of four antibiotics (cephaloridine, cephalothin, colistin, and kanamycin) is enhanced by coincidental administration of frusemide. In the case of cephaloridine and to a lesser extent, cephalothin, this damage occurs at blood levels of antibiotic within or near the normal therapeutic range, whereas with colistin and kanamycin the effects occur at considerably higher blood levels. It is possible, therefore, that an interaction between diuretics and antibiotics leading to renal damage is most likely to be detected among recipients of cephaloridine who have mild, preexisting renal disease.

The mechanism of the interaction has not yet been elucidated. However, one possible explanation is that the renin/angiotension mechanism is involved. Both glycerol and frusemide are known to stimulate renin release into the peripheral circulation. Were these antibiotics to do likewise, it is possible that the combined effect would be great enough to lead to the onset of acute renal failure.

Another possible cause is that suggested by Stewart (1967) who noted that the peptide antibiotics, penicillin, cephalosporin and bacitracin tend to polymerise in solution. Such polymers of cephaloridine contain the allergenic fraction of the drug, and they may also be responsible for the nephrotoxicity, since when injected into suitable animals at low doses, they are associated with the development of more severe renal damage than a similar dose of the depolymerised fraction (Stewart 1968) and do so at blood levels which are considerably lower than those obtained after injection of the depolymerised fraction. Injected cephaloridine is known to concentrate in the proximal renal tubules within one hour of administration (Currie et al 1966; Silverblatt 1970). If the concentration of this drug or its metabolites were increased in the proximal tubular cell by having water reabsorption into the cell inhibited, as for example, is known to occur with frusemide (Suzuki et al 1964), it is possible that polymerisation could take place in vivo in this cell. A third possible explanation is that the mild renal damage induced by glycerol rendered the rats more sensitive to the natriuresis induced by frusemide, resulting in considerable reduction in the intravascular space. This in turn could lead to significantly higher plasma (and later tissue) levels of the nephrotoxic antibiotics. In support of this hypothesis the plasma levels of both cephaloridine and cephalothin ninety minutes after the injections were somewhat higher in animals receiving glycerol and frusemide than in those not receiving these drugs. However, the differences in blood levels were not statistically significant and the time interval between the injections and this observed difference

was small (90 minutes) suggesting that factors other than simple dehydration of the animals would be required to explain the findings.

Whatever the pathophysiology of these effects, the above experiments give added confidence to the clinical observation that the administration of cephalosporin antibiotics, particularly cephaloridine, in combination with frusemide may be dangerous in patients with even mildly impaired renal function.

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CHAPTER 10

CEPHALORIDINE-INDUCED RENAL DAMAGE:

STUDIES IN RABBITS

Cephaloridine is known to be nephrotoxic both to man and to a wide range of animal species (Linsell et al 1967; Perkins et al 1968; Atkinson et al 1966a). This toxicity is related to the total dose administered at any single time, varies in magnitude from species to species, and is greatest in the rabbit (Currie 1967). Daily administration to rabbits of a subnephrotoxic dose of the drug over a prolonged period has been reported to be free of significant nephrotoxic effect (Atkinson et al 1966b).

The sensitivity of a species to the nephrotoxicity of cephaloridine appears to be directly related to the extent of metabolism of the drug by that species. In the rabbit, Silverblatt et al (1970) showed that histological damage confined to the proximal tubule could be observed under the electron microscope within one to five hours of an injection of 200 mg/kg cephaloridine. In addition these workers noted the appearance of membranous profiles in the proximal tubular cells of treated animals. The origin of these profiles was not fully determined, but in the opinion of the authors they could be either remnants of disrupted cell constituents or newly synthesised membranes such as endoplasmic reticulum.

Proliferation of smooth endoplasmic reticulum occurs in the liver cells of animals treated with barbiturates, DDT, alcohol and many other drugs (Conney 1967) and this effect is associated with increased activity of several groups of drug-metabolizing enzymes. The enzyme inducing

effect of phenobarbitone also can be shown in tissues other than liver (Conney 1971) and has been clearly demonstrated in rabbit kidney (Uehleke and Greim 1968).

The present studies were designed to assess both the effect of phenobarbitone on the metabolism and nephrotoxicity of cephaloridine in rabbits, and also the nephrotoxic effect of two doses of this drug separated by one week.

METHODS

Thirty female New Zealand white rabbits were used for the experiments. They weighed between 1.5 and 2.5 kg and had been reared in an antibiotic-free environment. During the course of the experiments they were given unlimited access to food and fluids.

At the onset, two animals were killed for control purposes. They were lightly anaesthetised using chloroform and then sacrifised by direct dislocation of the cervical spine. The kidneys were immediately removed, examined and fixed for histological examination.

Effect of repeated blood sampling on renal histology. Three animals were given an injection of 2 ml normal saline and serial blood samples (2 to 3 ml each time) were withdrawn from the marginal vein of the ear at regular intervals up to five hours after the injection. A total of nine samples were taken during this time. This process was repeated seven days later and the animals sacrifised 48 hours after the second injection of saline. The

kidneys were removed and examined as described above. In addition, blood was taken at the time of death for subsequent estimation of serum creatinine levels.

Effect of a single dose of cephaloridine (Group S animals). Four animals were given intravenous cephaloridine (50 mg/kg) directly into the marginal vein of the ear. Two were sacrifised at 48 hours and two at 220 hours after the injection. The kidneys were examined as described previously. A further five animals were then given 100 mg/kg cephaloridine in the same manner, three being sacrifised at 48 hours and two at 220 hours.

Effect of two doses of cephaloridine (Group C animals). Four animals were given two doses of 50 mg/kg cephaloridine intravenously separated by seven days and were then sacrifised 48 hours after the last dose (giving the time from the initial dose to sacrifise of approximately 220 hours). Later, a further group of four animals were given two doses of 100 mg/kg cephaloridine separated by seven days and sacrifised forty-eight hours after the last dose. In all cases blood was taken at the time of death for estimation of the serum creatinine levels.

Effect of phenobarbitone on cephaloridine metabolism and toxicity (Group P animals). The experiments outlined in the preceding paragraph were repeated with the addition that six hours after the initial dose of cephaloridine each animal was injected intraperitoneally with phenobarbitone in a dose of 15 mg/kg. This injection was repeated daily for six consecutive days.

Pharmacokinetic studies. These were performed on all animals receiving two injections of cephaloridine. During the studies the animals were kept in metabolic cages and all urine pased for the 24 hours after each injection was collected and assayed for antibacterial activity.

Immediately after each injection of cephaloridine and at regular intervals thereafter up to a maximum of five hours, blood was withdrawn from the marginal vein of the opposite ear, allowed to clot and the serum separated. The serum was then frozen at -4°C until it was assayed for cephaloridine level by the method described by Humphrey and Lightbown (1952), as modified by Bennett et al (1966). All assays were performed in quadruplicate.

The results were analysed with the aid of a computer which was programmed to give the following information:

1. An equation for the regression line between the logarithm of the observed plasma concentration of cephaloridine and the time from injection. This was calculated by the method of least squares and from it the half-life of the drug in serum was calculated ($t_{1/2}$).

2. The hypothetical serum concentration at the time of injection (C_{SO}) was calculated by extrapolating the regression line back to time zero.

3. From this calculated serum concentration at time zero (C_{SO}) the volume of distribution of the drug in the animal (V_d) was estimated:

$$V_d = \left[\frac{\text{Dose given (in } \mu g)}{C_{SO} \text{ (in } \mu g/L)} \right] \quad \text{litres}$$

4. From the observed elimination rate constant ($k_{el} = \frac{0.693}{t_{1/2}}$) and the volume of distribution (V_d), the body clearance of the drug (Cl_B) could be calculated:

$$Cl_B = K_{el} \cdot V_d$$

(Figure 10.1)

RESULTS

I. HISTOLOGICAL DATA

The appearance of normal rabbit kidney prepared under the conditions of this experiment is demonstrated in Figure 10.2. The histological appearances of the kidneys removed from animals who sustained repeated venepunctures following a control injection of saline were within normal limits.

Effect of a single dose of cephaloridine (Group S). Histological examination of the kidneys of animals receiving a single injection of antibiotic revealed no consistent abnormalities in individuals sacrifised at 48 hours after injection of 50 mg/kg or 100 mg/kg cephaloridine. In animals receiving the lower dose and killed at 220 hours, the appearances were again normal, whereas in those receiving the higher dose some dilatation of the distal

convoluted tubules and collecting ducts was present. In one of the latter group there was also mild fatty degeneration of the proximal convoluted tubule with patchy calcium debris in the lumen of both proximal and distal tubules.

Effect of two doses of cephaloridine. There were no significant differences between the histological appearances in the animals receiving phenobarbitone (Group P) and the controls (Group C).

Eight animals received 50 mg/kg cephaloridine on two separate occasions one week apart, and were killed 48 hours after the second injection. All animals showed evidence of mild proximal tubular damage with pyknosis of the nuclei and cloudy swelling of the cytoplasm. In addition, the majority of the animals had granular casts in the distal tubules and collecting ducts (Figure 10.3). Only one of these animals had calcification present in the tubular lumina.

Eight animals received 100 mg/kg cephaloridine on two occasions. All showed proximal convoluted tubular damage to a varying degree, with cloudy swelling, loss of brush border and nuclear pyknosis prominent in five animals. In six of the eight there was evidence of widespread calcified debris present in the tubular lumina particularly in the outer cortical segment of the kidney (Figures 10.4 and 10.5).

The mean serum creatinine level at death of animals receiving 50 mg/kg doses was 0.8 ± 0.1 mg/100 ml and of those receiving 100 mg/kg 1.4 ± 0.1 mg per 100 ml ($t = 7.99$, $p < 0.001$).

II. PHARMACOKINETIC DATA

The mean half-life of cephaloridine after the initial injection was similar in the animals assigned to Group P and Group C, being 41.7 $\pm$ 4.9 minutes and 37.3 $\pm$ 3.2 minutes, respectively. Following treatment with phenobarbitone of those animals assigned to Group P, the second serum half-life was again similar in the two groups being 44.3 $\pm$ 7.6 minutes in Group P and 43.9 $\pm$ 7.6 minutes in Group C (Tables 10.1 and 10.2).

The volume of distribution of cephaloridine in those animals assigned to Group C was similar after the first and second injections (669 $\pm$ 62 ml and 640 $\pm$ 75 ml, respectively). However, the mean volume of distribution of cephaloridine in the treated animals (Group P) was somewhat lower after the second injection (581 $\pm$ 40 ml) than after the first one (732 $\pm$ 63 ml) although the results were not statistically significant ($t = 1.99$; $0.1 > p > 0.05$).

The body clearance of cephaloridine was similar after each injection of drug both in Group P animals (13.1 $\pm$ 2.3 and 11.3 $\pm$ 2.2 ml/minute, respectively) and in Group C animals (12.7 $\pm$ 1.1 and 11.5 $\pm$ 2.0 ml/minute, respectively) (Tables 10.1 and 10.2).

As an indication of the accuracy of the regression lines from which the values of half-life and volume of distribution of drug were calculated, the observed and "expected" values for serum levels of drug at specific points of time in two rabbits are shown in Tables 10.3 and 10.4. The "expected" values are those calculated from the regression line derived from the observed data.

Urine cephaloridine concentration. Estimating the 24-hour urine volume and cephaloridine concentration proved difficult. The urine samples were occasionally contaminated with faeces and the assay plates from these samples were frequently overgrown with bacteria. In addition, there was considerable variation in the 24-hour urine volumes collected. In view of this, several attempts were made to catheterise each animal 24 hours after the injection of antibiotic to ensure that no residual urine was left in the bladder. These attempts were uniformly unsuccessful. Thus the observed total urinary excretion of cephaloridine in 24 hours was highly variable between animals and little weight can be placed on its accuracy (Tables 10.5 and 10.6).

DISCUSSION

These experiments confirm that cephaloridine is nephrotoxic when given in relatively small doses to rabbits. The results are similar to those described by Atkinson et al (1966a) and Silverblatt et al (1970). In a dose of 100 mg/kg given intravenously there was evidence of mild renal damage in all animals, with one individual showing patchy calcified debris in the tubular lumina 220 hours after injection. The presence of this debris is definite evidence of previous necrosis in the upper part of that nephron.

When two doses of 50 mg/kg were given one week apart, the animals all showed mild proximal tubular necrosis and this lesion was more marked when the dose of drug was increased to 100 mg/kg, when the majority of animals showed extensive calcified debris in the tubular lumina. These findings imply that the toxicity of cephaloridine is not purely a function of the dose received at any single point in time but rather that it may increase with repeated insults particularly of marginally subnephrotoxic doses. This finding is not fully in agreement with that of Atkinson et al (1966b) who failed to find evidence of increased toxicity of this drug when given in daily doses up to 50 mg/kg for periods of up to 56 days. The causes of this discrepancy are not clear but one possible explanation is that the cephaloridine was given intravenously in the studies reported here whereas it was given intramuscularly by Atkinson and his co-workers. It is possible that the intravenous route allowed a higher concentration of drug to be released into the proximal tubular cells in a shorter period of time than was the case with the intramuscular route. In addition, it has been observed that the toxicity of cephaloridine is variable even at a given dose, at least in the rat (Boyd et al 1971).

The cause of cephaloridine-induced proximal tubular damage is at present unclear and some of the possible factors have previously been discussed in Chapter 9. The finding of calcified debris in the tubular lumina particularly localised to the outer cortical compartment has also been reported by other workers (Atkinson et al 1966a; Currie 1967; Boyd et al 1971) and this is suggestive of a vascular contribution to the renal damage. However, the

present studies demonstrate the lesion to be a predominantly proximal tubular one and since cephaloridine has been shown to localise in this area of the kidney even after a single pass through that organ (Currie et al 1966) it is difficult to avoid the conclusion that the drug itself or one of its metabolites is toxic to that cell.

The present experiments failed to reveal a significant effect of phenobarbitone either on the metabolism or toxicity of cephaloridine. The finding of a somewhat lower volume of distribution of cephaloridine after treatment with phenobarbitone is likely to be due to a reduction in the animals' circulating blood volume as a result of moderate dehydration caused by excessive sedation.

Phenobarbitone is known to cause enzyme induction both in the rabbit liver (Cram et al 1965) and kidney (Uehleke and Greim 1968). Moreover, it has also been shown that enzyme induction can lead to increased toxicity of some compounds, particularly carbon tetrachloride (Brodie et al 1971). Phenobarbitone has been shown to influence the metabolism of another antibiotic - griseofulvin - both in rats and in man (Busfield et al 1963, 1964). For this reason it seemed possible that it might increase the rate of metabolism of cephaloridine and so account for the observations of Pryor et al (1967) and Curtis and Marshall (1970) that the half-life of cephaloridine decreased with duration of regular dialysis therapy in patients receiving this treatment. Unfortunately, this explanation does not seem to be correct and the cause of this effect of regular dialysis (be it direct or indirect via one of the accompanying by-products of dialysis) is currently unknown.

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CHAPTER 11

ANTIBIOTIC THERAPY IN PATIENTS WITH END-STAGE RENAL FAILURE

Patients with chronic renal failure are at constant risk from infections. This is particularly the case in those who require regular dialysis treatment (R.D.T.). The commonest offending organisms are staphylococci (giving skin infections including those around arterio-venous shunts), Escherichia coli (giving septicaemias) and a wide range of other gram-negative organisms. One particularly troublesome organism prevalent in the regular dialysis unit of the Western Infirmary, Glasgow, at the time of this investigation, was pseudomonas pyocyaneus.

While many antibiotics are available to treat infections in such patients, antibiotic therapy is not without its dangers in these individuals. On the one hand, toxic side-effects may arise because of impaired excretion of the drug leading to raised serum levels; such toxic effects as deafness from kanamycin, encephalopathy from penicillin and neurotoxicity from colistin are well known and will be reviewed in Chapter 12. On the other hand, inadequate serum levels resulting in ineffective therapy may occur if dosage is inappropriately reduced because of renal impairment. In addition, the use of regular dialysis treatment introduces yet another variable into the use of antibiotics in these patients, since dialysis may lead to a temporary increase in the clearance of these drugs.

Because of the dangers of toxicity, some workers have suggested that potentially dangerous antibiotics should not be given to patients with severe renal impairment (Goodman and Gilman 1965). However, it would seem preferable to give the therapeutic agent of choice in such a dose

as to maintain adequate serum levels without reaching toxic heights. In practice this could mean monitoring serum antibiotic levels in all patients with renal impairment. Clearly, however, this is impractical for many hospitals and difficult to adopt routinely even in the largest institutes. Moreover since patients undergoing R.D.T. are at enhanced risk of developing Australia antigen positive hepatitis with all its attendant risks to staff and patient, it would seem advisable to minimise the distribution of blood from such individuals where possible.

As a result of the development of a R.D.T. unit in the Western Infirmary, this investigation into the use of several antibiotics in such patients was undertaken in 1967.

PATIENTS AND METHODS

The nine patients studied all had end-stage renal disease and were being maintained by twice-weekly haemodialysis using Kolff twin coil artificial kidneys with Baxter-Travenol Chron-a-coils. No patient had received an antibiotic in the two weeks prior to the studies. All were fully informed of the nature of the investigation and their consent was obtained.

Blood was withdrawn immediately prior to the intramuscular injection of a single dose of the drug under study, and thereafter, samples were taken serially up to 100 hours. All samples were allowed to clot before the serum was separated and stored at -20°C. In addition, in selected individuals urine samples were collected for 24 hours after the injection

to determine the renal clearance of the antibiotic under study. The drugs chosen for study were streptomycin, kanamycin, carbenicillin, cloxacillin and colistin.

Antibiotic assays were performed using the methods described by Humphrey and Lightbown (1952) and Grove and Randall (1955). All assays were carried out in triplicate. The streptomycin serum levels were obtained using Bacillus subtilis as test organism and DIFCO Streptomycin assay agar. The kanamycin levels were assayed on similar agar using Bacillus subtilis NCIB 8054 as test organism. Carbenicillin levels were assayed as described by Knudsen et al (1967) using Pseudomonas pyocyaneus NCTC 10490 as test organism and Penassay seed agar No. 1. Assay of cloxacillin employed similar agar to the carbenicillin assay with Sarcina lutea NCTC 8340 as test organism. Finally, the colistin assay involved Bordetella bronchieseptica ATCC 4617 as test organism growing on polymixin seed agar.

RESULTS AND COMMENTS

Nine patients were studied of whom four were presumed to have chronic glomerulo-nephritis, one had severe acute glomerulo-nephritis, one systemic lupus erythematosus, one malignant hypertension, one obstructive uropathy with infection and one polycystic kidneys with infection. All had creatinine clearances below 3 ml per minute and urine volumes below 600 ml per day. Their ages ranged from 18 to 54 years, five were male and they weighed between 48 and 72 kg prior to dialysis.

Streptomycin. (Tables 11.1 and 11.2) Two patients were given streptomycin in doses of 0.25 gram intramuscularly half an hour prior to haemodialysis. The peak serum levels attained at two hours were 14 and 16 µg/ml and levels over 8 µg/ml were maintained only for 12 hours.

Three patients who received 0.5 gram intramuscularly preceeding dialysis had peak serum levels of 24, 26 and 26 µg/ml and maintained levels exceeding 8 µg/ml for over 72 hours.

Four patients each received a single dose of 0.5 gram intramuscularly after dialysis. Peak serum levels attained in these individuals were 30 to 34 µg/ml and levels exceeding 8 µg/ml were maintained for over eighty hours.

Since streptomycin would normally be used only to treat infections with M. tuberculosis blood levels exceeding 8 µg/ml would be required over a prolonged period. For this reason, monitoring of serum antibiotic levels would be required. Nevertheless, the results indicate that for adult patients weighing between 48 and 66 kg, a single dose of 0.5 gram streptomycin given before dialysis will result in adequate serum levels for 72 hours. A similar dose given after dialysis is likely to be associated with blood levels exceeding 30 µg/ml in the initial period and so should be avoided.

Kanamycin. (Tables 11.3 and 11.4) Five patients each received a single dose of 0.5 gram kanamycin intramuscularly half an hour before dialysis.

The dose received varied from 7.7 to 10.4 mg/kg body weight. Peak serum levels attained lay between 24 and 28 µg/ml. Levels exceeding 8 µg/ml were maintained for periods up to 60 hours after injection in all cases and over 72 hours in some (Figure 11.1).

Four patients each received 0.5 gram intramuscularly after completion of dialysis. Peak serum levels ranged from 22 to 32 µg/ml and levels exceeded 8 µg/ml for over 72 hours in all patients (Figure 11.1).

Kanamycin is indicated largely in the therapy of infections caused by E. coli and Proteus organisms. The majority of the former are sensitive to this drug at concentrations of 5 µg/ml and the latter at 8 µg/ml. The results indicate that for patients weighing between 49 and 65 kg, a single dose of 0.5 gram kanamycin given before dialysis will provide therapeutic levels in the serum for up to 72 hours in the majority of cases. A similar dose given after dialysis will give higher serum levels for a longer time at the risk of an initial potentially toxic serum level.

Colistin. (Tables 11.5 and 11.6) Three patients each received a single 100 mg dose of colistin intramuscularly before dialysis. Peak serum levels attained were between 3.6 and 4.6 µg/ml and levels over 3 µg/ml lasted for only eight to 12 hours after the injection. Because of the low serum levels attained, a further four patients were given a dose of 150 mg before dialysis. Peak serum levels attained were 6.5 µg/ml to 7.5 µg/ml with levels exceeding 3 µg/ml for over 40 hours in all cases.

Three patients received colistin 150 mg intramuscularly after dialysis. In all cases, peak serum levels were higher than when the drug was given before dialysis and levels over 3 µg/ml lasted up to fifty hours after the injection. The effect of dialysis on serum colistin levels was considerably less than with streptomycin or kanamycin (Figure 11.2).

Colistin may well be the drug of choice for treating an infection with pseudomonas pyocyaneus. The levels obtained with a dose of 100 mg were inadequate for this purpose. With a dose of 150 mg, higher, more sustained blood levels were obtained whether the drug was given before or after dialysis. The degree of retention of this drug was less than expected in view of the observation that it is excreted largely by the kidneys (Colley and Frankel 1963). Colistin levels over 5 µg/ml are bactericidal for 90% of pseudomonas strains and such levels can be attained by giving 150 mg each 24 hours, giving the dose before dialysis on that day.

Much higher levels can be attained by giving large doses intravenously but there have been reports of convulsions, coma, and respiratory arrest following such usage in uraemic patients (Greenberg and Sanford 1967).

Carbenicillin. (Tables 11.7 and 11.8) Four subjects received one gram intramuscularly half an hour before dialysis. Peak serum levels attained were 26 to 32 µg/ml and levels exceeding 12 µg/ml were maintained for twelve hours in all subjects (Figure 11.3).

When a similar dose was given to three patients after dialysis, the peak levels measured were 46 to 54 µg/ml and levels over 12 µg/ml were recorded in all patients for up to 30 hours after injection.

Carbenicillin is bactericidal for 90% of Proteus species at levels above 12 µg/ml. Thus when given in one gram doses to adults whose weights ranged from 53 to 69 kg, levels over 12 µg/ml resulted for twelve hours if given before dialysis, and 30 hours if given after the procedure. In view of the relative safety of the drug (see Chapter 12) it would seem advisable to give it in a dose of one gram daily, giving the dose on dialysis days after the completion of dialysis.

Cloxacillin. (Tables 11.9 and 11.10) Four patients were each given a single dose of cloxacillin--one gram intramuscularly--half an hour before dialysis commenced. Peak serum levels attained were 36 µg/ml to 42 µg/ml, with levels over 10 µg/ml being present for eight hours in all cases.

When a similar dose was given after dialysis, the peak serum levels were similar, but the duration of effective blood levels was increased to twelve hours (Figure 11.4).

The present study indicates that retention of cloxacillin is not marked in patients requiring R.D.T. Since 100% of penicillinase-producing staphylococci are destroyed at blood levels over 3 µg/ml, a single one gram dose given at the end of dialysis and repeated daily, will give sufficiently high blood levels for all such organisms.

Urine antibiotic levels. A 24-hour sample of urine was collected from a selected patient who received the studied antibiotic after dialysis. This sample was assayed for the specific antibiotic activity but in no case was such activity clearly demonstrated. This result indicates that the proportion of antibiotic removed by glomerular filtration in these patients was exceedingly small.

DISCUSSION

The results described above are limited because of the small numbers of patients available for study. Nevertheless, they indicate the blood levels of antibiotic which can be attained after a standard dose of drug is given to patients on R.D.T. Using this data, recommendations can be made concerning the dose of these drugs required by such individuals--Table 11.11. These recommendations are similar to others subsequently published in the literature (for review see Chapter 12).

The present results differ from others mainly in the case of colistin. Curtis and Eastwood (1968) found considerable prolongation of colistin half-life in patients on R.D.T. However, these workers were giving larger doses of this drug intravenously and consequently were dealing with higher serum levels. In addition, they reported an increased rate of removal of the drug during dialysis--a feature which was not prominent in the present study. This may in part be explained on the basis of the higher serum levels and in part on differences in the artificial kidneys used, since

these workers were treating patients with a two-layer Kiil dialyser using a cuprophane membrane which may well be more permeable than the cellophane one used in Baxter Chron-a-coils.

Finally, it should be emphasised that the data presented here reflect total serum concentrations of antibiotic present at the time of assay. No attempt was made to measure the fraction of drug which was protein-bound. It is possible that renal failure could alter the protein binding of antibiotics--a possibility which has recently been demonstrated for the sulphonamides (Anton and Corey 1971) and for diphenylhydantoin and demethylimipramine (Reidenberg et al 1971). Were this to be the case, then the blood levels reached in these patients could prove less effective at treating the target infection than similar levels in patients without renal impairment.

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CHAPTER 12

ANTIBIOTIC THERAPY IN RENAL FAILURE:

A REVIEW

The regulation of drug therapy in patients with renal disease is fraught with difficulties. Although it is well known that drugs normally excreted by the kidneys will be retained in the body for longer than normal periods in patients with renal failure, the dose modifications necessary to obtain therapeutic, non-toxic levels of drug over the required time intervals are difficult to calculate. As a result of this, incorrect dosage is not infrequently given to such patients who are therefore at a greater than normal risk of developing both adverse reactions to drugs and an ineffective response to therapy, due on the one hand to relative overdosage and on the other to relative underdosage. Although the latter is more difficult to prove, Smith, Siedl and Cluff (1966) in one of the earliest efficient prospective drug monitoring systems developed in the United States, reported that adverse reactions to all drugs were two and a half times more frequent in patients with presenting blood urea nitrogen levels of over 40 mg per 100 ml, than in those with presenting levels below 20 mg per 100 ml. This work has subsequently been confirmed by a similar group working in Boston (H. Jick, personal communication, 1971). Moreover, in a study of 178 episodes of acute central nervous system disease occurring in 103 uraemic subjects, Richet, deNovales and Verroust (1970) noted that 61 (34%) were definitely or probably drug related. Clearly the effect of renal damage on a patient's ability to effectively handle drugs is of immediate and practical importance. Particularly is this the case with antibiotics, the majority of which are excreted by the kidney to a variable extent.

Although it has been appreciated for some time that reduction either in the dosage of drug given or in its frequency, is necessary to avoid side-effects in such patients, these reductions must be sufficient to eliminate the hazards of drug accumulation, while permitting adequate dosage for therapeutic purposes. Furthermore, varying degrees of renal failure will demand different dose regimes and in those with virtually no renal function, the effect of dialysis on drug metabolism and elimination will further complicate the issue. Once therapy has started, other variables may assume importance. For example, effective therapy of a urinary tract infection may improve renal function with a subsequent increase in the patient's ability to handle the drug, resulting in a reduction in serum levels below those necessary to completely eradicate the initial infection. Conversely, renal damage may occur after administration of some antibiotics, leading to a cycle of events precipitating higher, more toxic blood levels of drug and so on.

Despite these hazards, antibiotic therapy is frequently required in patients with renal failure. Infection is a major cause of death in such patients. It may involve the urinary tract and result in deteriorating renal function, particularly in those with pre-existing renal disease (e.g. polycystic kidneys), or it may involve other systems such as lung or, in the case of regularly dialysed patients, an arterio-venous shunt site. For these reasons, it is clear that effective methods of calculating appropriate doses of antibiotics in patients with renal impairment must be developed. Although several workers had wrestled with this problem prior

to 1965 (Humphrey, 1944; McDermott, 1947; Anderson and Brodersen, 1949), it was not until the studies of Kunin and Finland (1959a), that a more rational, practical approach to the problem was developed. Since 1960, many workers have studied the use of antibiotics in renal disease; however, concise information on the dosage of these drugs is frequently lacking. To understand the reasons for this requires some knowledge of the mechanisms involved in drug elimination from the body.

MECHANISMS OF DRUG EXCRETION

At normal therapeutic concentrations, most drugs are removed from the body at a rate dependent upon the quantity present in the body. This rate of removal is proportional to the plasma concentration of the drug once tissue equilibration has taken place. The simplest method of expressing the rate of drug elimination is by calculating the time required for plasma concentrations of drug to fall to half the peak, post tissue-equilibration level (the $T_{1/2}$ of the drug). Such a calculation is readily performed in the clinical setting and is the basis of much of the work done on antibiotic dosages in patients with renal failure. Unfortunately, it has several drawbacks, of which two are of practical importance: firstly, the $T_{1/2}$ measured after a single dose of drug is frequently shorter than that measured after a multiple dosage schedule is interrupted to perform the calculation. This is due in part to a failure to obtain true blood-tissue equilibration during the period after the initial dose was given. Under these circumstances, the observed

half-life will reflect both the "true" half-life together with the rate at which the drug leaves the plasma to enter the tissues during the period of equilibration (Martin, 1965). Secondly, the above technique tends to underestimate the true excretion rate of strongly protein bound drugs, since after administration of such a drug a large reservoir of bound drug will be present in the tissues. As unbound drug is eliminated from the plasma, it will be replenished from this reservoir, resulting in an apparently low rate of fall in concentration of drug in the serum. If a drug is excreted entirely by the kidney, it has been shown that the half-life depends upon the rate at which the drug is removed from the plasma by the kidney and also upon its volume distribution (Goldstein et al, 1968).

Thus:

$$T_{1/2} = \frac{k \times \text{Distribution Volume}}{\text{Renal Clearance}}$$

where k = constant (0.693)

This distribution volume is equal to the amount of drug present in the body divided by the concentration of drug present in the plasma. It therefore depends upon a large number of variables such as the degree of protein binding and lipid solubility of the drug, the extra-cellular fluid volume of the treated patient, and the concentration of plasma proteins in this subject. Since there is no evidence that the degree of lipid solubility or water solubility of a drug is altered in patients with renal disease as compared to those with normal renal function, the most

important variables in this context are the extra cellular fluid volume, the extent of protein binding, and the plasma protein concentrations. Thus dehydration will lower the distribution volume of most drugs and overhydration will increase it.

Similarly, patients with markedly low serum protein levels, especially serum albumin levels (e.g. those with severe nephrotic syndrome) may have higher serum levels of unbound drug per unit dose, than those with normal serum albumin levels (Rolinson, 1967). In addition, the affinity of plasma proteins for certain drugs may be altered by disease states; examples of this are the reduction in protein binding of sulphonamides in uremic patients (Anton, 1968; Anton and Corey, 1971) and of diphenylhydantoin in uremic serum (Reidenberg et al, 1971).

Thus it can be seen that a large number of factors may interact to affect the handling of a drug in patients with renal impairment. Moreover, such patients who require hospitalization are likely to be given many drugs in that admission. The average in-patient in a British hospital may receive from four to nine drugs during his admission (Hurwitz, 1969), a figure similar to that observed in Boston by Jick and his colleagues (1970). When only those patients admitted with blood urea nitrogen levels over 40 mg per 100 ml are considered, the average number of drugs received per admission rises to around 12 (Jick, personal communication) and hence the possibility of a therapeutically significant interaction between drugs is increased in such patients.

In the remainder of this chapter, the indications, hazards, and dosage modifications necessary for the use of a wide variety of antibacterial substances in patients with renal failure will be reviewed, paying particular attention to the various variables discussed above.

Additional accounts of this subject may be found in works by Kunin (1967), Finegold et al (1969), Bennett et al (1970), and Reidenberg (1971). For a detailed account of the possible consequences of altering dosage schedules either by reducing the administered dose or by prolonging the time interval between doses, see the excellent review article by O'Grady (1971).

PENICILLIN

Penicillin is a remarkably non-toxic drug, a property which is shared to a lesser extent by the semi-synthetic penicillins. Eagle and Newman (1947)showed that the clearance of this drug by the kidney exceeded 500 ml/minute and noted that it accumulated in patients with renal failure. Given intramuscularly, penicillin G has a half life in normal subjects of about one hour rising to around 10 hours in the anuric subject (Kunin and Finland 1959b). Despite this, few cases of penicillin toxicity have been reported in patients with renal failure. Massive doses have been reported to cause neuromuscular excitability and convulsions (New and Wells 1965), but the evidence implicating penicillin is inconclusive, since the cases concerned all occurred in patients with previous renal dysfunction. It is conceivable that the excitability was caused not by the penicillin itself but rather by its accompanying cation. Twenty mega units of benzyl penicillin contain some 32-34 mEq potassium which, under rare circumstances, could if given intravenously, give rise to neurological problems. Baldwin et al (1968) reported seven cases of uraemia, fever, eosinophilia and infiltration of the renal interstitium with eosiniphils and mononuclear cells which occurred in patients given large doses of both penicillin and methicillin, however, these authors felt that the evidence against penicillin was not impressive (see later under methicillin). Bloomer et al (1967) reported four cases of "penicillin-induced encephalopathy" in patients with severe renal failure. Here again, the doses of drug used

were excessive even under conditions of normal renal function. It would appear therefore that within wide limits, penicillin can safely be given to those with renal failure, the only potential problem occurring in the anephric subject or in patients during regular dialysis, when large doses should be given slowly to avoid sudden increase in the concentration of the accompanying cation.

In patients with renal failure, therapeutic blood levels of penicillin may be obtained for most sensitive organisms by giving one million units of benzyl penicillin 12 hourly (Kunin and Finland 1959b). Since this drug is dialysable (Schreiner 1970), the dose should be given at the end of dialysis. If the drug is required in high doses, for example in the treatment of subacute bacterial endocarditis, the dose given should be regulated by blood level estimations of both penicillin and its accompanying cation and relating the former to the known minimum inhibitory concentration of the organism.

SEMI-SYNTHETIC PENICILLINS

Ampicillin. The most widely used of the semi-synthetic penicillins, at least in the United Kingdom and the United States, ampicillin has a wide spectrum of antibacterial activity (Goodman and Gilman 1970). It is highly effective against most strains of E. coli and some of Proteus species, although less effective than penicillin against sensitive strains of gram-positive cocci. The half life of this drug in normal individuals is about 1.8 hours, increasing to 18 hours in patients with creatinine clearance levels below 4 ml/minute (Kunin and Finkleberg 1970). The main adverse reaction occurring with ampicillin is skin rash. In a large series of consecutive hospitalised patients receiving ampicillin, rash occurred with a frequency of 9.5% compared to a frequency in those not receiving ampicillin of 1.8%, thus the risk attributable to ampicillin was 7.7% (Shapiro et al 1969). Although no comment upon dosage of drug received by their patients was made in the published report, there was no evidence that rash appeared more frequently either in patients with impaired renal function as manifested by a presenting blood urea nitrogen level of over 25 mg/100 ml, or in patients receiving a greater than normal dosage of two to three grams per day (Shapiro, personal communication). This finding is compatible with the postulated allergic basis of ampicillin-induced skin rash. Lee and Hill (1968) recorded an increased frequency of rash attributable to ampicillin in a small series of patients with renal failure. However, it is possible that this apparent increase in frequency over those without renal impairment was due in part to better observation of the former patients together with a somewhat greater baseline frequency of rash in patients with renal failure.

In serious infections in patients with severe renal impairment, therapy with ampicillin should be given in doses of up to 500 mg six hourly if required. Should rash be encountered, the usual course is a benign one, involving the patient in only minor discomfort. Although such discomfort should obviously be avoided where possible, it is to be preferred to the more serious complications which may arise if a substitute, more toxic antibiotic is employed. Kunin and Finkleberg (1970) made the additional observation, that while ampicillin reached good concentration in the urine of patients with mild to moderate renal failure, it did not do so when the creatinine clearance fell below 5 ml/minute. Thus ampicillin is likely to be ineffective against organisms causing urinary tract infection in such patients--a fact which may be of particular relevance to the early phase after cadaveric renal transplantation.

Since ampicillin is haemo-dialysable (Schreiner 1970), dosage of the drug given to patients requiring dialysis, should be given at the end of this procedure. Normal dosage may be given to patients with renal failure requiring peritoneal dialysis, since the drug is not substantially cleared by this technique (Ruedy 1966).

Carbenicillin. This drug is one of the newer semi-synthetic penicillins which is effective against many gram-negative organisms. Blood levels around 12 µg/ml are bactericidal for 90% of proteus species, and at this level, the drug is virtually non-toxic (Goodman and Gilman 1970). It has also been advocated for the treatment of pseudomonal infections when blood levels of 100 µg/ml are required; however these levels are difficult to achieve in

patients with normal renal function. Johny et al (1969) suggested that carbenicillin remains virtually non-toxic at such high serum levels, but Lurie et al (1970) and Waisbren et al (1971) reported the development of severe haemorrhagic diathesis in patients given high doses (up to 24 G/day), however, these patients were all suffering from renal failure and the association with carbenicillin may be coincidental.

Carbenicillin is retained in the body in renal failure and is fairly rapidly removed by haemodialysis (Schreiner 1970). In the treatment of infection with sensitive organisms (M.I.C. < 12 µg/ml) one gram 12 hourly will suffice in patients with creatinine clearances below 20 ml per minute. Those on regular dialysis therapy require doses of approximately one gram (14-15 mg/kg) daily the dose being given at the end of dialysis (see Chapter 11).

The high serum levels necessary to eradicate pseudomonal infections can be achieved in patients with renal failure with relative ease. Eastwood and Curtis (1968) suggest that patients with creatinine clearances below 5 ml/minute require 2 G eight to 12 hourly to maintain serum levels around 100 µg/ml with an increase in frequency of dosage to four hourly during dialysis. Such a policy is also advocated by Hoffman et al (1970) who demonstrated an increase in the half life of carbenicillin in the serum from the normal level of one hour to over 15 hours in severe oliguric renal failure.

Methicillin. Methicillin was the first penicillin which was effective against penicillinase producing staphylococci. Its use is largely confined to the treatment of infection with staphylococci which are frequently the cause of shunt infections or of pneumonia in patients undergoing regular dialysis treatment. This drug is retained in patients with severe renal failure (Bulger et al 1967), who require a reduction in dosage usually attained by increasing the normal interval between doses from four to eight or 12 hours. Serum levels of methicillin are not significantly affected by either peritoneal or haemo-dialysis (Gilbert and Sanford 1970). Baldwin et al (1968) and Brauninger and Remington (1968) described several patients who developed renal damage associated with allergic phenomena after administration of methicillin. While Baldwin and his co-workers suggested that this effect was dose-related, it is more likely that Brauninger and Remington are correct in implicating a hypersensitivity response independent of administered dose. For this reason, methicillin should probably be avoided in patients with renal involvement in systemic collagenoses or following transplantation.

Isoxazolyl Penicillins. Oxacillin, cloxacillin and dicloxacillin are all effective against penicillinase-producing staphylococci. They are given orally and are excreted in part by filtration by the glomeruli and secretion by the tubules (Marcy and Klein 1970). In the case of oxacillin, dosage reduction does not seem to be required when the drug is given to patients with renal failure (Bulger et al 1964), whereas with cloxacillin and dicloxacillin a reduction in dosage has been recommended (McCloskey and Hayes 1967,

Williams, et al 1967). When given to patients on regular dialysis treatment, one gram cloxacillin daily will maintain serum levels over 5 µg/ml for 24 hours--the dose being given after the procedure on dialysis days (see Chapter 11). This serum level should be sufficient to eradicate most sensitive strains of penicillinase-producing staphylococci (M.I.C. < 3 µg/ml).

CEPHALOSPORINS

Several cephalosporin antibiotics have come into general use since their initial discovery by Brotzu in 1948. In the United Kingdom, cephaloridine has been the most widely used drug, with cephalothin and cephalexin becoming available more recently. These drugs all have a wide antibacterial spectrum, being bactericidal to many gram-positive and gram-negative organisms. Their main clinical use is against penicillinase-producing staphylococci, but they are also effective aginst Clostridia, streptococci, and a variety of gram-negative organisms, including E. coli. (Muggleton and O'Callaghan 1967). Cephaloridine and cephalothin must be given by parenteral route, but cephalexin can be administered orally.

Cephaloridine. Within six hours of an intramuscular injection, 75% of cephaloridine is excreted in the urine, and this excretion is unaffected by the coincidental administration of Probenicid (Naumann 1967). Most of a single intramuscular dose is excreted within 24 hours by glomerular filtration. The half life of cephaloridine in the serum of normal subjects is 94 minutes. This is prolonged to three to four hours when the creatinine clearance falls below 40 ml/minute. With a creatinine clearance of 5 ml per minute the serum half life of cephaloridine is 20 to 24 hours. Urine concentrations of cephaloridine fall from over 1000 µg/ml at creatinine clearances of 70 ml/minute to under 80 µg/ml at creatinine clearances of less than 10 ml/min. (Pryor et al 1967). These authors also observed

a progressive decline in the half life of this drug in the serum of an anephric patient, from an initial value of 21.5 hours to one of 8.2 hours after a period of several months of regular dialysis treatment. This observation was confirmed by Curtis and Marshall (1970) who noted an inverse relationship between the serum half life and the duration of regular dialysis therapy. The reason for these observations is not clear, but it is possible that the observed increase in the half life of cephaloridine is due to an enzyme induction effect of barbiturates which are frequently given to these patients.

Cephaloridine resembles penicillin and methicillin with respect to its retention in the body in chronic renal failure since a significant portion of it may be inactivated by non-renal mechanisms (Kunin and Atuk 1966). For patients on regular dialysis treatment, Curtis and Marshall recommended a dose of one gram cephaloridine intravenously daily, increased to six-hourly during dialysis if the drug is given for staphylococcal infections. In the treatment of gram-negative infections in patients on regular dialysis, they recommend a dose of one gram 12-hourly intravenously, increased to one gram, four-hourly, intravenously during dialysis. They suggest that the drug be given slowly, dissolved in 20 ml of saline.

While the use of cephaloridine in patients with no significant residual renal function is probably safe, there is some evidence to suggest that its use in patients with renal impairment not yet requiring dialysis is potentially dangerous. Perkins et al (1968) showed that the drug was nephrotoxic in rabbits and monkeys when given in high doses.

Foord (1969), summarizing the evidence for nephrotoxicity of cephaloridine, concluded that serum levels over 100 µg/ml should be avoided. He noted also that in the 36 cases of acute renal failure in which cephaloridine was a suspected cause, two thirds of the patients were known to have impaired renal function at the beginning of treatment. Finally, he observed that in several of these patients cephaloridine had been given coincidentally with diuretics, particularly furosemide. The studies reported in Chapter 9 suggest that in the presence of minor degrees of renal damage, cephaloridine may produce severe acute tubular necrosis at serum levels which are below the suggested nephrotoxic level, at least in animals. This side effect of cephaloridine is enhanced by the coincidental administration of frusemide, and until further information is available, it may be advisable to avoid the use of this drug in patients with renal impairment where alternative therapy is possible.

Cephalothin. Cephalothin is normally excreted rapidly in the urine but in chronic renal failure it is metabolized in the liver, so that the normal half life in the serum of 0.85 hours is extended only to 2.9 hours in the anuric patient (Kunin and Atuk 1966). Dose modifications are therefore probably not required in patients with renal failure. There is at present no evidence available that cephalothin is nephrotoxic in man. Perkins et al (1968) failed to demonstrate a nephrotoxic effect in rabbits and monkeys. It would appear, therefore, that cephalothin is preferable to cephaloridine in patients with chronic renal failure, although its spectrum of antibacterial activity is not quite as wide as that of cephaloridine.

Cephalexin. Cephalexin, the orally administered cephalosporin, has an antibacterial spectrum similar to cephaloridine, and is likely to be effective against most organisms found in the urinary tract, except pseudomonads. The antibiotic is rapidly cleared from the body by glomerular filtration, and 95% of an oral dose can be recovered from the urine in normal patients within six hours. The half life of cephalexin in the serum is prolonged from one hour in normal subjects to approximately 20 to 30 hours in the anephric patient (Kabins et al 1970; Lindquist 1970). Serum levels achieved after a single oral dose become slightly higher as the creatinine clearance decreases, but at all levels of renal function the minimum level of cephalexin in the urine exceeded 32 µg/ml between four and 18 hours after the oral dose. At lower levels of creatinine clearance only approximately 60% of the ingested dose was recoverable in the urine, suggesting an extra-renal route of disposal. The serum half life of cephalexin is reduced to four to six hours during dialysis (Bailey et al 1970). Neither those workers nor Gower and Dash (1969) noted any evidence of deterioration in renal function during cephalexin therapy, but Galbraith and Pilsworth (1969) reported a fall in creatinine clearance in five out of 14 patients given this drug. Until further experience has been gained with cephalexin it is probable that the dosage should be reduced as the glomerular filtration rate falls. The dose schedule suggested by Bailey et al (1970) is to give 500 mg as a loading dose, repeated eight-hourly if the creatinine clearance exceeds 50 ml/minute; 12 hourly if the creatinine

clearance falls between 20 ml/minute and 50 ml/minute; and each day if the creatinine clearance is below 20 ml/minute. On dialysis days, an extra dose of 500 mg at the end of dialysis should be administered. Such doses of cephalexin will be adequate for most urinary tract infections, but should be approximately doubled for major systemic infections. A similar dosage schedule has been recommended by Lindquist et al (1970).

STREPTOMYCIN

Although most commonly used in the treatment of tuberculosis, streptomycin is also effective against many gram-negative organisms. It is given parenterally and the majority of each dose is excreted in the urine. Kunin and Finland (1959b) demonstrated that streptomycin accumulates in patients with renal failure, the half-life extending from a normal value of 2.4 hours to over 50 hours in the anuric subject. Streptomycin is cleared by glomerular filtration and is readily removed by haemodialysis (Edwards and Whyte 1959). Toxic effects are related to magnitude and duration of therapy and are rare if blood levels of the drug are kept below 25 µg/ml.

The major current use for this drug is in the therapy of tuberculosis, a not infrequent complication of chronic renal failure. During therapy streptomycin levels should be kept between 8 and 25 µg/ml (90% of strains of M. tuberculosis are sensitive at 8 µg/ml). To achieve this in patients with creatinine clearances below 10 ml/minute, Kunin and Finland (1959b) recommend a loading dose of 1 G followed by 0.5 G every two to three days. The dose should, however, be adjusted by frequent measurement of the blood level of drug to avoid dangerous accumulation.

In patients requiring regular dialysis treatment, safe, effective levels of streptomycin can be maintained by giving 10 mg/kg body weight at the end of each (twice-weekly) dialysis (see Chapter 11). Ogg et al (1968) described the treatment of tuberculosis in a patient on regular dialysis treatment. These workers gave similar doses to those recommended

here, but noted mild vestibular damage after a total of 11 G streptomycin were given in five weeks. Thus serial assays of serum streptomycin levels are required to regulate such long-term therapy.

Additonal Therapy for Tuberculosis. Ogg et al recommended isoniazid in a dose of 3 mg/kg body weight per day together with pyridoxine 20 mg/day to prevent deficiency of this vitamin during therapy (Robson and Sullivan 1963), and para amino salicylic acid (PAS) in a dose of 6 G/day. While such regimes give a guide to therapy, long term treatment of a chronic infection such as tuberculosis requires serial measurement of antibiotic levels.

More recently, McGeachie et al (1970) studied the use of rifampicin in patients with renal failure. This drug is excreted mainly in the bile and so can be given in normal doses to patients with renal failure. Thus there is a strong case for using it as a primary agent in the therapy of tuberculosis complicating renal failure.

KANAMYCIN

Kanamycin is an extremely effective drug in the treatment of gram-negative infections. Fekety et al (1962) demonstrated that 90% of E coli strains were sensitive to serum levels of 5 µg/ml and 80% of Proteus species to 8 µg/ml. However, the use of kanamycin in renal failure has been restricted because of its side effects--mainly oto-toxicity and nephrotoxicity (Kunin and Finland 1959b).

This drug is stable in the body and is almost entirely excreted by the kidney. Sørenen et al (1967) demonstrated a linear prolongation of the half life of this drug in the serum with falling creatinine clearance levels. Although toxic effects are usually recorded when serum levels exceed 25 µg/ml, there have been reports of such at lower blood levels (Toma and Main 1967). Sørenen et al suggested a complex dose regime based on serum creatinine levels to predict the optimal non-toxic dose of the drug to give to those with renal failure. However, elegant studies by Orme and Cutler (1969) gave more information on this drug's behaviour in patients with renal failure. By measuring simultaneous renal clearances of creatinine, inulin, PAH and kanamycin in 34 subjects, they noted that kanamycin clearance approached that of inulin and suggested that the drug was distributed in the inulin space (i.e. extracellular water). Thus changes in extracellular fluid volume will make significant differences to the half life of kanamcyin; a reduction in extracellular

fluid reducing the half life considerably when compared with the half life in an overhydrated patient with the same glomerular filtration rate. These workers suggested that the half life of kanamycin could be determined by the formula noted below:

$$T_{1/2\ (\text{hours})} = \frac{3.6 \times \text{body weight (kg)}}{C_{\text{creatinine}}\ (\text{ml/min})}$$

and recommended a dosage of 7 mg/kg body weight given at intervals of three times the half-life of kanamycin. Even this regime may require modification if gross overhydration or underhydration exists. While this work represents the most scientific approach to determining kanamycin dosage for those with renal failure who do not require regular dialysis, it is probably still advisable to check efficacy and safety of the dose given by regular estimations of serum kanamycin levels. Nevertheless, when McCloskey and Becker (1970) investigated the reliability of this method they found that in practise when the patients' serum creatinine level was below 9 mg/100 ml the method was highly reliable, although it was less so when initial serum creatinine levels were over 9 mg/100 ml. The finding that 83% of kanamycin orders prescribed for 12 patients behaved as predicted is impressive evidence in favour of this method.

In those patients requiring regular dialysis, 0.5 g kanamycin given at the beginning of dialysis will avoid dangerous levels of drug yet attain therapeutic concentrations for up to 80 hours (Ory et al 1966; Chapter 11).

GENTAMYCIN

Gentamycin is effective against a wide range of gram-positive and gram-negative bacteria including pseudomonads, proteus species, and various staphylococci. Serum levels above 4.5 µg/ml are bactericidal for these organisms (Weinstein 1967). Like kanamycin, gentamycin produces vestibular damage if excessive blood levels are reached (Jao and Jackson 1964) and it has been recommended that blood levels of greater than 10 µg/ml be avoided (Curtis et al 1967).

Gentamycin is excreted by glomerular filtration and there is a strong inverse correlation between serum half life and the glomerular filtration rate (Kunin 1968; Gingell and Waterworth 1968; Bergen et al 1971). For normal subjects, the mean daily dose of gentamycin is 2.4 mg/kg body weight. Gingell et al (1969) recommended modifications in the dose given to patients with varying degrees of renal failure, suggesting that, after an initial dose of 1 mg/kg body weight, subsequent doses be determined by altering the interval between doses:

Dose and Frequency	G.F.R. (ml/min)	Serum Creatinine (mg/100ml)
1 mg/kg 8 hrly	> 50	< 1.2
1 mg/kg 12 hrly	30-50	1.2-2
0.5 mg/kg 24 hrly	10-30	2-5
0.5 mg/kg 36 hrly	5-10	5-10
0.5 mg/kg 48 hrly	< 5	10+

As an alternative method of calculation McHenry et al (1971) noted that "for clinical purposes, the $T_{1/2}$ of gentamycin could be estimated by multiplying the value of the serum creatinine (mg/100 ml) by four." These authors recommended administering gentamycin in a dose of 1 mg/kg body weight at times equal to two half-lives.

Because of the considerable similarity between kanamycin and gentamycin, it is likely that variations in extracellular water will also influence the half-life of this drug and so estimations of serum levels will still be advisable during prolonged therapy.

In patients requiring regular dialysis treatment, satisfactory levels of gentamycin can be obtained by giving 1 mg/kg body weight at the end of each twice-weekly dialysis (Curtis et al 1967).

THE POLYMIXINS

Colistin (Polymixin E). This drug is active against many gram-negative bacteriae, but its use is largely confined to the treatment of pseudomonal infections. It is bactericidal to 90% of pseudomonads at serum levels of 5 µg/ml--a level which is readily attained in normal subjects by giving doses of 5 mg/kg body weight per day (Goodman and Gilman 1970).

MacKay and Kaye (1964) studied the effect of impaired renal function on the serum levels of this drug and recommended a dose regime for those with renal impairment:

Dose (mg/kg body weight)	Interval	$C_{creatinine}$ (ml/min)
2.5	12 hrs.	normal
1.5	12 hrs.	> 40
1.5	18-36 hrs.	< 40
2.0	given only once	0

Similar studies were performed by Goodwin and Friedman (1968).

Brumfitt et al (1966) recorded a fall in creatinine clearance lasting up to four weeks in patients with normal renal function given a single dose of colistin. While such a fall may, under certain circumstances, be tolerable in patients with normal renal function, it could prove disastrous in those with even mild pre-existing renal impairment. This was confirmed by Price and Graham (1970) who reported that, in 14 patients given the high dose of 26 mega units per day for the therapy of severe klebsiella infection,

all showed a considerable fall in creatinine clearance and several died as a result of this. At autopsy these patients showed evidence of acute tubular necrosis. Renal function gradually returned to normal following withdrawal of the colistin thus confirming the observations of Brumfitt and his co-workers.

In a recent comprehensive study of 288 consecutive patients receiving colistin in the Massachusetts General Hospital, Koch-Weser et al (1970) recorded an overall adverse reaction rate of 25.1%--that is, one in every four patients receiving the drug experienced unwanted effects as a result. While this figure is higher than that found within the Boston Collaborative Drug Surveillance Program (see page 95), the techniques used and the patients studied are not comparable. Of the patients studied by Koch-Weser, twenty per cent developed adverse reactions involving the kidney. Thus it is clear that this drug is nephrotoxic--a finding which has been denied by some workers (Taylor and Allison, 1962; Goury-Laffont 1962). In addition to their description of the prevalence of adverse reactions to this drug, Koch-Weser and his co-workers noted that these reactions were more common in heavier patients and concluded that the administration of colistin in doses proportional to the patients' weight resulted in relative overdose for heavy patients and relative underdose for light patients. Dosage calculation based on the square root of the patient's weight:--

$$\text{Daily Dose} = 15 \text{ mg} \times \sqrt{\text{weight in lbs.}}$$

was shown to be the most efficient method of adjusting the amount of drug required. While this calculation was based on the data obtained for colistin recipients, it is likely to have a more general relevance to the

topic of dose-weight relationships. As the rate of colistin excretion is a function of the glomerular filtration rate (MacKay and Kaye 1964) and as both the glomerular filtration rate and blood volume are more closely related to surface area (which is a function of $\sqrt{\text{body weight}}$) than to simple body weight, doses of drug which are related to surface area and the $\sqrt{\text{body weight}}$ are more likely to be of general applicability. At the present, for patients with normal renal function, it would seem reasonable to adopt Koch-Weser's dose criteria of:

Daily dose (mg) = $15\sqrt{\text{wt.(lb)}}$ or = $22\sqrt{\text{wt.(kg)}}$.

Where possible in patients with impaired renal function, the drug should be avoided.

In patients requiring regular dialysis treatment, Curtis and Eastwood (1968) consider the possible nephrotoxicity to be irrelevant and emphasise the value of this drug in treating pseudomonal infections. They suggest that a single dose of 2-3 mg/kg body weight given intravenously at the end of each twice-weekly dialysis will maintain therapeutically active blood levels in such patients. This regime is similar to that advocated in Chapter 11, however, it should be noted that it does produce transient high serum levels of antibiotic and there have been reports of convulsions, coma and respiratory arrest when colistin is given in high doses to uraemic patients (Greenberg and Sanford 1967).

Polymixin B. This drug is used under similar circumstances to colistin. Hoeprich (1970) has argued in favour of using it in preference to colistin, however, for all practical purposes, the two are interchangeable. In particular, dosage reduction for patients with renal impairment is similar with both drugs.

TETRACYCLINES

The tetracyclines are a group of broad-spectrum bacteriostatic antibiotics which show marked antagonism to concurrently administered penicillin. They may be given orally or parenterally, show a variable degree of protein binding and are excreted both in the urine and in the bile. The renal clearance of chlortetracycline is 35% of the creatinine clearance, while that of oxytetracycline is 85% of the creatinine clearance. The principal toxic effects of the tetracyclines are hepatic damage which occurs particularly if the drug is given parenterally (Dowling and Lepper 1964) and a rise in blood urea nitrogen (see Chapter 8). Photosensitivity has been recorded following demethylchlortetracycline therapy, as has persistent high fever and eosinophilia (Kasik and Thompson 1970).

Following a single intravenous dose of tetracycline Kunin et al (1959d) observed a relationship between creatinine clearance and the serum half life of the drug. In the anuric patient, the half life was approximately ten times the normal of 4.8 hours. In the case of chlortetracycline the serum half life is normal in patients with renal impairment. Thus, chlortetracycline in normal dosage would appear to be the tetracycline of choice in patients with renal impairment. However, in view of the evidence that the tetracyclines may cause a rise in blood urea nitrogen levels in a considerable proportion of those exposed, it would seem advisable to avoid these agents in patients with pre-existing renal disease.

ERYTHROMYCIN

Erythromycin is effective against many gram-positive organisms when given orally, although the organisms frequently develop resistance within a short period of time. The half life of erythromycin in the serum of anuric patients is prolonged to four to six hours, compared to a normal value of 1.4 hours (Kunin and Finland 1959b). This drug is relatively non-toxic, providing that the lauryl sulphate salt of the propionic acid ester is avoided since this derivative may cause an allergic cholestatic hepatitis (Goodman and Gilman 1970). With erythromycin stearate or lactobionate, no reduction in normal dosage is required for patients with renal failure, although data on the clearance of this drug is limited.

FUCIDIC ACID

This steroid antibiotic is bactericidal to most strains of staphylococci and is unaffected by penicillinase. Combined with penicillin, methicillin or perhaps tetracycline, it is particularly effective against gram-negative bacteriae, fungi and yeasts (Godtfredsen et al 1962; Goodman and Gilman 1970).

It is excreted by the liver, is not removed by the kidney, and is not known to be nephrotoxic. Since it is 97% protein bound, the drug is virtually unaffected by peritoneal or haemo-dialysis. No modification of dosage is required in patients with renal failure, before or during dialysis, although it has been suggested that gastrointestinal side effects may limit its oral use in patients with renal disease (Hobby et al 1970).

CHLORAMPHENICOL

Chloramphenicol is a bacteriostatic antibiotic which, at varying concentrations, is effective against some rickettsiae, many gram-negative organisms and some staphylococci and streptococci. It is rapidly absorbed when given orally, is approximately 60% protein bound and is excreted largely in the urine by glomerular filtration, where in normal individuals it attains a concentration of some 20 times that of the plasma levels. In patients with renal failure the concentration of active drug is little altered by falling creatinine clearance but the accumulation of inactive metabolites is inversely proportional to the glomerular filtration rate (Lindberg et al 1966). These metabolites are predominantly aryl amines and their derivatives which may be responsible for some of the toxic effects of chloramphenicol. They can be removed by dialysis with an efficiency of approximately half that of the removal of creatinine (Kunin et al 1959c). The most important adverse reaction to chloramphenicol is bone marrow depression which occurs with sufficient frequency to be considered a major reason for avoiding the drug where possible.

For this reason, it would seem advisable to prescribe other antibiotics to patients in renal failure, since the accumulation of potentially toxic metabolites may cause an increased frequency of adverse reactions under these circumstances. Where the drug must be used, it should be given in normal doses for as short a time as possible.

AMPHOTERICIN B

This antifungal antibiotic is effective against histoplasma, coccidiodes, candida species and cryptococcus. Although these organisms only rarely occur as systemic pathogens in Great Britain, the increasing use of renal and other transplantation procedures has lead to an increased frequency of opportunistic fungal infections with organisms likely to be sensitive to amphotericin.

In the normal individual, after a loading dose of 1 mg/kg body weight, maintenance doses of 0.5 mg/kg body weight per day will give serum levels of amphotericin considerably in excess of the necessary fungicidal levels. Unfortunately, the most frequent major adverse reaction with this drug is marked renal impairment which may occur in over one third of those treated. When given to normal individuals, amphotericin produces a wide variety of histopathological lesions in the kidney varying from glomerular proliferative changes to tubular degeneration associated with hypokalemia and renal tubular disorders (Douglas and Healy 1969). Utz et al (1964) reviewed the complications of amphotericin therapy and included hypersensitivity reactions, acute hepatocellular dysfunction, red cell aplasia and renal damage.

Bindschadler and Bennett (1969) investigated three patients with renal failure given amphotericin. They did not demonstrate a correlation between renal function and peak serum levels, nor did they demonstrate further deterioration in renal function or accumulation of the drug. Thus, despite the considerably toxicity of this drug, current evidence suggests that, if necessary, it may be given (in normal dosage) to patients with renal failure.

ETHAMBUTOL

This drug has its specific effect on mycobacteriae and on no other organisms. It is well absorbed when given orally and is excreted mainly by the kidneys. Its major toxic effect is that of a retrobulbar neuritis which results in decreased visual acuity and reduced visual fields. Fortunately this complication is reversible on withdrawal of the drug (Leibold 1966). The half life of this drug in the serum of normal subjects is four hours and this extends to 7-1/4 hours in the nephrectomised individual. Thus some reduction in dosage is necessary in patients with renal failure although exact recommendations have not yet been published. Dume et al (1971) recommended the following dosage schedules for patients requiring dialysis: 17.8 mg/kg per 24 hours during a 30-hour peritoneal dialysis; 23 mg/kg after an eight-hour haemo-dialysis; and 17.8 mg/kg per 24 hours during dialysis-free periods.

VANCOMYCIN

Vancomycin is a potent bactericidal agent used mainly in the treatment of severe staphylococcal infections, especially those due to strains resistant to other antibiotics. It is given systemically--usually intravenously--and is excreted predominantly in the urine. The half life of this drug in normal individuals is around six hours and this is prolonged in renal impairment (Lindholm and Murray 1966). Because of its considerable nephrotoxic and ototoxic properties, this drug should be avoided in those with renal impairment. Should it be required, serial blood levels are advisable. For anuric individuals, a dose of one gram intravenously may give persistent blood levels for ten days.

NITROFURANTOIN

This drug is a urinary antiseptic, effective against many gram-negative and some gram-positive organisms. When given orally, about 40% can be recovered in the urine of normal subjects (Paul et al 1959). The recovery in those with renal impairment is proportional to the creatinine clearance (Sachs et al 1968). Goff, Schlegel and O'Dell (1968) reported that blood levels of nitrofurantoin remained low after a dose of 100 mg six-hourly until the creatinine clearance fell below 14 ml/minute, when accumulation became obvious in the serum. There was an inverse relationship between creatinine clearance and urinary excretion in the patients. Schreiner (1970) noted that the drug was dialysible.

Side effects of nitrofurantoin therapy are haemolysis, hypersensitivity reactions, alimentary upsets and severe polyneuropathy, occurring particularly in patients with renal impairment (Martin et al 1962), although Craven (1971) reported five patients with peripheral neuropathy attributed to nitrofurantoin who developed symptoms in the absence of elevated levels of blood urea nitrogen.

Since therapy with this drug is likely to prove ineffective in patients with reduced creatinine clearances, because inadequate drug levels can be attained in the urine and since there is a risk of polyneuropathy complicating the therapy, the drug should not be given to patients with renal impairment. This conclusion was also reached by Felts et al (1971), who additionally demonstrated minor reduction in nerve conduction velocities in three of nine patients with urinary tract infection and impaired renal function.

NALIDIXIC ACID

This is an antibacterial substance excreted in the urine in concentrations which are sufficiently great to be bacteriostatic to many gram-negative organisms including E. coli, Klebsiella and proteus species, but excluding pseudomonas. Concentrations attained in body fluids other than the urine are insufficient to exert any antibacterial effect (Goodman and Gilman 1970). Given orally, this drug is relatively free of toxic effects. Its use in patients with renal failure has received little attention, however, Sachs et al (1968) reported 17 patients with creatinine clearances ranging from 8-121 ml/minute, who received nalidixic acid in doses of one gram six-hourly. They reported high urine concentrations even in patients with markedly diminished glomerular filtration rates. This work has subsequently been confirmed by Adam and Dawborn (1971) who noted an increased absorption and clearance of the drug when given with sodium bicarbonate. It seems likely, therefore, that nalidixic acid is a useful agent for the treatment of urinary tract infections even in those with severe renal impairment, however, under those circumstances, it is frequently desirable to attempt therapy with a bactericidal agent at first and then maintain success with a drug such as nalidixic acid. Finally, the rapid development of bacterial resistance may limit its usefulness (Ronald et al 1966).

Although most frequently given orally, some workers have given it intravenously under experimental conditions (Zinsser et al 1970). As yet however, such a procedure has not gained widespread acceptance and therefore cannot be recommended for patients with renal impairment.

SULPHONAMIDES

The sulphonamides are bacteriostatic agents effective against many gram-positive and gram-negative organisms and recently used principally in the treatment of urinary tract infection. Their antibacterial activity is inhibited by the presence of blood, pus or tissue breakdown products. Although a wide range of toxic effects has been reported with sulphonamides, including crystals of drug or metabolite in the urine and hypersensitivity reaction leading to nephropathy (Abramowicz and Edelmann 1968), these appear to be rare with the drugs currently in regular use (see Chapter 7 ; Koch-Weser et al 1971).

Sulphadimidine is a weak organic acid excreted by glomerular filtration, proximal tubular secretion, tubular reabsorption, and passive pH dependent non-ionic back diffusion. Williams et al (1968) studied the renal clearance of intravenously administered sodium sulphadimidine in normal and uraemic subjects. The clearance of this drug was found to be higher in patients with chronic renal failure than in normals, the mean clearance being 11.4 ml/minute in patients with renal impairment, and 6.3 ml/minute in normal subjects. There was no correlation between glomerular filtration rate and sulphadimidine clearance. Although in normal subjects the sulphadimidine clearance was related to urine pH this was not so in those with chronic renal failure. These authors concluded that sodium sulphadimidine was not retained in patients with chronic renal failure and that the urine levels achieved were adequate for the eradication of sulphonamide-sensitive organisms.

With sulphamethizole on the other hand, the serum half life is considerably prolonged in patients with low glomerular filtration rates (Goff et al 1968). Nevertheless these workers recorded that even with glomerular filtration rates of 8 ml/minute this sulphonamide attains bacteriostatic concentrations in the urine, thus the evidence suggests that some sulphonamides, notably sulphadimidine, can be given in normal dosage to patients with even severe renal impairment. Moreover, Koch-Weser et al (1971) noted that in a large series of prospectively monitored patients, adverse reactions to the sulphonamides sulfisoxazole and sulfamethazole, were infrequent, occurring in about 3.1-3.3% of the monitored patients. In this series no case of nephrotoxicity attributable to sulphonamides was observed.

Recently the sulphonamide-trimethoprim preparations have gained in popularity for the treatment of urinary tract infections. These drugs are however dispensed in fixed dose combinations which is unfortunate since there are substantial differences between the sulphonamides and trimethoprim in terms of their handling by the kidney. In particular, while sulphamethoxazole is not retained in moderate renal impairment, trimethoprim clearance falls sharply with declining renal function (Sharpstone 1969). Thus in such patients careful attention should be paid to possible adverse effects of trimethoprim on the bone marrow. Although there are reports of haematological reactions to this combination, the frequency with which these occur is at present ill defined (for review see under Evaluation on New Drugs 1971). In addition, it has been noted

that alimentary upsets are common when this drug is given to patients with renal impairment (see Chapter 4 ; McGeown 1970).

Finally because the concentration ratio of the two drugs in this combination vary with the glomerular filtration rate and with urine pH the effect of such variations on the efficacy of therapy is unknown.

PERITONEAL DIALYSIS

Patients undergoing peritoneal dialysis frequently have infections requiring therapy with antibiotics. In addition, many physicians adopt the practice of adding small amounts of antibiotics to the infused dialysis fluid in the hope of minimsing infection within the peritoneal cavity. Greenberg and Sanford (1967) studied the behaviour of four antibiotics--tetracycline, chlorampehnicol, kanamycin and colistin--given to patients during peritoneal dialysis. Of these four, only kanamycin was removed by dialysis in amounts sufficiently great to require a change in the normal dosage regime for patients with renal failure. The authors recommended an initial loading dose of 0.5 grams kanamycin followed by 0.25 grams per day during dialysis. When these antibiotics were administered in the dialysis solution, adequate therapeutic serum concentrations were obtained with all drugs, however, it was found that when tetracycline was administered in normal doses, it was readily absorbed and could attain potentially toxic serum levels if therapy was maintained during the entire dialysis.

In a similar study to that reported above, Buck and Cohen (1968) showed that cloxacillin, ampicillin, cephaloridine, kanamcyin and polymixin added to dialysis fluids all produced therapeutic serum levels during dialysis and for some hours thereafter. Only in the case of cloxacillin did the serum levels fall rapidly after the end of dialysis (half life 2.5 hours). Similarly, cephalothin, ampicillin, chloramphenicol and tetracycline in reduced dosage have been shown to produce therapeutic blood levels when administered directly in the peritoneal dialysis solution (Bulger et al 1964; Ruedy 1966).

Thus it would seem possible to attain adequate serum and tissue levels of various antibiotics by adding these to the dialysis fluids during such a procedure. However, it seems likely that most physicians would prefer to administer antibiotics in the normal manner even during peritoneal dialysis, rather than to adopt the fluid as a medium for introducing these drugs. One possible exception to this is where there is evidence of pre-existing inflammation in the peritoneal cavity when it is possible that direct administration of the drug to the inflamed area may be of additional importance (Linton, personal communication).

DISCUSSION

This review was undertaken in an endeavour to provide guidelines both on the choice of antibiotic and on the correct dosage of each antibiotic in patients with varying degrees of renal failure.

Analysis of the published work reveals considerable difficulties in attaining this aim since few of the studies are directly comparable in terms of the methods used. The classical papers by Kunin and his colleagues (1959) are good models of the type of study required, and more recently the studies of Bailey et al (1970), Curtis and Eastwood (1968), and Orme and Cutler (1969) illustrate how the pharmacology of any new antibiotic should be investigated in relation to the degree of renal impairment and the effect of haemodialysis. The pattern of absorption, metabolism and excretion of each drug should be defined in the normal, and studies on patients with reduced renal function should include peak serum levels obtained, serum half-life, urine antibiotic levels, effect of dialysis, and the effect of renal failure on the fraction of drug bound to serum proteins. Where the drug is ordinarily given orally, data on its absorption in such patients is also required.

Comparison of various dose regimes has also proven difficult, since some authors advocate reduced dosage at the normal frequency while others favour prolongation of the time between doses. Where possible, it would seem preferable to administer the drug at the regular time intervals in reduced dosage after an initial normal loading dose (O'Grady 1971).

In addition, it should be observed that an extrapolation from calculations based on the administration of a drug by one route, cannot be made to other routes of administration of the same drug. It has been shown, for example, that in the diabetic patient, penicillin given intramuscularly is poorly absorbed (Lerner and Weinstein 1964)--such studies have, however, not been reported in patients with renal failure in various stages of hydration.

In an attempt to rationalise this field of study, Dettli (1970) has considered the various factors which contribute to the disposition of a drug in patients with renal failure, and has derived somewhat complex mathematical expressions for calculating the optimum dose frequency of a drug. However, his calculations are based on the assumption that the patient's ability to handle a given drug does not vary from time to time, and that the metabolic pathways are not likely to change as a result of intervening factors such as other enzyme-inducing drugs. There is, however, already evidence that these assumptions cannot be made (Pryor et al 1967; Curtis and Marshall 1970). Nevertheless, this approach is of considerable theoretical interest and may prove to be clinically relevant in the near future, as indicated by the work of Mawer et al (1972).

At present, the factors which seem to be the most important in terms of assessing the effect of renal impairment on the handling of a given drug are summarised in Figure 12.1. In the case of most antibiotics, little work has been carried out either on the oral absorption of such drugs, or on alterations in their metabolism by the microsomal enzyme systems.

Furthermore, with the exception of the sulphonamides (see Anton and Corey 1971), little work has been done on possible alterations in the degree of protein binding of antibacterial agents in renal failure. Nevertheless, that such alterations may be of considerable importance in the case of other drugs has been shown in the work of Reidenberg and colleagues (1971), who studied the effect of uraemia on protein-binding of diphenylhydantoin. The lower half of Figure 12.1 briefly outlines possible consequences of alterations in the protein binding of drugs. This again emphasises the need for careful investigations into the role of protein binding of antibiotics in patients with renal failure.

Drug Interactions. Patients admitted to hospital with severe renal failure frequently require a prolonged period of hospitalisation resulting in the administration of a large number of pharmacologically active drugs. Thus the potential for drug interaction is unusually high in such patients. Since many individuals either have infections with several organisms at once or have infections with "resistant organisms," therapy with multiple antibiotics is not infrequent and so attention must be directed towards the compatibility of such drugs in terms of their effect on the target organisms. In addition, however, certain problems are more likely to arise in patients with chronic renal failure than in those with other conditions. Because of the frequency of fluid and electrolyte problems in these patients, the administration of either parenteral fluids or of potent diuretics is a frequent occurrence. Recently evidence is accumulating on the effect of such preparations upon coincidental antibiotic therapy.

When a patient with chronic renal failure is receiving fluids intravenously at the same time as he or she requires a parenteral antibiotic, it is tempting to inject the drug "intravenously" by injecting through the cuff of the venous line. While such a practise is reasonable, it has recently become acceptable, particularly in the United States, to add the antibiotic directly to the bottle of infusion fluid. Such a practise has been advocated by Professor O'Grady and his colleagues from St. Bartholomew's Hospital in London, since this technique allows for easier calculation of the dosage of drug required to provide predetermined serum levels (O'Grady et al 1971). However, it has been emphasised that penicillin rapidly loses its antibacterial activity if added to solutions containing both sodium bicarbonate and sucrose or dextrose (Simberkoff et al 1970). Both ampicillin and methicillin are also affected by addition to dextrose-containing solutions (Lynn 1971). Finally, when solutions of kanamycin and methicillin are mixed, the methicillin loses most of its antibacterial activity within minutes (Lynn 1971). Thus, until more information is available on the stability of antibacterial agents in infusion fluids, it would seem best to avoid this method of administration.

Turning now to the problem of the effect on antibiotic therapy of other drugs administered contemporaneously with the antibiotics, several clinically significant interactions are of importance. Firstly, the tetracyclines are inactivated when they form chelates with metallic ions. The ions most frequently involved are calcium, magnesium, and aluminium, and this interaction is of relevance only when tetracyclines are taken orally

(Goldberg 1965). Since tetracyclines are bacteriostatic and have been incriminated as a cause of significant rise in blood urea nitrogen, they should be avoided in patients with renal failure, particularly if such patients require therapy with aluminium hydroxide or other drugs containing those ions mentioned above. Secondly, sodium bicarbonate given orally increases the absorption of nalidixic acid (Adam and Dawborn 1971). The mechanism for this is unknown, but possibly it is one of altered intestinal pH. If this is so, it may be relevant to observe that Finland and his co-workers (1945) demonstrated enhanced blood levels of oral penicillin when comparing achlorhydric subjects with normal controls. If the gastric pH is an important factor in the absorption of orally administered antibiotics, then this alone will affect their handling in patients with renal failure. Thirdly, both frusemide and ethacrynic acid are known to produce ototoxicity under rare circumstances (Mathog and Klein 1969; Schwartz et al 1970). The aminoglycoside antibiotics have also been established as causing ototoxicity. It is therefore not surprising that claims of a possible potentiating effect of these drugs given together have been made (Mathog and Klein 1969; Johnson and Hamilton 1970). These claims have as yet remained unsubstantiated in any large body of data, however, the possibility of such an interaction should always be entertained, particularly if the diuretic is given intravenously, since it is thought that ototoxicity is greatest when this route is employed. Fourthly, it has recently been suggested that the nephrotoxicity of the cephalosporins is enhanced by coincidental diuretic therapy (Foord 1969; Lawson et al 1970). While certain experimental animal work has been reported which confirms this

possible interaction (Dodds and Foord 1970; Chapter 9) the observation awaits final confirmation in a large series of prospectively studied patients.

This review has emphasised that, while a large volume of work has been reported on the effects of renal impairment on the body's handling of antibiotics, much more remains to be done. In particular, it can be concluded that for most of the common antibiotics modified dose regimes can be prescribed for short periods of time, however, the position is much less clear when long term antibiotic therapy may be required. Possible interactions among antibiotics or between antibiotics and other drugs have been recorded. This field requires a considerable increase in the effort directed towards it particularly in patients receiving large numbers of other drugs or who have varying degrees of renal impairment (e.g. post-transplant patients or those in the diuretic phase of acute renal failure).

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SUMMARY AND CONCLUSIONS

The work described in this thesis was undertaken to elucidate certain aspects of the management of urinary tract infections. The early part of the thesis is concerned with assessing the role of screening tests in the identification of bacteriuria in the first trimester of pregnancy. This is important since it has been claimed that virtually all pregnant patients who develop urinary tract infections (U.T.I.) in late pregnancy have asymptomatic bacteriuria in the first trimester. Were this to be the case, then U.T.I. in pregnancy could become a preventable disease. To test this hypothesis, a simple routine screening procedure was carried out on a large population of pregnant patients attending a local maternity hospital. As a result a group of patients with asymptomatic bacteriuria was detected. Long-term follow-up of all patients screened revealed that the proportion of those developing U.T.I. in late pregnancy who had an initially positive screening test was low (i.e., the screening test for bacteriuria was not a sensitive predictor of subsequent U.T.I. in pregnancy). This result called in question the value of a single test as a means of preventing subsequent U.T.I.

In view of the importance of this finding for practitioners, a further theoretical assessment of the value of such screening tests was undertaken using as a basis the published data on the subject. This review indicated that, even under optimal conditions, the sensitivity of the screening test is unlikely to exceed 50% -- a finding which suggests that it is highly inefficient as a means of drastically reducing the incidence of U.T.I. in pregnancy.

Running contemporaneously with this study of screening tests in pregnancy, an assessment of the role of routinely screening the urine for cells and bacteria of all patients with symptoms of U.T.I. in general practise was performed. The patients came from two separate group practises in Glasgow. In the course of analysing the data, it was noted that the reported incidence of such symptoms was over twice as high in one practise than in the other. Several factors were felt to contribute to this finding. Firstly, the symptoms appeared to be commoner in patients of low social class. Secondly, the higher prevalence of symptoms occurred in the practise which serves an area of particularly low social class. Finally, the higher frequency of symptoms occurred in the practise solely run by female physicians--a factor which might lead to an increased frequency of reporting symptoms to the physician.

A review of the past history and present complaints of the patients failed to reveal any factor or group of factors which could be used to indicate whether the patients' urine was or was not sterile at the first visit. In addition, the response to therapy was good irrespective of the nature of the findings in the urine on presentation. Thus the study failed to provide evidence of the value of routinely screening the urine of all patients attending their practitioners with symptoms of U.T.I. The main benefit to accrue from the procedure was that those with a positive modified Addis count (as a reflection of the leucocyte excretion rate in the urine) and bacteriuria, had a higher recurrence rate than patients without these features. Nevertheless repeated recurrences were rare--only 2.7% of patients being referred to hospital for further investigation.

The result of long-term antibacterial therapy in 66 patients with established U.T.I. was then reviewed. All the patients had had recurrent U.T.I. with frequent demonstration of bacteriuria and failure to respond to short-term courses of therapy. A three-month course of sulphadimidine, ampicillin or nitrofurantoin was found to be effective in relieving symptoms and in sterilising the urine for a period of one year in 49% of patients. Those individuals with normal intravenous pyelograms fared better than those with abnormal ones. One half of the recurrences in the two years after therapy occurred within three months of stopping the drugs.

Several factors other than frank infection have been implicated in the development of U.T.I. For example, it has been suggested that long-term, high-dose analgesic consumption predisposes individuals to renal disease which then frequently becomes infected. Likewise, it has been suggested that diabetes mellitus predisposes patients to U.T.I. Certain aspects of these hypotheses were tested in two studies reported here. Firstly, using data collected by the Boston Collaborative Drug Surveillance Program (BCDSP), an investigation into the relationship between long-term analgesic intake, renal disease (as indicated by presenting blood urea nitrogen levels) was undertaken. This cross-sectional data failed to reveal a positive association between excessive analgesic intake and either renal disease or impaired renal function. Moreover, there was no evidence of a dose-response relationship between regular intake of over-the-counter analgesic preparations

and these, admittedly crude, parameters of renal disease. The data therefore suggest that if such a relationship exists, it is either a subtle one which rarely causes major renal disease or it occurs only in a sub-population of the large group of long-term analgesic users.

Secondly, an investigation was performed to test the hypothesis that recurrent U.T.I. might be associated with latent diabetes mellitus in a large proportion of cases. The data, however, indicate that such a relationship did not exist in a group of fifteen individuals with known established U.T.I. and suggest that latent diabetes mellitus is not a common predisposing factor in such individuals.

The latter half of the thesis is concerned with the hazards of antibiotic therapy in patients with urinary tract infection and renal impairment.

Using data collected by the BCDSP, two major investigations were carried out. Firstly, a simple overview of the reported adverse reaction rates to twenty commonly used antibacterial agents was undertaken. Included in this data is a general indication of the frequency with which physicians attribute renal damage to these drugs. Secondly, a more detailed analysis of the association between tetracycline receipt and subsequent rise in blood urea nitrogen (BUN) was undertaken. This revealed that in patients receiving diuretics, there was a three-fold increase in the frequency of reported rises in BUN amongst tetracycline recipients when compared with recipients of any other drugs excluding

the nephrotoxic antibiotics. As an addendum to this chapter, the data on nephrotoxic antibiotics was reviewed. This showed that the frequency of reported rises in BUN was greater amongst diuretic recipients than non-recipients, however, the number of patients involved was small and so no firm conclusions could be drawn, other than to suggest that the figures are compatible with the findings of animal experiments reported in the subsequent chapter.

The next two chapters deal with animal experiments designed to assess the nephrotoxic potential of cephaloridine. It has been suggested that this drug is nephrotoxic to man and to animals, that its toxicity depends on the dose received at any one time rather than on the cumulative dose received, that the half-life of the drug in anephric man varies according to the length of regular dialysis therapy and that its nephrotoxicity is enhanced by coincidental diuretic administration. The studies reported here confirm that the drug is nephrotoxic to rabbits and to rats, but suggest that the total dose of drug given to rabbits is of some importance in determining the degree of nephrotoxicity observed. In several animals subnephrotoxic doses of cephaloridine given on two occasions separated by one week gave definite evidence of renal damage. The half-life of this drug given to a group of rabbits was found to be variable. There was no evidence that phenobarbital enhanced the rate of metabolism of this drug in rabbits. Finally, experiments on rats whose kidneys were mildly damaged with glycerol indicated that the nephrotoxicity of cephaloridine was considerably enhanced by the simultaneous administration of the diuretic frusemide.

These data, derived from animal experiments, suggest that the cephalosporin antibiotic cephaloridine should be used with caution in patients with impaired renal function particularly when potent diuretics are also being administered.

A final group of experiments were performed on patients undergoing regular dialysis treatment. The rate of disappearance from the serum of five frequently used antibiotics was studied in such patients. In each case, the drug was studied both before and after dialysis procedures. On the basis of the findings, recommendations were made concerning the dosage of each drug required by regularly dialysed patients.

The thesis concludes with a detailed review of the place of antibiotic therapy in patients with renal failure. Each antibiotic is considered separately and the literature pertaining to its use in such individuals is critically evaluated.

PROBLEMS IN THE MANAGEMENT OF URINARY TRACT INFECTION

- Clinical Epidemiological and Laboratory Studies -

by

David H. Lawson, M.B., Ch.B., M.R.C.P.E.

SUMMARY

The work described in this thesis was undertaken to elucidate certain aspects of the management of urinary tract infections. The early part of the thesis is concerned with assessing the role of screening tests in the identification of bacteriuria in the first trimester of pregnancy. This is important since it has been claimed that virtually all pregnant patients who develop urinary tract infections (U.T.I.) in late pregnancy have asymptomatic bacteriuria in the first trimester. To test this hypothesis a simple screening procedure was carried out on a large proportion of pregnant patients attending a local maternity hospital. As a result a group of patients with asymptomatic bacteriuria was detected. Long-term follow-up of all patients screened revealed that the proportion of those developing U.T.I. in late pregnancy and who had an initially positive screening test was low. This result called in question the value of a single test as a means of preventing subsequent U.T.I. In view of the importance of this finding for practitioners a further theoretical assessment of the value of such screening tests was undertaken using as a basis the published data on the subject. This review indicated that even under optimal conditions the sensitivity of the screening test in predicting subsequent U.T.I. is low - a finding which suggests that it is inefficient as a means of drastically reducing the incidence of U.T.I. in pregnancy.

An assessment of the role of routinely screening the urine of all patients with symptoms of U.T.I. in general practice was then undertaken. The study failed to provide evidence of the value of

routinely screening the urine of all patients attending their practitioners with symptoms of U.T.I. The main benefit to accrue from this procedure was that those with a positive modified Addis count (as a reflection of the leucocyte excretion rate in the urine) and bacteriuria had a higher recurrence rate than patients without these features. Nevertheless repeated recurrences were rare - only 2.7% patients being referred to the hospital for further investigation.

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Using data collected by the B.C.D.S.P. two major investigations were carried out: firstly a simple over-view of the reported adverse reaction rates to twenty commonly used anti-bacterial agents was undertaken. Secondly a more detailed analysis of the association between tetracycline administration and subsequent rise in blood urea nitrogen was undertaken. This revealed that in patients receiving diuretics, there was a three-fold increase in the frequency of reported rises in blood urea nitrogen when compared with recipients of all other

drugs excluding the nephrotoxic antibiotics. As an addendum to this chapter the data on nephrotoxic antibiotics was reviewed. Unfortunately the number of patients involved was small and so no firm conclusions could be drawn other than to suggest that the figures were compatible with the findings of animal experiments reported in the subsequent chapter.

The next two chapters deal with animal experiments designed to assess the nephrotoxic potential with cephaloridine. It has been suggested that this drug is nephrotoxic to animals and to man, that its toxicity depends on the dose received at any one time rather than on the cumulative dose received, that the half-life of the drug in an anephric man varies according to the length of regular dialysis therapy and that its nephrotoxicity is enhanced by coincidental diuretic administration. The studies reported here confirm that the drug is nephrotoxic to rabbits and to rats, but suggest that the total dose of drug given to rabbits is of some importance in determining the degree of nephrotoxicity observed. In several animals sub-nephrotoxic doses of cephaloridine given on two occasions separated by one week gave definite evidence of renal damage. The half-life of this drug given to a group of rabbits was found to be variable and there was no evidence that phenobarbitone enhanced the rate of metabolism of this drug in rabbits. Finally experiments on rats whose kidneys were mildly damaged with glycerol indicated that the nephrotoxicity of cephaloridine was considerably enhanced by the simultaneous administration of the diuretic, frusemide. The data

suggests that the cephalosporin antibiotic cephaloridine should be used with caution in patients with impaired renal function particularly when potent diuretics are also being administered.

The final group of experiments were performed on patients undergoing regular dialysis treatment. The rate of disappearance from the serum of five frequently used antibiotics was studied in such patients. In each case the drug was studied both before and after dialysis procedures. On the basis of the findings recommendations were made concerning the dosage of each drug required by regularly dialysed patients.

The thesis concludes with a detailed review of the place of antibiotic therapy in patients with renal failure. Each antibiotic is considered separately and the literature pertaining to its use in such individuals is critically evalued.

TABLE 1.1

RELATIONSHIP OF URINARY TRACT INFECTION IN PREGNANCY
TO RESULTS OF INITIAL SCREENING TEST

SCREENING TEST	FREQUENCY OF URINARY TRACT INFECTION	
	DEFINED CLINICALLY	BACTERIOLOGICALLY CONFIRMED
BACTERIURIC (Group A)	15/54 = 27.7%	9/54 = 16.6%
DOUBTFUL (Group B)	9/89 = 10.1%	6/89 = 6.7%
NON-BACTERIURIC (Group C)	70/1017 = 6.9%	32/1017 = 3.1%
ALL GROUPS	94/1160 = 8.1%	47/1160 = 4.1%

TABLE 1.2

SENSITIVITY AND SPECIFICITY OF SCREENING TEST
IN PREDICTING URINARY TRACT INFECTION (U.T.I.)

SCREENING TEST	URINARY TRACT INFECTION	
	DEFINED CLINICALLY (94 Patients)	BACTERIOLOGICALLY CONFIRMED (47 Patients)
Sensitivity (%)	15.9	19.1
Specificity (%)	95.4	91.3

TABLE 1.3

RELATIONSHIPS OF HYPERTENSIVE DISORDERS OF PREGNANCY
TO RESULTS OF INITIAL SCREENING TESTS

(A) URINE CULTURE

	GROUP A		GROUP B		GROUP C	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Hypertension at first visit	15	27.8	16	18.0	162	15.9
Previous hypertension and/or pre-eclampsia	6	11.1	11	12.4	97	9.5
Hypertensive disorders of pregnancy	11	20.4	14	15.7	113	11.1
All patients	54	100.0	89	100.0	1017	100.0

Group A -- bacteriuric on screening test

Group B -- doubtful on screening test

Group C -- non-bacteriuric on screening test

TABLE 1.4

RELATIONSHIPS OF HYPERTENSIVE DISORDERS OF PREGNANCY
TO RESULTS OF INITIAL SCREENING TESTS

(B) ADDIS COUNT

	POSITIVE ADDIS COUNT		NEGATIVE ADDIS COUNT	
	NUMBER	PER CENT	NUMBER	PER CENT
Hypertension at first visit	14	15.5	139	16.0
Previous hypertension and/or pre-eclampsia	15	16.6	87	10.0
Hypertensive disorders of pregnancy	20	22.0	119	13.7
All patients	90	100.0	876	100.0

TABLE 1.5

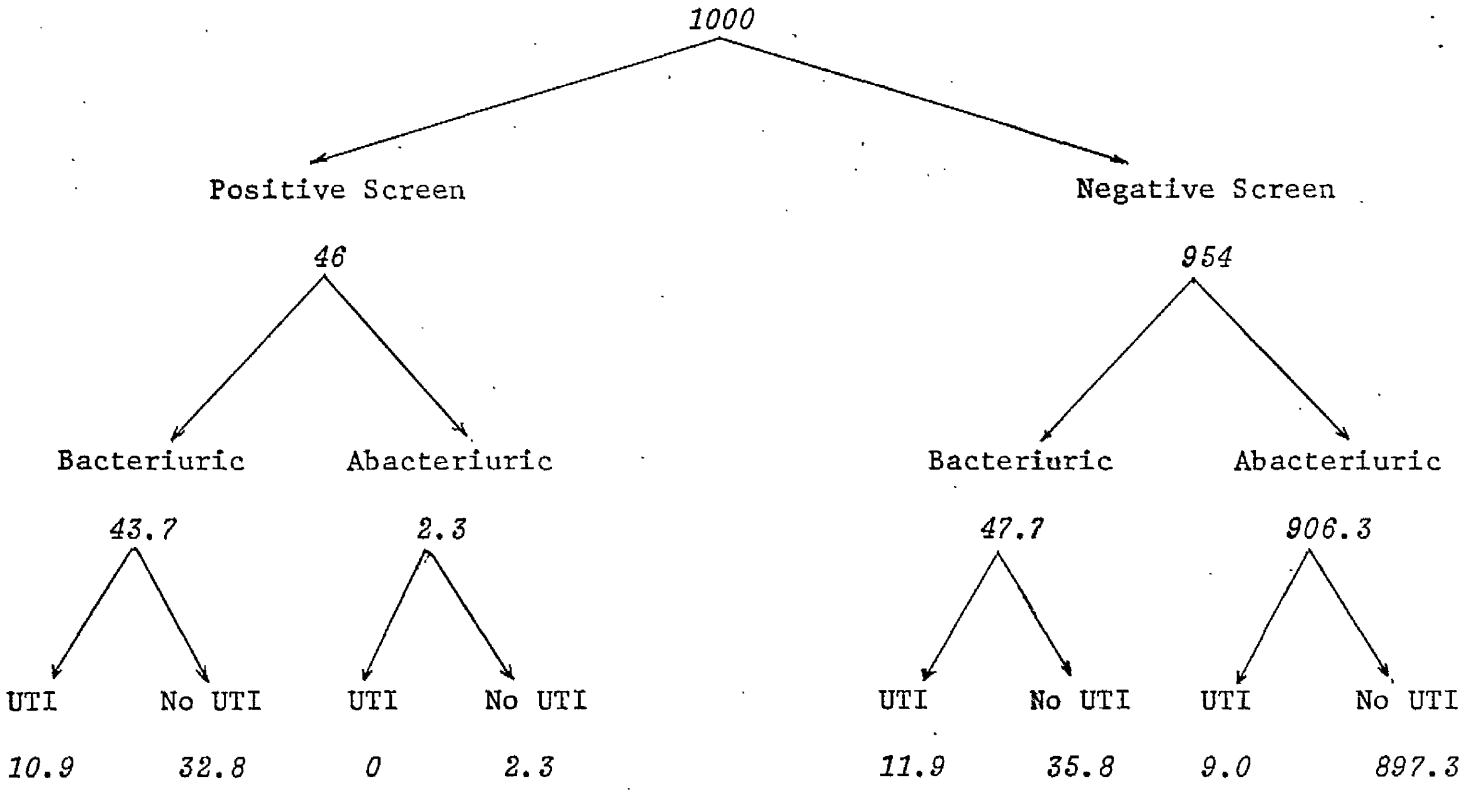
RELATIONSHIP BETWEEN HISTORY OF URETHRAL CATHETERISATION AND BACTERIURIA ON SCREENING

URETHRAL CATHETERISATION	GROUP A		GROUP B		GROUP C	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Never	32	59.3	53	59.6	641	63.1
Once	16	29.6	28	31.5	261	25.6
Twice	5	9.2	6	6.7	70	6.9
Three times or more	1	1.8	2	2.2	45	4.4
Total	54	100.0	89	100.0	1017	100.0

Group A - bacteriuric on screening test
Group B - doubtful on screening test
Group C - non-bacteriuric on screening test

FIGURE 2.1

RELATIONSHIP OF SCREENING TEST TO SUBSEQUENT DEVELOPMENT OF URINARY TRACT INFECTION*



Total number of patients developing UTI = 31.8

Numbers with UTI who had positive screen = 10.9

Numbers with UTI who had negative screen = 20.9

Frequency of UTI in those with positive screen = 23.7%

Frequency of UTI in those with negative screen = 2.0%

*assuming -- 95% accuracy of screening test

4.6% with positive screening test

25% bacteriurics develop urinary tract infection

1% non-bacteriurics develop urinary tract infection

TABLE 2.1

CALCULATED EFFICIENCY OF TESTS IN PREDICTING BACTERIURIA

Group	Test Accuracy (%)	Sensitivity for Bacteriuria (%)	Specificity for Bacteriuria (%)
A	80	16.2	98.8
B	90	30.3	99.4
C	95	47.8	99.7
D	97.5	65.3	99.9

Figures calculated on basis of 4.6% positive tests.

TABLE 2.2 (continued)

Based on variations in frequencies with which bacteriuric and non-bacteriuric patients subsequently develop urinary tract infection during pregnancy.

Group A_1 - A_3 - screening test accuracy of 80%

Group B_1 - B_3 - screening test accuracy of 90%

Group C_1 - C_3 - screening test accuracy of 95%

Group D_1 - D_6 - screening test accuracy of 97.5%

TABLE 2.2

CALCULATED SENSITIVITIES AND SPECIFICITIES OF VARIOUS SCREENING TESTS FOR BACTERIURIA IN PREDICTING DEVELOPMENT OF URINARY TRACT INFECTION DURING PREGNANCY*

Group	% Bact. →UTI	% Non-bact. →UTI	% Positive Screen →UTI	% Negative Screen →UTI	Sensitivity for UTI (%)	Specificity for UTI (%)
A_1	25	0.5	19.8	5.4	15.0	96.1
A_2	25	1.0	20.0	5.8	14.3	96.1
A_3	25	2.0	20.2	6.6	12.9	96.0
B_1	25	0.5	22.4	2.9	26.9	96.3
B_2	25	1.0	22.4	3.4	24.1	96.3
B_3	25	2.0	22.4	4.3	20.1	96.2
C_1	25	0.5	23.7	1.7	40.0	96.4
C_2	25	1.0	23.7	2.0	34.2	96.4
C_3	25	2.0	23.9	3.1	26.6	96.3
D_1	25	0.5	24.3	1.1	51.6	96.4
D_2	25	1.0	24.3	1.5	42.4	96.4
D_3	25	2.0	24.3	2.6	31.4	96.3
D_4	33	0.5	32.4	1.3	54.2	96.8
D_5	33	1.0	32.4	1.8	46.4	96.8
D_6	33	2.0	32.4	2.7	36.0	96.7

*see opposite page

FIGURE 2.2

RELATIONSHIP OF THE SENSITIVITY FOR DETECTION OF URINARY TRACT INFECTION TO THE ACCURACY OF THE SCREENING TEST IN DETECTING BACTERIURIA

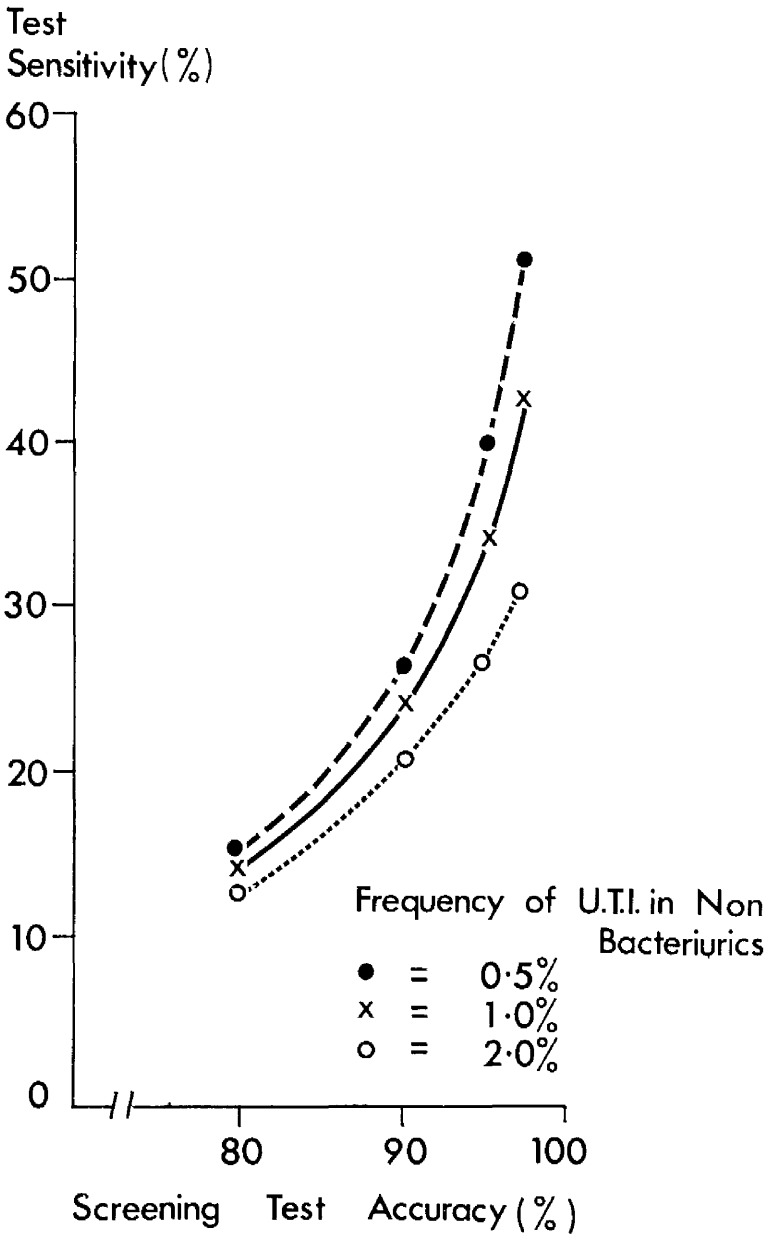


FIGURE 3.1

STANDARD FORM USED BY NURSE AND GENERAL PRACTITIONER
WHEN PATIENT ADMITTED TO STUDY

TRIAL NO._____

NAME:_____ AGE:_____ PARITY:_____

ADDRESS:_____ HUSBAND'S OCCUPATION:_____

SYMPTOMS: PYREXIA LOIN PAIN FREQUENCY DYSURIA NOCTURIA STRESS

Degree:
Comment:

PAST HISTORY: ENURESIS H'MOON CYSTITIS PREGNANCY CYSTITIS PREV.PYELONEPHRITIS

Frequency:
Comment:

URINE EXAMINATIONS:

DATE: __/__/__ __/__/__ __/__/__

Addis:
Bacteriology:
Therapy Group:

COMMENTS:

RECURRENCES:

SYMPTOMS:

Degree:
Comment:

URINE EXAMINATIONS:
Date: __/__/__ __/__/__ __/__/__
Addis:
Bacteriology:
Therapy Group:

REFERRAL TO HOSPITAL: YES/NO

TABLE 3.1

DISTRIBUTION OF PATIENTS BY REFERRING PRACTICE:
FINDINGS ON URINE EXAMINATION AND THERAPY RECEIVED

	GROUP A	GROUP B	GROUP C	GROUP D	ALL GROUPS
Practice R	45	22	29	105	201
Practice S	26	25	15	76	142
Total	71 (20.7%)	47 (13.7%)	44 (12.8%)	181 (52.8%)	343 (100%)
Therapy 1	27	13	14	61	115
Therapy 2	24	15	15	60	114
Therapy 3	20	19	15	60	114

Group A - Abnormal Addis; over 10^5 organisms/ml urine.
Group B - Normal Addis; over 10^5 organisms/ml urine.
Group C - Abnormal Addis; under 10^5 organisms/ml urine.
Group D - Normal Addis; under 10^5 organisms/ml urine.

Therapy 1 - Sulphadimidine 4 g daily.
Therapy 2 - Ampicillin 2 g daily.
Therapy 3 - Sulphadimidine 4 g daily with option to change later.

TABLE 3.2

RELATIONSHIP OF PRESENTING SYMPTOMS TO INITIAL FINDINGS ON URINE EXAMINATION

	GROUP A		GROUP B		GROUP C		GROUP D		ALL GROUPS	
SYMPTOMS	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Pyrexia	3	4.2	2	4.3	6	13.6	19	10.4	30	8.7
Loin Pain	27	38.0	27	57.0	17	38.6	71	39.2	142	42.0
Frequency	63	88.7	35	74.4	35	79.5	131	72.4	264	77.0
Dysuria	48	67.6	26	55.3	28	63.6	94	51.9	196	57.2
Nocturia	50	70.4	29	61.7	27	61.4	91	50.3	197	57.7
Stress Incontinence	16	22.5	20	42.5	13	29.5	44	24.3	93	27.0
All Symptoms	71	100.0	47	100.0	44	100.0	181	100.0	343	100.0

Group A - Abnormal Addis; over 10^5 organisms/ml urine.
Group B - Normal Addis; over 10^5 organisms/ml urine.
Group C - Abnormal Addis; under 10^5 organisms/ml urine.
Group D - Normal Addis; under 10^5 organisms/ml urine.

TABLE 3.3

COMPARISON OF ORGANISMS ISOLATED FROM PATIENTS BELONGING TO THE TWO PARTICIPATING PRACTICES

	PRACTICE R		PRACTICE S		BOTH PRACTICES	
ORGANISM	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Escherichia coli	47	70.0	29	57.0	76	64.0
Staph. albus	8	12.0	12	23.4	20	17.0
Micrococcus spp.	6	9.0	8	15.7	14	12.0
Proteus mirabilis	5	7.5	2	3.9	7	6.0
Pseudomonas aeruginosa	1	1.5	0	0	1	1.0

TABLE 3.4

COMPARISON OF RESULTS OF MODIFIED ADDIS COUNT PERFORMED ON EARLY- AND MID-STREAM SPECIMENS OF URINE

	EARLY SPECIMEN	MID-STREAM SPECIMEN
Addis positive*	27	23
Addis negative	48	52
Total	75	75

$\chi^2_1 = 0.37 \quad p > 0.5$

*Addis positive if over 10 white blood cells per counted area of Neubauer counting chamber.

TABLE 3.5

EFFECT OF THERAPY

	SULPHADIMIDINE (Therapy 1)	AMPICILLIN (Therapy 2)	SULPHADIMIDINE + OTHER (Therapy 3)
Number with recurrences	6 (5.2%)	15 (13.2%)	14 (12.3%)
Number with persistent symptoms at 14 days	14 (12.2%)	7 (6.3%)	16 (14.0%)
Number abnormal at 14 days	12 (10.4%)	10 (8.8%)	10 (8.8%)
Total exposed	115	114	114

TABLE 3.6

RECURRENCE OF SYMPTOMS DURING STUDY PERIOD

	GROUP A	GROUP B	GROUP C	GROUP D	ALL GROUPS
Numbers reviewed at 18 months	65	41	38	166	310
Numbers who reported recurrences to G.P. during study	15	4	3	13	35 (11.3%)
Numbers interviewed at 12 months	29	17	12	79	137
Number who spontaneously reported recurrences	6	1	0	11	17 (12.4%)
Number who admitted recurrences on questioning	10	3	6	19	38 (27.7%)

Group A - Abnormal Addis; over 10^5 organisms per ml urine.
Group B - Normal Addis; over 10^5 organisms per ml urine.
Group C - Abnormal Addis; under 10^5 organisms per ml urine.
Group D - Normal Addis; under 10^5 organisms per ml urine.

CASE REPORT 3i.

Patient: 25 year old unmarried female.

Comment: Frequent urinary tract symptoms for three years since first intercourse (with married man). Considerable conflict with family concerning extra-marital intercourse.

Symptoms respond to sulphadimidine for seven days, but recur frequently especially after intercourse.

Urine examination reveals $>10^5$ organisms per ml of urine (E. coli) and positive modified Addis count.

Blood urea = 30 mg/100 ml.

Serum creatinine = 0.7 mg/100 ml.

Intravenous pyelography: normal.

Cystoscopy: acute bladder inflammation; no evidence of tuberculosis.

Patient responded to three-month course of trimethoprim-sulphonamide followed by nightly nitrofurantoin (50 mg).

CASE REPORT 3ii.

Patient: 54 year old married female, para 1 + 1.

Comment: Frequent urinary tract symptoms for five years although no history prior to that. No catheterisation during pregnancy, no operations, no analgesic abuse.

Symptoms respond to seven-day course of ampicillin but recur regularly.

Urine culture reveals $>10^5$ organisms per ml of urine (E. coli) and positive modified Addis count.

Blood urea = 36 mg/100 ml.

Creatinine clearance = 75 ml/min.

Intravenous pyelography: normal.

Cystoscopy: normal.

Patient responded to three-month course of trimethoprim-sulphonamide.

CASE REPORT 3iii.

Patient: 47 year old married female, para 3 + 0.

Comment: Intermittent symptoms of urinary tract infection since birth of last child (a breech presentation, requiring pudendal block anaesthesiae, forceps delivery and urethral catheterisation).

Symptoms respond to seven-day course of sulphadimidine, but recur.

Urine culture $>10^5$ organisms per ml of urine (Staph. albus) and positive modified Addis count.

Blood urea = 34 mg/100 ml.

Serum creatinine 0.8 mg/100 ml.

Intravenous pyelography: clubbing of calyces in upper pole of (R) kidney with some scarring over those calyces.

Patient responded to three-month course of trimethoprim-sulphonamide for at least 18 months after course started.

CASE REPORT 3iv.

Patient: 28 year old married female, para 2 + 0.

Comment: Approximately three episodes of urinary tract symptomatology per annum since catheterisation following birth of first child. No history of U.T.I. prior to childbirth.

Symptoms respond to short courses of ampicillin or sulphonamides.

Urine sterile and microscopic examination negative (on eight occasions).

Blood urea 20 mg/100 ml.

Intravenous pyelography: normal.

Cystoscopy: normal

Micturating cystogram: normal.

Patient continues to have intermittent symptoms despite long-term nitrofurantoin therapy. Has been seen by many physicians all of whom observe the presence of marked "psychological overlay to symptoms." In support of this, symptoms became exacerbated when next-door neighbour (Case Report 3viii) required regular dialysis therapy.

CASE REPORT 3v.

Patient: 29 year old married Pakistani doctor of medicine, para 1 + 0.

Comment: Recurrent urinary tract symptomatology since birth of only child. No problems at delivery, not catheterised. Patient is bacteriologist and anxious about possibility of renal impairment.

Urine examinations - persistently normal.

Blood urea - 23 mg/100 ml.

Creatinine clearance - 90 ml/min.

Intravenous pyelography - dilated minor calyces on right side.

Cystoscopy - negative.

Patient continues to have symptoms despite several short courses and one long-term course of antibacterial therapy.

CASE REPORT 3vi.

Patient: 79 year old, extremely fit, married female, para 3 + 0.

Comment: Five-year history of recurrent episodes of frequency, dysuria, nocturia and stress incontinence. Symptoms do not respond to courses of antibacterial therapy for more than two months.

Urine examination persistently shows $>10^5$ E. coli per ml of urine with positive Addis counts.

Blood urea = 37 mg/100 ml.

Creatinine clearance: 64 ml/min.

Intravenous pyelography: normal.

Cystoscopy: evidence of chronic cystitis with increased vascularity of bladder wall and coarse trabeculation.

Patient only responded to long-term trimethoprim-sulphonamide after frequent bladder irrigations with neomycin.

CASE REPORT 3vii.

Patient: 33 year old married female, nulliparous.

Comment: Three episodes of urinary tract symptomatology in five months, no previous problems. No analgesic abuse.

Urine examination $>10^5$ E. coli per ml of urine with positive Addis count.

On referral to hospital, found to have pancytopenia with haematocrit of 21% and leucocyte count of 2,000 per cu.mm.
Peripheral blood film macrocytic RBC and bone marrow shows megaloblastic erythropoiesis.
Serum folate level < 1 µg/ml.
Serum B_{12} level 300 mg/ml.
Schilling test shows reduced absorption pattern not corrected by added intrinsic factor.
Glucose tolerance test - flat curve.
Faecal fat excretion abnormally high.
Reduced xylose tolerance.
Small bowel biopsy - flat mucosal pattern.

Excellent response to folic acid - reticulocyte count 35%.
No recurrence of urinary tract symptoms after therapy for malabsorption syndrome.

CASE REPORT 3viii.

Patient: 37 year old married female, para 3 + 0.

Comment: Four episodes of urinary tract symptomatology in last four years. No previous history. No analgesic abuse. No regular drug therapy. On this occasion given ampicillin, but symptoms recurred. Urine culture and microscopy negative on four occasions. On examination in hospital, showed classical signs of rapidly progressive renal failure (over four week course). Had hypertension, oliguria, proteinuria, haematuria. Investigations revealed a positive anti-nuclear factor antibody (1/256), and L.E. cells in peripheral blood.

Renal biopsy showed widespread sclerosis of glomeruli; patient failed to respond to steroids and was eventually taken on for regular dialysis therapy.

Currently, (four years later) is successfully being dialysed at home and is taking small dose of prednisone.

TABLE 3.7

COMPARISON OF FREQUENCY OF URINARY TRACT SYMPTOMS IN TWO PRACTICES

AGE RANGE	PRACTICE R			PRACTICE S			STATISTICAL SIGNIFICANCE	
(years)	NUMBER	TOTAL	PER CENT	NUMBER	TOTAL	PER CENT	χ^2_1	P
15 - 19	15	265	5.7	13	104	12.5	4.15	<0.05
20 - 29	34	707	4.8	42	485	8.3	6.24	<0.05
30 - 39	34	563	6.2	38	298	12.8	9.50	<0.005
40 - 49	37	630	5.9	32	196	15.8	17.19	<0.001
50 - 59	31	583	5.5	17	112	14.3	--	
60 - 69	37	670	5.7	--	--	--	--	
70 +	14	441	3.2	--	--	--	--	

TABLE 3.8

COMPARISON OF CALCULATED INCIDENCE RATES OF URINARY TRACT SYMPTOMS IN PATIENTS FROM TWO GENERAL PRACTICES

AGE RANGE (years)	INCIDENCE RATES† PRACTICE R	INCIDENCE RATES PRACTICE S
15 - 19	37.4	82.5
20 - 29	31.7	54.4
30 - 39	41.0	84.2
40 - 49	38.8	104.4
50 - 59*	36.2	94.3
60 - 69	37.4	--
70 +	20.9	--
All ages	35.1	76.2

†Derived from observed frequency of U.T.I. over 18-month period of admission to study and expressed as incidence per 1000 patients at risk per annum.

*Range 50 - 55 years in Practice S.

TABLE 3.9

COMPARISON OF SOCIAL STATUS OF PATIENTS WITH URINARY TRACT SYMPTOMS WITH THAT OF THE GENERAL FEMALE POPULATION OF GLASGOW CITY TAKEN FROM THE 1961 CENSUS*

	PRACTICE R		PRACTICE S		GLASGOW CITY	
SOCIAL CLASS**	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
1 + 2	18	8.9	12	8.4	2,157	12.0
3	103	51.3	70	49.2	9,488	53.0
4	38	18.8	31	21.8	4,532	25.3
5	29	14.2	20	14.2	1,619	9.0
Unknown	14	6.8	9	6.4	128	0.7
All classes	201	100.0	142	100.0	17,924	100.0

*Based on figures supplied by the Registrar General of Scotland.

**Based on husband's occupation where possible.

Class 1 - professional
Class 2 - intermediate
Class 3 - skilled
Class 4 - semi-skilled
Class 5 - unskilled

TABLE 4.1

PRESENTING DIAGNOSIS OF 66 PATIENTS
INCLUDED IN INITIAL TRIAL

DIAGNOSIS	NUMBER
Recurrent urinary tract infection	42
Analgesic abuse/urinary tract infection	12
Hypertension/urinary tract infection	4
Renal calculi	4
Prostatic obstruction	2
Paraplegia	2

TABLE 4.2

ORGANISMS ISOLATED FROM URINE OF 66 PATIENTS*

ORGANISM	NUMBER OF PATIENTS	PER CENT
Escherichia Coli	60	91
Proteus spp.	20	30
Klebsiellae	1	1.5
Streptococcus faecalis	3	4.5
Pseudomonas pyocyaneus	1	1.5

*19 patients had mixed infections.

TABLE 4.3

RECURRENCE RATES FOLLOWING A THREE MONTH COURSE OF ANTIBACTERIAL THERAPY

TIME AFTER COMPLETING THERAPY (months)	GROUP A		GROUP B		GROUP C		GROUP D		ALL GROUPS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
3	6	22	4	33	5	33	3	25	18	27
6	9	33	5	42	8	53	5	42	27	38
12	11	41	6	50	10	66	7	58	34	51
24	11	41	7	58	11	73	8	66	37	56

TABLE 4.4

RESULTS OF TRIAL OF THREE-MONTH COURSE OF TRIMETHOPRIM-SULPHAMETHOXAZOLE

	GROUP E	GROUP F
Numbers	15	15
Adverse reactions	2	6
Recurrence of infection*	5	4

*within six months of commencing therapy.

Group E - patients with normal I.V.P.

Group F - patients with abnormal I.V.P.

TABLE 5.1

BLOOD GLUCOSE VALUES OBTAINED DURING
100 G GLUCOSE TOLERANCE TEST (15 PATIENTS)

PATIENT	AGE	BLOOD GLUCOSE LEVEL (mg/100 ml)					
		Fasting	30 min.	60 min.	90 min.	120 min.	180 min.
1	16	72	142	133	118	84	79
2	19	86	110	94	87	81	77
3	20	75	125	102	96	93	69
4	22	81	148	134	120	103	91
5	25	77	129	117	98	90	85
6	27	76	110	82	76	69	59
7	29	80	98	110	108	102	78
8	34	91	154	141	131	114	96
9	34	79	136	101	96	93	69
10	39	80	110	97	89	83	73
11	40	71	132	110	94	89	77
12	46	81	137	133	101	87	79
13	48	69	120	111	97	85	72
14	48	72	119	116	96	90	84
15	53	85	135	129	120	114	93
Mean	33.4	78.3	127	114	101.8	91.8	78.7
S.E.M.	3.1	1.6	4.1	4.4	3.8	3.1	2.6

FIGURE 5.1

MEAN BLOOD GLUCOSE VALUES OBTAINED
DURING 100 g GLUCOSE TOLERANCE TEST IN 15 PATIENTS

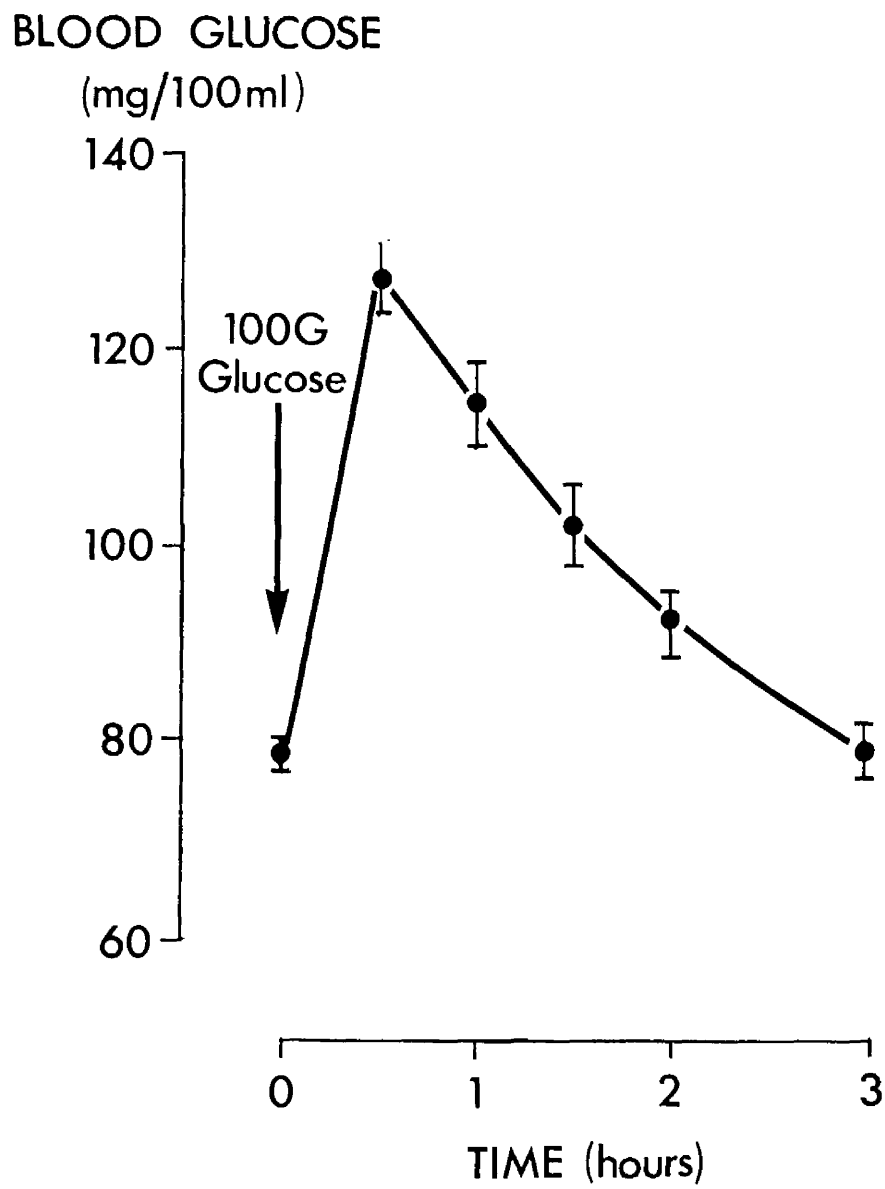


FIGURE 6.1

DISTRIBUTION OF 7017 PATIENTS WITH RECORDED MEDICATION HISTORY

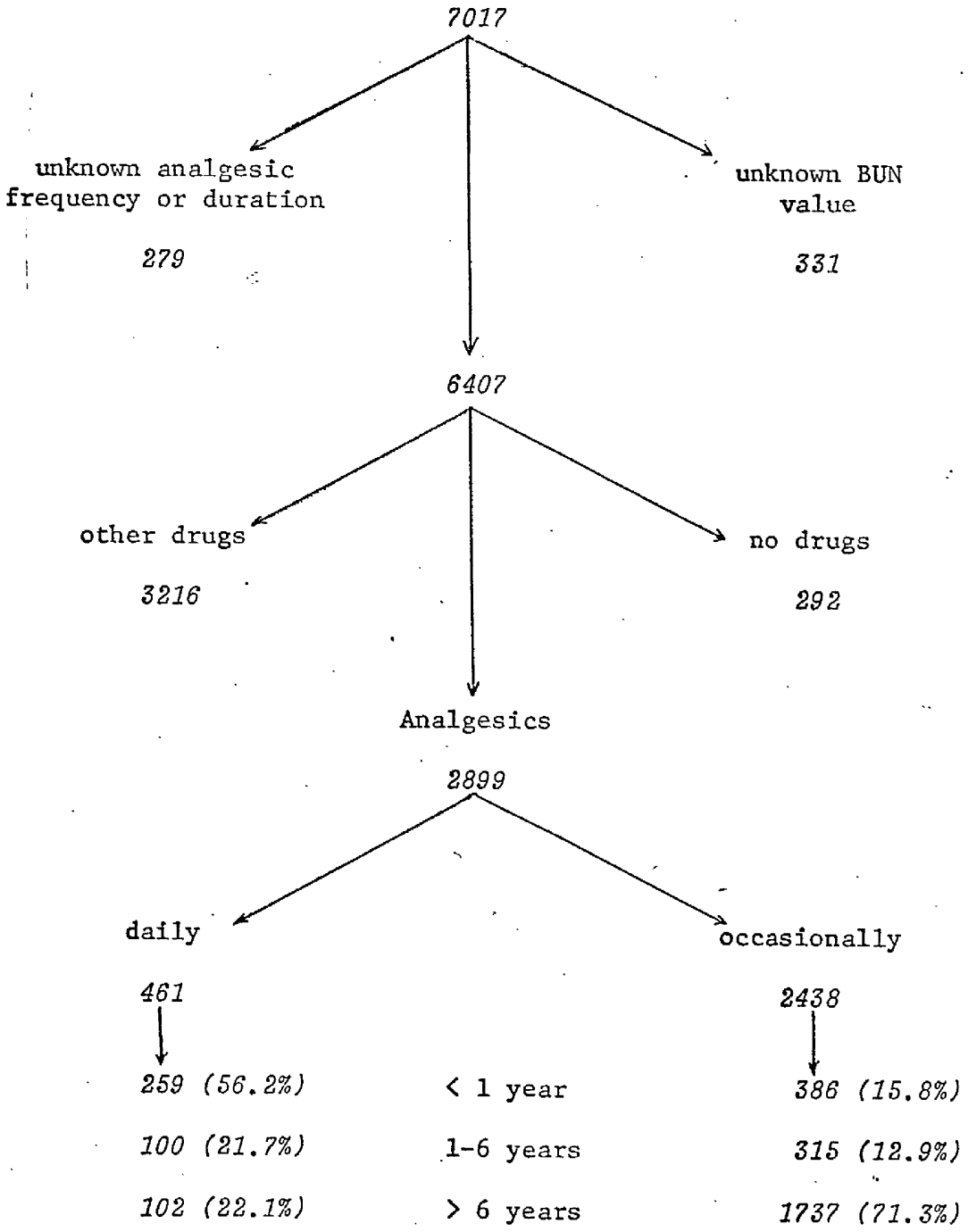


TABLE 6.1

DISTRIBUTION OF PATIENTS BY FIRST DISCHARGE DIAGNOSIS

DIAGNOSES	ANALGESICS DAILY		ANALGESICS OCCASIONALLY		OTHER DRUGS		NO DRUGS		ALL GROUPS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Cardiovascular	74	16.0	589	24.2	945	29.4	64	21.9	1672	26.1
Alimentary	63	13.6	298	12.2	412	12.8	38	13.0	811	12.7
Musculoskeletal	53	11.5	69	2.8	62	1.9	4	1.4	198	3.1
Renal	21	4.6	92	3.8	110	3.4	11	3.8	234	3.6
Neoplastic	44	9.5	211	8.7	278	8.6	22	7.5	555	8.7
Respiratory	54	11.7	259	10.6	377	11.7	40	13.7	730	11.4
Diabetes	9	2.0	100	4.1	151	4.7	7	2.4	267	4.2
Alcoholism	11	2.4	133	5.5	182	5.6	15	5.1	341	5.3
Other	132	28.6	677	27.8	699	21.7	91	31.2	1599	24.9
All	461	100.0	2438	100.0	3216	100.0	292	100.0	6407	100.0

TABLE 6.2

ANALGESICS MOST FREQUENTLY CONSUMED BY MONITORED PATIENTS[ø]

	Daily Analgesic Consumers (461 Patients)*		Occasional Analgesic Consumers (2,348 Patients)	
	No.	%	No.	%
Aspirin	210	45.5	1,221	50.1
Bufferin	58	12.6	351	14.4
Darvon Compound	42	9.1	79	3.2
Anacin	19	4.1	164	6.7
Tylenol	18	4.0	73	3.0
Exedrin	12	2.6	106	4.4
Compound Codeine	7	1.5	90	3.7
Aspirin-Phenacetin-Codeine	6	1.3	38	1.6
Codeine	5	1.1	17	0.7
Empirin	5	1.1	33	1.4

ø Patients may give a history of consumption of more than one analgesic.

* Of the 461 daily analgesic consumers, 114 (24.7%) consumed phenacetin-containing compounds, 307 (66.6%) consumed preparations containing salicylate without phenacetin, and 40 (8.7%) consumed preparations containing other drugs.

TABLE 6.3

RELATIONSHIP BETWEEN DISCHARGE DIAGNOSIS OF RENAL DISEASE AND HISTORY OF ANALGESIC INTAKE

	DAILY ANALGESICS	OCCASIONAL ANALGESICS	OTHER DRUGS	NO DRUGS
Renal Disease	21 (4.5)	92 (3.8)	110 (3.4)	11 (3.8)
Other Disease	440	2,346	3,106	281
All	461	2,438	3,216	292

TABLE 6.4

PATIENT CHARACTERISTICS

	DAILY ANALGESICS	OCCASIONAL ANALGESICS	OTHER DRUGS	NO DRUGS
Number of patients	461	2,438	3,216	292
Mean BUN (± SEM) mg/100 ml	19.3 ± 0.7	19.5 ± 0.4	23.4 ± 0.4	18.8 ± 0.9
Mean Age (± SEM) Years	53.3 ± 0.8	49.3 ± 0.3	56.5 ± 0.3	52.5 ± 1.2
Proportion Female (%)	38.0	37.7	35.6	25.3
Proportion Died (%)	4.5	4.2	8.0	5.8

TABLE 6.5

RELATIONSHIP BETWEEN MEDICATION HISTORY AND URINE PROTEIN CONCENTRATIONS*

URINE PROTEIN	DAILY ANALGESICS		OCCASIONAL ANALGESICS		OTHER DRUGS		NO DRUGS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
0	309	70.6	1574	67.9	1983	65.6	162	58.9
1 - 2, +	110	25.1	637	27.5	847	28.0	92	33.5
3 - 4, +	19	4.3	106	4.6	192	6.4	21	7.6
All	438	100.0	2317	100.0	3022	100.0	275	100.0

*as measured by Albustix (Ames Company).

TABLE 6.6

RELATIONSHIP BETWEEN MEDICATION HISTORY AND MICROSCOPIC FINDINGS IN THE URINE

URINE FINDINGS	DAILY ANALGESICS		OCCASIONAL ANALGESICS		OTHER DRUGS		NO DRUGS	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
White cells	91	21.1	380	16.7	640	21.4	72	26.6
Red cells/casts	13	3.0	85	3.7	124	4.1	13	4.8
Other	328	75.9	1823	79.6	2231	74.5	186	68.6
All	432	100.0	2288	100.0	2995	100.0	271	100.0

TABLE 6.7

CHARACTERISTICS OF DAILY ANALGESIC CONSUMERS

	DURATION OF CONSUMPTION (YEARS)		
	< 1	1 - 6	6 +
Number of Patients	259	100	102
Mean BUN (± SEM) (mg/100 ml)	18.9 ± 0.9	19.3 ± 1.6	20.2 ± 1.6
Mean Age (± SEM) (years)	49.7 ± 1.1	56.7 ± 1.7	59.2 ± 1.5
Proportion Female (%)	32.8	43.0	46.1

TABLE 6.8

RELATIONSHIP OF URINE PROTEIN CONCENTRATION* TO DURATION OF DAILY ANALGESIC CONSUMPTION

URINE PROTEIN	DURATION OF CONSUMPTION (years) < 1 NUMBER	< 1 PER CENT	1 - 6 NUMBER	1 - 6 PER CENT	6 + NUMBER	6 + PER CENT
0	178	71.5	67	71.3	64	67.4
1 - 2, +	59	23.7	24	25.5	27	28.4
3 - 4, +	12	4.8	3	3.2	4	4.2
All	249	100.0	94	100.0	95	100.0

*measured by Albustix (Ames Company)

TABLE 6.9

RELATIONSHIP BETWEEN MICROSCOPIC FINDINGS IN URINE AND DAILY ANALGESIC CONSUMPTION

URINE FINDINGS	DURATION OF CONSUMPTION (years) < 1 NUMBER	< 1 PER CENT	1 - 6 NUMBER	1 - 6 PER CENT	6 + NUMBER	6 + PER CENT
White cells	40	16.2	19	21.1	32	33.7
Red cells/casts	7	2.8	4	4.4	2	2.1
Other	200	81.0	67	74.5	61	64.2
Total	247	100.0	90	100.0	95	100.0

TABLE 6.10

COMPARISON AMONGST DAILY ANALGESIC USERS OF THE OBSERVED FREQUENCIES OF WHITE CELLS IN URINE TO THE EXPECTED FREQUENCIES WHEN THE POPULATION IS ADJUSTED FOR DIFFERENCES IN AGE AND SEX

(A) MALES

DURATION OF ANALGESIC USE (years)	0 - 39 YEARS			40 - 59 YEARS			60 + YEARS			TOTAL POPULATION[1]	
	TOTAL NUMBERS	ABNORMALITIES[2] OBSERVED	EXPECTED[3]	TOTAL NUMBERS	ABNORMALITIES OBSERVED	EXPECTED	TOTAL NUMBERS	ABNORMALITIES OBSERVED	EXPECTED	TOTAL NUMBERS	ABNORMALS OBSERVED
< 1	47	8	6.9	65	9	10.3	52	12	13.2	247	40
1-6	6	2	2.5	25	7	3.7	20	2	4.8	90	19
6 +	6	2	2.6	11	2	4.0	32	9	5.0	95	32
All	59	12	12	101	18	18	104	23	23	432	91

[1]Including both sexes.

[2]Abnormalities - number of patients with white cells in urine.

[3]Expected values calculated by applying rate observed in total population to the numbers in each cell, e.g., for males aged 0-39 years who consumed analgesics daily for up to one year, observed number of patients with abnormal white cells in urine = 8 and expected number = $\frac{247 \times 12}{432}$ or 6.9

TABLE 6.10

COMPARISON AMONGST DAILY ANALGESIC USERS OF THE OBSERVED FREQUENCIES OF WHITE CELLS IN URINE TO THE EXPECTED FREQUENCIES WHEN THE POPULATION IS ADJUSTED FOR DIFFERENCES IN AGE AND SEX

(B) FEMALES

DURATION OF ANALGESIC USE (years)	0 - 39 YEARS			40 - 59 YEARS			60 + YEARS			TOTAL POPULATION[1]	
	TOTAL NUMBERS	ABNORMALITIES OBSERVED	EXPECTED	TOTAL NUMBERS	ABNORMALITIES OBSERVED	EXPECTED	TOTAL NUMBERS	ABNORMALITIES[2] OBSERVED	EXPECTED	TOTAL NUMBERS	ABNORMALS OBSERVED
< 1	23	1	0.6	30	5	8.6	30	*5*	*12.6*	247	40
1-6	8	0	0.2	14	5	3.1	17	*3*	*4.6*	90	19
6 +	6	0	0.2	16	5	3.3	24	*14*	*4.8*	95	32
All	37	1	1	60	15	15	71	22	22	432	91

[1]Including both sexes.

[2]Observed and expected figures are similar in both sexes and at all age groups except in females over 60 years where a comparison between the observed and expected results (figures in italics) reveals a significant deficit of abnormalities amongst short term (< 1 year) daily analgesic users and a marked excess amongst long term (6+ years) daily users. ($\chi^2_2 = 22.8$, $p < 0.01$)

TABLE 6.11

CHARACTERISTICS OF OCCASIONAL ANALGESIC CONSUMERS

	DURATION OF CONSUMPTION (years)		
	< 1	1 - 6	6 +
Number of patients	386	315	1,737
Mean BUN (±SEM) (mg/100 ml)	20.4 ± 1.0	20.2 ± 1.1	19.2 ± 0.5
Mean age (± SEM) (years)	43.9 ± 2.3	43.8 ± 2.5	51.5 ± 1.2
Proportion female (%)	41.1	41.9	36.1

TABLE 6.12

RELATIONSHIP OF URINE PROTEIN CONCENTRATION* TO DURATION OF OCCASIONAL ANALGESIC CONSUMPTION

URINE PROTEIN	DURATION OF CONSUMPTION (years)					
	< 1		1 - 6		6 +	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
0	250	67.9	211	69.6	1113	67.6
1 - 2, +	97	26.4	79	26.0	461	28.0
3 - 4, +	21	5.7	13	4.4	72	4.4
All	368	100.0	303	100.0	1646	100.0

*measured by Albustix (Ames Company)

TABLE 6.13

RELATIONSHIP BETWEEN MICROSCOPIC FINDINGS IN URINE AND OCCASIONAL ANALGESIC CONSUMPTION

URINE FINDINGS	DURATION OF CONSUMPTION (years) < 1 NUMBER	< 1 PER CENT	1 - 6 NUMBER	1 - 6 PER CENT	6 + NUMBER	6 + PER CENT
White cells	54	14.8	39	12.9	287	17.7
Red cells/casts	13	3.6	14	4.6	58	3.6
Other	298	81.6	249	82.5	1276	78.7
Total	365	100.0	302	100.0	1621	100.0

TABLE 6.14

COMPARISON OF MEDICATION HISTORY IN THOSE WITH AND WITHOUT RECORDED BLOOD UREA NITROGEN (BUN) LEVELS

MEDICATION HISTORY	BUN NOT RECORDED		BUN RECORDED	
	Number	Per Cent	Number	Per Cent
Daily analgesics	22	6.6	461	6.9
Occasional analgesics	144	43.5	2438	36.5
Analgesics (unknown frequency)	12	3.6	279	4.2
Other drugs	139	42.1	3216	48.0
No drugs	14	4.2	292	4.4
All	331	100.0	6686	100.0

$\chi^2_4 = 7.159 \quad p > 0.1$

TABLE 6.15

ADMISSIONS DUE TO ANALGESIC ATTRIBUTED RENAL DISEASE

AGE/SEX	ADMISSION BUN	ADMISSION HCT	DRUG IMPLICATED	DAILY DOSAGE	DURATION OF INTAKE	DISCHARGE DIAGNOSES
43 F	132	26	"Phenacetin"	--	many years	Chronic renal failure
45 F	127	33	Exedrin	12	1-2 years	Chronic renal failure, hypertension
46 F	68	21	Fiorenal	--	many years	Chronic renal failure
48 F	160	25	"Phenacetin"	--	many years	Acute renal failure, pyelonephritis
52 F	14	41	Exedrin	--	6+ years	Nephrotic syndrome
			Vanquish	--	1 year	
55 F	--	22	Empirin	12	10 years	Chronic renal failure
61 M	95	--	"Phenacetin"	--	--	Chronic renal failure, cryptococcal meningitis
68 F	89	20	Frost 222	5	10 years	Chronic renal failure

TABLE 7.1

REPORTED ADVERSE REACTION RATES TO ANTIBIOTICS

Drug	Number Exposed	Adverse Reactions No.	(%)	Life Threatening A.R. No.	(%)	Allergy	Drug Fever	Alim[1] Sympt	Super[2] Infect	Rise in BUN	Tinni[3] Deaf.	Neur[4] A.R.	Inj[5] Comp	Ot
Aqueous Penicillin	590	27	4.6	5	0.8	10	1	1	5	0	0	1	8	
Procaine Penicillin	592	17	2.9	2	0.3	12	2	0	1	0	0	0	2	
Penicillin G K	299	11	3.7	1	0.3	3	1	2	0	0	0	2	3	
Penicillin V K	237	7	3.0	0	0	3	0	3	0	0	0	0	0	
Ampicillin	1322	147	11.1	3	0.2	85	0	45	12	0	0	0	2	
Oxacillin	228	15	6.6	0	0	3	2	5	0	0	0	2	3	
Cephalothin	530	64	12.1	11	2.1	10	6	3	8	3	0	0	32	
Streptomycin	295	11	3.7	1	0.3	3	2	1	0	0	1	2	1	
Kanamycin	238	34	14.3	12	5.0	2	2	1	3	17	5	1	1	
Gentamycin	97	8	8.2	4	4.1	2	0	0	0	4	2	0	0	
Neomycin	483	67	13.9	9	1.9	3	0	51	2	8	3	0	0	
Paromomycin	71	6	8.4	2	2.8	2	0	2	0	0	1	0	0	

TABLE 7.1 (continued)

REPORTED ADVERSE REACTION RATES TO ANTIBIOTICS

Drug	Number Exposed	Adverse Reactions No.	(%)	Life Threatening A.R. No.	(%)	Allergy	Drug Fever	Alim[1] Sympt	Super[2] Infect	Rise in BUN	Tinni[3] Deaf	Neur[4] A.R.	Inj[5] Comp	Oth
Polymixins (B and E)	128	21	16.4	6	4.7	1	0	0	1	9	0	7	3	0
Chloramphenicol	224	22	9.8	5	2.2	3	0	7	4	0	0	0	0	8
Tetracycline	705	45	6.4	5	0.7	4	1	22	5	7	0	0	3	2
Erythromycin	253	24	9.5	0	0	3	0	16	2	0	0	0	3	0
Isoniazid	361	16	4.4	3	0.8	2	2	1	0	0	0	1	0	10
Sulphisoxazole	298	16	5.4	0	0	3	0	7	1	1	0	0	0	4
Nitrofurantoin	83	10	12.0	0	0	5	0	5	0	0	0	0	0	0
Nalidixic Acid	50	2	4.0	0	0	0	0	2	0	0	0	0	0	0

[1]Alimentary symptoms; [2]Drug-attributed superinfection; [3]Tinnitus and/or deafness;

[4]Neurological complications (convulsions, extrapyramidal signs, paraesthesiae); [5]Injection complications;

[6]See Table 7.2.

TABLE 7.2

FURTHER DETAILS OF ADVERSE REACTIONS ATTRIBUTED TO ANTIBIOTICS

Drug	Adverse Reactions
Aqueous Penicillin	Haemolytic anaemia (1); extrapyramidal signs (1)
Penicillin G K	Convulsions (2) - Case reports 7i, 7ii.
Penicillin V K	Hyperkalemia (1) - Case report 7iii.
Ampicillin	Haematuria (1); petechial haemorrhages (1); heart block (1)
Oxacillin	Convulsions (2) - Case reports 7iv, 7v.
Cephalothin	Jaundice (2)
Streptomycin	Psychosis (2)
Kanamycin	Leucopenia (1); tachycardia (1)
Paromomycin	Proteinuria (1)
Polymixins (B and E)	Paresthesiae - peripheral (4) - circum-oral (3)
Chloramphenicol	Bone marrow depression (7); jaundice (1)
Tetracycline	Prolonged prothrombin time (1); jaundice (1)
Isoniazid	Psychosis (5); jaundice (3); depression (1); vasculitis (1)
Sulphisoxazole	Petechial haemorrhages (3); vertigo (1)

CASE REPORT 7i

Patient: 57 year old male with Hodgkin's disease and staphylococcal meningitis following septicemia.

Comment: Patient admitted to Lemuel Shattuck Hospital, Boston, with marked nuchal rigidity and profound shock, was shown to have staphylococcal septicemia and meningitis. Initially responded to therapy with penicillin G potassium 5 mega units four hourly intravenously. Two days after therapy commenced, he developed marked convulsions following an injection of penicillin. This responded to an injection of phenobarbitone followed by a five-day course of diphenylhydantoin. Dosage of penicillin was reduced to 2 mega units four hourly with good effect.

Initial BUN level on admission was 29 mg/100 ml. and this rose to 87 mg/100 ml on day of convulsions. At the time of reducing penicillin dosage serum potassium level was 5.2 m Eq/litre.

CASE REPORT 7ii

Patient: 54 year old female with mild alcoholic cirrhosis admitted with peritonitis.

Comment: Prior to admission, this patient had passed several melaena stools. On admission to Lemuel Shattuck Hospital, a diagnosis of peritonitis was made, the etiology of which was uncertain, but the presence of a colonic carcinoma was questioned. Presenting hematocrit was 29% and BUN level was 34 mg/100 ml. Patient was transfused 3 units of blood and penicillin G commenced in a dose of 5 mega units four hourly I.V. After an initial satisfactory response, she developed marked convulsions. These subsided following appropriate therapy. Dosage of penicillin G was reduced and patient recovered. BUN level on day of convulsions was 48 mg/100 ml, and serum creatinine level 2.9 mg/100 ml.

CASE REPORT 7iii

Patient: 87 year old female with pneumococcal pneumonia and congestive cardiac failure.

Comment: This patient was admitted to Peter Bent Brigham Hospital in marked congestive cardiac failure with a right lower lobe consolidation. Presenting hematocrit was 39%, BUN level was 48 mg/100 ml, and serum potassium was 4.0 m Eq/litre. She was given two days of therapy with penicillin G potassium one mega unit six hourly, and thereafter changed to penicillin V potassium 250 mg six hourly. After six days of penicillin therapy, her serum potassium level had risen to 6.4 m Eq/L, while BUN level remained at 45-50 mg/100 ml.

Hyperkalemia was attributed to penicillin V by the attending physician.

CASE REPORT 7iv

Patient: 21 year old female with rheumatoid arthritis, nephrotic syndrome and bacterial endocarditis.

Comment: Admitted to Peter Bent Brigham Hospital with the above diagnosis, this patient was gravely ill on arrival with BUN level of 70 mg/100 ml., serum albumin of 2.1 G/100 ml. and pancytopenia. She was given pencillin G potassium in a dose of 1 mega unit four hourly I.V. and oxacillin 1 G four hourly I.V. After seven doses of these drugs, she experienced marked convulsions which required paraldehyde and diphenylhydantoin to relieve them. Patient was then treated with cephalothin and subsequently recovered.

(Despite the clinical resemblance to disseminated lupus erythematosis no anti-nuclear factor or L.E. cells were demonstrated and the diagnosis could not be fully substantiated.)

CASE REPORT 7v

Patient: 52 year old female with staphylococcal septicemia following aspiration pneumonia secondary to amphetamine overdose.

Comment: On admission to Lemuel Shattuck Hospital, this patient was profoundly shocked and required emergency resuscitation. Following the diagnosis of staphylococcal septicemia, she was given oxacillin 2 G I.V. and ampicillin 2.5 G I.V. four hourly. After three days, patient sustained a severe convulsion which responded to appropriate therapy. Thereafter, the doses of antibiotics were reduced and she gradually recovered. BUN level on the day of the convulsions was 20 mg/100 ml. Convulsion was attributed to oxacillin by attending physician.

Table 8.1

Frequencies of administration of noted drugs to patients who did and did not develop a recorded rise in B.U.N. (irrespective of drug implicated in the observed rise).

Drug	No Rise in BUN		Rise in BUN	
	Numbers	Per Cent*	Numbers	Per Cent*
Neomycin	375	3.7	18	12.2
Kanamycin	174	1.7	17	11.6
Colistin	57	0.6	8	5.4
Polymixin B	34	0.3	4	2.7
Gentamycin	99	1.0	6	4.1
Cephalothin	426	4.2	16	10.9
Tetracycline	571	5.7	25	17.0
Frusemide	1,042	10.4	62	42.2
Triamterene	23	0.2	7	4.8
Ethacrynic Acid	219	2.2	14	9.5
Chlorothiazide	375	3.7	16	10.9
Hydrochlorothiazide	644	6.4	34	23.1
Spironolactone	508	5.0	46	31.3
All Patients	10,062	98.6†	147	1.4†

* Percentage calculated on basis of total number of patients in that group.

† This percentage calculated on basis of 10,209 patients in series.

Table 8.2

Distribution of First Discharge Diagnosis
by Treatment Group

DIAGNOSTIC CATEGORY	GROUP T	GROUP A	GROUP N
Cardiovascular	95 (46.6)	259 (43.5)	603 (52.1)
Respiratory	56 (27.4)	126 (21.1)	79 (6.8)
Hepatic	13 (6.3)	28 (4.7)	115 (9.9)
Neoplastic	17 (8.3)	59 (9.9)	86 (7.4)
Others	23 (11.2)	124 (20.8)	274 (23.7)
All categories	204	596	1157

Bracketed figures give percentages.

Group T - Tetracycline recipients
Group A - Recipients of other antibiotics
Group N - Recipients of other drugs

Table 8.3

Mean Admission BUN Level in Relation to Reported Rise in BUN
(expressed in mg/100 ml blood)

Group	Patients with Rise in BUN*	Patients without Rise in BUN*
T	34 ± 4	27 ± 2
A	41 ± 5	32 ± 1
N	31 ± 3	26 ± 1

*Results expressed as mean ± standard error of mean.

Group T - tetracycline recipients
Group A - other antibiotics recipients
Group N - recipients of other drugs

Table 8.4

Frequency of Recorded Rise in BUN among Recipients of Diuretics: In Relation to Admission BUN Levels

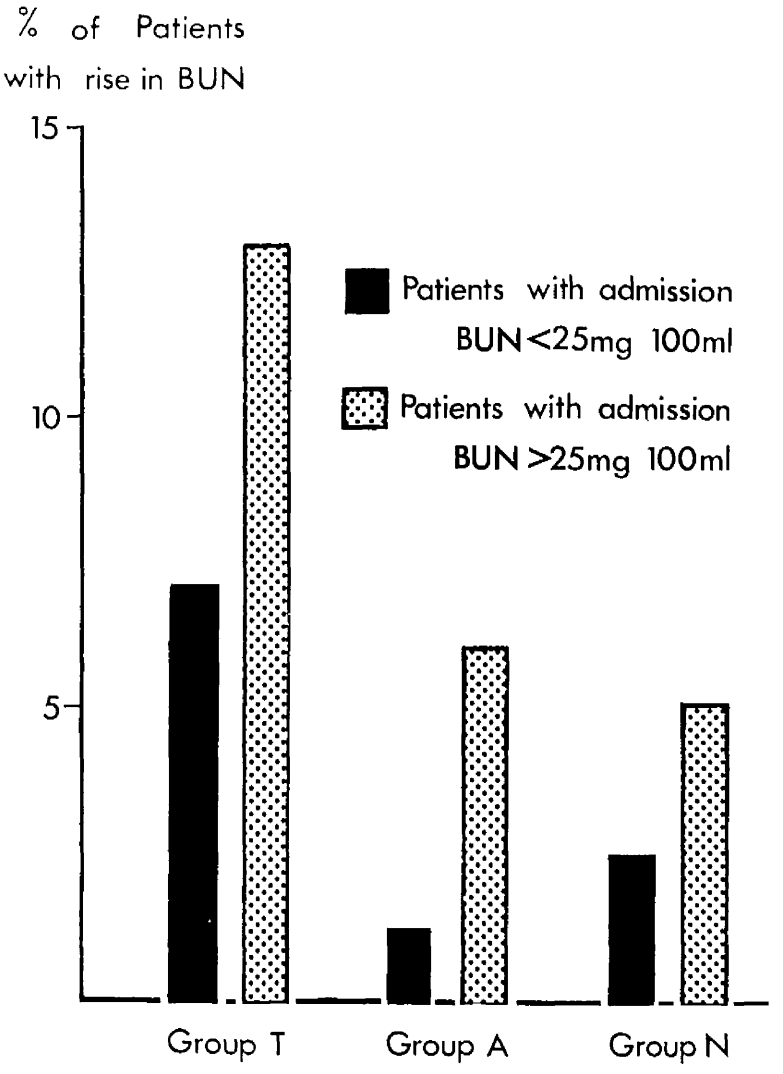
Admission BUN Level (mg/100 ml)	Group T	Group A	Group N
< 25	8/112 (7.1)	5/333 (1.5)	20/790 (2.5)
> 25	12/92 (13.0)	16/263 (6.1)	19/367 (5.2)
All levels	20/204 (9.8)	21/596 (3.5)	39/1157 (3.4)

Group T - tetracycline recipients
Group A - recipients of other antibiotics
Group N - recipients of other drugs

Bracketed figures give percentage of patients with recorded rise in BUN.

Figure 8.1

Frequency of Recorded Rise in BUN
among Recipients of Diuretics



Group T - Tetracycline recipients
Group A - Recipients of other Antibiotics
Group N - Recipients of other Drugs

Table 8.5

Mean Recorded Rise in BUN in Relation to Treatment Received

Group	Rise in BUN (mg/100 ml)	Range of Rise (mg/100 ml)
T	34 ± 5	10 - 77
A	33 ± 3	12 - 82
N	22 ± 2	6 - 75
All Groups	28 ± 3	6 - 77

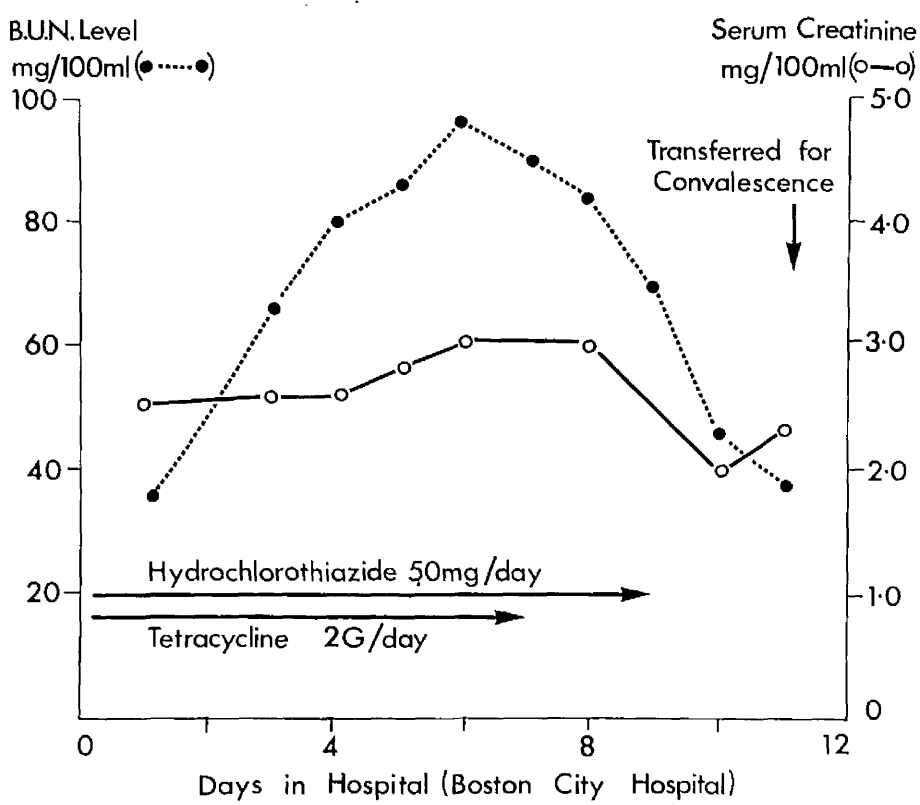
Group T - tetracycline recipients
Group A - recipients of other antibiotics
Group N - recipients of other drugs

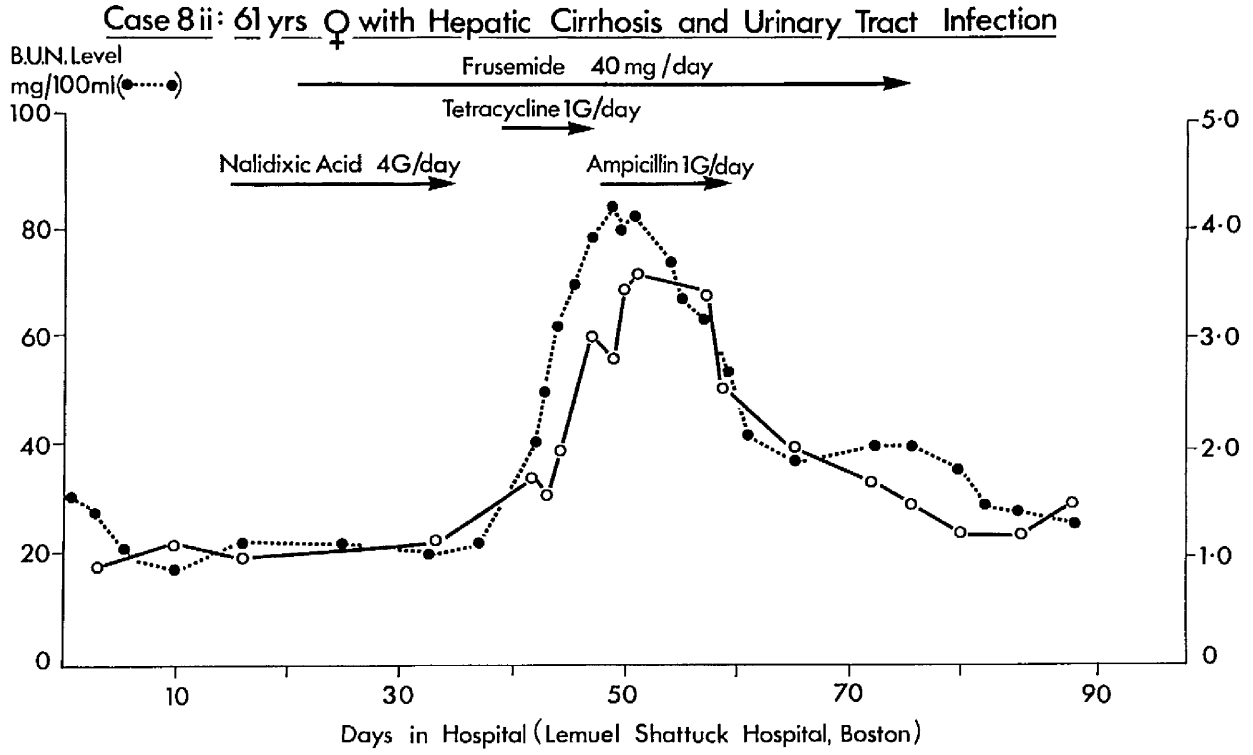
CASE REPORT 8i

Patient: 70 year old male with congestive cardiac failure and respiratory infection.

Comment: Admitted to Boston City Hospital suffering from an exacerbation of congestive cardiac failure associated with mild bronchitis. He was treated with hydrochlorothiazide, digoxin and tetracycline. After admission his BUN level was noted to rise from an initial level of 34 mg/100 ml to a maximum of 98 mg/100 ml. This rise was accompanied by a small rise in serum creatinine level (2.5 - 3.0 mg/100 ml).

On stopping tetracycline therapy, the BUN and creatinine levels returned to their admission values. The diuretic was implicated by the attending physician as a cause of the rise in BUN.




Case 8 ii: 61 yrs ♀ with Hepatic Cirrhosis and Urinary Tract Infection
B.U.N. Level
mg/100ml(●·····●)
Frusemide 40 mg / day
Tetracycline 1G/day
Nalidixic Acid 4G/day
Ampicillin 1G/day
100
80
60
40
20
0
5·0
4·0
3·0
2·0
1·0
0
10
30
50
70
90
Days in Hospital (Lemuel Shattuck Hospital, Boston)

CASE REPORT 8ii

Patient: 61 year old female with alcoholic cirrhosis and urinary tract infection.

Comment: Admitted to Massachusetts General Hospital suffering from her first episode of hepatic failure. On recovery was transferred for convalescence to Leumuel Shattuck Hospital (L.S.H.), where she was noticed to have symptoms of a urinary tract infection, which was initially treated with nalidixic acid. During her first month of convalescence, baseline BUN levels fluctuated around 20 mg/100 ml and creatinine levels around 1.0 mg/100 ml.

On the twentieth day after admission to L.S.H., she was started on diuretic therapy (frusemide 40 mg. per day) which was continued for 56 days.

BUN and creatinine levels remained constant until tetracycline therapy was commenced for a recurrence of urinary tract symptom - atology, whereupon both these levels rose, the former to a maximum of 82 mg/100 ml and the latter to 3.6 mg/100 ml.

When tetracycline therapy ceased (but diuretic therapy continued), the BUN and creatinine levels gradually returned to approximately their admission levels. During this recovery phase, a course of ampicillin was given without a further rise in BUN occurring.

The rise in BUN was attributed to frusemide by the attending physician.

Table 8.6

Frequency of drug-attributed rise in BUN in a group of selected antibiotic recipients*

	Kanamycin	Gentamycin	Polymixin	Colistin	Amphotericin	Neomycin	Paromomycin
No Diuretics	10/120 (8.3)†	3/72 (4.2)	1/22 (4.5)	5/39 (12.8)	1/5 (20.0)	4/237 (1.7)	2/26 (7.7)
Diuretics	12/67 (17.9)	6/39 (15.4)	6/18 (33.3)	4/23 (17.4)	2/3 (67.7)	21/169 (12.4)	9/29 (31.0)
All Groups	22/187 (11.8)	9/111 (8.1)	7/40 17.5)	9/62 (14.5)	3/8 (37.5)	25/406 (6.2)	11/55(20.0)

* patients may have received more than one of the target antibiotics, in which case they have been counted on more than one occasion, i.e., these groups are not mutually exclusive.

† bracketed figures give percentage of patients in group who developed drug-attributed rise in BUN

Table 8.7

Frequency of recorded rise in BUN among recipients of nephrotoxic drugs given for treatment of infection: with stratification by diuretic therapy.

	No Diuretics	Diuretics	Total
Rise in BUN	16 (7.4%)	16 (14.5%)	32 (9.8%)
No rise in BUN	201	94	295
Total	217	110	327

FIGURE 9.1

NORMAL RAT KIDNEY - STAINED WITH HAEMATOXYLIN AND EOSIN
(x350)

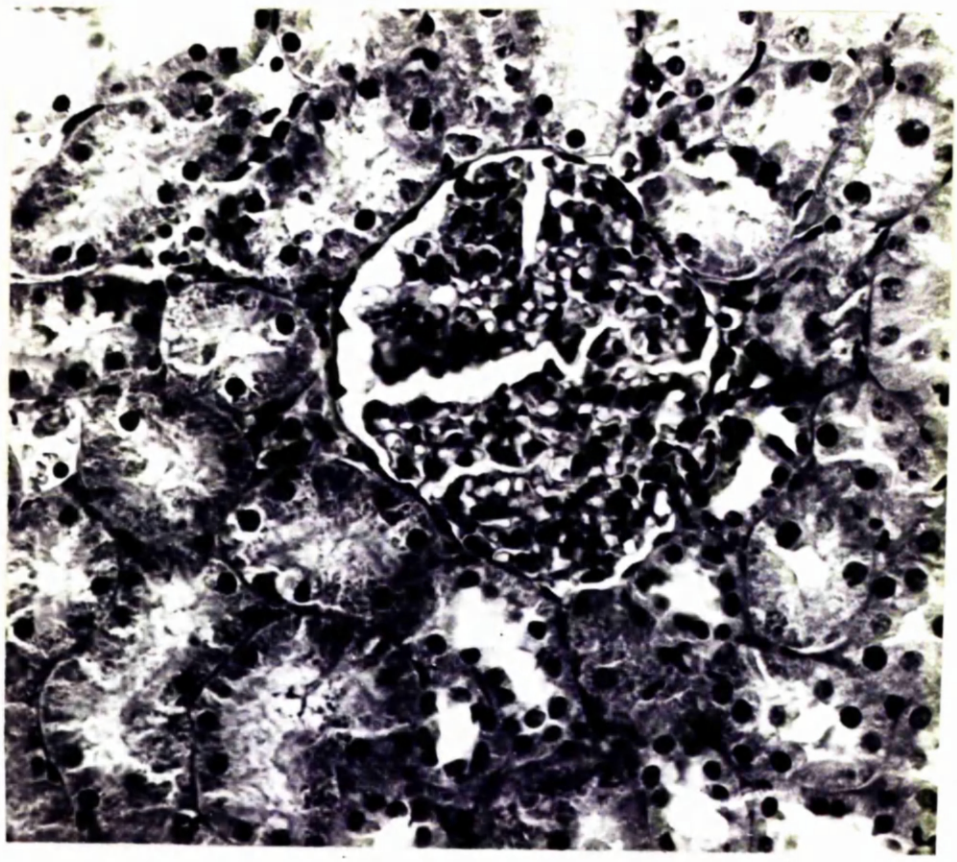


FIGURE 9.2

RAT KIDNEY SHOWING FOCAL PROXIMAL TUBULAR NECROSIS -
STAINED WITH HAEMATOXYLIN AND EOSIN
(x350)

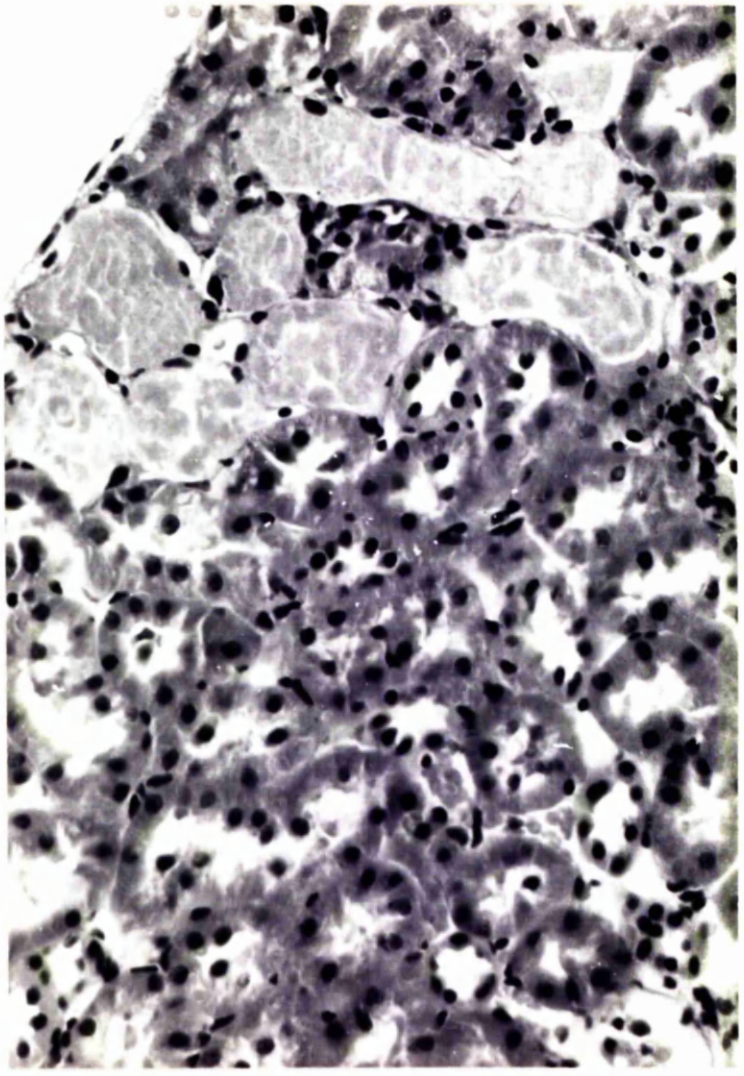


FIGURE 9.3

RAT KIDNEY SHOWING EXTENSIVE PROXIMAL TUBULAR NECROSIS -
STAINED WITH HAEMATOXYLIN AND EOSIN
(x145)

TABLE 9.1

EFFECT OF CEPHALORIDINE ON RENAL FUNCTION AND HISTOLOGY

Cephaloridine Dose	Number of Rats	Mean Weight (g)	Mean Blood Urea (mg/100 ml)	Extensive ATN	Focal ATN	Normal	Mean Antibiotic Level at 90 min. (µg/ml)
250 mg/kg	7	220	28	0	0	7	28
500 mg/kg	8	210	28	0	3	5	50
1 g/kg	6	250	32	0	6	0	78

ATN - acute tubular necrosis

TABLE 9.2

EFFECT OF COMBINATION OF CEPHALORIDINE, GLYCEROL AND FUROSEMIDE ON RENAL FUNCTION AND HISTOLOGY

Strain	Drugs	Number	Weight (g)	Mean Blood Urea (mg/100 ml)	Extensive ATN	Focal ATN	Normal	Mean Cephaloridine Levels at 90 mins. (μg/ml)
A	$C_{125}\ G_2\ F_{50}$	12	296	40	0	8	4	21
	$C_{250}\ G_2\ F_{50}$	12	250	56	0	10	2	18
	$C_{500}\ G_2\ F_{50}$	24	210	303	20	4	0	98
B	$C_{125}\ G_2\ F_{50}$	20	185	52	0	6	14	24
	$C_{250}\ G_2\ F_{50}$	20	200	48	1	12	7	--
	$C_{500}\ G_2\ F_{50}$	20	190	120	11	6	3	84

C - cephaloridine (mg/kg)

G - glycerol (ml/kg)

F - furosemide (mg/kg)

TABLE 9.3

EFFECT ON RENAL FUNCTION AND HISTOLOGY OF CEPHALOTHIN ALONE AND IN COMBINATION WITH GLYCEROL AND FUROSEMIDE

Drugs	Number	Weight (g)	Mean Blood Urea (mg/100 ml)	Extensive ATN	Focal ATN	Normal	Mean Cephalothin Levels at 90 mins. (µg/ml)
Ct_{1000}	6	185	28	0	0	6	--
Ct_{1500}	18	170	31	0	3	14	74
Ct_{500} G_2 F_{50}	18	205	36	1	3	14	72
Ct_{1000} G_2 F_{50}	18	185	105	9	7	2	113
Ct_{1500} G_2 F_{50}	10	200	190	9	1	0	--

Ct - Cephalothin (mg/kg)

G - Glycerol (ml/kg)

F - Furosemide (mg/kg)

TABLE 9.4

EFFECTS OF COLISTIN SULPHOMETHATE GIVEN ALONE AND WITH GLYCEROL AND FUROSEMIDE

Drugs	Number	Weight (g)	Mean Blood Urea (mg/100 ml)	Extensive ATN	Focal ATN	Normal	Mean Colistin Levels at 90 mins. (µg/ml)
C_{s24}	5	155	35	0	0	5	39
C_{s24} G_2	6	160	40	0	4	2	37
C_{s24} G_2 F_{50}	7	195	79	4	3	0	31

C_s - Colistin sulphomethate (mg/kg)

G - Glycerol (ml/kg)

F - Furosemide (mg/kg)

TABLE 9.5

EFFECTS OF KANAYMYCIN ON RENAL FUNCTION AND HISTOLOGY:
ALONE AND IN COMBINATION WITH FUROSEMIDE AND GLYCEROL

Drugs	Number	Weight (g)	Mean Blood Urea (mg/100 ml)	Extensive ATN	Focal ATN	Normal	Mean Kanamycin Levels at 90 mins. (µg/ml)
K_{500}	6	230	36	0	3	3	70
K_{1000}	6	210	40	0	6	0	92
K_{500} G_2 F_{50}	6	160	41	0	6	0	82
K_{1000} G_2 F_{50}	6	150	110	4	2	0	90
K_{500} G_2 F_{150}	8	150	95	6	2	0	60

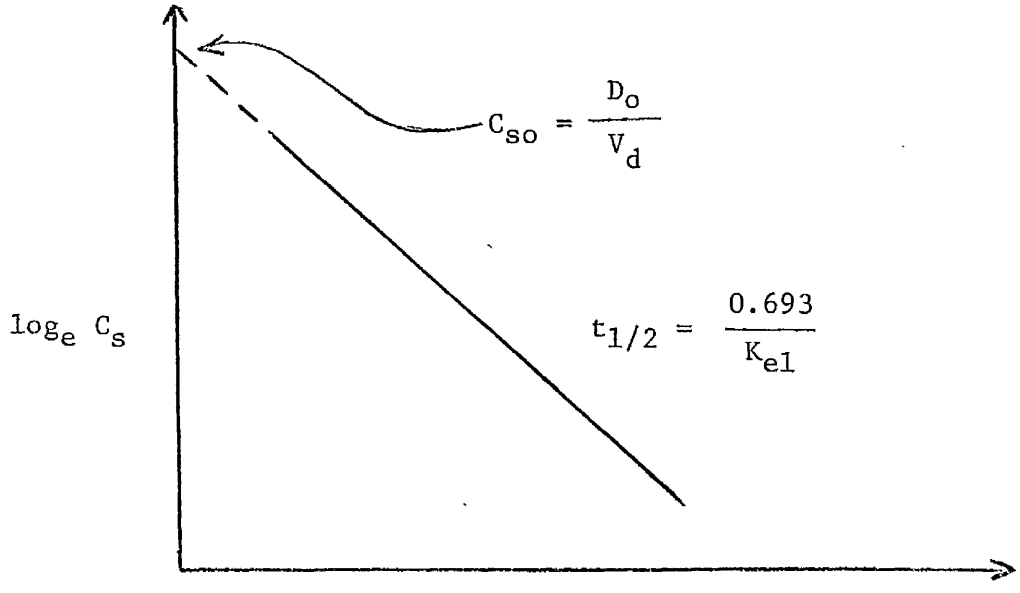
K - Kanamycin (mg/kg)

G - Glycerol (ml/kg)

F - Furosemide (mg/kg)

FIGURE 10.1

CALCULATED PHARMACOKINETIC DATA



where C_s = cephaloridine concentration in serum

$t_{1/2}$ = half-life of cephaloridine in serum (calculated from observed regression line)

C_{so} = original cephaloridine concentration in serum at time = zero - extrapolated from observed regression line

D_o = original dose administered

V_d = volume of distribution of drug

k_{el} = elimination rate constant $\left(\frac{0.693}{t_{1/2}}\right)$

FIGURE 10.2

NORMAL RABBIT KIDNEY STAINED WITH
HAEMATOXYLIN AND EOSIN (x560)

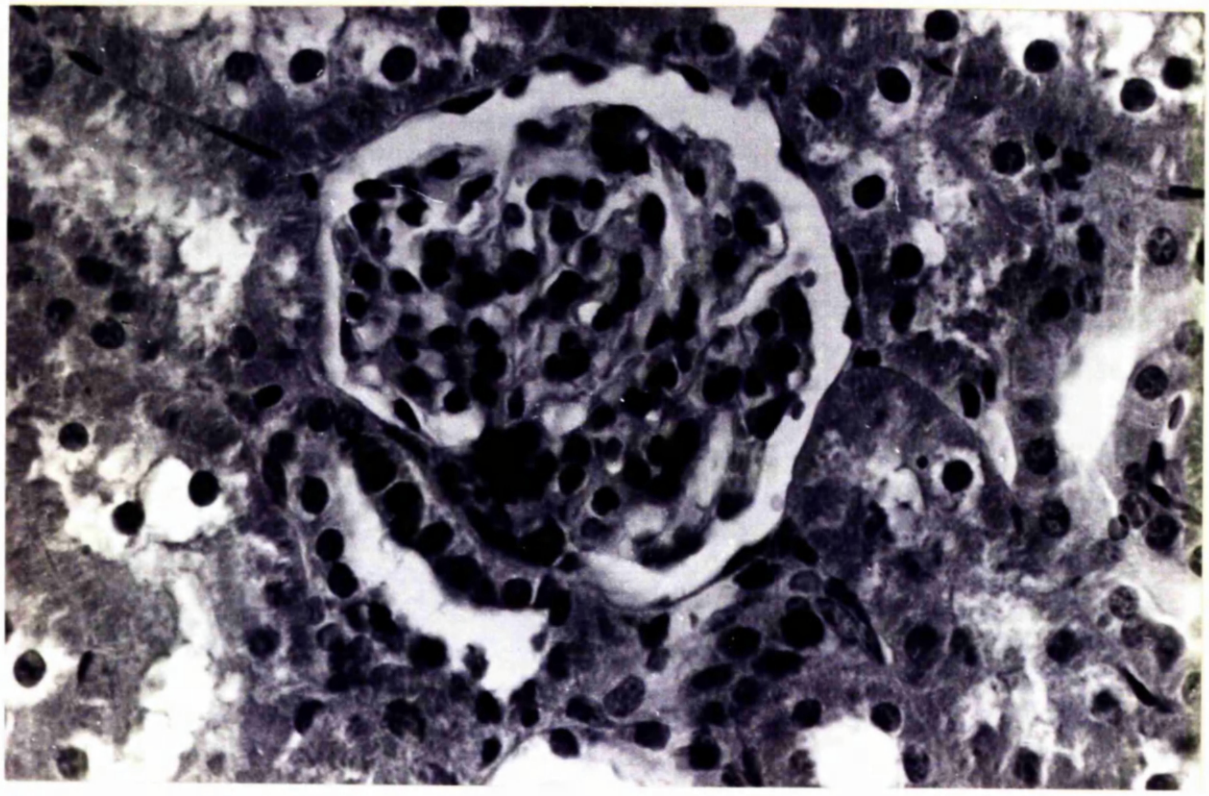


FIGURE 10.3

RABBIT KIDNEY STAINED WITH HEMATOXYLIN AND EOSIN
AND SHOWING GRANULAR AND CELLULAR CASTS IN COLLECTING TUBULES
(x 350)

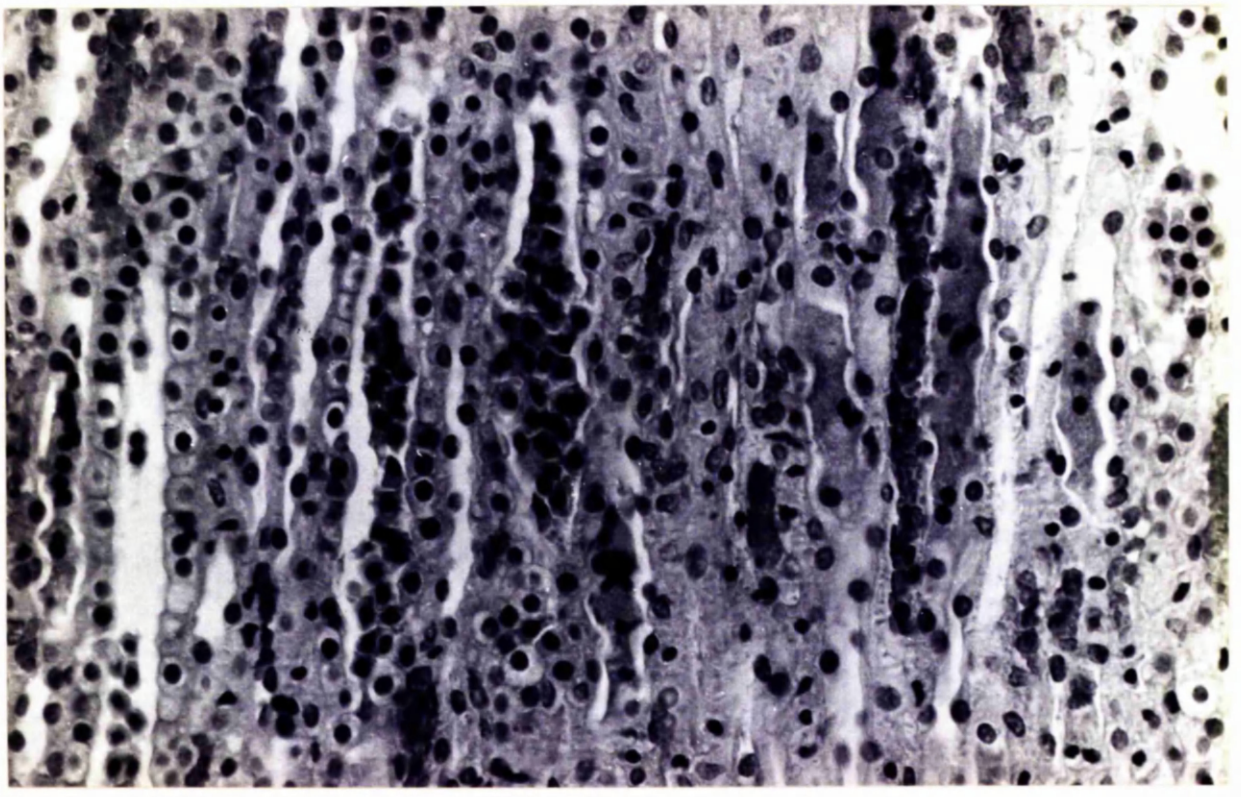


FIGURE 10.4

RABBIT KIDNEY STAINED WITH HAEMATOXYLIN AND EOSIN AND SHOWING WIDESPREAD CALCIFIED DEBRIS IN TUBULAR LUMINA PARTICULARLY IN OUTER CORTICAL SEGMENT OF KIDNEY (x 145)

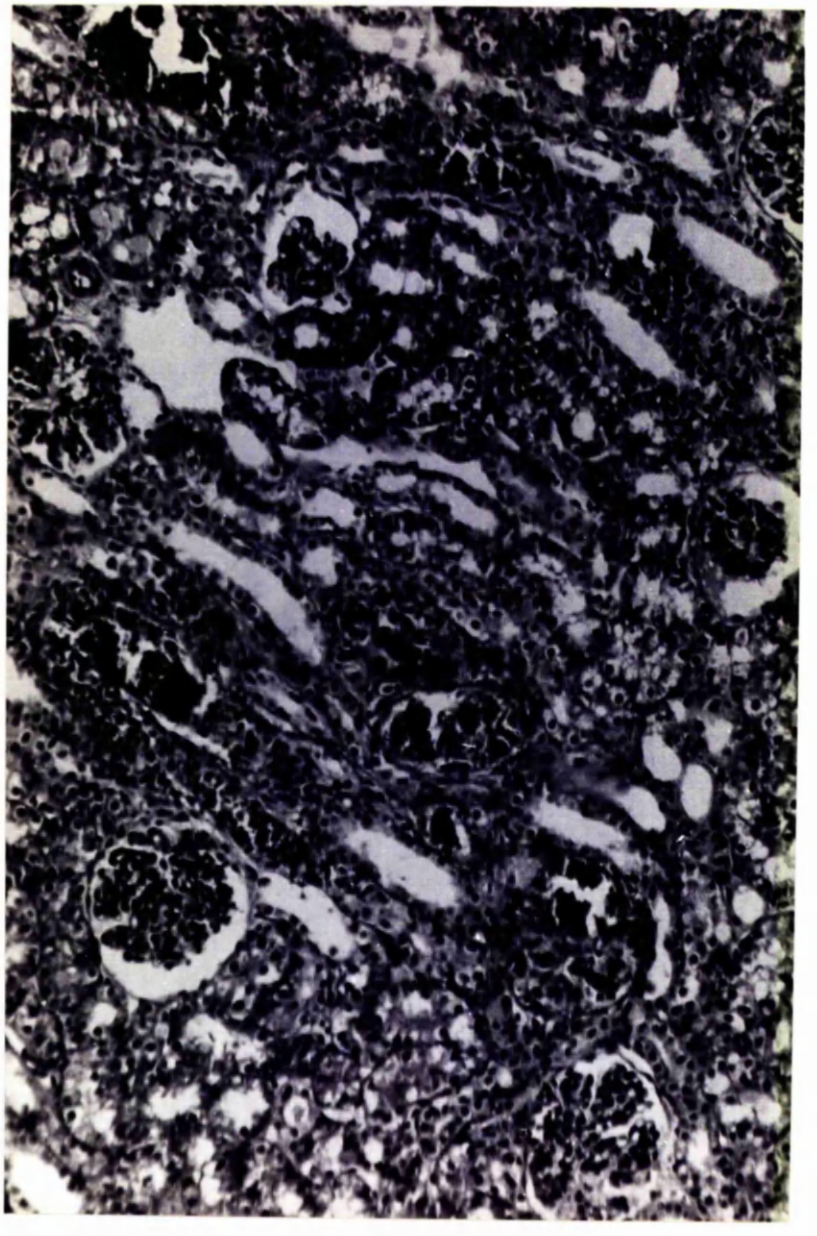


FIGURE 10.5

RABBIT KIDNEY STAINED WITH HAEMATOXYLIN AND EOSIN
SHOWING GREATER DETAIL OF LESION SEEN IN FIGURE 10.4
(x 350)

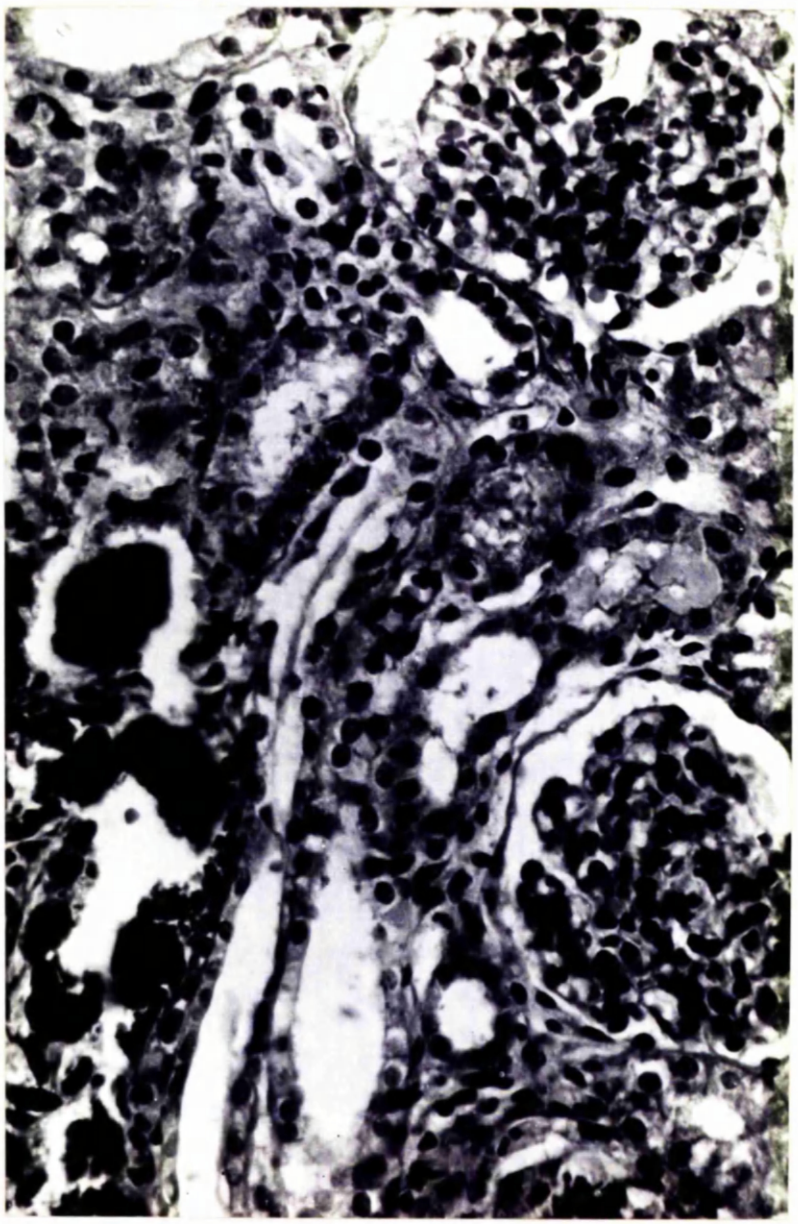


TABLE 10.1

PHARMACOKINETIC DATA ON ANIMALS OF GROUP P WHO RECEIVED TWO INJECTIONS OF CEPHALORIDINE TOGETHER WITH DAILY INTRAPERITONEAL PHENOBARBITONE

RABBIT	DOSE mg/kg	FIRST STUDY $t_{1/2}$(min)	FIRST STUDY V_d(ml)	FIRST STUDY Cl_B(ml/min)	SECOND STUDY $t_{1/2}$(min)	SECOND STUDY V_d(ml)	SECOND STUDY Cl_B(ml/min)
23	50	34.1	584	11.9	25.2	569	15.6
24	50	34.6	516	10.3	42.3	804	13.2
25	50	53.7	684	8.8	27.0	398	10.2
26	50	22.9	811	24.6	16.8	575	23.7
27	100	67.9	628	6.4	55.0	519	6.5
28	100	35.4	930	18.2	44.7	583	9.0
29	100	39.0	1038	18.5	63.0	641	7.1
30	100	46.2	662	6.2	80.6	563	4.8
Mean value		41.7	732	13.1	44.3	581	11.3
S.E.M.		4.9	63	2.3	7.6	40	2.2

$t_{1/2}$ = cephaloridine half-life in serum

Cl_B = body clearance of drug

V_d = volume of distribution of cephaloridine

TABLE 10.2

PHARMACOKINETIC DATA ON ANIMALS OF GROUP C WHO RECEIVED TWO INJECTIONS OF CEPHALORIDINE

RABBIT	DOSE mg/kg	FIRST STUDY $t_{1/2}$(min)	FIRST STUDY V_d(ml)	FIRST STUDY Cl_B(ml/min)	SECOND STUDY $t_{1/2}$(min)	SECOND STUDY V_d(ml)	SECOND STUDY Cl_B(ml/min)
15	50	28.8	542	13.1	28.3	637	15.6
16	50	29.7	590	13.7	30.4	708	16.3
17	50	54.6	829	10.5	36.7	1084	20.5
18	50	42.0	1014	16.7	33.8	432	8.9
19	100	43.0	455	7.3	41.0	589	9.9
20	100	36.1	645	12.4	38.5	463	8.3
21	100	27.2	676	17.2	48.1	477	6.9
22	100	37.1	600	11.2	94.5	731	5.4
Mean value		37.3	669	12.7	43.9	640	11.5
S.E.M.		3.2	62	1.1	7.6	75	2.0

$t_{1/2}$ = cephaloridine half-life in serum

Cl_B = body clearance of drug

V_d = volume of distribution of cephaloridine

TABLE 10.3

COMPARISON OF OBSERVED AND CALCULATED VALUES FOR SERUM CONCENTRATION OF CEPHALORIDINE IN RABBIT 24

FIRST STUDY[1]			SECOND STUDY[2]		
t	C_s	L	t	C_s	L
5	149	145	5	88	94
10	136	131	10	89	87
20	94	107	15	84	80
30	90	88	36	63	57
81	31	32	58	34	39
118	16	15	130	15	12
128	10	12	174	4.5	6
194	5	3	249	2.3	2
245	3.5	1			

[1]Correlation coefficient (C_s v L) = 0.995
[2]Correlation coefficient (C_s v L) = 0.994

C_s = serum concentration of cephaloridine at time t (µg/ml)
t = time after cephaloridine injection (minutes)
L = least squares estimate of cephaloridine concentration

TABLE 10.4

COMPARISON OF OBSERVED AND CALCULATED VALUES FOR SERUM CONCENTRATION OF CEPHALORIDINE IN RABBIT 20

FIRST STUDY[1]			SECOND STUDY[2]		
t	C_S	L	t	C_S	L
5	462	387	8	562	515
11	336	345	16	451	446
27	212	253	27	311	366
47	158	173	60	208	202
89	79	77	138	52	50
155	34	22	194	21	18
232	12	5	250	6	7

[1]Correlation coefficient (C_S v L) = 0.977
[2]Correlation coefficient (C_S v L) = 0.991

C_S = serum concentration of cephaloridine at time t (µg/ml)
t = time after cephaloridine injection (minutes)
L = least squares estimate of cephaloridine concentration

TABLE 10.5

URINARY RECOVERY OF CEPHALORIDINE IN ANIMALS OF GROUP P

RABBIT	FIRST STUDY			SECOND STUDY		
	URINE CEPHALORIDINE RECOVERY (mg)	ADMINISTERED DOSE (mg)	PROPORTION RECOVERED (%)	URINE CEPHALORIDINE RECOVERY (mg)	ADMINISTERED DOSE (mg)	PROPORTION RECOVERED (%)
23	8.6	82.5	1.0	30.7	82.5	38.0
24	31.4	82.5	37.3	20.0	82.5	24.2
25	14.8	82.5	18.0	--	--	--
26	37.4	82.5	45.3	26.3	82.5	32.0
27	122.4	220.0	55.0	--	--	--
28	--	--	--	50.2	275.0	18.2
29	32.5	275.0	11.8	--	--	--
30	120.0	275.0	44.7	--	--	--

Group P animals all received phenobarbitone (15 mg/kg) daily between studies.

TABLE 10.6

URINARY RECOVERY OF CEPHALORIDINE IN ANIMALS OF GROUP C

RABBIT	FIRST STUDY URINE CEPHALORIDINE RECOVERY (mg)	FIRST STUDY ADMINISTERED DOSE (mg)	FIRST STUDY PROPORTION RECOVERED (%)	SECOND STUDY URINE CEPHALORIDINE RECOVERY (mg)	SECOND STUDY ADMINISTERED DOSE (mg)	SECOND STUDY PROPORTION RECOVERED (%
15	1.3	138	0.9	48.2	138	35
16	4.0	138	2.9	--	--	--
17	31.9	136	22.7	7.3	136	5.4
18	36.9	136	27.0	9.4	136	6.9
19	62.5	275	22.7	20.8	275	7.6
20	--	--	--	10.0	275	3.7
21	--	--	--	14.4	264	5.5
22	18.2	275	6.6	10.9	275	4.0

TABLE 11.1

EFFECT OF STREPTOMYCIN GIVEN INTRAMUSCULARLY BEFORE DIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	STREPTOMYCIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS >8 µg/ml (hours)
B	M	43	66	200	16.0	3.8	16	12
B	M	43	65	160	16.5	7.7	24	72
C	F	37	49	600	10.0	5.1	14	12
C	F	37	50	600	10.5	10.0	26	72
D	F	18	48	375	5.0	10.4	26	72

TABLE 11.2

EFFECT OF 0.5 g STREPTOMYCIN GIVEN INTRAMUSCUARLY AFTER HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	STREPTOMYCIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 8 µg/ml (hours)
B	M	43	65	205	17	7.7	32	80
F	M	19	64	105	3.5	7.8	32	80
C	F	37	50	600	11	10.0	34	80
E	F	24	55	70	6	9.3	30	80

TABLE 11.3

EFFECT OF 0.5 g KANAMYCIN GIVEN INTRAMUSCULARLY BEFORE HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	KANAMYCIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 8 µg/ml (hours)
A	M	41	58	140	8	8.6	26	72
B	M	43	65	230	12	7.7	24	72
C	F	37	49	600	7	10.2	24	60
D	F	18	48	420	4	10.4	26	60
E	F	24	54	75	5	9.3	28	72

TABLE 11.4

EFFECT OF 0.5 g KANAMYCIN GIVEN INTRAMUSCULARLY AFTER HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	KANAMYCIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 8 µg/ml (hours)
A	M	41	58	115	9	8.6	30	80
B	M	43	65	280	15	7.7	26	80
F	M	19	63	100	3	8.0	22	72
C	F	37	49	570	9	10.2	32	80

FIGURE 11.1

EFFECT OF KANAMYCIN GIVEN BEFORE AND AFTER DIALYSIS TO PATIENT *A*

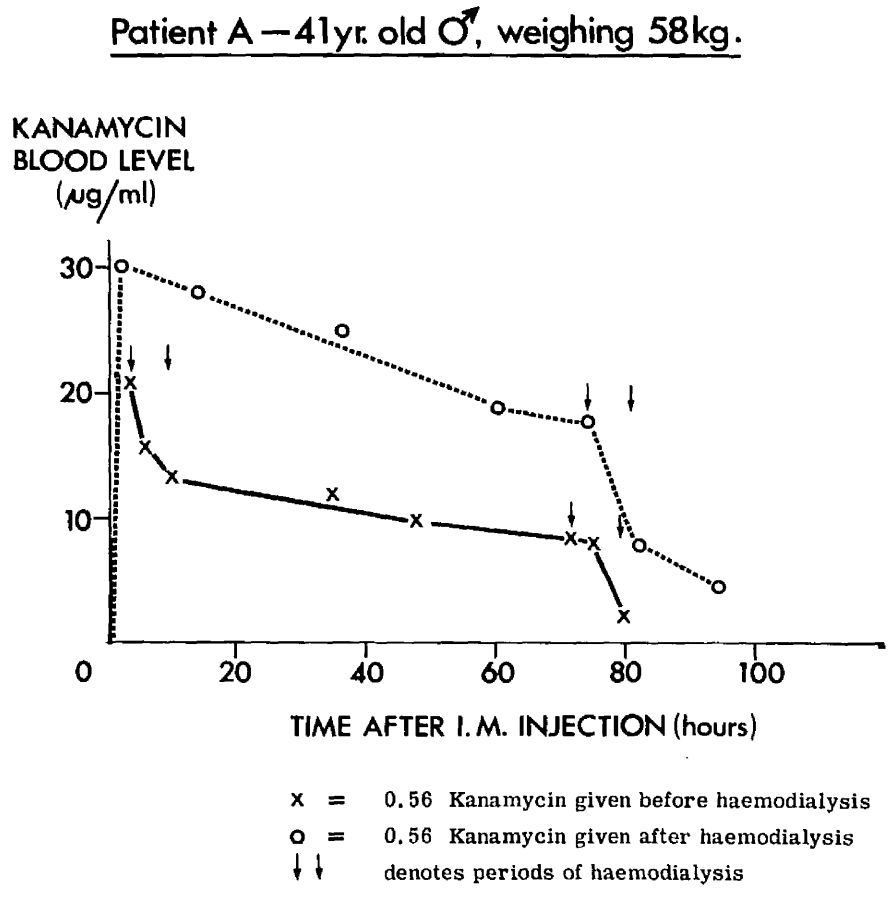


TABLE 11.5

EFFECT OF COLISTIN GIVEN INTRAMUSCULARLY BEFORE HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	COLISTIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 3 µg/ml (hours)
H	M	36	69	100	1.5	1.4	4.5	10
J	M	28	72	70	0.5	1.4	3.6	8
G	F	54	62	70	1.5	1.6	4.6	10
A	M	41	60	100	11.5	2.5	7.0	40
B	M	44	65	100	18.5	2.3	6.5	46
F	M	19	62	120	4.5	2.4	7.2	40
E	F	24	53	75	7.5	2.8	7.5	40

TABLE 11.6

EFFECT OF COLISTIN GIVEN INTRAMUSCULARLY AFTER HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	COLISTIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 3 µg/ml (hours)
B	M	44	66	120	19	2.3	9.0	50
F	M	19	60	190	5	2.5	9.8	50
E	F	24	54	125	8	2.8	10.2	50

FIGURE 11.2

EFFECT OF COLISTIN GIVEN BEFORE AND AFTER DIALYSIS TO PATIENT *F*

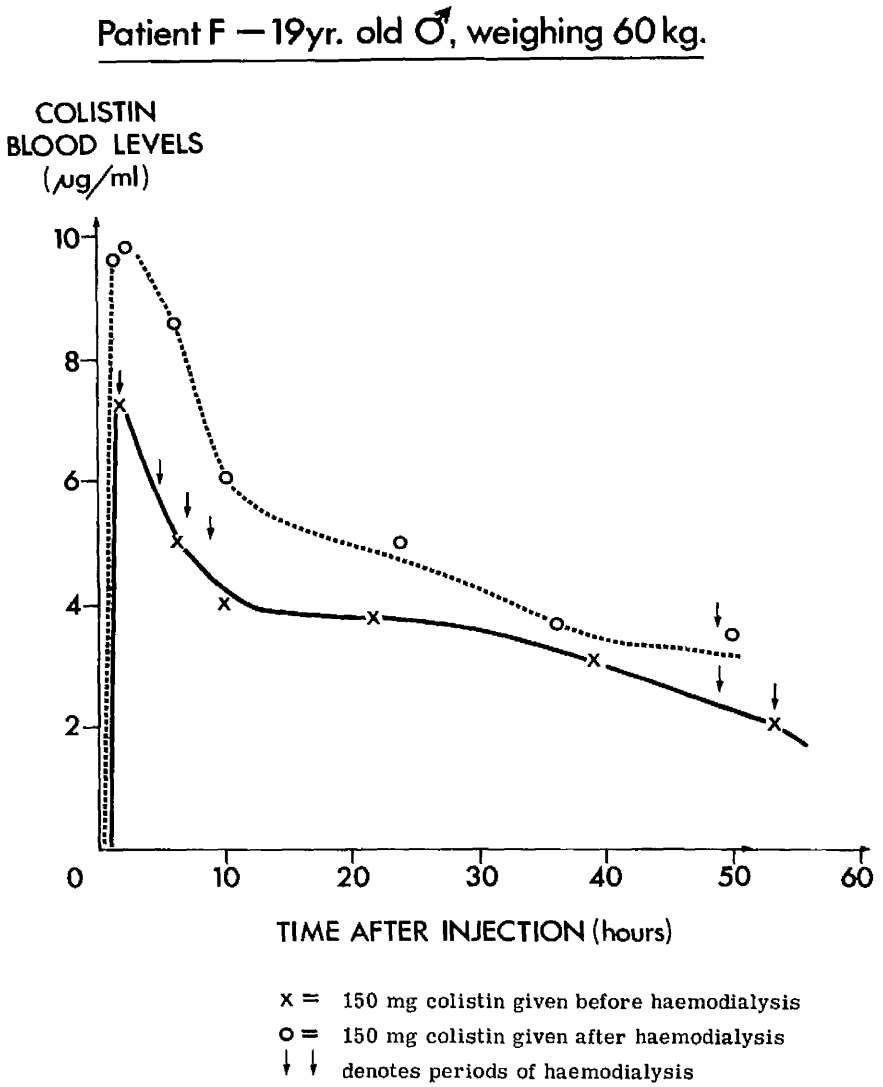


TABLE 11.7

EFFECT OF 1 g CARBENICILLIN GIVEN INTRAMUSCULARLY PRIOR TO HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	CARBENICILLIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 12 µg/ml (hours)
A	M	41	59	200	10.5	17	32	12
B	M	44	67	100	18.0	15	27	12
H	M	36	69	100	1.0	14.5	26	12
E	F	24	53	30	6.5	19	30	12

TABLE 11.8

EFFECT OF 1 g CARBENICILLIN GIVEN INTRAMUSCULARLY AFTER HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	CARBENICILLIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 12 µg/ml (hours)
A	M	41	59	170	11	17	54	30
B	M	44	65	145	17.5	15	46	30
D	F	19	54	200	5.5	18.5	48	30

FIGURE 11.3

EFFECT OF CARBENICILLIN GIVEN BEFORE AND AFTER DIALYSIS TO PATIENT *B*

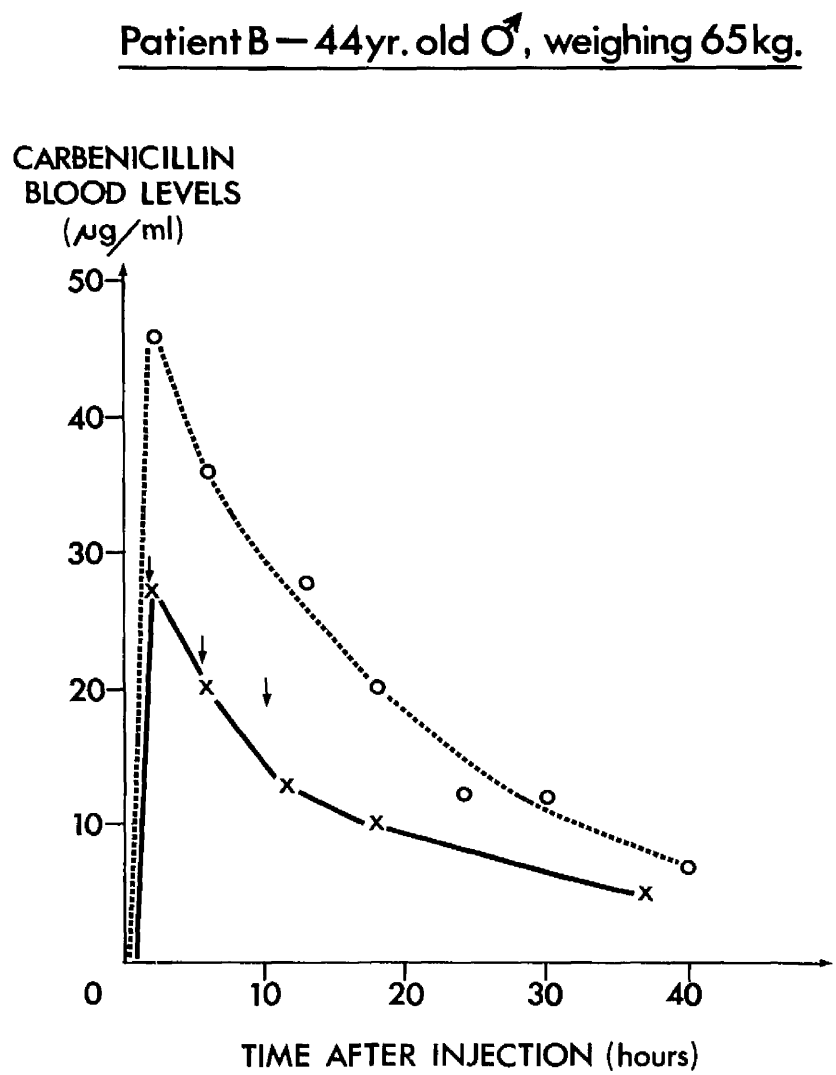


TABLE 11.9

EFFECT OF 1 g CLOXACILLIN GIVEN INTRAMUSCULARLY BEFORE HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	CLOXACILLIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 10 µg/ml (hours)
A	M	41	58	120	10	17	42	8
H	M	36	70	110	2.5	14	40	8
D	F	19	53	340	5	20	38	8
G	F	54	61	90	1	16	36	8

TABLE 11.10

EFFECT OF 1 g CLOXACILLIN GIVEN INTRAMUSCULARLY AFTER HAEMODIALYSIS

PATIENT	SEX	AGE (years)	WEIGHT (kg)	URINE VOLUME (ml)	DURATION OF RDT (months)	CLOXACILLIN DOSE (mg/kg)	PEAK SERUM LEVELS (µg/ml)	DURATION OF LEVELS > 10 µg/ml (hours)
A	M	41	59	100	9.5	17	40	12
D	F	18	51	300	4.5	20	42	12
G	F	54	63	70	0.5	16	36	12

FIGURE 11.4

EFFECT OF CLOXACILLIN GIVEN BEFORE AND AFTER DIALYSIS TO PATIENT *D*

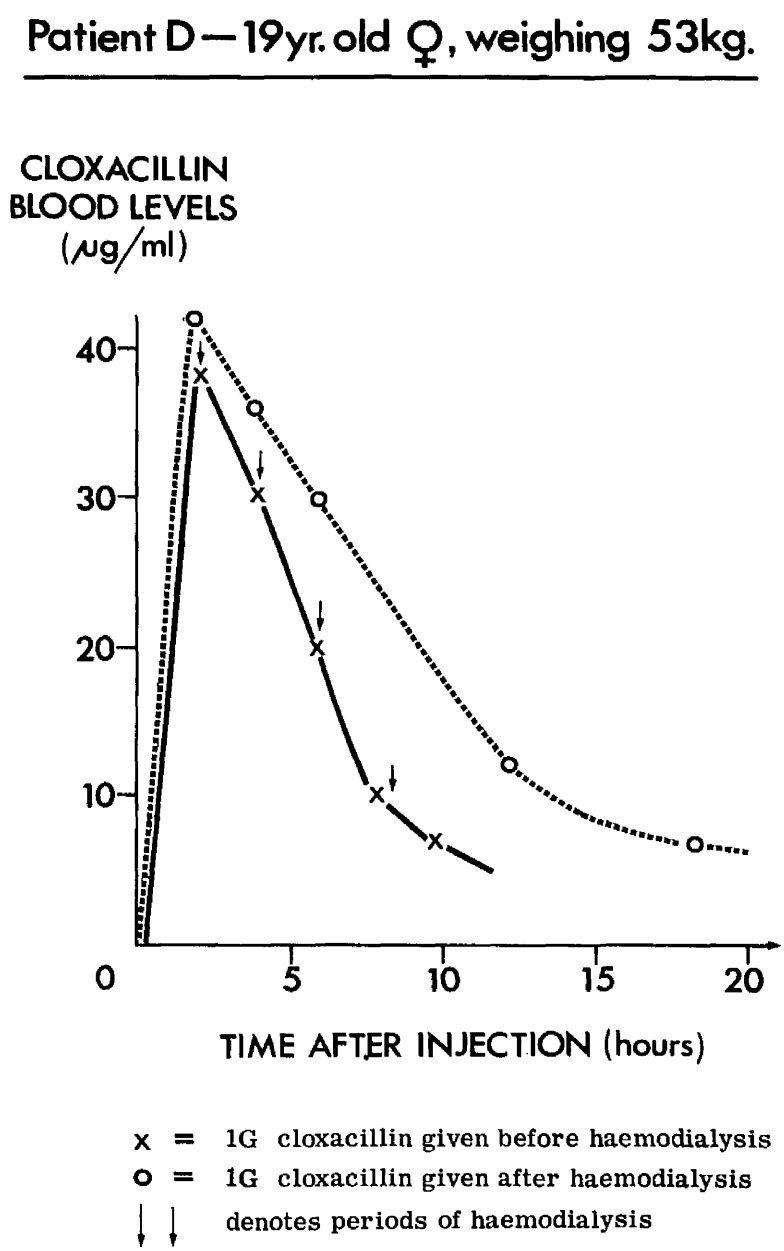


TABLE 11.11

RECOMMENDED DOSAGE OF ANTIBIOTICS IN ADULT PATIENTS REQUIRING REGULAR DIALYSIS TREATMENT: BASED ON DATA DERIVED FROM PATIENTS WEIGHING BETWEEN 48 AND 72 kg.

DRUG	DOSAGE (gram)	RELATIONSHIP TO DIALYSIS	BLOOD LEVELS EXCEED (µg/ml)	DURATION OF BLOOD LEVELS (hours)	SENSITIVE ORGANISMS
Kanamycin	0.5	before	8	70	90% *E.coli* at 5 µg/ml
	0.5	*after**	*8*	*80*	80% Proteus at 8 µg/ml
Streptomycin	0.5	before	8	72	90% M. tuberculosis
	0.5	after	8	80	at 8 µg/ml
Colistin	0.15	before	3	40	90% *E.coli* at 5 µg/ml
	0.15	after	3	50	90% Pseudomonads at 5 µg/ml
Carbenicillin	1.0	before	12	12	100% Staphylococci
	1.0	after	12	30	at 3 µg/ml
Cloxacillin	1.0	before	10	8	90% Proteus at 12 µg/ml
	1.0	after	10	12	44% *E.coli* at 12 µg/ml

*Avoid because of excessive peak serum levels.

FIGURE 12.1

DRUG METABOLISM IN RENAL FAILURE