RADIOACTIVE LEAD STUDIES

IN

THE HUMAN

by

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CAPE TOWN

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ABSTRACT

The differing susceptibility of individuals to the toxic effects of chronic lead exposure has never been fully understood. As the major intake of lead in the human is from food and beverages, any variation between individuals of the quantity of lead absorbed from the gut, and of the distribution and excretion of this lead, may account for the differences in individual susceptibility. The food and beverages themselves may have an influence, and to investigate their effects on absorption, distribution and excretion of lead, experiments were performed on normal subjects using a short lived radionuclide of lead, ^{203}Pb, and instruments generally available in Nuclear Medicine.

Lead absorption between different individuals showed a wide variation when ^{203}Pb was taken as a single dose between meals. The effect of fasting was to increase absorption and reduce the variation. This suggested that food with the lead in the gut was mainly responsible for the variation in lead absorption between individuals. This was confirmed when ^{203}Pb was mixed into a control meal and eaten by fasted subjects. Lead absorption was again low and variable. In contrast, ^{203}Pb taken in distilled water was avidly absorbed with little variation between subjects. The absorption of lead in water could be appreciably more than lead in food amongst the general population.

Minerals were found to be mainly responsible for affecting absorption when one subject ingested ^{203}Pb in control meals from which one dietary constituent at a time was omitted. The effect of minerals in reducing absorption of lead was greatest when they were ingested in distilled

water. Lead in water with a low mineral content, such as 'soft' water, could be a hazard to population groups living in 'soft' water areas. There were also indications from these experiments that dietary constituents may affect the distribution and excretion of lead.

Calcium and phosphorous were found to reduce the absorption of ^{203}Pb to approximately the same level as that produced by the total minerals. Calcium reduced absorption more than phosphorous when these minerals were ingested separately with ^{203}Pb. Paired kinetic experiments showed that calcium and phosphorous ingested at the same time as ^{203}Pb affected its distribution in the body but not its rate of excretion. Using the data from the kinetic experiments, a compartmental model was developed which adequately described the kinetics of orally ingested ^{203}Pb.

The model suggested that calcium is mainly responsible for reducing absorption of lead from the gut, but that the effect of phosphorous is to to increase soft tissue levels of lead at the expense of red cell lead. As susceptibility is related to soft tissue levels of lead, this suggests that the 'protective' effect of calcium in the gut is reduced. This could not be confirmed, however, as the kinetic data were insufficient for the model to distinguish the tissues particularly vulnerable to lead toxicity in the soft tissue compartment.

It was concluded that the calcium and phosphorous in the diet could influence susceptibility to lead toxicity through changes in the absorption of food and water lead and in the distribution of lead in the body. The results suggest that the prophylactic effect of calcium on lead absorption should be recognised and applied in this time of increased environmental levels of lead.

ABBREVIATIONS

(also defined in the text where relevant)

B	background count rate
C	combined count rate
CaBP	Calcium binding protein
cm	centimetre
d	deuteron
E.C.F.	extracellular fluid
FAO	Food and Agriculture Organization
F/U	ratio of faecal to urinary excretion
g	gram
γ-ray	gamma ray
HMSO	Her Majesty's Stationery Office
$hour^{-1}$	per hour
ICRP	International Commission on Radiological Protection
^{113m}In-S.C.	^{113m}In sulphur colloid
keV	thousand electron volts
kg	kilogram
l	litre
ℓn	Napierian logarithm
m	metre
M.C.A.	Multi-channel analyser
μCi	microcurie
μg	microgram
mCi	millicurie
MeV	million electron volts
mg	milligram
mm	millimetre
M HCl	molar hydrochloric acid

ABBREVIATIONS - cont'd

min	minute
ml	millilitre
msec	millisecond
N.E.	Nuclear Enterprises
n	neutron
P	probability
%A.D.	percentage administered dose
%I.D.	percentage ingested dose
%P.I.D.	percentage proportional ingested dose
Q	figure of merit
r	regression coefficient
SAAM	Simulation, Analysis and Modelling
SAAM25 (1967)	latest version of SAAM25
S.D.	standard deviation
S.E.	standard error of mean
sec	second
TRC	The Radiochemical Centre
USDHEW	United States Department of Health, Education and Welfare
USPHS	United States Public Health Service
WHO	World Health Organisation
x-s	xiphisternal joint

TABLE OF CONTENTS

TABLE OF CONTENTS - cont'd

TABLE OF CONTENTS - cont'd

TABLE OF CONTENTS - cont'd

TABLE OF CONTENTS - cont'd

TABLE OF CONTENTS - cont'd

LIST OF TABLES

LIST OF TABLES - cont'd

LIST OF TABLES - cont'd

LIST OF TABLES - cont'd

LIST OF TABLES - cont'd

LIST OF FIGURES

LIST OF FIGURES - cont'd

LIST OF FIGURES - cont'd

PREFACE

The purpose of this thesis was to investigate the gastrointestinal absorption of lead in the human, and the subsequent distribution and excretion of this lead. Studies on man's exposure to lead in air, therefore, have only been considered when there has been a direct relationship between air lead and gastrointestinal absorption.

The studies described in this thesis were done over a period of five years. In that time, very little work has been performed on the behaviour of ingested lead in the human which may be compared with the results in this thesis. Inevitably, many inferences have been drawn from animal studies, but, whenever possible, these were checked by further experiments on humans. However, some of the conclusions may not be entirely valid, as there may be differences between species.

A major portion of the work presented is concerned with modelling, and it is emphasised that a model is a conceptual representation based on observations and experiments, the elements of which may correspond to elements in a given real situation. It should be able to accomodate known data and to accept known facts as they are discovered, but no model is unique or exclusive, it is simply a tool which is used to obtain a better understanding of the biological system which is being studied. Nevertheless, it is possible using a model to

a) verify or reject a hypothesis

b) suggest new experiments

c) provide insight into unknown mechanisms, and

d) provide a framework from which better models can be developed.

The layout of the thesis has been planned to keep most of the details about methods, results, figures and computer programs away from the main text. Only figures and tables particularly relevant to discussion sections have been kept in the main section of the thesis.

SECTION 1

INTRODUCTION

Lead has been mined and worked by man since early antiquity. It was a very useful metal for ancient man, because of the widespread geographical distribution of lead bearing ore and the ease with which it could be extracted from this ore. Lead objects have been found dating from 3000 BC, but lead was not extensively used until Classical Greek times. The Greeks discovered that small amounts of silver could be parted from lead metal, after the metal had been smelted from lead ores. With the advent of silver coinage in 650 BC, silver became very important, and so the production of lead rose sharply. Huge piles of lead began to accumulate, and these were found a multitude of uses by the Greeks. Lead was used in warfare as sling bolts and arrow heads, in the transport and storage of drinking water, and in the cooking and storage of food and drink.

From Greek times until the present, the use of lead has become more widespread and diverse. It is an essential metal in present day industry because of its unique properties of ductility, high resistance to corrosion, and low melting point. Lead is the basic ingredient of solder, provides a protective sheath around intercontinental communication cables, protects against dangerous x-rays and atomic radiation, soundproofs buildings, ships and aircraft, produces efficient combustion of petrol and is the major component in batteries.

Although lead is a most useful metal, it is poisonous to man if ingested or inhaled in large quantities. Lead poisoning or 'plumbism' was first described by Nicander in the second century BC. It was always thought to be a disease of lead workers, as both the swallowing of lead compounds and the inhaling of fumes in smelting operations were recognised as dangerous. The danger of the domestic use of lead, however, appeared to have been overlooked. In the first century AD, Vitruius condemned its use for supplying drinking water, but his warning was ignored. The inappropriate use of lead in cooking and in the storage of food and drink in Greek and Roman times, therefore, caused many outbreaks of lead poisoning. It was not until 1498 that authorities began to restrict the culinary use of lead. The widespread and disastrous results of sweetening wine with lead compelled the authorities in Germany to evoke the death penalty for this particular practice.

The authorities in Great Britain introduced legislation to protect workers in the lead industry from lead poisoning in 1883. This was done because, from the Industrial Revolution onwards, the lead industry had expanded rapidly and had caused the incidence of lead poisoning to rise. Similar regulations were introduced in the pottery industry in 1894. Under the Factories Act of 1895, lead poisoning became a notifiable disease, so from this time onwards its incidence was to become widely known. Much has been achieved, therefore, in the disposal of, and protection from, lead dust and fume, the main hazards in the lead industry. The routine screening of all statutory workers for signs of developing lead toxicity is now required by law (Ministry of Labour, 1965).

The lead industry and the consumption and use of its products, however, has polluted the environment with lead, and further legislation had to be introduced to protect the general population from excessive exposure to lead. The World Health Organisation (WHO) has recommended a provisional tolerable weekly intake of 3 mg of lead per adult, which includes lead from all sources (WHO, 1972). Sources of lead which have caused isolated outbreaks of lead poisoning over the years are also controlled in some countries. The United States Potter's Association and the United States Food and Drug Administration have defined 7 µg/g as the maximum lead release of glazes recommended for use on ceramic items intended for food and drink (Ceramic Industry, 1970). The legal limit for lead in household paints has been set by the United States Congress at 0.5% (National Paint and Coatings Association, 1975).

The determination of environmental lead levels which are 'safe' for the general population is a complex task. The absorption of lead from the environment is not solely dependent on the amount of lead presented to the portals of entry. It also depends on the physical and chemical state of the lead, and it is influenced by age and physiological status of the host. The amount of food eaten, the amount of air breathed, together with the fraction of food and air lead absorbed into the body, will all be important influences. Manual workers breathe more air and eat more food than sedentary individuals of the same weight, and children eat almost as much food and breathe almost as much air as middle aged adults. There is also uncertainty about the degree to which individuals vary in their susceptibility, and the influence of the usual variables within and between populations

(WHO, 1972).

The fractions of lead absorbed in the respiratory and intestinal tracts have to be found, so that 'safe' environmental levels of lead can be established. Extensive experimental work has been performed to estimate these fractions. Most recent work has shown that the fraction of lead inhaled that is deposited in the lung can be as high as 50% (Chamberlain et al, 1978). In contrast, the accepted level of 10% absorption for lead in food and water is still based on the long term balance studies conducted by Kehoe (1961). The WHO Environmental Health Criteria 3 (1977), however, points out that this figure neglects endogenous faecal excretion. Chamberlain et al (1978) have shown that if it is taken into account, absorption from the gut is 15%. Percentage absorption may be even higher if lead is ingested in water independently of food (WHO, 1977), and the WHO (1972) recognised that dietary constituents such as calcium, phytic acid and protein may affect the absorption of ingested lead. However, no detailed work has been done to determine the degree by which absorption may be changed by dietary constituents.

1.1 Environmental pollution

The pollution of the environment by lead is caused by both the production and uses of lead. In the production of lead, the smelting of lead ore gives rise to lead emissions which may cover a considerable area. The zone of air pollution extended 5 km away from a smelter and soil contamination extended a further 5 km (Landrigan et al, 1975). It is the use of lead, however, which mainly contributes to air

pollution, and the combustion of alkyl lead additives in motor fuels accounts for the major part of all inorganic lead emissions.

Although the storage battery industry consumed most of the lead produced in the U.S.A. in 1970 (Mineral Year Book, 1970), it only contributed 3% of lead emissions into the air. The production of anti-knock additives contributed 11% of all emissions (Davis, 1973), even though the quantity of lead used was a third of that consumed by the battery industry. An examination of the annual snow strata in North Greenland has revealed that levels of airborne lead have increased markedly since the Industrial Revolution and very sharply since about 1940. This has been attributed mainly to combustion of lead alkyls in petrol (Bryce-Smith, 1971).

Other sources of pollution can arise from the vast number of lead containing items that are subjected to weathering or decomposition. It has been found that 50% of the paint was removed from surfaces protected by lead pigments in about seven years (Patterson, 1965). This will cause heavy contamination of the dust and soil around houses painted with lead paints (Ter Haar and Aronow, 1974).

Although it is probable that human exposure to lead in water pipes, food containers, insecticides, and other sources has decreased during the past 50 years (Schroeder and Balassa, 1961), it is likely that this has been more than compensated for by the additional exposure to airborne lead both directly and indirectly through food and water.

1.2 Lead levels in air, food and water

The emissions of lead from centres of human activity are diluted during transport away from these centres, but there is evidence that long-term global accumulation of lead has occurred. The levels of lead in the air have been assumed to be related to the concentration of lead in glacial ice and snow deposits, and a number of studies have shown that these concentrations have risen steadily since 800 BC. Ice layers examined in 1968 had a concentration 400 times greater than natural background (Murozumi et al, 1969).

The levels of lead in the air will be higher in urban areas than in rural areas, and urban levels will be influenced by traffic density and the presence of lead producing and consuming industries. Average concentrations of 1.1 $\mu g/m^3$ have been reported for urban areas, and these have fallen to 0.02 $\mu g/m^3$ in remote rural areas (McMullen et al, 1970). Near heavy traffic, however, the average concentration may be as high as 6 $\mu g/m^3$ (U.S. Department of Health, Education and Welfare, 1965). The air in the vicinity of a lead smelter may be appreciably polluted and may affect the general population, and this has been shown near a large smelter in the U.S.A. The annual mean concentration was approximately 80 $\mu g/m^3$ in the immediate vicinity of the smelter and it fell off rapidly to 1 $\mu g/m^3$ at 5 km away (Landrigan et al, 1973).

The fall-out of airborne lead will add to the lead present in food and water. If the pollution of the atmosphere by lead is world wide as suggested by the increase in the lead content of arctic snow (Murozumi et al, 1969), an increase in lead content of plants and lower forms of

animal life might be expected to be a natural sequel to increased lead in soil and water. Surprisingly, there has been no absolute confirmation of this trend. In Denmark, it has been reported that there was an overall decline in the lead content of cereals between 1962 and 1976 (Solgaard et al, 1978). Petrol consumption increased twofold during this period, and yet in only one area north of Copenhagen, where the traffic was heavy, was the lead content of cereals much above average. The decrease in lead was thought to be caused by a different technique in the manufacture of the fertilizer used on the crops.

Crops grown near a busy highway will probably have a high foliar deposition of lead from vehicle exhausts, whereas crops grown away from the highways will take up lead deposited in the soil by sedimentation and precipitation of exhaust lead. Only small quantities of lead are transferred from soil across the root membrane, as there is poor translocation of lead in plants (Ter Haar, 1975). An increase in soil levels, therefore should not have a dramatic effect on the lead content of crops, but an increase in foliar deposition of lead could be a potential hazard to man.

Grasses are efficient in capturing particulate lead from vehicle exhausts (Little and Wiffen, 1977), so it would be expected that cattle and sheep eating this grass would become contaminated. Fortunately, cattle 'filter' most of the lead from their diet giving low levels in milk (Potter et al, 1971), and, except in liver and kidney, low levels have been found in the meat from cows and sheep. The highest concentration of ^{203}Pb in the soft tissue of a calf fed ^{203}Pb in its diet was in the liver and kidneys.

(Potter et al, 1971). Ward et al (1978) found concentrations of lead up to 20 µg/g in the livers of sheep grazing near roadsides, whereas the typical lead content of beef is usually from 0.003 µg to 0.63 µg/g (De Treville, 1964).

It is difficult to decide whether airborne lead contributes significantly to lead present in food, because the concentration of lead in food is highly variable. There appears to be the same variation within specific items of food as between different categories of foods. Schroeder and Balassa (1961) found that the range was 0-1.5 mg/kg for condiments, 0.2-2.5 mg/kg for seafood, 0-0.37 mg/kg for meat and eggs, 0-1.39 mg/kg for grains, and 0-1.3 mg/kg for vegetables. Nevertheless, most studies show lead intake from dietary sources to be 200-300 µg/day (WHO, 1977). With such a large range, however, any significant contribution from airborne lead would have to be very large, such as that found by Kerin (1972) of between 670-2640 µg/day in areas exposed to smelter emissions.

There has been some concern expressed about the contamination of reservoirs by atmospheric lead, particularly in winter when decreased utilization of water may result in a doubling of lead content (Johnson et al, 1966). Most of the incidents of poisoning caused by lead contaminated water, however, have been from the domestic use of lead (Bacon et al, 1967; Beattie et al, 1972). The danger of poisoning from domestic lead pipes and lead storage tanks is enhanced by the degree of plumbosolvency of the water. In a study of overnight water in inhabited houses in 17 country boroughs of England and Wales, Crawford and Morris (1967) found that 31 out of 95 samples contained

more than 100 µg of lead per litre. The highest concentrations were found in soft waters, although some hard waters also contained excessive amounts. Acidity also appears to influence plumbosolvency although the relation is not a consistent one. The average intake of lead from drinking water is probably about 20 µg/day (Goyer and Rhyne, 1973) and the lead content of most municipal water supplies measured at the tap is below the WHO (1971) recommended limit of 100 µg/ℓ.

In certain circumstances, therefore, groups of people may consume food containing higher than average levels of lead, but the general population will only be exposed to a small increase of food and water lead attributable to the increase in airborne lead. The magnitude of this increase is difficult to determine, and, consequently, any potential hazard to the general population cannot be estimated.

1.3 Subclinical lead toxicity

The concern about the effect of increased levels of environmental lead on the population has been the result of an awareness that levels of lead in the body, not sufficient to cause the symptoms of classical lead poisoning, could cause insidious subclinical lead toxicity (Chisolm, 1974). More sensitive biochemical techniques, such as the measurements of δ-aminolevalinic acid and red cell protoporphyrin, have identified children with metabolic evidence of mental disorders but with none of the classical clinical signs of acute lead toxicity (Needleman et al, 1979).

The relationship between lead and mental development of children has been investigated by many workers, but with controversial results. Moncrieff et al (1964) showed that concentrations of lead in blood were frequently raised in mentally subnormal children. Bicknell et al (1968), however, found no evidence that moderately raised blood lead concentrations had any relation to the original cause of the mental retardation. These raised blood leads were found in subnormal children suffering from pica. Pica is more common in the disturbed retarded child, and if lead is present in his surroundings he will ingest an excessive amount (Clayton, 1975). Lansdown et al (1974) measured the blood lead concentration of children under 17 years living near a lead smelter, and found a relation between blood lead and distance from the smelter but no relation with the rate of behaviour disorders.

The relationship between lead and mental development is complicated

by the multifactorial aetiology of the latter, and it is only recently that stronger evidence has been found to support the relationship. Beattie et al (1975) measured the concentration of water in lead in the homes occupied, during the first year of life, by 77 mentally retarded children aged two to six years and 77 non-retarded matched controls and in the homes occupied by their mothers during pregnancy. The water lead content was significantly higher in the retarded group, and the probability of mental retardation was significantly increased when water lead exceeded 800 µg per litre. They concluded that lead contamination of water may be one factor in the multifactorial aetiology of mental retardation.

Another study was performed by the same group (Moore et al, 1977), in which they measured blood lead concentration retrospectively in blood contained on cards. This blood had been used to test for phenylketonuria in the first two weeks of life. 24 mental retardation/control pairs were compared, and there was a highly significant trend towards higher blood concentration in the mentally retarded children. The authors stressed that the blood lead concentrations in both groups of children were low, and in what would be regarded as the normal range. There was a highly significant regression of blood lead on domestic water lead concentrations from the maternal home during pregnancy. This was similar to that found in adults (Moore, 1977). The association of mental retardation with water lead concentrations, therefore, reflects principally intrauterine exposure with some postnatal exposure to lead.

Recently, Needleman et al (1979) compared the intellectual

performance of 58 children with high dentine lead levels and 100 children with low dentine lead levels. Tests such as the Wechsler Intelligence Scale for children, verbal subtests, auditory or speech processing, and non-adaptive classroom behaviour showed that children with high lead levels scored less well or were poorly behaved.

Lead exposure at levels which do not produce clinical symptoms of lead toxicity appears to be associated with neuropsychologic deficits in children. This has caused a revision of the lead levels assumed to be safe for children. The Centre of Disease Control (1978) has now defined a blood lead level of 30 µg/100 g as the threshold for undue lead absorption. The recognition of subclinical lead toxicity, especially in children, has caused a reappraisal of the environmental effects of lead released by the combustion of petrol. Some countries have either completely prohibited or considerably reduced the amount of lead added to petrol, and have reported substantial reductions in airborne lead levels (Waldron and Stöfen, 1974).

1.4 Differing susceptibilities to the toxic effects of lead

Susceptibility to lead toxicity is well known (WHO, 1972; WHO, 1977), but, with the recognition of subclinical toxicity, susceptible people exposed to the present environmental levels of lead may be more at risk. Although individual differences in susceptibility are known to occur, the degree by which these differences vary is unknown (WHO, 1977). Any assessment of these differences will be very dependent on determining the dose of lead that an individual receives. Susceptibility itself may be inherent and may be influenced by co-existent variables such as, age, sex and nutritional status, adding further complications to any assessment.

Early reports suggested that there were inborne differences in susceptibility and Oliver (1916), Legge and Goadby (1912) reported well established cases of family susceptibility. There appears to be inherent differences between the sensitivity of the nervous system of young children and that of adults, but it is also possible that these differences could be caused by the intensity of exposure (WHO, 1977). More direct evidence has been obtained of the influence of co-existent variables on susceptibility, such as nutritional status, from animal experiments. The absorption of lead from the gastrointestinal tract of animals has been shown to be influenced by diet which could alter susceptibility to the toxic effects of lead (Goyer and Mahaffey, 1972). Although animal studies have been helpful in the study of the biological effects of lead on man, they cannot be used to elucidate the exact dose-effect relationships in man as this is likely to be species specific (WHO, 1977).

There have been a number of reports in which individuals, with apparent similar levels of lead in their blood, have varied in their tendency to exhibit symptoms of poisoning. Beattie et al (1972) described lead poisoning in four families in rural Scotland. The source of lead was traced to the domestic water supply which in all cases was grossly contaminated from the lead plumbing systems. Two of the families used a common supply from a nearby stream. The three members of the first family had blood leads of 46.0 µg/100 g, with no symptoms, and 59.0 µg/100 g and 75.1 µg/100 g with symptoms of lead poisoning. The second family had blood lead levels of 46.4 µg/100 g, 67.5 µg/100 g and 69.3 µg/100 g with no symptoms of lead poisoning. In normal children, the upper limit of blood lead has usually been fixed at 60 µg/100 g (Chisolm and Harrison, 1956). Bradley et al (1956 a) however, found that eight children with blood lead levels between 50 and 80 µg/100 g and who were initially asymptomatic, were later admitted to hospital with lead encephalopathy and a mean blood-lead level of 43 µg/100 g.

There is, however, some doubt as to the validity of using blood lead levels as an indication of lead toxicity. Gibson et al (1968) examined three groups of men with presymptomatic state of lead exposure, mild symptoms or mild anaemia, and frank lead poisoning. Although the mean blood-lead levels of the three groups, 51.72, 73.69 and 83.94 µg/100 g were significantly higher than for normal men, 40 µg/100 g, there was considerable overlap of the three groups. They felt that the urinary excretion of coproporphyrin and δ-aminolevalinic acid were better indicators of 'metabolically active' and presumably

toxic lead in the body. They found no correlation between the urinary excretion of these substances and blood lead levels.

Apart from the validity of using blood lead levels as an indication of toxicity, there is also considerable analytical variability in the measurement of blood lead. Keppler et al (1970) reported on a study conducted by 66 laboratories, which analysed the same blood sample and obtained results varying from 0 to 29,000 µg/100 g. Berlin et al (1972) reported the results from 22 laboratories in which they found the lead analysis of blood ranged from 28% of the mean value to over twice the mean value.

The WHO (1977) has stressed, therefore, that blood lead should not be used as indication of even dose or exposure when dealing with individual subjects. It should only be used to assess the exposure of population groups in which biological effects may occur in a certain proportion of individuals.

1.5 Possible causes of different susceptibilities

Susceptibility to lead toxicity is known to be influenced by a number of physiological and environmental factors. These are

(a) Age and sex

(b) Nutrition

(c) Seasonal variations

(d) Intercurrent disease, alcohol and other metals (WHO, 1977).

They may influence both the dose of lead received by an individual and the response of the individual to that dose.

The toxicological effect of a dose has been defined as the amount or concentration of a given chemical at the site of effect (Nordberg , 1976), but it is often impossible to measure the dose defined in this way. Estimates would have to be made of the quantity of lead entering the body from air, food, water and various other contacts, including drugs and consumer products. In children, sources of lead such as in soil, settled dust and paint chips would also have to be considered. The quantity of lead entering the body is likely to be variable. The amount of food eaten, water drunk and air breathed may differ between individuals, and the levels of lead in air, food and water may vary considerably. Fortunately in experimental studies, it is possible to control the intake of lead into the body to a certain degree, and variation of intake is only a complication in general population studies.

The intensity of the toxic effect of lead will also depend on the

response of the individual. It has been suggested that there may be variations in the degree of resistance of tissues to lead intoxication (David et al, 1976), and that developing tissues may be more susceptible to damage (Bell, 1924). These may be the possible causes of the apparent increased susceptibility of children and women to the toxic effects of lead.

Children appear to be more susceptible to the toxic effects of lead than any other population group. It has been found that a blood lead level of 80 to 100 µg/100 g, which would produce no overt symptoms in the adult, can cause convulsions and coma in the child (Goyer and Mahaffey, 1972). Blood lead levels as low as 26 µg/100 g have been associated with mental disorders in children (Moore et al, 1977). The shift of lead into and out of growing bone of a child may also influence biological effects (Byers and Maloof, 1954), and the greater incidence of lead encephalopathy may reflect inherent sensitivity of the nervous system of a child to lead (Goyer and Rhyne, 1973).

Children, however, are likely to be exposed to lead from a greater number of sources and for a longer time than adults. Lead based paints in old buildings (Barltrop, 1968) and street dust in crowded urban areas (Grandjean, 1975) are two common sources, and the number of hours spent out of doors by children increases the risk of exposure to airborne lead.

Apart from the likelihood of increased exposure, there is evidence that children gastrointestinally absorb more lead than adults. Alexander et al (1973) found absorption of the order of 50% in

children aged from 3 months to 8.5 years, far higher than the accepted 10% for adults (Kehoe, 1961). Unfortunately, this work has been criticised because of the large scatter of values and because the conclusions were based on a short measurement period of 3 days (WHO, 1977). Increased absorption of lead in the young, however, has also been reported in animals. Kostial et al (1971) found that 5 - 7 day old rats absorbed at least 55% of oral doses of ^{203}Pb, and Forbes and Reina (1972) found that the absorption of tracer doses of ^{212}Pb were 83% at 16 days after birth, 74% at 22 days, and 16% at 89 days.

Although there is doubt about the inherent sensitivity of children to the toxic effects of lead (WHO, 1977), there appears to be stronger evidence to suggest that the tissues of women are more sensitive to the toxic effects of lead than those of men. Bell (1924) found in women the minimum toxic dose of intravenously injected lead was 40 mg, but in men it was 100 mg. Women are more likely to develop poisoning between the ages of 18 and 23 years, earlier than men and after a shorter exposure (Oliver, 1916). The manifestations of lead poisoning in women are also different. There is a higher incidence of encephalopathy and a lower incidence of paralysis and colic (Hardy, 1966).

In a recent experimental study (Stuik, 1974; Stuik and Zielhuis, 1975), groups of 5 males and 5 females aged 18 - 26 years received 20 µg/kg of lead acetate orally per day for a period of 21 days. The blood lead levels of control subjects remained approximately the same at 17.0 µg/100 g, those of the exposed males rose from 20.6 µg to 40.0 µg/100 g,

and those of the exposed females rose from 12.7 µg to 30.4 µg/100 g. The protoporphyrin IX content of the erythrocytes showed no change in either the control or the exposed male group, but in the female exposed group, however, it showed a rise during the third week of the experiment. It was suggested that this rise was caused by interference with the role of iron in the formation of haemoglobin, and that the synergism of lead exposure and iron deficiency might be responsible for this.

The dose of lead at a specific site or organ in the body will also be influenced by the fraction of the lead intake which is absorbed in the gastrointestinal and respiratory tracts, the distribution of this absorbed lead in the body, and its excretion. As the major fraction of environmental lead enters the body through the gastrointestinal tract, the effect of nutrition on gastrointestinal absorption, distribution and excretion of lead could be most important in affecting the susceptibility of individuals to toxic effects of lead.

1.5.1 Gastrointestinal absorption of lead

Lead is absorbed into the body mainly through the gastrointestinal and respiratory tracts, occasionally through the skin, and, rarely, from subcutaneous tissues. The dietary intake of lead is between 200 - 300 µg/day (WHO, 1977), and the intake from air lead is approximately 15 µg/day (Chamberlain et al, 1978). The percentage of ingested lead absorbed was shown to be 10% in the classical balance studies of (Kehoe, 1961). This low level of absorption was generally accepted and increases in dietary lead were not considered hazardous. Certain studies have shown, however, that uptake of lead from gut is variable and may be of considerable importance.

Hursh and Suomela (1968) were the first to challenge the accepted 10% absorption of ingested lead (Kehoe, 1961), when they found absorptions of 1.3, 8.1 and 16% in three subjects. Unfortunately, they did not measure the absorption of their tracer, ^{212}Pb, directly either by whole body counting or by total collection of excreta, but by measuring the percentage of the dose excreted in the urine in the first 24 hours after ingestion. ^{212}Pb was injected intravenously into the same subjects in order to define the percentage of the dose which would appear in the urine, and it was assumed that the fraction of the systemic ^{212}Pb excreted in the urine was the same whether entry was via the gut or by intravenous injection.

Uptake from the gut was also shown to be variable in the experiments of Rabinowitz (1974). Stable lead tracers as the nitrate, sulphide and cysteine were ingested by a fasting subject on separate

occasions, and absorption was affected by the chemical form of the lead. The greatest change occurred, however, when the different forms of lead were ingested with food. The uptake of ^{206}Pb cysteine, for instance, was reduced from 30% to 5.8% by the presence of food in the gut. Unlike the experiments of Hursh and Suomela (1968) absorption was measured directly, collecting and measuring unabsorbed stable-lead tracer in the faeces for 10 days following ingestion.

Further studies performed by Chamberlain et al (1978) confirmed those of Rabinowitz (1974). Six human subjects ingested, on separate occasions, ^{203}Pb chloride and the less soluble ^{203}Pb sulphide with food or after fasting. The mean uptake of ^{203}Pb chloride was 45 $\pm$ 7% (S.E.) of the ingested dose in fasting subjects, and this was reduced by presence of food by a factor of 6.5. A lower mean uptake of 12 $\pm$ 4% (S.E.) occurred with ^{203}Pb sulphide, but food reduced uptake by only a factor of 1.8. This smaller reduction was thought to be caused by the extra acidity of the stomach following the ingestion of food, making lead sulphide more soluble and, therefore, more available for absorption. The uptake of lead was found directly by measuring, with a whole body counter, the radioactivity of ^{203}Pb retained in the subject's body 5 days after ingestion.

Apart from the suggestion by Chamberlain et al (1978) that the acidity of stomach contents may affect gastrointestinal absorption of lead, there were no theories or detailed investigations into the possible causes of the effect of food on absorption, in any of the preceeding studies. There has been, however, extensive work performed with animals in which various constituents of food have been shown to

influence the absorption of lead.

Barltrop and Khoo (1975) performed experiments in which 30 day old rats were fed, ad libitum for 48 hr, a diet containing lead chloride (0.75 g/kg) labelled with ^{203}Pb and varying amounts of fibre, vitamin, protein, fat and minerals. They found that the absorption of lead, indicated by levels of ^{203}Pb in blood, kidneys, femur and liver, was increased when protein and minerals were excluded from the diet and when the fat content was increased by a factor of four. Absorption was reduced when minerals were increased by the same factor. Low fat, low fibre, high fibre, low vitamin and high vitamin diets had no effect on lead absorption.

As the greatest effect on absorption was caused by minerals, the response to the omission of major and minor components was determined, followed by experiments in which individual minerals were omitted. Diets that were deficient in calcium, phosphate, magnesium, sodium, potassium and chloride caused a marked increase in lead absorption but the omission of iron, manganese, copper, zinc, iodine and molybdenum from the diet had no effect. The individual minerals mainly responsible were found to be calcium and phosphate. Their effect was additive, when they were omitted from a diet which originally contained calcium and phosphorus concentrations of 7 g/kg and 5 g/kg, respectively.

Further experiments performed by Conrad and Barton (1978) enabled them to suggest how dietary constituents could affect the absorption of lead from the gut. Their experimental methods were different to that of

Barltrop and Khoo (1975), in that they injected the lead and dietary constituents into the isolated duodenal loop of fasting rats. A single dose of 1 µg of lead chloride labelled with ^{203}Pb was injected with millimolar concentrations of methionine, cysteine, ascorbic acid, tyrosine, arginine and each of these compounds increased the absorption of ^{203}Pb. These compounds were selected because they are known to bind lead *in vitro*. It was suggested that the increased absorption of lead was caused by its increased solubility in the duodenum making it more readily available for absorption. This supports the suggestion of Chamberlain et al (1978), that the effect of acidity of the stomach on lead sulphide was to make it more soluble and available for absorption.

Other compounds such as ferrous chloride, zinc chloride and calcium chloride decreased the absorption of ^{203}Pb, but because these compounds did not affect the solubility of lead in *in vitro* studies, it was suggested that their effect was caused by competition with lead for shared absorptive sites.

In contrast to the findings of Barltrop and Khoo (1975), phosphate did not reduce the absorption of ^{203}Pb, and the effect of iron was much greater than that of calcium. However, only the duodenum was included in the intestinal loop preparation, and Smith et al (1978) showed that lead was also absorbed in the distal small bowel of the rat. Phosphate absorption in the distal small bowel is stimulated by Vitamin D (Kowarski and Schachter, 1969), which suggests that it is actively transported at this site. Therefore, phosphate will probably inhibit lead absorption to the greatest extent in the distal small bowel. The

amount of iron used was greater than in the experiments of Barltrop and Khoo (1975). The human diet consists of calcium and iron in an approximate ratio of 100 to 1 (ICRP, 1971), so that the results of Barltrop and Khoo (1975), who gave a calcium to iron ratio of 330 to 1, are probably more relevant to the human.

The results of the studies of Barltrop and Khoo (1975) and Conrad and Barton (1978) show that, in a normal diet, calcium and possibly phosphorus are mainly responsible for reducing the absorption of lead. Their effect on absorption may be caused by their competition with lead for shared absorptive sites in the small bowel. The effect of calcium and phosphorus on the absorption of lead has been studied by many workers. Shields and Mitchell (1941) performed long term experiments (70 days) with stable lead (15 - 30 mg/kg), and showed that diets rich in calcium, phosphorus, calcium and phosphorus, reduced the amount of lead retained in the carcases of rats at the end of the experimental period.

Similar long term experiments were performed more recently by Quarterman and Morrison (1975). Larger doses of stable lead (200 mg/kg) were used and the rats were fed diets with calcium and phosphate levels lower than the normal requirements. Retention of lead in the carcass was several times greater than that obtained with a normal control diet, and the effects of both calcium and phosphate were the same and approximately additive.

Further experiments by this same group of workers (Quarterman et al, 1978a)showed that feeding rats diets containing levels of calcium and

phosphate above normal requirements reduced retention of lead. An increase in dietary content of both calcium and phosphate together, however, had an effect no greater than an increase of either one alone. It was suggested that the levels of calcium (19 g/kg) and phosphate (18 g/kg) used were each inhibiting the system which they influenced to the maximum possible extent.

In these long term absorption experiments, the effect of calcium and phosphorous on the absorption of lead from the gut may also be influenced by the nutritional status of the animal. Recent experiments have compared the effects of calcium supplemented diets to those of calcium and lead given simultaneously, on the absorption of lead measured by single tracer doses.

Meredith et al (1977) found that diets supplemented with calcium, to raise the content from 7 g/kg to 14 g/kg, significantly reduced the 10 day whole body retention of a single dose of 0.01 µg of lead labelled with ^{203}Pb given by stomach tube. The rats had been fed the supplemented diet for 21 days, and they had not been fasted before the lead was administered. In a second experiment, they found that giving 50 mg of calcium at approximately the same time as 1 mg of lead to fasting rats, also reduced the 5 day whole body retention of ^{203}Pb. The results of these experiments suggest that diet, and, hence, the nutritional status of the animal has some effect on the absorption of lead. This was not confirmed, however, by the studies of Barton et al (1978).

In their studies, Barton et al (1978) used fasting rats in both

sets of experiments. Three groups of rats were fed diets containing 2.39 g/kg, 4.6 g/kg and 13.8 g/kg calcium for 14 days, and a single dose of 1 µg of lead labelled with ^{203}Pb was injected into the isolated duodenal segment of each rat. There was no significant difference between the 4 hr whole body retention of these rats indicating no effect of diet. The 4 hour retention was significantly reduced, however, when 0.04 mg of calcium was injected simultaneously with 0.21 mg of labelled lead. The authors concluded that diet-induced calcium deficiency had little influence on lead absorption in the gastrointestinal tract, and any changes in absorption were caused by the levels of dietary calcium in the gut.

Unfortunately, no tracer experiments appear to have been performed in which the effect of dietary phosphorous deficiency on the absorption of lead has been compared to that of phosphorous given simultaneously with a single dose of tracer lead. Such a comparison, however, may be infered from the experiments of Quarterman et al (1978 a) and Meredith et al (1977).

In the experiments of Quarterman et al (1978 a), phosphorous reduced the retention of stable lead in rats by the same amount as calcium when rats were fed diets containing above normal requirements of both minerals. These experiments were comparable to those of Meredith et al (1977) in that the experimental period of 21 days and the concentration of calcium given in the normal and supplemented diets were approximately the same. The methods of administering the lead and estimating lead absorption, however, were different. Quarterman et al (1978a) fed the rats stable lead (0.4 g/kg) as part of their

diet and measured retained lead in the carcass at 21 days, whereas Meredith et al (1977) measured the 10 day retention of a single dose of ^{203}Pb given to non fasting rats at 21 days.

Even with these differences, Quarterman et al (1978a) and Meredith et al (1977) found the calcium reduced the retention of lead by factors of 2.3 and 2.8, respectively. In this section, these results of Meredith et al (1977) have been shown to be probably caused by the interactions of lead and calcium in the gastrointestinal tract of the rat and not by systemic calcium. The similar effect of phosphorous with that of calcium on the retention of carcass lead in the experiments of Quarterman et al (1978a), and the close agreement of the results of these stable lead experiments with those of the tracer lead experiments of Meredith et al (1977) suggests that the absence of a nutritional effect of calcium on the absorption of lead from the gut may also apply with phosphorous.

The results of the animal studies described in this section show that the effect of calcium, and probably phosphorous, on the gastrointestinal absorption of lead appears to be caused by interactions of these elements in the gut and not by the nutritional status of the animal. These interactions may be conveniently studied, therefore, by short term experiments in which tracer lead, calcium and phosphorous are ingested simultaneously into the gastrointestinal tract. The successful use of this type of experiment in animal studies suggests that similiar experiments may be conveniently performed with human subjects.

1.5.2 Distribution of lead in the body

In animals the normal dietary levels of calcium and phosphorous affected the fraction of ingested lead absorbed, which will influence the lead content of body tissues. Calcium and phosphorous may also affect the pattern of distribution of absorbed lead between these tissues. A change in distribution causing more soft tissue lead at the expense of bone lead may increase susceptibility to the toxic effects of lead (Goyer and Rhyne, 1973), over and above any changes in susceptibility caused by differences in the absorption of lead in the gut. The normal distribution of lead in man has been studied by Rabinowitz (1974) using stable lead tracers, but no studies appear to have been done to investigate the effect of dietary constituents on distribution. There have been a number of animal studies performed, however, whose results have shown changes in the distribution of lead attributed to dietary constituents.

In the experiments of Barltrop and Khoo (1975), already described in section 1.5.1, low protein, high fat and low mineral diets increased and high mineral diet decreased the blood lead concentration. The lead concentration of the liver showed a similar relationship, but the degree of change was much less. In the kidneys and femurs, however, a high protein diet caused an increased lead content compared to that in the blood. The greatest changes in lead concentration of the tissues occurred between those of rats fed low and high mineral diets. The effects of different dietary minerals were examined, and it was found that calcium and phosphate were mainly responsible for these changes.

The effect of calcium and phosphorous on the distribution of lead in animals has been investigated by several groups of workers. Shields and Mitchell (1941) performed long term experiments lasting 70 days in which rats ingested stable lead (15-30 mg/kg) as part of their diet. Lead was measured in bone and in the remainder of the carcass which the authors considered soft tissues. They found that decreasing the calcium and phosphorous content of a diet from 6.5 g/kg and 6.1 g/kg (normal requirements) to 1.0 g/kg and 3.7 g/kg, decreased the lead content of the soft tissues from 15.11% to 11.62% of the total body lead.

Quarterman and Morrison (1975) performed similar long-term rat experiments. The lead content of the diet, however, was higher at approximately 200 mg/kg, and they made a more comprehensive study of distribution by measuring the lead content of red cells, kidneys, liver and the remainder of the carcass which included bone. They reduced the calcium and phosphorous content of a diet satisfying normal requirements by approximately a third, and found a change in distribution such that the lead content of the kidneys increased by 6 times, the liver by 5 times, the red cells by 2.5 times, and the carcass by 7 times. The lead retained in the total body, compared to lead ingested, also increased 7 times, so that only red cells failed to follow the increasing lead content of other tissues and bone.

Unfortunately, it is impossible to directly compare the results of the two experiments because the distribution of lead has been considered differently. If it assumed, however, that the major

portion of carcass lead is in the bone, as found by Shields and Mitchell (1941), then the results of Quarterman and Morrison (1975) show that decreasing the calcium and phosphorous content of diet increases bone lead in relation to kidney, liver and blood lead. This agrees with the findings of Shields and Mitchell (1941) since kidney, liver and blood were included in their definition of soft tissues.

Quarterman et al (1978a) repeated their experiments with diets containing above normal requirements of calcium and phosphorous. An increase in these minerals by an approximate factor of 2 caused a decrease in the lead content of the red cells by a factor of 3.0, but the lead content of the carcass was only decreased by a factor of 1.8. Diets containing more than normal requirements of calcium and phosphorous change the distribution of lead differently to those containing less than normal requirements. A difference in the effects of such diets on gastrointestinal absorption of lead was also noted in section 1.5.1.

No animal experiments appear to have been performed showing the effect of the calcium and phosphorous content of a diet on the distribution in the body of a single oral dose of tracer lead. A similar experiment was performed by Meredith et al (1977), except they investigated the effect of systemic and not dietary calcium. They found no change in liver, kidney and femur radioactivities, measured 7 days after an oral dose of ^{203}Pb, of rats injected intraperitoneally each day for 10 days with 50 µg of calcium gluconate, compared with the radioactivities in the same organs of rats injected intraperitoneally with 0.9% NaCl. This suggests no effect of systemic calcium.

However, the rats consumed approximately 130 g of food a day with a calcium concentration of 7 g/kg. Therefore, their daily input of calcium was 0.91 g, so that a daily increment of 50 µg is unlikely to have caused any appreciable change in calcium levels of the body, and, consequently, any change in the distribution of ^{203}Pb.

From the results of animal studies, therefore, changes in dietary calcium and phosphorous appear to alter the distribution of stable lead in the body. The effect of such dietary changes on the distribution of a single dose of tracer lead is uncertain, and no experiments have investigated the effect on distribution of tracer lead of calcium and phosphorous ingested simultaneously with the tracer lead.

1.5.3 Excretion of lead

Changes in the calcium and phosphorous content of animal diets have been shown to have an effect on the gastrointestinal absorption of lead, and on the pattern of distribution of absorbed lead in animals. The quantity of lead retained in the body, which will influence susceptibility, will also depend on the rate of excretion of lead. An effect of calcium, and both calcium and phosphorous on excretion has been described in animal studies.

The experimental details of the studies performed by Quarterman and Morrison (1975), Quarterman et al (1978a), and Barton et al (1978) have already been described in sections 1.5.1 and 1.5.2. Only the relevant details of these experiments concerned with the excretion of lead will be considered in this section.

Quarterman and Morrison (1975) studied the effect of calcium and phosphorous on the retention of stable lead in a group of rats which were fed a diet containing stable lead for 8 weeks. At the end of this period, half the rats were killed and the lead retained in the carcasses was measured. The remaining rats were fed a lead free diet for a second period of 8 weeks, at the end of which carcass lead was again measured. They found retention at the end of the second period was lowest in control rats fed normal amounts of calcium and phosphorous, a third higher in the low calcium and low phosphorous group, and unchanged in the low calcium group.

Quarterman et al (1978a)repeated the experiment with diets supplemented with calcium and phosphorous. Retention again was lowest in the control group at the end of the second period, but it was 50% higher in both high calcium and high phosphorous, and in the high calcium groups of rats. The most rapid excretion of lead from the body, therefore, was found with dietary calcium and phosphorous at about requirement level.

In a tracer lead experiment, Barton et al (1978) intravenously injected 1.0 μCi ^{210}Pb nitrate (specific activity: 10 mCi/mg lead) into three groups of rats fed low, normal and high calcium diets. When lead retention was compared at 7 days and 6 weeks after injection, that of the high calcium group did not differ significantly from normal, whereas lead retention of the low calcium group was significantly enhanced at 7 days. This difference in lead retention persisted up to the final measurement at 6 weeks, showing that the effect of calcium on excretion occurred in the first 7 days.

The rate of excretion of stable and tracer lead in rats is affected by dietary calcium and phosphorous, but, again, the effect of the simultaneous ingestion of calcium, phosphorous and tracer lead on the excretion of the tracer does not appear to have been investigated.

SECTION 2

AIMS OF PRESENT STUDY

The studies described in this thesis were designed to investigate the effect of dietary constituents on the gastrointestinal absorption, distribution and excretion of lead in the human. The degree of change in these three processes will affect the size and the distribution of the body burden of lead in people and, therefore, influence susceptibility to lead toxicity.

The literature already reviewed has shown that the absorption of lead in man is variable and the cause was suggested to be food with the lead in the gut. The results of the animal studies suggested that the composition of the food was mainly responsible for the variation in the absorption of lead. The greatest effect on the absorption was caused by the dietary constituents, calcium and phosphorous, and they also affected the distribution and excretion of lead.

Experiments were designed, therefore, to establish the degree of variability of absorption of lead in the human, to investigate the effects of the main components of diet, and then, more specifically, the effect of calcium and phosphorous on absorption. Further experiments were designed to relate any effect of calcium and phosphorous on absorption to any possible effect on distribution and excretion. From the results of these experiments, it was planned to develop a compartmental model to describe the behaviour of lead in the body. A satisfactory model would provide a better understanding of the

interaction of lead, calcium and phosphorous in the human body.

2.1 Choice of experimental methods

The animal studies described in sections 1.5.1-1.5.3 can be divided into long term experiments in which lead was given as part of the diet, and short term experiments in which lead was given as a tracer in a single dose. Tracer studies were pioneered by Hevesy and, by coincidence, he used a natural radionuclide of lead to investigate the metabolism of lead in plants. By using a gold leaf electroscope, he was able to measure quantitatively the uptake of lead by using small quantities of radiolead which did not produce any toxic effects in the plants, the fundamental principle of tracer methodology.

The effects of dietary constituents on the absorption of lead from the gut were successfully studied in short-term animal experiments in which tracer lead was given at the same time as the constituents. It was decided, therefore, to use this type of experiment in the human studies presented in this thesis.

Both stable lead and radioactive lead nuclides can be used in tracer experiments. Rabinowitz (1974) used stable lead nuclides ^{204}Pb, ^{206}Pb and ^{207}Pb in human studies on the absorption and kinetics of oral lead, and he achieved a precision of measurement with a standard error of 1% using mass spectrometry. Radioactive lead nuclides, however, have an advantage over stable tracers when used in short term experiments. The kinetics of lead in part of a dynamic system can be studied without the need of samples. For example, an *in vivo* radiation detector can be placed over the liver

of a human subject to study the uptake and release of radioactive lead from this organ.

Three radioactive lead tracers are available commercially, ^{210}Pb, ^{212}Pb and ^{203}Pb. ^{210}Pb has a half life of 19 years and decays through the emission of a weak β-ray (197 keV) to the α-emitter ^{210}Po, which has a half life of 138.4 days. Its use in humans is restricted because of the high toxicity of ^{210}Pb, and measurement of the emitted radiations is difficult because of their nature and low energy. ^{212}Pb (ThB) has the disadvantage of having a short half life of 10.6 hours and decaying to ^{212}Bi which is an α-emitter and, therefore, toxic. ^{203}Pb decays by electron capture to stable ^{203}Tl, emitting a number of gamma rays. The main 279 keV gamma ray is suitable for imaging and <u>in vivo</u> counting, and the half life of 52 hours is long enough for studies up to two weeks in length.

^{203}Pb is the most suitable lead tracer for the type of experiment designed in this thesis. With the use of ^{203}Pb, it is assumed that the usual criteria of tracer methodology hold. These are that lead in the human body is in a steady state, that there is complete mixing of the tracer with stable lead in the body and that the amount of tracer added is negligible to the amount of stable lead in the diet and the body.

The tracer dictates the instrumentation which will be used to obtain the experimental data. As ^{203}Pb was the tracer of choice, its radioactivity in the body and in body fluids was measured using radiation detectors. The instruments used are available in most Nuclear Medicine departments, and most of the computer procedures are also readily available.

SECTION 3

VARIATION OF GASTROINTESTINAL ABSORPTION OF ^{203}Pb IN TEN SUBJECTS

3.1 Introduction

The gastrointestinal absorption of lead in man is variable and work confirming this has been reviewed in section 1.5.1. At the time the experiments described in this section were performed, only the results of Hursh and Suomela (1968) were available. As discussed in section 1.5.1., their results were based on an indirect measure of absorption. This experiment was intended to repeat their work, but a larger number of subjects were studied and the use of ^{203}Pb and a whole body counter provided a more direct measurement of absorption.

3.2. Materials and methods

The ten subjects M.W. to S.L., listed in order in table 11.1, ingested 10 µCi of ^{203}Pb chloride, without carrier lead, dissolved in 100 ml of distilled water two hours after a light breakfast of their choice. Whole body retention of ^{203}Pb was measured every day for the next 7 days using a 'shadow shield' whole body monitor (Warner and Oliver, 1966), and the 96 hour retention was calculated as described in section 11.3. A counting standard containing approximately the same radioactivity as the dose was diluted to 1 litre with distilled water.

3.3 Results

The whole body retention values at 48 and 96 hours after administration of ^{203}Pb are presented in table 3.3.1. In 6 of the subjects, there was appreciable retention at 48 hours after the oral dose of ^{203}Pb. At least 5 of the subjects had a 96 hour retention greater than 10%, and the mean value of the retention of the remaining 5 subjects was 11.47 ± 0.51 (S.E.). The study on subject K.B. was repeated because retention appeared to be so high, but the initial figures were confirmed.

3.4 Discussion

The International Commission on Radiological Protection (ICRP, 1959) gastrointestinal model is based on complete evacuation of an oral dose in 31 hours, but 6 of the subjects still retained most of the oral dose at 48 hours. Similar results were obtained by Hursh and Suomela (1968), and they suggested that the disagreement could be caused by different personal habits of the subjects. It was assumed that the unabsorbed fraction of ^{203}Pb was cleared by 96 hours as there was minimal reduction in retention after 4 days.

If no unabsorbed ^{203}Pb remains in the body at 96 hours, the percentage retention at this time can be regarded as an adequate measure of absorption. Hansky and Connell (1962) found that 8 out of 10 normal subjects excreted the total recoverable dose of non-absorbable radioactive chromic oxide and sodium chromate within 96 hours.

TABLE 3.3.1

% Whole body retention of orally ingested ^{203}Pb *in ten subjects

SUBJECT	% RETENTION AT 48 HOURS	% RETENTION AT 96 HOURS
M.W.	17.51 ± 0.44†	11.52 ± 0.72
M.P.	98.53 ± 0.81	13.19 ± 0.71
E.H.	30.12 ± 0.50	23.30 ± 0.79
C.H.	12.87 ± 0.46	10.10 ± 0.75
P.H.	41.84 ± 0.66	16.19 ± 0.90
A.F.	31.59 ± 0.48	11.17 ± 0.69
M.W.	18.90 ± 0.40	16.78 ± 0.79
K.B.	75.88 ± 0.81	63.40 ± 1.18
K.B. (Repeat)	74.60 ± 0.36	67.00 ± 0.44
B.S.	66.49 ± 0.74	11.15 ± 0.81
S.L.	31.96 ± 0.51	31.96 ± 0.80
Mean		17.87
S.D.		12.47
S.E.		3.94

* No carrier lead.

† ± 1 standard deviation.

The percentage retention at 96 hours does not equal the percentage of ^{203}Pb absorbed, because a fraction of this ^{203}Pb will have been excreted in the urine and faeces in the preceding 96 hours. This fraction is probably small if absorbed lead is excreted at approximately the same rate in the pre-96 hour as in the post-96 hour period.

The gastrointestinal absorption of ^{203}Pb in the ten subjects was variable, which agrees with the results of Hursh and Suomela (1968). The retention of 5 of the subjects was greater than the 10% absorption quoted in the WHO Environmental Health Criteria 3 (1977), but the mean value of the remaining 5 subjects agreed with the accepted value.

The variation of gastrointestinal absorption observed could have been caused by, using tracer quantities of ^{203}Pb, age, diet, intestinal contents and individual variation in absorption between subjects. The accepted level of absorption, 10%, is based on the long-term balance studies of Kehoe (1961) in which stable lead was ingested. As the intake of lead per day through the gastrointestinal tract is between 200 - 300 µg, it could be argued that the tracer amounts of lead used in the present experiment would not behave in the same way as larger amounts of stable lead. The tracer lead would mix with stable lead already present in the intestinal contents, and if the movement of lead through the gut was relatively slow, the tracer lead would no longer be 'carrier free'.

Any variations in the transit time of food through the gut would affect the mixing of tracer and stable lead, and, possibly, the fraction of

tracer lead absorbed. Hansky and Connell (1962) measured gastrointestinal transit times (mouth to excretion) and found a coefficient of variation in ten subjects of approximately 50%, and Garber and Wei (1973) found that in mice the dose of lead ingested can influence the percentage absorbed. It is possible, therefore, that some of the variation in absorption observed between subjects was caused by using tracer quantities of ^{203}Pb.

The ten subjects were healthy, active individuals and were aged between 25 and 40 years. There was no indication that absorption varied with age in this group, although it is known that absorption is increased in the young (section 1.5).

Each subject enjoyed a normal diet and as they were healthy and had no evidence of disease, it is probable that they all had the same nutritional status. Even if there were differences, they would be unlikely to affect absorption in such a short term experiment, particularly, as it has been shown in section 1.5.1 that, in animals, intestinal contents appeared to influence absorption much more than nutritional status.

The intestinal contents of each subject could have varied in both quantity and composition, as it was only specified that they ate a light breakfast of their own choice. These variables, together with the use of tracer lead and any individual differences in absorption, could all contribute to the variation in gastrointestinal absorption of ^{203}Pb found between subjects.

SECTION 4

EFFECT OF FASTING ON THE GASTROINTESTINAL ABSORPTION OF ^{203}Pb IN THREE SUBJECTS

4.1 Introduction

Rabinowitz (1974) found that the absorption of oral lead in a fasting subject was markedly reduced when the lead was ingested in food (section 1.5.1). Some of the variation in 96 hour retention observed in the last experiment could have been caused by different quantities of food in the subjects gastrointestinal tracts. A repeat experiment with fasting subjects should shown the same effects of food on the absorption of lead as that observed by Rabinowitz (1974).

Three subjects from the previous experiment, E.H., B.S. and M.W., were available for further absorption studies. Two of these, M.W. and B.S., had retained approximately 11% (table 3.3.1) of the oral dose of ^{203}Pb at 96 hours, and, therefore, their absorption of lead conforms to the accepted value of 10% (WHO, 1977). The third subject, E.H., retained approximately twice the dose of ^{203}Pb at 96 hours than that retained by the other two subjects. To reduce the likelihood that this increased retention could have been caused by tracer lead behaving differently to stable lead (section 3.4), the same weight of carrier, lead chloride, was added to the dose of ^{203}Pb given to each subject in the present experiment.

4.2 Materials and methods

An oral dose of 10 μCi of ^{203}Pb chloride with 300 μg of lead chloride was given in 100 ml of distilled water to the subjects. They fasted for 18 hours prior to the dose, and for a further 6 hours after the dose was given. Whole body counts were measured and 96 hour retentions were calculated in the same way as in the previous experiment (section 3.2).

4.3 Results

The 96 hour retentions of ^{203}Pb are presented in table 4.3.1, together with each subject's previous reading from table 3.3.1. In all subjects, there was a marked increase in retention of ^{203}Pb when the subjects had fasted, but the order of their percentage retentions remained the same. The differences between the higher retention of subject E.H. and the retentions of M.W. and B.S. were much less when they had all fasted compared to those found in the previous experiment (section 3.0).

4.4 Discussion

The results of the present experiment confirm the findings of Rabinowitz (1974) that the presence of food in the gut reduces the absorption of lead. Experiments performed by Chamberlain et al (1978), at a later date than the present one, showed the same effect of food on absorption of lead. These workers also confirmed that the order of percentage retention was the same in both fasting and non fasting experiments performed on the same subjects.

TABLE 4.3.1

% Whole body retention of orally ingested ^{203}Pb in three subjects.

SUBJECT	% RETENTION AT 96 HOURS* (Non-fasted)	% RETENTION AT 96 HOURS (Fasted)
E.H.	23.30 ± 0.79†	75.82 ± 0.69
M.W.	11.52 ± 0.72	69.95 ± 0.66
B.S.	11.15 ± 0.81	67.44 ± 0.38
Mean		69.50
S.D.		3.88
S.E.		2.24

* No carrier lead.

† ± 1 standard deviation.

The 96 hour retention values agree with those of 67.00% and 63.30% found with subject K.B. in section 3.3, but are higher than absorption and retention values reported by other workers. Rabinowitz (1974) obtained a maximum value of 52% absorption in a fasting subject who had ingested lead sulphide. Chamberlain et al (1978) showed that lead sulphide was not absorbed as readily as lead chloride in fasting subjects, so that if the subject in Rabinowitz's study had ingested lead chloride, a higher absorption may have resulted. Rabinowitz (1974) also measured absorption from the quantity of lead excreted in a 10 day faecal collection. He did not take into account endogenous excretion of previously absorbed lead, so that he overestimated the unabsorbed fraction of lead in the faeces.

The results of Chamberlain et al (1978) are more suitable for comparison, as they measured whole body retention of ^{203}Pb. In six subjects, they found a mean retention at 5 days of $45 \pm 17\%$ (S.D.) compared with a mean retention at 4 days of $69.50 \pm 3.88\%$ (S.D.), obtained in the present experiment. The extra day between measurements is unlikely to make any difference between the means, but the amount of carrier lead in the dose and the fasting regime followed by the subjects were different. They gave their subjects one quarter of the carrier lead which was given in the present experiment, and if absorption is influenced by the weight of the carrier, then their retention measurements should have been higher. Garber and Wei (1973) found in mice that decreasing the carrier lead given with a tracer dose increased absorption of the tracer. The fasting regime was different in that their subjects were fasted for 12 hours instead of 18 hours before the dose, and were not allowed to eat for $2\frac{1}{2}$ hours

instead of 6 hours after the dose had been given. It is possible that any food present in the gut, before and after the oral dose of ^{203}Pb had been given, could reduce the absorption of lead by a greater extent in these subjects than in those who took part in the present experiment.

It is also possible that the subjects chosen for the present experiment had, when fasted, a naturally high absorption of lead. Two of the 6 subjects who took part in the experiments of Chamberlain et al (1978), retained more than 60% of their oral dose of ^{203}Pb. A comparison of the two means, $45 \pm 17\%$ (S.D.) and $69.50 \pm 3.88\%$ (S.D.), shows that they are not different at the 5% level of significance. This suggests that the 25% difference between the means could be due to individual variation in absorption of lead between the two groups of subjects, and not to differing experimental conditions.

SECTION 5

EFFECT OF DIETARY CONSTITUENTS ON THE GASTROINTESTINAL ABSORPTION, DISTRIBUTION AND EXCRETION OF ^{203}Pb IN TWO SUBJECTS

5.1 Introduction

The last experiment and those of Rabinowitz (1974) and Chamberlain et al (1978) have all shown that, in man, the presence of food in the gut reduces the gastrointestinal absorption of lead. Absorption is also affected by chemical form of lead and possibly by the acidity of stomach contents, and these effects have been mentioned in section 1.5.1. No human studies appear to have been performed, however, in which the effects of different types of food on the absorption of lead have been studied.

Food could possibly reduce the gastrointestinal absorption of ^{203}Pb in a number of ways. It could reduce the probability of contact between lead in intestinal mucosa. Lead could combine with certain constituents in the food and form insoluble compounds that would render lead unavailable for absorption, or there could be competition between lead and constituents in the food for common intestinal transport mechanisms.

There is strong evidence in the animal studies reviewed in section

1.5.1 that dietary constituents can have a major influence on the gastrointestinal absorption of lead. These studies also showed that the effect of dietary constituents on absorption could be adequately demonstrated when they were ingested simultaneously with a single dose of tracer lead. Dietary constituents also affect the distribution and excretion of lead in animals (section 1.5.2 and 1.5.3), although there is no evidence from the animal studies that the same effects can occur with a single dose of tracer lead ingested simultaneously with the constituents.

The present experiment, therefore, was designed primarily to investigate the effect of dietary constituents on the absorption of ^{203}Pb by using a control meal devised by Barltrop and Khoo (1975) for their rat experiments, and their method of varying the composition of the control meal. Whole body retention, blood and urine levels of ^{203}Pb were measured in an attempt to find an effect of dietary constituents on the absorption, distribution and excretion of ^{203}Pb in two subjects.

5.2 Materials and methods

Subjects K.B. and D.W., whose details are listed in section 11.1, took part in experiments in which they ingested ^{203}Pb in the control meal with all its constituents (total meal). Five more were performed on subject K.B. in which protein, fat, fibre, minerals and vitamins were omitted, in turn, from the control meal. A further two experiments were performed on the two subjects in which the ^{203}Pb was given in distilled water with carrier and minerals, and with carrier and

without minerals. Finally, subject K.B. ingested ^{203}Pb in distilled water without carrier and without minerals.

The composition of the control meal is shown in table 5.2.1, and it was based on a diet used by Barltrop and Khoo (1975) in their rat experiments. Each meal was kept isogravic and isocaloric by adjusting corn starch and sucrose content, and each meal contained 300 µg of lead chloride and 50 µCi of ^{203}Pb. The meal was cooked for 45 minutes at 180°C to give a fudge texture, which was found to be the most palatable. Before each experiment, the subjects fasted for 18 hours and for a further 6 hours after the meal had been eaten. After eating the meal, the mouth was swilled with 150 ml of distilled water to dislodge any meal left between the teeth. The subjects ate a normal diet after the fasting period and in between experiments.

Approximately the same radioactivity as the ingested dose was diluted to 1 litre with distilled water. Blood and urine standards were made up from 1 ml and 2 ml of this solution, and diluted to 2ml and 150 ml with distilled water. The remainder was used as the whole body counting standard. Whole body retention of the ^{203}Pb was measured using a whole body counter, and the retention at 96 hours and the half times of retention from 96 hours onwards were calculated, as described in section 11.3. It was assumed that the fall in retention values could be described by a single negative exponential.

5 ml venous blood samples were taken every day, and urine was also collected over 24 hour periods during the study. Whole blood and urine ^{203}Pb radioactivities were measured as described in sections 11.8 and

TABLE 5.2.1

Composition of control meal

DIETARY CONSTITUENTS		WEIGHTS (g)
Protein	Casein	20.0
Fat	Corn oil	5.0
Fibre	Cellulose	3.0
Carbohydrate	Molasses	5.0
	Sucrose	28.0
	Corn starch	33.0
Minerals*		5.3
Vitamins (3 Multivites)		1.76
$PbCl_2$		0.0003
		101.0603

* The mineral mix provided the following quantities in g/kg of diet: $CaCO_3$, 17.5; $NaH_2PO_4.2H_2O$, 25.13; $MgCl_2.6H_2O$, 5.43; KCl, 3.43; NaCl, 1.27; $MnSO_4.H_2O$, 0.168; $FeSO_4.7H_2O$, 0.105; $ZnCO_3$, 0.050; $CuSO_4$, 0.020; KIO_3, 0.0003.

11.9, respectively. The total blood volumes of both subjects, K.B. and D.W., were measured as described in section 11.7.3, and recorded in section 11.1. The total ^{203}Pb content of blood could then be calculated for both subjects. The levels of ^{203}Pb in blood and urine were then expressed as percentages of 96 hour retention (retained dose).

5.3 Results

Some of the results of the experiment performed on subject D.W. (section 8.2.3) in which he ingested ^{203}Pb in distilled water have been included in this section. They are the 96 hour retention, half time of retention, blood and urine levels of ^{203}Pb and they are annotated in the tables. The inclusion of these results allows a better comparison to be made between subjects K.B. and D.W.

5.3.1 Gastrointestinal absorption of ^{203}Pb

The whole body retentions of ^{203}Pb at 48 and 96 hours of both subjects are presented in tables 5.3.1 and 5.3.2. As found in previous experiments, a comparison of the 48 hour and 96 hour readings shows that the unabsorbed fraction of the oral dose was not cleared completely in all studies at 48 hours. The 96 hour retentions of both subjects were highest after ^{203}Pb had been ingested with carrier lead in distilled water, and there was no significant change in the 96 hour retention of subject K.B. when carrier was omitted. In the series of retention experiments performed on subject K.B. (table 5.3.1), retention was below 10% except when minerals were absent from the

TABLE 5.3.1

% Whole body retention of orally ingested ^{203}Pb with different meals and fluids

Subject : K.B.

MEAL	% RETENTION AT 48 HOURS	% RETENTION AT 96 HOURS
Total	12.81 ± 0.06†	3.95 ± 0.06
No minerals	44.99 ± 0.14	34.82 ± 0.15
No protein	9.97 ± 0.065	3.67 ± 0.08
No fibre	20.76 ± 0.14	3.09 ± 0.07
No fat	5.58 ± 0.07	4.29 ± 0.11
No vitamins	20.04 ± 0.07	3.11 ± 0.05
FLUID		
Distilled water and minerals	4.43 ± 0.06	0.94 ± 0.06
Distilled water	86.50 ± 0.2	60.76 ± 0.19
Distilled water without carrier	71.56 ± 0.18	59.19 ± 0.19

All meals and fluids included carrier lead except where indicated.

† ± 1 standard deviation.

TABLE 5.3.2

% Whole body retention of orally ingested ^{203}Pb

Subject : D.W.

MEAL	% RETENTION AT 48 HOURS	% RETENTION AT 96 HOURS
Total	21.10 ± 0.07†	8.07 ± 0.06
FLUID		
Distilled water and minerals	20.86 ± 0.83	1.50 ± 0.05
Distilled water	94.06 ± 0.23§	71.60 ± 0.23§

All meals and fluids included carrier lead.

† ± 1 standard deviation.

§ Results from section 8.2.3 a).

control meal. The mean 96 hour retention found in experiments in which the minerals were present was 3.48 $\pm$ 0.48% (S.D.), giving a coefficient of variation of 14%. The lowest retentions were found in both subjects when they ingested ^{203}Pb with minerals in distilled water. Subject D.W. always retained more ^{203}Pb than subject K.B. in every experiment that they shared.

5.3.2 ^{203}Pb in total blood following ingestion

Tables 5.3.3 and 5.3.4 show the percentages of the ingested dose of ^{203}Pb in total blood. Values range from 30.26% to 0.19% corresponding to the highest and lowest values of 96 hour retention. There was no consistent time after ingestion at which blood radioactivity peaked in any of the experiments. In at least half the experiments, however, peaks occurred between 96 hours and 120 hours, and no peaks occurred later than 144 hours.

5.3.3 Urinary excretion and half time of retention of ^{203}Pb

Tables 5.3.5 and 5.3.6 list the percentages of the ingested dose of ^{203}Pb in 24 hour urine collections. Values range from 1.88% to 0.003% and, as with ^{203}Pb in the blood, correspond to the highest and lowest values of 96 hour retention. The half times of whole body retention from 96 hours onwards are shown in tables 5.3.7 and 5.3.8. There were not sufficient retention values to allow a half time to be calculated for subject D.W. in the experiment in which he ingested ^{203}Pb with minerals in distilled water. The regression coefficients (r) obtained from the least squares fits are generally close to 1.00, except those

TABLE 5.3.3

Percentage of ingested dose of ^{203}Pb in total blood with different meals and fluids

Subject : K.B.

TIME (hours)	TOTAL	NO MINERALS	NO PROTEIN	NO FIBRE	NO FAT	NO VITAMINS	WATER WITH MINERALS	WATER	WATER WITHOUT CARRIER
12	0.44±0.01†	5.44±0.03	1.69±0.02	0.64±0.01	1.68±0.04	0.63±0.01	0.20±0.01	24.97±0.12	22.82±0.13
24	0.47±0.01	5.20±0.03	1.79±0.02	0.65±0.01	1.99±0.04	0.73±0.01	0.21±0.01	28.22±0.13	25.83±0.13
48	0.56±0.01	5.14±0.04	1.74±0.02	0.71±0.02	1.76±0.04	0.80±0.01	0.20±0.04	27.19±0.11	26.84±0.16
72	0.55±0.07	5.35±0.04	1.67±0.02	0.69±0.02	1.93±0.03	0.73±0.01	0.27±0.01	28.79±0.10	23.07±0.16
96	0.58±0.01	4.93±0.05	1.89±0.03	0.76±0.03	1.74±0.04	0.64±0.01	0.39±0.01	29.09±0.12	21.94±0.17
120	0.52±0.02	4.55±0.05	1.72±0.04	0.83±0.05	1.6 ±0.05	0.80±0.01	0.32±0.02	29.28±0.14	23.52±0.18
144	0.45±0.02	4.53±0.05	1.54±0.03	0.67±0.05	1.59±0.07	0.69±0.01	0.30±0.02	26.11±0.15	22.38±0.18
168	0.48±0.03	4.18±0.06	1.49±0.04	0.57±0.05	1.33±0.06	0.70±0.02	0.26±0.02	20.87±0.14	-
192	-	4.03±0.05	1.26±0.05	-	-	0.55±0.02	0.19±0.02	19.98±0.17	-
216	-	3.78±0.06	-	-	-	-	-	-	16.84±0.20

All meals and fluids included carrier lead except where indicated.

† ± 1 standard deviation.

TABLE 5.3.4

Percentage of ingested dose of ^{203}Pb in total blood with different meals and fluids

Subject : D.W.

TIME (hours)	TOTAL	WATER AND MINERALS	WATER§
12	1.060 ± 0.004†	0.184 ± 0.001	26.16 ± 0.12
24	1.520 ± 0.005	0.234 ± 0.002	30.26 ± 0.09
48	1.434 ± 0.005	0.293 ± 0.002	27.82 ± 0.16
72	1.401 ± 0.007	0.316 ± 0.002	29.62 ± 0.21
96	1.400 ± 0.008	0.312 ± 0.003	26.84 ± 0.21
120	1.301 ± 0.008	0.300 ± 0.004	26.62 ± 0.24
144	-	0.340 ± 0.004	25.07 ± 0.27
168	1.283 ± 0.013	0.336 ± 0.007	24.58 ± 0.23
192	-	-	26.99 ± 0.28
216	1.216 ± 0.017	-	25.34 ± 0.31

All meals and fluids included carrier lead.

† ± 1 standard deviation.

§ Results from section 8.2.3 d).

TABLE 5.3.5

Percentage of ingested dose of ^{203}Pb in total urine with different meals and fluids

Subject : K.B.

TIME (hours)	TOTAL	NO MINERALS	NO PROTEIN	NO FIBRE	NO FAT	NO VITAMINS	WATER WITH MINERALS	WATER	WATER WITH-OUT CARRIER
0-24	0.029 ± 0.0005†	0.55 ± 0.007	0.061 ± 0.0004	0.041 ± 0.001	0.127 ± 0.002	0.049 ± 0.0005	0.009 ± 0.0003	1.88 ± 0.012	1.67 ± 0.004
24-48	0.015 ± 0.001	0.41 ± 0.004	0.046 ± 0.001	0.022 ± 0.002	0.050 ± 0.003	0.022 ± 0.0005	0.011 ± 0.0005	0.76 ± 0.008	0.63 ± 0.003
48-72	0.014 ± 0.0004	0.32 ± 0.004	0.063 ± 0.001	0.024 ± 0.001	0.058 ± 0.001	0.023 ± 0.001	0.008 ± 0.0005	0.68 ± 0.006	0.56 ± 0.003
72-96	0.013 ± 0.0004	0.25 ± 0.005	0.044 ± 0.001	0.026 ± 0.001	0.049 ± 0.001	0.016 ± 0.0005	0.007 ± 0.0005	0.38 ± 0.006	0.83 ± 0.005
96-120	0.013 ± 0.0006	0.20 ± 0.004	0.043 ± 0.002	0.020 ± 0.002	0.050 ± 0.002	0.017 ± 0.0005	0.009 ± 0.0007	0.64 ± 0.006	0.65 ± 0.004
120-144	0.013 ± 0.0006	0.19 ± 0.008	0.060 ± 0.001	0.018 ± 0.002	0.040 ± 0.003	0.014 ± 0.001	0.006 ± 0.001	0.48 ± 0.006	0.55 ± 0.005
144-168	0.013 ± 0.001	0.26 ± 0.01	-	0.027 ± 0.004	0.045 ± 0.005	0.011 ± 0.0005	0.007 ± 0.0007	0.98 ± 0.010	0.44 ± 0.008
168-192	-	0.28 ± 0.02	-	0.027 ± 0.006	0.045 ± 0.004	0.013 ± 0.0007	0.007 ± 0.001	0.56 ± 0.010	0.38 ± 0.007
192-216	0.015 ± 0.001	-	-	-	-	-	0.008 ± 0.001	-	0.49 ± 0.009

All meals and fluid included carrier lead except where indicated.

† $\pm$ 1 standard deviation.

TABLE 5.3.6

Percentage of ingested dose of ^{203}Pb in total urine with different meals and fluids

Subject : D.W.

TIME (hours)	TOTAL	WATER WITH MINERALS	WATER[§]
0-24	0.083 ± 0.0006	0.0100 ± 0.0001	1.35 ± 0.0065
24-48	0.036 ± 0.0004	0.0050 ± 0.0001	0.96 ± 0.0056
48-72	0.026 ± 0.0004	0.0074 ± 0.0002	0.79 ± 0.0067
72-96	0.024 ± 0.0004	0.0027 ± 0.0001	0.46 ± 0.0048
96-120	0.026 ± 0.0005	0.0090 ± 0.0011	0.55 ± 0.0071
120-144	0.026 ± 0.0004	0.0042 ± 0.0002	0.51 ± 0.0059
144-168	0.018 ± 0.0009	0.0037 ± 0.0001	0.58 ± 0.0071
168-192	0.024 ± 0.0006	0.0089 ± 0.0003	0.63 ± 0.0098
192-216	0.026 ± 0.0007	0.0045 ± 0.0002	0.74 ± 0.0097

All meals and fluids included carrier lead.

† ± 1 standard deviation.

§ Results from section 8.2.3 d).

TABLE 5.3.7

Half time of retention of ^{203}Pb from 96 hours onwards with different meals and fluids

Subject : K.B.

MEALS	HALF TIME (hours)	REGRESSION COEFFICIENT (r)
Total	29.49 ± 0.75† (4)	- 0.96
No minerals	364.74 ± 19.20 (6)	- 0.99
No protein	90.00 ± 9.35 (3)	- 0.91
No fat	62.43 ± 5.63 (4)	- 0.87
No vitamins	76.66 ± 4.58 (5)	- 0.96
No fibre	49.86 ± 3.95 (4)	- 0.92
Fluid		
Distilled water and minerals	37.26 ± 8.40 (3)	- 0.99
Distilled water	301.31 ± 1.31 (7)	- 0.99
Distilled water without carrier	771.70 ± 36.09 (6)	- 0.98

All meals and fluids included carrier lead except where indicated.
Figures in brackets are number of data points.

† ± 1 standard deviation.

TABLE 5.3.8

Half time of retention of ^{203}Pb from 96 hours onwards with different meals and fluids

Subject : D.W.

MEAL	HALF TIME (hours)	REGRESSION COEFFICIENT (r)
Total	$10.5 \pm 0.32^{\dagger}$ (6)	- 0.89
Fluid		
Distilled water and minerals	-	-
Distilled water	$630.00 \pm 57.27^{\S}$ (6)	- 0.99

All meals and fluids included carrier lead.
Figures in brackets are number of data points.

† $\pm$ 1 standard deviation.

§ Results from section 8.2.3 a).

found with retention values from the total meal experiment of subject D.W. and from the experiment in which subject K.B. ingested the meal without fat. In the total meal experiment, the half time of retention was extremely short at 10.5 hours. The longest half times are associated with the highest retentions, and it is noticeable that the half time of retention of subject K.B. was twice as long when carrier lead was absent from the ingested dose of ^{203}Pb.

5.3.4 ^{203}Pb content of blood and urine expressed as percentages of 96 hour retention

Tables 5.3.9 and 5.3.10 show the mean ^{203}Pb content of total blood and of 24 hour urine collections expressed as percentages of 96 hour retention. There is considerable variation between values obtained from the different meal experiments of subject K.B. The highest and lowest values are found when protein was omitted and every constituent was included in the total meal, respectively. There was good agreement between these last values and those obtained from the corresponding experiment performed with subject D.W. There is also good agreement between the ^{203}Pb content of blood and urine found in the two experiments in which subject K.B. ingested ^{203}Pb in distilled water with and then without carrier lead. Both blood and urine values obtained from total meal experiment and distilled water plus minerals experiment of subject D.W. agree well, but there is a marked discrepancy between these latter values and those found when ^{203}Pb was given in distilled water.

TABLE 5.3.9

Mean ^{203}Pb in blood and mean ^{203}Pb in 24 hour urine expressed as percentages of 96 hour retention for different meals and fluids

Subject : K.B.

MEAL	MEAN TOTAL BLOOD (% 96 hour retention)	MEAN 24 HOUR URINE (% 96 hour retention)
Total	12.89 ± 1.56†	0.405 ± 0.152
No minerals	14.19 ± 0.15	0.890 ± 0.316
No protein	46.32 ± 3.68	1.580 ± 0.200
No fibre	21.42 ± 1.41	0.906 ± 0.273
No fat	41.26 ± 4.55	1.380 ± 0.537
No vitamins	22.86 ± 2.38	0.707 ± 0.450
Fluid		
Distilled water and minerals	28.40 ± 8.29	0.957 ± 0.161
Distilled water	43.82 ± 5.12	1.080 ± 0.545
Distilled water without carrier	39.47 ± 4.55	1.250 ± 0.667

All meals and fluids included carrier lead except where indicated.

† ± 1 standard deviation.

TABLE 5.3.10

Mean ^{203}Pb in blood and mean ^{203}Pb in 24 hour urine expressed as percentages of 96 hour retention for different meals and fluids

Subject : D.W.

MEAL	MEAN TOTAL BLOOD (% 96 hour retention)	MEAN 24 HOUR URINE (% 96 hour retention)
Total	16.23 ± 2.36†	0.384 ± 0.198
Fluid		
Distilled water and minerals	15.80 ± 4.23	0.360 ± 0.187
Distilled water	39.05 ± 2.96§	1.010 ± 0.420§

All meals and fluids included carrier lead.

† ± 1 standard deviation.

§ Results from section 8.2.3.

5.4 Discussion

5.4.1 Gastrointestinal absorption of ^{203}Pb

The results clearly show that, in the two subjects studied, the simultaneous presence of food with lead in the gut reduces the gastrointestinal absorption of ^{203}Pb. The 96 hour retention of subject K.B. after he had ingested the total meal was approximately half the accepted value of absorption, whereas his retention in section 3.0 was the highest of the ten subjects in that experiment. The retention of subject D.W., however, agreed fairly well with the accepted value. The difference in retention between these two subjects was probably caused by individual variation in absorption of lead, as subject D.W. always retained a higher percentage of ^{203}Pb than subject K.B. in all the experiments they shared. This was observed in section 4.0 and confirms the same effect found by Chamberlain et al (1978).

The percentage of ^{203}Pb retained by subject K.B. was unaffected by the amount of carrier lead, 300 µg, present with the ^{203}Pb in the gut. In this subject, the absorptive mechanisms responsible for the absorption of lead can tolerate these lead levels in the gut without a change in the efficiency of absorption.

The absorption of lead was reduced, however, every time minerals were present with lead in the meals and fluids ingested by both subjects. The retention of subject K.B. dropped by a factor of 10 when minerals were present in the total meal. Barltrop and Khoo (1975) found that

the dietary regime of control meal with added minerals was the only one which decreased the gastrointestinal absorption of ^{203}Pb in rats.

When minerals were present in the meal, the absence, in turn, of protein, fat, fibre and vitamins did not appear to have any effect on the gastrointestinal absorption of ^{203}Pb in subject K.B. High and low protein diets have been shown to increase the absorption of lead in rats (Barltrop and Khoo, 1975), although Gontzea et al (1970) found that only a low protein intake increased absorption. Quarterman et al (1978b) however, accounted for this discrepancy when they found that the effect of protein on the absorption of lead in rats was influenced by several factors. These were the duration of both feeding by experimental diets and intake of lead, and whether or not the rats were fed to appetite. Their findings did not support the theory that a diet low in protein would necessarily increase lead absorption.

Fibre, in the form of cellulose, chelates zinc, iron and calcium and makes them unavailable for absorption by the human gut (Moynahan, 1977), but no effect on lead absorption was found in subject K.B. Diets deficient in vitamin C have been shown by Pillemer et al (1940) to increase lead toxicity, and diets with added vitamin D have produced increased lead absorption (Sobel et al, 1940). Barltrop and Khoo (1975), however, found no effect of vitamins on gastrointestinal absorption of lead in rats, and there was no effect on subject K.B.

The greatest reduction in gastrointestinal absorption of ^{203}Pb occurred after lead and minerals were taken orally in distilled water. This supports the theory that drinking water containing minerals

('hard water') is protective against the gastrointestinal absorption of water borne lead (Crawford and Clayton, 1973). This protective action was confirmed in studies on rats by Meredith et al (1977) when they found that 'hard water' decreased the retention of an oral dose of ^{203}Pb.

5.4.2 Distribution and excretion of ^{203}Pb

The levels of ^{203}Pb in blood and urine naturally reflected its percentage absorption in the gut. The different meals, however, also appeared to influence the percentage of the retained dose of ^{203}Pb in the blood, in the urine and the half time of retention from 96 hours onwards. The retained dose in the blood of subject K.B. was high when meals were consumed with no protein, no fat, and high in all the fluid experiments. Barltrop and Khoo (1975) obtained similiar results with low protein and low mineral diets in rats, but found, however, that high fat diets also gave high blood-lead concentrations.

The time taken to reach peak ^{203}Pb radioactivity in the blood was longer in most of the present experiments than that found by Chamberlain et al (1978) in their human studies. They observed peak blood radioactivities between 24 - 48 hours when ^{203}Pb chloride and ^{203}Pb sulphide were ingested by humans in fasting and non fasting experiments. The only experiments in which peak times were similiar to those found by Chamberlain et al (1978) were those in which fat and vitamins were absent from the meals ingested by K.B., and those in which the total meal and mineral-free fluid meal was ingested by D.W.

The percentage of retained ^{203}Pb in the urine followed the pattern of gastrointestinal absorption of ^{203}Pb observed with the blood. The half times of retention also showed a pattern, with the length of time corresponding to magnitude of 96 hour retention. The absence of carrier lead from the dose of ^{203}Pb increased the half time of retention in subject K.B. If it is assumed that the unabsorbed fraction of ^{203}Pb is cleared from the body in 96 hours and that the loss of ^{203}Pb by other routes of excretion, such as sweating, are negligible (Chamberlain et al, 1978), then the fall in retention values from 96 hours onwards represents urinary and endogenous faecal excretion of ^{203}Pb.

The mean endogenous faecal loss of ^{203}Pb per day, therefore, can be indirectly found by subtracting the mean urinary loss of ^{203}Pb per day from the mean reduction in whole body retention per day. The ratio of mean endogenous faecal to mean urinary loss per day ($^{F}/_{U}$) was 3.22 ± 1.01 (S.D.) when subject K.B. ingested ^{203}Pb with carrier lead, and 0.945 ± 0.306 (S.D.) when he ingested ^{203}Pb without carrier. This last result agrees with ratios found by Chamberlain et al (1978). The higher weight of carrier lead ingested may account for the higher value of F/U found in subject K.B., and suggests that the amount of lead absorbed with ^{203}Pb in the gut can influence rates of excretion. Klaasen and Shoeman (1974) showed in rats that the excretion rate of lead into bile was decreased by decreasing intravenous doses of carrier lead.

The fall in retention of ^{203}Pb from 96 hours onwards is generally well represented by a single negative exponential.

The shortest half times of retention were associated with meals and fluids containing minerals. Several of these half times, however, were calculated from very few data points. It has been assumed that the unabsorbed fraction of ^{203}Pb is cleared from the gut by 96 hours, but the effect of any residual unabsorbed tracer would be to decrease the half times obtained from retention figures. This could explain the short half times observed in experiments in which the unabsorbed fraction of lead is very large, resulting in low retentions and very few post 96 hour readings. The shortest half time of retention, however, was found in the total meal experiment of subject D.W. from 6 data points, but the regression coefficient was - 0.89, indicating that the fall in retention was poorly represented by a single negative exponential. This result cannot be compared to those found with the other subjects.

Comparing the results of the experiments that the two subjects shared, there is good agreement between the percentages of the retained dose in the total blood and urine found when ^{203}Pb was ingested in the total meal and between those when ^{203}Pb was ingested in distilled water. There is also good agreement between blood and urine levels found in the experiments in which subject D.W. ingested ^{203}Pb in the total meal and ^{203}Pb with minerals in distilled water. There is a difference, however, between the levels obtained from this last experiment and those found in the similiar experiment performed on subject K.B. In these experiments, the 96 hour retentions of both subjects was very low, 0.94% for subject K.B. and 1.50% for subject D.W., so that even a small fraction of unabsorbed ^{203}Pb in the gut

would have a substantial effect on retention. If this unabsorbed ^{203}Pb was present and could be accounted for, both retentions would be lower, and, with the subject K.B., it would make the difference greater, but with subject D.W., however, such a correction would give better agreement.

From the limited amount of data collected from the experiments in this section, there appears to be an effect of dietary constituents and carrier lead on the distribution and excretion of absorbed ^{203}Pb. However, the percentages of ^{203}Pb in blood and urine, expressed relative to 96 hour retention, do not entirely agree in the two subjects examined, indicating possible individual differences. Further experiments should be performed with more subjects and more comprehensive collection of data to confirm any effects.

SECTION 6

EFFECT OF CALCIUM AND PHOSPHOROUS ON THE GASTROINTESTINAL ABSORPTION OF ^{203}Pb IN FIVE SUBJECTS

6.1 Introduction

In the preceding experiment, the greatest reduction in 96 hour retention of ^{203}Pb in two human subjects occurred when they ingested the ^{203}Pb with minerals in food and water. Minerals produced a similiar effect on the absorption of tracer lead in the rat experiments of Barltrop and Khoo (1975), and, in further studies, these workers showed that calcium and phosphorous were mainly responsible for this effect. Meredith et al (1977) showed in rats that increasing weights of oral calcium reduced the retention of tracer lead in an exponential manner. They suggested that the effect of calcium on lead retention was caused by the existence of a common pathway for the absorption of calcium and other minerals, including lead, from the gut.

Other animal studies investigating the effect of calcium and phosphorous on the absorption of lead, were reviewed in section 1.5.1. A number of these studies showed that concomitant calcium markedly reduced the absorption of tracer lead, but no experiments had been performed to investigate a similar effect of phosphorous on absorption. Furthermore, no experiments using tracer lead have been performed on

human subjects to investigate the effects of calcium and phosphorous on lead absorption.

The experiments in this section, therefore, were prompted by the animal work of Barltrop and Khoo (1975) and Meredith et al (1977). The separate effects of calcium and phosphorous on the retention of ^{203}Pb were studied in one human subject, and the effect of them together was studied in the same subject and in four other human subjects. Finally, the effect of different weights of calcium and phosphorous on the retention of ^{203}Pb was examined in one subject in an attempt, similiar to that of Meredith et al (1977), to gain some insight into the mechanisms that may cause calcium and phosphorous to reduce the absorption of lead from the gut.

6.2 Materials and methods

The subjects K.B., J.B., B.C., G.E. and D.W., whose details are listed in section 11.1, took part in this experiment. Most of the experimental work was performed on subject K.B. He ingested $CaCO_3$ and $NaH_2PO_4.2H_2O$ in two separate experiments to compare their individual effects on retention, and then ingested different weights of them together to determine the response of retention to these different weights.

All subjects followed the same fasting regime used in section 5.0, and drank their doses of ^{203}Pb with 300 µg of carrier lead chloride in 100 ml of distilled water. Subject K.B. received 100 µCi of ^{203}Pb in each of his experiments in this section, and the doses of ^{203}Pb given to

the other subjects are listed in table 6.2.1. As the present experiments were a continuation of those performed in section 5.0, the weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ (maximum weights) used in the two separate retention experiments performed on subject K.B. are those listed in table 5.2.1. One tenth, one twentieth, one hundredth of these weights and weights equimolar to that of lead in the dose were then given to subject K.B. in separate experiments, but the ratio of $CaCO_3$ to $NaH_2PO_4.2H_2O$ was kept constant. These weights provided an adequate number and range of retention results, and they are listed in table 6.3.2. All four of the other subjects were given the maximum weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$, and three subjects were given one tenth of the maximum in separate experiments, as listed in table 6.2.1. The $CaCO_3$ and $NaH_2PO_4.2H_2O$ were mixed in 150 ml of distilled water and drunk immediately after the dose of ^{203}Pb. Whole body counts were performed, and the 96 hour retentions and the half times of retention were calculated, as described in previous sections.

6.3 Results

Results from experiments performed in other sections, but included here, have been annotated. The results of the experiments performed on subjects J.B., B.C., G.E., D.W. are shown in table 6.3.1 and those of subject K.B. in table 6.3.2. All subjects responded to the maximum weights of the minerals, 1.75 g $CaCO_3$ and 2.513 g $NaH_2PO_4.2H_2O$, with markedly low 96 hour retentions of ^{203}Pb, with a mean of $1.91 \pm 1.32\%$ (S.D.). There was also a definite but less marked response to the weights of 0.175 g $CaCO_3$ and 0.251 g $NaH_2PO_4.2H_2O$, with a mean of $23.88 \pm 8.07\%$ (S.D.).

TABLE 6.2.1

Weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ and doses of ^{203}Pb

SUBJECT	WEIGHT OF $CaCO_3$ (g)	WEIGHT OF $NaH_2PO_4.2H_2O$ (g)	^{203}Pb (µCi)
K.B.	-	-	50*
J.B.	-	-	247§
	0.175	0.251	100
	1.75	2.513	100
B.C.	-	-	250§
	0.175	0.251	100
	1.75	2.513	100
G.E.	-	-	250§
	0.175	0.251	450§
	1.75	2.513	100
D.W.	-	-	248§
	1.75	2.513	450§

All doses included carrier lead.

* Dose ingested in experiment, section 5.0.

§ Dose ingested in kinetic experiments, section 8.2.

The wide scatter of 96 hour retention values found in the subjects, when they were given calcium and phosphorous, is in marked contrast to the minimal variation of the mean, 72.28 $\pm$ 1.17% (S.D.), obtained in the non mineral experiments. In these latter experiments, however, even though retention values are approximately the same, there is considerable variation in the half times of retention, with a mean of 417.66 $\pm$ 157.12% (S.D.). Increasing weights of calcium and phosphorous caused half times of retention to decrease progressively.

The effect of $CaCO_3$ on the retention of ^{203}Pb in subject K.B. was much greater than that of $NaH_2PO_4.2H_2O$, but, when both were taken together, 0.175 g of $CaCO_3$ and 0.251 g of $NaH_2PO_4.2H_2O$ were sufficient to give the same 96 hour retention of ^{203}Pb as 1.75 g of $CaCO_3$ given on its own.

The response of 96 hour retention of subject K.B. to different weights of calcium and phosphorous can be fitted to a mathematical function of the form ($\chi^2 = 8.5$; $0.05 < P < 0.1$)

$$^{203}Pb \text{ retention at 96 hours} = 74.34e^{-44.40w} + 6.15e^{-1.90w}$$

where w is the weight of calcium in grams. The data and function are shown in figure 6.3.1, and figure 6.3.2 shows the same data plotted with 96 hour whole body retention as y-values against ℓn (weight of calcium).

There is considerable variation in the half times of retention found in the different experiments performed on the subject K.B., as shown in table 6.3.2. The lowest half time was found in the experiment in which the maximum weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ were given. It is

TABLE 6.3.1

Effect of $CaCO_3$ and $NaH_2PO_4.2H_2O$ on the retention of ^{203}Pb

SUBJECT	WEIGHT OF $CaCO_3$ (g)	WEIGHT OF $NaH_2PO_4.2H_2O$ (g)	96 HOUR RETENTION (%)	HALF TIME FROM 96 HOURS ONWARDS (hours)	REGRESSION COEFFICIENT (r)
J.B.	-	-	$71.70 \pm 0.27^{\dagger\S}$	$407.60 \pm 23.97^{\S}(6)$	- 0.99
	0.175‡	0.251‡	13.78 ± 0.15	198.00 ± 16.97 (6)	- 0.98
	1.75 ¶	2.513¶	1.50 ± 0.06	-	-
B.C.	-	-	$73.93 \pm 0.24^{\S}$	$702.84 \pm 30.43^{\S}(6)$	- 0.94
	0.175	0.251	41.38 ± 0.37	266.54 ± 20.50 (6)	- 0.84
	1.75	2.513	0.90 ± 0.10	-	-
G.E.	-	-	$71.71 \pm 0.27^{\S}$	$330.00 \pm 15.71^{\S}(6)$	- 0.97
	0.175	0.251	$26.48 \pm 0.10^{\S}$	$210.00 \pm 6.36^{\S}(6)$	- 0.98
	1.75	2.513	4.77 ± 0.10	111.77 ± 10.82 (6)	- 0.99
D.W.	-	-	$71.60 \pm 0.23^{\S}$	$630.00 \pm 57.27^{\S}(6)$	- 0.99
	1.75	2.513	$1.65 \pm 0.06^{\S}$	-	-
Mean (no minerals):		$72.28 \pm 1.17^{\dagger}(4)$		417.66 ± 157.12	
Mean (tenth max. weight):		23.88 ± 8.07 (3)			
Mean (max. weight):		1.91 ± 1.32 (4)			

All doses included carrier lead.
Figures in brackets are number of data points.
† ± 1 standard deviation.
§ Retention and half time of retention results from kinetic experiments, section 8.2.
‡ Tenth maximum weight.
¶ Maximum weight.

TABLE 6.3.2

Effect of $CaCO_3$ and $NaH_2PO_4.2H_2O$ on the retention of ^{203}Pb

Subject : K.B.

WEIGHT OF $CaCO_3$ (g)	WEIGHT OF $NaH_2PO_4.2H_2O$ (g)	96 HOUR RETENTION (%)	HALF TIME FROM 96 HOURS ONWARDS (hours)	REGRESSION COEFFICIENT (r)
-	-	60.76 ± 0.19†*	301.31 ± 1.31*(7)	- 0.99
0.0001	0.00016	65.31 ± 0.30	385.00 ± 21.39 (6)	- 0.99
0.0175	0.0251	66.19 ± 0.37	288.75 ± 12.03 (5)	- 0.94
0.087	0.126	31.43 ± 0.28	238.97 ± 16.48 (6)	- 0.96
0.175	0.251	6.51 ± 0.10	130.75 ± 17.27 (3)	- 0.93
1.75	2.513	1.51 ± 0.06	86.63 ± 22.74 (3)	- 0.99
-	2.513	47.24 ± 0.31	346.50 ± 34.65 (4)	- 0.99
1.75	-	6.51 ± 0.16	123.75 ± 24.31 (3)	- 0.96

All doses included carrier lead.

Figures in brackets are number of data points.

† ± 1 standard deviation.

* Retention and half time of retention results from section 5.0.

FIGURE. 6.3.1

96hour retention against weight of calcium

Subject K.B.

Calcium/phosphorous = 1.4

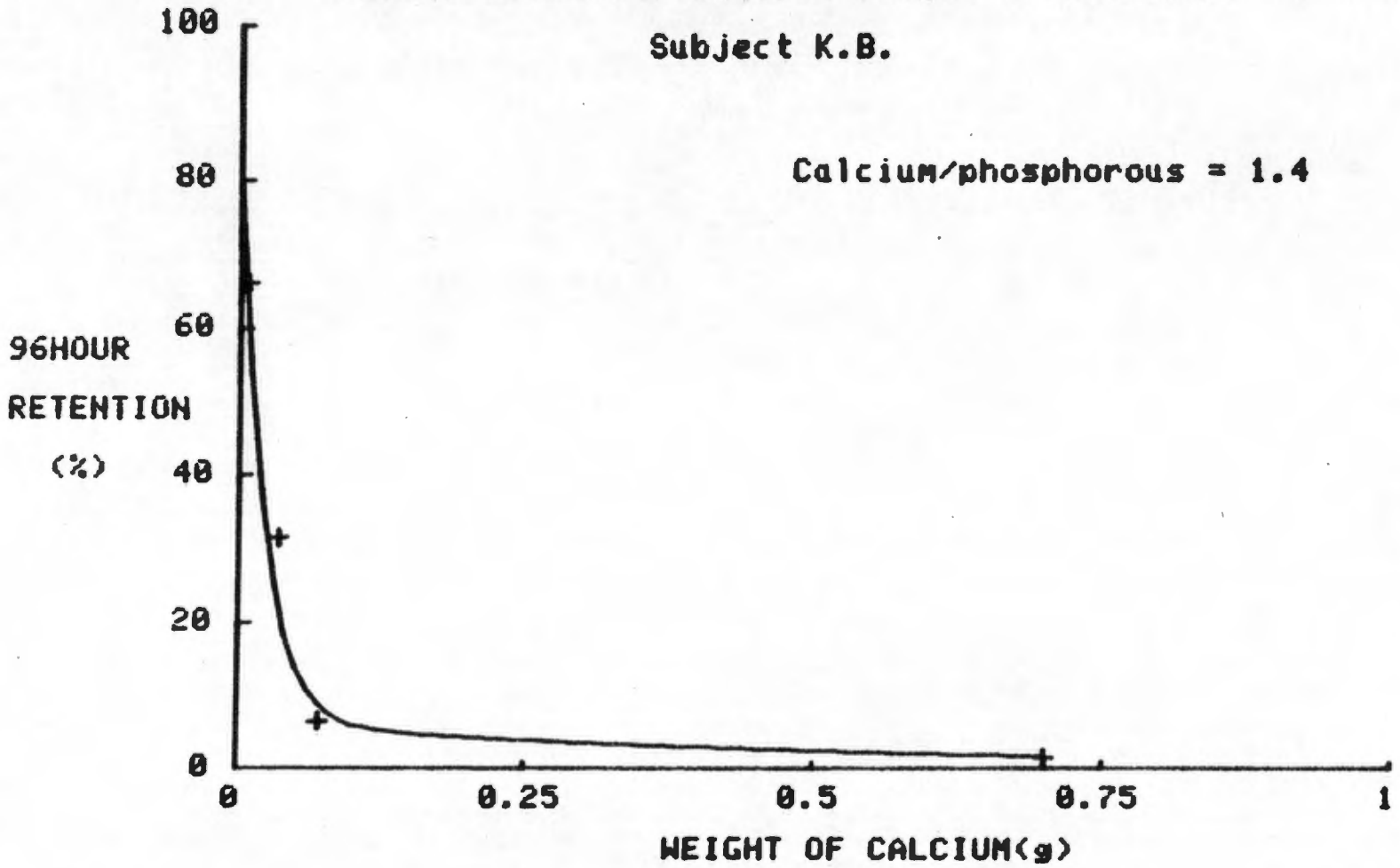
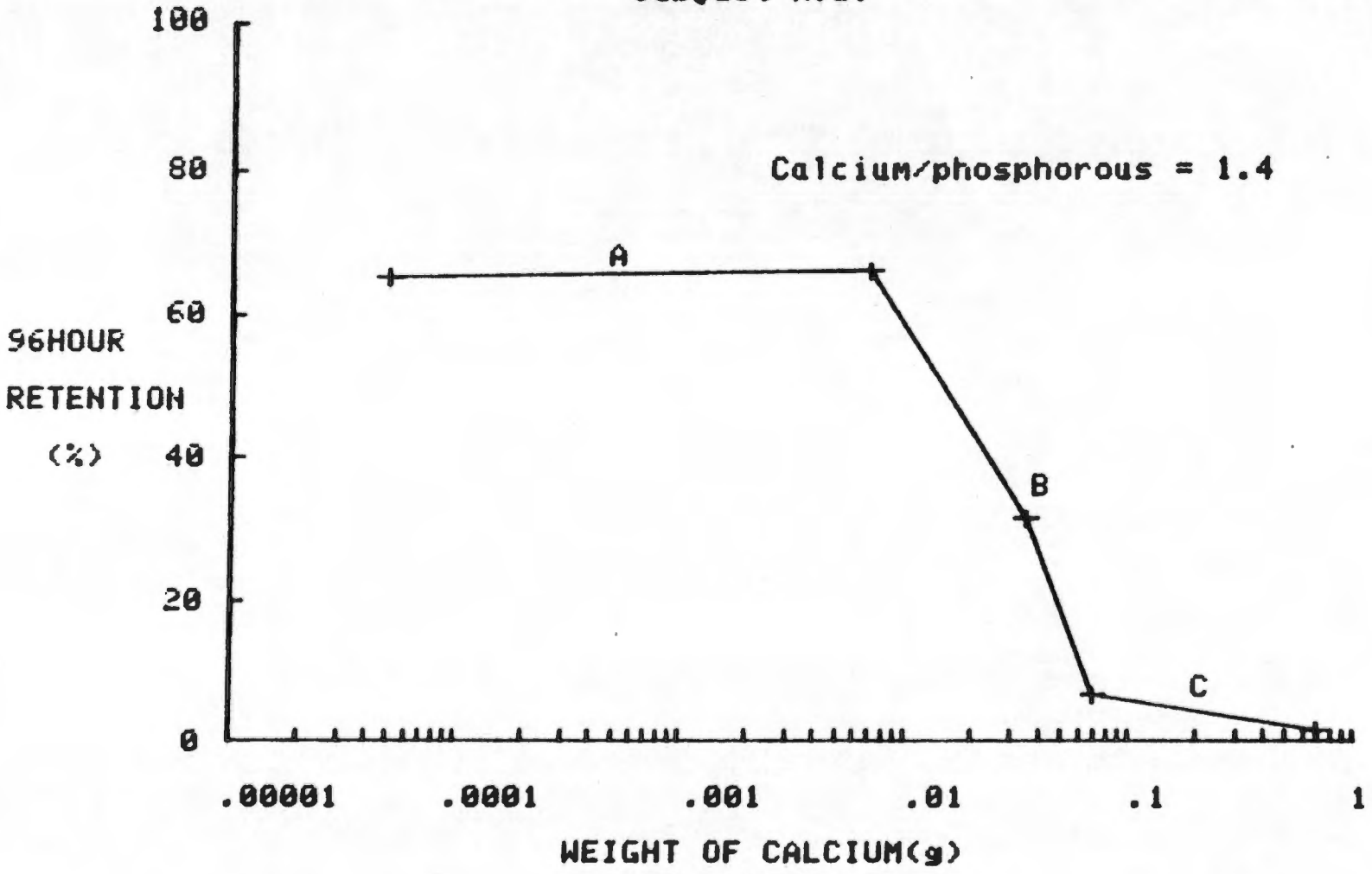


FIGURE. 6.3.2

96hour retention against ln(weight of calcium)

Subject K.B.



noticeable that there was no reduction in half time when only phosphorous was ingested with the ^{203}Pb, although retention dropped from 60.75% to 47.24% of the ingested dose.

6.4 Discussion

Barltrop and Khoo (1975) found that calcium and phosphorous were mainly responsible for reducing the gastrointestinal absorption of lead in rats, and the results of the present experiment confirm that this also occurs in humans. The 96 hour retentions of subjects K.B. and D.W. found in this experiment are comparable to those in section 5.0 (tables 5.3.1 and 5.3.2), even though, in the latter experiment, the dose of ^{203}Pb was ingested with all the minerals listed in table 5.2.1.

The gastrointestinal absorption of lead differed in subjects who had received the same weights of calcium and phosphorous with the lead. This caused a wide scatter in 96 hour retention values compared with values obtained, with the same subjects, when calcium and phosphorous were not ingested with the lead. The minimal variation of these last retention results suggests thatthe discrepancy noted between the results of the retention experiments of Chamberlain et al (1978) and those obtained in section 4.0 was not entirely caused, as suggested earlier, by individual variation in the absorption of lead. Their lower mean and greater scatter of retention values could be explained if, after the shorter fasting period of 12 hours, there were still traces of food containing calcium and phosphorous present in the gut when the dose of lead was ingested.

The reduction in the whole body retention of lead caused by calcium

and phosphorous was associated with a decrease in the half time of retention. In subject K.B., all the minerals, when ingested in distilled water (section 5.0), appear to reduce the half time of retention more than that found when only calcium and phosphorous were ingested. The standard deviations of both half times (tables 5.3.7 and 6.3.2), however, are both large, so there is unlikely to be any significant difference between them.

6.4.1 The effects of calcium, phosphorous and both calcium and phosphorous together on the gastrointestinal absorption of ^{203}Pb

The effect of separate weights of calcium and phosphorous on the absorption of lead was only investigated with one subject, K.B. The results of these two experiments, therefore, may not be representative of those obtained if more subjects had been used. These results, however, can be compared to animal experiments in which the separate effects of calcium and phosphorous on the absorption of lead have been examined.

Calcium reduced the 96 hour retention of subject K.B. much more than phosphorous, even though the actual weights of calcium, 0.7 g, and phosphorous, 0.5 g, were approximately the same. The percentage of the dose of lead retained at 96 hours is the difference between that absorbed in the gut and the percentage of absorbed lead excreted over 96 hours. Calcium reduced the half time of retention by a factor of 3 more than phosphorous (table 6.3.2), and this could be responsible for the lower 96 hour retention. However, if it is assumed that the same percentage of lead was absorbed in both experiments, and that absorbed lead was excreted at

approximately the same rate in the pre-96 hour as in the post-96 hour period, then the retention at 96 hours would only be different by a factor of 1.4 instead of the actual factor of 7.3. This suggests, therefore, that calcium also interferes more than phosphorous with the mechanisms which are responsible for the absorption of lead in the gut.

The greater effect of calcium than that of phosphorous on the absorption of lead was shown in the rat studies of Quarterman and Morrison (1975) and Barltrop and Khoo (1975). Three groups of rats were fed diets low in calcium, low in phosphorous and low in both calcium and phosphorous together for a period of 8 weeks (Quarterman and Morrison, 1975). The lead retained by the low calcium group was 3.7 times, and that retained by the low phosphorous group was 2.6 times, the lead retained by rats fed lead in a normal diet. Although the calcium and phosphorous contents of the diet were below the minimum estimated requirements of the rat, it is unlikely that the nutritional status of the rats had an effect as Barltrop and Khoo (1975) confirmed the findings of Quarterman and Morrison (1975) in a more acute diet experiment. They found that a low calcium diet given to rats over 48 hours increased the retention of oral ^{203}Pb by a factor of 3.1. A low phosphorous diet also increased retention but by only a factor of 1.8.

The presence of both calcium and phosphorous with ^{203}Pb in the gut reduced the retention of ^{203}Pb in subject K.B. considerably more than calcium or phosphorous alone. This was also shown in the rat experiments of Quarterman and Morrison (1975) and Barltrop and Khoo (1975), and both groups of workers found the effects of calcium and phosphorus together on the absorption of lead were additive. In

contrast to these two animal experiments, Quarterman et al (1978a) found that in rats an increase above normal requirements in the dietary content of calcium and phosphorous together had an effect no greater than an increase of either one alone.

The results of these animal studies suggest certain characteristics about the gastrointestinal absorption of lead, if we assume, as argued in the start of this section, that calcium and phosphorous reduce retention primarily by affecting the absorption of lead from the lumen of the gut. The effects of calcium and phosphorous suggest competition with lead for absorption by a common pathway, with calcium competing more efficiently than phosphorous. As their effects were shown by Quarterman and Morrison (1975) and Barltrop and Khoo (1975) to be additive, the quantities of calcium, phosphorous and lead used in these studies were not sufficient to cause any saturation of the common pathway. The effects observed by Quarterman et al (1978a),however, do suggest that saturation can occur if larger quantities of calcium and phosphorous are used.

In the present experiment performed on subject K.B., calcium and phosphorous reduced the 96 hour retention by factprs of 9.3 and 1.3, respectively, so that a reduction of 10.6 would be expected if the effect of both was additive when ingested together. Retention was actually reduced 40 times. Although it has been reported that the transport of phosphorous in the upper duodenum of the rat is increased by a factor of 3 by the presence of calcium (Chen et al, 1974), it is unlikely that such a synergistic effect could be totally responsible for the large reduction in retention observed. However, if lead is

absorbed by two separate pathways, one which it shares specifically with calcium and the other specifically with phosphorous, then the absolute changes in percentage retention of lead in subject K.B., caused by separate doses of calcium and phosphorous each saturating its specific pathway, could easily account for the change which occurred when they were both taken together.

6.4.2 Effect of different weights of calcium and phosphorous on the gastrointestinal absorption of ^{203}Pb

Although the full study on the response of retention of lead against weights of calcium and phosphorous was only performed on subject K.B., the effect of different weights of these minerals on retention was examined in four other subjects at the maximum weights and in three of these subjects at one tenth the maximum weights of calcium and phosphorous. Even though the scatter of the retention results of these subjects was considerable at these two different weights, the means were sufficiently far apart to confirm the overall response of the retention of subject K.B. against different weights of calcium and phosphorous.

Increasing weights of calcium and phosphorous resulted in progressively lower retentions of ^{203}Pb in the subject K.B. A similar effect was observed in rats by Meredith et al (1977) when ^{203}Pb was administered orally with different concentrations of calcium chloride. They found that the 5 day retention of ^{203}Pb decreased exponentially as calcium concentration increased, and that doses of calcium above a certain concentration did not reduce retention further. In the present experiment, however, the relationship between weights of calcium and

phosphorous and retention could be described by two negative exponentials. Unlike the results of Meredith et al (1977), increasing weights of calcium and phosphorous continued to reduce retention. The fit of the exponential function was not unique, but the presence of the more slowly changing second exponential does suggest that phosphorous was still reducing retention at high weights of these two minerals.

The shape of the curve of 96 hour retention of subject K.B. against weight of minerals could be explained by the early rapid fall of retention caused by calcium and the later slower reduction caused by phosphorous. Meredith et al (1977) concluded that two mechanisms for the transport of lead across the gut wall were responsible for the relationship between retention and calcium concentration found in their experiment. One of the mechanisms was suggested to be a common pathway for the absorption of calcium and other minerals, such as lead, from the gut. This had been suggested before by Six and Goyer (1970). In the present experiment, the other mechanism could be a common pathway for the absorption of phosphorous and lead as suggested by Smith et al (1978). The results could again be explained, therefore, if lead is absorbed by two separate pathways, one which it shares specifically with calcium and the other specifically with phosphorous.

The response of 96 hour retention with different weights of calcium and phosphorous has three distinct regions, A, B, and C shown in figure 6.3.2.

a) Region A

In this region, calcium and phosphorous did not reduce the retention of ^{203}Pb, even though the weights of minerals were approximately 150 times the weight of lead at the shoulder of the curve between region A and B. A similar effect was observed by Conrad and Barton (1978) in rats given ^{203}Pb intragastrically with different amounts of carrier, lead chloride. Absorption was not reduced until a carrier weight was used 10^5 times greater than the lowest carrier weight. This suggests that, in region A, the common pathways for lead, calcium and phosphorous are able to accommodate the concentrations of these elements present in the lumen, or it suggests pathways that are separate for all three. Barton et al (1978) found, however, that when equimolar quantities of ^{203}Pb chloride and calcium chloride were injected into isolated duodenal segments of the rat, absorption of ^{203}Pb was reduced. Approximately the same reduction in absorption was found by Meredith et al (1977) when they gave rats oral ^{203}Pb chloride and calcium chloride, except that a calcium/lead ratio of 10:1 was required. Although these results were obtained from animal experiments, they appear to contradict the finding of no effect of calcium and phosphorous on retention in region A.

In these three animal experiments of Conrad and Barton (1978), Barton et al (1978) and Meredith et al (1977), however, there are differences in the percentage of ^{203}Pb absorbed by control rats. The retention of lead by control rats in the experiments of Conrad and Barton (1978) and Barton et al (1978) was 4% and 18%, respectively, of the administered dose, and it was 2.3% in those of Meredith et al (1977).

Although the methods used to measure the gastrointestinal absorption of lead differed in the two experiments of Conrad and Barton (1978) and Barton et al (1978) when compared with that of Meredith et al (1977), the results are comparable as both sets of workers effectively measured ^{203}Pb in the body without the unabsorbed fraction of ^{203}Pb. Conrad and Barton (1978) and Barton et al (1978) measured whole body radioactivity, with intestinal segments removed from the carcass, at the time of maximal absorption of ^{203}Pb (4 hours) after administration of the dose. Meredith et al (1977) measured whole body retention at 120 hours, by which time the unabsorbed fraction of ^{203}Pb should have been excreted. The excretion of previously absorbed lead in this last experiment would produce a slight under estimation of absorption. All the rats were fasted overnight in each of the experiments, so it is unlikely that the presence of food in the gut influenced absorption.

There were differences, however, in the solutions administered to the rats. Conrad and Barton (1978) and Meredith et al (1977) gave rats lead doses in 1 ml of distilled water (neutral pH), but Barton et al (1978) administered the doses in a solution of pH 4.0. In the same work, Barton et al (1978) found that the solubility of lead was dependent on the pH of the solution; lead precipitating at neutral pH. Conrad and Barton (1978) showed that the solubility of lead in the intestinal contents increased absorption, and that there was a difference in absorption of lead from an oral dose compared to that from an isolated duodenal loop. The increased absorption of lead from the duodenal loops was attributed to differences in the pH of the lead solution, prolonged exposure of lead to absorptive cells of closed loop, or a possible gastric inhibitor of lead absorption.

The low pH of the solutions administered by Barton et al (1978) would render lead and calcium more soluble in the intestinal contents. Calcium, like lead, is more soluble in solutions of low pH (Wilkinson, 1976). A larger fraction of lead and calcium would be more available for absorption, than if the doses had been given in neutral pH solutions. The common pathways of absorption would not be able to accommodate these larger fractions, and competitive inhibition of lead absorption by calcium would occur. The result would be a higher absorption of lead in the absence of calcium and marked reduction of lead absorption with concomitant calcium. These were the differences between the results of Barton et al (1978) and those of the other two groups.

Therefore, the absence of any effect of increasing weights of calcium and phosphorous on absorption of tracer lead in region A, although similar to the effect of increasing weight of intragastrically administered carrier lead in rats, has not been entirely confirmed in animal studies. There is a suggestion that such a non interactive region exists but the different experimental conditions of the animal studies hinder any positive confirmation.

b) Region B

Over the region B, the whole body retention of ^{203}Pb fell very rapidly with increasing weight of calcium and phosphorous, so that it is unlikely that lead, calcium and phosphorous have separate absorptive pathways. Doubling the weight decreased retention by a factor of 5. Barton et al (1978), however, observed a decrease by only a factor of

2 on increasing the weight of calcium by a factor of 10^4, and the same decrease in retention occurred in the work of Meredith et al (1977) when the weight of calcium was increased tenfold. Both groups of workers, therefore, observed much smaller reductions in retention than that found in this study.

As the effect of calcium on the absorption of lead in subject K.B. was found to be much greater than that of phosphorous, calcium was probably responsible for most of the reduction in retention in region B, by competing with lead for some common transport mechanism (Six and Goyer, 1970). Competitive inhibition of this type is a characteristic of active transport, but cannot be used solely to distinguish this from other types of membrane permeation (Wilson, 1962). Nevertheless, calcium is mainly absorbed by active transport across the intestinal wall (Schachter et al, 1960), and the inhibition of lead absorption could be caused by lead partially sharing the same active transport system.

Although the bulk of the evidence from animal experiments suggests that lead is passively diffused across the intestinal wall (Grunden and Stantic, 1975; Blair et al, 1978), most is derived from an <u>in vitro</u> procedure, the everted sac preparation of Wilson and Wiseman (1954). A ratio of serosal-to-mucosal concentration of lead above unity indicates the existence of active transport. Grunden and Stantic(1975) found ratios of 1.10 ± 0.16, 1.15 ± 0.12 and 1.32 ± 0.09 for the duodenum, jejenum and ileum which does suggest slight active transport even if the ratios are not as great as that achieved using calcium, which was 7.57 ± 1.26 for the duodenum segement.

The everted sac technique has been used extensively in research into intestinal absorption (Smyth, 1972), but there are indications that the application of the technique may be invalid in the work of Grunden and Stantic (1975). They used an incubation time of 90 minutes in their experiments, and it has been found that after 60 minutes of incubation, sac preparations can deteriorate (Smyth, 1972). It was also not clear from their work how the serosal-to-mucosal ratios were measured. If the concentration of ^{203}Pb was measured then the results may be in error, as Blair et al (1979) have shown that with the everted sac preparation the transport of lead is related to water movement. Serosal-to-mucosal ratios should be measured using the total fluid content of ^{203}Pb, as dilution of the serosal lead would decrease the ratio if concentrations were measured.

It has been shown that the presence of bile in the intestinal lumen can increase the gastrointestinal absorption of ^{203}Pb in the rat by a factor of 2 (Cikrt and Tichý, 1975; Conrad and Barton, 1978). There was no reference to the presence of bile in the sac preparations in either of the work of Grunden and Stantic (1975) or Blair et al (1979). Therefore, the conclusion of Grunden and Stantic (1975) that active transport of lead does not exist, may not be true.

Evidence that suggests lead may share the same active transport system of calcium was found by Barton et al (1978). They discovered that, in vivo, lead bound to two heat-stable intestinal mucosal fractions which also bound calcium. Substantial amounts of lead and calcium were found in both fractions with 35.9% of the lead bound to the higher molecular weight fraction and 8.0% bound to the lower molecular weight

vitamin D-induced calcium binding protein (CaBP). The addition of calcium diminished the amounts of lead bound to the high molecular weight protein and vitamin D dependent CaBP by factors of 2.5 and 8, respectively. Vitamin D has also been shown to increase lead absorption in rats (Sobel et al, 1940), which supports the findings of Barton et al (1978) that lead binds to vitamin D-induced CaBP. The sharing of binding sites with calcium and the vitamin D dependence suggests that lead has an affinity for the active transport responsible for calcium absorption.

In summary, region B of the response of whole body retention against weights of calcium and phosphorous could describe competitive inhibition of lead by calcium for binding sites on the vitamin D-dependent CaBP (Quarterman et al 1978a; Waldron and Stöfen, 1974), which is part of the active transport mechanism known to be responsible for calcium absorption from the small bowel.

c) Region C

In this region, the reduction in retention by increasing weights of calcium and phosphorous was much less than in region B. A change in retention by a factor of 4 was only achieved by increasing the weights by a factor of 10. The marked discontinuity between regions B and C could be explained if the shared binding sites on the vitamin D-induced CaBP become saturated with calcium, another characteristic of an active transport system (Wilson, 1962). The maximum capacity of the active transport component of calcium absorption in normal humans has been calculated to be 8.2 mg/kg/day (Marshall, 1976 a). With subject K.B.,

weighing 72 kg, and assuming a transit time through the small bowel of 4 hours (Eve, 1966), saturation would occur with an ingested calcium dose of 98 mg. This agrees quite well with the actual dose of 70 mg calcium ingested by the subject at the discontinuity of the response curve. The reduction in retention in region C, therefore, could be primarily caused by competition between lead and phosphorous for common pathways of absorption as suggested earlier.

SECTION 7

DISCUSSION

7.1 Results of the four gastrointestinal absorption experiments

The results of the preceding four sections (3.0-6.0) show that eight human subjects, who had fasted adequately, absorbed approximately 70% (table 7.1.1) of a quantity of lead comparable to that of the normal intake per day of dietary lead. Food in the gut, particularly the calcium and phosphorous content of that food, reduces the gastrointestinal absorption of lead considerably.

Variation in the gastrointestinal absorption of lead is small between subjects who have fasted adequately. The coefficient of variation for the 96 hour retentions of the eight subjects is 4.6% (table 7.1.1). When there is competition between lead, calcium and phosphorous for absorption in the gut, however, individuals absorb different amounts of lead. This effect may be caused by differences in the efficiency of absorption of calcium and phosphorous between individuals, if there are common pathways of absorption of these elements and lead in the gut.

Phang et al (1969) found individual variation in the ability of human subjects to utilize an increased dietary calcium load, and Marshall (1976 a) showed, by using a simple compartmental model, that the fractional rate of absorption of calcium in 152 normal subjects showed

TABLE 7.1.1

% Whole body retention of orally ingested ^{203}Pb

in eight fasted subjects

SUBJECT	96 HOUR RETENTION (%)
K.B.	65.42 ± 0.23†
J.B.	71.70 ± 0.27
B.C.	73.93 ± 0.24
G.E.	71.71 ± 0.27
E.H.	75.82 ± 0.69
B.S.	67.44 ± 0.38
D.W.	71.60 ± 0.23
M.W.	69.95 ± 0.66
Mean	70.56
S.D.	3.27
S.E.	1.16

All doses included carrier lead.

† ± 1 standard deviation.

a log normal distribution with values ranging from 0.2 $hour^{-1}$ to 1.4 $hour^{-1}$. Similarly the fractional rate of absorption of phosphorous was also shown to be log normally distributed in normal humans, with a similar range to that of calcium (Marshall, 1976 a).

Although the solubility of lead in intestinal contents was shown by Conrad and Barton (1978) to affect the absorption of lead, and, likewise, the presence of chelating agents (Garber and Wei, 1974), the experiments in section 6.0 were designed to study the effect on absorption of only calcium and phosphorous. Any differences in absorption observed between different subjects were probably caused by individual differences in the efficiency of shared absorptive pathways used by lead.

The effects of calcium and phosphorous on the gastrointestinal absorption of lead were produced with levels of these three elements which are physiological, and which occur in a normal human diet. The weight of carrier lead, 300 µg of lead chloride, is at the top of the range, 200-300 µg, estimated by the WHO (1977) to be the dietary lead consumed per day by humans. The maximum weights of calcium and phosphorous were 0.7 g and 0.5 g, respectively, whereas the calcium and phosphorous intake of reference man is 1.1 g calcium per day and 1.4 g phosphorous per day (ICRP, 1975). Even a tenth of the maximum weights of calcium and phosphorous produced a considerable reduction in absorption, and the large range of percentage lead absorbed, when taken between meals by the subjects in section 3.0, was probably caused by residual calcium and phosphorous in the gut.

These findings may significantly affect any assessment of the possible risks of environmental lead to certain population groups and to the population as a whole. It is emphasised, however, that experiments were not carried out with dietary lead in its natural state. Dietary lead will exist in different chemical forms which have been shown to affect the absorption of lead, and this has not been investigated in this thesis. Rabinowitz (1974), however, found that the greatest effect on lead absorption was produced by the presence of food in the gut and not by different chemical forms of lead.

Lead must be in solution before it is absorbed and even the most 'insoluble' lead salts and metallic lead if finely divided are soluble in digestive juices (Sollman, 1957). Chamberlain et al (1978) showed that 14% of insoluble ^{203}Pb chromate was absorbed in a human subject, which they regarded as typical for unspecified compounds and dietary states. Rabinowitz (1974) found that the absorption rates of the tracer, lead nitrate, and of food lead when eaten together were nearly the same.

The lead was ingested as a single dose by the subjects in this thesis unlike the normal exposure of humans to multiple intake of unknown frequency and duration. The effects of calcium and phosphorous on the absorption of lead would be considerably greater in a single dose, but even low concentrations of calcium and phosphorous, probably more representative of multiple intake, were shown to reduce the absorption of lead.

The effects of calcium and phosphorous on the absorption of oral lead

have a special significance in children, women and individuals who appear to be susceptible to the toxic effects of lead (section 1.4). Dietary surveys of urban poor groups have observed low calcium intakes in children. In one study by Stubbs (1965) in Texas, mean calcium intakes of pre-school children of white urban poor were 73 percent and those of negro pre-school children were 47 percent, respectively, of that recommended by the National Research Council (1968) as the daily allowance for calcium. In a nationwide survey conducted in the United States in 1965, it was shown that the average diets of girls (15 to 17 years) and of women (from 35 years on) were about 35 percent below Recommended Dietary Allowances for calcium (Krause and Mahan, 1979). Diets deficient in calcium would cause increased absorption of food and water lead, higher body burdens of lead and, consequently, apparent increased susceptibility to the toxic effects of lead.

The doubts expressed by the WHO that the accepted level of 10% absorption may not apply to lead in water and that dietary constituents may also alter this percentage (section 1.0), have been substantiated by the present findings. The highest percentage absorption of lead occurred, seven times the accepted level, when it was ingested in water with no added minerals. Lead in water, particularly in 'soft water', may present a serious hazard to the general population. The accepted level of 10% absorption would certainly not apply if diets were deficient in calcium, and, to a lesser extent, deficient in phosphorous. Because of the relatively large quantities of calcium and phosphorous consumed in food compared to lead, they have a profound effect on the absorption of lead which can vary from individual to individual. Therefore, to establish a mean percentage uptake of

dietary lead is extremely difficult, but it should be recommended that, particularly in children, the dietary levels of calcium and phosphorous should not fall below normal requirements.

7.2 Interrelationship between lead, calcium and phosphorous absorption

From the review of the literature and the results of the lead absorption experiments performed so far, it is possible to suggest the mechanisms by which lead is gastrointestinally absorbed, and how calcium and phosphorous interfere with lead absorption. It must be emphasised that none of the experimental work performed can directly prove the suggested interrelationship between lead, calcium and phosphorous. Before describing this proposed interrelationship, it is necessary to summarize the present concepts of calcium and phosphorous absorption in the gut.

7.2.1 Active and passive transport of calcium and phosphorous

Both calcium and phosphorous are absorbed by active and passive transport. Active transport of calcium is dominant in the upper small intestine, while diffusion appears to make a relatively greater contribution to absorption in the lower small intestine (Marshall, 1976 a). Phosphorous is absorbed throughout the whole small intestine but the active component is small in comparison to the diffusion component (Marshall, 1976 a). There is a correspondence between CaBP levels and the efficiency of calcium absorption, with CaBP levels highest in the upper small intestine and lowest in the lower small intestine (Wasserman and Corradino, 1973). Although phosphorous does

not appear to bind the CaBP and no phosphorous binder was found in the lower small intestine of the chick (Wasserman and Taylor, 1973) there is evidence to suggest that phosphorous may be transported by a carrier mediated transport in the upper small intestine of man. In the normal human, the plasma levels of calcium and phosphorous rise at the same rate and reach a maximum at approximately 2 hours after their oral administration. It is unlikely that such rapid absorption of phosphorous could occur by diffusion alone. In a human with calcium malabsorption, however, plasma levels of calcium and phosphorous remain low and do not peak at 2 hours. Plasma levels of phosphorous rise later and continue to rise over a 2-4 hour period which suggests diffusion of phosphorous in the lower small intestine (Marshall, 1976 a).

7.2.2 Inhibition of the absorption of lead by calcium and phosphorous

Approximately 70% of an oral dose of ^{203}Pb, mixed with normal dietary quantities of lead, is retained at 96 hours when there is no concomitant calcium and phosphorous present in the gut. If lead and calcium shared the same pathway of absorption in the upper small intestine, it should be expected that small amounts of dietary lead should be absorbed with the same efficiency as small amounts of calcium. The net amount of calcium absorbed in normal humans, however, is lower at approximately 31% (Saville, 1973), but the net amount is less than true absorbed calcium by an amount equal to the endogenous faecal calcium. True absorbed calcium can be as high as 60% when the amount of dietary calcium is very low (Wilkinson, 1976). The measurement of gastrointestinal absorption of lead is not complicated by large amounts of endogenous lead, as both the normal body content of

lead and, consequently, the amount of endogenous faecal lead are much lower than those of calcium. Small amounts of lead and calcium, therefore, appear to be absorbed by the gut with the same efficiency.

The addition of calcium and phosphorous to the oral lead dose will mean competitive inhibition between lead and calcium, and to a lesser extent between lead and phosphorous giving rise to low absorption of lead. The synergistic effect obtained by adding phosphorous to calcium could be caused by increased competition of both calcium and phosphorous with lead for specific-carrier binding sites in the upper small intestine or by an intracellular enhancement of calcium absorption by phosphorous. Calcium is thought to be transported across the intestinal cell by the mitochondria (Wilkinson, 1976), on which it is taken up by an energy dependent process (Mela, 1969; Chance and Mela, 1966; Ghosh and Chance, 1970). Increasing the concentration of phosphate in a bathing medium containing monkey kidney cells increased the uptake of calcium in the mitochondrial compartment (Borle, 1971), and this may also occur in the intestinal absorption cell. Lead may utilise the calcium carrier system of the mitochondria in isolated heart mitochondria (Scott et al, 1971), so that the increased uptake of calcium in the presence of phosphate could reduce the uptake of lead on the mitochondria in the intestinal cell. Lead is also passively bound to isolated heart mitochondria, and in the presence of phosphate virtually no lead is available to interact with the mitochondrion (Koeppe and Miller, 1970; Brierley et al, 1971; Cardona et al, 1971). If intracellular binding of lead is reduced, lead transported into the cell could diffuse out again into the lumen of the small bowel when the concentration of lead in the lumen was

lower than that in the cell. The result would be a reduction in the amount of lead absorbed giving lower whole body retention.

Unabsorbed lead further down the small bowel beyond the region of maximal calcium absorption, could still be absorbed by the phosphorous transport system. The true absorption of phosphorous at low dietary levels is approximately 100% (Wilkinson, 1976). If the absorption pathways of phosphorous and lead are shared, the remaining unabsorbed lead should be completely absorbed giving nearly 100% retention. As this does not occur, lead may have less affinity for the absorption pathways of phosphorous than those of calcium. This was suggested by the greater effect of calcium than that of phosphorous on the absorption of lead in subject K.B.

A fraction of the remaining lead, however, may be unavailable for absorption. The solubility of lead in the intestinal contents affects absorption (Conrad and Barton, 1978). As the pH of the small intestinal contents rises from upper to lower regions (Fordtran and Locklear, 1966), lead may complex with phosphate and oxalate becoming less available for absorption. The remaining unabsorbed or complexed lead passes into the large bowel from which it is eventually excreted in the faeces.

SECTION 8

COMPARTMENTAL ANALYSIS OF THE KINETICS OF ORAL ^{203}Pb INGESTED WITH AND WITHOUT CALCIUM AND PHOSPHOROUS IN FIVE SUBJECTS

8.1 Introduction

In animals, changes in the dietary levels of calcium and phosphorous affect the absorption, distribution and excretion of lead (sections 1.5.1-1.5.3). The results so far in the present work have shown that, in humans, minerals also affect absorption, and, possibly, distribution and excretion of tracer lead when they are ingested with a single dose of tracer. In section 5.0, the ingestion of minerals with ^{203}Pb was found to reduce the levels of ^{203}Pb in the blood of two subjects, K.B. and D.W., when these levels were expressed as percentages of 96 hour retention. The degree of change in subject D.W., however, was much greater, which could indicate possible individual variation in the distribution of ^{203}Pb between the two subjects. However, his levels of ^{203}Pb in urine were also reduced when expressed in the same way as blood, whereas those of subject K.B. were not. It was suggested that the discrepancy could be caused by the 96 hour retentions of these two subjects not reflecting the absorption of ^{203}Pb accurately. As these retentions were very low, any unabsorbed ^{203}Pb in the body would have a considerable effect on the measurement of retention. The problem could not be resolved, however, with the

limited data available on distribution of ^{203}Pb in section 5.0.

These changes in the distribution of ^{203}Pb were caused by the total minerals, and direct evidence of an effect of only calcium and phosphorous has not been demonstrated. However, the change in absorption and excretion in ^{203}Pb caused by all the minerals (section 5.0) was very similar in degree to that caused by calcium and phosphorous alone (section 6.0), which suggests that these two minerals were mainly responsible for the distributive changes.

As calcium and phosphorous are mainly responsible for reducing the absorption of lead in the gut of humans, it is important, as outlined in section 1.5, that their effect on the distribution and excretion of lead should be examined more closely. This will help to evaluate their overall influence on the behaviour of lead in the body and on the susceptibility of individuals to the toxic effects of lead.

The different states of a tracer, characterized by the distribution (in a body fluid, in an organ) or by chemical form (protein bound, free state or by-product), may be described by a system with a finite number of compartments. A model can be built with these compartments and with defined probabilities of transfer of tracer between the compartments. This model can then be used to describe the kinetics of the tracer in the system. The model may be developed from some a priori knowledge about the system, from the experimental data, or by trial and error and the intuition of the research worker. Once the appropriate model is decided upon, it can be represented in a mathematical form. The response of any system, even non linear, to a tracer is always linear (Berman et al, 1968 a),

provided the following assumptions hold.

(1) the system is in a steady state,

(2) there is complete mixing of tracer and tracée material in each compartment and this mixing is rapid in comparison with the rates of transfer of material between compartments,

(3) the amount of tracer added to any compartment is negligible in comparison to the size of the compartment (Jacquez, 1972).

The system can be described mathematically by linear differential equations, which can be solved by either analytical or numerical procedures. The solution of these equations gives values of the model parameters that can be used to reproduce the experimental data. If satisfactory agreement is not obtained between calculated and experimental data, the model may be revised until agreement is reached.

The advantages and disadvantages of compartmental analysis have been described by Berman (1974). Mechanistic, biochemical and mathematical descriptions of systems may be obtained as an aid in understanding physiological processes, such as metabolism. Compartmental models can be built compatible with the resolution of data, they can handle discrete as well as incomplete data, and all the information contained in a tracer response curve can be used. However, care should be taken interpreting the results of analysis, as model parameters are frequently identified with physiological entities without adequate confirmation, and this can be highly speculative. Compartmental modelling may also be cumbersome, and models are sometimes arbitrary in structure or loosely defined.

8.1.1 Review of models in literature

Several attempts have been made to describe the kinetics of lead in the human by linear compartmental models. Bernard (1977) used a mammillary compartmental model, and, with published data on baboons and reference man (ICRP, 1975), generated equations describing the distribution of lead in organs and tissues and the retention of lead in the human body. However, no details were given of how the number of compartments or pathways between compartments were chosen.

An attempt by Rabinowitz et al (1976) was based on experimental studies on five healthy men using stable lead tracers. The subjects ate constant low lead diets for 1-124 days, and each day the diets were supplemented with ^{204}Pb nitrate. The concentration and isotopic composition of lead was determined serially in blood, urine, faeces and diet, and less frequently in hair, nails, sweat, bone and alimentary secretions. A three compartmental model consisting of blood, soft tissue and bone was developed from the observed isotopic composition. The authors stressed, however, that there could be many more physiological pools of lead. Linear differential equations with time-independent rate constants were used to describe the observed concentration of tracer lead in blood and in other tissues and fluids. Their results included the steady-state pool sizes, mean lives, and the transport of lead in their model.

Batschelet et al (1979) used the model developed by Rabinowitz et al (1976) to assess the effect of increasing daily input from the air on lead levels in the blood. They included two more compartments to

represent the lungs and gastrointestinal tract, and, using the data and the results of kinetic analysis given in Rabinowitz et al (1973), obtained a solution to the differential equations describing their model. Their results showed that the blood level of lead depended linearly on the intake of lead from the air, provided the kinetics of lead could be described by linear processes.

All these models were developed to describe the behaviour of lead in a steady state, and not that of a single dose of tracer lead taken up in the body. Rabinowitz et al (1974), however, had performed one experiment in which a human subject received a single dose of ^{204}Pb. They found that the isotopic composition of ^{204}Pb and normal lead in red cells and plasma differed widely in blood samples taken at 6 hours after ingestion of ^{204}Pb. They were also unable to account for all the absorbed ^{204}Pb in the blood compartment at 6 hours. They concluded that the lead temporarily 'disappeared' into a compartment different to blood and returned to the blood during the next day or two. They suggested that for short term studies a model suitable for analysis of lead kinetics would have to include a plasma, red cell and another compartment different to that of the blood compartments.

Chamberlain et al (1978) suggested a similiar change to the three compartmental model of Rabinowitz et al (1974). They proposed that as the initial uptake of lead from lung and gut was in plasma, the lead would distribute from the plasma to red cells, bone and other storage sites.

Compartmental models developed to describe the steady state levels of

lead in the human appear to be inadequate to describe the short term kinetics of a single tracer dose of lead. Furthermore, two of the models assumed constant input of lead from the environment, and the third allowed for changes to occur in the input of lead from the air. None of the models allowed for changes in the input of lead from gut and the effect of such changes on the model parameters. A model that describes the short term kinetics of ^{203}Pb and the effect of calcium and phosphorous on the absorption of ^{203}Pb could be complicated. The two extra compartments suggested by Rabinowitz et al (1974) and the two compartments added to their three compartmental model by Batschelet et al (1979), gives a model with 7 compartments.

8.1.2 Choice of compartments

The first step in the compartmental analysis of the kinetics of a tracer in a system is to determine the compartments of the model. The response of the tracer in the system can often be used to find the number of compartments. For example, when a tracer is injected rapidly into the blood circulation, the number of exponentials required to fit the plasma clearance curve of the tracer is chosen as the number of compartments (Berman et al, 1962 a). However, when the entry of the tracer into the blood is relatively slow, as in gastrointestinal absorption, no information may be obtained from the exponential analysis of tracer levels in the plasma. The initial selection of the compartments of a model describing the behaviour of gastrointestinally absorbed lead in the human will have to be made from the known distribution of tracer lead in humans and animals.

Rabinowitz et al (1974; 1976) developed a compartmental model consisting of blood, soft tissue and bone compartments. They found that their model was inadequate to explain the short term kinetics of tracer lead in humans. They suggested, however, that such a model would require the blood compartment divided into plasma and red cell compartments. A separate plasma compartment was also suggested by Chamberlain et al (1978). Other compartments may be found from animal studies in which the distribution of tracer lead has been extensively examined. Lloyd et al (1970) measured the distribution of intravenously administered ^{210}Pb in a beagle at 28 days post injection. They determined the ^{210}Pb content of 19 different bones, and 24 different tissues, and found that 24% of the administered dose was in the skeleton, 8% in the liver, 3% in the blood and 0.5% in the kidneys. The liver and kidneys were the organs with the highest ^{210}Pb content. Cohen (1970) administered intravenous ^{210}Pb to baboons, and, in one baboon sacrified at 24 hours, he measured the ^{210}Pb content in 13 different tissues. He found that the ^{210}Pb contents of liver and kidney were the highest of all tissues at 12.8% and 3.48% of the administered dose, respectively. Another study on the distribution of tracer lead was performed by Potter et al (1971), in which a single dose of oral ^{203}Pb was administered to a calf. The distribution of ^{203}Pb was measured in bone and 17 different tissues and fluids, and 0.4% of the administered dose was in the liver, 0.4% in the bone and 0.1% in the kidneys. Barltrop and Khoo (1975) fed rats ^{203}Pb as part of their diet for 48 hours, and sacrificed the animals at this time. They measured 0.06% of the administered dose in the liver, 0.03% in the kidneys, 0.02% in the femur and 0.002% in the blood.

The liver and kidneys of different animals, therefore, appear to accumulate tracer lead, even when it was administered by different routes. If it is assumed that the excretory function of these two organs is the same in the human as in animals, it suggests that the liver and kidneys will also accumulate tracer lead in man as they have been found to do with stable lead (Goyer and Rhyne, 1973). The wall of the small bowel has also been shown to accumulate tracer lead, although this has been mainly demonstrated in in vitro studies. Grunden and Stantic (1975) showed that 55% of the initial mucosal radioactivity of ^{203}Pb was accumulated in the wall of everted sacs prepared from the small bowel of rats. Although doubts were raised about the long incubation time of 90 minutes in this study (section 6.4.2), accumulation of lead in the wall of the small bowel was confirmed by the similar studies of Blair et al (1979). They showed rapid and massive binding of tracer amounts of stable lead after incubating everted sacs for the more accepted length of time of 60 minutes. Conrad and Barton (1978) confirmed the findings of these in vitro studies in experiments on rats injected intravenously with ^{210}Pb. The ^{210}Pb content of the small bowel remained at approximately 3% of the injected dose for the first 8 hours, and then decreased rapidly with a 24-hour half life.

The evidence from animal studies suggests that compartments representing wall of small bowel, liver and kidney should be added to the steady state model of Rabinowitz et al (1974; 1976). The original blood compartment should be divided into plasma and red cells, and the bone and soft tissue compartments retained. These compartments may then be sufficient to build a preliminary model describing the short

term kinetics of tracer lead in the human.

8.1.3 Experimental data requirements

Once the compartments have been chosen, it is necessary to determine the interconnections or pathways between compartments. The most general model would result if tracer is allowed to move in both directions between compartments, and only more information about the system may decide the selection of a particular model. Such information might come from experimental data describing the kinetics of the tracer from the system, or from certain physiological and biochemical restrictions known about the system which might impose a certain structure upon the model.

The experimental data should be measures of the response of the tracer in each compartment of the system, and, if this is the case, the parameters of the model can be determined uniquely (Berman et al, 1962 a). If the data are insufficient, assumptions may be introduced making the model simple and of a certain class, but this is not always sufficient for uniqueness (Berman, 1963).

In the model suggested in section 8.1.2, serial measurements of tracer can be made directly from plasma and red cells. When radioactive tracers are used, external measurements of radioactivity can be performed over selected areas of the body that predominantly include the compartments of interest. Surface radioactivity measurements over small bowel, liver and kidney will provide information on tracer levels in these three organs, and information on soft tissue and bone levels may

be obtained from areas in which these tissues predominate, such as the calf and ankle. Similiar measurements were performed by Neer et al (1967) and Cohn et al (1965), to obtain information on the kinetics of ^{47}Ca in normal adult males. In addition, Cohn et al (1965) measured whole body radioactivity of ^{47}Ca to provide information on tracer levels in all the compartments.

Once all the information on the system has been collected, it can be used to decide on a preliminary structure of the model. This can then be represented mathematically by a set of linear differential equations.

8.1.4 Model solution

The solution of the set of linear differential equations, which characterize the model, gives values of the parameters that can be used to reproduce the experimental data. The solution may be obtained analytically, but, if the model is complex, the mathematical operations required can be difficult. A solution may be found numerically, however, and Berman et al (1962 b; 1965) have developed an integrated methodology of general use, programmed for digital computers in such a way that it can be used without understanding the sophisticated hardware and the complex mathematics. The program is called SAAM (Simulation, Analysis and Modelling), and the final version is SAAM25 (Berman and Weiss, 1967).

The SAAM25 program is described in Appendix D, but, in essence, it allows the setting up of the differential equations directly and allows the values of the variable parameters, such as rate constants between

compartments, to be adjusted until a satisfactory fit to the experimental data is obtained. This method is highly desirable because it calculates the final values of the variable parameters directly, yields measures of their uncertainties, can accept data in 'raw' form and requires no intermediate calculations. However, it has several disadvantages. It may be both difficult to decide on the number of compartments for the model, and to assign initial estimates for the values of the parameters. These initial estimates are required for a numerical solution. Convergence may also be slow due to interdependence of parameters when fitting the experimental data.

The SAAM25 program was originally developed for the solution of linear compartmental models, such as encountered in radionuclide tracer experiments, and has been used extensively to study the kinetics of calcium (Cohn et al, 1965; Neer et al, 1967; Phang et al, 1969; Birge et al, 1969). Of particular relevance to the proposed compartmental analysis in this thesis, was the work of Birge et al (1969) on the gastrointestinal absorption of ^{47}Ca in humans. They obtained an input function, representing the entry of ^{47}Ca into the plasma, by the deconvolution of ^{47}Ca levels in the plasma, and the characteristics of this input function were described by a compartmental model with 11 compartments. Using this model, they were able to distinguish clearly between the effects of disease and calcium loading on calcium absorption in human subjects. Similar results will be required from the compartmental analysis of the kinetics of orally ingested tracer lead, to explain the effects of calcium and phosphorous on the behaviour of the tracer in the body.

8.1.5 Testing the model

Finally, the model should be judged to be consistent and unique. Systematic deviations between calculated and observed values indicate the model is inconsistent and needs a greater degree of freedom. This can be done by the addition of new parameters. When systematic deviations do not occur, but the calculated parameter values have large standard deviations, the model is not unique. This can occur when the quantity of information contained in the experimental data is inadequate to completely define the model. New experimental data or additional physiological and biochemical information about the system is required to change the model. Convergence to a least squares solution should be obtained. Failure to do so may be caused by interdependence of parameters, which will occur when there are a number of compartments in series, and how well the initial estimates of the variable parameters have been chosen (Berman et al, 1962 b). A poor choice of initial estimates will mean that the adjustment of parameters in the iterative procedures will not be sufficient to significantly change the sum of squares, so that the solution will terminate with no convergence.

8.1.6 Summary

It appears possible that effects of calcium and phosphorous on the gastrointestinal absorption of lead may be studied by using a compartmental model. There is enough information in the literature to suggest a model to describe the distribution of lead in the human, and there should be enough experimental data available to test such a model

if a radioactive tracer such as ^{203}Pb is used in kinetic studies. Therefore, it was planned to perform paired kinetic experiments on five subjects, one experiment in which they ingested ^{203}Pb, and the other in which they ingested ^{203}Pb with calcium and phosphorous. Experimental data will be obtained from various *in vitro* and *in vivo* procedures, to test a linear compartmental model developed from information in the literature and observations from the experiments.

A successful model will then be used to try and explain the experimental anomalies described in section 8.1. It will also be used to check the theory that lead is absorbed by two pathways, one which it shares specifically with calcium and the other specifically with phosphorous. This theory was developed in sections 6.4.1 and 6.4.2 mainly from the results of experiments performed on one subject. Therefore, it is important that the theory should be supported by the results of further experiments using more subjects. Finally the model may provide further insights into the mechanisms responsible for the gastrointestinal absorption of lead and reasons why the susceptibilities of individuals to lead toxicity should vary.

8.2 Kinetic experiments

8.2.1 Introduction

The kinetic experiments were performed to provide sufficient data to help develop a compartmental model to describe the behaviour of oral lead in the body. This model may also show any effects on this behaviour of calcium and phosphorous ingested with the lead. The necessary requirements of the experimental data have already been outlined in section 8.1.3.

In section 6.4, it was suggested that, in the human, lead is absorbed by two pathways in the gut, one which it shares specifically with calcium and the other specifically with phosphorous. Using a model, the characteristics of these two absorptive pathways would be best studied at the region of the response curve of retention of lead against weights of calcium and phosphorous where the action of these minerals on retention is greatest. It was also suggested in the same section that the common lead/calcium pathway was saturated by the maximum weights of calcium and phosphorous, whereas the common lead/phosphorous pathway was not. If possible, this should also be confirmed by the use of the model.

8.2.2 Materials and methods

a) Oral doses of ^{203}Pb chloride, $CaCO_3$ and $NaH_2PO_4.2H_2O$

The five subjects, K.B., J.B., B.C., G.E. and D.W., whose details are listed in section 11.1, took part in the paired kinetic experiments

performed in this section. The subjects followed the same fasting regime described in previous sections and, in the first of the paired experiments (Kinetic 1.), ingested ^{203}Pb chloride and 300 µg of lead chloride in 100 ml of distilled water. In the second experiment (Kinetic 2.), they ingested $CaCO_3$ and $NaH_2PO_4.2H_2O$ mixed in 150 ml of distilled water immediately after the dose of lead.

Four of the subjects, K.B., J.B., B.C. and G.E., received weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ ('half weights') calculated to reduce their 96 hour retentions by 50% of those found in the Kinetic 1. experiments. A reduction of this order should give retentions at the region of the response curve of 96 hour retention against weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ where the effects of these minerals on lead absorption are probably greatest. The response of subject K.B. was found to be approximately exponential in this region, and the contribution of the second exponential term was only 8% (section 6.3). Therefore, the approximate 'half weights' were calculated using exponential interpolation or extrapolation from the 96 hour retention of each subject obtained with no $CaCO_3$ and $NaH_2PO_4.2H_2O$ added to the dose of ^{203}Pb and those values obtained with one tenth of the maximum weights added (table 6.3.1). One of the subjects, D.W., received the maximum weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ to investigate the responses of the absorptive pathways of lead to these large weights.

The doses of ^{203}Pb given to the subjects in the Kinetic 1. experiments were the same as that given the first subject studied, D.W. This dose was found to be sufficient to allow <u>in vivo</u> measurements, particularly surface radioactivity measurements, to be performed up to 8-9 days after

the ingestion of the dose. The statistical error of the surface radioactivity measurements at 8-9 days was just acceptable (section 11.12) with a counting time of 20 minutes, which the subjects could comfortably tolerate without undue movement.

As the 96 hour retentions of ^{203}Pb in the Kinetic 2. experiments were expected to be 50% lower than those found in the Kinetic 1. experiments, the doses of ^{203}Pb given were approximately 50% higher. The measurements performed in both experiments, therefore, should be statistically comparable. It was expected that fewer in vivo measurements would be performed on subject D.W. in his Kinetic 2. experiment, as his retention will be less than the other subjects because of the larger weights of calcium and phosphorous he ingested. The doses of ^{203}Pb and weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ given to each subject are shown in table 8.2.1.

b) Whole body counts

Whole body counts were performed as described in section 11.3, and at least six readings on separate days were obtained from 96 hours onwards. The retentions of 96 hours and the half times of retention from 96 hours onwards were calculated as in previous sections.

c) Gamma camera studies

Gastrointestinal tract images were recorded, as described in section 11.4, at approximately every hour for the first 12 hours, at 16, 20 and 24 hours and then on every day up to 96 hours. Satisfactory images could not be recorded on later days because of low count rates.

TABLE 8.2.1

^{203}Pb doses and weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$

SUBJECT	KINETIC 1.	KINETIC 2.		
	^{203}Pb (μCi)	^{203}Pb (μCi)	$CaCO_3$ (g)	$NaH_2PO_4.2H_2O$ (g)
K.B.	258	504	0.087	0.126
J.B.	247	521	0.110	0.158
B.C.	250	500	0.200	0.290
G.E.	250	450	0.175	0.251
D.W.	248	450	1.750	2.513

d) Profile scan studies

Profile scans of ^{203}Pb radioactivity in subjects and standards, and of backgrounds were performed, as described in section 11.5, at approximately every hour up to 12 hours, at 16, 20 and 24 hours and then once a day until the end of the study. In addition to the serial profile scans performed on the subjects after they had ingested ^{203}Pb, single profile scans were also performed on each subject after the administration of ^{113m}In, ^{113m}In colloid and ^{82}Br on separate occasions. Profile-scanner counting conditions for the appropriate radionuclide were set using the values listed in table 11.5.1. Data was punched on to paper tape, which was then fed into a Univac 1100 computer via a Tektronix 4051 intelligent terminal.

Profile scans were first aligned using the digital marker corresponding to the position of the xiphisternal joint, and marker counts were edited from the scans. Backgrounds were subtracted and the profiles were smoothed and restored by the methods described in Appendix A.1. The number of points chosen to smooth the profiles depended on the convergence of the restoration procedure, and it varied from 13 points for the first profile, 45 minutes after the ingestion of ^{203}Pb, to 25 points for the last profile, 9 days later. The total counts in the profiles were also calculated.

The contributions of ^{203}Pb in the blood and 'soft' tissue extracellular fluid (E.C.F.) were then subtracted from these profiles. The term 'soft' tissue E.C.F. and the rational for subtraction is discussed in section 11.7. Blood and 'soft' tissue E.C.F. backgrounds were

represented by the profiles obtained with ^{113m}In and ^{82}Br, respectively, after these profiles had been smoothed, restored and modified by the appropriate factors. The reasons and assumptions for using ^{113m}In and ^{82}Br are described in section 11.7.1 and the calculations required to obtain the factors are given in section 11.7.5. Subtractions were performed using computer programs in Appendix E. After subtraction of the ^{203}Pb blood and 'soft' tissue E.C.F., there was still a background of residual ^{203}Pb. However, the 'soft' tissue E.C.F. background was fitted by eye to this residual ^{203}Pb background and subtraction gave a profile consisting of peaks with no significant background.

These final profile scans were then compared to scintigrams performed at approximately the same time, and the distribution of peaks in the profile scans was correlated anatomically to the distribution of ^{203}Pb uptake in the scintigrams. Any profile peak which could be identified with a particular organ visualised in the scintigram, such as the liver, was then selected for further analysis. Modified Gaussian functions, specific to particular organs, were then fitted to the corresponding organ profile peaks, and only height and position of peak parameters were allowed to vary. The fitting was done using parametric and non-linear least squares procedures from SAAM 25 (1967). The number of counts under each function and the standard deviation of that number (Bevington, 1969), were calculated using computer program E.1.14. The percentages of ingested dose of ^{203}Pb in the organs, at particular times after the start of the experiment, were calculated from the ratio of the counts in the organ profile to the counts in the whole body profile, multiplied by the percentage retention of ^{203}Pb in the body.

e) Surface radioactivity measurements

Surface radioactivity measurements were performed (section 11.6) at time intervals similar to those used for profile scan measurements, to give information on the ^{203}Pb radioactivity in small bowel, liver, kidney, soft tissue and bone. As with profile scans, the contributions of ^{203}Pb in blood and 'soft' tissue E.C.F. were subtracted from surface radioactivity measurements. The measurements of surface radioactivity of the blood and E.C.F. tracers, ^{113m}In and ^{82}Br, are described in sections 11.7.3 and 11.7.4. The factors required to adjust these measurements so that they represented ^{203}Pb blood and 'soft' tissue E.C.F. backgrounds were derived as shown in section 11.7.6. Blood and 'soft' tissue E.C.F. backgrounds were subtracted from surface radioactivity measured over the organs and medial malleolus, but only blood background was subtracted from calf-surface radioactivity measurements, as the 'soft' tissue compartment included E.C.F. as explained in section 11.7.

f) Measurement of ^{203}Pb radioactivities in blood and urine

Venous blood samples were taken from each subject at 1, 2, 3, 6, 16, 20, 24 hours and on each day until the end of the study. ^{203}Pb radioactivities in plasma and red cells were measured as described in section 11.8. Urine was collected over 24 hour periods during the study, and ^{203}Pb radioactivities in urine were measured as described in section 11.9. The half lifes of the loss of ^{203}Pb from the red cells were determined from post 72 hour readings i.e. from data after the maximum level of ^{203}Pb in red cells had been reached. The loss of

^{203}Pb from the red cells was assumed to be represented by a single negative exponential.

g) Calculation of faecal excretion of ^{203}Pb from 96 hours onwards

Faecal excretion of ^{203}Pb was calculated by subtracting mean urinary loss per day of ^{203}Pb from mean reduction in percentage retention of ^{203}Pb per day, both calculated from 96 hours onwards. It was assumed that the excretion of ^{203}Pb by other routes, such as in sweat, were negligible (Rabinowitz, 1974; Chamberlain et al, 1978).

8.2.3 Results

Detailed results obtained from the kinetic experiments are shown in columns labelled 'experimental data' in the tables in section 12. All results on the maximum levels of ^{203}Pb in blood, mean urinary loss per day and calculated mean faecal loss per day of ^{203}Pb are expressed as percentages of 96 hour retention (retained dose).

a) Whole body counts

The percentage reduction in 96 hour retention produced by the weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ are shown in table 8.2.2, and in only one subject, J.B., was a true prediction made of subject response. However, the mean reduction was 50.93 ± 9.10 %(S.E.) which agrees with that planned. Table 8.2.3 shows the 96 hour retentions and the half times of retention of ^{203}Pb in all the subjects. The coefficient of variation of 96 hour retentions found in the Kinetic 1. experiments is only 4.8% whereas that of the half times of retention is 32.9%. The

TABLE 8.2.2

Weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$ used in Kinetic 2. experiment and percentage reduction in 96 hour retention resulting from weights

SUBJECT	WEIGHT OF $CaCO_3$ (g)	WEIGHT OF $NaH_2PO_4.2H_2O$ (g)	% REDUCTION IN 96 HOUR RETENTION
K.B.	0.087	0.126	26.08 ± 0.45†
J.B.	0.11	0.158	48.91 ± 0.44
B.C.	0.2	0.29	66.06 ± 0.44
G.E.	0.175	0.251	63.07 ± 0.47
Mean			50.93
S.D.			18.20
S.E.			9.1

† $\pm$ 1 standard deviation.

TABLE 8.2.3

96 Hour whole body retentions and half times of retention

of ^{203}Pb from 96 hours onwards

SUBJECT	KINETIC 1.			KINETIC 2.		
	96 Hour retention (%)	Half time (hours)	Regression coefficient (r)	96 Hour retention (%)	Half time (hours)	Regression coefficient (r)
K.B.	$65.42 \pm 0.23^{\dagger}$	$407.00 \pm 24.12(6)$	- 0.97	48.36 ± 0.17	$346.50 \pm 17.33(6)$	- 0.99
J.B.	71.70 ± 0.27	$407.65 \pm 23.97(6)$	- 0.99	36.63 ± 0.10	$301.30 \pm 13.10(6)$	- 0.99
B.C.	73.93 ± 0.24	$702.84 \pm 30.43(6)$	- 0.94	25.09 ± 0.09	$173.25 \pm 4.33(6)$	- 0.96
G.E.	71.71 ± 0.27	$330.00 \pm 15.71(6)$	- 0.97	26.48 ± 0.10	$210.00 \pm 6.36(6)$	- 0.98
D.W.	$71.60 \pm 0.23^{\S}$	$630.00 \pm 57.27(6)^{\S}$	- 0.99	$1.65 \pm 0.06^{\S *}$	-	-
Mean	70.71	415.61		30.95	198.84	
S.D.	3.37	136.73		8.62	51.25	
S.E.	1.51	61.15		4.31	25.62	

Kinetic 1. 96 hour retentions different to Kinetic 2. 96 hour retentions ($P < 0.05$).
Figures in brackets are number of data points.

† ± 1 standard deviation.

§ Results excluded from paired 't' test.

* Result excluded from mean.

96 hour retentions found in Kinetic 2. experiments were all significantly lower and although the half times of retention were all shorter, the differences between them and those found in Kinetic 1. experiments were not significant. A half time of retention could not be calculated for subject D.W., as his retention could not be measured later than 120 hours in the Kinetic 2. experiment.

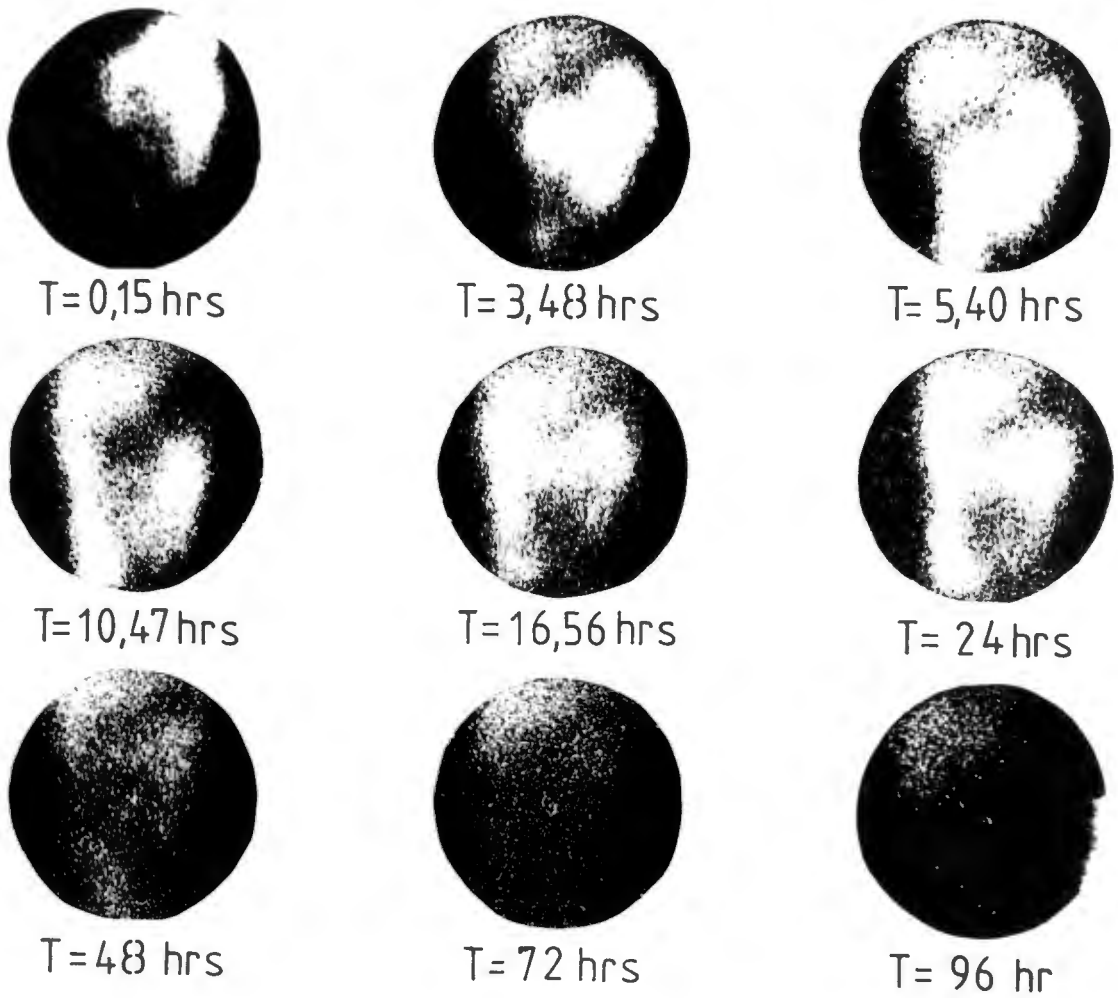
b) Gamma camera images

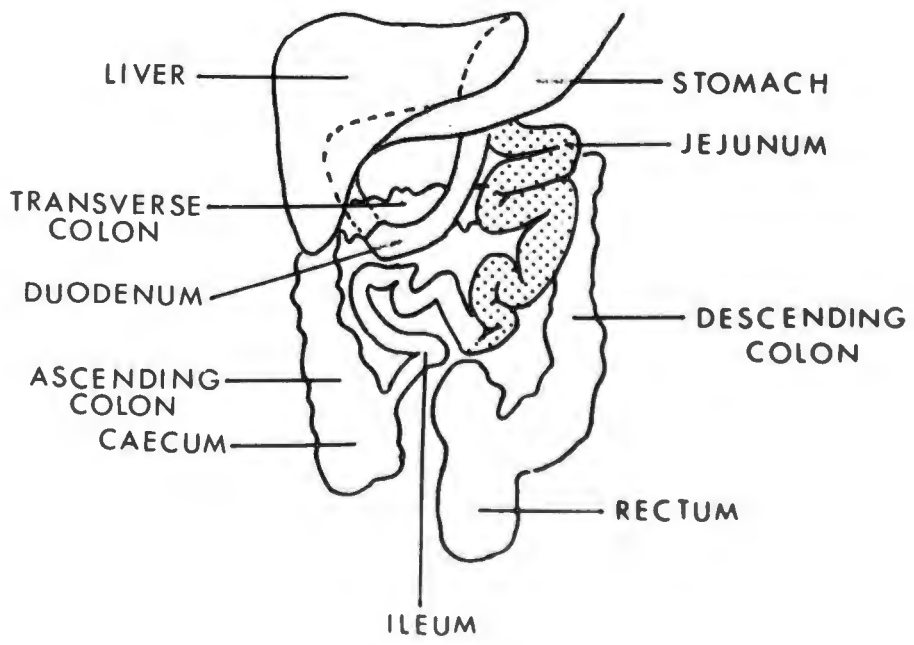
The gamma camera scintigrams obtained with subjects J.B., B.C., G.E. and D.W., were recorded on small scale photographs, and these have been enclosed in the folder at the front of this thesis. Those of subject K.B. are shown in the large scale photograph, figure 8.2.1, and these will be used to describe the changing distribution of ^{203}Pb. The scintigrams chosen in the first 24 hours of the study were those in which major changes in distribution occurred.

In figure 8.2.1, it is seen that at 0.15 hour after ingestion, most of the ^{203}Pb had already left the stomach and reached the small bowel. By 3.48 hours, there was a clear image of ^{203}Pb in the liver, indicating significant gastrointestinal absorption of the ^{203}Pb. At 10.47 hours, there was still ^{203}Pb in the small bowel, and this persisted up to 16.56 hours when it was masked by radioactivity from the unabsorbed fraction of ^{203}Pb in the large bowel. The unabsorbed fraction had reached the caecum at 5.40 hours and, by 10.47 hours, it filled the ascending portion of the large bowel. At 16.56 hours, the transverse section of the large bowel had filled with unabsorbed ^{203}Pb, and at 24 hours practically the whole of the large bowel was filled. Liver and body background radioactivities continued to increase in every image up

FIGURE 8.2.1

Gamma camera images of the distribution of ^{203}Pb in gastrointestinal tract.





to 24 hours.

At 48 hours, there was residual radioactivity in the splenic flexure of the large bowel and in the rectum, and at 72 hours, there was still some radioactivity at the splenic flexure. By 96 hours, the gastrointestinal tract appeared clear of unabsorbed ^{203}Pb, and ^{203}Pb radioactivity persisted only in the liver. There appears to be no uptake of ^{203}Pb in the scintigrams which can be identified with the anatomical positions of the kidneys. However, low uptake may have occurred which could not be discerned because of the proximity of ^{203}Pb in liver and gut. The stomach, small bowel and large bowel were identified using an oral dose of ^{99m}Tc sulphur colloid, and the relationship between these organs and the liver was found with an intravenous injection of ^{99m}Tc sulphur colloid.

c) Profile scans

In the Kinetic 2. experiment of subject D.W., the profile scans only showed a large peak due to the unabsorbed fraction of ^{203}Pb. Once this fraction was cleared from the body, there was insufficient radioactivity in the body to allow profile scans to be performed. The series of profile scans obtained from all the other subjects were very similar, and only those of subject K.B. have been included as an example. These are shown in figures 8.2.2 to 8.2.10, and were selected from the Kinetic 1. experiment. They were performed at approximately the same times as the gamma camera images shown in figure 8.2.1, so that profile peaks may be identified with regions of uptake on the scintigrams.

FIGURE. 8.2.2

Profile scan of Pb-203 radioactivity in body

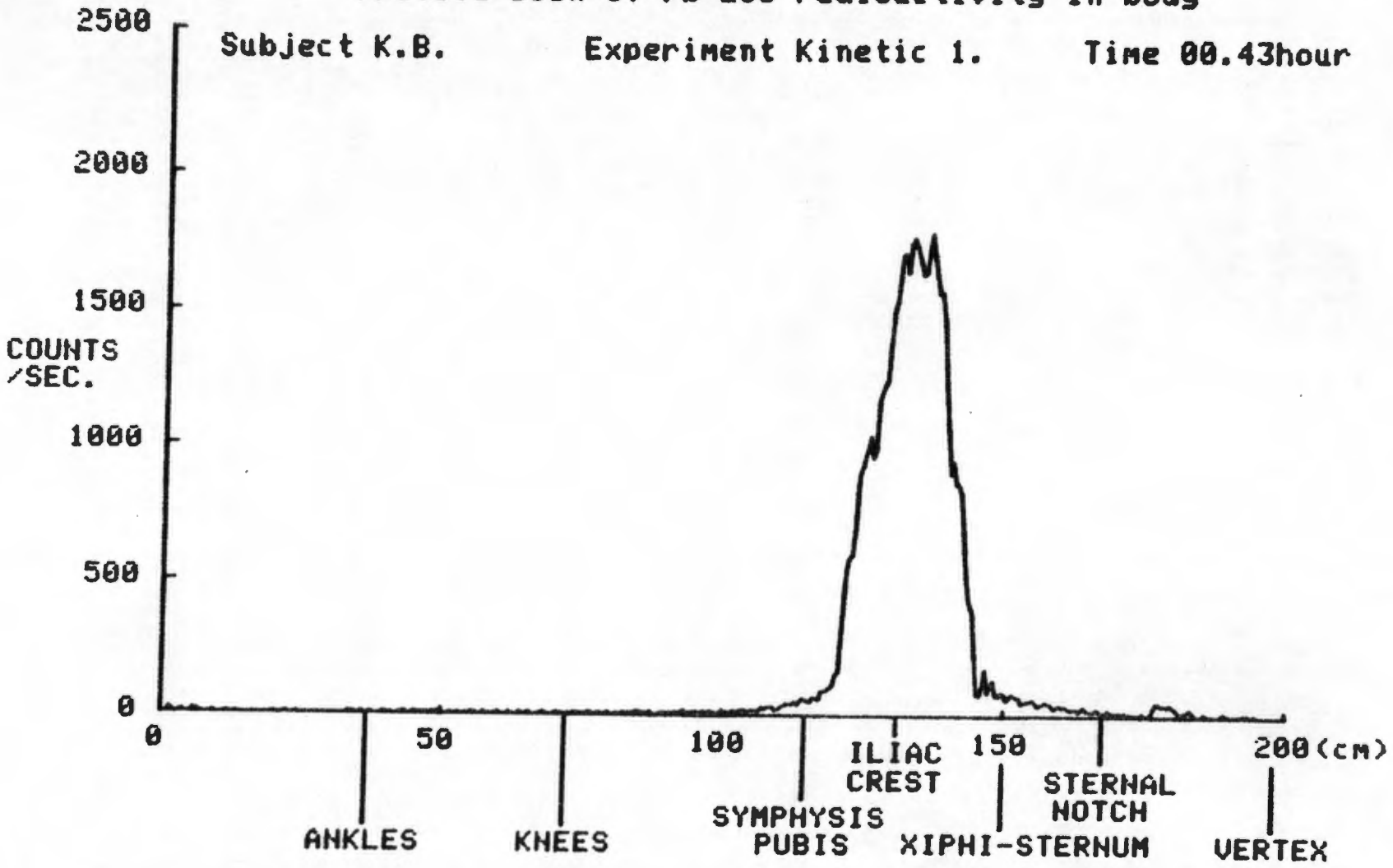


FIGURE. 8.2.3

Profile scan of Pb-203 radioactivity in body

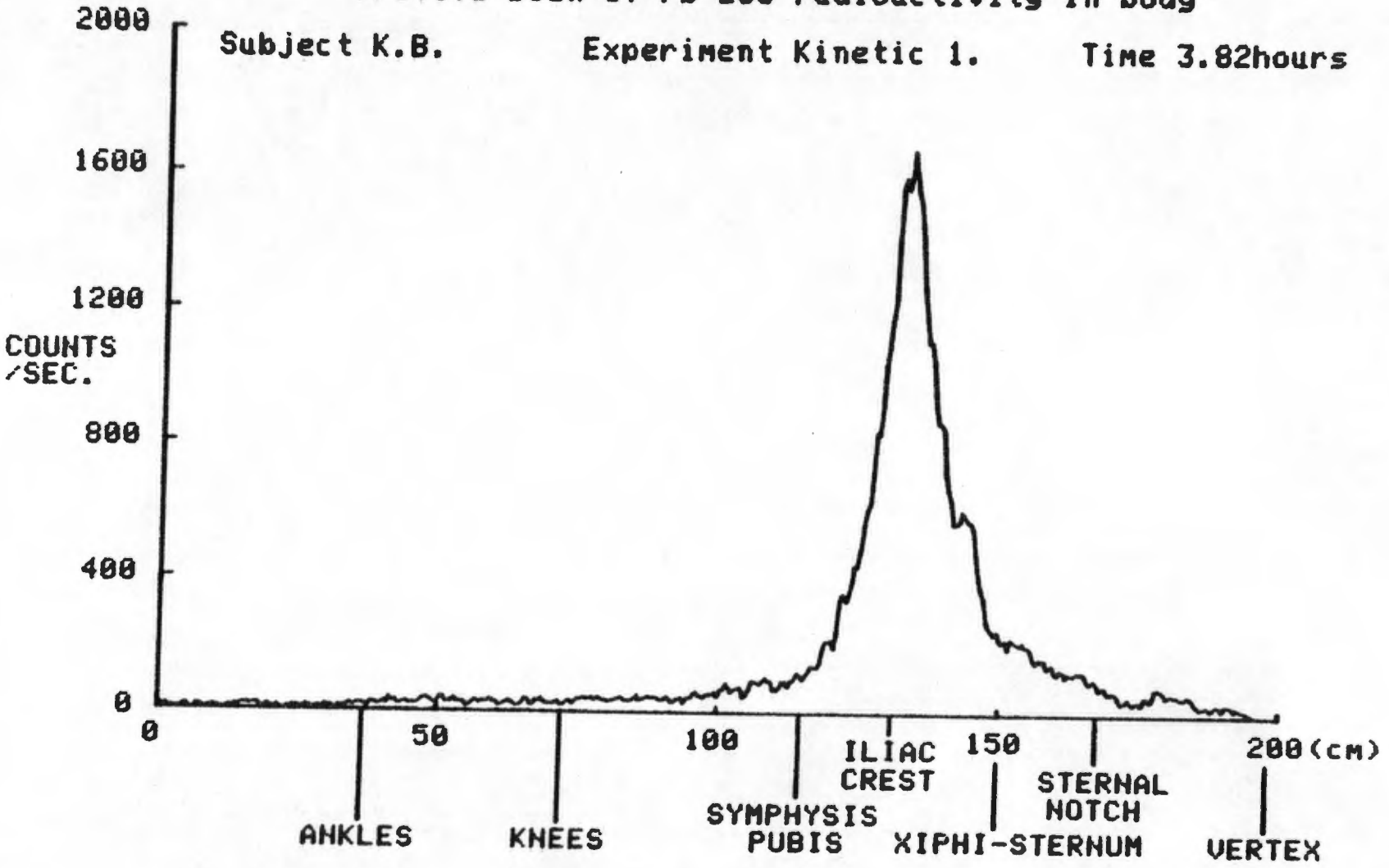


FIGURE. 8.2.4

Profile scan of Pb-203 radioactivity in body

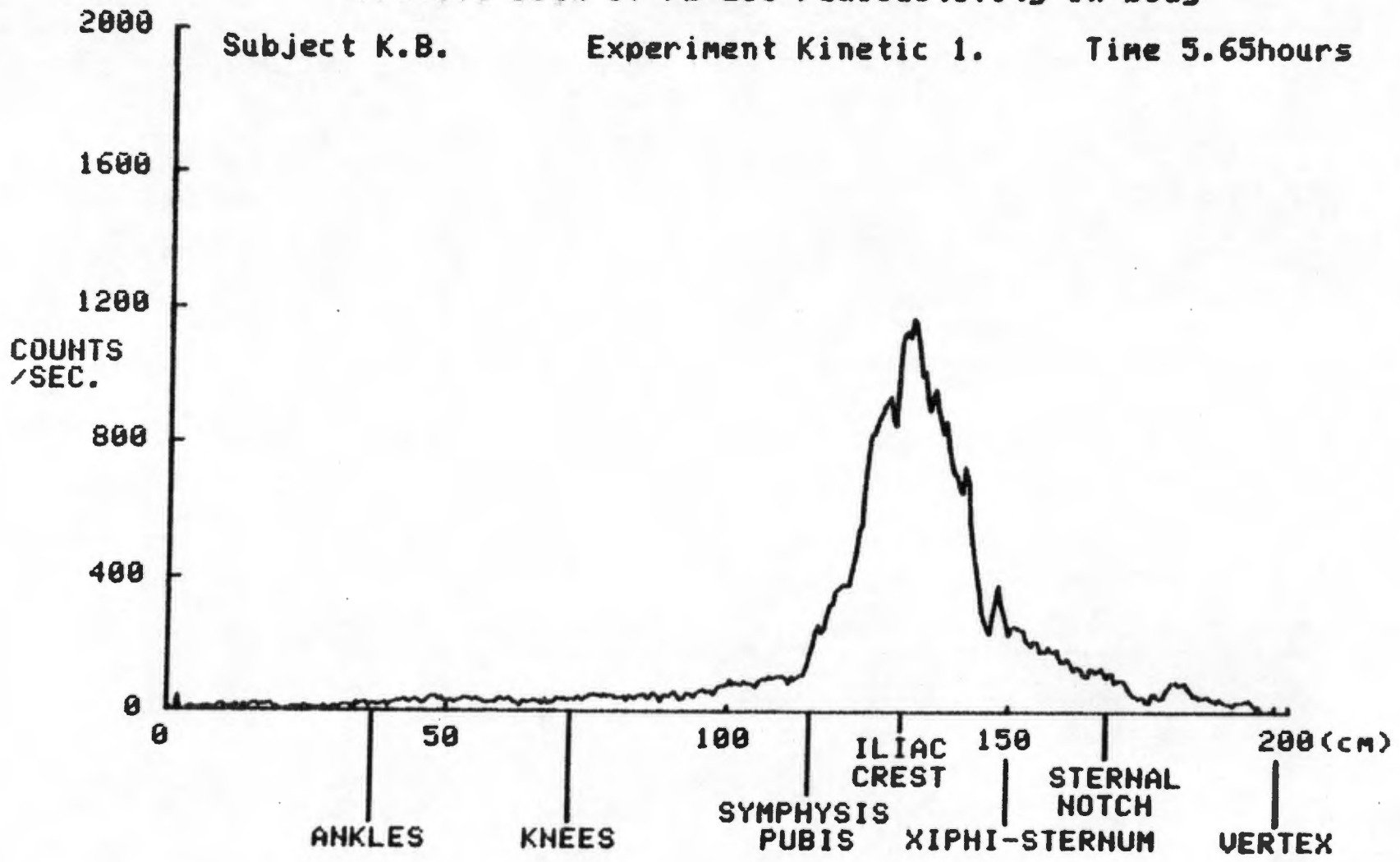


FIGURE. 8.2.5

Profile scan of Pb-203 radioactivity in body

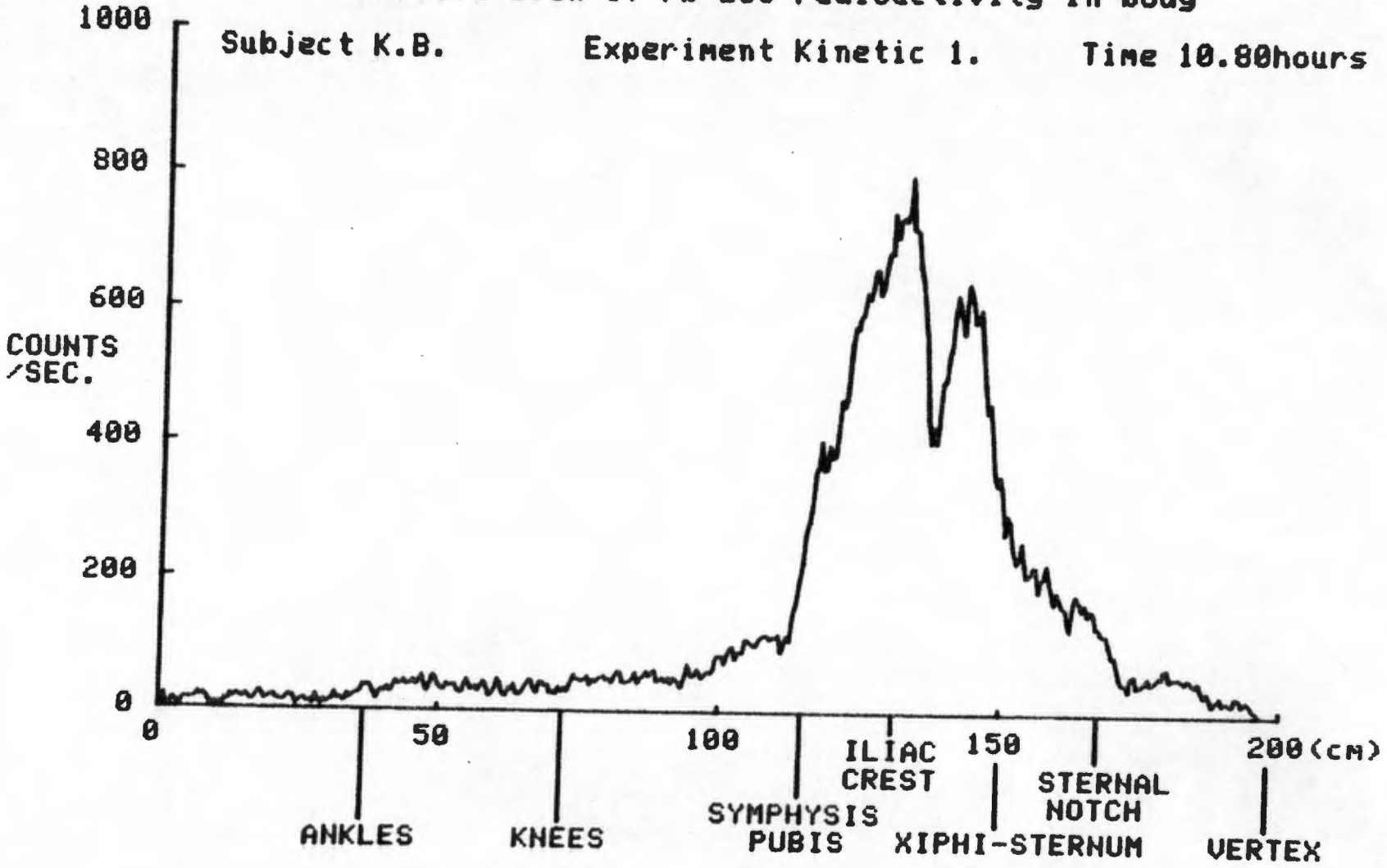


FIGURE. 8.2.6

Profile scan of Pb-203 radioactivity in body

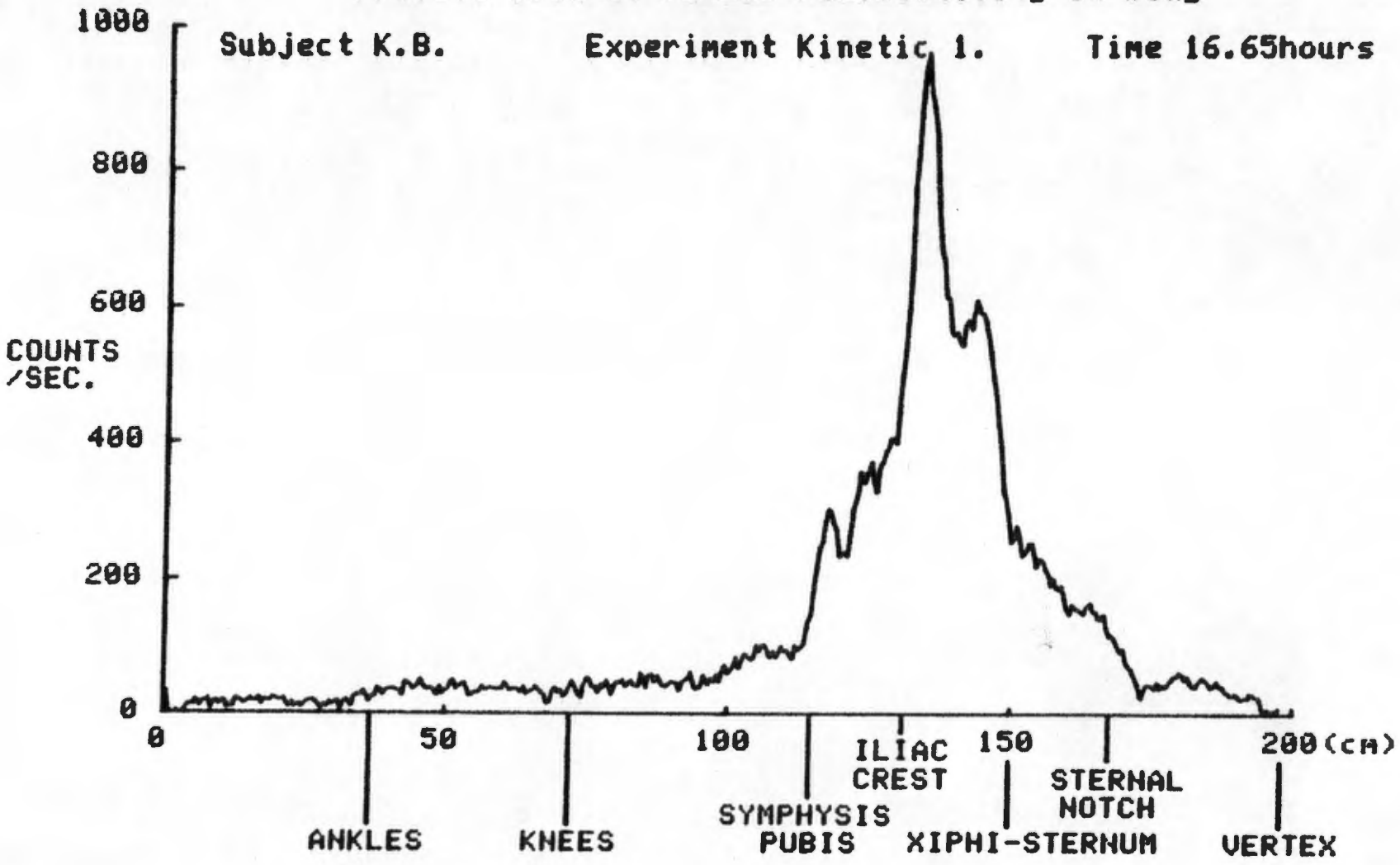


FIGURE. 8.2.7

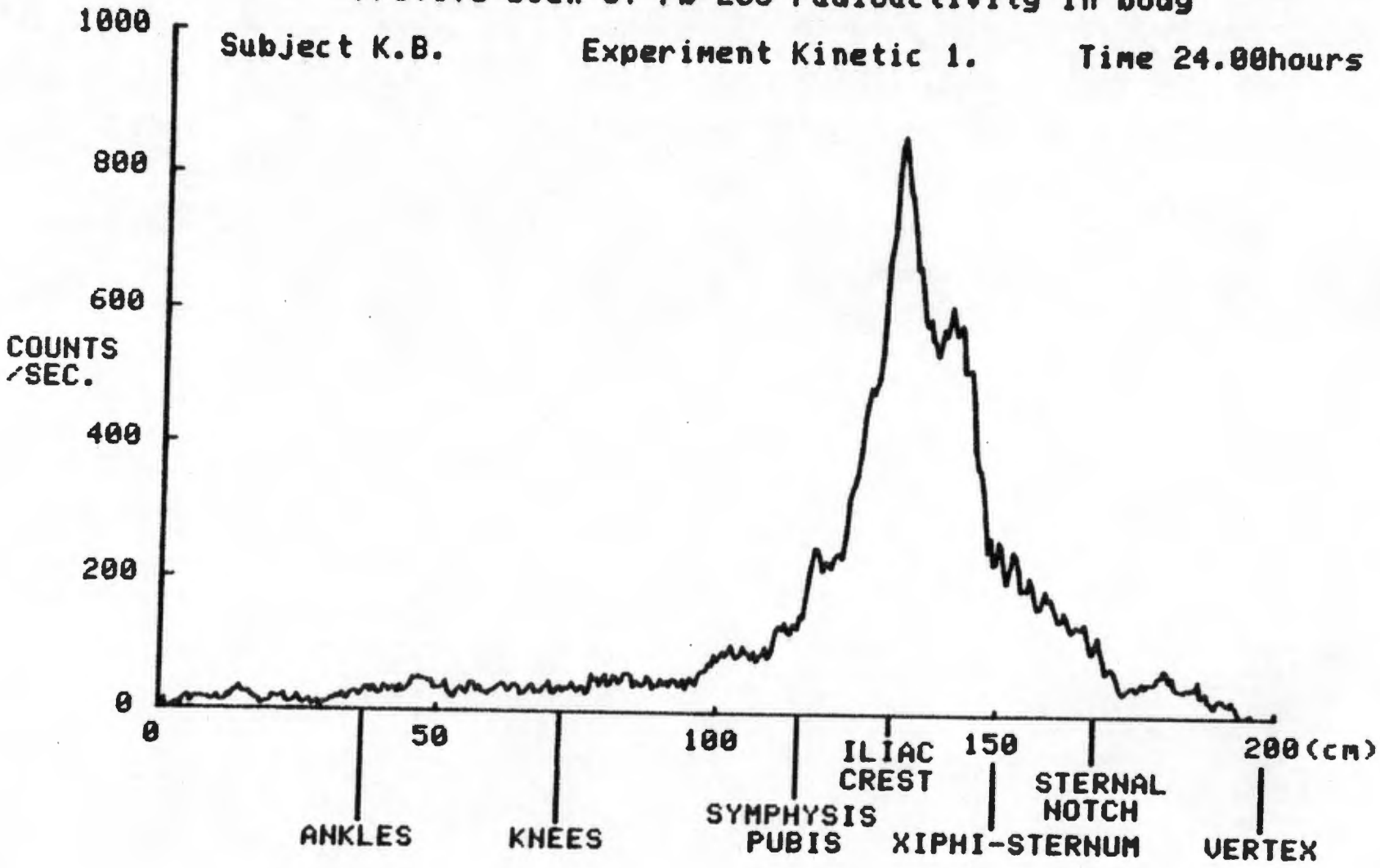

Profile scan of Pb-203 radioactivity in body
Subject K.B.
Experiment Kinetic 1.
Time 24.00hours
1000
800
600
COUNTS /SEC.
400
200
0
0
50
100
150
200(cm)
ANKLES
KNEES
SYMPHYSIS PUBIS
ILIAC CREST
XIPHI-STERNUM
STERNAL NOTCH
VERTEX

FIGURE. 8.2.8

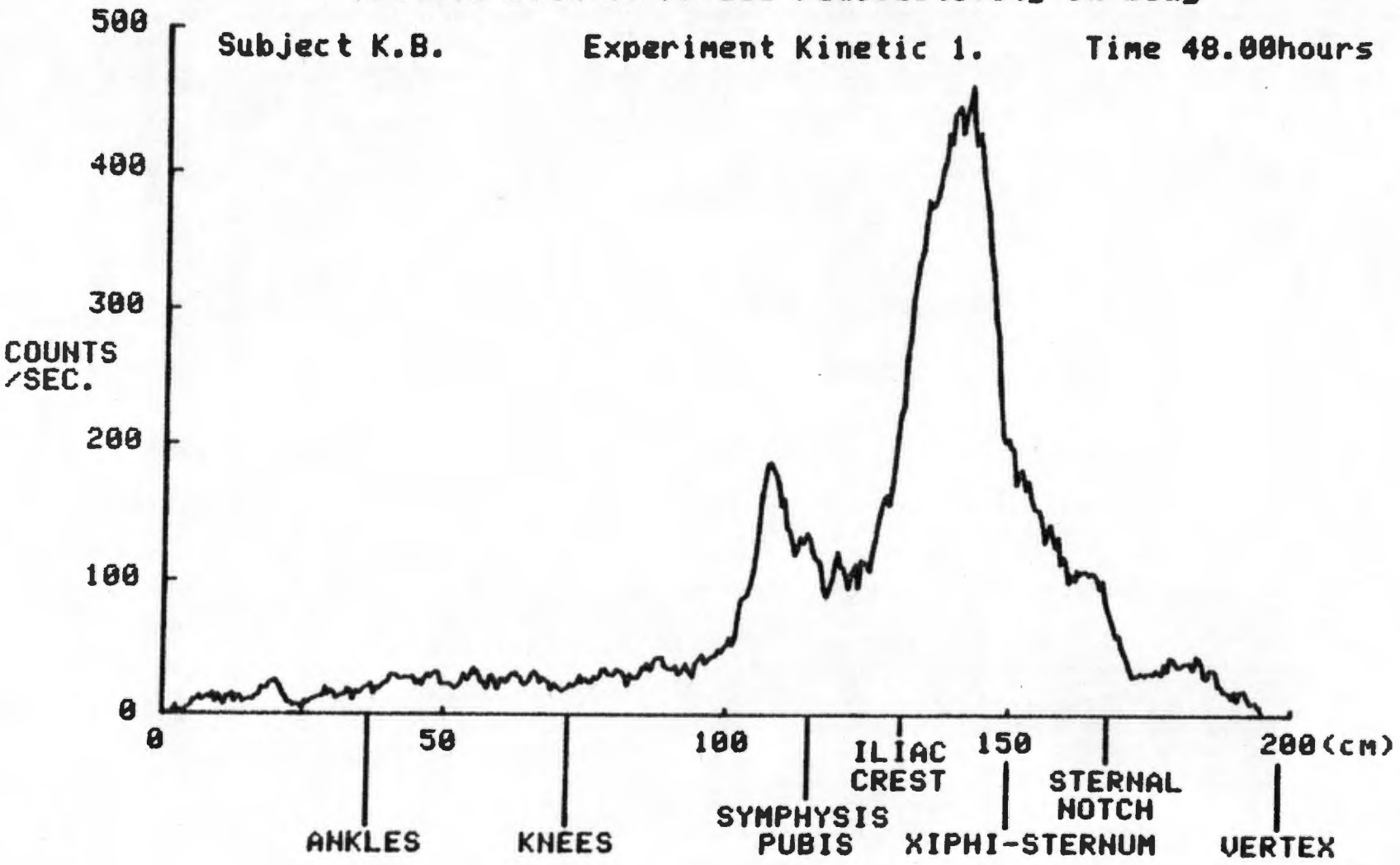

Profile scan of Pb-203 radioactivity in body
Subject K.B.
Experiment Kinetic 1.
Time 48.00hours
500
400
300
200
100
0
COUNTS /SEC.
0
50
100
150
200(cm)
ANKLES
KNEES
SYMPHYSIS PUBIS
ILIAC CREST
XIPHI-STERNUM
STERNAL NOTCH
VERTEX

FIGURE. 8.2.9

Profile scan of Pb-203 radioactivity in body

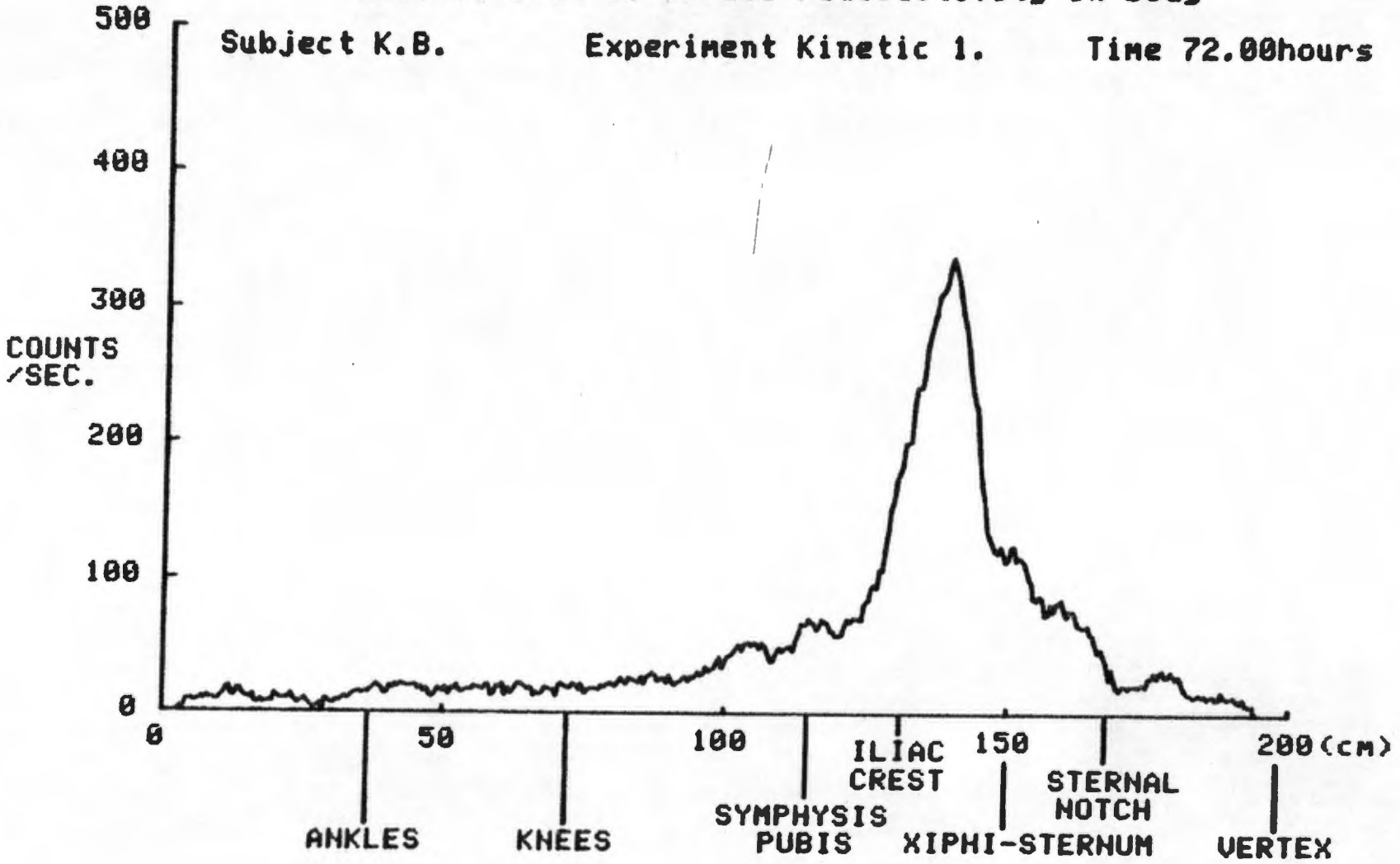
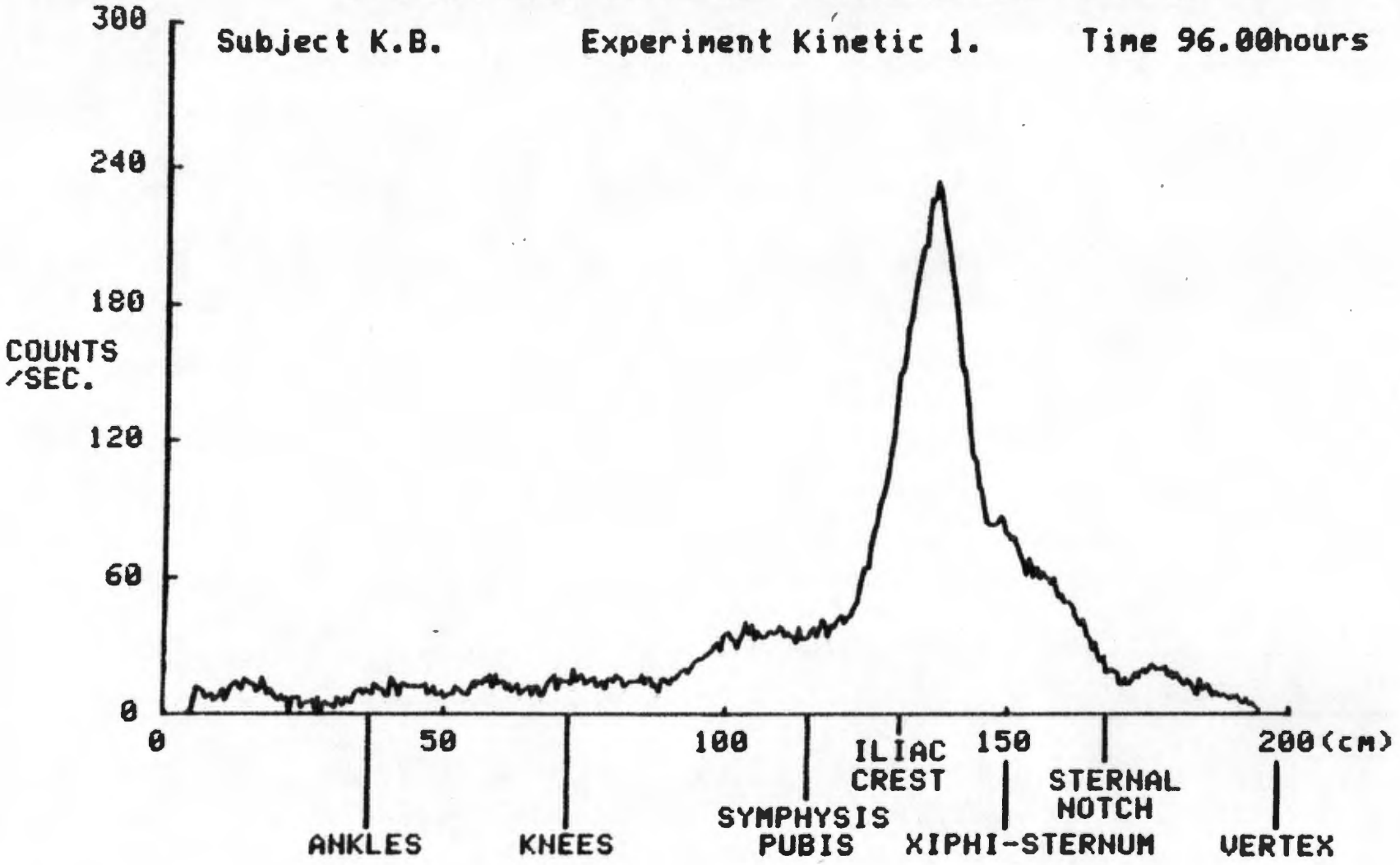


FIGURE. 8.2.10

Profile scan of Pb-203 radioactivity in body



The first profile scan, at 0.43 hour, shows a broad peak and a background spreading the whole length of the body due to ^{203}Pb absorbed and distributed through the body. At 3.82 hours, the single peak has narrowed and lies at the level of the iliac crest, and it was produced by ^{203}Pb in the wall and lumen of the small bowel. There is a small peak just below the xiphisternal joint caused by ^{203}Pb in the liver, as this organ is clearly seen on the 3.48 hour scintigram. The 5.65 hour profile scan shows that ^{203}Pb distributed through the body was still increasing, that the peak at the iliac crest has decreased, and that the main peak has spread towards the symphysis pubis which corresponds to ^{203}Pb near the caecum on the 5.40 hour scintigram. At 10.80 hours, a peak due to ^{203}Pb in the liver can be seen below the xiphisternal joint, and although ^{203}Pb can be seen in the small bowel on the corresponding scintigram, the small bowel peak is superimposed on the unabsorbed fraction of ^{203}Pb in the ascending large bowel. This unabsorbed fraction of ^{203}Pb can also be seen in the transverse large bowel in the 16.56 hour scintigram, and has caused a distinctive peak superimposed on that due to ^{203}Pb in the liver in the 16.65 hour profile scan.

There is no appreciable change between the 16.65 hour profile and the 24 hour profile, and there is very little difference between the corresponding scintigrams. At 48.00 hours, the peak due to ^{203}Pb in the liver can be clearly seen, although the scintigram shows some residual ^{203}Pb in the splenic flexure of the large bowel which can be seen superimposed on the inferior edge of the liver peak. The same profile distribution occurs in the 72 hours profile, although residual ^{203}Pb in the large bowel appears to be much less in the corresponding scintigram.

By 96 hours, the peak due to liver ^{203}Pb can be clearly seen, and profile scans performed on later days were an identical shape to the 96 hour profile. In both the 96 hour gamma-camera image and the 96 hour profile scan, there is no indication of unabsorbed ^{203}Pb in the gastrointestinal tract of subject K.B. or in those of the other subjects.

Thus, only ^{203}Pb radioactivity in liver gave profile peaks which could be clearly seen in the profile scans. The profile peak caused by small bowel radioactivity was always superimposed on the peak due to the unabsorbed fraction of ^{203}Pb in the large bowel. There appeared to be no profile peak caused by radioactivity in the kidneys.

Profile scan analysis could only be performed, therefore, on the liver profile peak, and as the peak and the superior edge of the liver profile peak could only be clearly seen in profile scans from 48 hours onwards, these profile scans were the only scans which could be analysed. The factors required to transform the ^{113m}In and ^{82}Br profile scans into blood and 'soft' tissue E.C.F. backgrounds are shown in tables 8.2.4 and 8.2.5, and the result of the subtraction of these backgrounds is shown for the 96 hour profile in figure 8.2.11. The final subtraction, with a 'soft' tissue E.C.F. background adjusted by eye, gave one peak caused by liver ^{203}Pb radioactivity as shown in figure 8.2.12. A modified Gaussian function, which was determined from the ^{113m}In-colloid liver profile as described in Appendix A.3, was fitted to this single profile peak. Figure 8.2.13 shows the fit between calculated values and experimental data for the 96 hour profile. The fit is good on the superior side of the peak, but on the inferior side, there appears to be a superposition of gut radioactivity. The percentages of the ingested

TABLE 8.2.4

Factor to transform ^{113m}In profile scan to ^{203}Pb blood background profile scan

Subject : K.B. Experiment: Kinetic 1.

TIME OF ^{203}Pb PROFILE (hours)	FACTOR
48.00	0.107
72.00	0.074
96.00	0.051
120.00	0.035
144.00	0.026
168.00	0.022
192.00	0.012
216.00	0.008

TABLE 8.2.5

Factors to transform ^{82}Br profile scan to ^{203}Pb

'soft' tissue E.C.F. background profile scan

Subject : K.B. Experiment : Kinetic 1.

TIME OF ^{203}Pb PROFILE (hours)	FACTOR
48.00	0.0013
72.00	0.0009
96.00	0.0005
120.00	0.0004
144.00	0.0003
168.00	0.0002
192.00	0.0002
216.00	0.0001

Factor to transform ^{113m}In profile scan to ^{82}Br blood background profile scan = 0.237.

FIGURE. 8.2.11

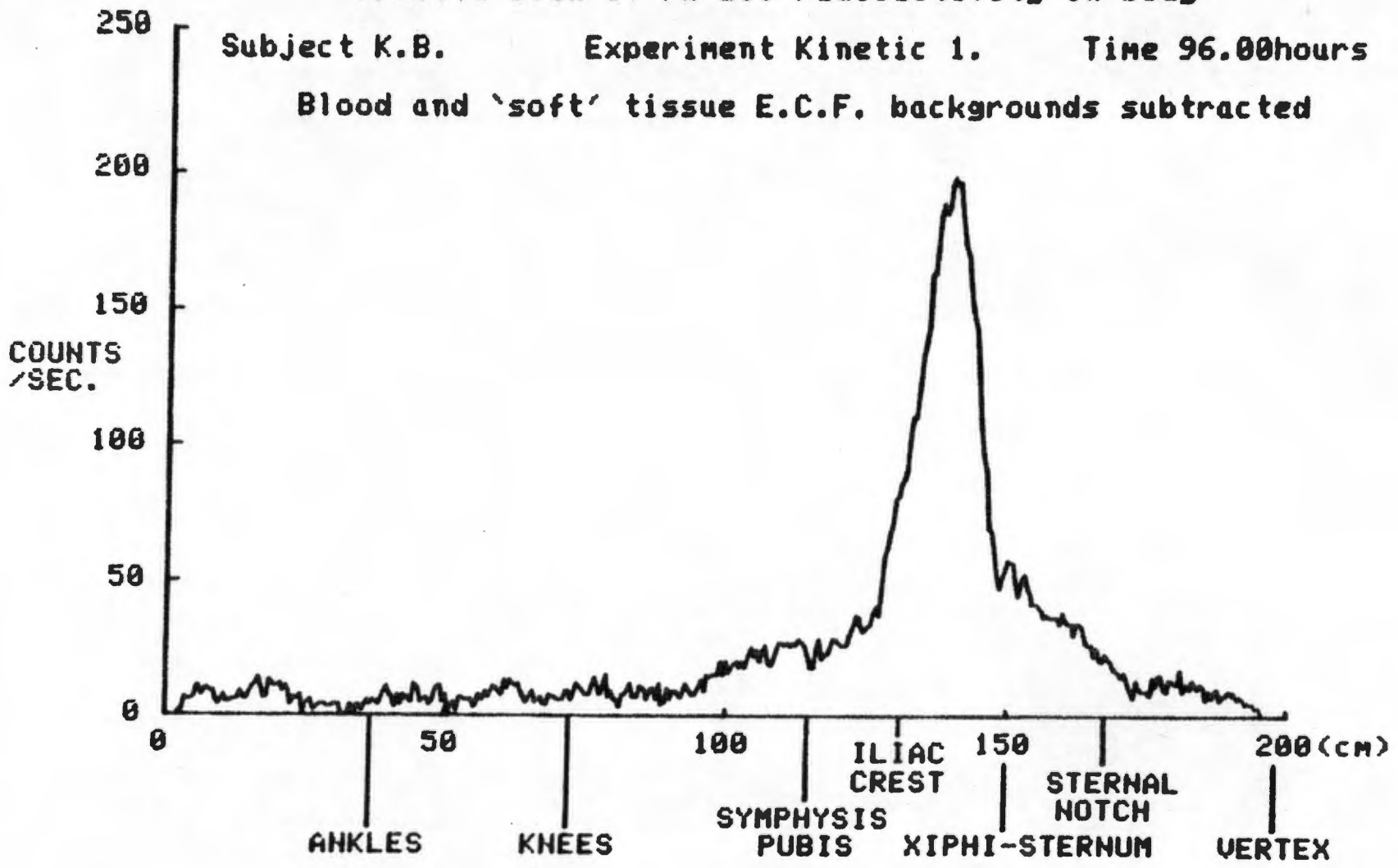

Profile scan of Pb-203 radioactivity in body
Subject K.B.
Experiment Kinetic 1.
Time 96.00hours
Blood and 'soft' tissue E.C.F. backgrounds subtracted
250
200
150
COUNTS /SEC.
100
50
0
0
50
100
150
200(cm)
ANKLES
KNEES
SYMPHYSIS PUBIS
ILIAC CREST
XIPHI-STERNUM
STERNAL NOTCH
VERTEX

FIGURE. 8.2.12

Profile scan of Pb-203 radioactivity in body

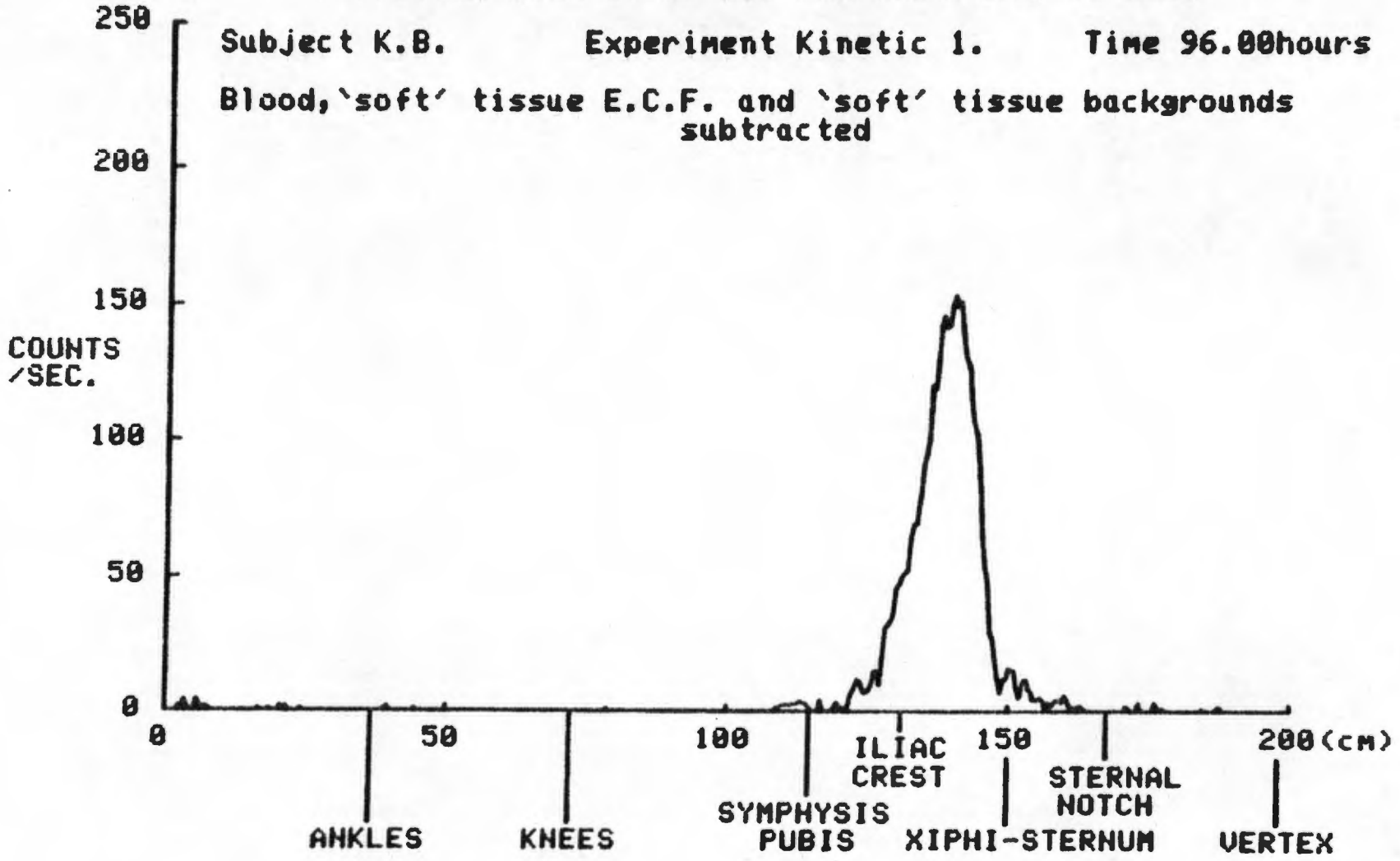
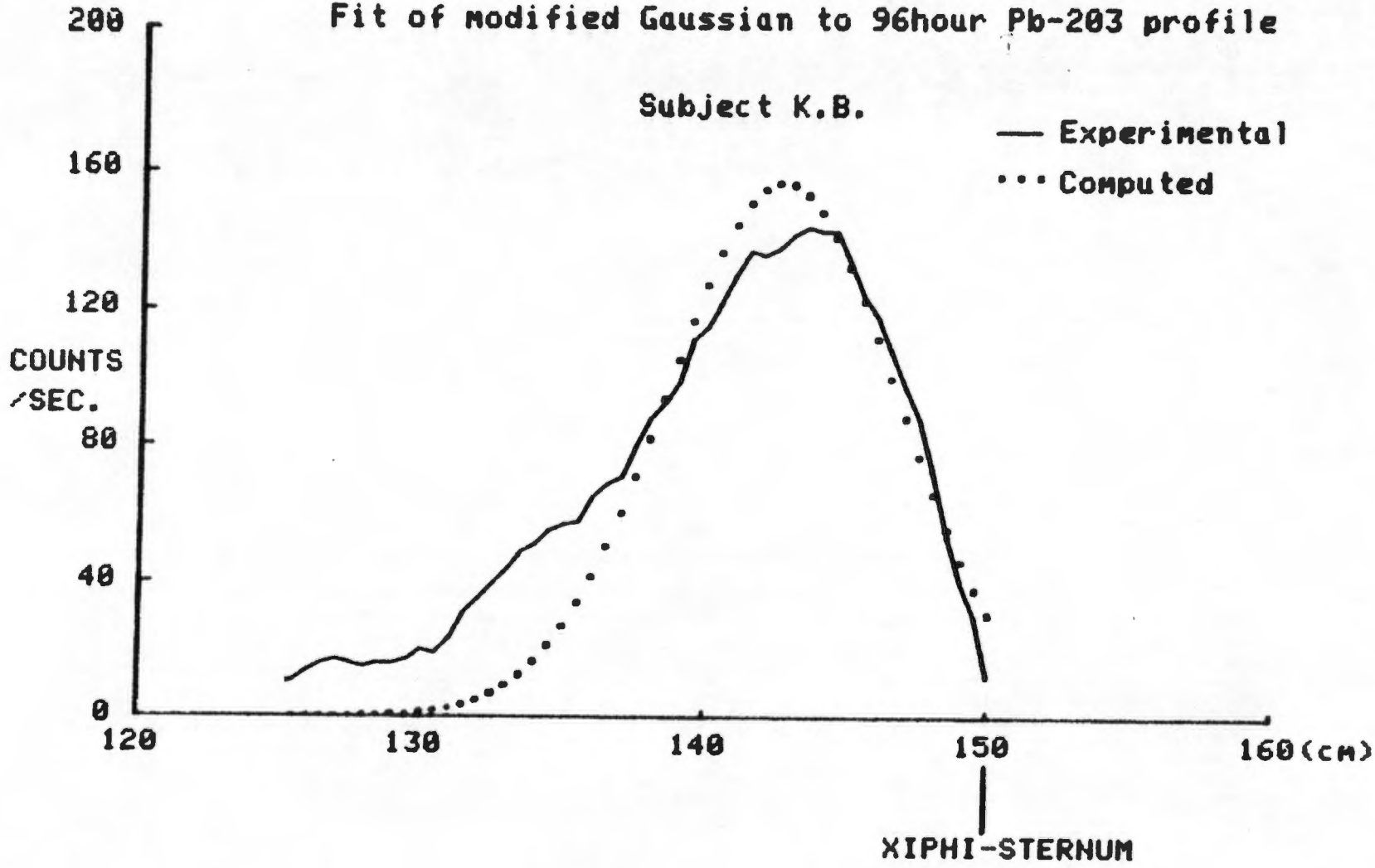


FIGURE 8.2.13


Fit of modified Gaussian to 96hour Pb-203 profile
Subject K.B.
Experimental
Computed
200
160
120
COUNTS /SEC.
80
40
0
120
130
140
150
160(cm)
XIPHI-STERNUM

dose of ^{203}Pb calculated to be in the liver of subject K.B. are shown in table 8.2.6.

c) Surface radioactivity measurements

In the Kinetic 2. experiment of subject D.W., only some of the surface radioactivity measurements performed during the first 24 hours over his small bowel had sufficient statistical accuracy (section 11.12). This was due to the presence of the large unabsorbed fraction of ^{203}Pb, which at various times during the first 24 hours, was in the 'field of view' of the in vivo detector. Surface radioactivity measurements performed over the other sites all had large statistical errors and could not be used. Although surface radioactivity measurements were continued up to 9 days after the ingestion of ^{203}Pb with all the other subjects, a number of measurements, particularly the later ones performed over the calf, had to be rejected because of large statistical counting errors.

In the other subjects, small bowel surface radioactivity decreased very rapidly over the first 12 hours after ingestion of ^{203}Pb. However, a sharp increase occurred at 16 hours which persisted until 48 hours. From 72 hours onwards, the measurements decreased very slowly. Surface radioactivity over the liver rose rapidly to a peak within 24 hours, and either remained at this level or increased slightly over the rest of the study. A more rapid rise in surface radioactivity occurred over the medial calf in comparison to that which occurred over the liver. A peak was reached within 12 hours, but there was considerable scatter in the results, so no particular trend could be identified from post-24 hour results. The rise in surface radioactivity over the medial malleolus was very similar to that which occurred over the calf during

TABLE 8.2.6

Percentage of ingested dose in liver profile peaks

determined by profile scan analysis

Subject : K.B. Experiment : Kinetic 1.

TIME (hours)	% INGESTED DOSE
48	15.11 ± 0.25†
72	17.11 ± 0.30
96	14.98 ± 0.27
120	13.85 ± 0.31
144	9.67 ± 0.24
168	13.38 ± 0.46
192	13.66 ± 0.51
216	14.63 ± 0.60

† ± 1 standard deviation.

the first 12 hours. However, unlike the calf, post-24 hour results continued to rise steadily to the end of the study.

d) ^{203}Pb levels in blood and urinary and faecal losses of ^{203}Pb

The ^{203}Pb levels in total plasma were always less than 0.1% of the ingested dose in all experiments. These levels generally peaked at 24 hours and then decreased fairly rapidly. Unfortunately, the ^{203}Pb levels in plasma of subject D.W. in his Kinetic 2. experiment were too low to be measured with sufficient statistical accuracy (section 11.12). With the other subjects, there was sufficient ^{203}Pb radioactivity in the plasma for measurements to be performed to at least 96 hours. The ^{203}Pb levels in total red cells rose rapidly to peak between 24 and 48 hours in the Kinetic 1. experiments, but in the Kinetic 2. experiments, levels rose more slowly and peaks generally occurred later. The levels of ^{203}Pb in accumulative urine rose linearly over the period of study for all subjects.

The maximum ^{203}Pb content of total plasma, total red cells, the urinary loss per day and the calculated faecal loss per day of ^{203}Pb are shown in tables 8.2.7 - 8.2.10, respectively. Table 8.2.11 shows the half life of ^{203}Pb in the red cells. All regression coefficients are close to unity except that found from the Kinetic 1. experimental data of subject D.W. Results from the Kinetic 1. and Kinetic 2. experiments were compared using a paired 't' test (Mould, 1976), and there was a significant decrease ($P < 0.05$) in only the maximum red cell content of ^{203}Pb.

TABLE 8.2.7

Maximum ^{203}Pb content of plasma expressed as a percentage of 96 hour retention

SUBJECT	MAXIMUM ^{203}Pb CONTENT OF PLASMA (% 96 hour retention)	
	Kinetic 1.	Kinetic 2.
K.B.	$0.113 \pm 0.002^{\dagger}$	0.130 ± 0.001
J.B.	0.102 ± 0.002	0.139 ± 0.001
B.C.	0.062 ± 0.002	0.060 ± 0.003
G.E.	0.074 ± 0.002	0.117 ± 0.002
D.W.	$0.101 \pm 0.003^{\S}$	-
Mean	0.089	0.129
S.D.	0.022	0.019
S.E.	0.010	0.010

† $\pm$ 1 standard deviation.

§ Result excluded from paired 't' test.

TABLE 8.2.8

Maximum ^{203}Pb content of red cells expressed as a percentage of 96 hour retention

SUBJECT	MAXIMUM ^{203}Pb CONTENT OF RED CELLS (% 96 hour retention)	
	Kinetic 1.	Kinetic 2.
K.B.	$35.97 \pm 0.18^{\dagger}$	28.56 ± 0.14
J.B.	45.17 ± 0.22	34.53 ± 0.14
B.C.	30.80 ± 0.12	24.07 ± 0.10
G.E.	47.87 ± 0.21	29.27 ± 0.81
D.W.	$44.60 \pm 0.19^{\S}$	$20.36 \pm 0.81^{\S}$
Mean	37.95	28.12
S.D.	7.74	4.32
S.E.	3.46	1.93

Kinetic 1. results different from Kinetic 2. results ($P < 0.05$).

$\dagger \pm$ 1 standard deviation.

§ Results excluded from paired 't' test.

TABLE 8.2.9

Urinary loss of ^{203}Pb per day expressed as a percentage of 96 hour retention

SUBJECT	URINARY LOSS OF ^{203}Pb PER DAY (% 96 hour retention)	
	Kinetic 1.	Kinetic 2.
K.B.	1.37 ± 0.007†	0.99 ± 0.004
J.B.	1.14 ± 0.006	1.00 ± 0.004
B.C.	0.94 ± 0.004	0.82 ± 0.004
G.E.	1.13 ± 0.007	1.00 ± 0.006
D.W.	1.02 ± 0.005§	0.37 ± 0.015§
Mean	1.07	0.934
S.D.	0.15	0.127
S.E.	0.07	0.057

† ± 1 standard deviation.

§ Results excluded from paired 't' test.

TABLE 8.2.10

Faecal loss of ^{203}Pb per day expressed as a percentage of 96 hour retention

SUBJECT	FAECAL LOSS OF ^{203}Pb PER DAY (% 96 hour retention)	
	Kinetic 1.	Kinetic 2.
K.B.	2.39 ± 0.17†	3.37 ± 0.12
J.B.	2.53 ± 0.15	4.16 ± 0.12
B.C.	1.91 ± 0.20	6.37 ± 0.17
G.E.	3.30 ± 0.44	4.89 ± 0.17
D.W.	1.28 ± 0.28§	-
Mean	2.55	4.38
S.D.	0.67	1.19
S.E.	0.30	0.59

† ± 1 standard deviation.

§ Result excluded from paired 't' test.

TABLE 8.2.11

Half life of ^{203}Pb in red cells following ingestion of ^{203}Pb

SUBJECT	KINETIC 1.		KINETIC 2.	
	Half life (days)	Regression coefficient (r)	Half life (days)	Regression coefficient (r)
K.B.	22.00 ± 0.31†(7)	- 0.88	7.80 ± 0.06 (7)	- 0.98
J.B.	28.88 ± 0.72 (6)	- 0.98	9.02 ± 0.08 (6)	- 0.98
B.C.	14.44 ± 0.14 (5)	- 0.97	12.03 ± 0.10 (7)	- 0.95
G.E.	20.09 ± 0.18 (7)	- 0.99	16.04 ± 0.18 (7)	- 0.89
D.W.	28.88 ± 2.90§(7)	- 0.73	-	-
Mean	17.44		9.34	
S.D.	3.92		2.56	
S.E.	1.75		1.28	

Figures in brackets are number of data points.

† ± 1 standard deviation.

§ Result excluded from paired 't' test.

8.2.4 Discussion

The Kinetic 2. experiment of subject D.W. was not a complete success. The maximum weights of calcium and phosphorous reduced his absorption of ^{203}Pb to such an extent that no whole body counts from 120 hours onwards, useful profile scans, useful surface radioactivity or plasma measurements could be performed with sufficient statistical accuracy. Although it was anticipated that his lead absorption would be low, from his results when he ingested ^{203}Pb with minerals (section 5.0), it was hoped that sufficient in vivo and plasma measurements could be done for future compartmental analysis.

In only one subject, J.B., was a 50% reduction in 96 hour retention achieved between Kinetic 1. and Kinetic 2. retention values. The mean reduction, however, was approximately 50%. The calculation of the 'half weights' of calcium and phosphorous was based on the response curve of 96 hour retention against weights of calcium and phosphorous of one subject, K.B. The shape of this response curve would appear to be different for the other subjects for which the calculation was not correct. However, this does not explain why the retention of subject K.B. was not reduced by 50%. At this time, this last discrepancy is unresolved.

The paired experiments were designed, however, to only investigate the effects of added calcium and phosphorous on the behaviour of an oral dose of ^{203}Pb in the body. The actual reductions in retention caused by these minerals were all statistically significant. The values of the retentions probably correspond to those in the region of the response

curve where the effects of calcium and phosphorous on lead absorption are considerable, even if they did not exactly agree with the 50% values.

a) Whole body retention

The 96 hour whole body retentions of all subjects were significantly reduced by the simultaneous presence of calcium and phosphorous with ^{203}Pb in the gut, but the half times of retention were not. The variation of 96 hour retentions in Kinetic 1. was low as found earlier in section 4.0, and the mean of 70.71 $\pm$ 1.51% (S.E.) agrees well with the mean of 69.50 $\pm$ 2.24% (S.E.) obtained in that earlier section.

b) Gamma camera images, profile scans and surface radioactivity measurements

The gamma camera studies in all subjects were characterised by very rapid emptying of ^{203}Pb from the stomach, uptake in the wall of the small bowel and liver, and no evidence of localised uptake due to unabsorbed ^{203}Pb in the gut at 96 hours. The only exception was the study obtained in the Kinetic 2. experiment of subject D.W., in which only the distribution of the unabsorbed fraction of ^{203}Pb in the gastrointestinal tract was visualised.

A similar pattern of the uptake found in the gamma camera images was observed in the profile scans, except that it was difficult to distinguish between uptake in the wall of the small bowel, in the liver and the unabsorbed fraction of ^{203}Pb in the early scans. As with the gamma camera images, there was no indication of peaks due to localised

unabsorbed ^{203}Pb in the gut at 96 hours. However, there was a generalised superposition of gut radioactivity on the inferior side of the liver profile peak, which occurred even in the analysis of the last profile scans at 9 days in all subjects. This could have been caused by endogenous ^{203}Pb in the gut.

Surface radioactivity measurements could be easily performed over liver and small bowel as count rates were moderately high, in contrast to those found over medial calf and medial malleolus which were low. Surface radioactivity measurements of subjects B.C. and G.E. were mainly affected by their lower than planned retentions.

There was no evidence of appreciable ^{203}Pb uptake in the kidneys of any of the subjects, in either gamma camera images or profile scans. However, any uptake occurring before the gastrointestinal tract was clear of large amounts of radioactivity, may have been masked. In post-48 hour profile scans, any appreciable uptake would have been seen as a distinct peak on the inferior side of the liver peak. During the surface radioactivity measurements, the posterior anatomical positions of the kidneys of each subject were surveyed by the <u>in vivo</u> detector, but, on the right of the body, count rates from ^{203}Pb in the liver predominated. On the left side, count rates were affected by ^{203}Pb in the gut, but even when that had cleared from the body, no appreciable uptake could be found in that region.

c) ^{203}Pb radioactivity in plasma and red cells

The mean of the maximum retained dose of ^{203}Pb in the plasma found in the Kinetic 1. experiments was 0.089 ± 0.01% (S.E.), which is lower than that found by Chamberlain et al (1978) of 0.3% and Hursh et al (1969) of 1.5%. These last two studies were performed on subjects who received tracer lead by other routes not orally, which could possibly account for the differences. There was no significant difference between the plasma levels of ^{203}Pb found in the Kinetic 1. and Kinetic 2. experiments, and Rabinowitz (1974) found that plasma levels remained constant despite changes in whole blood lead. Rosen et al (1974) reported that the plasma lead levels in normal and lead intoxicated children were nearly the same.

The mean of the maximum retained dose of ^{203}Pb in the red cells found in the Kinetic 1. experiments was 37.95 ± 3.46% (S.E.) and agrees with that found by Chamberlain et al (1975) in similar experiments of 44.5 ± 4.6% (S.E.) of absorbed dose of ^{203}Pb in whole blood. However, in later work Chamberlain et al (1978) obtained a higher percentage of 52 ± 2% (S.E.). The differences between means could have been caused by the selection of subjects with differing red cell volumes or different estimations of these volumes. There was a significant decrease in the ^{203}Pb levels in the red cells found in the Kinetic 2. experiments compared with those found in the Kinetic 1. experiments. The mean half life of ^{203}Pb in the red cells was 17.44 ± 1.75 days (S.E.) in the Kinetic 1. experiments, which agrees with that found by Chamberlain et al (1978) of 15.4 ± 2.7 days (S.E.).

d) Urinary and faecal excretion of ^{203}Pb

The mean urinary loss per day of 1.07 ± 0.07% (S.E.) of the retained dose of ^{203}Pb found in Kinetic 1. experiments is comparable to that found by Chamberlain et al (1978) of 1.08 ± 0.08% (S.E.) in their experiments with fasted subjects. In the same work, a faecal loss of 0.86 ± 0.03% (S.E.) was found in fasted subjects, which is less than the mean faecal loss per day of 3.01 ± 0.28% (S.E.) found in the Kinetic 1. experiments. However, the subjects in the present experiment ingested 300 µg of carrier lead with the ^{203}Pb, compared to 75 µg ingested in the experiments of Chamberlain et al (1978). This may account for the differences in faecal loss of ^{203}Pb, as explained in section 5.4.2.

The ratio of mean faecal to mean urine loss per day (F/U) in the Kinetic 1.experiments was 2.81, and this is comparable to that found in patients with chronic plumbism after their removal from exposure to lead (Cantarow and Trumper, 1944). There is considerable variation in F/U values from other published work. 0.7 and 1.1 have been found in baboons injected with ^{210}Pb (Cohen, 1970; Strehlow, 1971). In rats injected with ^{210}Pb, a F/U of 2.2 was obtained (Castellino and Aloj, 1964), and in rats injected with ^{203}Pb a F/U of 1.0 was found (Morgan et al, 1977). Similarly in dogs ratios of 0.2 (Stover, 1959) and 1.85 (Hursh, 1973) have been found. Klaasen and Schoeman (1974) showed that the rate of biliary excretion varied in animals of different species. They also observed that increasing intravenous doses of carrier lead increased the rate of biliary excretion. Therefore, the differences of F/U values of animals of the same species could be

caused by different levels of systemic lead.

e) Distribution and excretion of ^{203}Pb

Calcium and phosphorous ingested simultaneously with ^{203}Pb caused a significant decrease, in all subjects, of the ^{203}Pb content of red cells. In the four subjects, K.B., J.B., B.C., G.E., there was a decrease in urinary excretion and an increase in the faecal excretion of ^{203}Pb, and in the three subjects K.B., J.B., and G.E. there was also an increase in plasma levels of ^{203}Pb. However, these changes were not statistically significant. The half time of ^{203}Pb in red cells was also reduced, but the change was only significant at the 10% level of probability.

These results can be compared to those in section 5.0, in which the two subjects K.B. and D.W. ingested ^{203}Pb with minerals. A decrease in the retained dose of ^{203}Pb in the red cells was also observed in both subjects, but a decrease in the retained dose in the urine was only found in subject D.W. These decreases were questioned at that time, however, because the 96 hour retentions of the two subjects were below 2%. It was argued that the possible presence of some of the unabsorbed fraction of ^{203}Pb in the body would have a significant effect on such low values of 96 hour retention.

The results described in the present section show that a decrease in the retained dose of ^{203}Pb in the red cells can occur with 96 hour retentions of approximately 40%, so that the decrease found in section 5.0 is probably correct. However, the magnitude of that decrease may still be influenced by the unabsorbed fraction of ^{203}Pb as argued above.

8.3 Compartmental model describing the kinetics of orally ingested ^{203}Pb

8.3.1 Structure of compartmental model developed from the literature and results of kinetic experiments (section 8.2)

The adequacy of the experimental data from the kinetic experiments to define the proposed model is unknown. The preliminary model, therefore, should be simple and restricted to one class (Berman, 1963). The least number of compartments and pathways between compartments should be chosen that are compatible with the known distribution of lead from the literature and the results of the kinetic experiments.

The mammillary model was the class of compartmental model chosen in the studies reviewed in section 8.1.1. The central compartment of the model proposed by Bernard (1977) represented mainly blood lead, although there was not a direct one-to-one correspondence. A fraction of another compartment also contributed to the blood lead. Rabinowitz et al (1974) chose blood as their central compartment, as did Batschelet et al (1979). All these models had pathways in both directions between the central compartment and the other compartments.

These models describing steady state levels of lead in the human, however, were found to be inadequate to explain the short term kinetics of tracer lead. Rabinowitz et al (1974) suggested that plasma and red cells should be regarded as separate compartments to explain the early distribution of tracer lead. Chamberlain et al (1978) implied that plasma should be the central compartment with lead entering from lung and gut and rapidly distributing to red cells, bone and other storage

sites. A further refinement of the mammillary model with a central plasma compartment was suggested by Baloh (1974). In his model, the central compartment was diffusible plasma lead and the other compartments were non diffusible lead, red cell lead, 'soft' tissue lead (brain, kidney, bone marrow, etc.), and 'hard' tissue lead (dense bone, hair, teeth, etc.)

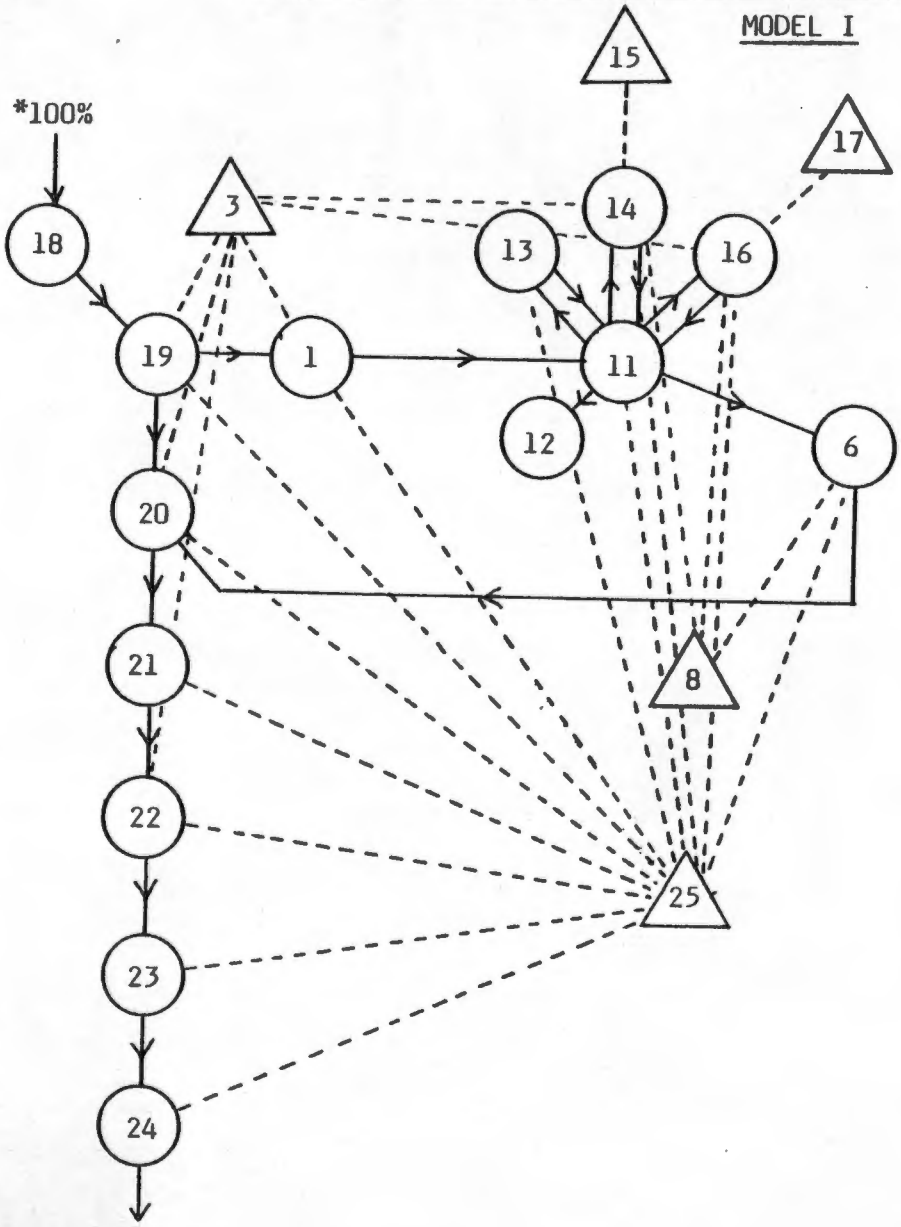
The mammillary model with plasma as the central compartment was chosen as the basis of the preliminary model, and the number of compartments in series was kept to a minimum. The compartments and the pathways of the simplest model that may be constructed from basic physiology, the literature and observations from the kinetic experiments is shown in figure 8.3.1. The development of the model and the relationship between experimental data and the model is explained in the following sections. The SAAM 25 nomenclature and symbols used are shown in figure 8.3.2.

a) Lead in the gut

^{203}Pb enters the stomach (18) and clears rapidly into the small bowel (19), as there was no evidence of radioactivity in the stomach on the 3.22 hours scintigram (figure 8.2.1). Lead is not absorbed from the stomach, but it is absorbed from the small bowel (Cantarow and Trumper, 1944), ^{203}Pb also appears to be temporarily stored in the wall of the small bowel (1), as shown in the scintigrams taken between 3.22 hours and 16.08 hours. This was suggested by the everted sac studies of Grunden and Stantic (1975) and Blair et al (1979) and the *in vivo* rat experiments of Conrad and Barton (1978), reviewed in section 8.1.2. The relationship between the model and the surface radioactivity data

FIGURE 8.3.1

Compartment model developed from literature and experimental observations



COMPARTMENTS

1 Wall of small bowel

6 Liver

11 Plasma

12 Accumulative urine

13 Red Cells

14 'Soft' tissue

16 'Hard' tissue

18 Stomach

19 Lumen of small bowel

20 24 Large bowel

SUMMERS

3 Small bowel

8 Liver

15 'Soft' tissue

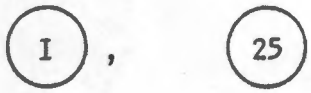
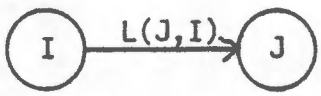
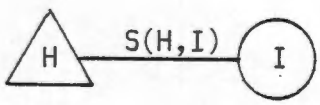
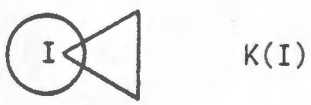
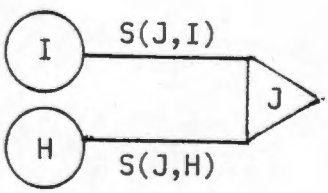
17 'Hard' tissue

25 Whole body

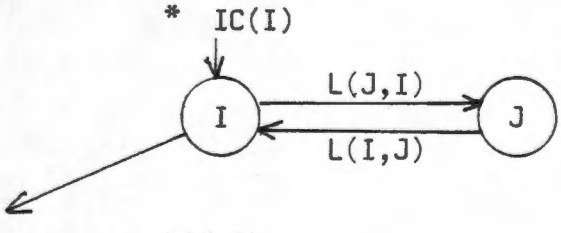
*100% oral ^{203}Pb

FIGURE 8.3.2

SAAM nomenclature and symbols

PROGRAM ELEMENT	DESCRIPTION	SYMBOL
	Compartment	
I	Independent variable	
F(I,T)	F-function I	
IC(I)	Value of F(I,T) at start of solution (Input of tracer)	
L(J,I)	Primary (non-linear) parameter	
S(H,I)	Secondary parameter (linear), summing coefficient	
K(I)	Secondary (linear) parameter, proportionally coefficient	
Qc(J,T)	Function generated from the F(I,T), T and other parameters. For a SUMMER $Qc(J,T) = \sum_{I} S(J,I) \times F(I,T)$	

TWO COMPARTMENT MODEL



L(Ø,I)

obtained over the region of the small bowel is described in the section, Summer compartments (f).

The unabsorbed fraction of ^{203}Pb passes through the small bowel to a series of compartments (20) - (24) representing large bowel, where it is assumed no absorption occurs (ICRP, 1959).
Compartments (20) - (24) provide a delay segment to simulate the transit of the lead through the large bowel to the rectum, from which it is excreted in the faeces. The movement of the unabsorbed fraction of ^{203}Pb through the large bowel can be clearly seen in the scintigrams from 10.47 hours to 48 hours.

b) Lead in plasma and red cells

^{203}Pb enters the plasma (11) from the wall of the small bowel (1), and is rapidly taken up by red cells (13). This occurred in all subjects. Hursh and Suomela (1968) and Chamberlain et al (1978) found the same avidity of lead for red cells, when human subjects were injected with ^{212}Pb and ^{203}Pb, respectively. Lead is lost from the red cells by red cell death (Hursh and Suomela, 1968), but Chamberlain et al (1978) found a biological half life of 15.4 days for their human subjects, and a mean half life of 17.44 days was found in section 8.2.3. These are less than the half life of 20 - 35 days of ^{51}Cr in normal human blood (Waldron, 1966), which suggests another loss mechanism apart from red cell death.

The percentages of ingested dose measured in the total plasma and red cells were absolute data, which were found by directly 'sampling' the plasma (11) and red cell (13). This data was used directly in the

solution of the model.

c) Lead in 'soft' and 'hard' tissues

Baloh (1974) suggested a broad classification of 'soft' and 'hard' tissues, and this was adopted as it reduces the number of compartments required to explain the distribution of lead. Lead transfers very rapidly from plasma to extracellular spaces and 'soft' tissue (14), but as the plasma lead concentration drops, there is a partial return from this compartment (Stover, 1959). Lead is also taken up in 'hard' tissue (16), and although bone lead is thought to be 'metabolically inactive', it may be released to the 'soft' tissue or plasma under conditions of bone resorption (Byers and Maloof, 1954). Surface radioactivity measurements over the medial aspect of the left calf ('soft' tissue) and left medial malleolus ('hard' tissue) represent proportional data, and they require the summers (15) and (17) to make them compatible with the model.

d) Lead in liver and kidneys

Appreciable uptake of ^{203}Pb occurred in the liver (6), which can be clearly seen in the scintigrams from 3.22 hours onwards. This agrees with the findings in the animal studies described in section 8.1.2. Lead has been assumed to be transferred to the liver from the plasma (Klaasen and Shoeman, 1974). The relationship between the model and the surface radioactivity data obtained from measurements over the liver is described in the section, Summer coefficients (f).

There was no evidence of kidney uptake of ^{203}Pb in the kinetic experiments performed in section 8.2. Although kidney uptake of lead was found in animal studies (section 8.1.2), it was always much less than liver uptake when lead was taken by mouth. Slight uptake of ^{203}Pb in the kidney could have occurred, which was undetected in the kinetic experiments. Kidneys were assumed, however, to be part of the 'soft' tissue compartment, as suggested by Baloh (1974).

e) Excretion of lead

Lead is primarily excreted in the bile (Blaxter and Cowie, 1946; Castellino et al, 1966; Cikrt, 1972; Klaasen and Shoeman, 1974) and in the gastric and intestinal secretions (Rabinowitz, 1974; 1976). Although Rabinowitz et al (1976) found that gastric juices may be a major source of endogenous faecal excretion of lead, secretin and cholecystokinin were used to stimulate secretions, so their results may not reflect the normal state. They also found in human subjects that only after a few months of continuous tracer uptake was there appreciable amounts of tracer lead in bile and gastrointestinal secretions. Other work described by Chamberlain et al (1968), suggested that endogenous faecal excretion is established at the same time as urinary excretion. Therefore, the results of Rabinowitz et al (1976) may not be relevant in a short-term tracer study.

In the present study, the gamma camera scintigrams from 3.22 hours onwards show appreciable uptake of ^{203}Pb in the liver, which could cause substantial biliary excretion of ^{203}Pb. Klaasen and Shoeman (1974) found in rats injected with low doses of lead that the positive concentration gradient of lead from liver to bile was one tenth that from plasma to liver. They also found that biliary excretion

is the major route of excretion of lead in the rat. In the preliminary model (figure 8.3.1), endogenous faecal excretion of ^{203}Pb was assumed to only occur from the liver (6).

Although it has been suggested that there may be entero-hepatic circulation of lead (Cantarow and Trumper, 1944), it has not been studied in man (Goyer and Mahaffey, 1972), and in rats it has been found to be very low (Cikrt and Tichý, 1975) or non existent (Conrad and Barton, 1978). It has been assumed not to occur in this preliminary model, so that clearance of lead from the liver is directly into non absorbing segments of the large bowel (20). The relationship of data on ^{203}Pb radioactivity in the liver to the model is discussed in the section, Summer coefficients (f).

Lead is excreted in the urine, and compartment (12) represents the accumulative urine excreted over the period of study. The urine data is absolute and it was used directly in the solution of the model. Lead is also excreted in sweat but the amount lost by this route is negligible in comparison to faecal and urinary losses (Rabinowitz, 1974; Chamberlain et al, 1978).

f) Summer compartments

The whole body counter data represents the sum of all compartments, summer (25), and the contribution of each compartment in the model to this summer is unity. Data obtained from surface radioactivity measurements are proportional data, representing the ^{203}Pb radioactivity in the fraction of the various compartments 'seen' by the *in vivo* detector. Therefore, summer or proportionality coefficients are

required to make these data compatible with the model.

Over the region of the small bowel, surface radioactivity measurements represented by summer (3) will consist of count rates arising from ^{203}Pb in the lumen (19), ^{203}Pb in the wall of the small bowel (1), endogenous ^{203}Pb (20), and will include contributions from ^{203}Pb in the 'soft' tissue (14) and 'hard' tissue (16). The presence of the unabsorbed fraction of lead which passes through the field of view of the *in vivo* detector between 16 - 48 hours is represented by either summer S(3,21) or (3,22).

Proportional data from surface radioactivity measurements performed over the liver are represented by summer (8), and they will include contributions from ^{203}Pb in 'soft' tissue (14) and 'hard' tissue (16). Proportional data from surface radioactivity measurements were used instead of the absolute data from the profile scan analysis, because only profile scans from 48 hours onwards could be analysed, as discussed in section 8.2.3. The profile scan analysis was not completely rigorous, because of the fit by eye of an adjusted 'soft'-tissue background profile to enable the liver profile peaks to be isolated. The mean values and standard deviations of the percentages of ingested dose calculated to be in the liver, therefore, were only used to define the maximum and minimum limits of the summer coefficient S(8,6), as shown in table 8.3.1.

TABLE 8.3.1

Summer coefficients for proportional liver data

SUBJECT	KINETIC 1.			KINETIC 2.		
	Liver* (Absolute %I.D.)	Liver¶ (Proportional %I.D.)	Summer coefficient	Liver* (Absolute %I.D.)	Liver¶ (Proportional %I.D.)	Summer coefficient
K.B.	14.05 ± 2.00†	2.27 ± 0.18	0.162 ± 0.026	10.08 ± 0.25	1.24 ± 0.08	0.123 ± 0.008
J.B.	18.64 ± 1.30	2.93 ± 0.15	0.157 ± 0.014	9.00 ± 0.98	1.29 ± 0.13	0.143 ± 0.021
B.C.	11.78 ± 2.11	3.15 ± 0.26	0.267 ± 0.053	3.05 ± 0.61	0.791 ± 0.061	0.259 ± 0.055
G.E.	17.76 ± 2.16	2.81 ± 0.10	0.158 ± 0.020	5.70 ± 0.91	0.853 ± 0.022	0.150 ± 0.024
D.W.	16.69 ± 3.26	3.49 ± 0.23	0.209 ± 0.043	-	-	-

* Mean of liver profile scan contents from 48 hours onwards.

¶ Mean of liver surface radioactivity data from 48 hours onwards.

† ± 1 standard deviation.

8.3.2 Solution, testing and adjusting of compartmental model

In this section, all the work on developing the final model was performed with data from the experiments performed on subject K.B. He was the first subject to complete the paired kinetic experiments, and most of the work was done using the data from his Kinetic 1. experiment. Any major changes in the model were checked for compatability with the data from his Kinetic 2. experiment.

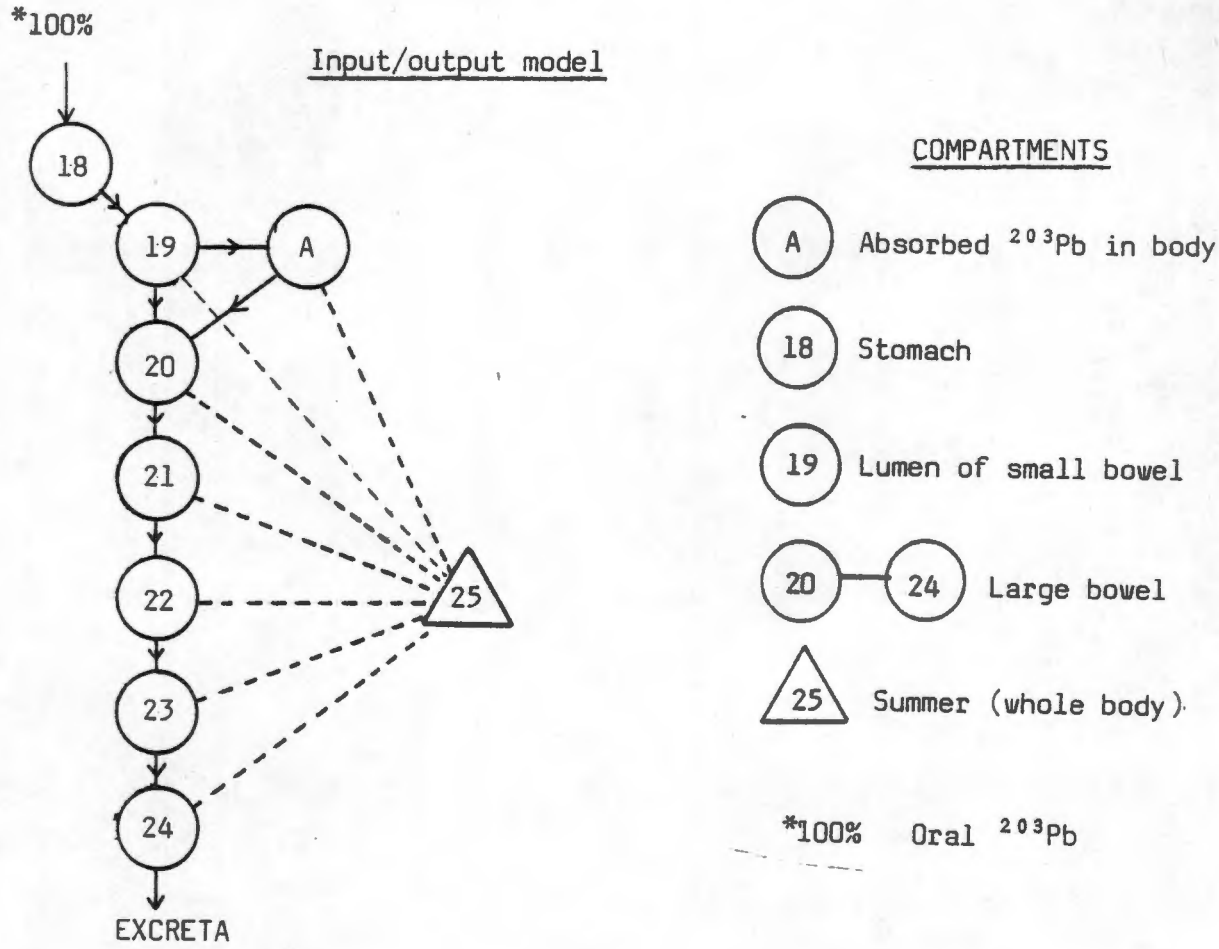
a) Initial values of variable parameters

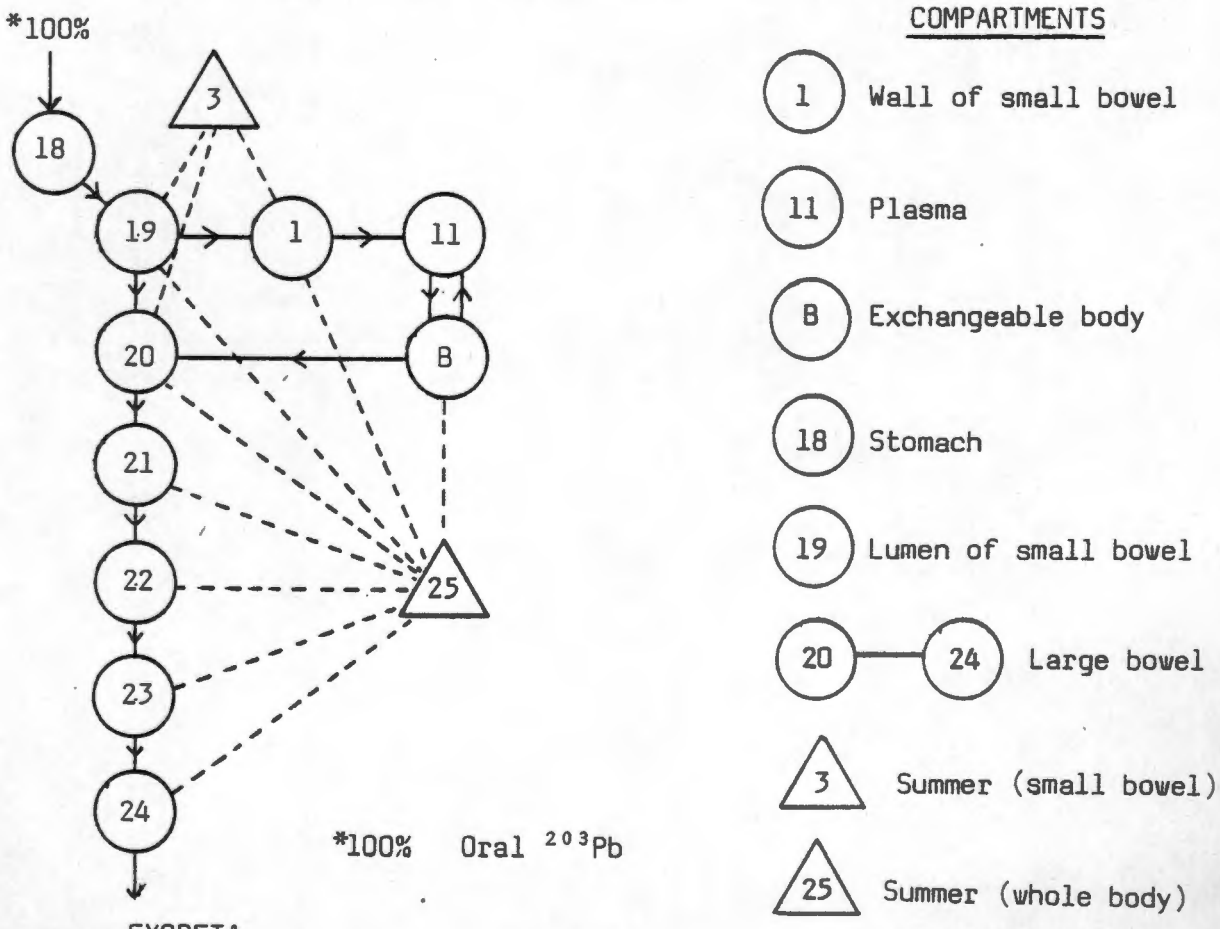
It was stated in section 8.1.4 that it is necessary to find initial values for the variable parameters when the model is set up in terms of the differential equations directly, and when the solution of these equations is achieved by numerical procedures.

First, the compartmental model proposed in section 8.3.1 was reduced to a basic input/output system. This was used to find initial values for the rate constants representing the transfer of ^{203}Pb between small bowel and stomach, L(19,18), wall of small bowel and lumen, L(1,19), and large bowel and lumen of small bowel, L(20,19). This is shown in figure 8.3.3 where (A) and (20) represent the absorbed and the unabsorbed fractions of ingested lead in the body, respectively. A solution was obtained using only whole body radioactivity data.

The next step was to use an exchangeable body compartment (B) to find initial values for pathways exchanging with plasma (11), as shown in figure 8.3.3. Whole body and small-bowel surface radioactivity data were used in this solution. With these estimates of initial values and

FIGURE 8.3.3


*100%
Input/output model
18
19
A
20
21
22
25
23
24
EXCRETA
COMPARTMENTS
A
Absorbed 203Pb in body
18
Stomach
19
Lumen of small bowel
20
24
Large bowel
25
Summer (whole body)
*100%
Oral 203Pb


Input/output model with exchangeable body compartment
*100%
3
18
19
1
11
20
B
21
22
25
23
24
*100%
Oral 203Pb
COMPARTMENTS
1
Wall of small bowel
11
Plasma
B
Exchangeable body
18
Stomach
19
Lumen of small bowel
20
24
Large bowel
3
Summer (small bowel)
25
Summer (whole body)

using the data from other compartments as a guide to their order of magnitude, it was possible to estimate L(J,I) parameters for other pathways.

b) MODEL I

The preliminary model developed in section 8.3.1 was called MODEL I, and a solution was obtained giving the parameter values and the residual sums of squares shown in table 8.3.2. The standard deviations of the L(J,I) parameters are very low, except for L(16,11), rate constant representing transfer of lead to 'hard' tissue from plasma. However, the residual sums of squares are high for  and  , representing liver and red cells. The fits between calculated values and early experimental data were poor, suggesting that the rates of input of ^{203}Pb into these compartments were too low.

As they both directly communicate with plasma  , it was decided to try a solution excluding plasma data. In effect, this removes constraints on the plasma compartment, which should allow the other communicating compartments to receive ^{203}Pb at higher rates. The result is shown in table 8.3.3, and the values of L(6,11) and L(13,11), rate constants representing the transfer of ^{203}Pb to liver from plasma and to red cells from plasma, respectively, have increased from 11.43 and 30.57 to 352.91 and 500.00, and the residual sums of squares for  and  have improved from 0.0389 and 0.0187 to 0.0068 and 0.0037.

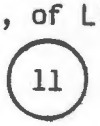
There are very large standard deviations, however, of L(J,I) parameters associated with the output of tracer from plasma  . This

TABLE 8.3.2

RESULTS OF COMPARTMENTAL ANALYSIS USING ALL EXPERIMENTAL DATA

SUBJECT:K.B. MODEL:I

PARAMETER	VALUE (HR-1)	S.D.*
L (1,19)	2.517	0.119
L (11, 1)	0.022	0.001
L (6,11)	11.430	0.334
L (12,11)	1.228	0.033
L (13,11)	30.569	1.384
L (11,13)	0.040	0.002
L (14,11)	0.687	0.044
L (11,14)	0.411	0.032
L (16,11)	1.217	3.174
L (11,16)	0.163	0.009
L (20, 6)	0.025	0.001
L (19,18)	1.068	0.079
L (20,19)	0.154	0.045
L (21,20)	0.078	0.005

RESIDUAL SUMS OF SQUARES	
TOTAL	0.08239
COMP. 3	0.00271
COMP. 8	0.03887
COMP.11	0.00403
COMP.12	0.00322
COMP.13	0.01870
COMP.15	0.00445
COMP.17	0.00829
COMP.25	0.00213

* +- 1 STANDARD DEVIATION

TABLE 8.3.3

RESULTS OF COMPARTMENTAL ANALYSIS USING

ALL EXPERIMENTAL DATA EXCEPT PLASMA DATA

SUBJECT:K.B. MODEL:I

PARAMETER	VALUE (HR-1)	S.D.*
L (1,19)	3.679	23.973
L (11, 1)	3.454	17.958
L (6,11)	352.906	3764.696
L (12,11)	52.761	561.529
L (13,11)	500.000	5337.419
L (11,13)	0.011	0.001
L (14,11)	939.825	10018.230
L (11,14)	0.014	0.001
L (16,11)	1.387	14.757
L (11,16)	0.007	0.001
L (20, 6)	0.012	0.001
L (19,18)	0.183	0.008
L (20,19)	0.100	0.700
L (21,20)	0.376	0.020

RESIDUAL SUMS OF SQUARES	
TOTAL	0.02741
COMP. 3	0.00449
COMP. 8	0.00682
COMP.12	0.00211
COMP.13	0.00367
COMP.15	0.00414
COMP.17	0.00525
COMP.25	0.00093

* +- 1 STANDARD DEVIATION

suggests that the quantity of tracer leaving (11) is not sufficient to satisfy the calculated values needed to fit the experimental data of liver (6). Reducing this output would allow more ^{203}Pb to enter the compartments communicating with (11), and this may be achieved by introducing a second liver compartment, (4), between (1) and (11). The calculated values required to fit the experimental liver data are now generated from two compartments, and the contribution of these two compartments to the summer (8) will be the same. Therefore, S(8,4) was allowed to vary and S(8,6) was kept equal to the value of S(8,4) by a dependence equation. With these changes, the rate constant representing output of ^{203}Pb from (11) to (6), L(6,11), should now decrease in magnitude. These changes were included in a new model, MODEL II (figure 8.3.4).

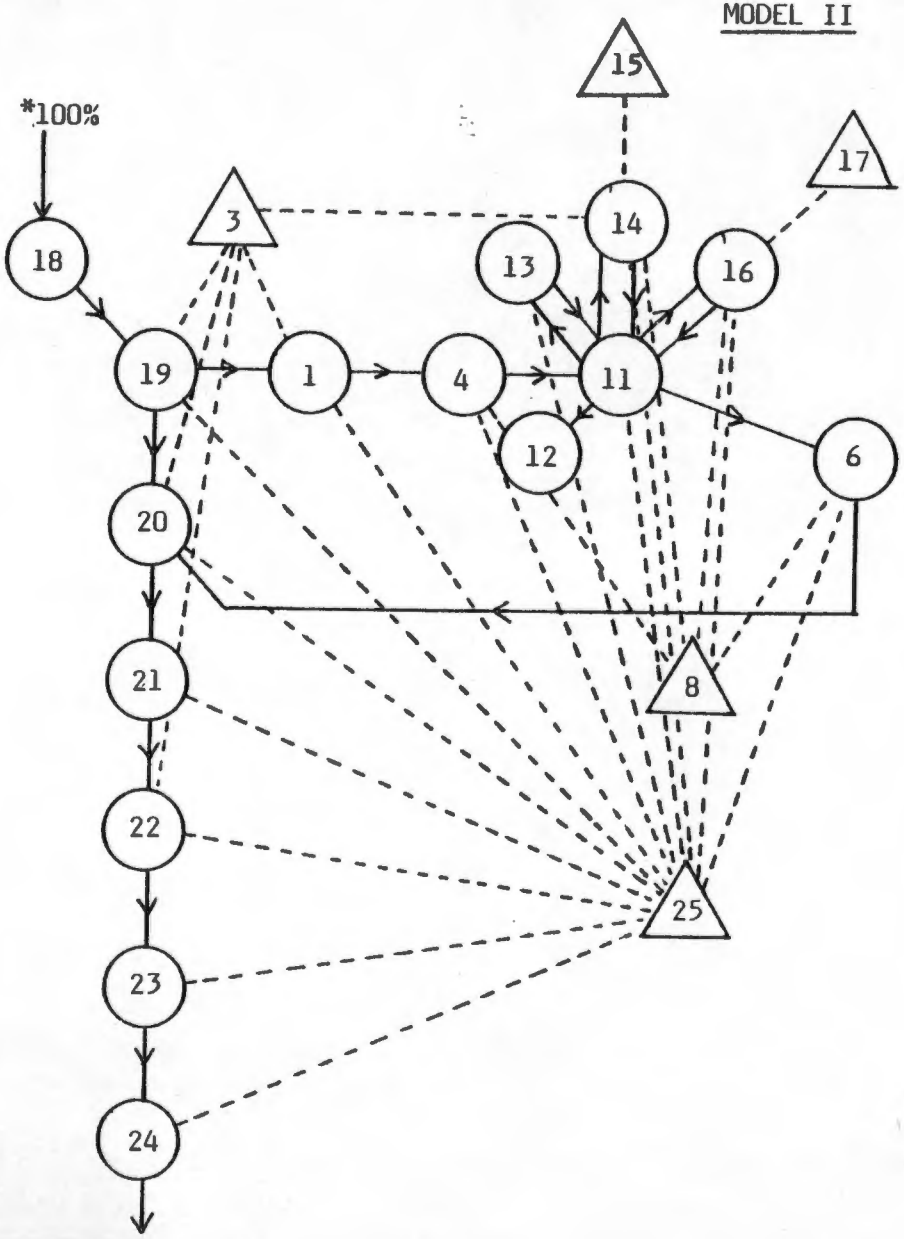
c) MODEL II

i) Absorbed fraction of ^{203}Pb

A solution was obtained using MODEL II, which gave values of parameters and residual sums of squares as shown in table 8.3.4. L(6,11) and the standard deviations of the L(J,I) parameters are reduced, and the residual sums of squares have improved for all compartments. However, the percentage of the ingested dose of ^{203}Pb absorbed, L(1,19) x 100/ (L(1,19) + L(20,19)), is 94.55 which does not agree with the percentage of 65.42 retained at 96 hours, measured by whole body counting (table 8.2.3). Therefore, the rate constants describing the transport of ^{203}Pb to wall from lumen of small bowel, L(1,19), and movement of ^{203}Pb to large bowel from lumen of small bowel, L(20,19), have to assume values that satisfy the division of ^{203}Pb between

FIGURE 8.3.4

MODEL II



COMPARTMENTS

1 Wall of small bowel

4 6 Liver

11 Plasma

12 Accumulative urine

13 Red cells

14 'Soft' tissue

16 'Hard' tissue

18 Stomach

19 Lumen of small bowel

20 24 Large bowel

SUMMERS

3 Small bowel

8 Liver

15 'Soft' tissue

17 'Hard' tissue

25 Whole body

*100% oral ^{203}Pb

TABLE 8.3.4

RESULTS OF COMPARTMENTAL ANALYSIS USING

ALL EXPERIMENTAL DATA EXCEPT PLASMA DATA

SUBJECT:K.B. MODEL:II

PARAMETER	VALUE (HR-1)	S.D.*
L (1,19)	2.969	0.229
L (4, 1)	3000.000	6898.865
L (11, 4)	6.141	0.740
L (6,11)	164.380	126.238
L (12,11)	23.437	18.064
L (13,11)	277.142	214.799
L (11,13)	0.015	0.001
L (14,11)	559.613	435.125
L (11,14)	0.020	0.001
L (16,11)	0.766	8.644
L (11,16)	0.006	0.001
L (20, 6)	0.015	0.001
L (19,18)	0.253	0.007
L (20,19)	0.171	0.043
L (21,20)	0.433	0.022

RESIDUAL SUMS OF SQUARES	
TOTAL	0.01251
COMP. 3	0.00440
COMP. 8	0.00118
COMP.12	0.00082
COMP.13	0.00128
COMP.15	0.00280
COMP.17	0.00167
COMP.25	0.00036

* +- 1 STANDARD DEVIATION

absorbed and unabsorbed fractions, and the rate at which the ^{203}Pb is absorbed into the wall of the small bowel. This rate will depend on the calculated levels of ^{203}Pb required in the body compartments to fit the experimental data. Therefore, L(1,19) and L(20,19) should not be allowed to vary between wide limits, but they should be constrained so that initial values of absorbed and unabsorbed fractions of ^{203}Pb are the same as those found by whole body counting.

ii) Plasma levels of ^{203}Pb

The solution of MODEL II was found without the constraints of experimental plasma data. In order to examine the behaviour of plasma ^{203}Pb in MODEL II, a simulation was performed with the values of the variable parameters listed in table 8.3.4. This simulation gave 96 hour values of ^{203}Pb in various compartments as shown in table 8.3.5. The agreement between simulated and experimental values is good, except for the plasma compartment for which the simulated value is approximately 10^{-2} smaller than the experimental value. This discrepancy could be explained if the ^{203}Pb in the plasma was in two different forms.

Baloh (1974) suggested that plasma lead is made up of two fractions, the plasma protein-bound fraction and the diffusible fraction, and that probably the diffusible form is a very small percentage of the total plasma lead. A similar suggestion was made by Goyer and Mahaffey (1972) that lead in the body must exist in two forms; a diffusible or mobile form and a non diffusible or fixed form. They also suggested that lead in the plasma can be chelated to small diffusible ligands, a form of plasma lead which could correspond to the diffusible fraction mentioned by

TABLE 8.3.5

Comparison of simulated and experimental ^{203}Pb levels at 96 hours in various compartments of MODEL II

COMPARTMENT	% INGESTED DOSE (Simulation)	% INGESTED DOSE (Experimental)
3*	0.862	0.563
8*	2.18	2.08
11	4.4×10^{-4}	0.042
12	4.17	4.65
13	20.12	21.46
15*	0.072	0.081
17*	0.100	0.117
25	68.00	65.42

* Summer compartments - proportional percentage ingested dose.

Baloh.

The level of plasma ^{203}Pb found by the simulation of MODEL II is the result of ^{203}Pb exchanging with the red cell, 'soft' tissue and 'hard' tissue compartments. This behaviour and the low level of simulated plasma ^{203}Pb compared to the experimentally determined level are similar to that of the diffusible plasma lead suggested by Baloh (1974) and Goyer and Mahaffey (1972). The experimentally determined level probably arises from a slowly diffusible fraction of plasma ^{203}Pb.

d) MODEL III

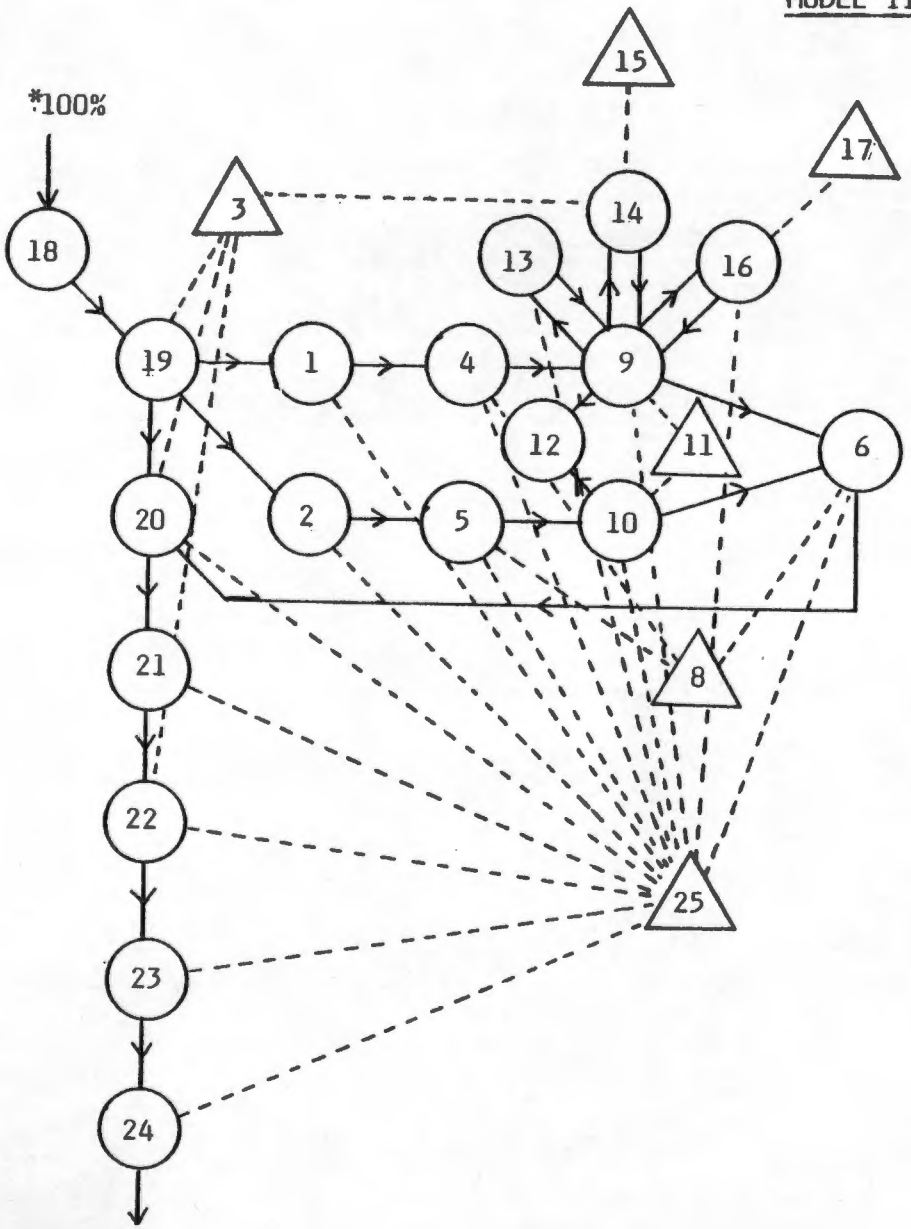
i) Changes to model

The two forms of plasma lead could arise from two different absorptive pathways for lead in the small bowel. Two pathways were suggested by the results of experiments performed in section 6.0, one that lead shares specifically with calcium and the other specifically with phosphorous. In the model, therefore, a second pathway was introduced to a second compartment, representing wall of small bowel, from the lumen of the small bowel. Lead was transferred to a second plasma compartment from the new wall compartment via a second liver compartment.

Figure 8.3.5 shows the schematic for MODEL III with pathways to the small-bowel wall compartments (1) and (2) from the lumen of small bowel compartment (19). Therefore, the rate constants L(1,19) and L(2,19) represent the common lead/calcium and common lead/phosphorous absorptive pathways, which have been suggested to exist. Each wall

FIGURE 8.3.5

MODEL III



COMPARTMENTS

1 2 Wall of small bowel

4 6 Liver

9 10 Plasma

12 Accumulative urine

13 Red cells

14 'Soft' tissue

16 'Hard' tissue

18 Stomach

19 Lumen of small bowel

20 24 Whole body

SUMMERS

3 Small bowel

8 Liver

11 Plasma

15 'Soft' tissue

17 'Hard' tissue

25 Whole body

*100% oral ^{203}Pb

compartment communicates with one of the two plasma compartments (9) and (10). The experimental plasma data is now represented by the summer 

, and contributions from (9) and (10) to 

are both unity. The liver compartment (5) has been introduced to maintain compatibility between the two pathways from (1) and (2) to the plasma compartments (9) and (10). Compartment (5) contributes to 

by the summer coefficient S(8,5). This coefficient was made equal to S(8,4) by a dependence equation. Uptake of ^{203}Pb in liver compartment (6) also occurs from (10), and urinary excretion of ^{203}Pb from (10) is by a pathway represented by the rate constant L(12,10).

Summer coefficients S(3,1), S(3,2), S(3,16) and S(8,14) were all very small and removed from the model. The values of S(3,19) and S(3,20) were very close, so only S(3,19) was allowed to vary and S(3,20) was made equal to S(3,19) by a dependence equation.

ii) <u>Constraints on L(1,19), L(2,19) and L(20,19)</u>

The constraints on L(1,19), L(2,19) and L(20,19), rate constants describing the transport of ^{203}Pb to wall from lumen of small bowel and movement of ^{203}Pb to large bowel from lumen of small bowel, were imposed by using the intercept from the equation of the regression line fitted to the whole body retention from 96 hours onwards (table 11.1.2). The absorbed percentage of ^{203}Pb in the model,

$(L(1,19)) + L(2,19)) \times 100 / (L(1,19) + L(2,19) + L(20,19))$, was made equal to the intercept value, and the unabsorbed percentage,

$L(20,19) \times 100 / (L(1,19) + L(2,19) + L(20,19))$, equal to 100% minus

the intercept value. A solution using these contraints was obtained giving an absorbed fraction consistent with whole body retention of ^{203}Pb.

The rates of input and output of ^{203}Pb in the body compartments have to be satisfied and these are reflected in the magnitudes of L(1,19) and L(2,19). A further solution was found in which L(1,19) was allowed to vary between wide limits, but dependence equations were used to ensure that L(2,19) and L(20,19) were always a fixed fraction of L(1,19). This maintained the percentages of absorbed and unabsorbed ^{203}Pb found in the previous solution.

Finally, the values of L(1,19), L(2,19) and L(20,19) found in this last solution were used as initial values in a solution in which they were allowed to vary freely. In this way, it was possible to produce the necessary absorbed and unabsorbed fractions consistent with whole body retention, and still allow the magnitudes of L(1,19) and L(2,19) to vary to enable the calculated values from the model solution to fit the experimental data. The results of the final solution of MODEL III are shown in table 8.3.6.

e) MODEL IV

From the results of the solution of MODEL III, it can be seen that the rate constant describing urinary excretion from plasma (10), L(12,10), is very small. This pathway can be removed from the model without affecting the fit of the calculated values to experiment data. The standard deviation of the rate constant L(16,9), representing transfer of ^{203}Pb between the 'hard tissue' compartment (16) and

TABLE 8.3.6

RESULTS OF COMPARTMENTAL ANALYSIS USING ALL EXPERIMENTAL DATA

SUBJECT:K.B. MODEL:III

PARAMETER	VALUE (HR-1)	S.D.*
L (1,19)	0.142	0.015
L (2,19)	0.025	0.013
L (4, 1)	175.000	4400.000
L (5, 2)	1710.000	33500.000
L (9, 4)	12.000	13.100
L (10, 5)	0.007	0.001
L (6, 9)	78.000	44.100
L (12, 9)	27.700	8.210
L (12,10)	0.001	0.170
L (13, 9)	333.000	97.600
L (9,13)	0.014	0.005
L (14, 9)	366.000	146.000
L (9,14)	0.015	0.006
L (16, 9)	1.920	13.300
L (9,16)	0.006	0.004
L (6,10)	0.933	0.451
L (19,18)	2.310	1.520
L (20, 6)	0.012	0.004
L (20,19)	0.070	0.007
L (21,20)	0.100	0.015

RESIDUAL SUMS OF SQUARES	
TOTAL	0.04693
COMP. 3	0.00442
COMP. 8	0.00995
COMP.11	0.00351
COMP.12	0.00380
COMP.13	0.00150
COMP.15	0.00431
COMP.17	0.01521
COMP.25	0.00447

* +- 1 STANDARD DEVIATION

plasma compartment (9) is still high, and the fit between calculated values and experimental data is poor. The rate constant L(12,9), representing urinary excretion of ^{203}Pb from (9), had a low standard deviation, and as both the experimental accumulative urine and 'hard' tissue data increased continuously over the period of the study, it was decided to try a solution without L(9,16).

With the introduction of the second absorption pathway and its associated compartments, the fit to the liver and whole body data has deteriorated. The fit was poor at later times for both sets of data, indicating that a delay compartment may be necessary between (6) and (20). Therefore, the changes to the model were the exclusion of pathways L(12,10) and L(9,16) and the introduction of a liver delay compartment (7), to give MODEL IV.

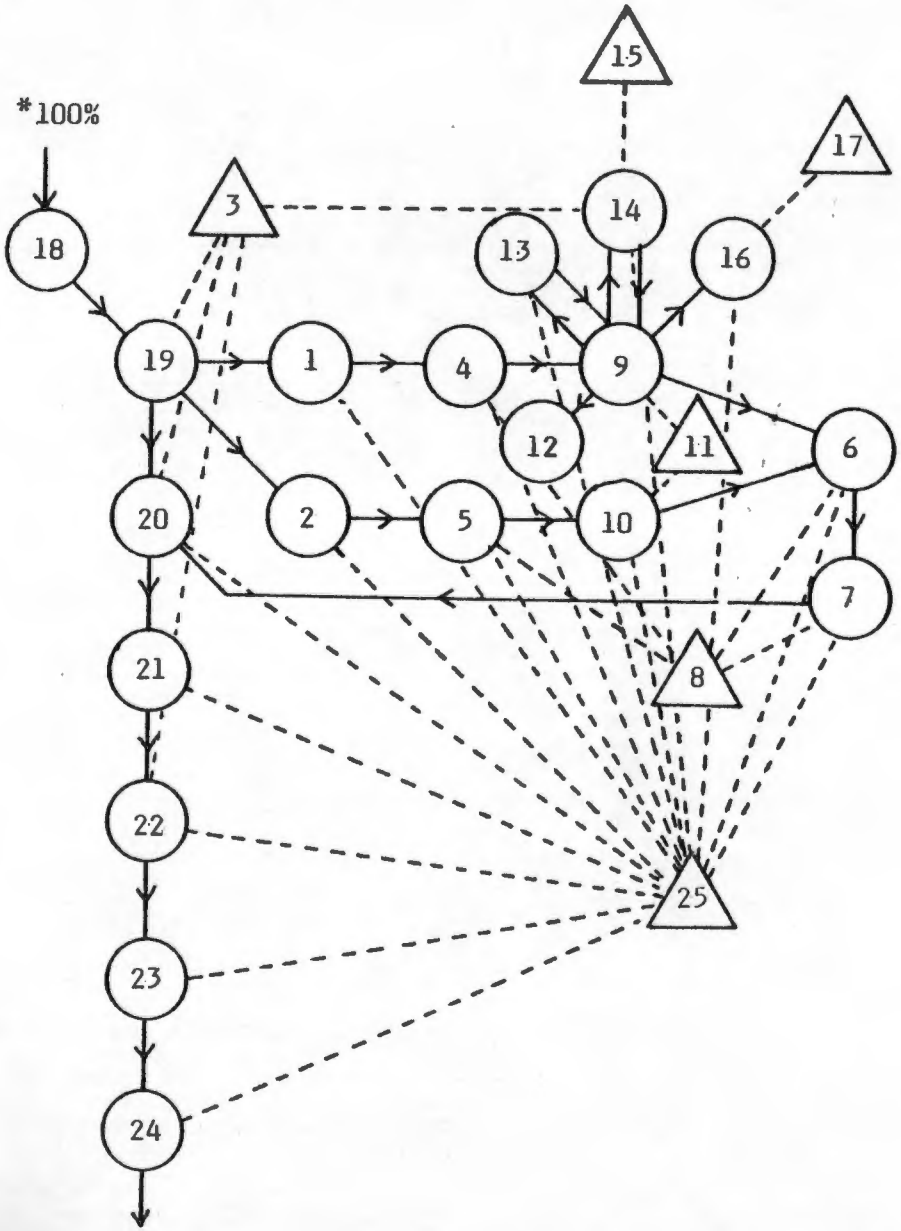
Figure 8.3.6 shows the schematic for MODEL IV with an extra summer S(8,7) so that (7) may contribute to the calculated data for the liver. As with the other liver summer coefficients, S(8,7) was made equal to S(8,4) by a dependence equation. Therefore, all liver compartments contribute equally to (8). This assumes that the in vivo detector 'sees' the same fraction of ingested dose in each liver compartment. Table 8.3.7 shows the results of the solution with a better fit to whole body and liver data.

f) Other subjects

MODEL IV was used in the compartmental analysis of the experimental data from both Kinetic 1. and Kinetic 2. experiments of all the other subjects. The exception was the Kinetic 2. experiment of subject D.W.,

FIGURE 8.3.6

MODEL IV



COMPARTMENTS

1 2 Wall of small bowel

4 7 Liver

9 10 Plasma

12 Accumulative urine

13 Red Cells

14 'Soft' tissue

16 'Hard' tissue

18 Stomach

19 Lumen of small bowel

20 24 Whole body

SUMMERS

3 Small bowel

8 Liver

11 Plasma

15 'Soft' tissue

17 'Hard' tissue

25 Whole body

*100% oral ^{203}Pb

TABLE 8.3.7

RESULTS OF COMPARTMENTAL ANALYSIS USING

ALL EXPERIMENTAL DATA

SUBJECT:K.B. MODEL:IV

PARAMETER	VALUE (HR-1)	S.D.*
L (1,19)	0.135	0.009
L (2,19)	0.025	0.008
L (4, 1)	724.182	17413.300
L (5, 2)	632.800	10570.300
L (9, 4)	1.404	0.302
L (10, 5)	0.006	0.001
L (6, 9)	50.373	25.109
L (12, 9)	29.468	8.666
L (13, 9)	409.412	124.568
L (9,13)	0.018	0.002
L (14, 9)	510.557	151.111
L (9,14)	0.021	0.002
L (16, 9)	0.899	0.262
L (6,10)	0.842	0.211
L (7, 6)	32.167	694.352
L (20, 7)	0.008	0.002
L (19,18)	2.317	1.522
L (20,19)	0.070	0.008
L (21,20)	0.099	0.004

RESIDUAL SUMS OF SQUARES	
TOTAL	0.03023
COMP. 3	0.00317
COMP. 8	0.00214
COMP.11	0.00333
COMP.12	0.00156
COMP.13	0.00140
COMP.15	0.00411
COMP.17	0.01442
COMP.25	0.00010

* +- 1 STANDARD DEVIATION

as there was insufficient experimental data. Even with the lower than planned absorption of ^{203}Pb in the Kinetic 2. experiments of subjects B.C. and G.E., there was sufficient in vivo data to perform compartmental analysis.

There were a few minor changes required in the model, and these involved only summer coefficients. A better fit between calculated values and experimental small bowel data from the Kinetic 2. experiment of subject B.C. was obtained using the summer coefficient S(3,21) instead of S(3,22). This was caused by the faster transit time of ^{203}Pb in the large bowel of subject B.C. in his Kinetic 2. experiment, as indicated by the high value of L(21,20) compared with those found in the analysis of data from other subjects.

The contribution of ^{203}Pb in the 'hard' tissue to the liver surface radioactivity measurements, represented by summer coefficient S(8,16), was only significant in subject G.E. There was also little contribution to the surface radioactivity measurements performed over the small bowel of 'soft' tissue ^{203}Pb, represented by summer coefficient S(3,14), in this same subject.

8.3.3 Results

a) Compatibility of MODEL IV with kinetic data

Tables comparing and figures showing the fits between model calculated values and experimental data are listed in sections 12 and 13, respectively. Visual inspection shows that, overall, fits are generally good. The exceptions are those to the red cell data from

the Kinetic 2. experiments of subjects, K.B., J.B. and B.C., to the 'hard' tissue data from both experiments of subjects K.B. and G.E. and, at later times, to the 'soft' tissue data from both experiments of subject B.C. There were also poor fits to small bowel data from the Kinetic 2. experiments of all subjects except subject K.B. These were the result of the large unabsorbed fraction of ^{203}Pb moving back through the field-of-view of the in vivo detector between 16 - 48 hours.

Table 8.3.8 shows the residual sums of squares for the fits to all the experimental data, and the total values are lower for absolute data than for proportional data. It is noticeable that if the residual sums of squares of the fits to red cell data are compared between Kinetic 1. and Kinetic 2. experiments, those of the latter are usually smaller. This contradicts the visual inspection, but the discrepancy occurred because the model was unable to fit the early rapid phase of red cell uptake of ^{203}Pb in the first 3 hours during the Kinetic 1. experiments. This same effect occurred with the fits to the early phases of 'soft' and 'hard' tissue data.

Tables 8.3.9-13 list the variable parameters obtained from the compartmental analysis, using experimental data from the paired kinetic experiments. There was insufficient data from the Kinetic 2. experiment of subject D.W. to allow a full compartmental analysis. There are very large uncertainties in the variable parameters L(4,1), L(5,2) and L(7,6), rate constants representing the transfer of ^{203}Pb between wall of the small bowel and liver, and between liver compartments in the route of biliary excretion of ^{203}Pb. All model solutions converged to a minimum least squares.

TABLE 8.3.8

Residual sums of squares from model solutions

DATA	SUBJECTS										TOTAL
	K.B.		J.B.		B.C.		G.E.		D.W.		
	Kinetic 1.	Kinetic 2.	Kinetic 1.	Kinetic 2.	Kinetic 1.	Kinetic 2.	Kinetic 1.	Kinetic 2.	Kinetic 1.	Kinetic 2.	
Whole Body*	0.97§	0.52	0.72	1.63	4.63	1.34	2.25	0.82	1.25	-	14.13
Plasma*	33.28	4.19	27.57	4.10	29.05	3.79	3.14	8.11	28.19	-	141.42
Red Cells*	13.99	12.18	9.32	9.48	42.17	5.72	17.21	4.46	23.66	-	138.19
Urine*	15.61	2.78	6.68	0.08	4.59	0.35	8.99	1.52	34.50	-	75.10
Small Bowel¶	31.73	10.44	69.42	9.07	17.91	10.81	14.78	20.91	13.37	-	198.44
Liver¶	21.36	5.55	32.66	1.38	30.62	3.37	8.33	119.35	23.54	-	246.16
'Soft'Tissue¶	41.14	18.70	38.05	18.18	31.89	6.44	19.29	11.17	103.82	-	288.68
'Hard'Tissue¶	144.25	28.27	43.27	8.38	18.12	3.56	87.16	13.30	25.08	-	371.39

§ All readings are multiples of 10^{-4}
* Absolute data
¶ Proportional data

TABLE 8.3.9

COMPARISION OF VARIABLE PARAMETERS FROM

PAIRED KINETIC EXPERIMENTS

SUBJECT:K.B.

PARAMETER	KINETIC 1. (HR-1)		KINETIC 2. (HR-1)	
L (1,19)	0.135+-	0.009*	0.124+-	0.010
L (2,19)	0.025+-	0.008	0.013+-	0.005
L (4, 1)	724.182+-	17413.300	5582.019+-	9998.821
L (5, 2)	632.800+-	10570.300	1023.827+-	6109.701
L (9, 4)	1.404+-	0.302	9.865+-	2.985
L (10, 5)	0.006+-	0.001	0.009+-	0.001
L (6, 9)	50.373+-	25.109	80.878+-	21.225
L (12, 9)	29.468+-	8.666	22.278+-	4.031
L (13, 9)	409.412+-	124.568	242.384+-	42.874
L (9,13)	0.018+-	0.002	0.014+-	0.001
L (14, 9)	510.557+-	151.111	728.346+-	119.019
L (9,14)	0.021+-	0.002	0.020+-	0.002
L (16, 9)	0.899+-	0.262	0.537+-	0.096
L (6,10)	0.842+-	0.211	0.699+-	0.282
L (7, 6)	32.167+-	694.352	758.821+-	2101.035
L (20, 7)	0.008+-	0.002	0.008+-	0.005
L (19,18)	2.317+-	1.522	2.020+-	0.350
L (20,19)	0.070+-	0.008	0.130+-	0.009
L (21,20)	0.099+-	0.004	0.103+-	0.005
S (3,14)	0.010+-	0.004	0.006+-	0.002
S (3,19)	0.119+-	0.012	0.153+-	0.009
S (3,22)	0.282+-	0.038	0.126+-	0.015
S (8, 4)	0.161+-	0.028	0.131+-	0.030
S (15,14)	0.003+-	0.000	0.002+-	0.000
S (17,16)	1.000+-	0.000	1.000+-	0.026

* +- 1 STANDARD DEVIATION

TABLE 8.3.10

COMPARISION OF VARIABLE PARAMETERS FROM

PAIRED KINETIC EXPERIMENTS

SUBJECT:J.B.

PARAMETER	KINETIC 1. (HR-1)		KINETIC 2. (HR-1)	
L (1,19)	0.220+-	0.014*	0.114+-	0.013
L (2,19)	0.020+-	0.005	0.010+-	0.002
L (4, 1)	5043.850+-	25854.320	2.801+-	0.554
L (5, 2)	15.041+-	40.446	289.596+-	19547.510
L (9, 4)	5.630+-	1.184	859.211+-	13867.920
L (10, 5)	0.009+-	0.001	0.005+-	0.001
L (6, 9)	113.004+-	25.120	79.832+-	21.835
L (12, 9)	32.805+-	5.776	21.922+-	5.838
L (13, 9)	460.188+-	82.189	230.818+-	60.737
L (9,13)	0.014+-	0.002	0.014+-	0.001
L (14, 9)	534.720+-	110.035	760.356+-	204.848
L (9,14)	0.018+-	0.002	0.029+-	0.003
L (16, 9)	0.876+-	0.154	0.530+-	0.141
L (6,10)	0.844+-	0.219	0.357+-	0.068
L (7, 6)	100.000+-	1282.824	897.751+-	55454.160
L (20, 7)	0.006+-	0.001	0.007+-	0.001
L (19,18)	2.061+-	0.461	2.490+-	1.040
L (20,19)	0.064+-	0.008	0.200+-	0.015
L (21,20)	0.090+-	0.007	0.075+-	0.004
S (3,14)	0.000+-	0.002	0.005+-	0.001
S (3,19)	0.186+-	0.012	0.185+-	0.015
S (3,22)	0.410+-	0.083	0.051+-	0.009
S (8, 4)	0.171+-	0.005	0.171+-	0.004
S (15,14)	0.002+-	0.000	0.001+-	0.000
S (17,16)	1.000+-	0.025	1.000+-	0.027

* +- 1 STANDARD DEVIATION

TABLE 8.3.11

COMPARISION OF VARIABLE PARAMETERS FROM

PAIRED KINETIC EXPERIMENTS

SUBJECT:B.C.

PARAMETER	KINETIC 1. (HR-1)		KINETIC 2. (HR-1)	
L (1,19)	0.191+-	0.013*	0.124+-	0.021
L (2,19)	0.010+-	0.004	0.003+-	0.002
L (4, 1)	9989.000+-	22208.450	1.917+-	0.671
L (5, 2)	151.254+-	428.238	50.000+-	524.609
L (9, 4)	7.604+-	1.409	350.251+-	1506.506
L (10, 5)	0.005+-	0.001	0.004+-	0.001
L (6, 9)	30.824+-	14.296	119.636+-	25.904
L (12, 9)	22.444+-	2.532	15.629+-	4.655
L (13, 9)	241.939+-	25.742	176.467+-	56.429
L (9,13)	0.014+-	0.001	0.014+-	0.002
L (14, 9)	494.816+-	68.061	1177.003+-	330.459
L (9,14)	0.011+-	0.001	0.036+-	0.003
L (16, 9)	0.570+-	0.062	0.670+-	0.201
L (6,10)	0.415+-	0.115	0.244+-	0.109
L (7, 6)	6.621+-	24.153	6.457+-	85.298
L (20, 7)	0.004+-	0.002	0.014+-	0.001
L (19,18)	2.010+-	1.281	2.303+-	1.258
L (20,19)	0.070+-	0.010	0.318+-	0.042
L (21,20)	0.070+-	0.008	0.355+-	0.019
S (3,14)	0.014+-	0.001	0.014+-	0.001
S (3,19)	0.075+-	0.006	0.074+-	0.009
S (3,22)	0.093+-	0.024	0.106+-	0.003
S (8, 4)	0.320+-	0.009	0.204+-	0.000
S (15,14)	0.002+-	0.000	0.001+-	0.000
S (17,16)	1.000+-	0.025	1.000+-	0.025

* +- 1 STANDARD DEVIATION

TABLE 8.3.12

COMPARISION OF VARIABLE PARAMETERS FROM

PAIRED KINETIC EXPERIMENTS

SUBJECT:G.E.

PARAMETER	KINETIC 1. (HR-1)		KINETIC 2. (HR-1)	
L (1,19)	0.143+-	0.011*	0.098+-	0.007
L (2,19)	0.024+-	0.004	0.005+-	0.002
L (4, 1)	318.251+-	4052.469	9.550+-	2.518
L (5, 2)	7334.979+-	221460.200	67.302+-	204.789
L (9, 4)	5.640+-	1.653	2.705+-	0.213
L (10, 5)	0.009+-	0.001	0.030+-	0.002
L (6, 9)	35.370+-	14.787	139.175+-	22.840
L (12, 9)	21.613+-	2.849	22.695+-	4.428
L (13, 9)	602.990+-	77.277	244.795+-	49.290
L (9,13)	0.025+-	0.002	0.014+-	0.001
L (14, 9)	354.887+-	74.514	877.931+-	170.929
L (9,14)	0.016+-	0.002	0.030+-	0.003
L (16, 9)	0.990+-	0.126	0.899+-	0.176
L (6,10)	1.663+-	0.257	1.246+-	0.401
L (7, 6)	688.693+-	11486.660	11.532+-	30.003
L (20, 7)	0.017+-	0.013	0.020+-	0.004
L (19,18)	2.061+-	0.782	2.210+-	0.914
L (20,19)	0.055+-	0.010	0.227+-	0.011
L (21,20)	0.093+-	0.017	0.117+-	0.004
S (3,19)	0.063+-	0.007	0.083+-	0.008
S (3,22)	0.109+-	0.075	0.131+-	0.017
S (8, 4)	0.174+-	0.008	0.126+-	0.002
S (8,16)	6.569+-	2.872	6.077+-	0.765
S (15,14)	0.003+-	0.001	0.002+-	0.000
S (17,16)	1.000+-	0.025	1.000+-	0.022

* +- 1 STANDARD DEVIATION

TABLE 8.3.13

COMPARISION OF VARIABLE PARAMETERS FROM

PAIRED KINETIC EXPERIMENTS

SUBJECT:D.W.

PARAMETER	KINETIC 1. (HR-1)	KINETIC 2. (HR-1)
L (1,19)	0.139+-	0.007*
L (2,19)	0.036+-	0.003
L (4, 1)	10000.000+-	32015.560
L (5, 2)	167.729+-	453.455
L (9, 4)	10.076+-	3.657
L (10, 5)	0.005+-	0.001
L (6, 9)	43.477+-	10.823
L (12, 9)	20.724+-	2.411
L (13, 9)	471.259+-	52.096
L (9,13)	0.020+-	0.002
L (14, 9)	256.998+-	39.321
L (9,14)	0.018+-	0.002
L (16, 9)	0.660+-	0.074
L (6,10)	1.573+-	0.216
L (7, 6)	11.045+-	27.405
L (20, 7)	0.003+-	0.001
L (19,18)	2.069+-	0.118
L (20,19)	0.068+-	0.006
L (21,20)	0.080+-	0.005
S (3,14)	0.024+-	0.007
S (3,19)	0.177+-	0.010
S (3,22)	0.313+-	0.050
S (8, 4)	0.171+-	0.004
S (15,14)	0.004+-	0.000
S (17,16)	1.000+-	0.022

* +- 1 STANDARD DEVIATION

b) Comparison of variable parameters obtained from MODEL IV solutions using kinetic data from the paired experiments

Rate constants from L(1,19) to L(21,20) have been compared with the paired Student's 't' test (Mould, 1976), for the subjects K.B., J.B., B.C. and G.E., and the results are shown in table 8.9.14. Significant changes between Kinetic 1. and Kinetic 2. values occurred in rate constants, L(2,19), representing the transport of ^{203}Pb to wall from lumen of small bowel via the common lead/phosphorous pathway, L(13,9) and L(14,9), representing the uptake of ^{203}Pb in red cells and 'soft' tissue compartments and L(20,19), representing the movement of the unabsorbed fraction of ^{203}Pb to large bowel from lumen of small bowel.

The only consistent changes in the values of the summer coefficients were in S(15,14), the 'soft' tissue coefficient. The values found in the model solutions using data from Kinetic 2. experiments were always lower by an approximate factor of 2 than those found using data from Kinetic 1. experiments.

c) Comparison of percentages of ingested dose of ^{203}Pb absorbed in common lead/calcium and common lead/phosphorous absorptive pathways in paired kinetic experiments

The percentages of ingested dose absorbed in the common lead/calcium and common lead/phosphorous absorptive pathways were calculated from their representative rate constants L(1,19) and L(2,19), respectively, and L(20,19), rate constant representing the movement of unabsorbed ^{203}Pb from lumen of small bowel to large bowel. These percentages are listed in table 8.3.15 for both kinetic experiments. The reduction in

TABLE 8.3.14

Results of paired Student's 't' test of rate constant changes between the results of the paired kinetic experiments

RATE CONSTANT	't'
L(1,19)	2.87
L(2,19)*	4.40
L(4,1)	1.04
L(5,2)	0.91
L(9,4)	1.49
L(10,5)	0.85
L(6,9)	1.50
L(12,9)	2.34
L(13,9)*	4.04
L(9,13)	1.45
L(14,9)*	3.69
L(9,14)	2.31
L(16,9)	1.58
L(6,10)	1.98
L(7,6)	1.13
L(19,18)	1.05
L(20,7)	1.63
L(20,19)*	3.67
L(21,20)	1.04

* $(0.01 < P < 0.05)$

TABLE 8.3.15

Percentages of ingested dose of ^{203}Pb absorbed via model pathways L(1,19) and L(2,19) in paired kinetic experiments

SUBJECT	KINETIC 1.		KINETIC 2.	
	L(1,19)	L(2,19)	L(1,19)	L(2,19)
K.B.	58.70 ± 3.97†	10.87 ± 3.46	46.44 ± 4.44	4.83 ± 2.08
J.B.	72.54 ± 5.96	6.60 ± 1.69	35.19 ± 4.56	3.09 ± 0.58
B.C.	70.48 ± 6.34	3.69 ± 1.49	27.87 ± 5.56	0.787 ± 0.369
G.E.	64.41 ± 6.65	10.81 ± 1.78	29.70 ± 2.43	1.51 ± 0.52
D.W.	57.20 ± 3.86§	14.81 ± 1.37§	-	-

Reduction in absorbed dose significant for both pathways ($0.01 < P < 0.05$).

† ± 1 standard deviation.

§ Results excluded from paired 't' test.

percentages of ingested dose absorbed in both pathways was significantly reduced in the Kinetic 2. experiments.

d) Model derived percentages of absorbed dose of ^{203}Pb in liver, 'soft' and 'hard' tissue compartments

Experimental data obtained from surface radioactivity measurements performed over liver, medial aspect of calf and medial malleolus were proportional data. Summer coefficients relating this data to absolute calculated values of percentage ingested dose in the liver, 'soft' and 'hard' tissue compartments were estimated in the compartmental analysis. These absolute calculated values can either be derived from simulations of the model, or from the proportional calculated values matched to the experimental data and the values of the corresponding summer coefficients. Table 8.3.16 shows the maximum ^{203}Pb contents of liver, 'soft' and 'hard' tissue compartments expressed as percentages of calculated absorbed dose. There were significant increases in 'soft' tissue levels of absorbed dose of ^{203}Pb found in the Kinetic 2. experiments compared with those found in the Kinetic 1. experiments. There were no other significant changes.

e) Rate constants of MODEL IV pathways determined with data from Kinetic 1. experiments

Table 8.3.17 lists the values of the rate constants obtained from the solution of MODEL IV using the data from the Kinetic 1. experiments of all subjects. The means and standard deviations of each set of rate constants were calculated and are also listed in the table.

TABLE 8.3.16

Maximum ^{203}Pb content of liver, 'soft' and 'hard' tissues expressed as percentages of absorbed dose calculated from model parameters

SUBJECT	KINETIC 1. (% Absorbed dose)			KINETIC 2. (% Absorbed dose)		
	Liver	'Soft' tissue	'Hard' tissue	Liver	'Soft' tissue	'Hard' tissue
K.B.	20.63	40.81	0.244	19.25	58.24	0.137
J.B.	20.32	40.45	0.203	19.80	59.01	0.178
B.C.	10.72	59.40	0.169	14.27	72.40	0.206
G.E.	22.12	33.40	0.360	20.12	59.47	0.227
D.W.	28.61§	25.37§	0.276§	-	-	-
Mean	20.48	39.89	0.250	18.43	62.28	0.187
S.D.	6.40	12.60	0.073	2.79	6.77	0.039
S.E.	2.86	5.63	0.033	1.39	3.38	0.020

Kinetic 1. 'soft' tissue results different from Kinetic 2. 'soft' tissue results ($P < 0.05$).

§ Results excluded from paired 't' test.

TABLE 8.3.17

Rate constants of MODEL IV pathways determined from Kinetic 1. experiments

RATE CONSTANT ($hour^{-1}$)	SUBJECT					MEAN ± S.D.
	K.B.	J.B.	B.C.	G.E.	D.W.	
L(1,19)	0.135 ± 0.009†	0.220 ± 0.014	0.191 ± 0.013	0.143 ± 0.011	0.139 ± 0.007	0.154 ± 0.032
L(2,19)	0.025 ± 0.008	0.020 ± 0.005	0.010 ± 0.004	0.024 ± 0.004	0.036 ± 0.003	0.025 ± 0.011
L(4,1)	724.2 ± 17413	5044 ± 25854	9989 ± 22208	318.3 ± 4052	9990 ± 32016	863.3 ± 2315
L(5,2)	632.8 ± 10570	15.04 ± 40.44	151.25 ± 428.2	7335 ± 22146	167.7 ± 453.5	17.35 ± 20.62
L(9,4)	1.404 ± 0.302	5.630 ± 1.184	7.604 ± 1.409	5.640 ± 1.653	10.08 ± 3.657	2.051 ± 1.950
L(10,5)	0.006 ± 0.001	0.009 ± 0.001	0.005 ± 0.001	0.009 ± 0.001	0.005 ± 0.001	0.007 ± 0.002
L(6,9)	50.37 ± 25.11	113.0 ± 25.12	30.82 ± 14.30	35.37 ± 14.79	43.48 ± 10.82	44.57 ± 22.87
L(12,9)	29.47 ± 8.666	32.81 ± 5.776	22.44 ± 2.532	21.61 ± 2.849	20.71 ± 2.411	22.45 ± 3.361
L(13,9)	409.4 ± 124.6	460.2 ± 82.19	241.9 ± 25.74	603.0 ± 77.28	471.3 ± 52.10	325.3 ± 138.0
L(9,13)	0.018 ± 0.002	0.014 ± 0.002	0.014 ± 0.001	0.025 ± 0.002	0.020 ± 0.002	0.018 ± 0.001
L(14,9)	510.6 ± 151.1	534.7 ± 110.0	494.8 ± 68.06	354.9 ± 74.51	257.0 ± 39.32	344.4 ± 122.6
L(9,14)	0.021 ± 0.002	0.018 ± 0.002	0.011 ± 0.001	0.016 ± 0.002	0.018 ± 0.002	0.015 ± 0.004
L(16,9)	0.899 ± 0.262	0.876 ± 0.154	0.570 ± 0.062	0.990 ± 0.126	0.660 ± 0.074	0.675 ± 0.160
L(6,10)	0.842 ± 0.211	0.844 ± 0.219	0.415 ± 0.115	1.663 ± 0.257	1.573 ± 0.216	0.827 ± 0.529
L(7,6)	32.17 ± 694.4	100.0 ± 1283	6.621 ± 24.15	688.7 ± 11487	11.05 ± 27.41	8.581 ± 3.132
L(19,18)	2.317 ± 1.522	2.061 ± 0.461	2.010 ± 1.281	2.061 ± 0.782	2.008 ± 0.449	2.069 ± 0.118
L(20,7)	0.008 ± 0.002	0.006 ± 0.001	0.004 ± 0.002	0.017 ± 0.013	0.003 ± 0.001	0.005 ± 0.002
L(20,19)	0.070 ± 0.008	0.064 ± 0.008	0.070 ± 0.010	0.055 ± 0.010	0.068 ± 0.006	0.066 ± 0.005
L(21,20)	0.099 ± 0.004	0.090 ± 0.007	0.070 ± 0.008	0.093 ± 0.017	0.080 ± 0.005	0.089 ± 0.012

† ± 1 standard deviation.

Rate constants with high mean values are L(4,1), representing transfer of ^{203}Pb from wall of small bowel of the common lead/calcium pathway to liver, L(14,9) and L(13,9), representing uptake of ^{203}Pb in 'soft' tissue and red cell compartments. Low mean values were found for rate constants L(10,5), representing transfer of ^{203}Pb, absorbed in common lead/phosphorous pathway, from liver to plasma, and L(20,7), representing biliary excretion of ^{203}Pb.

Coefficients of variation were low for L(19,18), representing transfer of ^{203}Pb from stomach to lumen of small bowel, L(20,19), representing movement of unabsorbed ^{203}Pb from lumen of small bowel to large bowel, L(21,20), representing movement of ^{203}Pb in the lumen of the large bowel and L(12,9), representing urinary excretion of ^{203}Pb.

Rate constants L(4,1) and L(5,2) had extremely large coefficients of variation, and L(2,19), rate constant representing transport of ^{203}Pb in common lead/phosphorous pathway, and L(13,9), L(9,13) and L(20,7) had large coefficients of variation.

8.3.4 Discussion

A 'universal' model was developed to fit the experimental data from all subjects and experiments. The fitting of a full model to all the data simultaneously reduces the possibility of overlooking inconsistencies that are not apparent intuitively. The complexity of the final model evolved after efforts to derive a compatible, less complicated model, failed.

It may appear that a model consisting of many compartments should be

able to fit any data. However, when the experimental data are extensive, such as the eight data curves in the present work, have sufficient structure and when the model contains constraints, it may be quite difficult to fit data to a particular model, even if it contains a large number of compartments (Berman et al, 1968 b).

The model was developed on the assumption that there exists a 'universal' model to represent the kinetics of lead in the body. Differences in kinetics between individuals and those caused by the effects of calcium and phosphorous are also assumed to be reflected in quantitative changes in the values of model parameters.

All transport processes in the compartmental model have been represented by one rate constant for each process, and this is probably a simplification as long-term animal studies have shown that these processes may consist of two or even three rate constants. Barton et al (1978) injected ^{210}Pb into rats and measured retention over a period of six weeks which showed at least two phases of elimination. Cohen (1970) fitted a two exponential function to the whole body retention of baboons that had been injected with ^{210}Pb and measured over a year. In the same work, the release of ^{210}Pb from the blood was best fitted by a two exponential function, and Hursh (1973) needed three exponentials to fit the release of injected ^{210}Pb from the blood of dogs over a period of 9 months.

Rabinowitz et al (1976) measured the blood levels of the stable tracer ^{204}Pb in five subjects whose food intake had been supplemented each day by ^{204}Pb from 1-124 days. They were able to fit the blood data with a two compartmental model, after discontinuing the ingestion of lead

tracer by the subjects. However, the blood ^{204}Pb did not decrease as rapidly towards zero as predicted from the two compartmental model. The authors suggested that there existed a component of blood with a long biological half-life of lead, and that this was caused by the return of ^{204}Pb from a third compartment with a slow turnover of lead, namely, the dense cortical bone of the skeleton. However, the discrepancy in the fit occurred at about 100 days after the cessation of tracer lead input, so that the loss of lead from the blood can probably be represented by a single exponential up to 100 days.

The number of exponentials required to fit the data from long term studies is influenced by the resorption of lead from the skeleton, a pathway which it was not necessary to include in the final compartmental model in this thesis. The transport processes can be adequately described by one rate constant for each process over the study length of nine days, and probably even longer from the evidence of Rabinowitz et al (1976).

The rate of lead absorption along the small bowel was represented by two pathways in the model, but it is unlikely to be discontinuous occurring at only two rates. However, it is significant that attempts to produce a compatible model with less than two independent rates were unsuccessful.

a) Compatibility of MODEL IV with kinetic experimental data

The fits between model calculated values and the experimental data were generally good with few systematic deviations, indicating that the degrees of freedom of the model were sufficient (section 8.1.5). The

best fits were obtained between absolute experimental data and calculated values. Both the closer relationship between absolute data and the model, and the lower statistical error of the data were responsible for the better fits.

The model was unable to represent the early rapid partitioning between red cells, 'soft' and 'hard' tissue compartments. However, this occurred within the first 3 hours after the ingestion of ^{203}Pb, which represents a small fraction of the total study time of 8-9 days. Another discrepancy was the poor fit at later times between calculated values and the experimental red-cell data from the Kinetic 2. experiments of subjects K.B., J.B. and B.C.

The structure of the red cell data curves from the Kinetic 2. experiments, however, was generally different to those from the Kinetic 1. experiments. Those from the latter had one initial slope rising sharply to a peak, and from this peak the ^{203}Pb content decreased in a single exponential manner. The ^{203}Pb content of red cells in the Kinetic 2. experiments had the same first phase as that found in the Kinetic 1. experiments, except that the slope was less. However, there was also a second phase, with content rising at a slower rate before the peak was reached. This second phase was most noticeable in the red cell data from the Kinetic 2. experiment of subject D.W. In this experiment, subject D.W. ingested the maximum weights of calcium and phosphorous with ^{203}Pb, and the second phase was particularly long as the maximum ^{203}Pb content of red cells was not reached until 144 hours.

In the analysis of data from the Kinetic 2. experiments, the model was

able to match the slope of the first phase of red cell uptake of ^{203}Pb by decreasing the values of rate constants L(1,19), describing the transfer of ^{203}Pb to wall from lumen of small bowel via the common lead/calcium pathway, and L(13,9), describing the uptake of ^{203}Pb by the red cells. However, it could not accomodate the slower second phase. There appears to be a delay in the uptake of ^{203}Pb in the red cells when it is ingested with calcium and phosphorous, and Chamberlain et al (1978) observed a similar delay when their subjects ingested ^{203}Pb in food.

To investigate the two phases of red cell uptake of ^{203}Pb, compartments which had represented the large bowel were used as delay compartments between plasma (9) and the red cell (13). These delay compartments would allow the model to still match the initial slope of the red cell data curve, and allow longer storage of ^{203}Pb. The curve could now continue to rise to the peak at a slower rate during the second phase before the release of ^{203}Pb back into the plasma compartment. A solution was attempted without whole body data, with model parameters fixed except those communicating with the plasma compartment and with experimental data from the Kinetic 2. experiment of subject J.B. The results showed a much better fit between calculated values and the experimental red cell data as seen in figure JB-RC-2A. There were no significant changes in any of the important variable parameters, such as L(13,9) and L(14,9).

Poor fits were obtained between calculated values and experimental 'hard' tissue data of subjects K.B. and G.E. Their 'hard' tissue data initially rose rapidly as in the other subjects, but did not rise as

rapidly over the remainder of the study period. The discrepancies in the fits showed the same trends for both subjects and both kinetic experiments. This suggests that experimental errors were not the source of the discrepancies, but that the behaviour of lead in the 'hard' tissues of the two subjects was different to that which occurred in the other subjects.

The poor fits to some of the small bowel data were caused by the inability of the model to describe the unabsorbed fraction of ^{203}Pb moving through the transverse portion of the large bowel. The values of the rate constants representing the movement of ^{203}Pb in the lumen of the large bowel were primarily obtained from the fit to the whole body data. The faecal excretion of unabsorbed ^{203}Pb is a much slower process than its movement in the transverse portion of the large bowel.

The transport of the contents of the transverse colon is thought to be by a mass movement which may occur one to four times a day, and the contents are then stored in the descending colon and rectum (Eve, 1966). Both gamma camera and profile scan studies in section 8.2.3 had shown both the fast movement through the large bowel and storage in rectum of unabsorbed ^{203}Pb.

The movement of unabsorbed ^{203}Pb in the transverse colon would be better described by the model if the rate constants representing the movement of ^{203}Pb in the lumen of large bowel were allowed to vary individually and more compartments were included in the large bowel segment. The values of some of the rate constants could rise to give a faster input and output in a number of compartments to suit the

relatively fast movement of ^{203}Pb in transverse colon. The increase in the number of compartments would maintain the overall delay in the excretion of the unabsorbed fraction of ^{203}Pb.

A solution was attempted with compartments that had been used as summer compartments, (8), (15) and (17), included with the other large bowel compartments (20) - (24). Only those parameters in the large-bowel delay segment were allowed to vary, all others were fixed. The experimental data used was that from the Kinetic 2. experiment of subject G.E., without data on liver, 'soft' and 'hard' tissue compartments. The results show a much better fit between calculated values and the experimental small-bowel data, as shown in figure GE-SB-2A.

The 'soft' tissue data of subject B.C. was poorly fitted by model calculated values, because the data kept rising from 24 hours onwards. This subject was the most heavily built of all the subjects who took part in the kinetic experiments. Therefore, it is possible that his tibia and fibula, representing a fraction of the 'hard' tissue compartment, may have been included in the field of view of the in vivo detector, even though the detector was carefully positioned to avoid this possibility. This was checked by allowing the 'hard' tissue to contribute to the 'soft' tissue calculated values, by including in the model the summer coefficient S(15,16). A good fit was obtained to the experimental data as seen in figures BC-ST-1A and BC-ST-2A. However, there was no significant change in the model derived percentages of absorbed dose in the 'soft' tissue compartments.

The rate constants representing movement of ^{203}Pb from wall of small bowel to liver, L(4,1) and L(5,2), and the rate constant representing transfer of lead between the two liver compartments in the route of biliary excretion, L(7,6), all had consistently large uncertainties. The experimental liver data was inadequate, therefore, to completely define the structure of the liver compartments in the model (section 8.1.5).

The uncertainties were also associated with compartments in series, so that there would be a certain interdependence of parameters. Such interdependence affects the precision with which the parameters may be estimated (Berman et al, 1968). The experimental data describing the kinetics of ^{203}Pb in the liver was proportional, and the results of the profile scan analysis could only be used to provide constraints on the liver summer coefficients. Therefore, the model solutions obtained would give the parameters, associated with the liver, larger uncertainties than if the experimental liver data were absolute.

Convergence to a least squares solution was obtained with the compartmental analysis of all the kinetic data from every subject and every experiment. The methods used in section 8.3.2 (a) helped to obtain a good choice of initial values for the variable parameters, and, consequently, convergence of the model solutions.

The compatibility is satisfactory between MODEL IV and most of the experimental data from the Kinetic 1. experiment, according to the criteria described in section 8.1.5. It is not as good between the model and the experimental data from the Kinetic 2. experiment.

Supplementary analysis showed, however, that additional compartments were required to improve compatibility, but these could not be included in MODEL IV because of the limited number of compartments and variable parameters allowed in SAAM25 (1967). As the additional compartments required were operational, i.e. delay compartments, and no significant changes occurred in the values of important parameters in the supplementary analysis, the results of the compartmental analysis of the Kinetic 2. data can be used to examine the effect of calcium and phosphorous on model parameters.

b) Effect of calcium and phosphorous on model parameters

Calcium and phosphorous ingested simultaneously with ^{203}Pb significantly reduced the percentages of ingested ^{203}Pb absorbed via pathways L(1,19) and L(2,19), representing the transport of ^{203}Pb by the common lead/calcium pathway and the common lead/phosphorous pathway, respectively. This reduction was reflected in the lower 96 hour retentions of all subjects in the Kinetic 2. experiments. The relative change in these model derived percentages absorbed via the two pathways was by a factor of 1.3 for L(1,19) and by a factor of 3.2 for L(2,19), showing that the second pathway was more sensitive to the effect of calcium and phosphorous on lead absorption. The rate of absorption of ^{203}Pb via L(1,19) was not significantly reduced by calcium and phosphorous. A significant reduction occurred, however, in the rate for the L(2,19) pathway. The different responses of the rate constants suggest that the nature of the transport mechanisms mainly responsible for lead absorption, which they represent, are different.

The value of L(20,19) was increased significantly by the presence of calcium and phosphorous with ^{203}Pb in the gut. However, the value of this rate constant represents the fraction of ^{203}Pb unabsorbed with which it correlates very well (r=0.92).

There were significant reductions in the values of L(13,9) and a significant increases in the values of L(14,9), rate constants representing the uptake of ^{203}Pb in the red cell and 'soft' tissue compartments, respectively. As both these compartments are connected to the diffusible-plasma lead compartment, it is possible that their changes are dependent. The significance of these changes will be discussed in section 9.0.

It is impossible to compare the variable summer coefficients for a given compartment between subjects. These summer coefficients relate the surface radioactivity measurements to the model, and these measurements depend on local tissues and detector geometry, gamma ray absorption in the tissues, and the sensitivity of the detector. These uncontrolled variables will be different for different subjects and for different measurement sites on the same subject. It is valid to compare the coefficients of compartments at the same site, and there was a consistent reduction by a factor of 2 in the value of the 'soft'-tissue summer coefficient, S(15,14), found in the Kinetic 2. experiments for each subject. This shows that a lower fraction of the ingested dose of lead in the 'soft' tissue compartment was 'seen' by the <u>in vivo</u> detector in the Kinetic 2. experiments. The significance of this effect will be discussed in section 9.0.

c) Model derived percentages of ^{203}Pb in liver, 'soft' tissue and 'hard' tissue compartments

i) Liver compartments

There was no significant effect of calcium and phosphorous on the model derived percentages of the absorbed dose of ^{203}Pb found in the liver. The mean value of these percentages, 20.48 $\pm$ 2.86% (S.E.), was comparable to the 20% found in dogs at 28 days after an injection of ^{210}Pb (Lloyd et al, 1970). Cohen (1970) measured a lower ^{210}Pb content of 12.8% in a baboon who received the lead intravenously and was sacrificed 24 hours later. A ^{203}Pb content of liver, 10.8%, was found by Meredith et al (1977), when rats ingested ^{203}Pb and were sacrificed at 7 days. Similarly, a liver content of 10.48% was found by Conrad and Barton (1978) after the intravenous injection of ^{210}Pb in rats. This last measurement was done, however, at 1 hour post injection and the liver content at a time comparable to that used by Meredith et al (1977) was only 0.42%. This suggests that ingested and intravenous lead behave differently in the liver. As the liver removes lead from the portal blood, it would be expected that the fraction of ingested lead stored in the liver would be greater than that stored of injected lead (Cantarow and Trumper, 1944).

ii) 'Soft' and 'hard' tissue compartments

Although the mean percentage of absorbed ^{203}Pb in the 'hard' tissue was reduced in the Kinetic 2. experiment, the change was not significant. In the 'soft' tissue compartment, however, there was a significant increase in the mean percentage of absorbed dose, and this

will be discussed later in section 9.0.

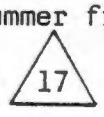
The model derived values of absorbed dose of ^{203}Pb in the 'hard' tissue compartment were much less than those in the 'soft' tissue compartment. It was expected that they would be higher as the 'hard' tissue compartment represented bone, and it has been shown in animal studies that the early distribution of tracer lead is towards high uptake in bone. Hammond et al (1967) injected ^{210}Pb into rats and found at 72 hours that 53.4% of the injected dose was in bone and only 6.5% was in total soft tissues. The results of the present work show that, in the Kinetic 1. experiment, the mean percentage of absorbed dose of ^{203}Pb is 0.15% in the 'hard' tissue compartment and 37.36% in the 'soft' tissue compartment at 72 hours after the ingestion of ^{203}Pb.

The significance of the differences in the percentages of absorbed dose calculated to be in the 'hard' and 'soft' tissue compartments will depend on the structure of the model, how these compartments are defined in the model and how they relate to the different tissues in the field-of-view of the in vivo detector.

As the experimental data representing ^{203}Pb radioactivity in the 'hard' and 'soft' tissue compartments were proportional, the model derived values of absorbed dose in these compartments will depend on how they are arranged in the structure of the model. During the development of the model (section 8.3), different configurations of the 'soft' tissue, 'hard' tissue and the diffusible-plasma lead compartments were tried, such as connecting the 'hard' tissue to the 'soft' tissue and not to the plasma compartment. Model solutions obtained using these different combinations were all inferior to the final structure (figure 8.3.6), in

both the uncertainties in the estimates of the 'soft' tissue and 'hard' tissue variable parameters and residual sums of squares.

Both the 'soft' and 'hard' tissue compartments are connected to the diffusible-plasma lead compartment, and they are two of a total of five receiving lead from this plasma compartment. The others are liver, red cells and accumulative urine compartments, and the last two are well defined by absolute experimental data. The output from the plasma to the liver compartment is constrained by proportional liver data, but as this output affects the biliary excretion of lead in the model, it is also defined by the absolute whole body data. The 'hard' and 'soft' tissue compartments are, therefore, less well defined, and they represent all lead in the body apart from red cell, liver, and plasma lead, i.e. lead in the bone and other soft tissues.

The experimental data describing the ^{203}Pb radioactivity in the 'hard' tissue compartment was obtained from surface radioactivity measurements performed over the medial malleolus. The different tissues 'seen' by the <u>in vivo</u> detector placed over this site were 'soft' tissue, trabecular bone, cortical bone, and blood and 'soft' tissue E.C.F. ^{203}Pb. These last two are subtracted from surface radioactivity measurements before the data is used in analysis. In the development of the model, it was found unnecessary to include a summer from 'soft' tissue compartment (14) to the 'hard' tissue summer 

, indicating that the contribution of 'soft' tissue to 'hard' tissue data is negligible. The remaining tissues are, therefore, trabecular and cortical bone, and the behaviour of lead in these two tissues has been suggested to be different.

Baloh (1974) suggested that bone lead may exist in two compartments, the readily exchangeable fraction in trabecular bone and the relatively non exchangeable fraction in the dense cortex. Rabinowitz et al (1976) found in their studies of steady state levels of lead in humans, that the ratio of tracer to total lead was about two to three times greater in trabecular than in the cortex. Cantarow and Trumper (1944) have suggested that the lead stored in the trabeculae is more mobile than that stored in the cortical bone. They reported that there was 52% more lead in the cortex than in the trabecular portion of the sternum of a normal human subject, but 78% more lead in the trabecular than in the cortical bone in a subject with active lead poisoning. This suggests that recently absorbed lead is deposited as a loosely bound compound in the trabeculae, before it is eventually deposited as a relatively fixed compound in the cortical bone. This last type of bone receives a relatively small percentage of the circulation (Baloh, 1974), and may be expected to be the site of long term storage of lead (Chamberlain, 1975).

The low value of the rate constant describing the uptake of ^{203}Pb in the 'hard' tissue compartment, L(16,9), and the low percentage of absorbed dose derived from the model in this compartment, suggests that the experimental data obtained from measurements over the medial malleolus was mainly from ^{203}Pb radioactivity in cortical bone. The bony structures included in the field-of-view of the in vivo detector were the ends of the tibia and fibula and the talus bone. All three consist of trabecular bone with a surface covering of the more dense cortical bone. The surface area of these three bony structures will be greater than that of the same volume of bone in a single bony structure,

such as the calcaneum. Therefore, the fraction of cortical bone 'seen' by the in vivo detector placed over the medial malleolus will be greater than that 'seen' over the calcaneum.

Osteodensitometry measurements (section 11.11) performed over the medial malleolus and calcaneum in four of the subjects who took part in the kinetic studies, gave mean values of 1.11 ± 0.02 g/cm² (S.E.) and 0.567 ± 0.039 g/cm² (S.E.), respectively. The higher mean found over the medial malleolus indicates a higher density of bone in that region reflecting a larger proportion of cortical bone.

The experimental data describing the ^{203}Pb radioactivity in the 'soft' tissue compartment was obtained from surface radioactivity measurements over the medial aspect of the calf. The predominant tissue in the field-of-view of the in vivo detector was muscle, as the detector was positioned carefully to exclude bone from the field-of-view. From the work of Hammond et al (1967), the ^{210}Pb content of muscle in rats injected with ^{210}Pb was only 0.12% of the injected dose at 72 hours. If this low lead content of muscle also occurs with tracer lead in man, which is suggested by low steady-state lead levels (Barry, 1975), then the major fraction of ^{203}Pb in the 'soft' tissue compartment must be in some other types of tissue in this compartment. However, this assumes that the changing lead content of muscle reflects that occurring in the remainder of the tissues which constitute the 'soft' tissue compartment.

If surface radioactivity measurements performed over the medial malleolus mainly represent ^{203}Pb radioactivity in cortical bone, then the 'soft' tissue compartment will include the readily exchangeable fraction of trabecular bone lead. This is also suggested by the levels

of absorbed lead found in the 'soft' tissue compartment which are of the same order as those found in the bone of animals a few days after the administration of lead. Apart from the experiments of Hammond et al (1967) already described, Hackett and Sikov (1977) found that rats injected with ^{210}Pb had 30% of the injected dose in the skeleton at 90 minutes, and 40% at 11 days.

The trends of the ^{203}Pb radioactivity in the 'hard' and 'soft' tissue compartments are similar to those found by Knop et al (1977) in their compartmental model describing the kinetics of ^{47}Ca injected into normal humans. The levels of ^{47}Ca in their 'fixed' bone calcium compartment rose slowly over the 10 day period of study, whereas those in the 'exchangeable' bone calcium compartment rose to a peak within 48 hours and decreased slowly from that time onwards.

d) Rate constant values obtained from the compartmental analysis of experimental data from Kinetic 1. experiments

The data from the Kinetic 1. experiments were obtained, as far as possible, with identical experimental conditions. The compartmental model was found to be compatible with most of this kinetic data, so that it adequately represents the behaviour of ^{203}Pb in the body. Therefore, any differences in parameter values obtained from the analysis of data from each subject, could be caused by individual variation between subjects.

The rate constant describing the transport of ^{203}Pb from lumen of small bowel to wall, L(1,19), has a mean value of $0.154 \pm 0.032\ hr^{-1}$, which is of the same order as those found by Birge et al (1969) for the

rate constants describing the absorption of ^{47}Ca from the small bowel in 6 normal humans. This suggests a similar transport mechanism for calcium and lead, and strengthens the hypothesis advanced in section 6.4.1 that lead and calcium share the same absorptive pathways.

The large value of L(4,1), rate constant describing the transfer of ^{203}Pb from wall of small bowel of the common lead/calcium pathway to liver, cannot be commented on because of a very large coefficient of variation. The large values of L(14,9) and L(13,9), rate constants describing the uptake of ^{203}Pb in 'soft' tissue and red cells, are consistent with the observations of other workers that lead rapidly exchanges between plasma and extracellular fluid (Stover, 1959), and is taken up avidly by red cells (Hursh and Suomela, 1968). They are of the same order, as suggested by Chamberlain et al (1975) and Hursh et al (1969). The low values of rate constants L(10,5) and L(20,7), representing transfer of ^{203}Pb, absorbed via the common lead/phosphorous pathway, from liver to plasma, and biliary excretion of lead are consistent with suggestions that the liver acts as a storage compartment for lead (Barltrop, 1968; Cantarow and Trumper, 1944).

The low coefficients of variation of L(19,18) and L(21,20), representing transfer of lead from stomach to lumen of small bowel and movement of ^{203}Pb in the lumen of large bowel, respectively, are not surprising. It was assumed in the model that these pathways did not involve absorption and the 'mechanical' process of stomach emptying and movement of lead in the lumen of the large bowel should show little variation. The rate constant, L(20,19), representing the unabsorbed fraction of lead, should have a small coefficient of variation as the

absorption of ^{203}Pb in all the subjects was approximately the same in the Kinetic 1.experiments.

The coefficient of variation of the rate constant describing the urinary excretion of ^{203}Pb, L(12,9), is surprisingly low at 15%. This suggests that the wide range of urine lead concentrations found in community studies is probably caused by differences in the absorption of lead from the gut. This small variation is in direct contrast to that found with the rate constants describing uptake and release of ^{203}Pb in red cells, L(13,9) and L(9,13), of approximately 45%. Waldron and Stöfen (1974) have reported work which shows that the capacity of red cells to hold lead may show variation from one person to another. Mylroie et al (1977) maintained that not only were blood lead measurements inappropriate as the sole criterion in therapy and toxicological studies, as suggested by Chisolm et al (1975), but that blood lead measurements should not be used as a sole measure of environmental exposure to lead. As mentioned in section 1.4, the WHO (1977) have accepted that blood lead should not be used as an indication of exposure when dealing with individual subjects.

The large coefficients of variation of the mean values of L(4,1) and L(5,2), rate constants representing the transfer of ^{203}Pb from wall of small bowel to liver compartments, reflect the large uncertainties of these rate constants found in the solutions of the model. The rate constant representing biliary excretion of lead, L(20,7), also has a large coefficient of variation which may account for the large scatter in the half times of retention found in the subjects who took part in the Kinetic 1. experiments.

8.4 Use of compartmental MODEL IV

8.4.1 Introduction

Throughout this thesis, the 96 hour whole body retention of ^{203}Pb has been regarded as a reliable measure of ^{203}Pb absorption. The results of the compartmental analysis can now be used to check this assumption. The 96 hour retentions of the subjects who took part in the kinetic experiments can be compared with the percentages of ingested ^{203}Pb absorbed by these subjects, calculated from the values of their model parameters.

If there is any discrepancy between retentions and calculated absorbed doses, the cause may be the presence of some unabsorbed ^{203}Pb still in the gut at 96 hours. It was suggested in section 5.4.2 that some of the short half times of retention calculated with retention data from 96 hours onwards could have been caused by such unabsorbed ^{203}Pb. Simulations of MODEL IV with and without the unabsorbed fraction of ^{203}Pb in the gut should show any effects of unabsorbed ^{203}Pb on 96 hour retentions and half times of retention.

The interrelationship between lead, calcium and phosphorous absorption in the gut, suggested in section 7.2, may be further examined by using the model. As minimal changes were required in model parameters to describe the effect of calcium and phosphorous on the kinetics of ^{203}Pb in the body, it should be possible to analyse the limited kinetic data from the Kinetic 2. experiment of subject D.W. This could be done by using model parameter values obtained in the analysis of his Kinetic 1. experimental data. Such an analysis would be an important check on the

flexibility of the model and on the responses of model parameters to the maximum weights of calcium and phosphorous. The effect of carrier lead on lead absorption in subject K.B. may be investigated in a similar manner, using the experimental data obtained from this subject in section 5.0.

The maximum weights of calcium and phosphorous ingested together by subject K.B. reduced his 96 hour retention of ^{203}Pb from 60.76% to 1.51% (table 6.3.2). This indicates an inhibition of lead absorption which is nearly complete. The effects of separate doses of the same weights of calcium and phosphorous were much less, reducing retention to 6.51% and 47.24%, respectively. However, if lead shares the common pathways of calcium and phosphorous absorption, then the effects of separate doses may be explained by the complete inhibition of lead absorption in the lead/calcium pathway by calcium and in the lead/phosphorous pathway by phosphorous. This can be checked by simulations of the model giving calculated values of retention that can be compared with the data from the separate dose experiments.

The experimental data of ^{203}Pb levels in plasma and liver were fitted to a linear combination of calculated values from the two plasma and four liver compartments. The calculated values from each compartment can be found by a simulation of MODEL IV. A comparison of the levels of ^{203}Pb in these compartments may provide a better understanding of the behaviour of the two different forms of lead suggested to exist in the body.

8.4.2 Methods

a) Effect of the unabsorbed fraction of ^{203}Pb on 96 hour retentions and half times of retention

Simulations were performed for all subjects and experiments using the model parameters listed in tables 8.3.9-13, allowing the unabsorbed ^{203}Pb to move down the large bowel compartments (20) - (24) in the normal manner, and then repeated, removing the unabsorbed ^{203}Pb from the large bowel. This was done in the model by changing pathway L(20,19) to L(0,19). The half times of retention from 96 hours onwards were then calculated from the simulated whole body retention values using a non-weighted least squares regression.

b) Compartmental analysis of limited kinetic data

Because of the low percentage of ^{203}Pb absorbed by subject D.W. in the Kinetic 2. experiment, whole body counts could only be performed up to 120 hours and useful profile scans, plasma and surface radioactivity measurements could not be obtained. The ^{203}Pb content of the red cells and the ^{203}Pb excreted in the urine, however, could be measured with acceptable statistical accuracy up to 9 days. Data from the experiment in which subject K.B. ingested ^{203}Pb without carrier lead (section 5.0), included measurements on ^{203}Pb radioactivity in the whole body, whole blood and urine performed up to 8-9 days after the ingestion of ^{203}Pb.

Solutions were tried using MODEL IV, allowing parameters to vary that had shown a significant change between paired experiments. The other parameters were fixed to the values obtained from the compartmental

analysis of the data from Kinetic 1. experiments. The parameters allowed to vary were the input rate constants L(2,19) and L(20,19), describing the transport of ^{203}Pb to wall from lumen of small bowel via the common lead/phosphorous pathway and the movement of ^{203}Pb to large bowel from small bowel, respectively. Internal rate constants allowed to vary were L(13,9) and L(14,9), rate constants describing uptake of lead in red cell and 'soft' tissue compartments, respectively.

c) Simulation of the effects of separate doses of $CaCO_3$ and $NaH_2PO_4.2H_2O$ on the whole body retention of subject K.B.

Subject K.B. had ingested ^{203}Pb with $CaCO_3$ and then with $NaH_2PO_4.2H_2O$ in two separate experiments (section 5.0). Whole body retention measurements found in these two experiments were simulated using MODEL IV and the parameter values obtained from the compartmental analysis of the Kinetic 1. data of subject K.B. In the first simulation, the rate constant representing the transport of ^{203}Pb via the common lead/calcium pathway, L(1,19), was set equal to zero. The rate constant representing the transport of ^{203}Pb via the common lead/phosphorous pathway, L(2,19), was then set equal to zero in a second simulation. These conditions represented the complete inhibition of ^{203}Pb absorption by the maximum weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$, respectively.

d) Simulation of ^{203}Pb levels in compartments with summer coefficients

A simulation was performed using MODEL IV and the mean values of the variable parameters found in the compartmental analysis of the experimental data from the Kinetic 1. experiments of all subjects. The

compartments chosen for the simulation were the two plasma compartments, (9) and (10), and the four liver compartments (4), (5), (6) and (7).

8.4.3 Results

Table 8.4.1 shows the 96 hour retentions found in each of the kinetic experiments, except the Kinetic 2. experiment of D.W., and the percentages of the ingested dose calculated to have been absorbed by the subjects in these experiments. These percentages were determined from the values of the model parameters L(1,19), L(2,19) and L(20,19), representing transport of ^{203}Pb to wall from lumen of small bowel and movement of ^{203}Pb from lumen of small bowel to large bowel. A linear regression of 96 hour retention on the percentage of the ingested dose absorbed gave the following equation.

96 hour retention = 1.003 x % ingested dose absorbed - 3.06

with a regression coefficient, r = 0.99.

Figure 8.4.1 shows a plot of 96 hour retention against the percentage of the ingested dose absorbed, and the regression line.

The simulated 96 hour retentions and half times retention found with and without the unabsorbed fraction of ^{203}Pb present in the gut of MODEL IV are shown in table 8.4.2. The experimental values of retentions and half times are also included for comparison. There is good agreement between experimental and simulated values obtained using the normal model configuration, except between values found in the Kinetic 2. experiment of subject D.W. There are differences between the experimental and simulated values of the half times of retention,

TABLE 8.4.1

Comparison of 96 hour whole body retentions with percentages of ingested dose calculated from model parameters

SUBJECT	EXPERIMENT	96 HOUR RETENTION (%)	CALCULATED INGESTED DOSE (%)
K.B.	Kinetic 1.	65.42 ± 0.23†	69.57 ± 5.27
	Kinetic 2.	48.36 ± 0.17	51.27 ± 4.90
J.B.	Kinetic 1.	71.70 ± 0.27	79.14 ± 6.19
	Kinetic 2.	36.63 ± 0.10	38.28 ± 4.60
B.C.	Kinetic 1.	73.93 ± 0.24	74.17 ± 6.51
	Kinetic 2.	25.09 ± 0.09	28.66 ± 5.57
G.E.	Kinetic 1.	71.71 ± 0.27	75.22 ± 6.88
	Kinetic 2.	26.48 ± 0.10	31.21 ± 2.49
D.W.	Kinetic 1.	71.60 ± 0.23	72.01 ± 4.10
	Kinetic 2.	1.65 ± 0.06	-

† ± 1 standard deviation.

FIGURE. 8.4.1

96hour retention against %ingested dose absorbed

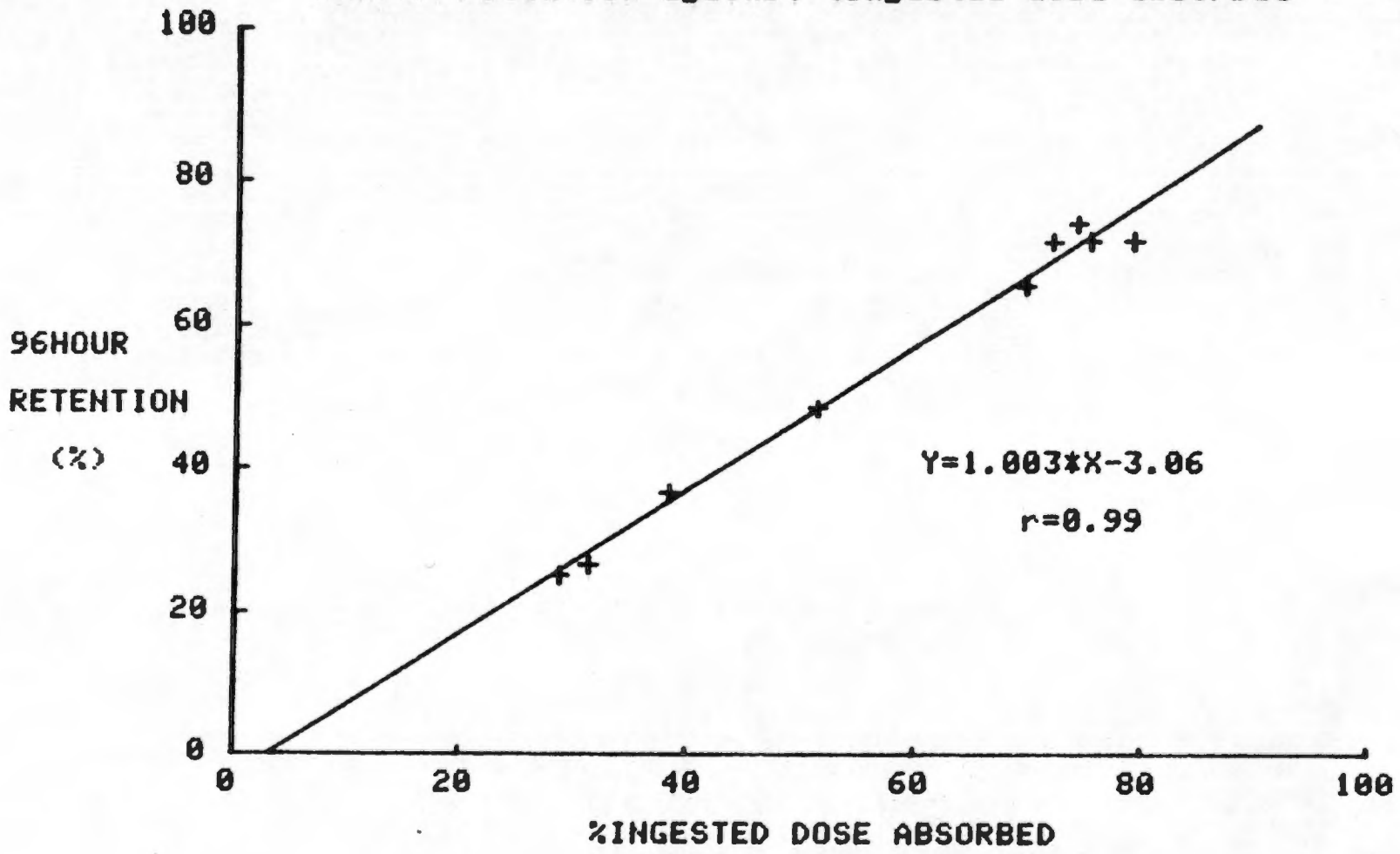


TABLE 8.4.2

Comparison of 96 hour whole body retentions and half times of retention measurements with values simulated using MODEL IV

SUBJECT	EXPERIMENT	96 HOUR RETENTION (%) Experimental	96 HOUR RETENTION (%) Simulation (L(20,19))	96 HOUR RETENTION (%) Simulation (L(0,19))	HALF TIME OF RETENTION (hours) Experimental	HALF TIME OF RETENTION (hours) Simulation (L(20,19))	HALF TIME OF RETENTION (hours) Simulation (L(0,19))
K.B.	Kinetic 1.	65.42 ± 0.23†	65.32	63.59	407.00 ± 24.12	421.59	477.04
	Kinetic 2.	48.36 ± 0.17	49.33	47.26	346.50 ± 17.33	373.36	451.16
J.B.	Kinetic 1.	71.70 ± 0.27	74.26	72.24	407.65 ± 23.97	423.42	478.22
	Kinetic 2.	36.63 ± 0.10	36.80	35.52	301.30 ± 13.10	349.13	490.41
B.C.	Kinetic 1.	73.93 ± 0.24	75.88	69.84	702.84 ± 30.43	728.69	1210.44
	Kinetic 2.	25.09 ± 0.09	24.20	24.19	173.25 ± 4.33	275.87	276.02
G.E.	Kinetic 1.	71.71 ± 0.27	70.94	69.00	330.00 ± 15.71	378.53	421.64
	Kinetic 2.	26.48 ± 0.10	27.17	25.99	210.00 ± 6.36	192.63	213.63
D.W.	Kinetic 1.	71.60 ± 0.23	71.83	67.66	630.00 ± 57.27	569.77	798.88
	Kinetic 2.	1.65 ± 0.06	1.17	0.77	-	-	-

† ± 1 standard deviation.

but they are probably only significant for the values found in the Kinetic 2. experiment of subject B.C.

When the unabsorbed fraction of ^{203}Pb was removed from the gut by simulation, the 96 hour retentions were always lower than those obtained by simulation of the normal model configuration. However, the differences are only large between experimental and simulated values for the Kinetic 2. experiment of subject D.W. and the Kinetic 1. experiment of subject B.C. The simulated half times of retention were always longer when the unabsorbed fraction of ^{203}Pb was removed from the gut. The mean percentage decrease in simulated 96 hour retention values, excluding the Kinetic 2. experiment of subject D.W., caused by the absence of the unabsorbed fraction of ^{203}Pb is $3.76 \pm 0.75\%$ (S.E.), whereas the mean percentage increase in half times of simulated retention is $24.00 \pm 6.94\%$ (S.E.).

Table 8.4.3 shows a comparison between the values of the parameters allowed to vary in the compartmental analysis of the limited data from the Kinetic 2. experiment of subject D.W., and the values of the same parameters found in the analysis of the data from his Kinetic 1. experiment. The rate constants L(1,19), representing transport of ^{203}Pb from lumen to wall of small bowel via the common lead/calcium pathway, L(20,7), describing the biliary excretion of ^{203}Pb, and L(21,20), representing the movement of ^{203}Pb in the lumen of the large bowel, had to be included in the variable parameters to give a good fit between calculated values and experimental data. There is a marked decrease in both L(1,19) and L(2,19), rate constants describing the transport of ^{203}Pb from lumen to wall of small bowel. However, only the difference in L(1,19) is significant, as the uncertainty of L(2,19) is very large. Both L(20,19) and L(21,20), representing the magnitude and

TABLE 8.4.3

Comparison of variable parameters from model solutions using experimental data from Kinetic 1. and Kinetic 2. experiments of subject D.W.

RATE CONSTANT	KINETIC 1. ($hour^{-1}$)	KINETIC 2. ($hour^{-1}$)
L(1,19)	$0.139 \pm 0.007^{\dagger}$	0.0007 ± 0.0001
L(2,19)	0.036 ± 0.003	$10^{-5} \pm 3 \times 10^{-5}$
L(13,9)	471.26 ± 52.10	560.55 ± 12.70
L(14,9)	257.00 ± 39.32	775.56 ± 293.72
L(20,7)	0.003 ± 0.001	0.110 ± 0.08
L(20,19)	0.068 ± 0.006	0.084 ± 0.004
L(21,20)	0.080 ± 0.005	0.206 ± 0.007

$^{\dagger} \pm$ 1 standard deviation.

movement of the unabsorbed fraction of ^{203}Pb in the gut, respectively, and L(20,7) are all increased in the analysis of Kinetic 2. data. Reasonable fits were obtained between model calculated values and experimental data as shown in figures 8.4.2-8.4.4.

A comparison between parameter values found in the compartmental analysis of the kinetic data from the experiment in which subject K.B. ingested ^{203}Pb without carrier lead, and the corresponding values from his Kinetic 1. experiment is shown in table 8.4.4. L(1,19), L(20,7) and L(21,20) were again included as variable parameters. ^{203}Pb radioactivity in the red cells was not directly measured in the experiment. Plasma levels of ^{203}Pb were found to be less than 0.1% of the ingested dose in subject K.B., in the Kinetic 1. experiment. Therefore, whole blood radioactivity approximates ^{203}Pb radioactivity in the red cells, and whole blood data was used in the model solution. There was no change in the rate of ^{203}Pb absorption in pathway L(1,19). The percentage of the ingested ^{203}Pb absorbed in this pathway, calculated from model parameters, was 62.58 $\pm$ 19.98% (S.D.), and agrees well with that calculated using the parameter values found in the Kinetic 1. experiment, of 60.08 $\pm$ 7.75% (S.D.) (table 8.3.15). The greatest change occurred in the value of L(2,19), rate constant representing transport of ^{203}Pb by the common lead/phosphorous pathway. This decreased to practically zero. The second greatest change occurred by a factor of 2 in L(20,7), but the uncertainty of this parameter was high. The changes in the other parameters were not significant.

Table 8.4.5 compares the calculated values of 96 hour retention and half time of retention with the experimental data, and there is good agreement. Figures 8.4.5-8.4.7 show the good fits between calculated values and experimental data.

FIGURE. 8.4.2

Fit of calculated values to experimental data

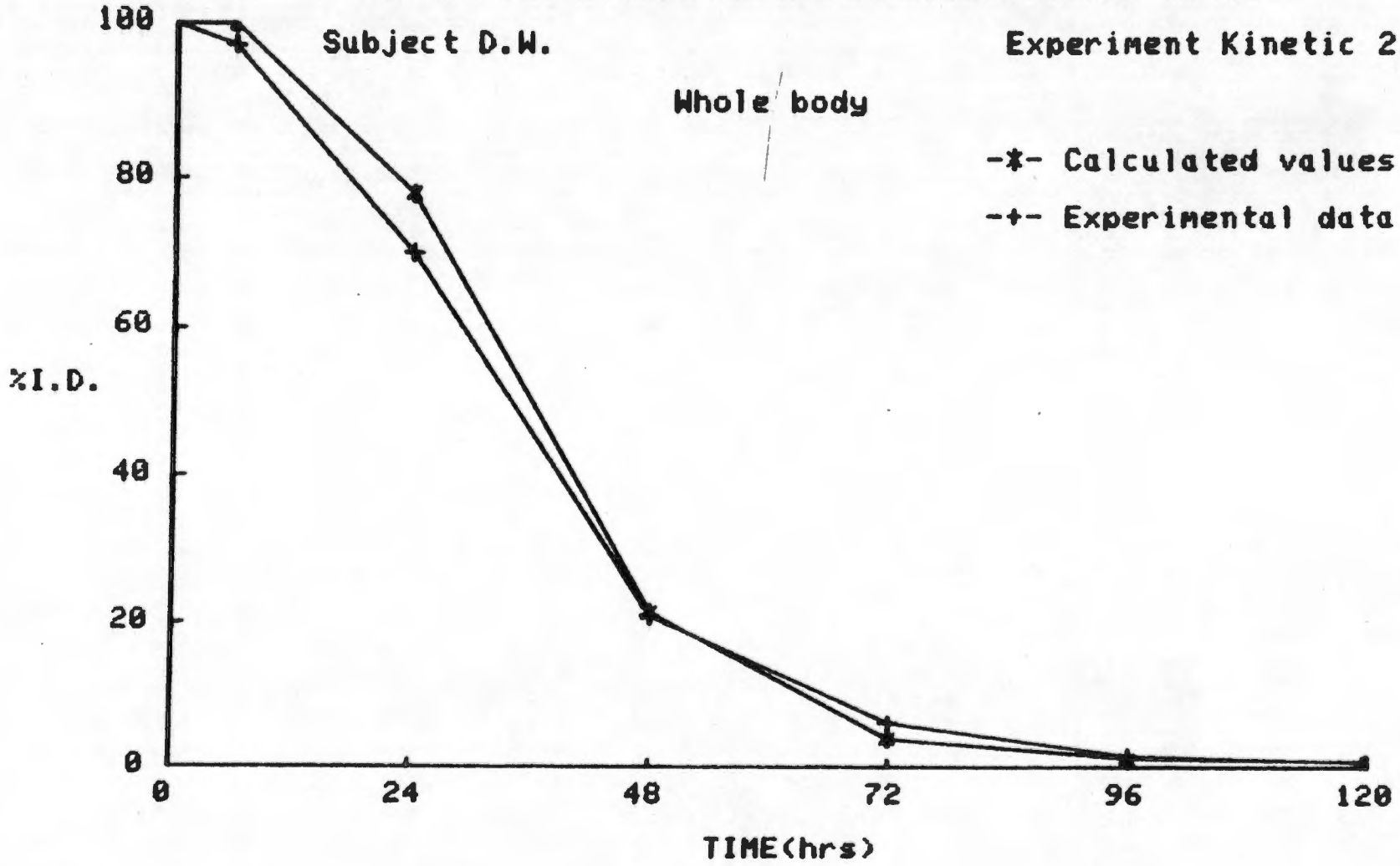


FIGURE. 8.4.3

Fit of calculated values to experimental data

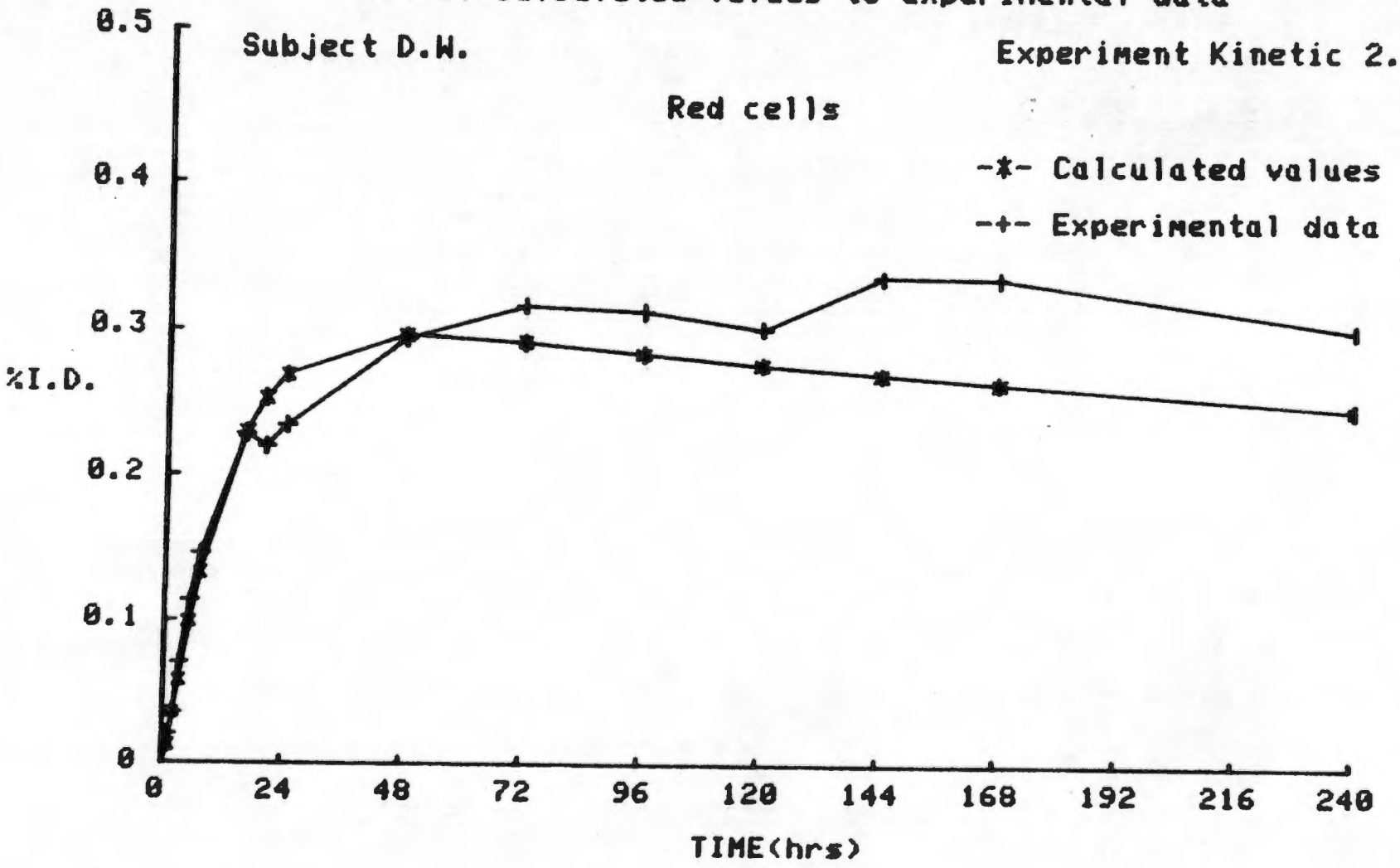


FIGURE. 8.4.4

Fit of calculated values to experimental data

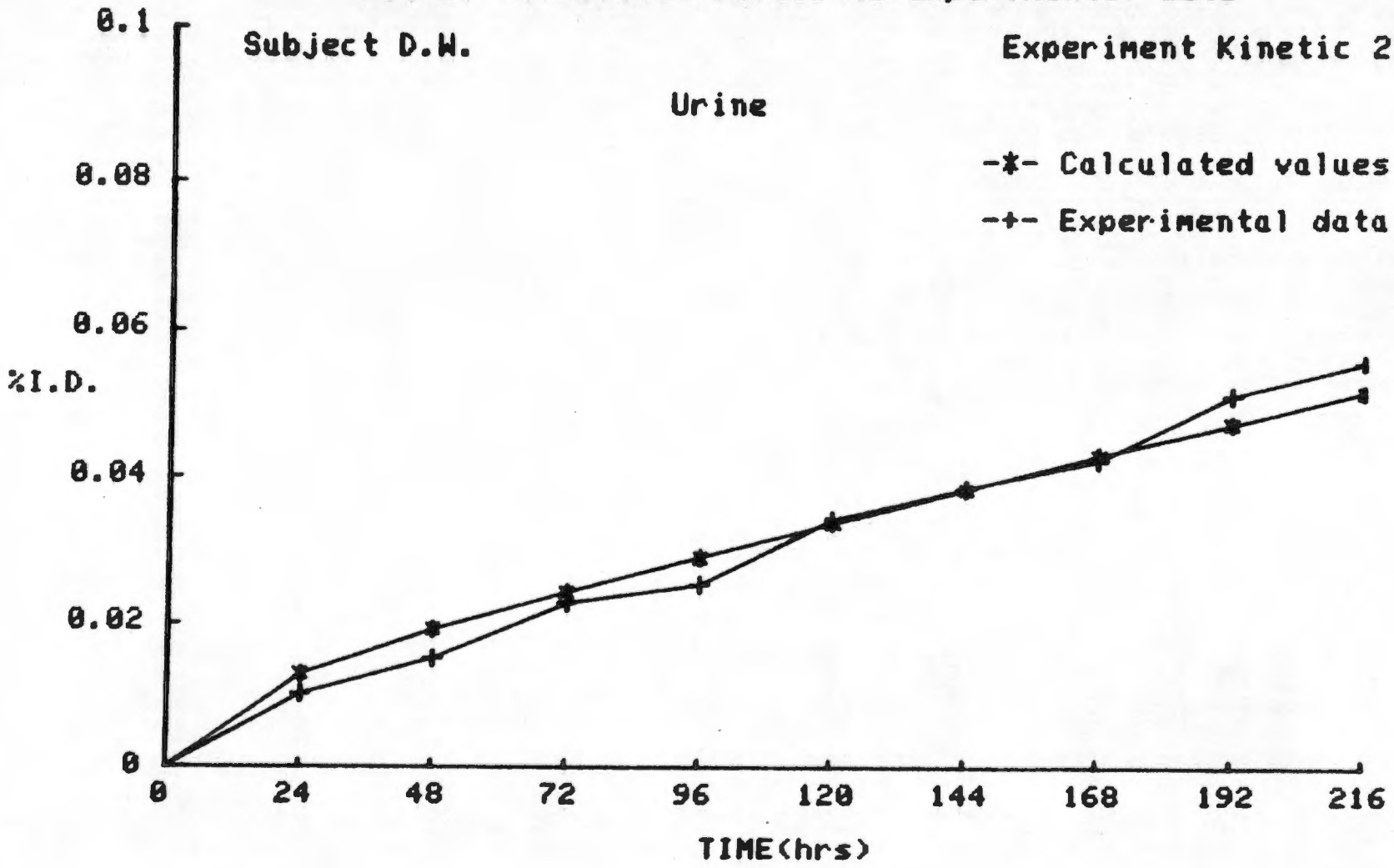


TABLE 8.4.4

Comparison of variable parameters from model solutions using experimental data from Kinetic 1. experiment and no carrier lead experiment of subject K.B.

RATE CONSTANT	KINETIC 1. ($hour^{-1}$)	NO CARRIER LEAD ($hour^{-1}$)
L(1,19)	$0.135 \pm 0.009^{\dagger}$	0.138 ± 0.036
L(2,19)	0.025 ± 0.008	$5 \times 10^{-6} \pm 4 \times 10^{-5}$
L(13,9)	409.41 ± 124.57	509.00 ± 12.39
L(14,9)	510.56 ± 151.11	725.75 ± 70.46
L(20,7)	0.008 ± 0.002	0.004 ± 0.005
L(20,19)	0.070 ± 0.008	0.083 ± 0.021
L(21,20)	0.099 ± 0.004	0.121 ± 0.015

$^{\dagger} \pm$ 1 standard deviation.

TABLE 8.4.5

Comparison of ^{203}Pb retention measurements from no carrier lead experiment of subject K.B. with model derived values

	96 HOUR RETENTION (%)	HALF TIME OF RETENTION (hours)	REGRESSION COEFFICIENT (r)
EXPERIMENTAL	$59.20 \pm 0.19^{\dagger}$	771.70 ± 36.09	- 0.98
MODEL DERIVED	58.88	820.95	- 0.99

$^{\dagger} \pm$ 1 standard deviation.

FIGURE. 8.4.5

Fit of calculated values to experimental data

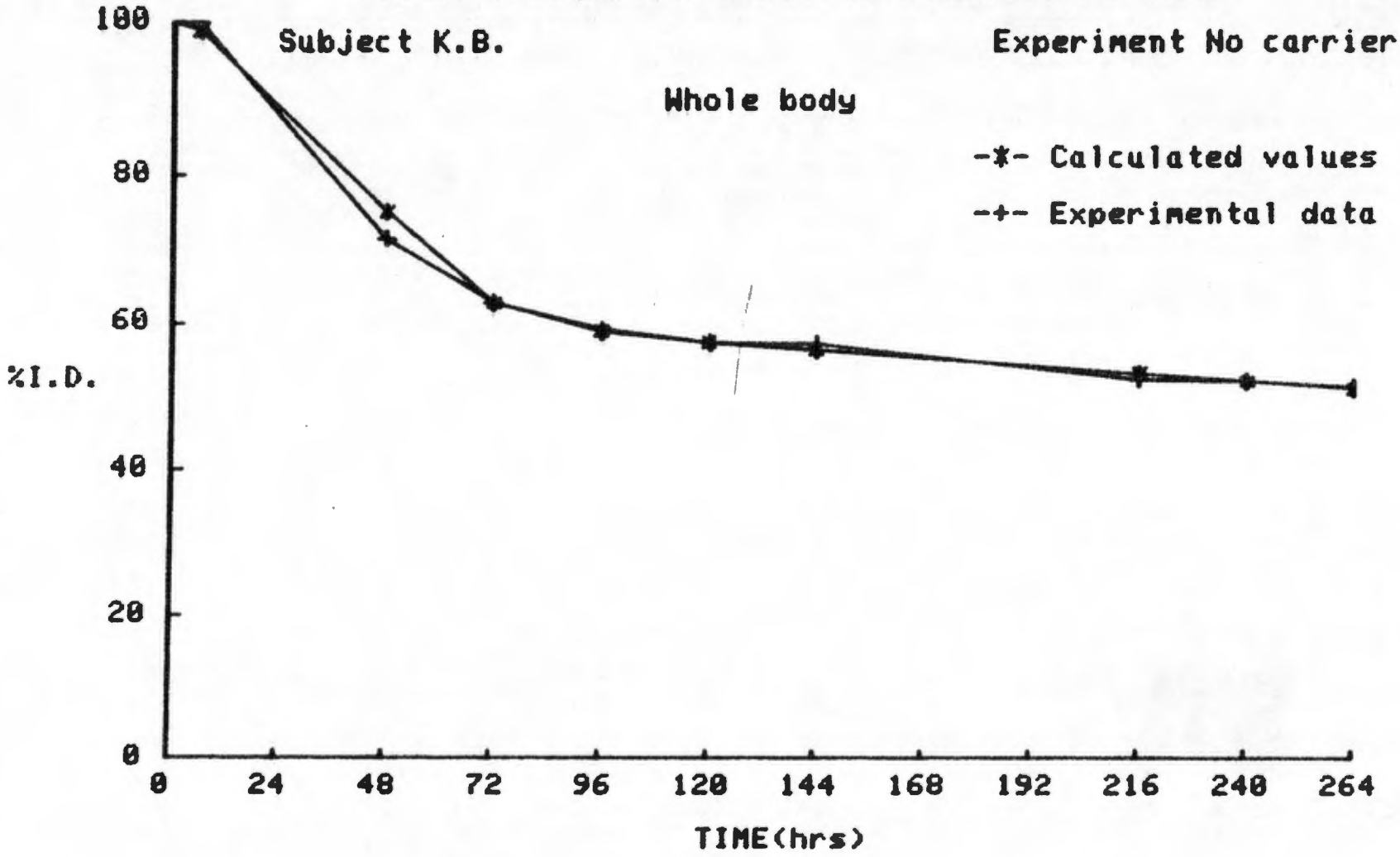


FIGURE. 8.4.6

Fit of calculated values to experimental data

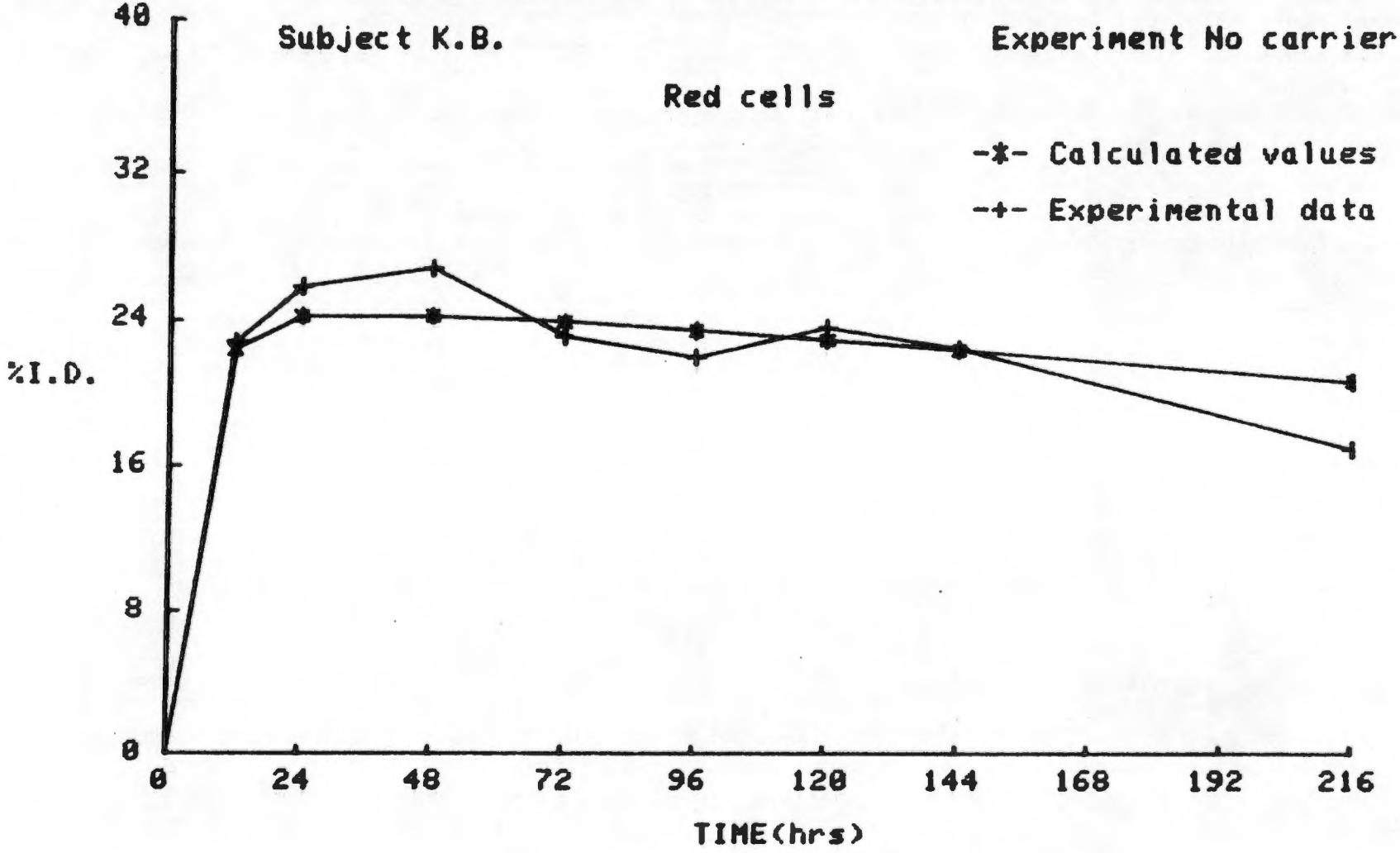


FIGURE. 8.4.7

Fit of calculated values to experimental data

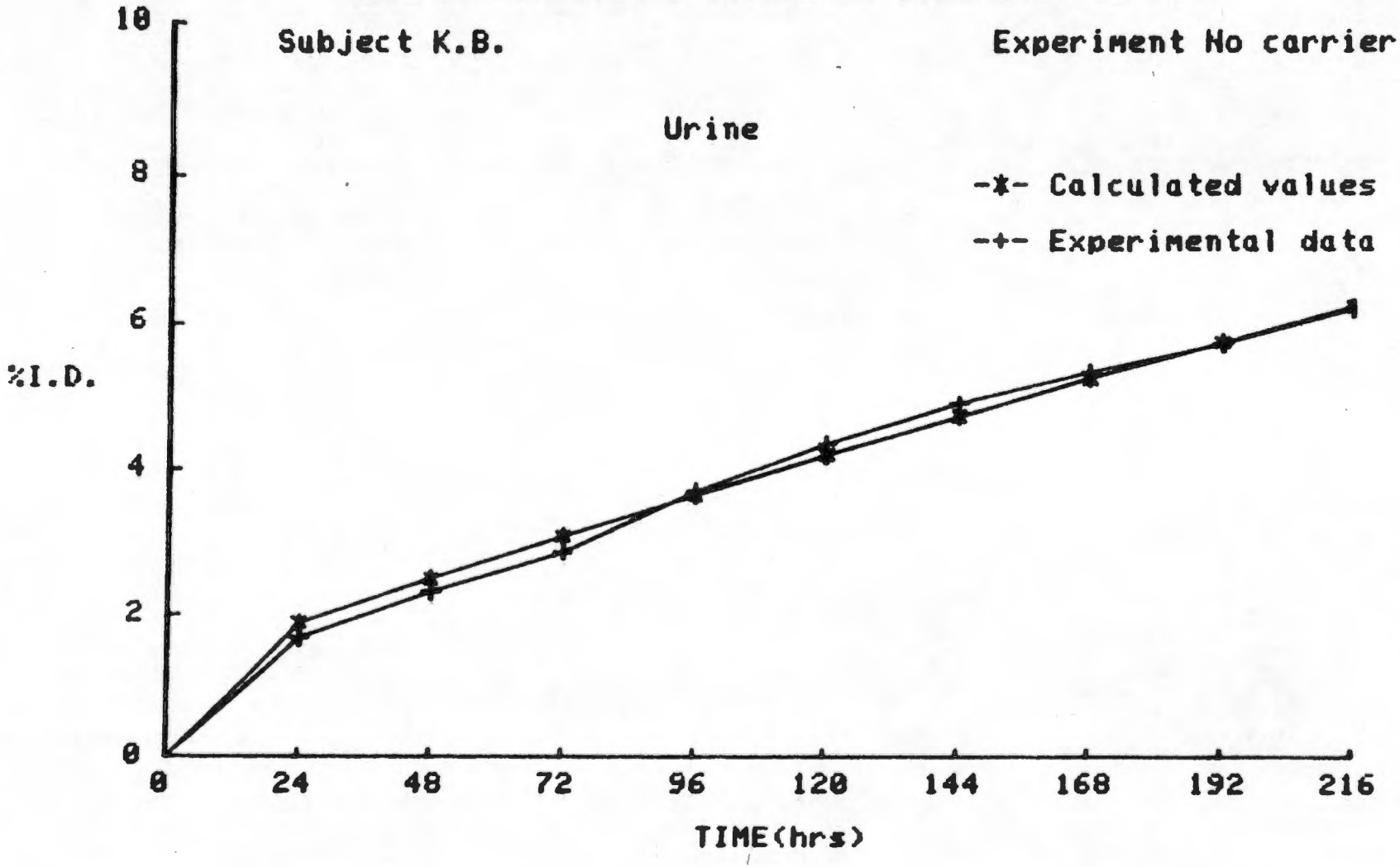


Table 8.4.6 shows the experimental retention data and simulated values for the two experiments in which subject K.B. ingested ^{203}Pb with calcium and phosphorous separately (section 6.0). Table 8.4.7 shows the values of the few rate constants, L(20,7), L(20,19) and L(21,20) which were required to change for both simulations. Figures 8.4.8 and 8.4.9 show the good fits between simulated and experimental whole body data.

The simulated levels of ^{203}Pb at 96 hours found in all the plasma and liver compartments are shown for comparison in table 8.4.8. The level of ^{203}Pb in plasma (9) is only 2% of that in plasma (10). There was no ^{203}Pb found in liver (4), a low level in liver (6), and approximately the same level of ^{203}Pb in liver compartments (5) and (7). Figures 8.4.10-15 show the levels of ^{203}Pb in each of the compartments. It is noticeable that the ^{203}Pb peaks very rapidly in plasma (9), within 2 hours of ingesting the dose of ^{203}Pb, whereas the peak occurs at approximately 16 hours in plasma (10). The uptake and release of ^{203}Pb in liver (4) is extremely rapid. The ^{203}Pb in liver (5) peaks at 15 hours and gradually falls away, whereas in liver (6), it follows the trends of plasma lead in the plasma compartments (9) and (10), and in liver (7), it rises continuously over the period of study.

TABLE 8.4.6

Comparison of ^{203}Pb retention measurements from separate calcium and phosphorous experiments of subject K.B. with simulated values using MODEL IV

WEIGHT OF $CaCO_3$ (g)	WEIGHT OF $NaH_2PO_4.2H_2O$ (g)	96 HOUR RETENTION (%)		HALF TIME OF RETENTION (hours)	
		Experimental	Simulated	Experimental	Simulated
-	2.513	47.24 $\pm$ 0.31†	47.22	346.50 $\pm$ 34.65	364.10
1.75	-	6.51 $\pm$ 0.10	6.93	123.75 $\pm$ 24.31	133.21

† $\pm$ 1 standard deviation.

TABLE 8.4.7

Rate constant changes required to simulate the ^{203}Pb whole body retention of subject K.B. found with separate weights of $CaCO_3$ and $NaH_2PO_4.2H_2O$

RATE CONSTANT ($hour^{-1}$)	$CaCO_3$ EXPERIMENT (1.75 g)	$NaH_2PO_4.2H_2O$ EXPERIMENT (2.513 g)
L(1,19)	Ø	-
L(2,19)	-	Ø
L(20,7)	0.025	0.020
L(20,19)	0.286	0.113
L(21,20)	0.159	0.144

FIGURE. 8.4.8

Fit of calculated values to experimental data

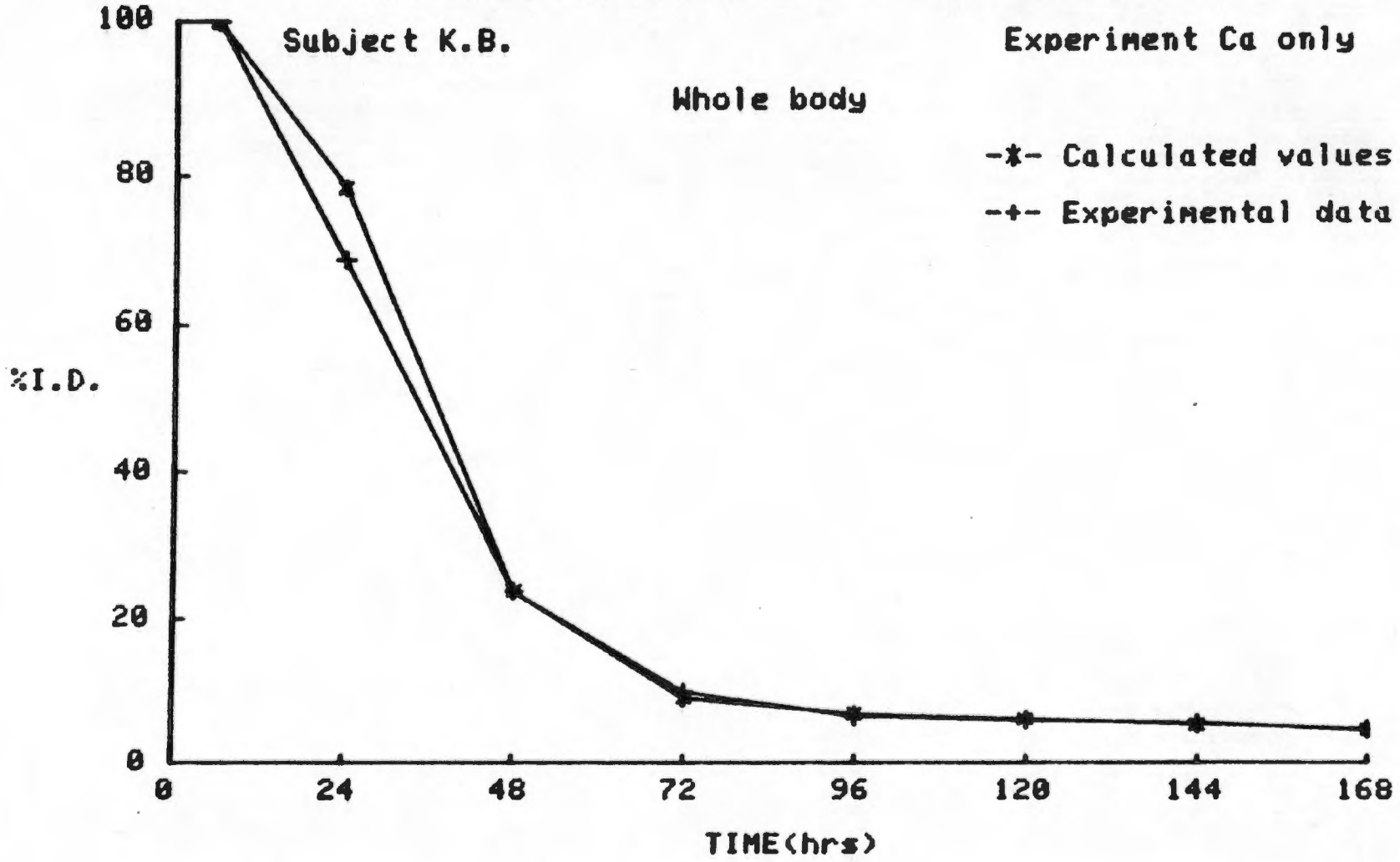


FIGURE. 8.4.9

Fit of calculated values to experimental data

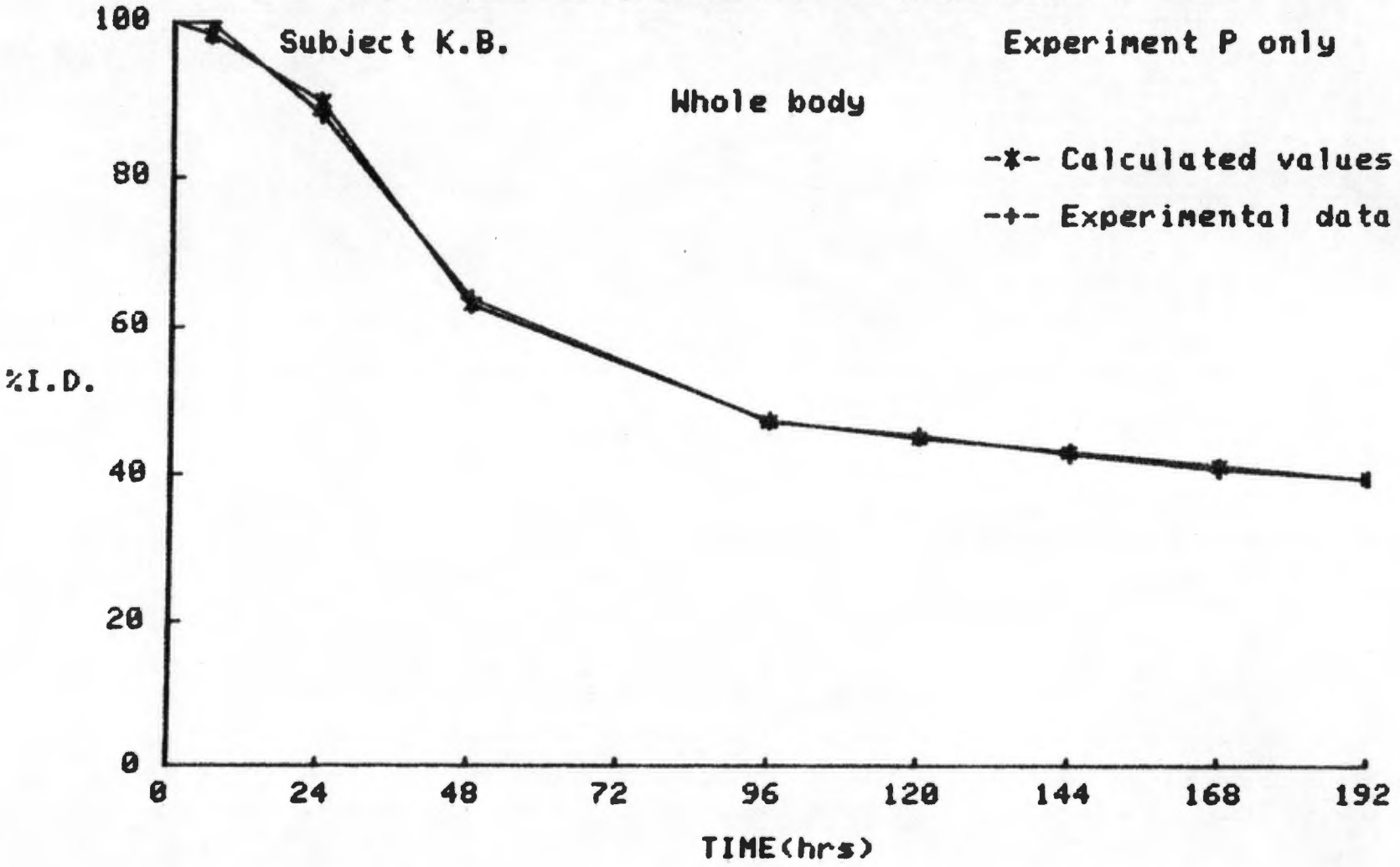


TABLE 8.4.8

Simulated 96 hour percentages of ingested dose of ^{203}Pb in plasma and liver compartments of MODEL IV determined using means of rate constants from Kinetic 1. experiments

COMPARTMENT		INGESTED DOSE ^{203}Pb (%)
Liver	4	Ø
Liver	5	5.53
Liver	6	0.010
Liver	7	9.89
Plasma	9	0.001
Plasma	10	0.045

FIGURE. 8.4.10

Simulated Pb-203 levels in plasma compartment 9

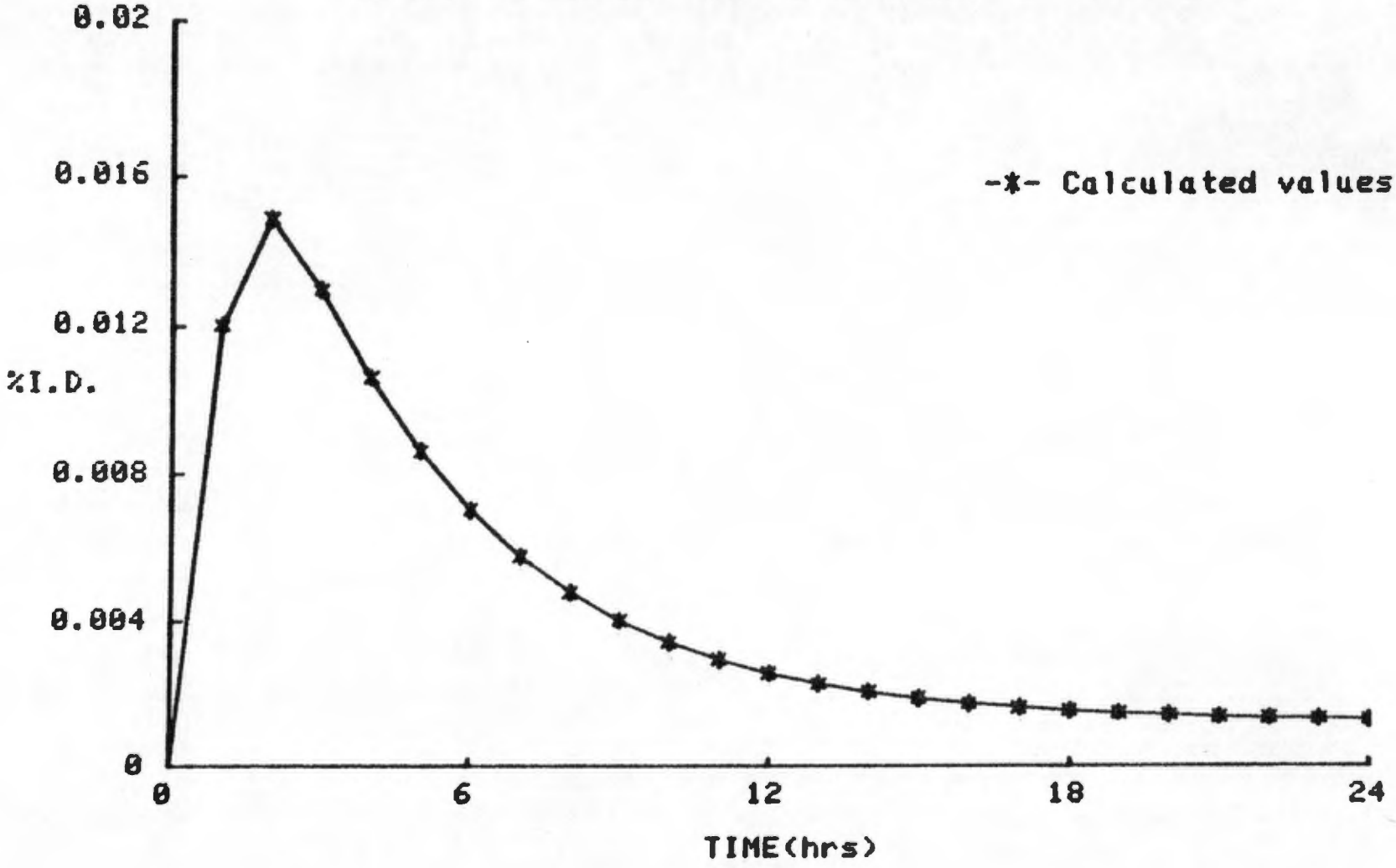


FIGURE. 8.4.11

Simulated Pb-203 levels in plasma compartment 10

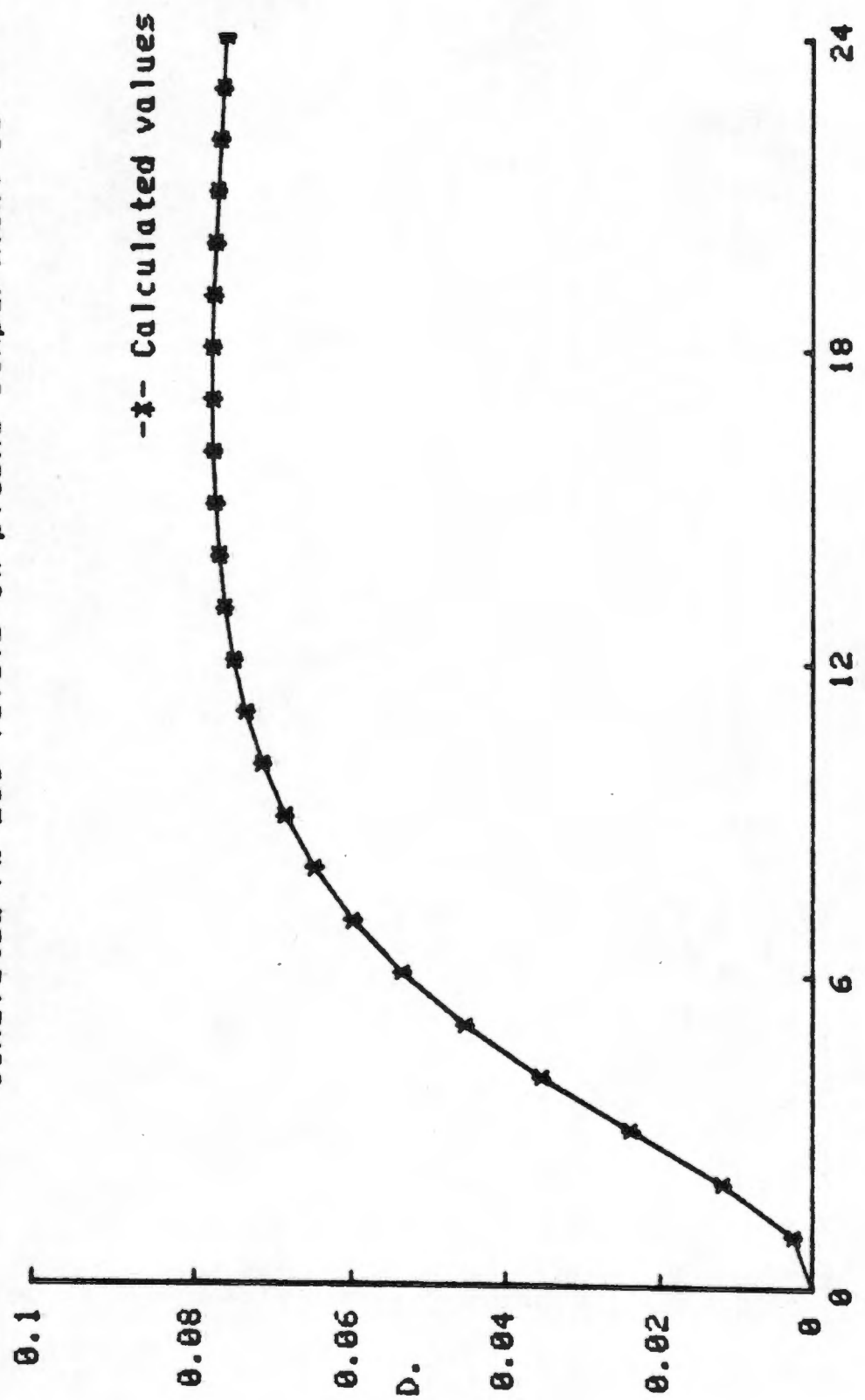


FIGURE. 8.4.12

Simulated Pb-203 levels in liver compartment 4

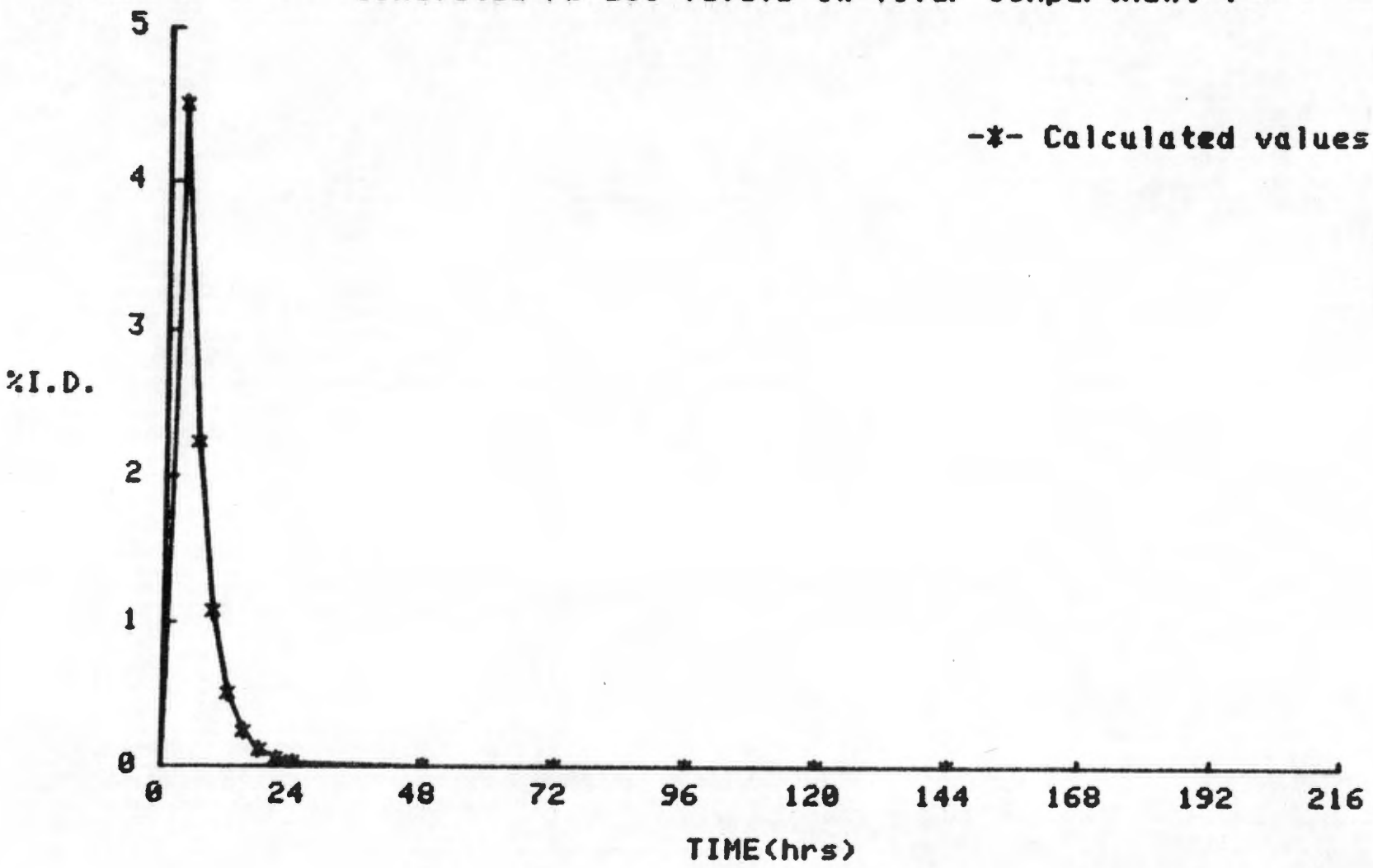


FIGURE. 8.4.13

Simulated Pb-203 levels in liver compartment 5

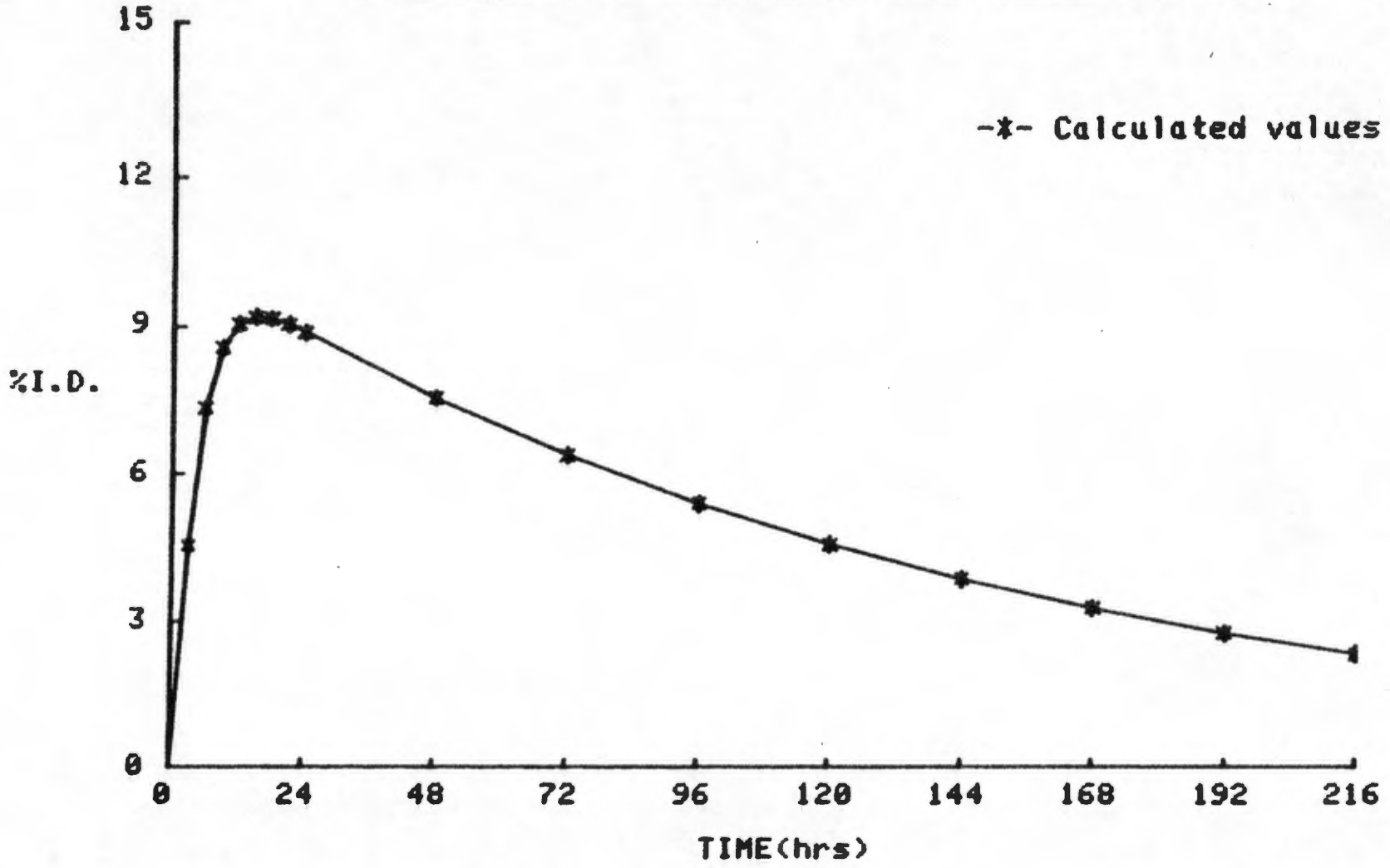


FIGURE. 8.4.14

Simulated Pb-203 levels in liver compartment 6

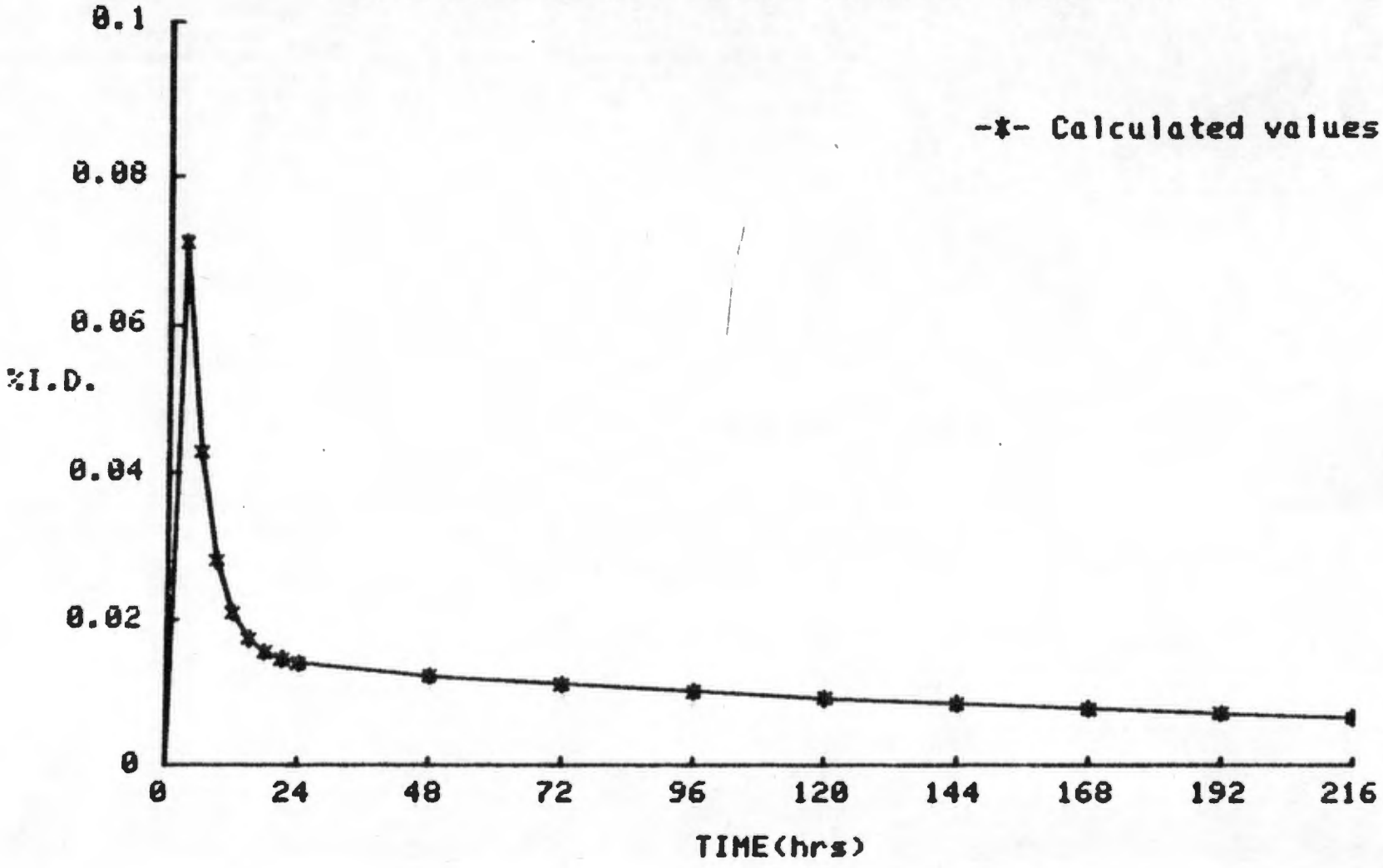
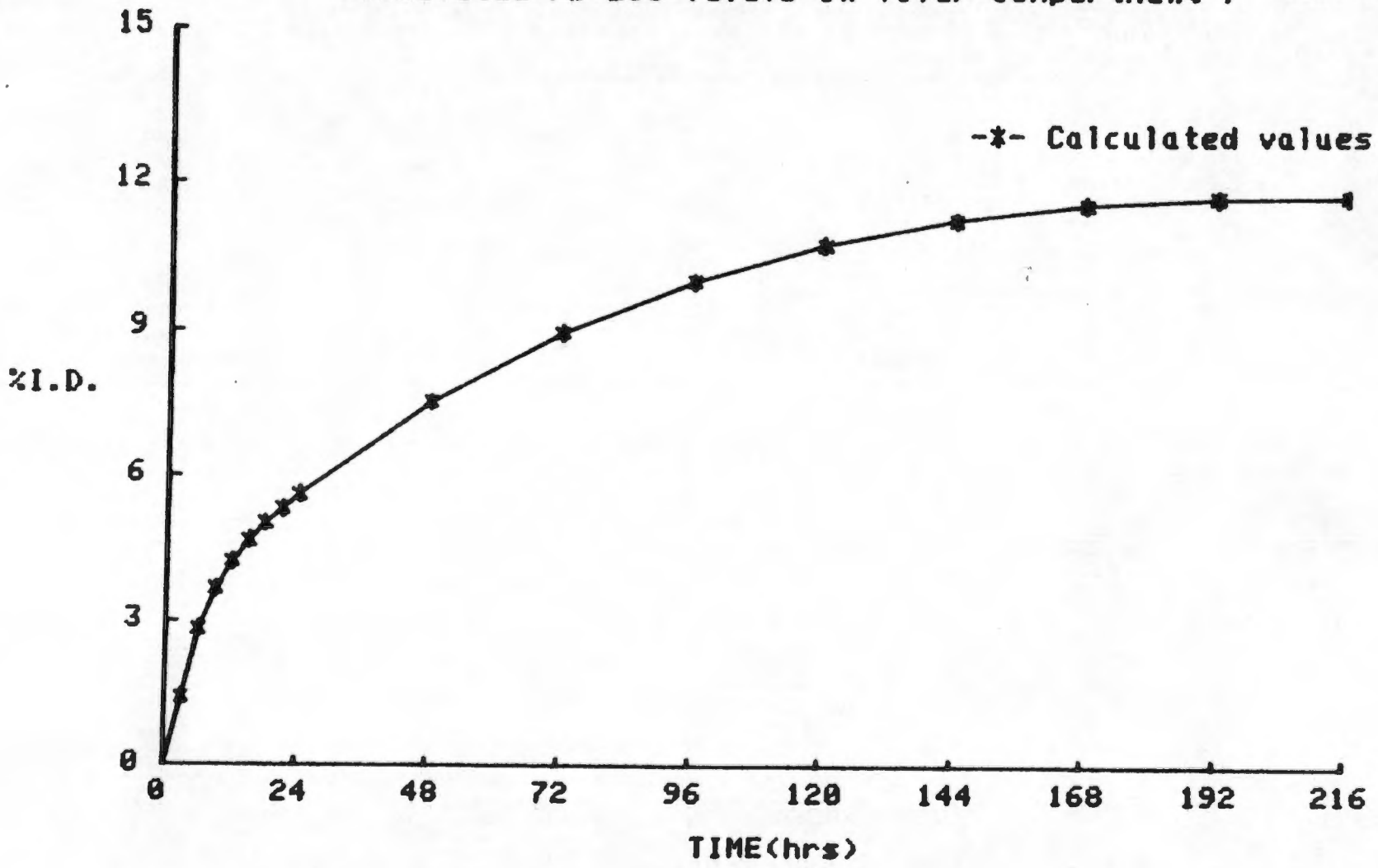


FIGURE. 8.4.15

Simulated Pb-203 levels in liver compartment 7



8.4.4 Discussion

a) 96 Hour whole body retention as a measure of absorption of ^{203}Pb and the effect of unabsorbed ^{203}Pb on 96 hour retention and half time of retention

The assumption that the 96 hour retention of ingested ^{203}Pb is a reliable measure of lead absorption appears to be valid. There was a good correlation between 96 hour retentions and the percentages of ingested dose absorbed that were calculated from model parameters. The 96 hour retention of subject D.W. found in the Kinetic 2. experiment was excluded, as there was doubt about the reliability of very low retentions as measures of lead absorption.

In the development of MODEL IV, retention values were used to constrain the percentages of ingested dose absorbed, but this was only done for the first model solution. The final solution was performed with rate constants L(1,19), L(2,19) and L(20,19) allowed to vary independently, and in which calculated values were fitted to all experimental whole body data from 6 hours to at least 216 hours. These rate constants represented the transport of lead from lumen to wall of small bowel and the movement of unabsorbed lead from lumen of small bowel to large bowel.

Although gamma camera and profile scan studies showed no localised ^{203}Pb radioactivity in the large bowel and rectum of each subject at 96 hours, the results of the simulations suggested that some unabsorbed ^{203}Pb may have been present. The effect of such unabsorbed ^{203}Pb on 96 hour retention was minimal, however, in most of the subjects.

It only appreciably affected the simulated 96 hour retentions of the Kinetic 1. experiment of subject B.C. and the Kinetic 2. experiment of subject D.W.

The presence of the unabsorbed ^{203}Pb in the simulation of the retention found in the Kinetic 1. experiment of subject B.C. caused an 8% increase in 96 hour retention. In contrast, the simulation of retention found in the Kinetic 2. experiment of the same subject showed no effect of unabsorbed ^{203}Pb. In this experiment, the unabsorbed ^{203}Pb cleared rapidly from the body. This was shown by the rapid decrease of whole body retention (figure BC-WB-2) and the large value of the rate constant L(21,20). This rate constant represents the movement of ^{203}Pb in the lumen of the large bowel, and it had a value of 0.36 $hour^{-1}$ in the Kinetic 2. experiment compared with its value of 0.075 $hour^{-1}$ in the Kinetic 1. experiment. The movement of the unabsorbed ^{203}Pb in the lumen of the large bowel of this subject was well described by the model.

If there is an even larger unabsorbed fraction of ^{203}Pb present in the gut, as in the Kinetic 2. experiment of subject D.W., 96 hour retention can be increased by a far greater amount i.e. 50%. If such a correction is applied to the 96 hour retention of this subject when he ingested ^{203}Pb with minerals (section 5.0), the reduction in retained doses of ^{203}Pb in his red cells and urine caused by the minerals would be much less. The magnitude of the changes would be comparable to those which occurred with the retained doses of ^{203}Pb in the red cells and urine of the other subject in that section, K.B. Therefore, 96 hour retentions of 1-2% may be considerably influenced by unabsorbed ^{203}Pb in the gut, and they may not be reliable measures of absorption of lead.

The presence of unabsorbed ^{203}Pb in the gut was shown by the simulations to have a considerable effect on the half times of retention calculated with retention data from 96 hours onwards. When the unabsorbed ^{203}Pb was removed from the gut by simulation, the mean increase in half times of retention was greater by a factor of 6 than the decrease in 96 hour retentions. Half times of retention, therefore, may not be as good a measure of urinary and endogenous faecal excretion of ^{203}Pb, as 96 hour retentions are a measure of absorption of ^{203}Pb.

There was still a decrease in the half times of retention when calcium and phosphorous were ingested with ^{203}Pb, which cannot be completely explained by the presence of a 'tailing edge' from the unabsorbed fraction of ^{203}Pb. The simulated half times of retention for the Kinetic 2. experiments were always less than those found for the Kinetic 1. experiments, and, in three subjects, still less even when there was no unabsorbed fraction of ^{203}Pb in the simulation.

It is surprising that the presence of unabsorbed ^{203}Pb in the large bowel of subject B.C. was not detected as a peak of localised radioactivity in the 96 hour profile scan performed on this subject in the Kinetic 1. experiment. Although the presence of the unabsorbed ^{203}Pb at 96 hours was only suggested by simulations of the model, the movement of the unabsorbed ^{203}Pb in the lumen of the large bowel of this subject was well described by the model.

Non-endogenous faecal ^{203}Pb in the gut at 96 hours may have come from another source apart from the unabsorbed fraction of ^{203}Pb, and it is necessary to discuss the delayed passage of unabsorbed lead in more

detail. Some idea of the dynamic behaviour of unabsorbed ^{203}Pb in the gut can be found in radiological studies of barium described by Eve (1966). It is thought that the transport of the contents of the transverse colon is by a mass movement effect which may occur one to four times a day. This mass movement would cause the unabsorbed ^{203}Pb to move quickly through the transverse colon into the descending colon, and this was confirmed by the peak of short duration between 16-24 hours in the surface radioactivity measurements performed over the small bowel. In the perfect physiological reflex, the peristaltic wave which sweeps the contents of the transverse colon into the descending colon will empty the transverse colon completely, but frequently some fragments are left in its wake. Such fragments of the unabsorbed ^{203}Pb probably caused the areas and peaks of localised radioactivity frequently seen in the region of the descending colon in the 48 hour and 72 hour scintigrams and profile scans.

The delayed passage of unabsorbed tracer in the gut of the human was investigated by Rabinowitz et al (1976). They administered a tracer, ^{207}Pb, for 10 days to two subjects who had already ingested the tracer ^{204}Pb daily for a length of time sufficient to produce steady state conditions of ^{204}Pb in the body. Ingestion of both tracers was discontinued simultaneously, and faecal excretion of ^{207}Pb was not detected 20 days after it had been discontinued. The authors presumed that the excretion of the ^{204}Pb more than 20 days after ingestion of both tracers was stopped, represented endogenously excreted ^{204}Pb. This suggests that it took 20 days for the unabsorbed fraction of ^{207}Pb to be cleared.

This study was based on certain assumptions, and the first was that there was no endogenous faecal excretion of the absorbed fraction of ^{207}Pb in the 20 days. Although this is consistent with the compartmental model of Rabinowitz et al (1974; 1976), in that endogenous faecal excretion of tracer is delayed by about 40 days after ingestion, work described by Chamberlain et al (1978) suggested that the only delay in endogenous faecal excretion is because of the time taken for the passage of faecal matter through the gut.

The second assumption was that the rate of reabsorption of endogenously excreted lead tracer was similar to the absorption of the ingested lead tracer. This has not been confirmed in animal studies. Experiments on rats have shown that very little if any reabsorption of endogenous lead occurs (Cikrt and Tichý, 1975; Conrad and Barton, 1978), and in the compartmental model developed in this thesis, no pathway for reabsorption was necessary to explain the kinetics of orally ingested ^{203}Pb.

Rabinowitz et al (1976) were probably measuring unabsorbed and endogenous faecal ^{207}Pb during the 20 days after ingestion of ^{207}Pb was stopped. After this time, they probably were unable to detect the presence of endogenous faecal ^{207}Pb as it was only ingested for a period of 10 days so that the levels of ^{207}Pb in the body would be much lower than those of ^{204}Pb. In another work, Rabinowitz et al (1974) had stated that the experimental error in the determination of endogenous faecal lead is significant. This would also make it difficult to detect small quantities of endogenous ^{207}Pb in faecal matter.

The suggested increase in 96 hour retentions, shown by the simulations and attributed to the 'tailing edge' of unabsorbed ^{203}Pb, may be due to exfoliation of mucosal cells of the small bowel. Exfoliation of mucosal cells as a mechanism of lead excretion was suggested by Conrad and Barton (1978). They found in fasting rats injected with ^{210}Pb that the disappearance of ^{210}Pb from the small intestine approximated the 2-day life span of mucosal cells.

This mechanism of excretion together with the storage of ^{203}Pb in the wall of the small bowel observed in the kinetic studies (section 8.2), would probably not cause a localised pattern of ^{203}Pb in the gut, but a more generalised distribution. Such a distribution was observed in the inferior edge of the isolated profiles of ^{203}Pb radioactivity in the liver during profile scan analysis (section 8.2.3). In that section, the distribution was attributed to endogenous faecal ^{203}Pb.

However, whether the suggested increase in 96 hour retentions was caused by the 'tailing edge' of the unabsorbed fraction of ^{203}Pb or exfoliation of mucosal cells containing ^{203}Pb from the small bowel, cannot be proved from the experiments performed in this thesis.

b) Compartmental analysis of data from Kinetic 2. experiment of subject D.W.

The effect of the maximum weights of calcium and phosphorous ingested by subject D.W. was to dramatically reduce the absorption of lead in both the common lead/calcium and common lead/phosphorous absorptive pathways. The percentage of ingested dose absorbed was calculated to be 0.83%, and it agrees well with the simulated 96 hour retention of 0.77% of this same subject when the unabsorbed fraction of ^{203}Pb was removed

from the gut by simulation. The values of the rate constants representing absorption of ^{203}Pb were considerably lower than those which were found from the analysis of the data from the Kinetic 1. experiment of this subject.

From the results of the dose response experiment performed on subject K.B. (section 6.4.2), it was suggested that no absorption of ^{203}Pb occurred via the common lead/calcium pathway but it did via the common lead/phosphorous pathway when ^{203}Pb was ingested with the maximum weights of calcium and phosphorous. The use of the model with the data from the Kinetic 2. experiment of subject D.W., however, has shown that absorption still appears to occur via the common lead/calcium pathway, as indicated by the ^{203}Pb radioactivities in red cells and urine. The extremely low value of the rate constant representing absorption of ^{203}Pb via the common lead/phosphorous pathway suggests no absorption, but as the uncertainty of the value was very high, this cannot be confirmed. The value of the rate constant representing absorption via the common lead/calcium pathway was also greatly reduced, which may suggest a change in the nature of the transport mechanisms responsible for the absorption of ^{203}Pb in this pathway.

There was the expected increase in L(14,9), rate constant representing the uptake of ^{203}Pb in the 'soft' tissue compartment, as this had occurred in the other subjects in their Kinetic 2. experiments. The rate constant representing the uptake of ^{203}Pb in the red cell compartment, L(13,9), was also increased, which is the opposite to which occurred in the other subjects. However, the model was unable to completely describe the changing levels of ^{203}Pb in the blood, as these

levels rose very slowly with time.

The large changes in the values of L(20,7) and L(21,20), rate constants representing the biliary excretion of ^{203}Pb and movement of ^{203}Pb in the lumen of the large bowel, and the large uncertainty of L(20,7) are the result of the lack of experimental data, particularly on liver ^{203}Pb radioactivity and on post-96 hour whole body radioactivity. The value of L(20,19) is very low, as it represents the fraction of ^{203}Pb which is unabsorbed and, hence, its value will depend on that of L(1,19).

c) Effect of carrier lead on absorption and excretion of ^{203}Pb in subject K.B.

Both the value of the rate constant and the percentage of ingested dose of ^{203}Pb absorbed via the common lead/calcium pathway, L(1,19), were unchanged by the presence of carrier lead with ^{203}Pb. This confirms the suggestion made in section 5.4.1 that the weight of carrier lead used, 300 µg lead chloride, can be tolerated by the transport mechanisms responsible for the absorption of lead. There appeared to be no absorption via the common lead/phosphorous pathway.

Although both L(13,9) and L(14,9), rate constants describing the uptake of ^{203}Pb in red cell and 'soft' tissue compartments, are increased compared with their values from the analysis of data from the Kinetic 1. experiment, the changes are not significant.

Of the other rate constants allowed to vary, the only large change occurred in the rate constant L(20,7), representing biliary excretion of ^{203}Pb. This was decreased by a factor of 2. However, the

uncertainty of this rate constant was large, and this was caused by the lack of experimental data on liver ^{203}Pb radioactivity.

The half time of retention was decreased by an approximate factor of 2 by the presence of carrier lead with the dose of ingested ^{203}Pb. The 96 hour retentions were approximately 60%, and the results of the simulation of the effect of unabsorbed ^{203}Pb on the retention data of subject K.B. showed a possible 20% increase in half times of retention. The effect of any unabsorbed ^{203}Pb present in the gut, therefore, could not completely account for the difference in half times. Only by the inclusion of L(20,7) in the model solution and a marked change in its value could the calculated values of retention be made to match the experimental data.

Although this application of MODEL IV with the limited data from the experiment in which subject K.B. ingested ^{203}Pb without carrier lead suggests that carrier lead increases the biliary excretion of ^{203}Pb, more experimental data from more subjects are required to confirm this effect.

d) <u>Effects of separate doses of calcium and phosphorous on the absorption of ^{203}Pb in subject K.B.</u>

The whole body retention data of subject K.B. were successfully simulated using MODEL IV by not allowing any absorption of ^{203}Pb by the common lead/calcium pathway and the common lead/phosphorous pathway in two separate simulations. This suggests that the maximum weights of calcium, 1.75 g $CaCO_3$, and phosphorous, 2.513 g $NaH_2PO_4.2H_2O$, ingested with the lead in these two experiments, almost completely inhibited the

absorption of lead in the pathway common to either of the minerals and lead. This supports the theory advanced in section 6.4.1 that lead is probably absorbed by at least two pathways, one which it shares specifically with calcium and the other specifically with phosphorous.

The value of L(20,19) will be different between the two experiments as it represents the percentage of ingested dose not absorbed. The values of L(20,7) and L(21,20), rate constants representing the biliary excretion of ^{203}Pb and movement of ^{203}Pb in the lumen of the large bowel, are comparable between the two experiments, although they are larger than the values found from the analysis of data from the Kinetic 1. experiment of subject K.B.

The different value of L(20,7) is not unexpected, as no other experimental data apart from the whole body retention was available. Other rate constants such as L(13,9) and L(14,9), representing uptake of ^{203}Pb in red cell and 'soft' tissue compartments could not be included. Such rate constants could have changed the levels of ^{203}Pb in body compartments and influenced the value of L(20,7). The larger value of L(21,20) could have occurred because of a difference in the bowel motility of subject K.B. between the times of these experiments and the kinetic experiments.

The half times of retention for each experiment were very different. The 96 hour retentions were not of the order of 1-2%, and the results of the simulation of the effect of unabsorbed ^{203}Pb on the retention data of subject K.B. showed a possible 20% increase in half times of retention. The effect of any unabsorbed ^{203}Pb present in the gut from

96 hours onward cannot completely account for the differences in half times. Even the values of L(20,7), rate constant representing biliary excretion of ^{203}Pb, are too close to account for the difference between half times.

Therefore, the fraction of ^{203}Pb ingested in each of the two pathways in the small bowel has a great effect on the half times of retention. This could explain the shorter half times of retention found in experiments in which ^{203}Pb was ingested with calcium and phosphorous.

e) Possible physiological roles of plasma and liver compartments

Lead and calcium have been suggested to share the same metabolism (Aub et al, 1926; Six and Goyer, 1970). Similarities of behaviour in the gut have also been described (Barton et al, 1978), and work in this thesis has shown that lead appears to share the same active transport as calcium. Baloh (1974) suggested that plasma lead probably exists in two forms, diffusible and protein bound, in an analogous manner to plasma calcium. Two forms of plasma lead had to be introduced into the compartmental model developed in this thesis, to make the model compatible with experimental data on the kinetics of lead in the body.

The results of simulating the levels of ^{203}Pb in the plasma and liver compartments shows that the two forms of lead in the plasma appear to behave quite differently. In the model, the lead entering the plasma from the common lead/calcium pathway has been defined as the diffusible form, and it reaches a peak in the plasma at approximately 2 hours after ingestion of ^{203}Pb. Plasma levels of ^{47}Ca reach a peak in a similar time after the ingestion of ^{47}Ca by fasted normal humans (Tothill et

al, 1970). Calcium is actively transported in the ionised form (Schachter et al, 1960), and the similarity between the trends of ^{47}Ca plasma levels and the simulated levels of diffusible plasma ^{203}Pb suggests that lead may also be transported in the ionised form.

The non-diffusible plasma lead has been suggested to enter the plasma via the common lead/phosphorous pathway. From the simulation, this form of plasma lead appears to constitute 98% of the total plasma lead. It peaks at approximately 16 hours, which suggests a delayed absorption. At this time, this could mean absorption from the large bowel or absorption from the small bowel, uptake in an organ and subsequent release into the general circulation. The most likely mechanism is small bowel absorption and uptake in and release from the liver. This is the first organ that receives the portal circulation, which will contain the gastrointestinally absorbed lead. This mechanism was adopted in the compartmental model, which was able to generate calculated values satisfactorily matching the experimental liver data.

As the liver is the site of albumin synthesis in the body (Samson Wright, 1965), the lead released slowly from the liver could be protein bound and, therefore, non diffusible. Calcium also exists in the plasma mainly bound to albumin (Pedersen, 1972), and, similarly, lead has been found predominantly in the albumin and α_1 - globin fractions of the plasma proteins (Waldron and Stöfen, 1974).

The simulation showed that the diffusible plasma lead was approximately 2% of the non diffusible or protein bound lead. The levels of diffusible and non-diffusible plasma calcium are approximately the same

(Marshall, 1976 b). Calcium does not bind to red cells, however, as avidly as lead. The relatively lower level of diffusible plasma lead compared to that of diffusible plasma calcium could be caused by the greater uptake of lead in the red cells. Measureable uptake of calcium by red cells only occurs in non physiological conditions (Robertson, 1976). This difference in the behaviour of calcium and lead with red cells could be caused by the lower affinity of calcium for sulphydryl groups. Red cells are rich in sulphydryl groups, and the order of activity for different metals is Hg > Ag > Pb > Cd > Zn > Ca > Mg (Waldron and Stöfen, 1974).

The behaviour of lead in the liver was described by four compartments in the model. Two of the compartments appear to have no recognised physiological roles. The uptake and release of lead is extremely rapid in the liver compartment in the pathway by which the diffusible lead enters the plasma of the general circulation. The use of this compartment appears to be operational as does the use of the other liver compartment that combines the outputs from the two plasma compartments of the model.

The behaviour of lead in the other two compartments may be physiological. The slow rate of release of lead from the compartment in the pathway by which non diffusible lead enters the plasma of the general circulation is consistent with the suggestion made earlier that lead is bound to albumin in the liver. The storage of lead in the compartment from which lead is biliary excreted is also consistent with the suggestion of Barltrop (1968) that lead is stored in the liver. Lead in this compartment of the liver may be compared to the mitochondria

fraction of lead isolated by Castellino and Aloj (1969), which was found to be strongly bound to the mitochondria.

SECTION 9

DISCUSSION

9.1 Interrelationship between lead, calcium and phosphorous absorption

The interrelationship between lead, calcium and phosphorous absorption discussed in section 7.2 was based on the hypothesis suggested in section 6.4.1 that oral lead was absorbed by two pathways, one which it shares specifically with calcium and the other specifically with phosphorous. The effects of calcium and phosphorous, singly and together, on the retention of ^{203}Pb in one subject, K.B., was explained by this hypothesis (section 6.4.1).

Later work on the compartmental analysis of the kinetics of orally ingested ^{203}Pb in five subjects (section 8.0), confirmed that at least two pathways of lead absorption were necessary to make a 'universal' model compatible with the kinetic data from these five subjects. Furthermore, the effects of separate doses of calcium and phosphorous on the retention of subject K.B. were explained by using the model and assuming that calcium and phosphorous would specifically inhibit absorption of lead in the appropriate common lead/calcium and common lead/phosphorous pathways.

The responses of the suggested common lead/calcium and common lead/phosphorous absorptive pathways to increasing weights of calcium and phosphorous were investigated in section 6.0. The results were

discussed in section 6.4.2, and it was suggested that as the weights of calcium and phosphorous given with the oral dose of ^{203}Pb were increased, calcium specifically inhibited the absorption of ^{203}Pb in the common lead/calcium pathway, but there was little effect of phosphorous on ^{203}Pb absorption in the common lead/phosphorous pathway. With large weights of calcium and phosphorous, calcium completely inhibited the absorption of ^{203}Pb in the common lead/calcium pathway, but absorption still occurred in the other pathway. This theory was used to explain the shape of the response curve of 96 hour retention of subject K.B. against weights of calcium and phosphorous.

The results of the compartmental analysis of the data from the paired kinetic experiments suggests that this theory should be re-examined. The analysis of data from the Kinetic 1. experiments showed that the fraction of ingested lead absorbed by the common lead/calcium pathway was approximately 7 times that absorbed by the common lead/phosphorous pathway. This ratio was increased to approximately 14 to 1 when lead was ingested with the intermediate weights of calcium and phosphorous given in the Kinetic 2. experiments of all the subjects except D.W. This shows that phosphorous inhibits lead absorption in the common lead/phosphorous pathway much more than calcium does in its respective pathway. At large weights of calcium and phosphorous, it is unlikely that any measurable absorption of lead would occur by the common lead/phosphorous pathway, as suggested above.

Furthermore, the analysis of the limited data from the Kinetic 2. experiment of subject D.W. showed that absorption of lead by the common lead/calcium pathway could still occur at large weights of calcium and

phosphorous. This contradicts the suggestion made earlier that large weights of calcium would completely inhibit the absorption of lead in the common lead/calcium pathway.

The results of the compartmental analysis of the data from the paired kinetic experiments also showed that the values of the rate constants describing the transport of lead via the two pathways changed. There were no significant changes in the rate constant representing the common lead/calcium pathway caused by intermediate weights of calcium, but when large weights were ingested by subject D.W., the value of this rate constant was reduced. This suggests a change in the nature of the transport mechanism represented by this rate constant. It was noticeable that the value of the rate constant representing the common lead/phosphorous pathway was reduced by intermediate weights of phosphorous.

A reduction in the fraction of lead absorbed by a pathway but no change in the rate constant representing absorption suggests that competitive inhibition of active transport is taking place. A reduction in both the fraction absorbed and in the rate constant suggests competition for a slower transport process, which could be diffusion. If lead were to share both active and passive transport mechanisms of calcium and phosphorous, the results above would be compatible with the known characteristics of calcium and phosphorous absorption.

Calcium is predominantly absorbed at low calcium concentrations by active transport in the upper small bowel, that saturates at high calcium concentrations. Absorption then takes place by a concentration-dependent

diffusion transport, which is unsaturable (Marshall, 1976 a). Phosphorous is absorbed lower down the small bowel than calcium, and the saturable component of phosphorous absorption is small in comparison with the diffusion component (Marshall, 1976 a).

Small quantities of lead entering the small bowel will be mainly absorbed by the active transport of calcium, and unabsorbed lead will move further down the bowel and be absorbed by the active transport of phosphorous. However, certain 'digestive' factors appear to affect the absorption of phosphorous (Wilkinson, 1976), so that some of the lead will pass out of the small bowel into the large bowel and will be excreted in the faeces. This could explain the high absorption of lead in the Kinetic 1. experiments, and the larger fraction of this lead absorbed by the common lead/calcium pathway.

The presence of intermediate weights of calcium and phosphorous with lead in the small bowel would correspond to region B of the dose response curve of 96 hour retention against weights of calcium and phosphorous of subject K.B. (figure 6.3.2). There would be competitive inhibition of lead absorption by calcium in the common lead/calcium pathway, but active transport would still exist, as shown by little change in the value of the rate constant representing this pathway. The large change in the value of the rate constant representing the common lead/phosphorous pathway shows that the active transport of phosphorous is already saturated and absorption is probably taking place by diffusion. As the fraction of ingested lead absorbed by the common lead/calcium pathway is much greater than that absorbed by the common lead/phosphorous pathway, the absolute change in total

absorption produced by calcium will be much greater. Region B, as suggested in section 6.0, does appear to represent the interaction of mainly calcium and lead in the small bowel.

In region C, the large weights of calcium will have saturated the active transport of calcium, as suggested in section 6.4.2. Lead absorption can now only take place by the diffusion pathways of calcium. This was shown in the Kinetic 2. experiment of subject D.W., with a drop in the value of the rate constant representing the common lead/calcium pathway indicating that active transport had ceased. Lead may still be absorbed by the diffusion pathways of phosphorous, but the fraction of ingested lead absorbed is probably minute. Region C, therefore, appears to represent the competition of lead and calcium for the diffusion pathways of calcium.

9.2 Possible systemic effect of calcium and phosphorous on the distribution and excretion of lead

In section 5.0, two subjects ingested ^{203}Pb with and without minerals in separate experiments, and the levels of ^{203}Pb in their blood and urine were measured. When these ^{203}Pb levels were expressed as percentages of each subject's 96 hour retention (retained dose), minerals had reduced the retained dose in the blood of both subjects and that in the urine of one subject, respectively. The 96 hour retentions of the subjects when they had ingested ^{203}Pb with minerals were approximately 1-2% of the ingested dose. Subsequent work showed that unabsorbed ^{203}Pb in the body at 96 hours could have a considerable effect on such low measurements of retention and, therefore, on any result expressed as a percentage of retention.

More comprehensive experiments were performed in section 8.2 to study the effect of calcium and phosphorous on the kinetics of ^{203}Pb in five subjects. The results of these experiments (section 8.2.3) confirmed the changes in retained dose of ^{203}Pb in blood but not those in the urine found in section 5.0.

9.2.1 Distribution

The compartmental model showed the effect of ingesting calcium and phosphorous simultaneously with lead caused a significant reduction in the rate constant representing the uptake of lead in the red cell compartment and a significant increase in the rate constant representing the uptake of lead in the 'soft' tissue compartment.

The changes in these rate constants were associated with a significant decrease in retained dose of ^{203}Pb in the red cells and a significant increase in the model derived levels of absorbed dose in the 'soft' tissue compartment. A reduction in the value of the summer coefficient relating the experimental 'soft' tissue data to the absolute calculated values accompanied the increase in 'soft' tissue levels. This summer coefficient represents the fraction of the ingested dose of ^{203}Pb in the 'soft' tissue compartment 'seen' by the *in vivo* detector. A reduction in this fraction suggests that the apparent size of the 'soft' tissue compartment may have increased.

The changes in the rate constants representing uptake of lead in the red cells and 'soft' tissue compartments may have been caused by differences in plasma levels of calcium and phosphorous between the paired kinetic experiments. In the Kinetic 2. experiments, the calcium ingested will

be absorbed by active transport in the upper small bowel, and increasing levels of ionised calcium in the plasma will cause a homeostatic response in the three organs, intestine, bone and kidney. Parathyroid hormone will be released which will reduce the absorption of calcium from the gut, reduce the release of calcium from the bone and increase the excretion of calcium. The effectiveness of these mechanisms is such that variations in plasma calcium due to absorbed calcium are extremely difficult to detect (Nordin, 1976).

The absorption of phosphorous ingested in the Kinetic 2. experiments will increase as it moves from upper to lower small bowel, and plasma levels of phosphorous will increase. These levels are highly dependent on the amount of phosphorous in the gut (Robertson, 1976), and the normal levels of plasma phosphorous are less controlled than those of calcium (Robertson, 1976). Intestinal absorption of phosphorous will influence the plasma concentration of phosphorous throughout the day (Robertson, 1976). Therefore, plasma phosphorous will probably be raised compared to plasma calcium.

If the early partitioning of gastrointestinally absorbed ^{203}Pb between red cells and soft tissues is assumed to be competitive, then the raised plasma levels of phosphorous may have a considerable effect on the uptake of ^{203}Pb in red cells and soft tissues. It is known that phosphorous, as phosphate, inhibits the uptake of lead by red cells. Lead suspended in whole blood caused less damage to red cells than lead suspended with red cells in phosphate-free Ringer suspension, owing to the protection afforded by the plasma inorganic phosphate (Clarkson and Kench, 1958).

Diets rich in phosphorous have been shown to decrease blood lead levels in animals. Sobel et at (1940) fed rats diets with different quantities of calcium and phosphorous to which large amounts of lead carbonate (8 g/kg) were added. After 29 days on the diets, the rats were sacrificed and lead levels in blood and bone were measured. They found that the addition of phosphorous to the diet caused a significant decrease in blood lead levels. Morrison et al (1974) fed smaller amounts of lead (0.2 g/kg) as part of the diet to lambs for 1 year. A group of lambs were fed phosphate supplements, and, in this group, blood lead was lower than in a group fed a diet with normal amounts of calcium and phosphate. There was no difference in the lead content of livers and kidneys between the two groups, which suggests that the phosphate caused a change in distribution of lead away from blood in favour of soft tissues other than liver and kidney.

The high plasma levels of phosphorous, which probably occurred in the Kinetic 2. experiments, could have reduced the uptake of ^{203}Pb in the red cells. An extra delay compartment was required in the model between plasma and red cell compartments to obtain a good fit between calculated values and experimental data from the Kinetic 2. experiments. The slower uptake of ^{203}Pb in the red cells caused the model to respond by decreasing the rate constant describing this uptake. More ^{203}Pb will be transfered by the competing pathway to the 'soft' tissue compartment, and this was reflected in an increase in the rate constant representing uptake in this compartment.

The levels of ^{203}Pb in the red cell and 'soft' tissue compartments will be affected by the change in the rate constants representing uptake of

^{203}Pb in these two compartments. There were no significant changes in the rate constants representing the release of ^{203}Pb from the red cell and soft tissue compartments. Therefore, the result will be a decrease in levels of ^{203}Pb in the red cell compartment, and an increase in levels in the 'soft' tissue compartment, the changes which occurred.

Apart from the increases in the rate constant representing uptake of ^{203}Pb and the levels of ^{203}Pb in the 'soft' tissue compartment, there was an apparent increase in the size of this compartment. A similar effect was described by Nordin (1976), when calcium was intravenously infused into normal subjects. The weights of calcium per hour infused were of the same order as the weights of calcium given to the subjects in the Kinetic 2. experiments. The plasma concentration of calcium resulting from the infusion did not increase at a rate which would be expected if the size of the labile calcium compartment remained constant. The apparent size of the compartment increased as infusion progressed, and it was suggested that this was caused by extracellular calcium moving into bone. Bone was also though to contribute to plasma calcium homeostasis by acting as a buffer which resisted changes in plasma calcium above the prevailing level determined by the kidney.

Aub (1935) suggested that the deposition of lead in the bone is analogous to that of calcium. The buffering effect of bone will probably be caused by calcium moving into an 'exchangeable' bone calcium compartment which will be physiologically represented by trabecular bone. The ^{203}Pb absorbed with calcium from the gut, which is not taken up by the red cells, will probably move into the soft tissues and, like calcium, also move into the trabecular bone (Aub, 1935).

This type of bone has been suggested to be part of the 'soft' tissue compartment (section 8.3.4 c). The result will be an apparent increase in size of the 'soft' tissue compartment.

9.2.2 Excretion

The results of the compartmental analysis of the data from the kinetic experiments showed that there was no significant effect of calcium and phosphorous on the rate constants describing urinary and biliary excretion of ^{203}Pb. The half times of retention calculated from 96 hours onwards in the Kinetic 2. experiments were all shorter than those found with retention data from the Kinetic 1. experiments. It was shown that the presence of unabsorbed ^{203}Pb in the gut at 96 hours could have a considerable effect on half times calculated with retention data from 96 hours onwards. However, the reduction found in three of the subjects could not be explained by the presence of unabsorbed ^{203}Pb.

The simulations of the retention data obtained in the two experiments in which subject K.B. ingested ^{203}Pb with only calcium and then with only phosphorous, showed that the different half times calculated from the retention data of these two experiments were associated with changes in the fraction of ^{203}Pb absorbed in the two absorptive pathways. When no absorption of calcium was simulated in the common lead/calcium pathway, the half time of retention was approximately a third shorter than when no absorption of phosphorous was simulated in the common lead/phosphorous pathway. This occurred with no change in the rate constant representing urinary excretion and a small change in the rate

constant representing biliary excretion.

There appears to be very little systemic effect of calcium and phosphorous on excretion of ^{203}Pb, but half times of retention are influenced by the gut interactions of lead, calcium and phosphorous.

9.3 Speculation on the overall influence of calcium and phosphorous on susceptibility to the toxic effects of lead

The overall influence of calcium and phosphorous on susceptibility to the toxic effects of lead will depend on the interactions between lead, calcium and phosphorous in the gut and the systemic effect of calcium and phosphorous on lead. The experiments performed in this thesis have shown that the absorption of lead from the gut can be dramatically reduced by calcium and phosphorous. This will result in lower body burdens of lead, which should reduce susceptibility to the toxic effects of lead. Evidence from experiments on the kinetics of lead in the body performed in this thesis suggests that soft tissue levels of lead may be increased by a systemic effect of calcium and phosphorous. Susceptibility will also depend on the distribution of absorbed lead, and a change in distribution causing more soft tissue lead at the expense of bone lead could increase susceptibility.

In the kinetic experiments, the weights of calcium and phosphorous ingested with the lead caused a mean reduction of 50% in the gastrointestinal absorption of ingested lead in four subjects. Compartmental analysis of the data from these experiments showed that the calcium and phosphorous also caused a mean increase of 56% in the absorbed lead levels in the 'soft' tissue compartment of the model.

Therefore, the absolute mean reduction in the levels of ingested lead in this compartment is 22%.

Susceptibility to lead toxicity is influenced by soft tissue lead (Goyer and Rhyne, 1973), so that the 'protection' afforded by calcium and phosphorous in reducing gastrointestinal absorption of lead appears to have been lessened by the systemic effect of these minerals in raising soft tissue levels of lead. This systemic effect, however, was shown in the compartmental analysis of data on the kinetics of the tracer ^{203}Pb in the body, and the analysis was based on a number of assumptions.

The compartmental model itself is only a conceptualisation of the lead system in the human body as 'seen' by the radionuclide kinetic technique. It was assumed that the 'soft' tissue compartment of the model included all the lead in body except for lead in plasma, red cells, liver and cortical bone. The levels of lead in this compartment were also assumed to be represented by those in muscle. The experimental data on lead levels in muscle were proportional, and, therefore, the structure of the model influenced the model derived values of lead in the 'soft' tissue compartment. Even with all these assumptions, the model was found to be compatible with most of the kinetic data, and it was accepted that the model adequately represented the behaviour of lead in the body.

The compartments of the model developed in this thesis were assumed to correspond to physiological and anatomical entities, although this is not always true of compartmental models. However, even if the 'soft'

tissue compartment can be defined in this manner, the significance of any change in lead levels on susceptibility to the toxic effects of lead will depend on the lead content of the different tissues represented by this compartment.

The symptoms of lead toxicity are related to the content of lead in the haematopoietic system, the liver and the kidneys (Goyer and Rhyne, 1973). The liver was represented in the model as an individual organ, and the compartmental analysis of the data from the kinetic experiments showed no systemic effect of calcium and phosphorous on levels of absorbed lead in the liver. The haematopoietic system and the kidneys were included in the 'soft' tissue compartment, and the experimental data from the kinetic experiments was inadequate to enable the different tissues to be distinguished in the 'soft' tissue compartment.

The increase in the levels of absorbed lead in the 'soft' tissue compartment was mainly caused by an apparent increase in the size of this compartment. It was suggested in section 9.2 that this may have resulted from a movement of lead into the trabecular bone, analogous to that of calcium. The levels of absorbed lead in the other tissues in the compartment could remain unchanged. These tissues would include the haematopoietic system and kidneys, and the absence of any systemic effect of calcium and phosphorous on the levels of absorbed lead in these tissues would agree with the same result found with the liver. Similar findings were obtained by Morrison et al (1974) when they fed lambs diets rich in phosphate and found no effect of phosphate supplementation on the lead contents of liver and kidney.

The overall influence of calcium and phosphorous on susceptibility to the toxic effects of lead cannot be accurately assessed, as the experimental data was inadequate to define the lead content of all the organs and tissues which are particularly vulnerable. However, the reduction in the absorption of lead by calcium and phosphorous in the gut could still be most important in protecting people against the toxic effects of lead exposure.

SECTION 10

CONCLUSIONS

The results of this thesis have been obtained from experiments using the relatively short lived radionuclide of lead, ^{203}Pb. Any conclusions drawn can only strictly apply to short term processes acting in the first nine days after the ^{203}Pb was ingested. Gastrointestinal absorption in man is a short term process, and any influences of single doses of tracer lead and normal dietary constituents on absorptive mechanisms should have ended within 9 days after ingestion. The distribution and excretion of lead have been represented by transport processes described by one rate constant. Long term animal experiments, however, have shown that these processes may consist of two or even three rate constants. Changes in distribution and excretion found during the nine day experimental period, therefore, may not be significant in the long term.

The results show that the gastrointestinal absorption of lead between normal humans is variable, and the major cause is the presence of food with lead in the gut. After fasting, the absorption of dietary levels of lead is high and the amount absorbed does not vary appreciably between individuals. Lead absorption, however, can be dramatically reduced by calcium and, to a lesser extent, by phosphorous in the food in the gut. The effect of these two minerals was explained by assuming that they compete with lead for shared absorptive pathways in the small bowel. Calcium and phosphorous absorption is known to vary between normal individuals. This will affect the competitive inhibition of lead absorption

by calcium and phosphorous and could account for the variable absorption of food lead in man.

Variations in gastrointestinal absorption of dietary lead and in the calcium and phosphorous content of diet would be sufficient to explain the wide scatter of blood and urine lead levels found in community studies. Furthermore, the different amounts of dietary lead absorbed by people will change their body burdens of lead, and, indirectly, influence the susceptibility of individuals to the toxic effects of lead.

Susceptibility to the toxic effects of lead does not solely depend on the body burden. The major symptoms of lead intoxication are related to the content of lead of the soft tissues, so that the distribution and excretion of lead will influence susceptibility. By using a compartmental model, calcium and phosphorous ingested at the same time as a single dose of tracer lead were shown to affect the distribution of the tracer in the body.

The distribution of lead between the red cells and the soft tissues was changed, with a reduction of red cell uptake and an increase in soft tissue levels of lead. These changes were suggested to have been caused by systemic phosphorous. The release of lead from the red cells and soft tissues was also shown by the model to be relatively slow compared to uptake. The levels of lead in the red cells and soft tissues, therefore, will mainly depend on the initial partitioning of lead between them, so that the changes shown by this short term study may be significant in the long term.

The changes in the distribution of lead shown by the model could reduce the 'protective' effect of calcium and phosphorous on the absorption of lead in the gut. The experimental data were inadequate, however, to enable the model to determine the changes in lead levels of particular soft tissues which are vulnerable to the toxic effects of lead. The changes were also shown by using a compartmental model, and the limitations and assumptions inherent in mathematical modelling should be taken into account. The reduction in gastrointestinal absorption of lead mainly caused by calcium was still sufficient to substantially reduce the absolute levels of soft tissue lead found in the model.

The compartmental model suggested that lead is absorbed from the gut by at least two pathways, one which it shares specifically with calcium and the other specifically with phosphorous. Lead appears to share both the active and passive transports of calcium and phosphorous. Absorption of lead in the different pathways gives rise to at least two different forms of plasma lead, analogous to those of calcium. It must be emphasised, however, that there was no direct proof of these concepts from the work in this thesis, but that they were suggested by the compartmental analysis of the kinetics of orally ingested lead tracer.

In conclusion, short term studies with a single dose of tracer lead are adequate to investigate the gastrointestinal absorption of lead in man. They show that dietary calcium at requirement level will minimise the absorption of lead from food and beverages. The result will be lower soft tissue levels of lead, which should reduce susceptibility to the toxic effects of lead exposure. There are groups of the population, however, whose diets contain less than the Recommended Dietary

Allowance for calcium. The children of the urban poor form one of these groups, so that it is essential for the health of these children that the prophylactic effect of calcium on lead absorption should be recognised and applied in this time of increasing environmental levels of lead.

SECTION 11

DETAILED MATERIALS AND METHODS

11.1 Subjects

All the subjects were male with an age range of 23-40 years, a weight range of 58-100 kg and a height range of 1.63-1.91 m, as shown in table 11.1.1. There were no abnormalities detected on full history and clinical examination, urinalysis, full blood count, serology and blood electrolytes. Red cell porphyrins were normal in all subjects. Table 11.1.2 shows the results of the measurements of red cell, plasma and E.C.F. volumes of the subjects who took part in the kinetic experiments. The intercept of the regression equation fitted to their whole body retention from 96 hours onwards is also shown. All studies were performed with the informed consent of the subjects, who were members of the professional and technical staff from the Departments of Medical Physics, Nuclear Medicine, Biomedical Engineering and Radiotherapy, University of Cape Town.

11.2 Radionuclide ^{203}Pb

^{203}Pb has a half life of 52.1 hours, decays by electron capture emitting a main gamma ray of energy 279 keV (81%), gamma rays with energies of 401 keV (5%) and 680 keV (1%) and characteristic x-rays of Tℓ from 70 to 84 keV.

TABLE 11.1.1

Subject details

SUBJECT	AGE (years)	WEIGHT (kilograms)	HEIGHT (metres)
M.W.	40	65	1.68
M.P.	27	72	1.72
E.H.	30	80	1.82
C.H.	26	82	1.63
P.H.	26	85	1.90
A.F.	25	74	1.75
M.W.	30	68	1.73
K.B.	35	72	1.82
B.S.	40	100	1.81
S.L.	39	75	1.65
J.B.	23	58	1.74
B.C.	30	95	1.80
G.E.	30	66	1.91
D.W.	29	70	1.80

TABLE 11.1.2

Details of subjects who took part in kinetic experiments

SUBJECT	HAEMATOCRIT* (%)	PLASMA VOLUME (ml)	RED CELL VOLUME (ml)	E.C.F. VOLUME (ml)	REGRESSION INTERCEPT (% retention)	
					Kinetic 1.	Kinetic 2.
K.B.	44.0	2234 ± 7†	1428 ± 4	14991 ± 41	76.06 ± 0.61	58.32 ± 0.36
J.B.	45.0	1907 ± 5	1266 ± 4	12662 ± 64	84.42 ± 1.27	43.67 ± 0.43
B.C.	48.2	2341 ± 5	1744 ± 2	18638 ± 80	81.88 ± 0.54	35.78 ± 0.35
G.E.	46.3	2403 ± 4	1670 ± 3	17904 ± 54	87.15 ± 0.87	35.64 ± 0.30
D.W.	46.7	2209 ± 6	1559 ± 4	17632 ± 69	79.37 ± 0.57	-

* Measured.

† ± 1 standard deviation.

^{203}Pb was prepared by bombarding natural Thallium (as the metal) with 16 MeV deuterons. The production reaction was

$$^{203}Tl\ (d, 2n)^{203}Pb$$

and after bombardment 0.2-0.3 mm of the surface of the target was removed for chemical separation of the ^{203}Pb. This was done by an ion exchange method based on that of Strelow and Toerien (1966). The final chemical form of the carrier free ^{203}Pb was the chloride dissolved in a solution of 1M HCl.

The production and chemical processing of the ^{203}Pb chloride was performed by the National Accelerator Centre, Council for Scientific and Industrial Research, Pretoria, South Africa.

11.3 Whole body counts

Whole body, standard, body background and counter background counts were measured using a NE 8108 Whole Body Monitor (Warner and Oliver, 1966) fitted with four 102 mm x 76 mm NaI (Tℓ) crystals, two above and two below the movable couch top. The pulse height analyser was set to detect both the Compton and photopeak pulses of the 279 keV gamma ray of ^{203}Pb. This reduced the variation in count response with changing distribution of a radionuclide in the body (Warner and Oliver, 1966). Couch speed was set at 500 mm/min giving a whole body counting time of 6 minutes, which was sufficiently long enough to give a coefficient of variation of less than 10% on 96 hour readings.

Although both Compton and photopeak pulses were included in pulse-height analyser window, the count response of the whole body monitor was still

affected by the early redistribution of the ^{203}Pb in the body. A maximum change of 10% occurred in series of retention results done on one subject (table 11.3.1). The count at 6 hours was taken as the 100% ingested dose reading in all subjects, and readings were normalised to this value. The percentage retention and its standard deviation were calculated by the method of Anderson and Warner (1970) using computer program E.1.1.

Whole body counts were performed, when possible, once a day. From 96 hours onwards, at least six readings were obtained for estimating the half time of retention. Half times were calculated using a weighted linear regression of ℓn (% retention) on time (hours) with post-96 hour data using computer program E.1.2.

11.4 Gamma camera studies

A Nuclear Chicago Pho Gamma IV gamma camera was used to image the ^{203}Pb in the gastrointestinal tracts of the subjects. Uniformity, resolution and linearity measurements were done on the gamma camera before each study to check that its performance was optimal. The camera was set to detect the 279 keV gamma ray of ^{203}Pb and fitted with a 1200 hole medium-energy diverging collimator. The collimator-to-subject distance was adjusted so that the whole of the gastrointestinal tract appeared in the field-of-view of the camera. The images of the distribution of ^{203}Pb in the body each contained an accumulated count of 50 000, and they were recorded on polaroid film. At approximately 48 hours after the oral dose, an image was recorded of the distribution of ^{203}Pb in the liver of each subject. This was performed with a 1200 hole medium-energy parallel holed collimator to produce a larger image

TABLE 11.3.1

Variation of percentage retention of orally ingested ^{203}Pb

Subject : K.B.

TIME (hours)	PERCENTAGE RETENTION (Normalised to 6 hour reading)
0	90.33 ± 0.25†
1	91.74 ± 0.25
2	96.58 ± 0.26
3	98.23 ± 0.27
4	98.28 ± 0.27
5	99.24 ± 0.27
6	100.00 ± 0.27
7	100.35 ± 0.28
8	100.59 ± 0.28
10	99.78 ± 0.28
12	99.91 ± 0.28

† ± 1 standard deviation.

of the liver. The same procedure was used to image the distribution of ^{113m}In colloid in the liver of each subject, except for changing the camera settings to detect the 393 keV gamma ray of ^{113m}In.

11.5 Profile scans

The NE 8108 whole body monitor was used for producing profile scans of the radioactivities in the subjects. Specially constructed collimators (Appendix B) were fitted between upper and lower NaI(Tℓ) crystals to improve the spatial resolution of the system. These collimators were designed to focus at the approximate mid-line (150 mm above the couch) of a subject lying on the couch top. The Full Width at Half Maximum was 21 mm at this mid-line, and the 50% isocount contours were continuous between both collimators.

The pulse height analyser was set to detect the major gamma ray emitted from the radionuclide used. Settings are shown in table 11.5.1. The logic output of the pulse height analyser was fed into a 400 channel Intertechnique multi-channel analyser (M.C.A.) set in multiscaling mode with a time increment of 1 second. The couch speed was set at 300 mm/min to give a scanning time of 400 seconds, which was long enough to enable a profile of the total length of each subject to be recorded. On every occasion that a profile scan of a subject was performed, profiles of standard and background were done. All profile data was punched on paper tape for further analysis.

The outputs from top and bottom NaI(Tℓ) crystals were separately recorded on two ratemeters attached to two Labograph recorders running at chart speeds of 50 mm/min. The following anatomical landmarks were

TABLE 11.5.1

Pulse height analyser settings of profile scanner

RADIONUCLIDE	GAMMA RAY ENERGY (keV)	THRESHOLD*	WINDOW*
^{203}Pb	279	90	100
^{113m}In	393	150	70
^{82}Br	777	230	220

* 2 MeV expansion of pulse-height analyser settings.

marked on the recorder paper:

1. Vertex of head
2. Suprasternal notch
3. Xiphisternal joint
4. Iliac crest
5. Symphysis pubis
6. Knee
7. Ankle

The position of the xiphisternal joint (x-s) was marked digitally in the profile recorded in the M.C.A. system. This was done by a pulse generator, which was activated manually when the x-s passed through the centre of the field of view of the detectors. The landmarks were used to align profile scans correctly for the computer analysis of profile scans (Appendix A).

11.6 Surface radioactivity measurements

Surface radioactivity was measured using a Ohio Nuclear Series 84 rectilinear scanner. Table 11.6.1 shows the pulse height analyser settings used to detect ^{203}Pb, ^{113m}In and ^{82}Br. Two analysers were used to detect both the x-rays and gamma ray of ^{203}Pb, so that if necessary, the statistical accuracy of counting could be improved by summing the count rates from both pulse height analysers. A focussing collimator was used with a 127 mm geometrical focal length. This gave sufficient depth response to measure radioactivity at depth in the liver.

TABLE 11.6.1

Pulse height analyser settings of rectilinear scanner

RADIONUCLIDE	PHOTON ENERGY (keV)	THRESHOLD*	WINDOW*
^{203}Pb	70-84 (x-rays)	50	45
	279 (γ-ray)	250	100
^{113m}In	393 (γ-ray)	350	100
^{82}Br	777 (γ-ray)	650	500

* 1 MeV expansion of pulse-height analyser settings.

The approximate position of organ measurement sites were found by using a scintigram image in which the organs could be clearly seen. From these approximate positions, the organs were surveyed individually with the probe of the rectilinear scanner immediately after the scintigram was taken, until the positions giving the highest count rates were found. These were marked on the skin and on a polythene template to help with future positioning of the probe. At all measurement sites, the collimator was placed in contact with the subject's skin, and subsequent repositioning was done by using skin marks and the collimator light beam.

The precision of surface radioactivity measurements could be affected by an error in repositioning the detector at a counting site. Therefore, at 24 hours, when count rates were high, each subject was counted and repositioned several times. A typical set of readings from one subject is shown in table 11.6.2. Overall, the coefficients of variation were only slightly greater than that due to statistical variation, so that error due to repositioning was negligible.

On every occasion surface radioactivity measurements were performed, standard and background count rates were also recorded. Body background measurements were also performed at all sites with each subject, when no radioactivity was present in the body. Counter backgrounds recorded during surface radioactivity measurements were then corrected by the ratio of body to counter backgrounds. The ratios for subject K.B. are shown in table 11.6.3. The standard was used to avoid correcting surface counts for radioactive decay of ^{203}Pb and to compensate for any change in the sensitivity of the detector. The standard was not

TABLE 11.6.2

Variation in surface radioactivity measurements due to repositioning

Subject : K.B.

	LIVER (counts/300sec.)	SMALL BOWEL (counts/60sec.)	MEDIAL CALF (counts/300sec.)	MEDIAL MALLEOLUS (counts/300sec.)
	14112 ± 127†	15023 ± 124	2479 ± 69	1989 ± 66
	14329 ± 128	14256 ± 121	2315 ± 68	1924 ± 65
	14520 ± 129	14496 ± 122	2395 ± 69	2080 ± 66
Mean	14318	14585	2396	1997
S.D.	204	391	82	78
S.E.	118	226	47	45
Coefficient of Variation	1.4	2.7	3.4	3.9

† ± 1 standard deviation.

Background was subtracted from all readings.

TABLE 11.6.3

Body background / counter background ratios

Subject : K.B.

LIVER	SMALL BOWEL	MEDIAL CALF	MEDIAL MALLEOLUS
0.94 ± 0.03(3)†	0.95 ± 0.03(3)	0.99 ± 0.05(3)	0.99 ± 0.05(3)

Figures in brackets are number of data points.

† ± 1 standard deviation.

intended to simulate an aliquot of the ingested dose in the region or organ of interest. Surface radioactivity measurements, therefore, were expressed as proportional units of percentage ingested dose not as absolute units, and these were calculated using computer program E.1.3.

11.7 Subtraction of blood and 'soft' tissue backgrounds from profile scans and surface radioactivity measurements

Radioactivity in the field of view of the detector is usually distributed in the organ of interest, the circulating blood and other extracellular or intracellular compartments. Therefore, the net counts due to radioactivity in the organ can only be obtained by subtracting the contribution from the other compartments. This may be done by using other radionuclides, such as ^{113m}In and ^{82}Br, that are known to be confined to spaces which approximate to the circulating blood and extracellular compartments.

Profile scan and surface radioactivity measurements were performed on the subjects after the radionuclide of interest ^{203}Pb, and the blood and extracellular fluid (E.C.F.) tracers, ^{113m}In and ^{82}Br, had been administered to them on different occasions. The estimation of blood and 'soft' tissue backgrounds from these measurements depend on how the blood and 'soft' tissue compartments are defined. In the compartmental model developed in this study, the red cells, plasma and 'soft'tissues are all separate compartments. Blood background will consist of ^{203}Pb radioactivities in red cells plus plasma, whereas 'soft' tissue background will be caused by intracellular plus extracellular minus plasma ^{203}Pb radioactivities. This last entity represents a 'soft' tissue E.C.F. In the determination of 'soft' tissue E.C.F. backgrounds, it has been assumed that the concentration of ^{203}Pb in the E.C.F. was the same as in the plasma, and that the 'soft' tissue E.C.F. volume equals total E.C.F. volume minus plasma volume.

The profile scan and surface radioactivity measurements of ^{113m}In and ^{82}Br radioactivities in the body have to be adjusted to make them represent the radioactivity of ^{203}Pb in the blood and 'soft' tissue E.C.F. It was first of all necessary to determine the detector responses of each of the radionuclides, and this was done using phantoms to simulate the organ of interest and its adjacent tissues as regards position, size and shape. Using the relative detector responses of ^{113m}In and ^{82}Br to that of ^{203}Pb and the radioactivities of these radionuclides, the profile scan and surface radioactivity measurements of ^{113m}In and ^{82}Br were adjusted to represent 100% of the ingested dose of ^{203}Pb in blood and 'soft' tissue E.C.F. These measurements were then reduced in proportion to the actual percentage ingested doses of ^{203}Pb measured in the blood and 'soft' tissue E.C.F. compartments during the experiments. This gave the ^{203}Pb backgrounds required to be subtracted from the gross profile scan and surface radioactivity measurements.

The measurement times of the blood and 'soft' tissue E.C.F. data were often different to those of the surface radioactivity and profile scan measurements. It was necessary, therefore, to interpolate between data points to find the percentage of ingested dose at the required time, and this was done using computer program E.1.4.

11.7.1 Radionuclides used as blood and extracellular tracers

a) Blood tracer

The accepted method of measuring plasma volume is by using labelled proteins such as ^{131}I or ^{125}I-human serum albumin. Hosain et al (1969) used ^{113m}In, which binds plasma transferrin, to estimate plasma volume

and found it very satisfactory except that it overestimated the plasma volume obtained by using ^{131}I-human serum albumin. Wootton (1976) found the same over estimation of plasma volume using ^{113m}In chloride but he derived a regression equation to correct it. In the present study, ^{113m}In chloride was used as a blood tracer to measure plasma volume and to estimate blood ^{203}Pb backgrounds. Its 393 keV gamma ray is more convenient for in vivo experiments than ^{125}I, and it gives a much lower absorbed radiation dose to the body than ^{131}I (Hosain et al 1969).

b) Extracellular fluid tracer

The chloride ion has been regarded as most suitable for the measurement of extracellular volume, provided the chloride space is corrected for the chloride content of the red cells. A more convenient ion is the bromide ion through its radionuclide ^{82}Br, which has a half life of 36 hours. The gamma rays emitted from ^{82}Br are also convenient for in vivo measurements. Corrections have to be applied for urinary loss, presence of proteins in plasma and entry of bromide into red cells. ^{82}Br was used as the extracellular tracer to measure E.C.F. volumes and to estimate the 'soft' tissue E.C.F. backgrounds of ^{203}Pb.

11.7.2 Determination of in vivo detector responses of ^{203}Pb, ^{113m}In and ^{82}Br

An Alderson whole body phantom was used to determine the detector responses of the rectilinear and profile scanners. Unfortunately, this phantom has a 'modified gastrointestinal tract' which does not simulate small bowel, so that it was only possible to measure detector responses over the liver, calf and ankle of the phantom. The detector

responses over the small bowel were assumed to be the same as those measured over the liver. The lower left leg and liver of the phantom were filled, on different occasions, with measured radioactivities of ^{203}Pb, ^{113m}In and ^{82}Br, and surface radioactivity measurements were performed at the chosen sites using the procedures described in section 11.6. In a similar way, profile scans were also performed (section 11.5) of the radioactivities of the three radionuclides in the liver of the phantom. Detector responses were expressed as counts/second/μCi and profile counts/μCi and responses were normalised to the ^{203}Pb readings as shown in tables 11.7.1 and 11.7.2.

11.7.3 Measurement of plasma and red cell volumes and surface radioactivities using ^{113m}In

1 mCi of ^{113m}In chloride was injected intravenously over a period of about a minute as recommended by Hosain et al (1969). The ^{113m}In chloride was obtained by elution from a generator (TRC, Code: TFC3) with 0.05 MHCl. Approximately the same radioactivity as injected was diluted with distilled water to a final volume of 1 litre, and 1 ml of this volume was used as a standard for blood, 50 ml as a standard for surface radioactivity measurements and the remainder used as the profile scan standard.

Venous blood was taken from an antecubital vein in the arm opposite to that used for injection. 5 ml blood samples were obtained at 10, 20, 40, and 60 minutes post injection. The blood was then centrifuged, the plasma was separated and known volumes of plasma and standard were counted in a Packard automatic counter (Model 3002) set to detect the 393 keV gamma ray of ^{113m}In. All measurements of radioactivity were

TABLE 11.7.1

In vivo detector responses of ^{203}Pb, ^{113m}In and ^{82}Br

RADIONUCLIDE		RECTILINEAR SCANNER			PROFILE SCANNER
		Ankle (counts/sec/μCi)	Calf (counts/sec/μCi)	Liver (counts/sec/μCi)	Liver (counts/μCi)
^{203}Pb	x-rays	1.05 ± 0.01†	1.28 ± 0.01	1.60 ± 0.02	-
	γ-rays	0.651 ± 0.009	0.802 ± 0.010	1.05 ± 0.02	289 ± 2
^{113m}In		0.352 ± 0.004	0.431 ± 0.005	0.563 ± 0.006	103 ± 1
^{82}Br		22.24 ± 0.13	25.38 ± 0.13	22.27 ± 0.19	914 ± 4

† ± 1 standard deviation.

TABLE 11.7.2

In vivo detector responses normalised to that of ^{203}Pb

(Response Factor)

RADIONUCLIDE		RECTILINEAR SCANNER			PROFILE SCANNER
		Ankle	Calf	Liver	Liver
^{203}Pb	x-rays	1.00	1.00	1.00	1.00
	γ-rays	1.00	1.00	1.00	
^{113m}In		0.331 ± 0.006†	0.341 ± 0.005	0.353 ± 0.006	0.356 ± 0.004
		0.542 ± 0.009	0.543 ± 0.005	0.531 ± 0.010	
^{82}Br		21.18 ± 0.28	19.82 ± 0.24	13.92 ± 0.21	3.16 ± 0.03
		34.22 ± 0.52	31.73 ± 0.43	21.21 ± 0.35	

† ± 1 standard deviation.

made to a coefficient of variation of less than 1%, after correction had been made for background and physical decay.

Plasma volume was calculated from the intercept at zero time of the weighted regression line fitted to the serial radioactivity measurements. The plasma volume measured using ^{113m}In chloride is greater than that measuring using ^{125}I-human serum albumin, and it was corrected using the regression equation determined by Wootton (1976). Venous haematocrit was measured in each subject, corrected for trapped plasma and corrected to body haematocrit (Belcher and Vetter, 1971), which was then used to calculate the red cell volume from the plasma volume. The regression and calculations were done with computer program E.1.5.

Profile scan and surface radioactivity measurements were performed at least 20 minutes after the injection, as described in sections 11.5 and 11.6, respectively. The pulse height analysers were set to detect the 393 keV gamma ray of ^{113m}In, and the times of each measurement were noted. Profile scans were smoothed and restored by the methods described in Appendix A.1.

11.7.4 Measurement of extracellular fluid volume and surface radioactivities using ^{82}Br

100 µCi of ^{82}Br in the form of ammonium bromide was given orally after a 4 hour fast. The same radioactivity was diluted with distilled water to a final volume of 1 litre, and 1 ml of this volume was used as a standard for blood and urine sample counting and 50 ml as a standard for surface radioactivity measurements. The remainder was used as the

profile scan standard. A period of 6 hours was allowed for equilibration (Belcher and Vetter, 1971), during which time all urine was collected. A 5 ml specimen of blood was then taken into a heparinised tube. The blood was centrifuged immediately and the plasma separated.

The total volume of urine collected was measured, and known volumes of plasma, red cells, urine and the standard were measured in a Packard automatic counter (Model 3002) with the pulse-height analyser window set to detect the multiple gamma rays emitted from ^{82}Br in the range 400 - 900 keV. Enough counts were collected to give a coefficient of variation of the net counts of 1%. The apparent bromide space was calculated from the equation.

$$\text{Apparent bromide space (ml)} = \frac{(sd - vu)}{p}$$

where s is the counting rate of diluted standard, d the dilution factor of standard, v the volume of urine collected (ml), u the counting rate of urine sample and p the counting rate per ml of the plasma sample.

A correction factor must be used for the concentration of ^{82}Br in the plasma being less than its mean concentration in extracellular fluid and for the ^{82}Br content of the circulating red cells. For the first correction, a factor of 0.90 has been used on an empirical basis by Bradley et al (1956b) to estimate extracellular fluid volume from the apparent bromide space. The ^{82}Br content of the red cells was estimated from the count rate per ml of the red cell sample and the calculated red cell volume.

Combining these two corrections, the extracellular fluid volume is given by

$$\text{Extracellular fluid volume (ml)} = \frac{((sd - vu) - rV)}{p} \times 0.90$$

where r is the count rate of 1 ml of red cells and V the red cell volume in ml. Calculations were done using computer program E.1.6.

Profile scan and surface radioactivity measurements were performed as described in sections 11.5 and 11.6, respectively, with pulse height analysers set to detect the main 777 keV gamma ray ^{82}Br. Profile scans were smoothed and restored by the methods described in Appendix A.1.

11.7.5 Derivation of blood and 'soft' tissue E.C.F. background factors for profile scans

a) ^{203}Pb blood background factor

The method of adjusting the profile scan of the blood tracer, ^{113m}In, to represent the ^{203}Pb blood background has been outlined in section 11.7. In addition, the percentage ingested dose of ^{203}Pb measured or calculated to be in the blood at the time of a particular profile scan must be reduced by the decay of ^{203}Pb, which had occurred by the time the profile scan was recorded. The blood content of ^{203}Pb must also be corrected by the efficiency of the profile scanner in detecting ^{203}Pb radioactivity in the body. Efficiency will vary from subject to subject, and it was found by comparing the total counts in the 6 hour profile scan of each subject with the total counts in the corresponding profile scan of the standard.

The blood background factor to adjust the profile scan of ^{113m}In radioactivity in the whole blood was derived as follows.

Let P_i = ^{113m}In profile scan

T_i = time of ^{113m}In injection

T_p = time of ^{113m}In profile

λ_i = decay constant of ^{113m}In

C_i = ^{113m}In response factor for profile scanner from table 11.7.2

D_i = ^{113m}In injected dose

D_p = ^{203}Pb ingested dose

S_i = ^{203}Pb profile standard count at T = 6 hours

S_p = ^{203}Pb profile standard count at time T.

E_p = efficiency of detection of ^{203}Pb by profile scanner for a particular subject.

$$\text{Then blood background factor} = \frac{Dp \times \exp(\lambda_i (Tp - T_i))}{C_i \times D_i} = F_i$$

^{203}Pb blood background profile to be subtracted at time T

$$= \frac{P_i \times Ep \times F_i \times Sp}{100\ S_i} \times (\%\ \text{I.D. of } ^{203}Pb \text{ in blood at time T})$$

Calculation of blood background factors was done using computer program E.1.7.

b) <u>^{203}Pb 'soft' tissue E.C.F. background factor</u>

To obtain a 'soft' tissue E.C.F. background profile, it was first of all necessary to subtract from the original ^{82}Br profile scan the contribution from ^{82}Br in the blood. The profile scan obtained using

the blood tracer, ^{113m}In, was transformed to represent a ^{82}Br profile using the appropriate response factor from table 11.7.2, reduced by the measured ^{82}Br content of plasma plus red cells and then subtracted from the original ^{82}Br profile scan. This subtracted ^{82}Br profile scan was transformed into the ^{203}Pb 'soft' tissue E.C.F. background by the same methods used in section 11.7.5 (a).

The 'soft' tissue E.C.F. background factor was derived as follows:

Let V_p = plasma volume

V_r = red cell volume

V_e = E.C.F. volume

P_b = ^{82}Br profile scan

P_{br} = % I.D. of ^{82}Br in plasma

R_{br} = % I.D. of ^{82}Br in red cells

U_{br} = % I.D. of ^{82}Br in urine

D_b = ^{82}Br ingested dose

C_b = ^{82}Br response factor for profile scanner from table 11.7.2.

S_i = ^{203}Pb profile standard count at T = 6 hours

S_p = ^{203}Pb profile standard count at time T

E_p = efficiency of detection of ^{203}Pb by profile scanner for a particular subject

Blood background factor of $^{113m}In = F_i$

Fraction of total ^{82}Br counts which was due to ^{82}Br blood content

$$= \frac{(P_{br} + R_{br})}{(100 - U_{br})}$$

^{113m}In profile was multiplied by the following factor to make it represent the percentage ingested dose of ^{82}Br in whole blood.

$$\frac{F_i\ (P_{br} + R_{br})\ C_b\ D_b}{Dp\quad (100 - U_{br})}$$

This ^{82}Br blood profile was then subtracted from the original ^{82}Br profile to give a 'soft' tissue E.C.F. profile (P_e). Adjustment to 100% of the ingested dose of ^{82}Br in 'soft' tissue E.C.F. and transformation to represent 100% of the ingested dose of ^{203}Pb, gave the following background factor

$$F_b = \frac{100\ Dp}{(100 - P_{br} - R_{br} - U_{br})\ C_b\ D_b}$$

^{203}Pb 'soft' tissue E.C.F. background profile to be subtracted at time T

$$= \frac{P_e \times E_p \times F_b \times Sp}{100\ S_i} \times (\%\ \text{I.D. of } ^{203}\text{Pb in 'soft' tissue E.C.F. at time T})$$

Calculation of 'soft' tissue E.C.F. background factors was done using computer program E.1.8.

11.7.6 Derivation of blood and 'soft' tissue E.C.F. background factors for surface radioactivity measurements

a) ^{203}Pb blood background factor

In addition to the manipulations described in section 11.7, ^{113m}In surface radioactivity measurements were first corrected for

radioactive decay from the time of the standard count. Surface radioactivity measurements are expressed in proportional units of percentage ingested dose, so that it was unnecessary to adjust the percentage ingested dose in the blood for the decay of ^{203}Pb.

The blood background factor was derived as follows.

Let S_i = ^{113m}In surface radioactivity measurements expressed as percentage injected dose

T_s = Time of ^{113m}In surface radioactivity measurement

T_{st} = Time of ^{113m}In standard measurement

λ_i = decay constant of ^{113m}In

C_i = ^{113m}In response factor for rectilinear scanner from table 11.7.2

D_i = ^{113m}In injected dose

D_p = ^{203}Pb ingested dose

$$\text{Blood background factor} = \frac{Dp\ S_i\ \exp\ (\lambda_i\ (Ts - Tst))}{C_i\ D_i} = F_i$$

^{203}Pb blood background to be subtracted at time T

= F_i x (% I.D. of ^{203}Pb in blood at time T) / 100

Calculation of blood background factors was done using computer program E.1.9.

b) <u>^{203}Pb 'soft' tissue E.C.F. background factors</u>

To obtain a 'soft' tissue E.C.F. background measurement, it was necessary to subtract from the original ^{82}Br surface radioactivity

measurement the contribution from ^{82}Br in the blood. This was done with the surface radioactivity measurements obtained using the blood tracer, ^{113m}In, which were first of all changed to represent ^{82}Br surface radioactivity measurements by using the appropriate response factor from table 11.7.2. They were then reduced by the measured ^{82}Br content of plasma plus red cells and subtracted from the original ^{82}Br measurements. This subtracted ^{82}Br surface radioactivity measurement was made to represent the ^{203}Pb 'soft' tissue E.C.F. background, as described in section 11.7.

The 'soft' tissue E.C.F. background factor was derived as follows:

Let V_p = plasma volume

V_r = red cell volume

V_e = E.C.F. volume

S_b = ^{82}Br surface radioactivity measurements expressed as % ingested dose

P_{br} = % I.D. of ^{82}Br in plasma

R_{br} = % I.D. of ^{82}Br in red cells

U_{br} = % I.D. of ^{82}Br in urine

D_b = ^{82}Br ingested dose

C_b = ^{82}Br response factor for rectilinear scanner from table 11.7.2

Surface radioactivity from 100% ^{82}Br in blood - derived from ^{113m}In measurements

$$= \frac{C_b D_b F_i}{Dp}$$

Surface radioactivity from measured ^{82}Br in blood

$$= \frac{C_b\ D_b\ F_i\ (P_{br} + R_{br})}{D_p\ (100 - U_{br})}$$

Surface radioactivity from ^{82}Br in 'soft' tissue E.C.F.

$$= S_b - \frac{C_b\ D_b\ F_i\ (P_{br} + R_{br})}{Dp\ (100 - U_{br})}$$

containing $(100 - U_{br} - P_{br})$ % of ingested ^{82}Br

$\therefore$ Surface radioactivity from 100% ^{82}Br in 'soft' tissue E.C.F.

$$= \left(S_b - \frac{C_b\ D_b\ F_i\ (P_{br} + R_{br})}{Dp\ (100 - U_{br})}\right) / (100 - U_{br} - P_{br})$$

Surface radioactivity from 100% ^{203}Pb in 'soft' tissue E.C.F.

$$= Dp\left(S_b - \frac{C_b\ D_b\ F_i\ (P_{br} + R_{br})}{Dp\ (100 - U_{br})}\right) / \quad C_b\ D_b\ (100 - U_{br} - P_{br})$$

= 'soft' tissue E.C.F. background factor (F_b)

$\therefore$ ^{203}Pb 'soft' tissue E.C.F. background to be subtracted at time T

= F_b x (% I.D. of ^{203}Pb in 'soft tissue' E.C.F. at time T) / 100

Calculation of 'soft' tissue E.C.F. background factors was done using computer program E.1.10.

11.8 ^{203}Pb radioactivity in blood

5-10 ml of venous blood samples were taken into heparinised containers. When the ^{203}Pb content of plasma and red cells were required, the blood was centrifuged immediately after sampling, and the plasma was separated carefully from the red cells. A known volume of whole blood or red cells was lysed with saponin. Measured volumes of whole blood or red cells and plasma were counted in a Packard automatic counter (Model 3002). For all measurements, background and a known aliquot of the oral dose of ^{203}Pb were counted.

The pulse height analyser of the counter was set for maximum counting efficiency with a threshold of 10 and a window of 340. This window included the 70 - 84 keV x-rays as well as the 279 keV gamma ray of ^{203}Pb. The window levels were set by using the figure of merit, $Q = \sqrt{C} - \sqrt{B}$ (Belcher and Vetter, 1971), as shown in table 11.8.1.

The ^{203}Pb radioactivity in the plasma samples was usually so low that the counting time of the gamma counter was set to its maximum of 100 minutes. Red cell samples were counted in the same run as plasma samples, but the ^{203}Pb radioactivity in red cells was much higher than that in plasma, so that the maximum preset count limit of 9×10^5 counts was usually reached during red cell sample counting. Consequently, the coefficient of variation of red cell counts, usually less than 5%, was considerably lower than that of plasma counts.

The percentage ingested dose of ^{203}Pb in total blood or in red cells and plasma was calculated by computer program E.1.11-12, using the red cell and plasma volumes determined by the ^{113m}In plasma volume method

TABLE 11.8.1

Calibration of Packard gamma counter (blood) and N.E. 5502 counter (urine) for maximum sensitivities (^{203}Pb)

Threshold*	Window*	Packard gamma counter (Q)	N.E. 5502 Counter (Q)
250	100	83.54	233.92
200	150	91.91	261.82
150	200	95.92	272.45
100	250	105.51	281.22
50	300	131.25	288.35
40	310	133.85	284.94
30	320	133.75	294.76
20	330	132.80	279.32
10	340	134.05	271.20
0	350	122.52	263.52

* 1 MeV expansion of pulse-height analyser settings.

(section 11.7.3). The half life of ^{203}Pb in the red cells was calculated with a weighted linear regression of ℓn (% ingested dose) on time (hours), using computer program E.1.2.

11.9 ^{203}Pb radioactivity in urine

Urine was collected over 24 hour periods, and 150 ml samples of these 24 hour collections were counted in a Nuclear Enterprises (N.E.) 5502 counter with a 5 cm diameter flat-topped NaI(Tℓ) crystal. For all measurements, background and a known aliquot of the oral dose of ^{203}Pb were counted. The pulse height analyser was set with a threshold of 30 and a window of 320 to include both the 70 - 84 keV x-rays as well as the 279 keV gamma ray of ^{203}Pb. These settings were found using the figure of merit, Q, as shown in table 11.8.1. Coefficient of variation using these settings was usually less than 5%. The total volume of urine excreted in the 24 hour periods was measured, and the accumulative ^{203}Pb radioactivity excreted in the urine was then calculated as a percentage of the ingested dose, using computer program E.1.13.

11.10 Summation of rectilinear-scanner count rates arising from x-rays and gamma ray emitted from ^{203}Pb

Because of the low count rates obtained over the medial calf and medial malleolus, the count rates from both windows, set to detect the x-rays and gamma ray of ^{203}Pb, of the rectilinear scanner were summed to improve statistical accuracy. Subtraction of blood and 'soft' tissue E.C.F. backgrounds depend on the ratios of the detector responses of ^{203}Pb to those of the vascular and E.C.F. tracers, ^{113m}In and ^{82}Br. The ratios

are different for the x-rays and gamma ray of ^{203}Pb (table 11.7.2). Therefore, the blood and 'soft' tissue E.C.F. backgrounds were subtracted from each count rate arising from the x-rays and gamma ray, before the count rates were summed.

11.11 Osteodensitometry measurements

Osteodensitometry measurements were performed using a Norland-Cameron 178 Bone Mineral Analyser. The sites surveyed were the medial malleolus and calcaneum, and a water bag was used to compensate for the irregular shape of these structures. Four measurements were done at each site, and the mean readings were expressed as g/cm^2 by dividing the bone mineral reading by the measured bone width. The units are arbitrary and are only relevant to measurements made with this type of bone mineral analyser. Table 11.11.1 shows the results obtained from four of the subjects who took part in the kinetic experiments.

11.12 Statistical considerations

Counts arising from radioactivity were rejected if the net counts above background were less than three times the standard deviation of the background count (Mehl, 1967). The experimental data obtained from all experiments was assumed to be normally distributed. The standard deviations of measurements were calculated by the method of sums of variances and relative variances (Belcher and Vetter, 1971). The standard deviations of the results of calculations, except for whole body retention, were calculated by the method of partial differentials and principle of superposition of errors (Topping, 1972). The mean and

TABLE 11.11.1

Measurement of bone mineral content of left medial malleolus and left calcaneum

SUBJECT	LEFT MEDIAL MALLEOLUS			LEFT CALCANEUM		
	Bone mineral content (g/cm)	Bone width (cm)	Bone mineral content / Bone width (g/cm^2)	Bone mineral content	Bone width (cm)	Bone mineral content / Bone width (g/cm^2)
K.B.	6.42 ± 0.19†	5.16 ± 0.10	1.24 ± 0.04	2.37 ± 0.07	4.51 ± 0.03	0.525 ± 0.016
J.B.	5.46 ± 0.05	4.39 ± 0.22	1.24 ± 0.06	3.03 ± 0.12	4.39 ± 0.05	0.690 ± 0.028
B.C.	5.59 ± 0.17	4.59 ± 0.05	1.22 ± 0.04	2.20 ± 0.18	4.15 ± 0.04	0.530 ± 0.044
G.E.	5.99 ± 0.01	5.46 ± 0.04	1.10 ± 0.01	3.04 ± 0.21	4.89 ± 0.05	0.622 ± 0.043
Mean			1.11			0.567
S.D.			0.04			0.078
S.E.			0.02			0.039

† ± 1 standard deviation.

standard deviation of combined data were calculated using the relative weights of individual data (Bevington, 1969). If means were compared, they were checked for equal variances and the appropriate test was selected from Documenta Geigy (6th edition).

The parameter values obtained from the compartmental analysis are a 'best estimate' and as such are the maximum value of a likelihood function (Brandt, 1976). This function has been assumed to have a normal distribution, so that the 'best estimate' is the mean of this distribution and the square root of the variance of the distribution about the 'best estimate' can be taken as the uncertainty of that estimate. Statistical comparisons were made by Student's 't' test for paired data (Mould, 1976).

SECTION 12

TABLES

Tables

The tables in this section list a comparison of experimental data and calculated values found from the compartmental analysis of the data from kinetic experiments performed in section 8.0.

They are listed in subject order,

K.B., J.B., B.C., G.E. and D.W.,

experiment order for each subject,

Kinetic 1. and Kinetic 2.,

and compartment order for each experiment,

whole body, plasma, red cells, urine, small bowel, liver,

'soft' tissue and 'hard' tissue.

All tables have been named with the following format.

Subject initials-compartment initials-kinetic experiment

e.g. Subjects K.B.'s small bowel data from Kinetic 1. experiment

KB-SB-1

Experimental data is shown with $\pm$ 1 standard deviation.

Abbreviations

hrs - hours

%I.D. - percentage ingested dose

%P.I.D. - percentage proportional ingested dose

TABLE:KB-WB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)		CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +-	0.237	98.785	0.98
24.00	94.647 +-	0.237	96.134	1.01
48.00	80.817 +-	0.224	83.881	1.03
72.00	73.094 +-	0.232	71.604	0.98
96.00	65.418 +-	0.234	65.317	0.99
120.00	61.104 +-	0.261	62.154	1.01
144.00	58.679 +-	0.294	59.865	1.02
168.00	56.432 +-	0.336	57.721	1.02
192.00	56.720 +-	0.412	55.583	0.98
216.00	53.118 +-	0.488	53.445	1.00

TABLE:KB-PL-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.019 +- 0.001	0.009	0.47
2.00	0.030 +- 0.001	0.020	0.65
3.00	0.031 +- 0.001	0.030	0.95
6.00	0.065 +- 0.001	0.052	0.78
10.00	0.056 +- 0.001	0.066	1.15
17.00	0.073 +- 0.001	0.071	0.96
24.00	0.058 +- 0.001	0.070	1.19
48.00	0.053 +- 0.002	0.061	1.13
72.00	0.052 +- 0.002	0.053	0.99
96.00	0.041 +- 0.003	0.046	1.10
120.00	0.043 +- 0.004	0.040	0.91

TABLE:KB-RC-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	4.445 +- 0.015	1.209	0.27
2.00	8.696 +- 0.029	4.564	0.52
3.00	11.752 +- 0.040	8.195	0.69
10.00	20.531 +- 0.070	20.813	1.01
17.00	22.367 +- 0.077	23.334	1.04
24.00	23.253 +- 0.080	23.783	1.02
48.00	23.525 +- 0.081	23.531	1.00
72.00	22.423 +- 0.077	22.980	1.02
96.00	21.457 +- 0.075	22.330	1.04
120.00	21.031 +- 0.072	21.630	1.02
144.00	20.357 +- 0.086	20.908	1.02
168.00	21.139 +- 0.071	20.184	0.95
192.00	17.335 +- 0.060	19.468	1.12
216.00	15.912 +- 0.057	18.767	1.17

TABLE:KB-UR-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	1.900 +- 0.012	2.287	1.20
48.00	2.906 +- 0.015	3.006	1.03
72.00	3.725 +- 0.017	3.689	0.99
96.00	4.557 +- 0.020	4.347	0.95
120.00	4.989 +- 0.021	4.980	0.99
144.00	5.797 +- 0.023	5.589	0.96
168.00	6.523 +- 0.025	6.175	0.94
192.00	7.259 +- 0.027	6.740	0.92
216.00	8.037 +- 0.029	7.283	0.90

TABLE:KB-SB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.57	12.531 +-	0.175	8.890	0.70
3.15	6.869 +-	0.108	6.541	0.95
4.07	4.884 +-	0.087	5.418	1.10
4.98	5.246 +-	0.091	4.543	0.86
5.90	3.195 +-	0.065	3.859	1.20
8.07	2.323 +-	0.041	2.841	1.22
9.07	2.796 +-	0.049	2.577	0.92
10.07	2.631 +-	0.045	2.403	0.91
10.98	3.016 +-	0.049	2.306	0.76
16.80	2.735 +-	0.051	2.346	0.85
19.98	2.142 +-	0.051	2.483	1.15
24.00	2.726 +-	0.051	2.570	0.94
48.00	1.354 +-	0.033	1.463	1.08
72.00	0.794 +-	0.027	0.648	0.81
96.00	0.563 +-	0.028	0.452	0.80
120.00	0.491 +-	0.036	0.422	0.85
144.00	0.447 +-	0.046	0.417	0.93
168.00	0.371 +-	0.059	0.413	1.11
192.00	0.322 +-	0.078	0.406	1.26

TABLE:KB-LI-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.57	1.161 +- 0.023	1.439	1.24
3.15	1.587 +- 0.035	1.915	1.20
4.07	1.800 +- 0.039	2.001	1.11
4.98	2.015 +- 0.041	2.050	1.01
5.90	2.176 +- 0.044	2.086	0.95
8.07	2.283 +- 0.041	2.144	0.93
9.07	2.389 +- 0.046	2.163	0.90
10.07	2.055 +- 0.040	2.179	1.06
10.98	1.887 +- 0.038	2.192	1.16
16.80	2.834 +- 0.054	2.241	0.79
19.98	2.336 +- 0.047	2.256	0.96
24.00	2.509 +- 0.050	2.270	0.90
48.00	2.468 +- 0.049	2.305	0.93
72.00	2.262 +- 0.044	2.291	1.01
96.00	2.084 +- 0.045	2.243	1.07
120.00	2.381 +- 0.055	2.172	0.91
144.00	2.191 +- 0.064	2.085	0.95
168.00	2.357 +- 0.082	1.989	0.84
192.00	1.959 +- 0.099	1.887	0.96
216.00	2.534 +- 0.133	1.784	0.70

TABLE:KB-ST-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
1.57	0.032 +- 0.010	0.011	0.35
3.15	0.044 +- 0.006	0.033	0.75
4.07	0.050 +- 0.007	0.044	0.86
4.98	0.059 +- 0.007	0.053	0.88
5.90	0.069 +- 0.007	0.060	0.86
8.07	0.070 +- 0.007	0.072	1.01
9.07	0.071 +- 0.008	0.075	1.06
10.07	0.072 +- 0.007	0.078	1.08
10.98	0.078 +- 0.007	0.080	1.02
16.80	0.096 +- 0.009	0.086	0.89
19.98	0.067 +- 0.008	0.087	1.28
24.00	0.080 +- 0.009	0.087	1.07
48.00	0.075 +- 0.011	0.082	1.09
72.00	0.074 +- 0.015	0.078	1.05
96.00	0.080 +- 0.019	0.075	0.92
120.00	0.064 +- 0.028	0.072	1.10

TABLE:KB-HT-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:1.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
1.57	0.019 +-	0.010	0.007	0.34
3.15	0.035 +-	0.006	0.020	0.54
4.07	0.041 +-	0.007	0.026	0.63
4.98	0.044 +-	0.007	0.032	0.71
5.90	0.055 +-	0.007	0.037	0.65
8.07	0.067 +-	0.007	0.045	0.66
9.07	0.063 +-	0.008	0.048	0.75
10.07	0.063 +-	0.007	0.051	0.80
10.98	0.068 +-	0.007	0.053	0.76
16.80	0.106 +-	0.009	0.062	0.58
19.98	0.070 +-	0.008	0.066	0.93
24.00	0.078 +-	0.009	0.070	0.89
48.00	0.093 +-	0.011	0.092	0.97
72.00	0.087 +-	0.015	0.113	1.28
96.00	0.117 +-	0.020	0.133	1.13
120.00	0.093 +-	0.029	0.152	1.62
144.00	0.104 +-	0.040	0.170	1.63

TABLE:KB-WB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)		CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +-	0.181	99.217	0.99
24.00	98.877 +-	0.187	95.696	0.96
48.00	79.754 +-	0.168	75.394	0.94
72.00	57.793 +-	0.140	57.221	0.99
96.00	48.360 +-	0.137	49.328	1.02
120.00	45.409 +-	0.148	46.161	1.01
144.00	42.579 +-	0.164	44.243	1.03
168.00	41.700 +-	0.191	42.560	1.02
192.00	39.882 +-	0.220	40.910	1.02
216.00	37.814 +-	0.256	39.279	1.03

TABLE:KB-PL-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)			CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.011	+-	0.000	0.011	0.95
2.00	0.019	+-	0.000	0.016	0.85
6.00	0.039	+-	0.000	0.040	1.02
9.00	0.063	+-	0.000	0.049	0.77
12.00	0.062	+-	0.000	0.053	0.83
16.00	0.060	+-	0.000	0.053	0.88
24.00	0.049	+-	0.000	0.051	1.02
48.00	0.036	+-	0.000	0.042	1.14
72.00	0.040	+-	0.000	0.034	0.85
96.00	0.033	+-	0.000	0.028	0.83
120.00	0.030	+-	0.001	0.023	0.74
144.00	0.018	+-	0.001	0.019	0.98
168.00	0.012	+-	0.001	0.015	1.19

TABLE:KB-RC-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	1.419 +- 0.004	1.336	0.94
2.00	3.066 +- 0.010	3.370	1.09
3.00	4.385 +- 0.014	5.038	1.14
6.00	7.857 +- 0.026	8.094	1.03
9.00	10.327 +- 0.034	9.501	0.92
12.00	11.347 +- 0.038	10.165	0.89
16.00	10.718 +- 0.036	10.563	0.98
24.00	11.994 +- 0.040	10.839	0.90
48.00	13.535 +- 0.045	11.061	0.81
72.00	13.806 +- 0.056	11.057	0.80
96.00	12.638 +- 0.046	10.917	0.86
120.00	12.549 +- 0.049	10.686	0.85
144.00	11.394 +- 0.038	10.401	0.91
168.00	9.856 +- 0.033	10.083	1.02
192.00	8.835 +- 0.029	9.747	1.10
216.00	8.428 +- 0.032	9.404	1.11

TABLE:KB-UR-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	1.135 +- 0.005	1.267	1.11
48.00	1.558 +- 0.006	1.625	1.04
72.00	1.932 +- 0.006	1.965	1.01
96.00	2.276 +- 0.007	2.290	1.00
120.00	2.641 +- 0.008	2.601	0.98
144.00	3.015 +- 0.009	2.899	0.96
168.00	3.380 +- 0.010	3.184	0.94
192.00	3.797 +- 0.011	3.458	0.91
216.00	4.316 +- 0.013	3.721	0.86

TABLE:KB-SB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.65	14.981 +- 0.151	10.762	0.71
1.62	12.144 +- 0.127	11.005	0.90
2.60	6.918 +- 0.079	8.908	1.28
3.52	5.856 +- 0.069	7.167	1.22
4.58	7.301 +- 0.085	5.618	0.76
5.55	5.727 +- 0.070	4.559	0.79
8.28	2.894 +- 0.036	2.821	0.97
9.30	2.673 +- 0.032	2.482	0.92
10.15	2.154 +- 0.027	2.281	1.05
11.00	2.122 +- 0.028	2.138	1.00
16.00	2.156 +- 0.029	1.899	0.88
24.00	1.518 +- 0.018	1.913	1.26
48.00	1.318 +- 0.019	0.929	0.70
72.00	0.452 +- 0.010	0.374	0.82
96.00	0.377 +- 0.014	0.250	0.66
120.00	0.248 +- 0.016	0.227	0.91
144.00	0.218 +- 0.020	0.220	1.00
168.00	0.173 +- 0.028	0.214	1.22
192.00	0.183 +- 0.034	0.207	1.13

TABLE:KB-LI-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.65	0.360 +- 0.006	0.188	0.52
1.62	0.572 +- 0.009	0.417	0.72
2.60	0.584 +- 0.009	0.586	1.00
3.52	0.652 +- 0.010	0.709	1.08
4.58	0.774 +- 0.012	0.818	1.05
5.55	0.855 +- 0.013	0.895	1.04
8.28	1.058 +- 0.015	1.035	0.97
9.30	1.006 +- 0.013	1.067	1.06
10.15	1.104 +- 0.014	1.089	0.98
11.00	1.078 +- 0.014	1.107	1.02
16.00	1.217 +- 0.016	1.169	0.96
24.00	1.211 +- 0.017	1.209	0.99
48.00	1.217 +- 0.020	1.266	1.04
72.00	1.193 +- 0.020	1.290	1.08
96.00	1.168 +- 0.023	1.293	1.10
120.00	1.307 +- 0.026	1.282	0.98
144.00	1.177 +- 0.029	1.260	1.07
168.00	1.165 +- 0.037	1.232	1.05
192.00	1.343 +- 0.046	1.200	0.89
216.00	1.358 +- 0.057	1.166	0.85

TABLE:KB-ST-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.65	0.018 +- 0.002	0.003	0.16
1.62	0.025 +- 0.003	0.013	0.49
2.60	0.022 +- 0.003	0.021	0.91
3.52	0.023 +- 0.003	0.027	1.17
4.58	0.030 +- 0.003	0.033	1.07
5.55	0.036 +- 0.003	0.037	0.99
8.28	0.041 +- 0.003	0.043	1.05
9.30	0.055 +- 0.003	0.044	0.80
10.15	0.050 +- 0.003	0.045	0.90
11.00	0.044 +- 0.003	0.046	1.03
16.00	0.044 +- 0.003	0.048	1.06
24.00	0.047 +- 0.004	0.047	1.00
48.00	0.060 +- 0.004	0.044	0.72
72.00	0.051 +- 0.007	0.042	0.80
96.00	0.029 +- 0.010	0.040	1.32
120.00	0.034 +- 0.013	0.038	1.07
144.00	0.032 +- 0.018	0.036	1.10

TABLE:KB-HT-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:K.B. KINETIC:2.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.65	0.011 +- 0.002	0.001	0.12
1.62	0.011 +- 0.002	0.006	0.53
2.60	0.012 +- 0.003	0.010	0.82
3.52	0.014 +- 0.003	0.013	0.87
4.58	0.017 +- 0.003	0.016	0.90
5.55	0.018 +- 0.003	0.018	0.95
8.28	0.030 +- 0.003	0.022	0.72
9.30	0.029 +- 0.003	0.023	0.78
10.15	0.034 +- 0.003	0.024	0.68
11.00	0.027 +- 0.003	0.024	0.89
16.00	0.034 +- 0.003	0.027	0.78
24.00	0.036 +- 0.004	0.031	0.83
48.00	0.057 +- 0.004	0.039	0.67
72.00	0.042 +- 0.007	0.047	1.10
96.00	0.043 +- 0.010	0.055	1.27
120.00	0.053 +- 0.013	0.063	1.16
144.00	0.043 +- 0.018	0.070	1.61

TABLE: JB-WB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT: J.B. KINETIC: 1.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA (QO) (%I.D.)	CALCULATED RESULTS (QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.238	98.260	0.98
24.00	95.011 +- 0.240	96.494	1.01
48.00	92.930 +- 0.257	88.858	0.95
72.00	86.596 +- 0.264	79.919	0.92
96.00	71.701 +- 0.268	74.257	1.03
120.00	69.206 +- 0.284	70.823	1.02
144.00	66.359 +- 0.315	68.191	1.02
168.00	63.221 +- 0.358	65.733	1.04
192.00	61.818 +- 0.432	63.290	1.02
216.00	58.571 +- 0.451	60.844	1.03

TABLE:JB-PL-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.028 +- 0.000	0.016	0.55
2.00	0.034 +- 0.000	0.024	0.69
3.00	0.025 +- 0.000	0.033	1.29
6.00	0.051 +- 0.000	0.053	1.01
16.00	0.073 +- 0.001	0.064	0.87
22.00	0.064 +- 0.001	0.061	0.95
25.00	0.049 +- 0.001	0.060	1.19
48.00	0.044 +- 0.001	0.049	1.09
72.00	0.048 +- 0.002	0.039	0.81
96.00	0.024 +- 0.003	0.032	1.27
144.00	0.019 +- 0.006	0.021	1.05

TABLE:JB-RC-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)		CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	4.509 +-	0.014	3.426	0.76
2.00	9.951 +-	0.031	9.513	0.95
3.00	12.666 +-	0.040	14.577	1.15
6.00	18.177 +-	0.058	23.314	1.28
16.00	29.528 +-	0.095	28.916	0.97
22.00	27.661 +-	0.088	29.115	1.05
25.00	30.507 +-	0.098	29.113	0.95
48.00	32.392 +-	0.104	28.718	0.88
72.00	28.881 +-	0.101	28.022	0.97
96.00	28.378 +-	0.105	27.157	0.95
120.00	26.697 +-	0.109	26.188	0.98
144.00	25.387 +-	0.085	25.176	0.99
192.00	23.817 +-	0.114	23.117	0.97
216.00	23.721 +-	0.128	22.106	0.93

TABLE:JB-UR-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	2.344 +- 0.014	2.641	1.12
48.00	3.085 +- 0.015	3.283	1.06
72.00	3.927 +- 0.016	3.892	0.99
96.00	4.626 +- 0.017	4.470	0.96
120.00	5.375 +- 0.020	5.020	0.93
144.00	5.800 +- 0.021	5.543	0.95
168.00	6.314 +- 0.022	6.041	0.95
192.00	6.748 +- 0.022	6.516	0.96
216.00	7.383 +- 0.024	6.968	0.94

TABLE:JB-SB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.33	13.013 +- 0.148	13.524	1.03
2.43	9.520 +- 0.125	11.085	1.16
3.25	8.915 +- 0.121	9.109	1.02
4.30	8.663 +- 0.117	7.100	0.81
5.18	6.142 +- 0.092	5.839	0.95
5.83	6.410 +- 0.095	5.109	0.79
7.67	3.428 +- 0.052	3.719	1.08
8.50	2.755 +- 0.040	3.331	1.20
9.58	3.272 +- 0.046	2.978	0.91
10.72	3.322 +- 0.045	2.743	0.82
11.75	3.865 +- 0.053	2.616	0.67
17.08	2.844 +- 0.044	2.556	0.89
21.88	4.110 +- 0.059	2.661	0.64
24.00	4.452 +- 0.075	2.671	0.60
48.00	3.032 +- 0.049	1.567	0.51
72.00	1.100 +- 0.032	0.703	0.63
96.00	0.548 +- 0.030	0.470	0.85
120.00	0.400 +- 0.035	0.441	1.10
144.00	0.367 +- 0.044	0.451	1.22
192.00	0.288 +- 0.072	0.464	1.60

TABLE:JB-LI-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.33	1.046 +-	0.018	0.939	0.89
2.43	1.860 +-	0.031	1.372	0.73
3.25	2.057 +-	0.034	1.595	0.77
4.30	2.316 +-	0.036	1.810	0.78
5.18	2.580 +-	0.040	1.946	0.75
5.83	2.757 +-	0.042	2.027	0.73
7.67	2.863 +-	0.052	2.189	0.76
8.50	2.975 +-	0.046	2.240	0.75
9.58	3.013 +-	0.048	2.292	0.76
10.72	2.733 +-	0.043	2.334	0.85
11.75	3.073 +-	0.049	2.364	0.76
17.08	2.972 +-	0.051	2.453	0.82
21.88	2.936 +-	0.051	2.497	0.85
48.00	2.700 +-	0.047	2.646	0.98
72.00	2.945 +-	0.051	2.720	0.92
96.00	3.099 +-	0.063	2.749	0.88
120.00	3.101 +-	0.073	2.745	0.88
192.00	2.892 +-	0.114	2.601	0.89
216.00	2.812 +-	0.143	2.527	0.89

TABLE:JB-ST-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.33	0.035 +- 0.004	0.014	0.37
2.43	0.050 +- 0.004	0.030	0.58
3.25	0.050 +- 0.005	0.039	0.76
4.30	0.053 +- 0.004	0.048	0.89
5.18	0.055 +- 0.005	0.053	0.95
5.83	0.054 +- 0.005	0.057	1.04
7.67	0.060 +- 0.005	0.063	1.03
11.75	0.062 +- 0.005	0.068	1.08
17.08	0.059 +- 0.004	0.069	1.14
21.88	0.061 +- 0.005	0.068	1.11
24.00	0.058 +- 0.006	0.068	1.15
48.00	0.050 +- 0.007	0.062	1.24
72.00	0.066 +- 0.010	0.058	0.86
96.00	0.057 +- 0.013	0.054	0.95

TABLE:JB-HT-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:1.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.33	0.027 +-	0.004	0.010	0.37
2.43	0.019 +-	0.004	0.023	1.16
3.25	0.035 +-	0.004	0.030	0.84
4.30	0.032 +-	0.004	0.038	1.15
5.18	0.051 +-	0.005	0.043	0.83
5.83	0.037 +-	0.004	0.046	1.20
7.67	0.064 +-	0.005	0.052	0.80
8.50	0.062 +-	0.004	0.054	0.87
9.58	0.060 +-	0.004	0.056	0.92
10.72	0.070 +-	0.004	0.058	0.82
11.75	0.077 +-	0.005	0.060	0.77
17.08	0.068 +-	0.004	0.065	0.94
21.88	0.084 +-	0.005	0.069	0.81
24.00	0.066 +-	0.006	0.071	1.05
48.00	0.064 +-	0.008	0.088	1.36
72.00	0.094 +-	0.010	0.104	1.10
96.00	0.111 +-	0.014	0.119	1.06
120.00	0.122 +-	0.017	0.134	1.09
144.00	0.154 +-	0.024	0.148	0.95
168.00	0.168 +-	0.032	0.161	0.95

TABLE:JB-WB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.176	99.200	0.99
24.00	88.654 +- 0.162	86.490	0.97
48.00	48.214 +- 0.105	58.579	1.21
96.00	36.633 +- 0.104	36.796	1.00
120.00	33.429 +- 0.110	34.218	1.02
144.00	31.248 +- 0.120	32.667	1.04
168.00	29.334 +- 0.139	31.359	1.06
192.00	28.204 +- 0.164	30.098	1.06
216.00	27.202 +- 0.191	28.849	1.06

TABLE:JB-PL-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.007 +- 0.000	0.007	0.90
2.00	0.015 +- 0.000	0.011	0.74
3.00	0.017 +- 0.000	0.015	0.84
6.00	0.035 +- 0.000	0.027	0.74
10.00	0.039 +- 0.000	0.037	0.94
16.00	0.037 +- 0.000	0.041	1.10
24.00	0.051 +- 0.000	0.041	0.79
48.00	0.035 +- 0.000	0.036	1.03
72.00	0.032 +- 0.000	0.032	0.99
96.00	0.019 +- 0.000	0.028	1.45
120.00	0.035 +- 0.000	0.025	0.70
144.00	0.019 +- 0.001	0.022	1.15
168.00	0.022 +- 0.001	0.020	0.86
216.00	0.021 +- 0.002	0.016	0.72

TABLE:JB-RC-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.801 +- 0.002	0.710	0.88
2.00	1.980 +- 0.006	2.281	1.15
3.00	2.990 +- 0.009	3.690	1.23
6.00	6.171 +- 0.019	6.175	1.00
10.00	8.636 +- 0.027	7.447	0.86
16.00	10.250 +- 0.032	8.121	0.79
24.00	11.853 +- 0.037	8.561	0.72
48.00	12.653 +- 0.039	9.319	0.73
72.00	11.378 +- 0.035	9.630	0.84
96.00	10.765 +- 0.034	9.658	0.89
120.00	9.762 +- 0.030	9.511	0.97
144.00	9.463 +- 0.029	9.256	0.97
168.00	8.958 +- 0.028	8.938	0.99
216.00	7.041 +- 0.024	8.220	1.16

TABLE:JB-UR-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	1.006 +- 0.004	1.022	1.01
48.00	1.329 +- 0.005	1.373	1.03
72.00	1.694 +- 0.006	1.697	1.00
96.00	2.034 +- 0.007	1.999	0.98
120.00	2.332 +- 0.007	2.282	0.97
144.00	2.597 +- 0.008	2.549	0.98
168.00	2.866 +- 0.009	2.801	0.97
192.00	3.044 +- 0.009	3.039	0.99
216.00	3.288 +- 0.009	3.265	0.99

TABLE:JB-SB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.75	15.455 +- 0.148	12.658	0.81
1.78	14.355 +- 0.142	12.614	0.87
2.75	15.785 +- 0.155	10.216	0.64
3.75	8.656 +- 0.095	8.067	0.93
4.83	5.197 +- 0.063	6.326	1.21
5.50	4.400 +- 0.050	5.496	1.24
7.72	2.975 +- 0.039	3.675	1.23
8.58	2.994 +- 0.039	3.233	1.08
9.67	3.216 +- 0.041	2.808	0.87
10.42	2.995 +- 0.039	2.583	0.86
16.50	2.431 +- 0.035	1.759	0.72
24.00	5.423 +- 0.067	1.475	0.27
48.00	0.640 +- 0.015	0.832	1.29
72.00	0.430 +- 0.014	0.379	0.88
96.00	0.232 +- 0.014	0.195	0.84
120.00	0.159 +- 0.016	0.137	0.85
144.00	0.086 +- 0.019	0.120	1.38
168.00	0.135 +- 0.026	0.114	0.84
192.00	0.152 +- 0.035	0.111	0.72

TABLE:JB-LI-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.75	0.099 +- 0.004	0.080	0.80
1.78	0.282 +- 0.007	0.292	1.03
2.75	0.429 +- 0.008	0.470	1.09
3.75	0.600 +- 0.011	0.610	1.01
4.83	0.719 +- 0.014	0.721	1.00
5.50	0.820 +- 0.015	0.774	0.94
7.72	1.077 +- 0.019	0.890	0.82
8.58	1.099 +- 0.019	0.919	0.83
9.67	1.023 +- 0.020	0.948	0.92
10.42	1.058 +- 0.020	0.964	0.91
16.50	1.040 +- 0.023	1.036	0.99
24.00	0.996 +- 0.021	1.083	1.08
48.00	1.033 +- 0.023	1.186	1.14
72.00	1.149 +- 0.027	1.250	1.08
96.00	1.325 +- 0.028	1.285	0.96
120.00	1.321 +- 0.032	1.297	0.98
144.00	1.300 +- 0.033	1.292	0.99
168.00	1.363 +- 0.040	1.274	0.93
192.00	1.430 +- 0.050	1.247	0.87
216.00	1.471 +- 0.058	1.214	0.82

TABLE:JB-ST-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
0.75	0.013 +- 0.002	0.002	0.12
1.78	0.022 +- 0.002	0.008	0.37
2.75	0.021 +- 0.002	0.014	0.66
3.75	0.024 +- 0.002	0.019	0.80
4.83	0.026 +- 0.002	0.023	0.86
5.50	0.028 +- 0.002	0.025	0.85
7.72	0.033 +- 0.002	0.028	0.85
8.58	0.030 +- 0.002	0.029	0.94
9.67	0.027 +- 0.002	0.029	1.07
10.42	0.026 +- 0.002	0.030	1.10
16.50	0.021 +- 0.002	0.030	1.42
24.00	0.020 +- 0.002	0.029	1.44
48.00	0.018 +- 0.004	0.026	1.41
72.00	0.031 +- 0.004	0.023	0.74
96.00	0.036 +- 0.006	0.022	0.59

TABLE:JB-HT-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:J.B. KINETIC:2.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.75	0.004 +- 0.002	0.001	0.22
1.78	0.008 +- 0.002	0.004	0.52
2.75	0.010 +- 0.002	0.008	0.77
3.75	0.014 +- 0.002	0.011	0.73
4.83	0.014 +- 0.002	0.013	0.91
5.50	0.015 +- 0.002	0.014	0.88
7.72	0.016 +- 0.002	0.017	1.00
8.58	0.022 +- 0.002	0.018	0.78
9.67	0.022 +- 0.002	0.018	0.81
10.42	0.017 +- 0.002	0.019	1.07
16.50	0.024 +- 0.002	0.022	0.87
24.00	0.023 +- 0.003	0.025	1.04
48.00	0.025 +- 0.004	0.033	1.29
72.00	0.037 +- 0.005	0.041	1.08
96.00	0.054 +- 0.006	0.048	0.88
120.00	0.070 +- 0.008	0.055	0.77
144.00	0.050 +- 0.011	0.062	1.21
168.00	0.068 +- 0.015	0.068	0.99

TABLE:BC-WB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.221	99.999	1.00
24.00	99.287 +- 0.231	97.158	0.97
72.00	83.535 +- 0.237	83.144	0.99
96.00	73.931 +- 0.239	75.876	1.02
168.00	71.331 +- 0.360	67.478	0.94
192.00	68.594 +- 0.405	66.305	0.96
216.00	64.770 +- 0.468	65.242	1.00
288.00	59.749 +- 0.886	62.113	1.04
336.00	52.844 +- 1.453	60.008	1.13

TABLE:BC-PL-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.020 +- 0.001	0.018	0.86
2.00	0.026 +- 0.001	0.020	0.76
3.00	0.030 +- 0.001	0.022	0.70
5.00	0.034 +- 0.001	0.027	0.76
7.00	0.039 +- 0.001	0.031	0.78
16.00	0.026 +- 0.001	0.040	1.51
24.00	0.045 +- 0.001	0.040	0.86
41.50	0.042 +- 0.001	0.037	0.86
72.00	0.038 +- 0.002	0.032	0.82
96.00	0.036 +- 0.003	0.029	0.79

TABLE:BC-RC-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	3.939 +- 0.007	2.451	0.62
2.00	7.397 +- 0.014	6.586	0.89
3.00	9.920 +- 0.019	10.062	1.01
5.00	13.663 +- 0.026	14.782	1.08
7.00	15.907 +- 0.031	17.484	1.09
16.00	19.100 +- 0.037	20.553	1.07
24.00	21.388 +- 0.041	20.438	0.95
41.50	22.770 +- 0.045	19.664	0.86
72.00	21.431 +- 0.042	18.518	0.86
96.00	17.895 +- 0.036	17.795	0.99
120.00	18.446 +- 0.040	17.183	0.93
168.00	15.931 +- 0.047	16.192	1.01
216.00	14.140 +- 0.058	15.396	1.08

TABLE:BC-UR-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	2.131 +- 0.010	2.432	1.14
48.00	3.043 +- 0.013	2.956	0.97
72.00	3.379 +- 0.014	3.465	1.02
96.00	4.053 +- 0.015	3.964	0.97
120.00	4.605 +- 0.016	4.451	0.96
144.00	5.140 +- 0.017	4.929	0.95
168.00	5.485 +- 0.018	5.397	0.98
192.00	5.833 +- 0.019	5.857	1.00
216.00	6.273 +- 0.021	6.307	1.00

TABLE:BC-SB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.68	7.025 +- 0.065	6.097	0.86
2.58	4.650 +- 0.047	5.631	1.21
3.57	4.660 +- 0.047	5.041	1.08
4.60	5.254 +- 0.051	4.515	0.85
5.77	4.088 +- 0.044	4.033	0.98
7.77	3.586 +- 0.038	3.424	0.95
8.67	3.710 +- 0.040	3.216	0.86
9.97	3.600 +- 0.040	2.969	0.82
10.93	3.550 +- 0.040	2.819	0.79
17.03	1.720 +- 0.020	2.241	1.30
20.57	1.840 +- 0.022	2.059	1.11
24.00	1.970 +- 0.024	1.927	0.97
48.00	1.384 +- 0.019	1.296	0.93
72.00	1.090 +- 0.020	0.903	0.82
96.00	0.828 +- 0.017	0.728	0.87
120.00	0.645 +- 0.015	0.665	1.03
144.00	0.682 +- 0.018	0.643	0.94
168.00	0.614 +- 0.023	0.633	1.03
192.00	0.520 +- 0.027	0.626	1.20
216.00	0.675 +- 0.035	0.619	0.91

TABLE:BC-LI-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.68	1.436 +- 0.017	1.105	0.76
2.58	1.705 +- 0.019	1.332	0.78
3.57	1.762 +- 0.019	1.508	0.85
4.60	1.916 +- 0.020	1.646	0.85
5.77	2.060 +- 0.022	1.764	0.85
7.77	2.108 +- 0.027	1.900	0.90
8.67	2.366 +- 0.029	1.942	0.82
9.97	2.215 +- 0.028	1.990	0.89
10.93	2.243 +- 0.028	2.017	0.89
17.03	2.199 +- 0.025	2.111	0.96
20.57	2.258 +- 0.025	2.140	0.94
24.00	2.645 +- 0.030	2.162	0.81
48.00	2.890 +- 0.039	2.278	0.78
72.00	3.673 +- 0.057	2.368	0.64
96.00	3.151 +- 0.046	2.435	0.77
120.00	2.912 +- 0.037	2.484	0.85
144.00	3.387 +- 0.047	2.517	0.74
168.00	3.090 +- 0.053	2.536	0.82
192.00	2.873 +- 0.054	2.544	0.88
216.00	3.244 +- 0.063	2.543	0.78

TABLE:BC-ST-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)			CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.68	0.033	+-	0.003	0.022	0.64
2.58	0.046	+-	0.003	0.036	0.76
3.57	0.046	+-	0.003	0.048	1.03
4.60	0.048	+-	0.003	0.058	1.20
5.77	0.071	+-	0.003	0.067	0.93
7.77	0.058	+-	0.003	0.076	1.29
8.67	0.069	+-	0.003	0.079	1.12
9.97	0.090	+-	0.003	0.082	0.90
10.93	0.086	+-	0.003	0.083	0.96
17.03	0.095	+-	0.003	0.088	0.92
20.57	0.076	+-	0.003	0.089	1.15
24.00	0.112	+-	0.003	0.089	0.78
48.00	0.072	+-	0.004	0.089	1.22
72.00	0.080	+-	0.007	0.088	1.09
96.00	0.124	+-	0.008	0.087	0.69
120.00	0.098	+-	0.009	0.086	0.87
144.00	0.127	+-	0.013	0.085	0.66

TABLE:BC-HT-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:1.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
1.68	0.019 +- 0.003	0.013	0.65
2.58	0.021 +- 0.002	0.021	0.97
3.57	0.025 +- 0.002	0.028	1.10
4.60	0.031 +- 0.002	0.034	1.09
5.77	0.043 +- 0.003	0.039	0.91
7.77	0.049 +- 0.003	0.046	0.91
8.67	0.051 +- 0.003	0.048	0.91
9.97	0.051 +- 0.003	0.050	0.96
10.93	0.057 +- 0.003	0.052	0.89
17.03	0.050 +- 0.003	0.057	1.14
20.57	0.073 +- 0.003	0.060	0.81
24.00	0.085 +- 0.003	0.062	0.72
48.00	0.060 +- 0.004	0.075	1.23
72.00	0.082 +- 0.008	0.088	1.06
96.00	0.117 +- 0.008	0.101	0.86
120.00	0.114 +- 0.010	0.113	0.98
144.00	0.113 +- 0.013	0.125	1.09

TABLE:BC-WB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.113	98.331	0.98
24.00	35.822 +- 0.093	37.858	1.05
48.00	31.110 +- 0.086	26.827	0.86
72.00	26.542 +- 0.086	25.524	0.96
96.00	25.090 +- 0.093	24.196	0.96
120.00	20.842 +- 0.095	22.859	1.09
144.00	19.867 +- 0.108	21.544	1.08
168.00	18.483 +- 0.124	20.271	1.09
192.00	16.591 +- 0.160	19.052	1.14
216.00	16.069 +- 0.187	17.891	1.11

TABLE:BC-PL-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
3.00	0.003 +- 0.000	0.006	1.79
16.00	0.015 +- 0.000	0.012	0.81
24.00	0.014 +- 0.000	0.012	0.84
48.00	0.009 +- 0.001	0.011	1.16
72.00	0.008 +- 0.000	0.010	1.15
96.00	0.010 +- 0.001	0.009	0.88
120.00	0.009 +- 0.001	0.009	0.85
144.00	0.009 +- 0.001	0.008	0.79
168.00	0.010 +- 0.001	0.007	0.65
192.00	0.007 +- 0.002	0.006	0.81

TABLE:BC-RC-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
2.00	0.677 +- 0.001	1.209	1.78
3.00	1.109 +- 0.002	1.946	1.75
6.00	3.025 +- 0.005	3.082	1.01
16.00	5.883 +- 0.011	3.880	0.65
24.00	6.037 +- 0.011	4.169	0.69
48.00	5.883 +- 0.011	4.732	0.80
72.00	5.428 +- 0.010	4.978	0.91
96.00	5.303 +- 0.015	5.025	0.94
120.00	5.049 +- 0.017	4.946	0.98
144.00	4.716 +- 0.013	4.792	1.01
168.00	4.146 +- 0.009	4.595	1.10
192.00	3.974 +- 0.009	4.376	1.10
216.00	4.298 +- 0.017	4.147	0.96

TABLE:BC-UR-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	0.567 +- 0.003	0.467	0.82
48.00	0.624 +- 0.003	0.652	1.04
72.00	0.745 +- 0.003	0.820	1.10
96.00	0.959 +- 0.004	0.975	1.01
120.00	1.157 +- 0.004	1.118	0.96
144.00	1.236 +- 0.004	1.251	1.01
168.00	1.531 +- 0.006	1.374	0.89
192.00	1.701 +- 0.006	1.489	0.87
216.00	1.851 +- 0.006	1.597	0.86

TABLE:BC-SB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.53	16.117 +-	0.136	4.561	0.28
1.58	5.166 +-	0.057	4.886	0.94
2.70	4.950 +-	0.056	4.158	0.84
4.03	3.035 +-	0.040	3.660	1.20
4.85	2.546 +-	0.031	3.421	1.34
5.75	2.115 +-	0.027	3.154	1.49
7.92	4.880 +-	0.058	2.455	0.50
8.92	5.041 +-	0.060	2.133	0.42
9.75	4.258 +-	0.053	1.881	0.44
10.67	2.254 +-	0.035	1.624	0.72
16.67	1.197 +-	0.019	0.621	0.51
24.00	0.694 +-	0.011	0.325	0.46
48.00	0.443 +-	0.010	0.254	0.57
72.00	0.225 +-	0.009	0.231	1.02
96.00	0.234 +-	0.012	0.213	0.90
120.00	0.159 +-	0.014	0.196	1.23
144.00	0.139 +-	0.018	0.182	1.31

TABLE:BC-LI-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.58	0.224 +- 0.006	0.183	0.81
2.70	0.230 +- 0.005	0.344	1.49
4.03	0.293 +- 0.006	0.471	1.60
4.85	0.635 +- 0.009	0.522	0.82
7.92	0.634 +- 0.009	0.620	0.97
8.92	0.653 +- 0.011	0.636	0.97
9.75	0.740 +- 0.012	0.646	0.87
10.67	0.809 +- 0.012	0.656	0.81
16.67	0.609 +- 0.011	0.697	1.14
24.00	0.642 +- 0.011	0.733	1.14
48.00	0.684 +- 0.013	0.807	1.17
72.00	0.757 +- 0.014	0.835	1.10
96.00	0.872 +- 0.018	0.834	0.95
120.00	0.780 +- 0.019	0.814	1.04
144.00	0.847 +- 0.024	0.784	0.92
168.00	0.822 +- 0.029	0.748	0.91
192.00	0.810 +- 0.043	0.709	0.87
216.00	0.778 +- 0.054	0.669	0.85

TABLE:BC-ST-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.58	0.013 +- 0.002	0.006	0.45
2.70	0.015 +- 0.002	0.013	0.81
4.03	0.017 +- 0.002	0.018	1.03
4.85	0.017 +- 0.002	0.020	1.14
5.75	0.014 +- 0.002	0.021	1.46
7.92	0.018 +- 0.002	0.023	1.24
8.92	0.024 +- 0.002	0.023	0.94
9.75	0.021 +- 0.002	0.023	1.09
10.67	0.021 +- 0.002	0.023	1.07
16.67	0.029 +- 0.002	0.023	0.77
24.00	0.019 +- 0.002	0.022	1.13
48.00	0.026 +- 0.003	0.020	0.74
72.00	0.030 +- 0.005	0.018	0.57
96.00	0.032 +- 0.005	0.016	0.49

TABLE:BC-HT-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:B.C. KINETIC:2.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.58	0.009 +- 0.002	0.003	0.34
2.70	0.011 +- 0.002	0.007	0.61
4.03	0.011 +- 0.002	0.010	0.87
4.85	0.009 +- 0.002	0.011	1.13
5.75	0.008 +- 0.002	0.012	1.39
7.92	0.015 +- 0.002	0.014	0.90
8.92	0.014 +- 0.002	0.014	0.95
9.75	0.016 +- 0.002	0.015	0.87
10.67	0.015 +- 0.002	0.015	0.95
16.67	0.022 +- 0.002	0.017	0.78
24.00	0.020 +- 0.002	0.020	0.95
48.00	0.024 +- 0.003	0.028	1.12
72.00	0.036 +- 0.005	0.035	0.95
96.00	0.041 +- 0.006	0.042	1.01
120.00	0.040 +- 0.007	0.048	1.17
144.00	0.055 +- 0.010	0.054	0.97

TABLE:GE-WB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.289	98.883	0.98
24.00	98.590 +- 0.298	97.104	0.98
48.00	98.551 +- 0.316	88.030	0.89
72.00	79.274 +- 0.286	77.462	0.97
96.00	71.709 +- 0.272	70.942	0.98
120.00	68.629 +- 0.297	67.070	0.97
144.00	62.791 +- 0.327	64.137	1.02
168.00	61.241 +- 0.354	61.496	1.00
192.00	60.037 +- 0.433	59.003	0.98
240.00	52.651 +- 0.528	54.431	1.03

TABLE:GE-PL-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.011 +- 0.001	0.013	1.09
2.00	0.022 +- 0.001	0.021	0.95
3.00	0.032 +- 0.001	0.028	0.85
14.00	0.045 +- 0.001	0.050	1.10
20.00	0.051 +- 0.001	0.050	0.95
24.00	0.052 +- 0.001	0.048	0.91
48.00	0.045 +- 0.002	0.040	0.87
72.00	0.029 +- 0.003	0.033	1.12
96.00	0.027 +- 0.007	0.027	0.97

TABLE:GE-RC-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	4.120 +- 0.010	3.435	0.83
2.00	10.398 +- 0.025	9.727	0.93
3.00	14.657 +- 0.035	15.261	1.04
6.00	21.403 +- 0.051	26.092	1.21
14.00	32.474 +- 0.078	34.796	1.07
20.00	34.332 +- 0.083	35.434	1.03
24.00	33.678 +- 0.081	35.218	1.04
48.00	32.574 +- 0.079	32.797	1.00
72.00	33.122 +- 0.081	30.848	0.93
96.00	31.963 +- 0.079	29.339	0.91
120.00	30.601 +- 0.076	28.112	0.91
144.00	28.492 +- 0.071	27.071	0.95
168.00	25.878 +- 0.068	26.154	1.01
192.00	25.994 +- 0.069	25.321	0.97
240.00	22.816 +- 0.064	23.821	1.04

TABLE:GE-UR-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	1.600 +- 0.012	1.882	1.17
48.00	2.600 +- 0.015	2.527	0.97
72.00	3.500 +- 0.017	3.140	0.89
96.00	3.640 +- 0.017	3.732	1.02
120.00	4.310 +- 0.017	4.305	0.99
144.00	4.900 +- 0.020	4.861	0.99
168.00	5.530 +- 0.023	5.400	0.97
192.00	6.110 +- 0.025	5.923	0.96
216.00	7.310 +- 0.033	6.432	0.88

TABLE:GE-SB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.75	5.924 +- 0.088	6.103	1.03
2.91	5.545 +- 0.085	6.077	1.09
3.85	7.616 +- 0.108	5.897	0.77
4.88	6.330 +- 0.094	5.655	0.89
5.87	5.593 +- 0.086	5.405	0.96
7.95	4.739 +- 0.069	4.865	1.02
8.91	4.337 +- 0.057	4.623	1.06
9.91	4.271 +- 0.057	4.380	1.02
10.75	3.763 +- 0.052	4.185	1.11
11.58	3.615 +- 0.035	4.002	1.10
16.76	3.252 +- 0.050	3.061	0.94
21.00	2.596 +- 0.044	2.512	0.96
24.00	4.048 +- 0.060	2.210	0.54
48.00	0.822 +- 0.018	0.990	1.20
72.00	0.784 +- 0.028	0.645	0.82
96.00	0.573 +- 0.029	0.568	0.99
120.00	0.522 +- 0.033	0.545	1.04

TABLE:GE-LI-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.75	1.141 +- 0.019	0.961	0.84
2.91	1.698 +- 0.028	1.362	0.80
3.85	1.921 +- 0.035	1.615	0.84
4.88	2.115 +- 0.033	1.839	0.86
5.87	2.277 +- 0.041	2.013	0.88
7.95	2.555 +- 0.041	2.280	0.89
8.91	2.583 +- 0.042	2.369	0.91
9.91	2.723 +- 0.044	2.445	0.89
10.75	2.749 +- 0.045	2.499	0.90
11.58	2.732 +- 0.031	2.544	0.93
16.76	2.630 +- 0.047	2.710	1.03
21.00	2.598 +- 0.047	2.773	1.06
24.00	2.498 +- 0.046	2.801	1.12
48.00	2.500 +- 0.040	2.885	1.15
72.00	2.640 +- 0.050	2.896	1.09
96.00	2.914 +- 0.059	2.881	0.98
120.00	2.887 +- 0.061	2.861	0.99
144.00	2.904 +- 0.071	2.847	0.98
168.00	2.823 +- 0.081	2.846	1.00
192.00	2.719 +- 0.103	2.859	1.05

TABLE:GE-ST-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.75	0.019 +- 0.004	0.015	0.74
2.91	0.034 +- 0.005	0.027	0.78
3.85	0.035 +- 0.005	0.035	0.97
4.88	0.042 +- 0.006	0.042	0.99
5.87	0.034 +- 0.005	0.048	1.39
7.95	0.051 +- 0.005	0.056	1.09
8.91	0.054 +- 0.005	0.059	1.07
9.91	0.052 +- 0.005	0.061	1.17
10.75	0.067 +- 0.005	0.063	0.92
11.58	0.051 +- 0.005	0.064	1.25
16.76	0.068 +- 0.006	0.070	1.01
21.00	0.083 +- 0.005	0.072	0.86
24.00	0.085 +- 0.005	0.073	0.84
48.00	0.078 +- 0.008	0.076	0.96
72.00	0.084 +- 0.010	0.077	0.90
96.00	0.090 +- 0.012	0.076	0.84
120.00	0.083 +- 0.016	0.076	0.90
144.00	0.087 +- 0.021	0.074	0.85

TABLE:GE-HT-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:1.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.75	0.023 +- 0.005	0.014	0.58
2.91	0.024 +- 0.005	0.025	1.04
3.85	0.024 +- 0.005	0.033	1.36
4.88	0.024 +- 0.006	0.040	1.60
5.87	0.039 +- 0.005	0.046	1.16
7.95	0.070 +- 0.005	0.055	0.77
8.91	0.088 +- 0.005	0.058	0.66
9.91	0.096 +- 0.006	0.061	0.63
10.75	0.118 +- 0.006	0.064	0.53
11.58	0.123 +- 0.006	0.066	0.53
16.76	0.159 +- 0.007	0.076	0.47
21.00	0.126 +- 0.006	0.082	0.65
24.00	0.142 +- 0.006	0.086	0.60
48.00	0.157 +- 0.008	0.116	0.73
72.00	0.195 +- 0.010	0.144	0.73
96.00	0.177 +- 0.013	0.171	0.96
120.00	0.173 +- 0.017	0.197	1.13
144.00	0.184 +- 0.022	0.223	1.20
168.00	0.243 +- 0.029	0.247	1.01
192.00	0.203 +- 0.041	0.271	1.33

TABLE:GE-WB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.202	99.534	0.99
24.00	91.900 +- 0.191	92.217	1.00
48.00	66.866 +- 0.155	57.488	0.86
72.00	38.411 +- 0.111	34.823	0.90
96.00	26.483 +- 0.097	27.170	1.02
120.00	23.551 +- 0.106	24.188	1.02
144.00	21.535 +- 0.116	22.217	1.03
168.00	19.978 +- 0.135	20.532	1.02
192.00	19.468 +- 0.162	19.014	0.97
216.00	18.667 +- 0.198	17.635	0.94

TABLE:GE-PL-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.004 +- 0.000	0.006	1.33
2.00	0.010 +- 0.000	0.013	1.27
3.00	0.024 +- 0.000	0.019	0.77
6.00	0.030 +- 0.000	0.028	0.89
16.50	0.014 +- 0.000	0.026	1.71
20.00	0.020 +- 0.000	0.023	1.11
24.00	0.015 +- 0.000	0.021	1.32
48.00	0.010 +- 0.000	0.010	0.95
72.00	0.011 +- 0.001	0.005	0.46
96.00	0.005 +- 0.001	0.003	0.53

TABLE:GE-RC-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.390 +- 0.001	0.462	1.18
2.00	1.653 +- 0.004	1.667	1.00
3.00	2.118 +- 0.005	2.767	1.30
6.00	4.143 +- 0.010	4.683	1.13
16.50	7.083 +- 0.017	6.144	0.86
20.00	6.350 +- 0.015	6.287	0.99
24.00	6.974 +- 0.017	6.418	0.92
48.00	7.037 +- 0.017	6.879	0.97
72.00	7.749 +- 0.018	6.995	0.90
96.00	6.649 +- 0.016	6.898	1.03
120.00	6.736 +- 0.019	6.674	0.99
144.00	6.140 +- 0.018	6.380	1.03
168.00	6.344 +- 0.018	6.048	0.95
192.00	5.918 +- 0.019	5.703	0.96
216.00	5.857 +- 0.020	5.357	0.91

TABLE:GE-UR-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	0.615 +- 0.005	0.752	1.22
48.00	0.944 +- 0.006	1.002	1.06
72.00	1.172 +- 0.006	1.228	1.04
96.00	1.368 +- 0.007	1.435	1.04
120.00	1.622 +- 0.007	1.625	1.00
144.00	1.799 +- 0.008	1.800	1.00
168.00	2.045 +- 0.008	1.961	0.95
192.00	2.221 +- 0.009	2.111	0.95
216.00	2.393 +- 0.010	2.251	0.94

TABLE:GE-SB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.75	9.658 +- 0.101	5.759	0.59
1.50	6.053 +- 0.068	5.616	0.92
2.60	5.804 +- 0.067	4.191	0.72
3.58	3.039 +- 0.042	3.167	1.04
5.08	1.773 +- 0.024	2.203	1.24
6.00	1.824 +- 0.026	1.881	1.03
7.50	1.554 +- 0.019	1.643	1.05
8.33	1.499 +- 0.019	1.615	1.07
9.58	1.645 +- 0.021	1.658	1.00
11.30	1.116 +- 0.016	1.811	1.62
16.75	7.112 +- 0.086	2.338	0.32
20.17	6.602 +- 0.084	2.465	0.37
24.00	7.083 +- 0.091	2.405	0.34
48.00	3.668 +- 0.049	0.821	0.22
72.00	0.619 +- 0.014	0.241	0.39
96.00	0.313 +- 0.013	0.145	0.46
120.00	0.194 +- 0.015	0.124	0.63
144.00	0.128 +- 0.020	0.112	0.86
168.00	0.070 +- 0.026	0.102	1.45

TABLE:GE-LI-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.75	0.091 +- 0.004	0.235	2.58
1.50	0.189 +- 0.005	0.454	2.40
2.60	0.365 +- 0.007	0.574	1.57
3.58	0.457 +- 0.008	0.620	1.35
5.08	0.569 +- 0.009	0.664	1.16
6.00	0.795 +- 0.013	0.683	0.85
7.50	0.797 +- 0.013	0.705	0.88
8.33	0.889 +- 0.014	0.714	0.80
9.58	0.873 +- 0.014	0.725	0.83
11.30	0.813 +- 0.014	0.736	0.90
16.75	0.816 +- 0.015	0.757	0.92
20.17	0.847 +- 0.016	0.766	0.90
24.00	0.838 +- 0.016	0.773	0.92
48.00	0.865 +- 0.016	0.791	0.91
72.00	0.894 +- 0.018	0.791	0.88
96.00	0.836 +- 0.018	0.787	0.94
120.00	0.856 +- 0.022	0.786	0.91
144.00	0.890 +- 0.026	0.788	0.88
168.00	0.838 +- 0.032	0.793	0.94
192.00	0.845 +- 0.043	0.800	0.94
216.00	0.854 +- 0.053	0.809	0.94

TABLE:GE-ST-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
0.75	0.025 +- 0.002	0.002	0.06
1.50	0.020 +- 0.001	0.007	0.34
2.60	0.024 +- 0.002	0.016	0.65
3.58	0.028 +- 0.002	0.022	0.78
5.08	0.028 +- 0.002	0.028	0.98
6.00	0.033 +- 0.002	0.031	0.91
7.50	0.027 +- 0.002	0.033	1.23
8.33	0.036 +- 0.002	0.034	0.94
9.58	0.030 +- 0.002	0.035	1.17
11.30	0.042 +- 0.002	0.036	0.84
16.75	0.029 +- 0.002	0.036	1.18
20.17	0.031 +- 0.002	0.035	1.09
24.00	0.032 +- 0.002	0.034	1.04
48.00	0.022 +- 0.003	0.030	1.32
72.00	0.030 +- 0.004	0.027	0.88
96.00	0.040 +- 0.006	0.024	0.59

TABLE:GE-HT-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:G.E. KINETIC:2.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/Q0
0.75	0.008 +- 0.002	0.001	0.10
1.50	0.005 +- 0.002	0.004	0.66
2.60	0.012 +- 0.002	0.009	0.70
3.58	0.025 +- 0.002	0.012	0.47
5.08	0.026 +- 0.002	0.016	0.61
6.00	0.025 +- 0.002	0.018	0.70
7.50	0.027 +- 0.002	0.020	0.73
8.33	0.031 +- 0.002	0.021	0.67
9.58	0.028 +- 0.002	0.022	0.78
11.30	0.046 +- 0.002	0.023	0.50
16.75	0.029 +- 0.002	0.026	0.91
20.17	0.031 +- 0.002	0.028	0.87
24.00	0.032 +- 0.002	0.030	0.92
48.00	0.038 +- 0.003	0.040	1.03
72.00	0.041 +- 0.004	0.049	1.17
96.00	0.043 +- 0.006	0.057	1.30
120.00	0.062 +- 0.011	0.064	1.03
144.00	0.051 +- 0.011	0.071	1.39

TABLE:DW-WB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +- 0.210	98.844	0.98
22.00	97.708 +- 0.215	97.582	0.99
48.00	94.062 +- 0.227	89.768	0.95
72.00	82.881 +- 0.225	79.158	0.95
96.00	71.604 +- 0.228	71.826	1.00
120.00	69.246 +- 0.255	67.917	0.98
144.00	68.385 +- 0.298	65.698	0.96
192.00	64.238 +- 0.415	62.521	0.97
288.00	58.091 +- 1.192	56.190	0.96
353.00	53.459 +- 2.218	51.776	0.96

TABLE:DW-PL-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

PLASMA

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	0.014 +- 0.001	0.016	1.09
2.00	0.028 +- 0.001	0.023	0.79
3.00	0.031 +- 0.001	0.029	0.91
5.00	0.028 +- 0.001	0.037	1.31
7.00	0.036 +- 0.001	0.043	1.16
16.50	0.057 +- 0.001	0.048	0.83
19.50	0.072 +- 0.001	0.048	0.66
22.00	0.033 +- 0.002	0.048	1.44
48.00	0.054 +- 0.001	0.042	0.76
72.00	0.053 +- 0.003	0.037	0.68
96.00	0.046 +- 0.003	0.032	0.69
120.00	0.023 +- 0.004	0.029	1.19

TABLE:DW-RC-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
1.00	4.910 +- 0.046	3.774	0.76
2.00	10.985 +- 0.075	9.815	0.89
3.00	14.577 +- 0.089	14.936	1.02
5.00	19.473 +- 0.108	22.148	1.13
7.00	22.133 +- 0.118	26.531	1.19
16.50	30.828 +- 0.150	32.353	1.04
19.30	31.932 +- 0.095	32.510	1.01
22.00	30.229 +- 0.089	32.497	1.07
48.00	27.773 +- 0.163	31.022	1.11
72.00	29.572 +- 0.212	29.668	1.00
96.00	26.791 +- 0.208	28.438	1.06
120.00	26.603 +- 0.240	27.302	1.02
144.00	25.073 +- 0.268	26.242	1.04
168.00	24.576 +- 0.226	25.234	1.02
192.00	26.989 +- 0.280	24.276	0.89
216.00	25.341 +- 0.312	23.361	0.92

TABLE:DW-UR-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

URINE

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/Q0
24.00	1.351 +- 0.006	1.991	1.47
48.00	2.316 +- 0.008	2.599	1.12
72.00	3.110 +- 0.010	3.180	1.02
96.00	3.566 +- 0.011	3.740	1.04
120.00	4.112 +- 0.013	4.278	1.04
144.00	4.624 +- 0.015	4.795	1.03
168.00	5.206 +- 0.016	5.294	1.01
192.00	5.834 +- 0.019	5.775	0.99
216.00	6.577 +- 0.021	6.237	0.94

TABLE:DW-SB-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

SMALL BOWEL

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)		CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.87	18.679 +-	0.162	13.469	0.72
1.50	11.068 +-	0.103	14.016	1.26
2.62	11.811 +-	0.108	12.204	1.03
3.67	10.166 +-	0.096	10.382	1.02
4.67	9.320 +-	0.089	8.958	0.96
5.58	8.404 +-	0.083	7.908	0.94
6.80	7.883 +-	0.079	6.802	0.86
7.92	6.697 +-	0.068	6.029	0.90
8.67	5.855 +-	0.062	5.614	0.95
9.52	5.785 +-	0.063	5.226	0.90
10.65	4.811 +-	0.056	4.821	1.00
11.63	3.893 +-	0.046	4.550	1.16
20.07	3.269 +-	0.046	3.703	1.13
23.00	3.883 +-	0.053	3.613	0.93
48.00	2.234 +-	0.035	2.286	1.02
72.00	1.327 +-	0.024	1.163	0.87
96.00	1.039 +-	0.022	0.743	0.71
120.00	0.598 +-	0.017	0.636	1.06
144.00	0.591 +-	0.017	0.618	1.04
168.00	0.678 +-	0.021	0.619	0.91
192.00	0.535 +-	0.025	0.621	1.16
216.00	0.605 +-	0.035	0.620	1.02

TABLE:DW-LI-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

LIVER

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
1.50	1.489 +- 0.020	0.840	0.56
2.62	1.659 +- 0.022	1.372	0.82
3.67	2.222 +- 0.028	1.758	0.79
4.67	2.904 +- 0.040	2.047	0.70
5.58	3.653 +- 0.047	2.256	0.61
6.80	2.945 +- 0.041	2.476	0.84
7.92	3.077 +- 0.042	2.629	0.85
8.67	3.114 +- 0.043	2.712	0.87
9.52	3.093 +- 0.044	2.790	0.90
9.88	3.250 +- 0.046	2.819	0.86
10.65	3.246 +- 0.046	2.874	0.88
11.63	3.381 +- 0.049	2.931	0.86
20.07	3.323 +- 0.051	3.153	0.94
23.00	3.321 +- 0.052	3.184	0.95
48.00	3.611 +- 0.054	3.331	0.92
72.00	3.434 +- 0.048	3.422	0.99
96.00	3.560 +- 0.054	3.481	0.97
120.00	2.937 +- 0.039	3.513	1.19
144.00	3.767 +- 0.050	3.522	0.93
168.00	3.465 +- 0.060	3.512	1.01
192.00	3.569 +- 0.068	3.486	0.97
216.00	3.593 +- 0.076	3.446	0.95

TABLE:DW-ST-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

'SOFT' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.87	0.032 +- 0.003	0.007	0.21
1.50	0.034 +- 0.003	0.016	0.46
2.62	0.042 +- 0.003	0.030	0.71
3.67	0.043 +- 0.004	0.041	0.94
4.67	0.046 +- 0.004	0.049	1.05
5.58	0.043 +- 0.004	0.055	1.27
6.80	0.080 +- 0.004	0.061	0.75
7.92	0.086 +- 0.004	0.065	0.75
8.67	0.117 +- 0.004	0.067	0.57
9.52	0.056 +- 0.004	0.069	1.23
9.88	0.069 +- 0.004	0.070	1.01
10.65	0.047 +- 0.004	0.072	1.50
11.63	0.076 +- 0.005	0.073	0.95
20.07	0.055 +- 0.005	0.077	1.39
23.00	0.084 +- 0.005	0.078	0.92
48.00	0.077 +- 0.005	0.076	0.98
72.00	0.068 +- 0.007	0.074	1.09
96.00	0.076 +- 0.009	0.072	0.94
120.00	0.055 +- 0.010	0.070	1.24
144.00	0.128 +- 0.012	0.067	0.52

TABLE:DW-HT-1

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:1.

'HARD' TISSUE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%P.I.D.)	CALCULATED RESULTS(QC) (%P.I.D.)	QC/QO
0.87	0.011 +- 0.003	0.004	0.37
2.62	0.017 +- 0.003	0.019	1.10
3.67	0.029 +- 0.003	0.026	0.88
4.67	0.028 +- 0.003	0.031	1.08
5.58	0.030 +- 0.004	0.035	1.15
6.80	0.041 +- 0.004	0.040	0.95
7.92	0.044 +- 0.004	0.043	0.96
8.67	0.045 +- 0.004	0.045	0.97
9.52	0.048 +- 0.004	0.047	0.96
9.88	0.048 +- 0.004	0.047	0.98
10.65	0.056 +- 0.004	0.049	0.85
11.63	0.057 +- 0.004	0.050	0.87
20.07	0.048 +- 0.005	0.060	1.24
23.00	0.062 +- 0.005	0.063	0.99
48.00	0.103 +- 0.006	0.083	0.79
72.00	0.115 +- 0.007	0.101	0.87
96.00	0.141 +- 0.009	0.119	0.84
120.00	0.112 +- 0.010	0.136	1.21
144.00	0.164 +- 0.013	0.153	0.92
168.00	0.159 +- 0.017	0.169	1.05
192.00	0.186 +- 0.023	0.184	0.98
216.00	0.168 +- 0.033	0.199	1.18

TABLE:DW-WB-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:2.

WHOLE BODY

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)		CALCULATED RESULTS(QC) (%I.D.)	QC/QO
6.00	100.000 +-	0.215	99.941	1.00
24.00	70.175 +-	0.171	78.044	1.11
48.00	20.857 +-	0.838	21.292	1.02
72.00	6.114 +-	0.066	3.944	0.64
96.00	1.651 +-	0.062	1.167	0.70
120.00	0.594 +-	0.078	0.776	1.30

TABLE:DW-RC-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:2.

RED CELLS

TIME (HRS)	EXPERIMENTAL DATA(Q0) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/Q0
1.00	0.020 +- 0.001	0.013	0.62
2.00	0.035 +- 0.001	0.036	0.99
3.00	0.070 +- 0.001	0.059	0.83
5.00	0.113 +- 0.001	0.099	0.87
7.00	0.145 +- 0.001	0.133	0.91
16.00	0.228 +- 0.001	0.229	1.00
20.00	0.219 +- 0.001	0.253	1.15
24.00	0.233 +- 0.001	0.269	1.14
48.00	0.293 +- 0.001	0.296	1.00
72.00	0.316 +- 0.002	0.291	0.92
96.00	0.312 +- 0.002	0.283	0.90
120.00	0.300 +- 0.003	0.276	0.91
144.00	0.335 +- 0.004	0.270	0.80
168.00	0.335 +- 0.007	0.263	0.78
240.00	0.300 +- 0.015	0.247	0.82

TABLE:DW-UR-2

COMPARISON OF EXPERIMENTAL DATA AND CALCULATED VALUES

FROM COMPARTMENTAL ANALYSIS

SUBJECT:D.W. KINETIC:2.

URINE

TIME (HRS)	EXPERIMENTAL DATA(QO) (%I.D.)	CALCULATED RESULTS(QC) (%I.D.)	QC/QO
24.00	0.010 +- 0.000	0.013	1.27
48.00	0.015 +- 0.000	0.019	1.25
72.00	0.022 +- 0.000	0.024	1.06
96.00	0.025 +- 0.000	0.029	1.14
120.00	0.034 +- 0.000	0.034	0.98
144.00	0.038 +- 0.000	0.038	0.99
168.00	0.042 +- 0.000	0.043	1.01
192.00	0.051 +- 0.000	0.047	0.92
216.00	0.055 +- 0.000	0.051	0.92

SECTION 13

FIGURES

Figures

The figures in this section show the fits between experimental data and calculated values found from the compartmental analysis of the data from kinetic experiments performed in section 8.0.

They are listed in subject order,

K.B., J.B., B.C., G.E. and D.W.,

experiment order for each subject,

Kinetic 1. and Kinetic 2.,

and compartment order for each experiment,

whole body, plasma, red cells, urine, small bowel, liver,

'soft' tissue and 'hard' tissue.

All figures have been named with the following format.

Subject initials-compartment initials-kinetic experiment

e.g. Subjects K.B.'s small bowel data from Kinetic 1. experiment

KB-SB-1

Abbreviations

hrs - hours

%I.D. - percentage ingested dose

%P.I.D. - percentage proportional ingested dose

FIGURE. KB-WB-1

Fit of calculated values to experimental data

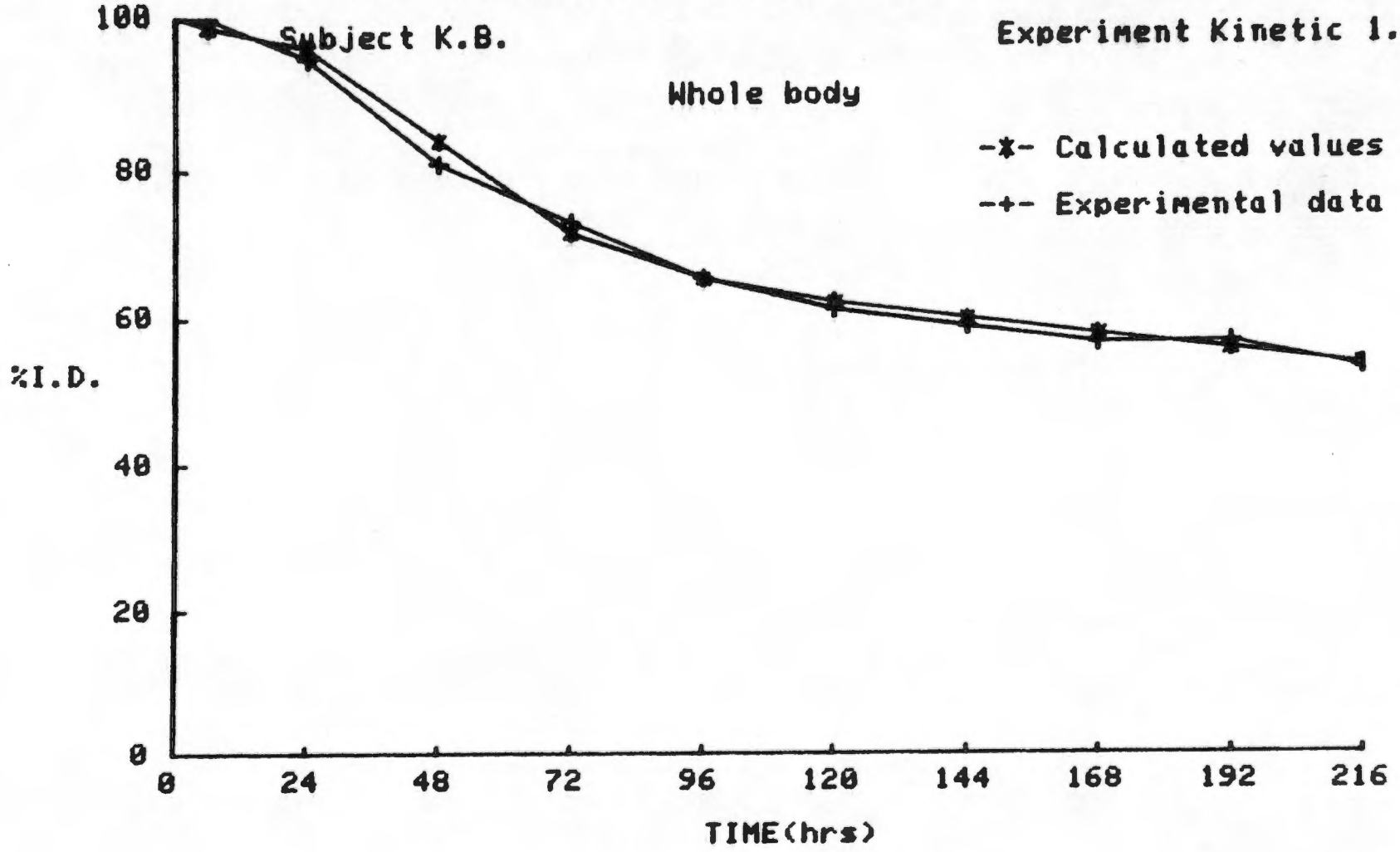


FIGURE. KB-PL-1

Fit of calculated values to experimental data

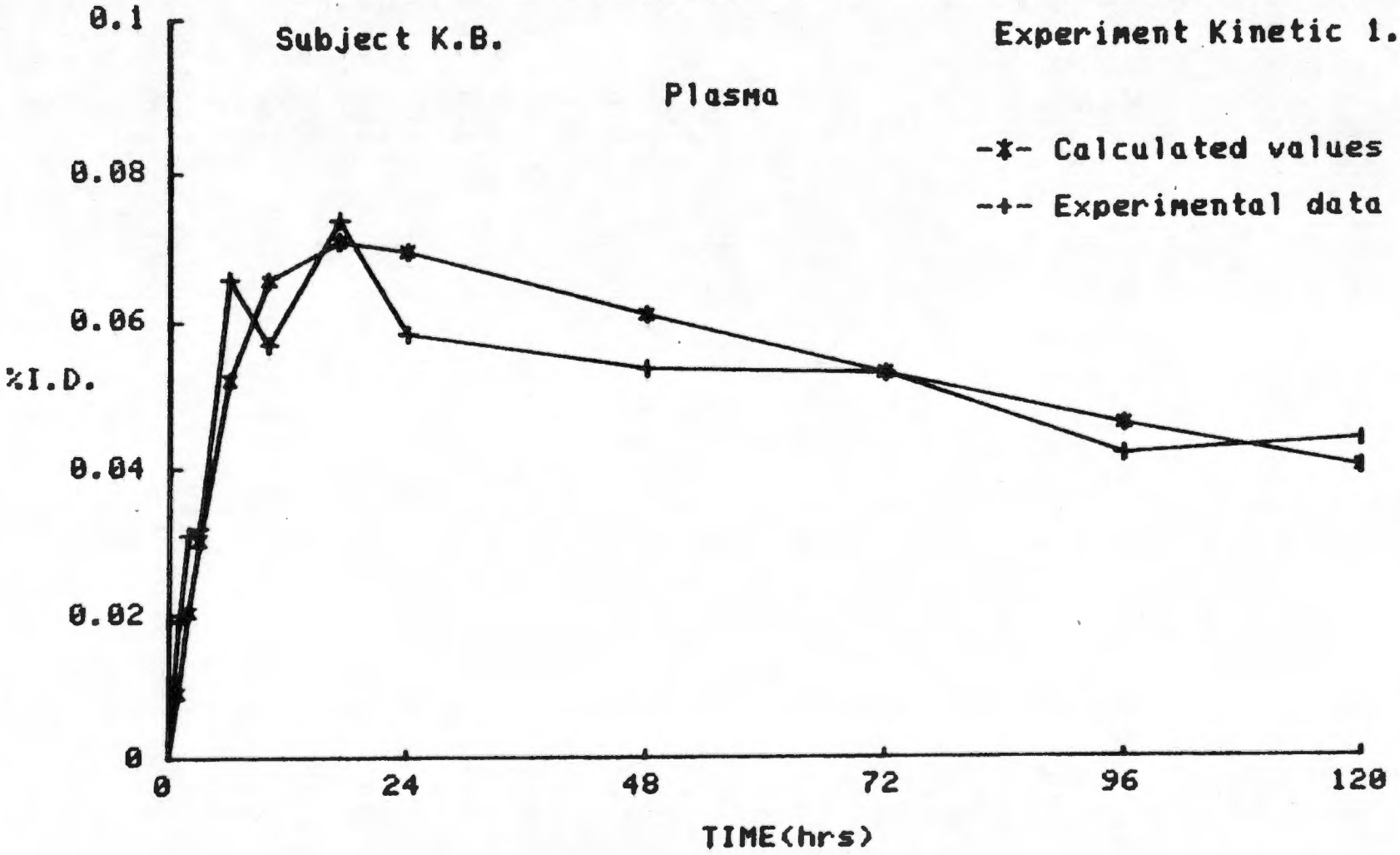


FIGURE. KB-RC-1

Fit of calculated values to experimental data

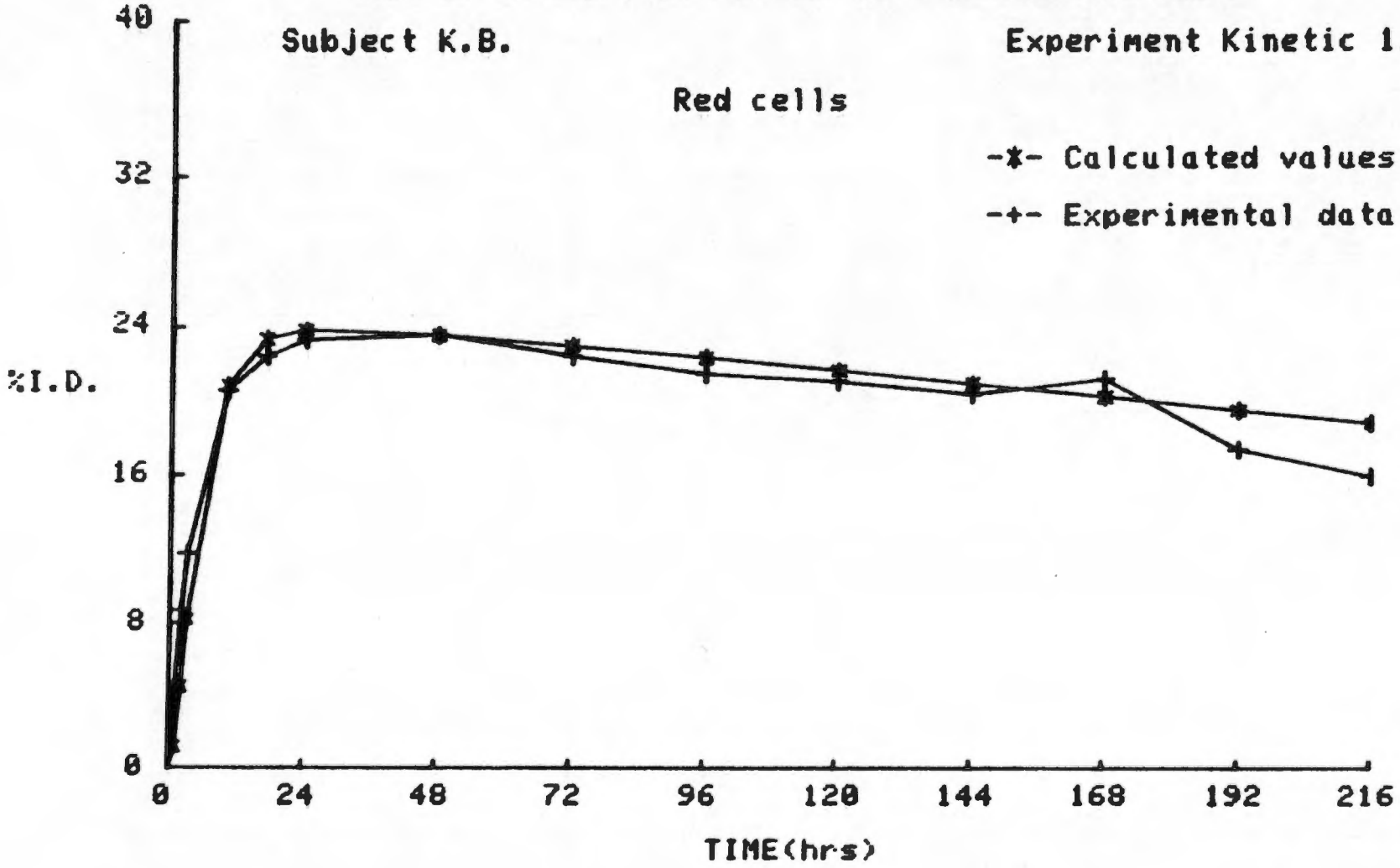


FIGURE. KB-UR-1

Fit of calculated values to experimental data

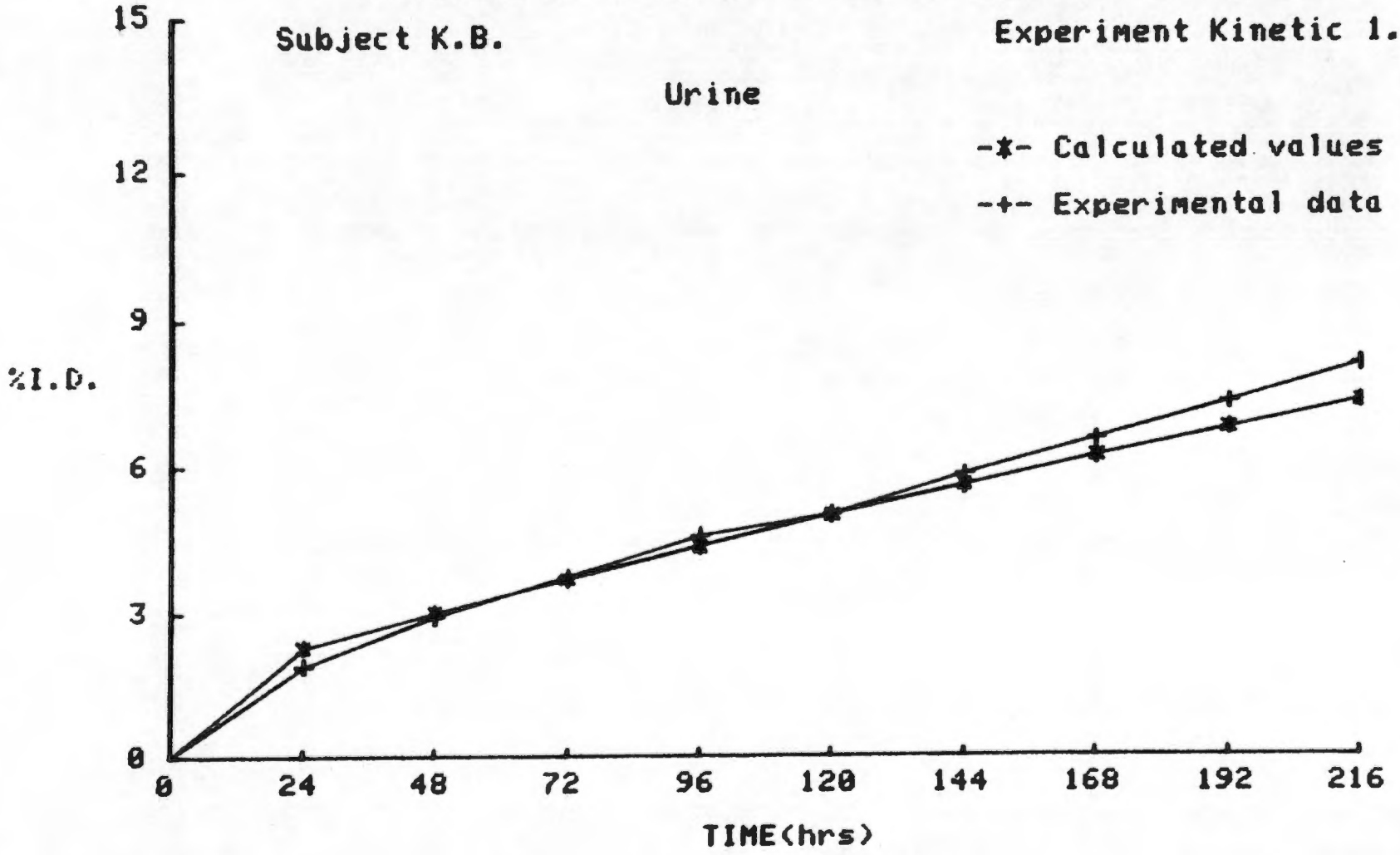


FIGURE. KB-SB-1

Fit of calculated values to experimental data

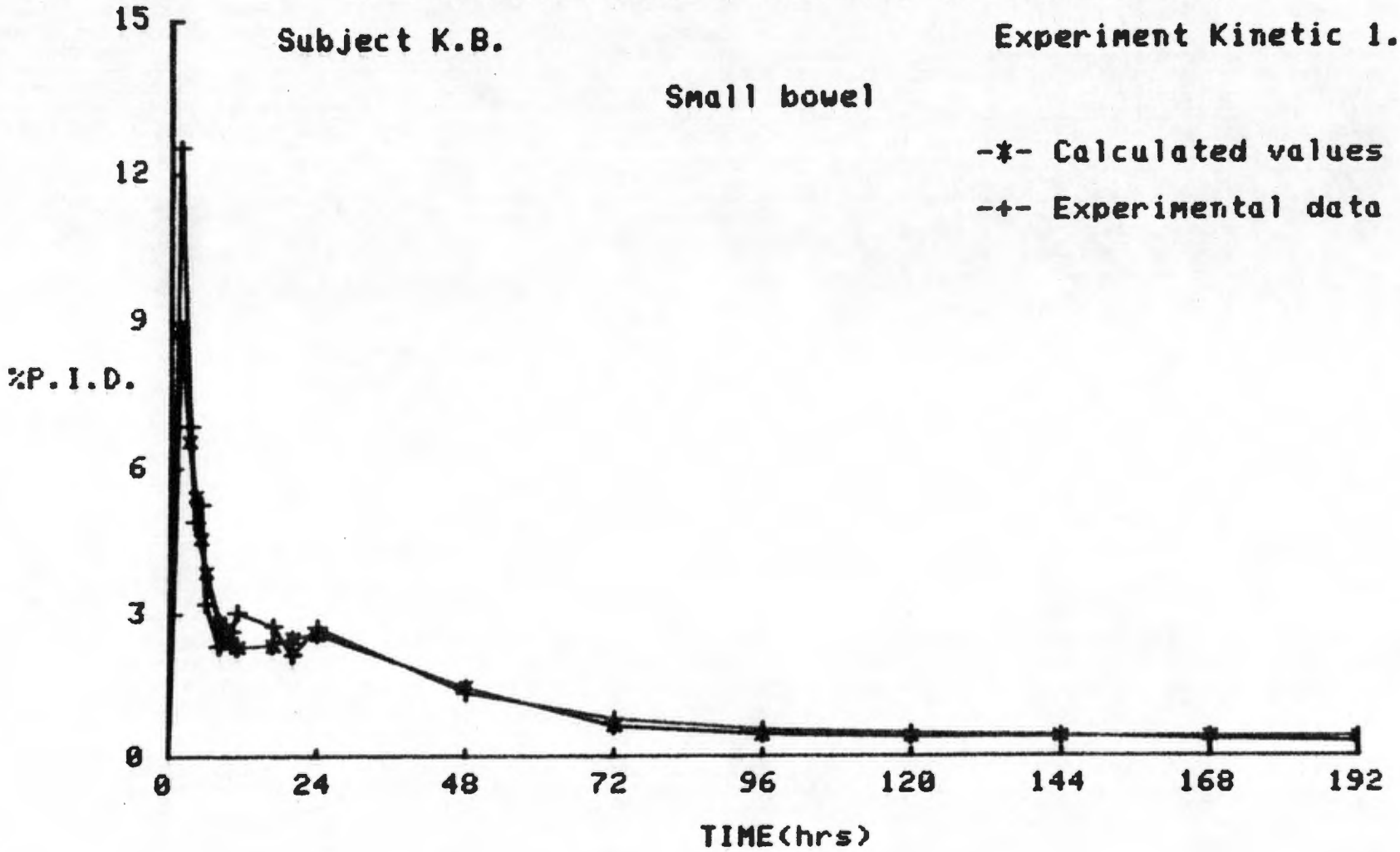


FIGURE. KB-LI-1

Fit of calculated values to experimental data

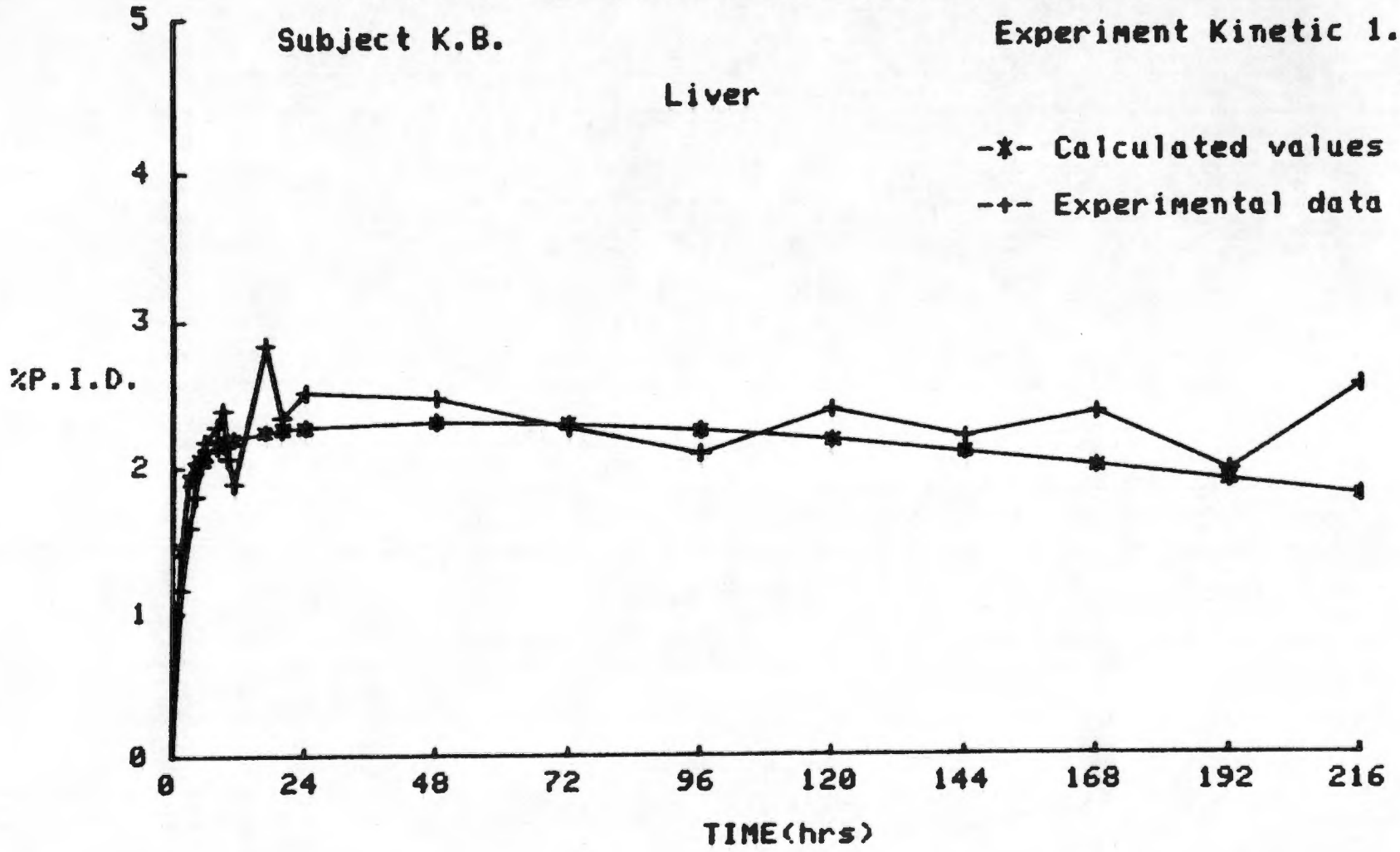


FIGURE. KB-ST-1

Fit of calculated values to experimental data

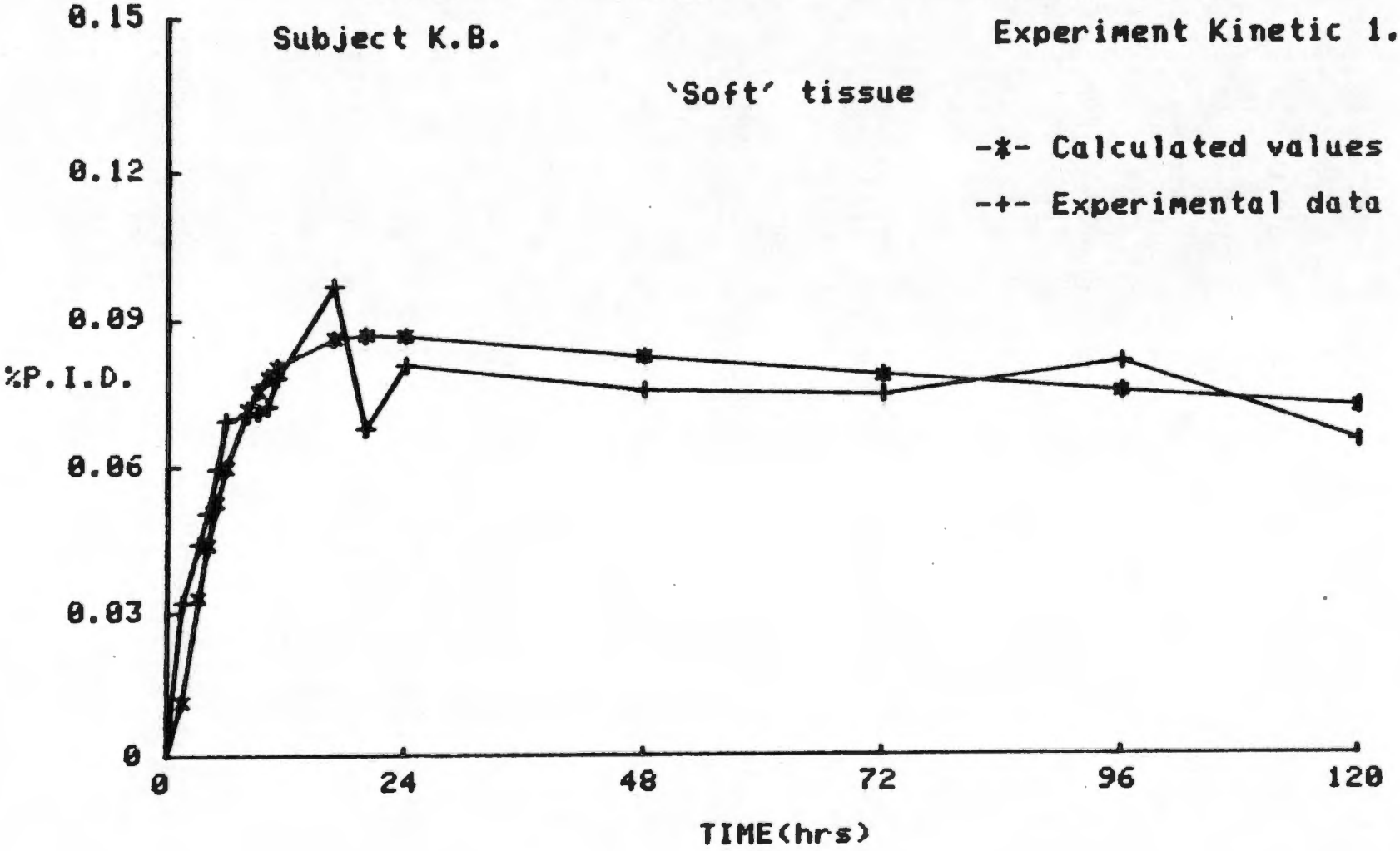


FIGURE. KB-HT-1

Fit of calculated values to experimental data

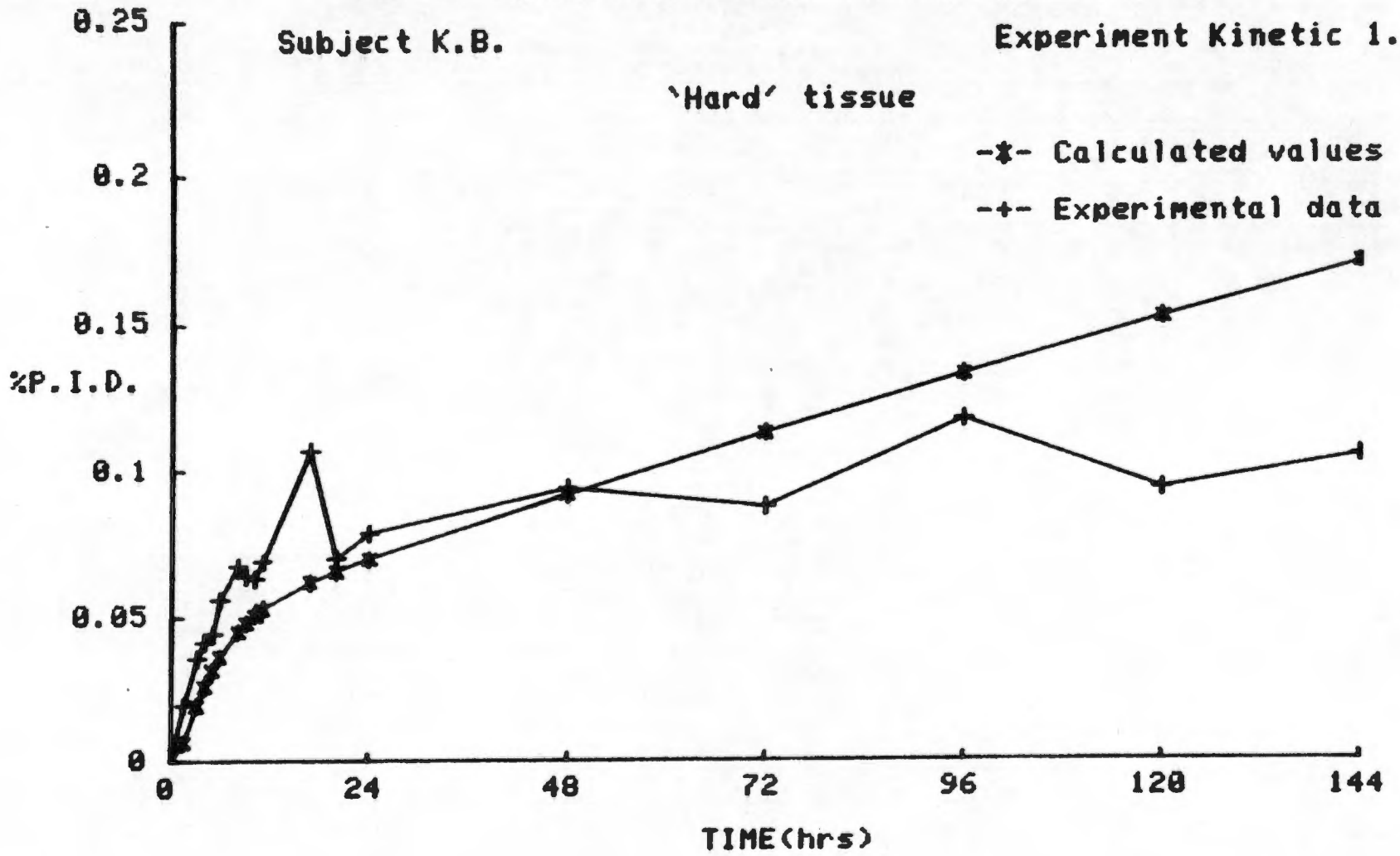


FIGURE. KB-WB-2

Fit of calculated values to experimental data

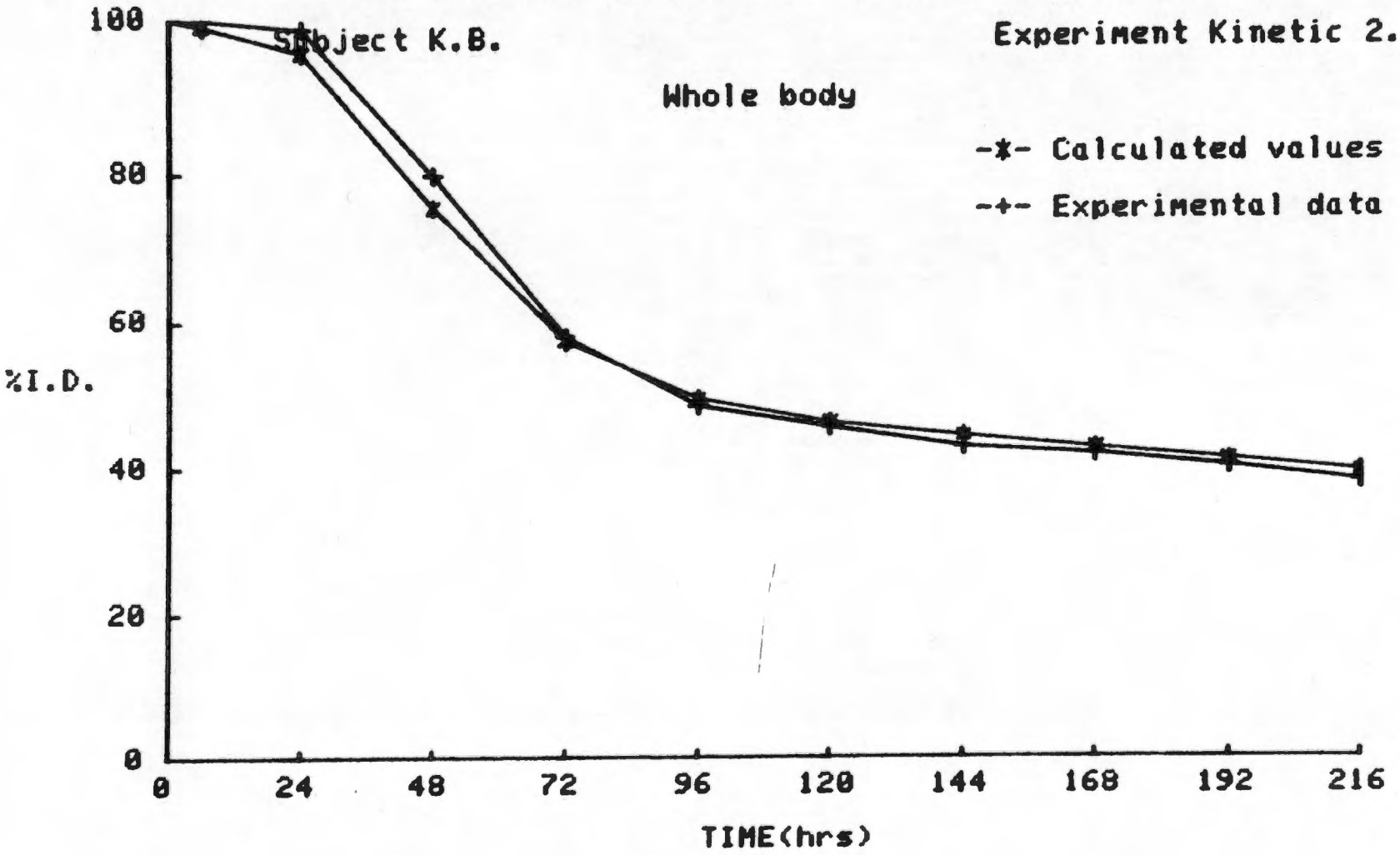


FIGURE. KB-PL-2

Fit of calculated values to experimental data

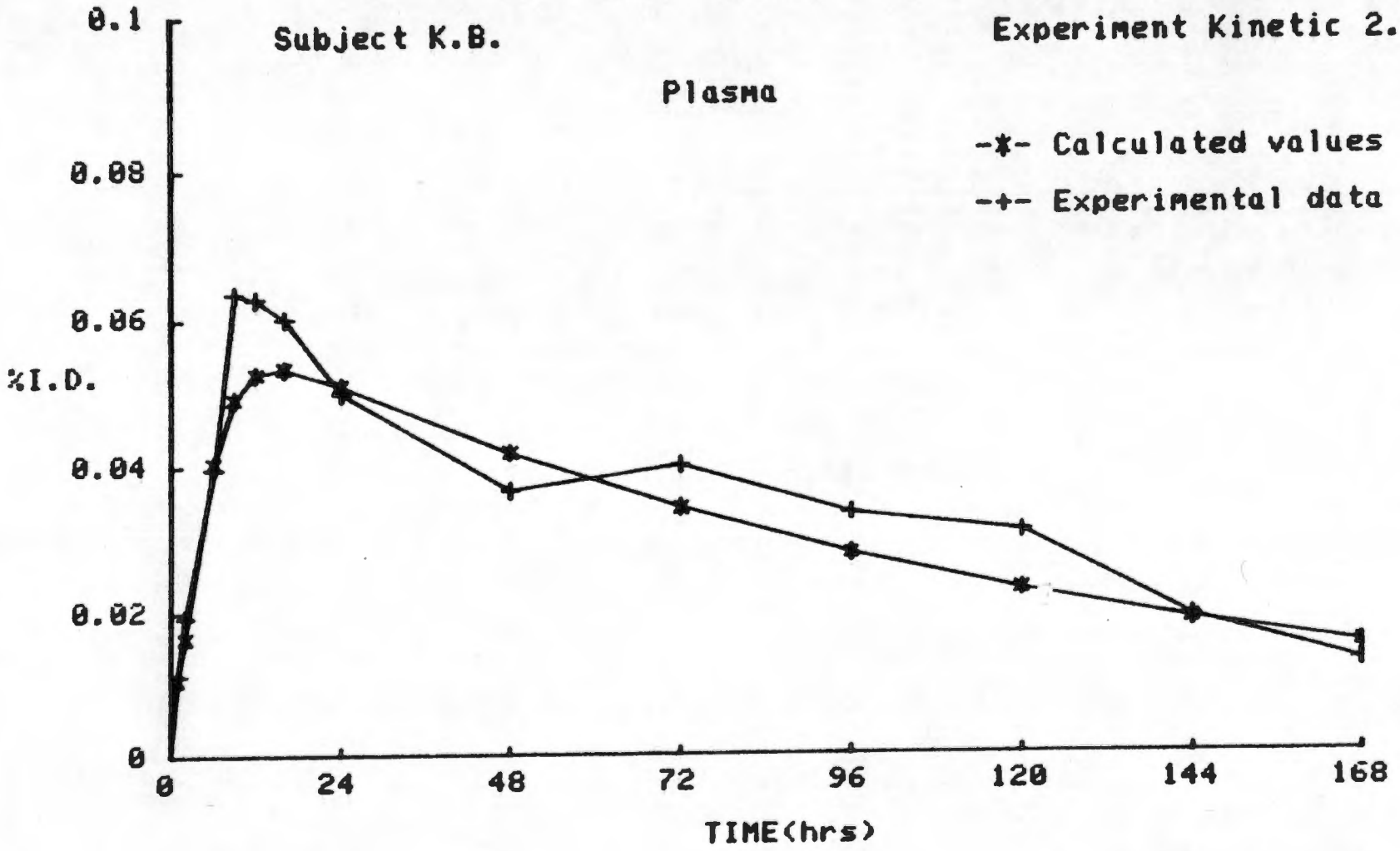


FIGURE. KB-RC-2

Fit of calculated values to experimental data

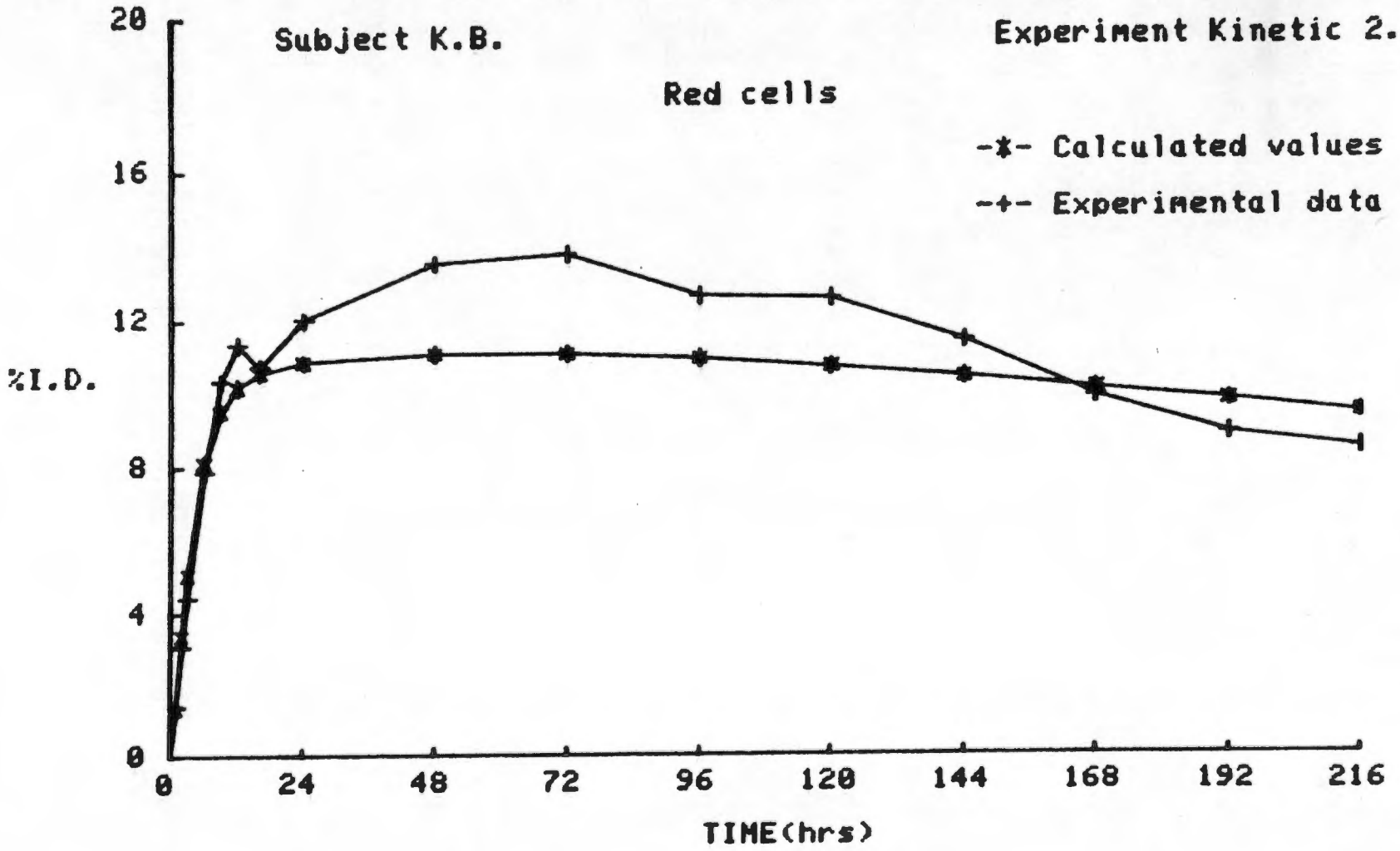


FIGURE. KB-UR-2

Fit of calculated values to experimental data

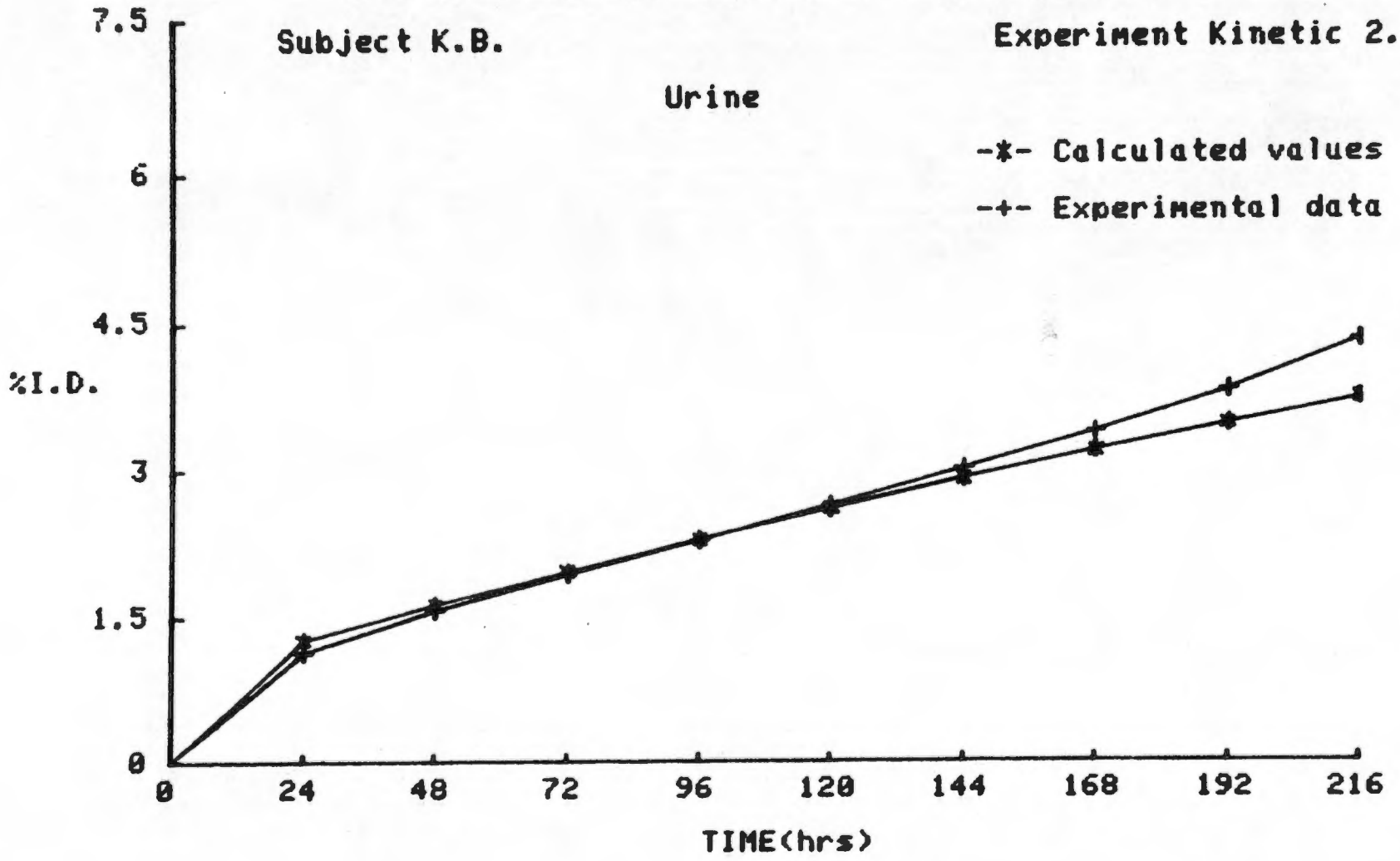


FIGURE. KB-SB-2

Fit of calculated values to experimental data

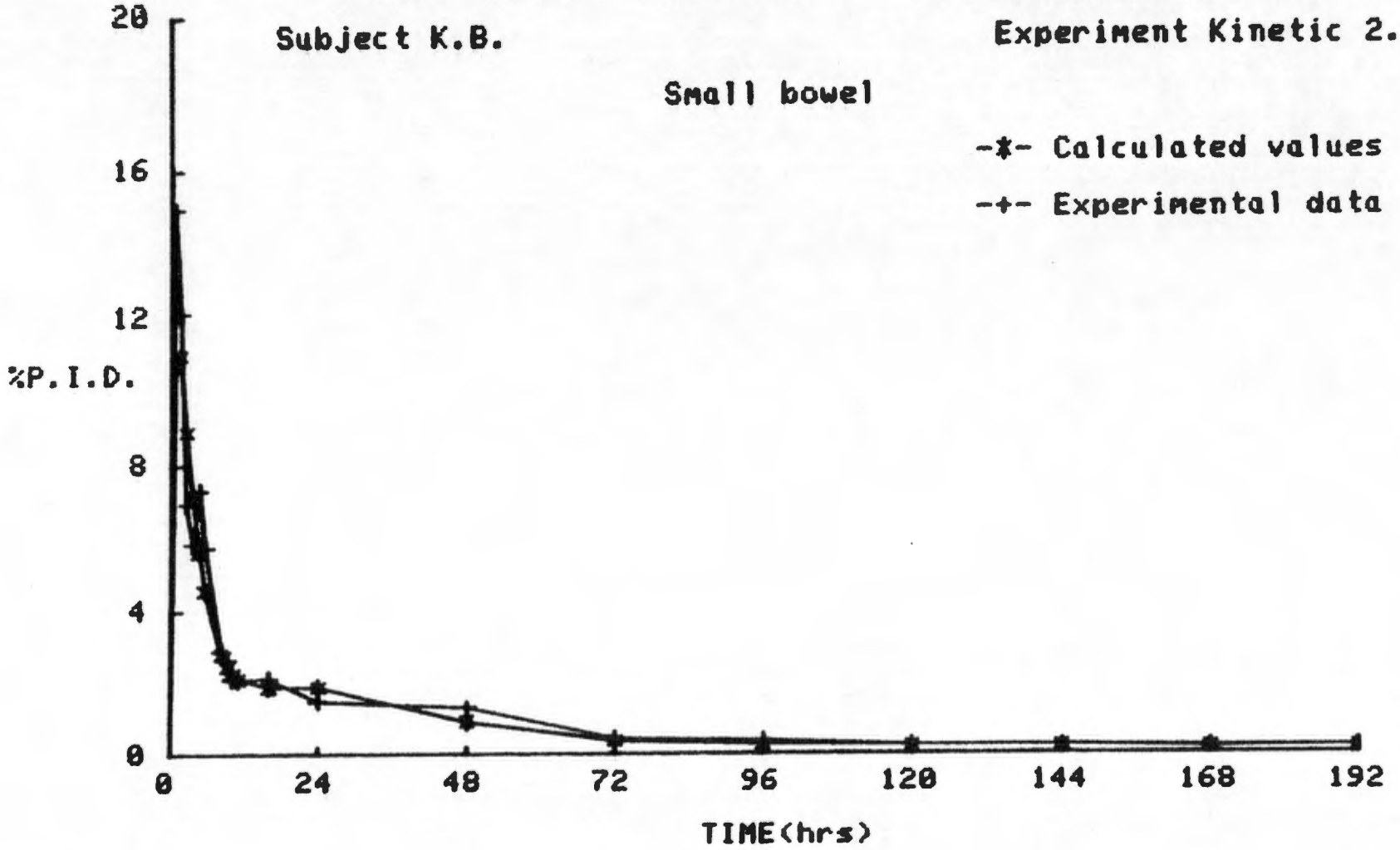


FIGURE. KB-LI-2

Fit of calculated values to experimental data

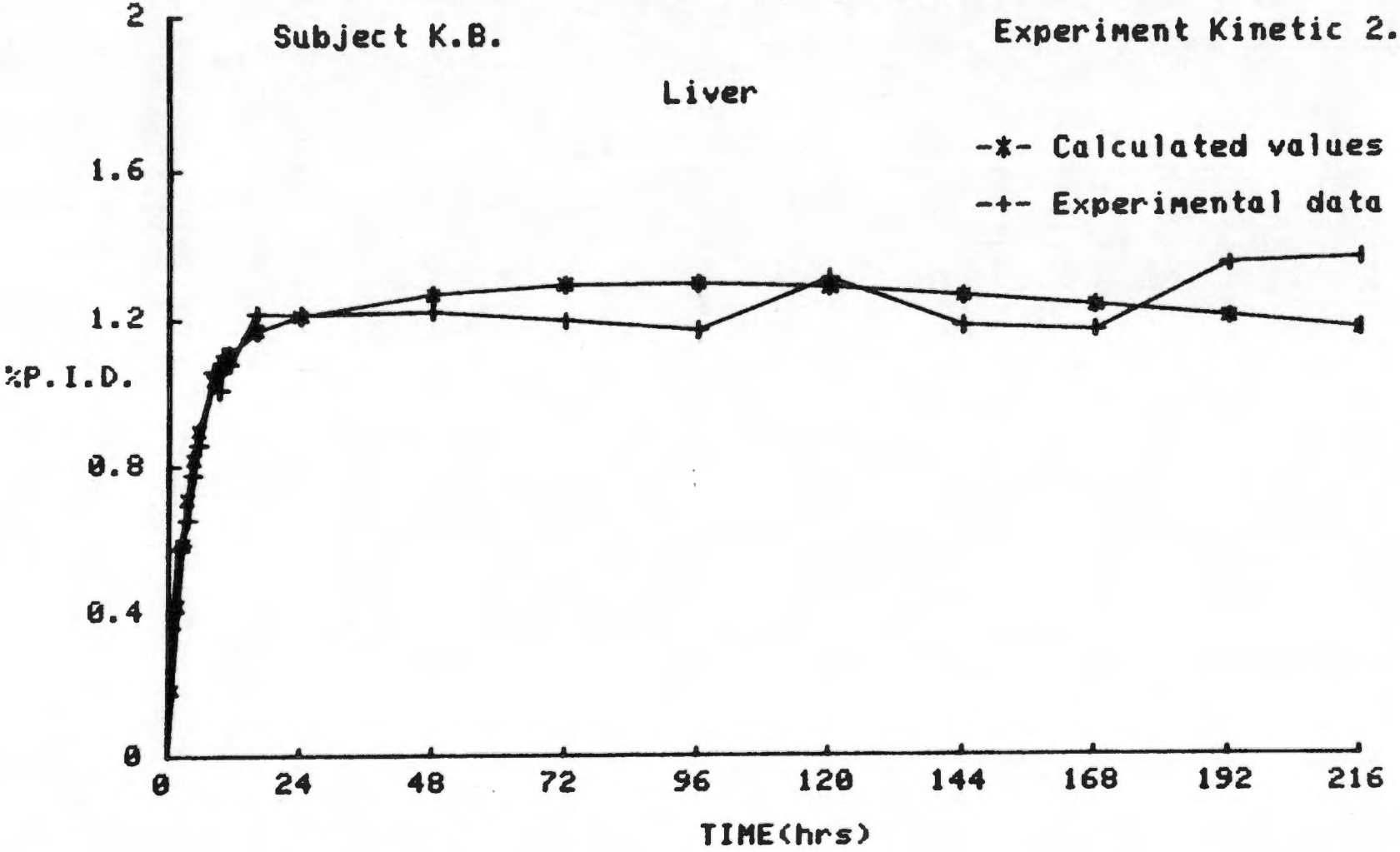


FIGURE. KB-ST-2

Fit of calculated values to experimental data

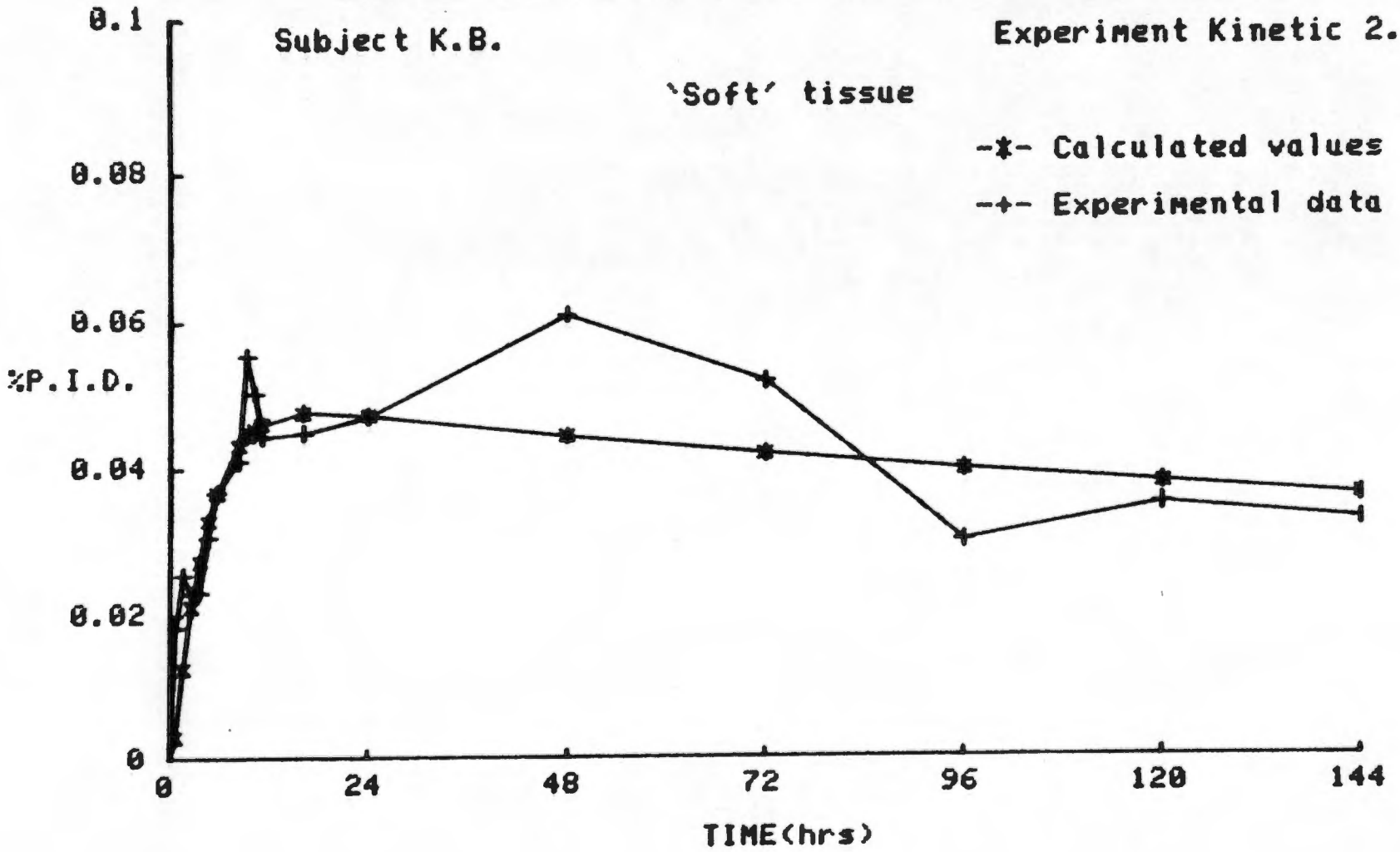


FIGURE. KB-HT-2

Fit of calculated values to experimental data

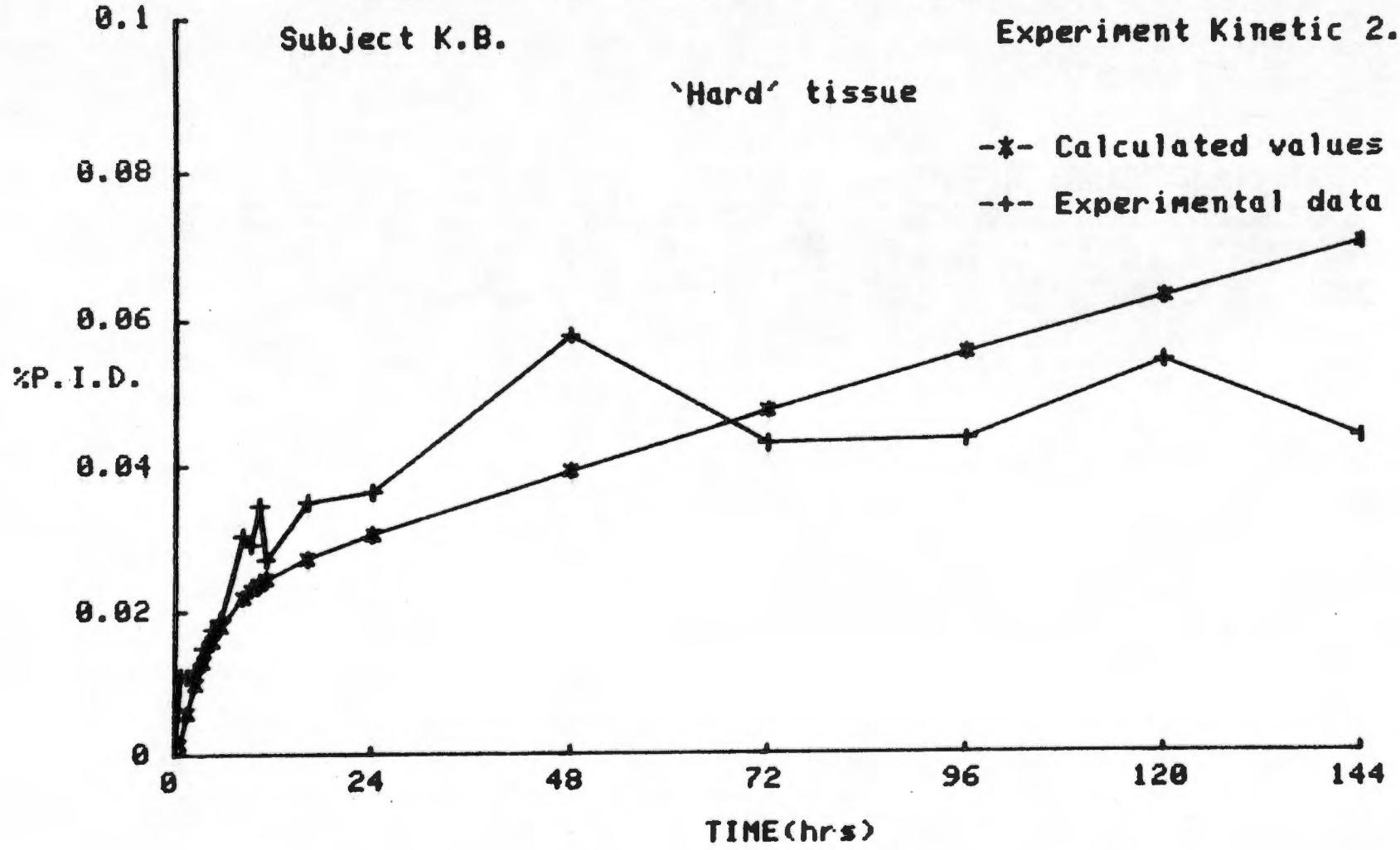


FIGURE. JB-WB-1

Fit of calculated values to experimental data

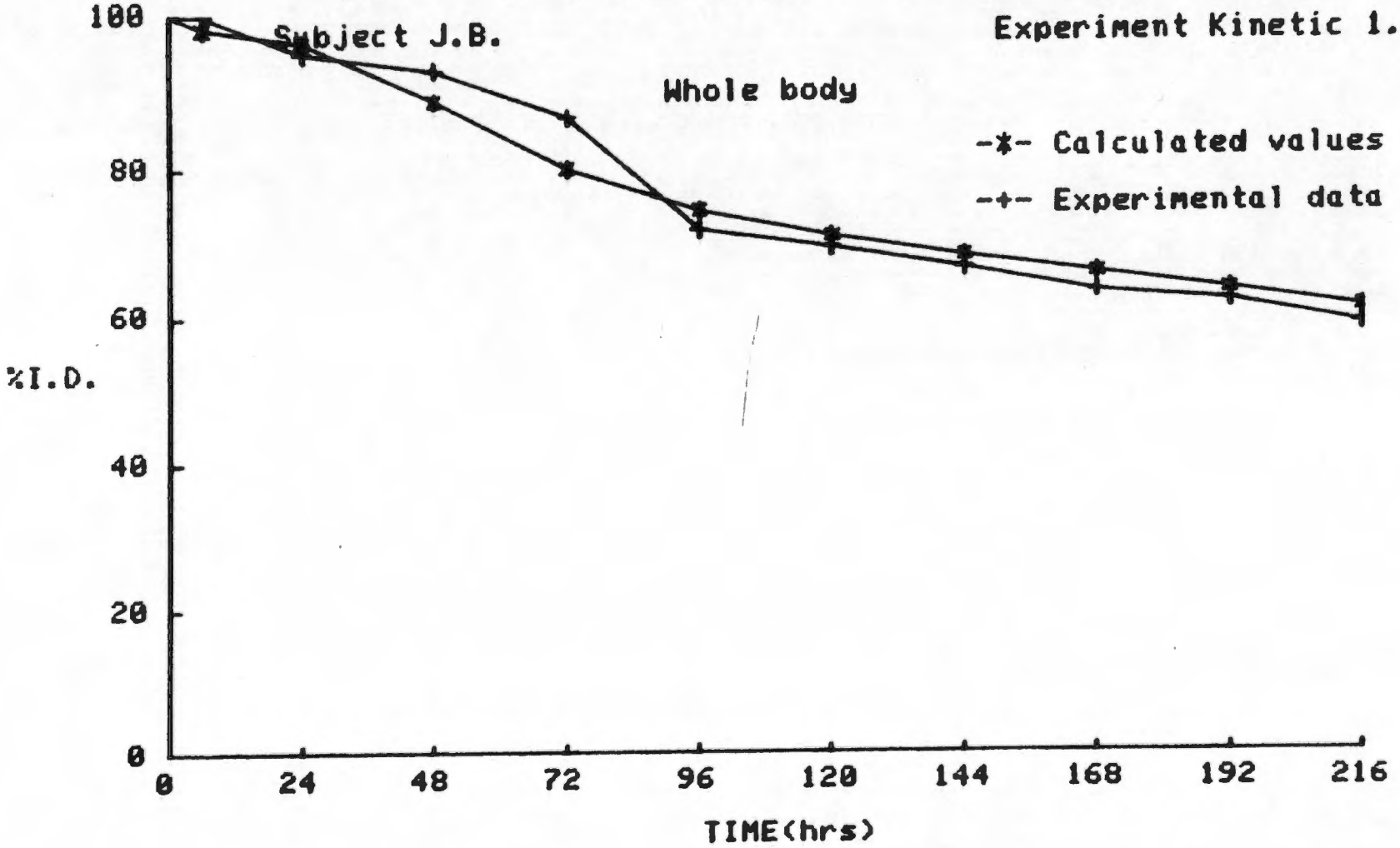


FIGURE. JB-PL-1

Fit of calculated values to experimental data

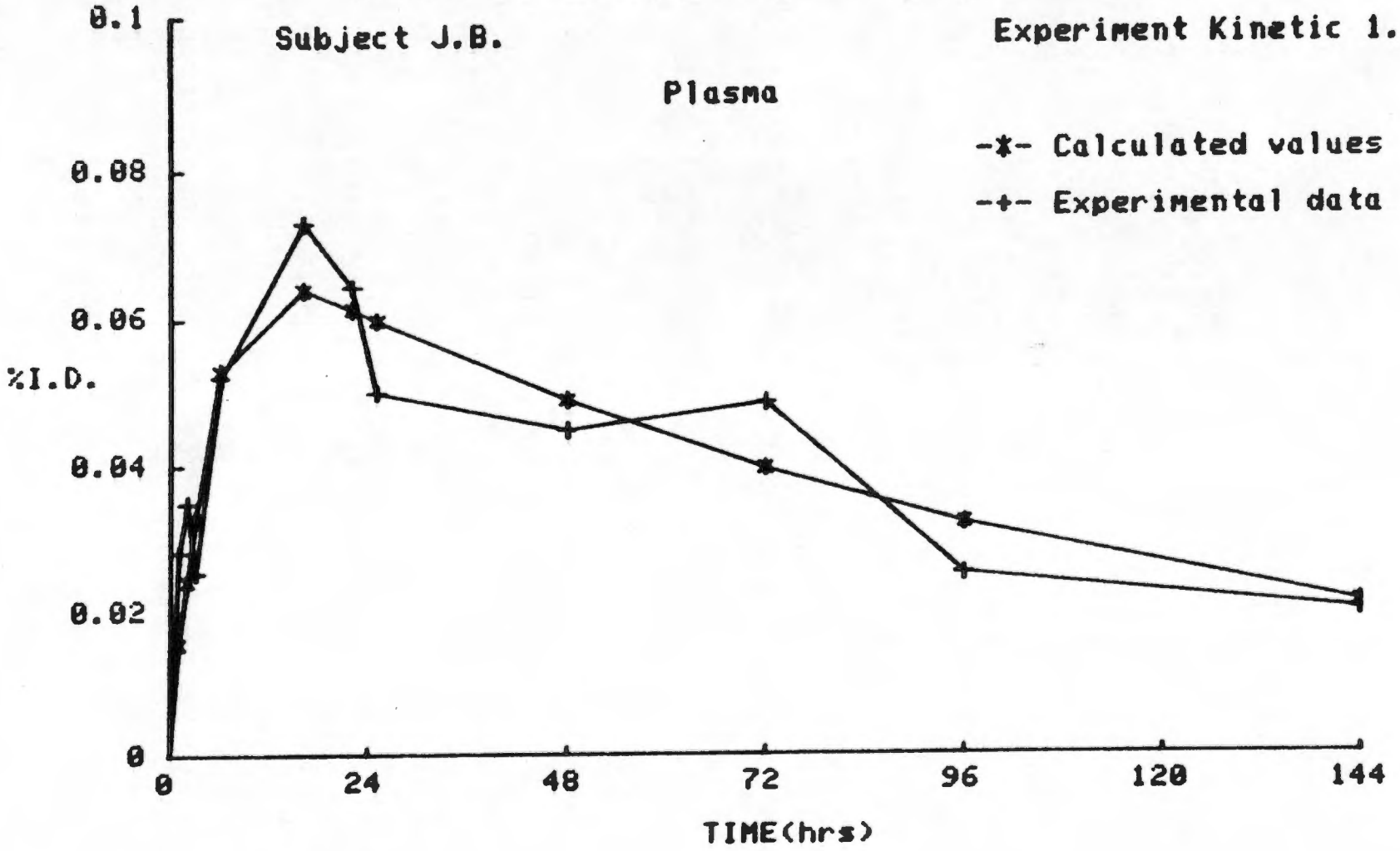


FIGURE. JB-RC-1

Fit of calculated values to experimental data

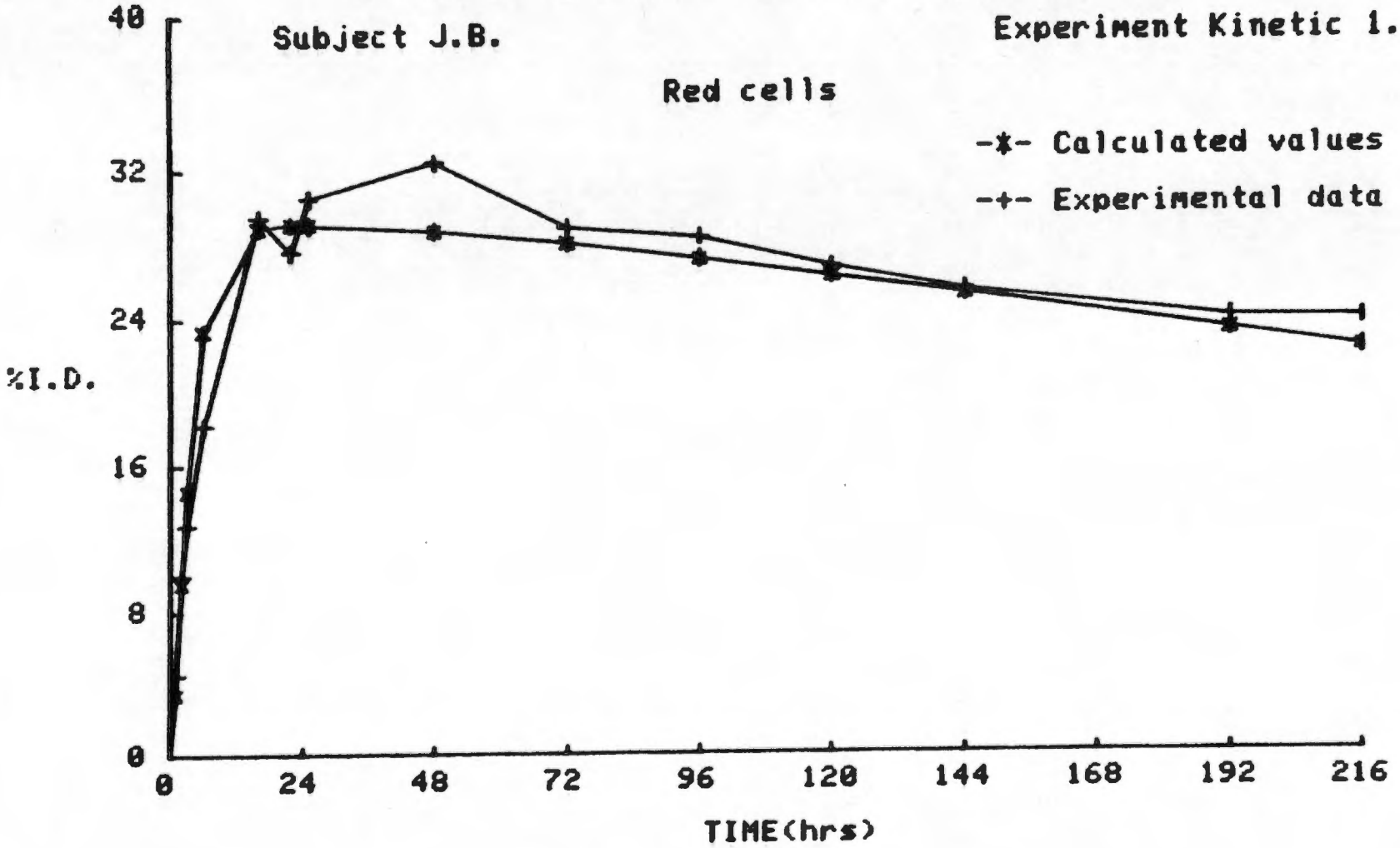


FIGURE. JB-UR-1

Fit of calculated values to experimental data

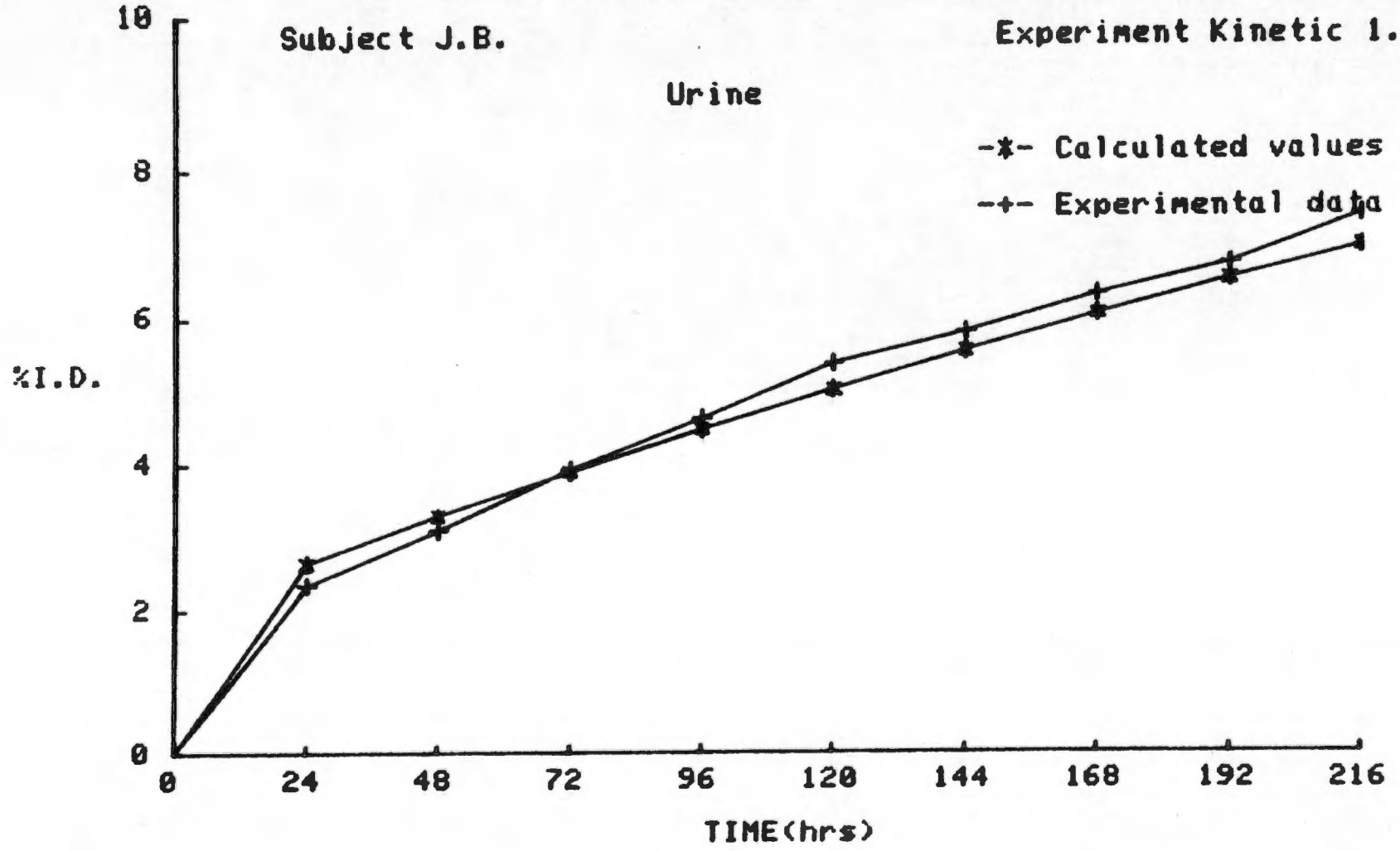


FIGURE. JB-SB-1

Fit of calculated values to experimental data

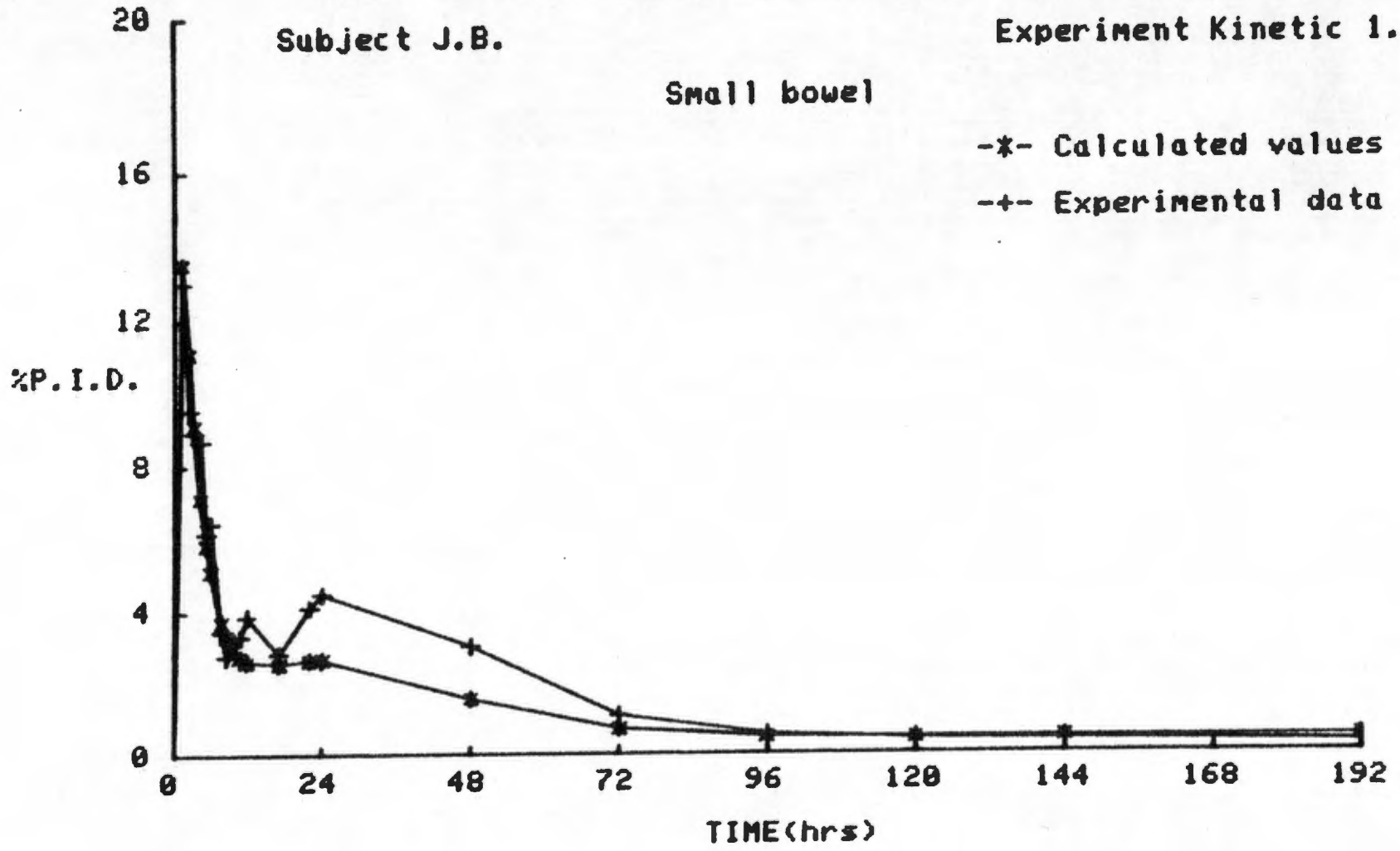


FIGURE. JB-LI-1

Fit of calculated values to experimental data

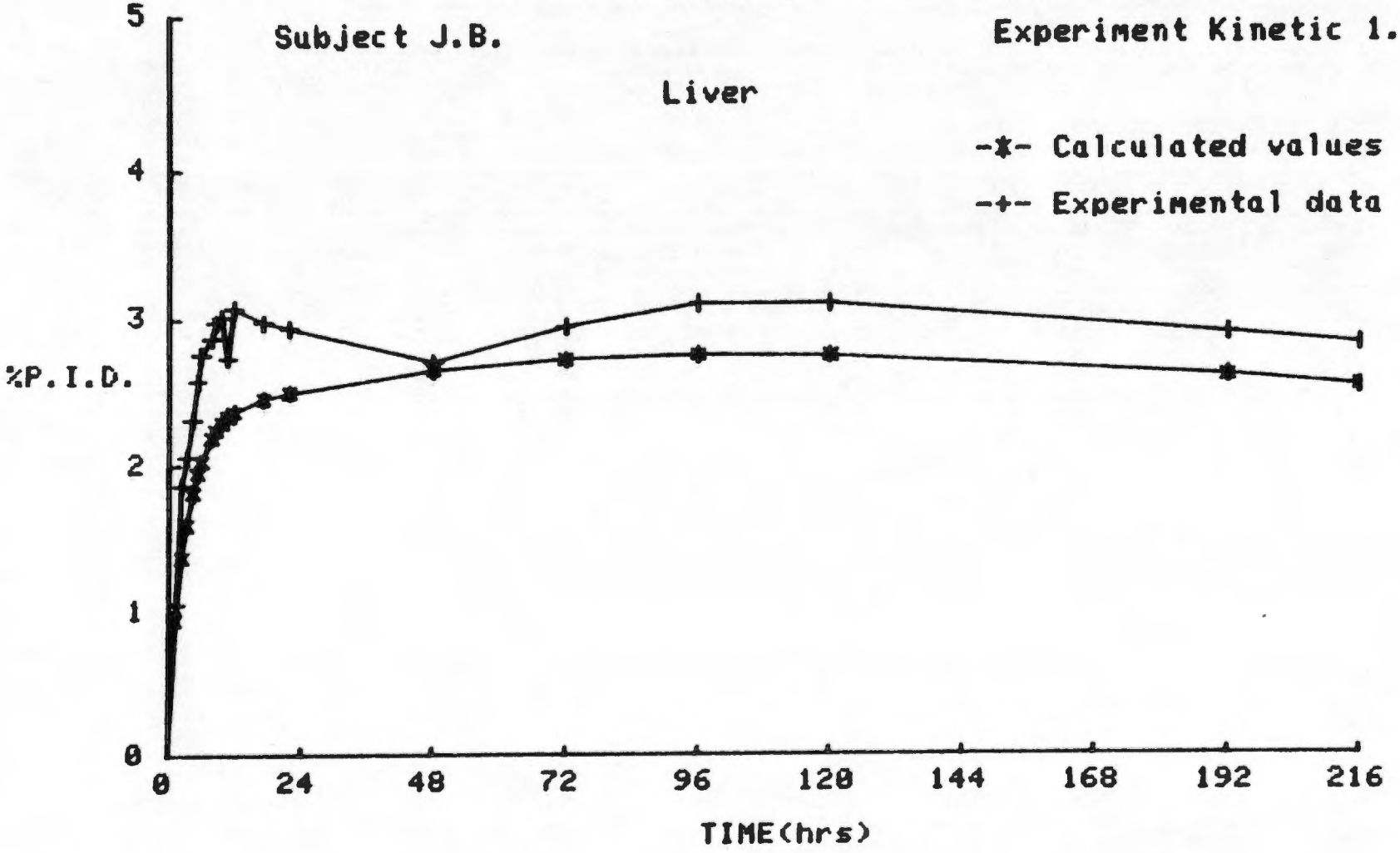


FIGURE. JB-ST-1

Fit of calculated values to experimental data

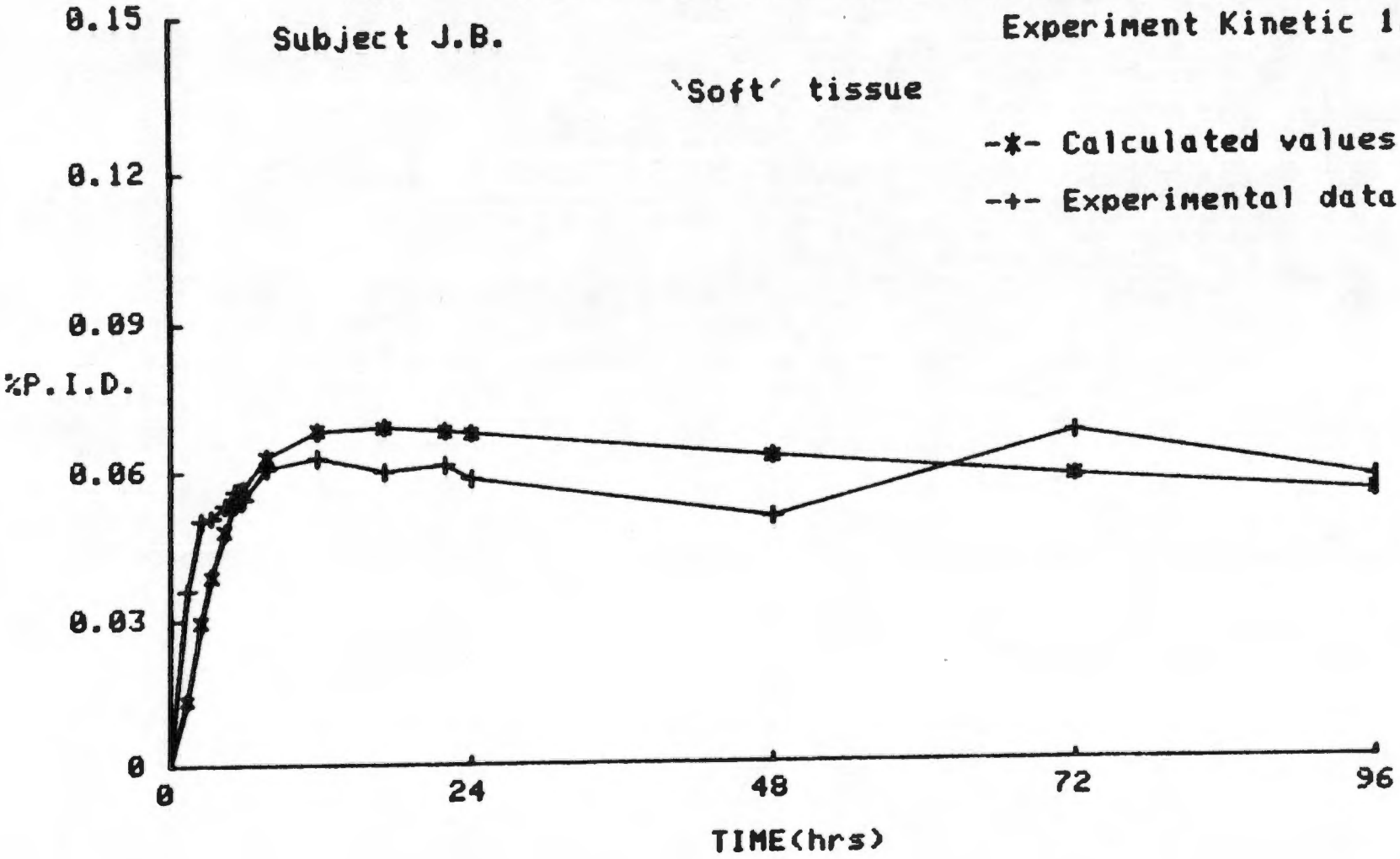


FIGURE. JB-HT-1

Fit of calculated values to experimental data

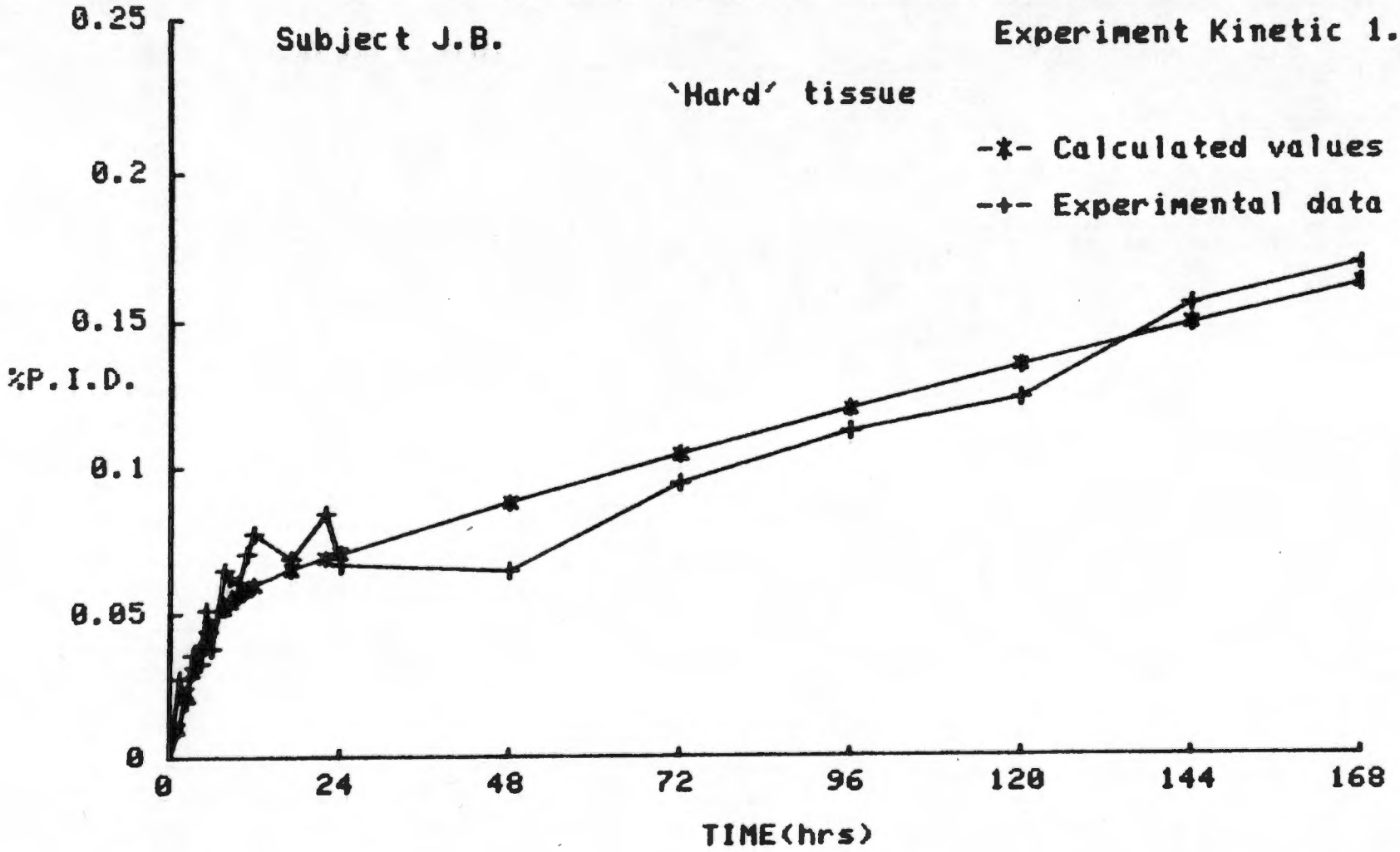


FIGURE. JB-WB-2

Fit of calculated values to experimental data

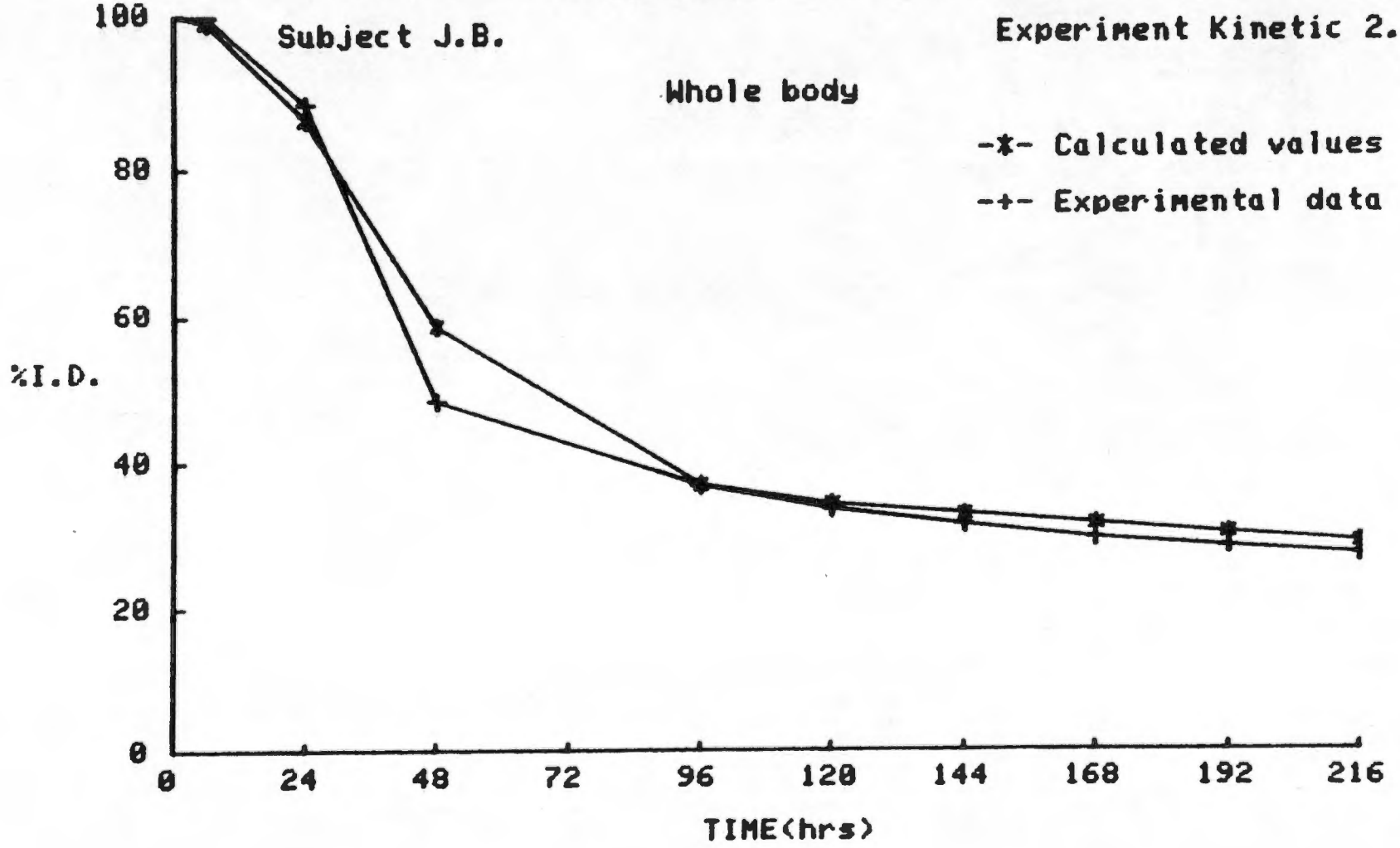


FIGURE. JB-PL-2

Fit of calculated values to experimental data

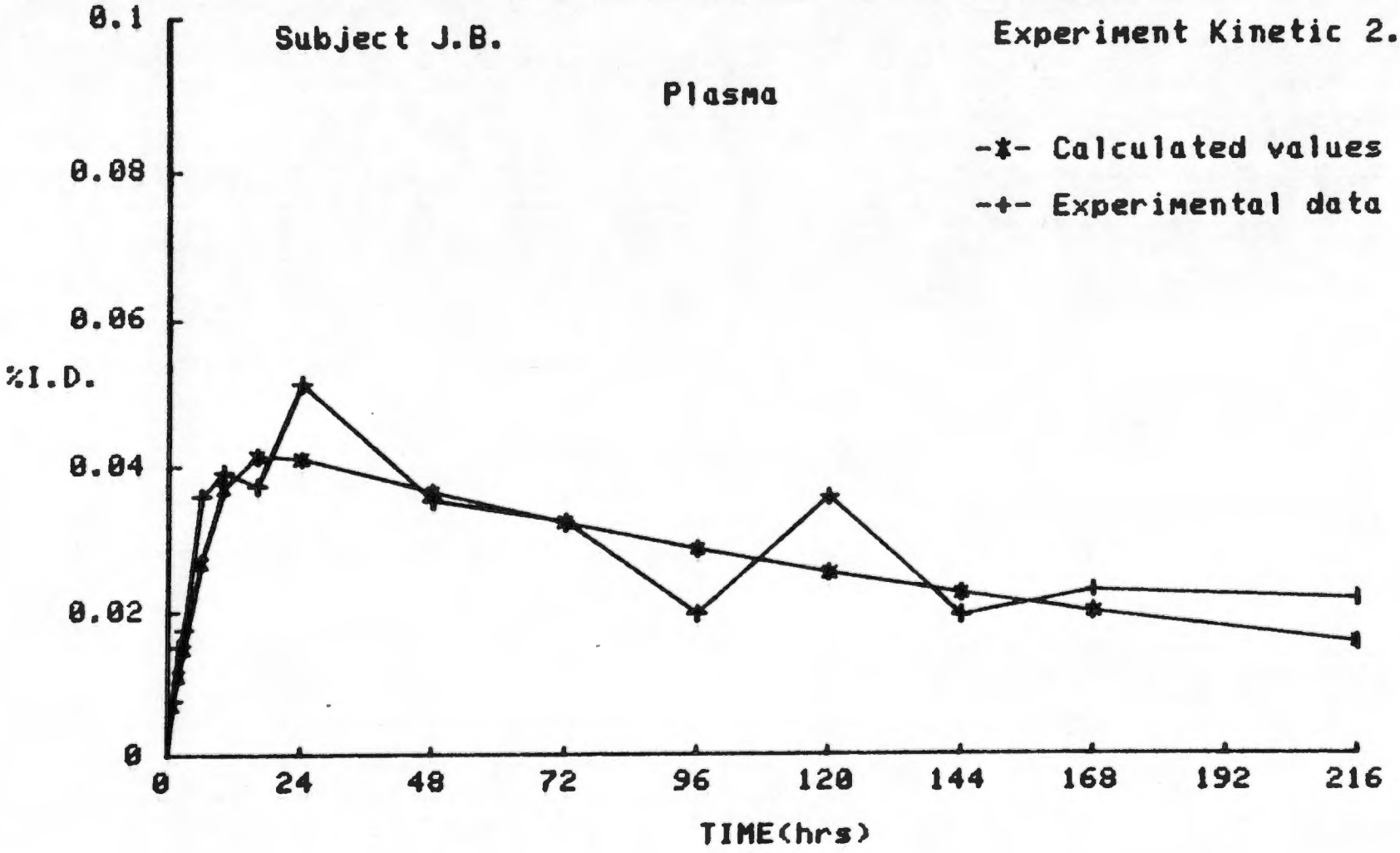


FIGURE. JB-RC-2

Fit of calculated values to experimental data

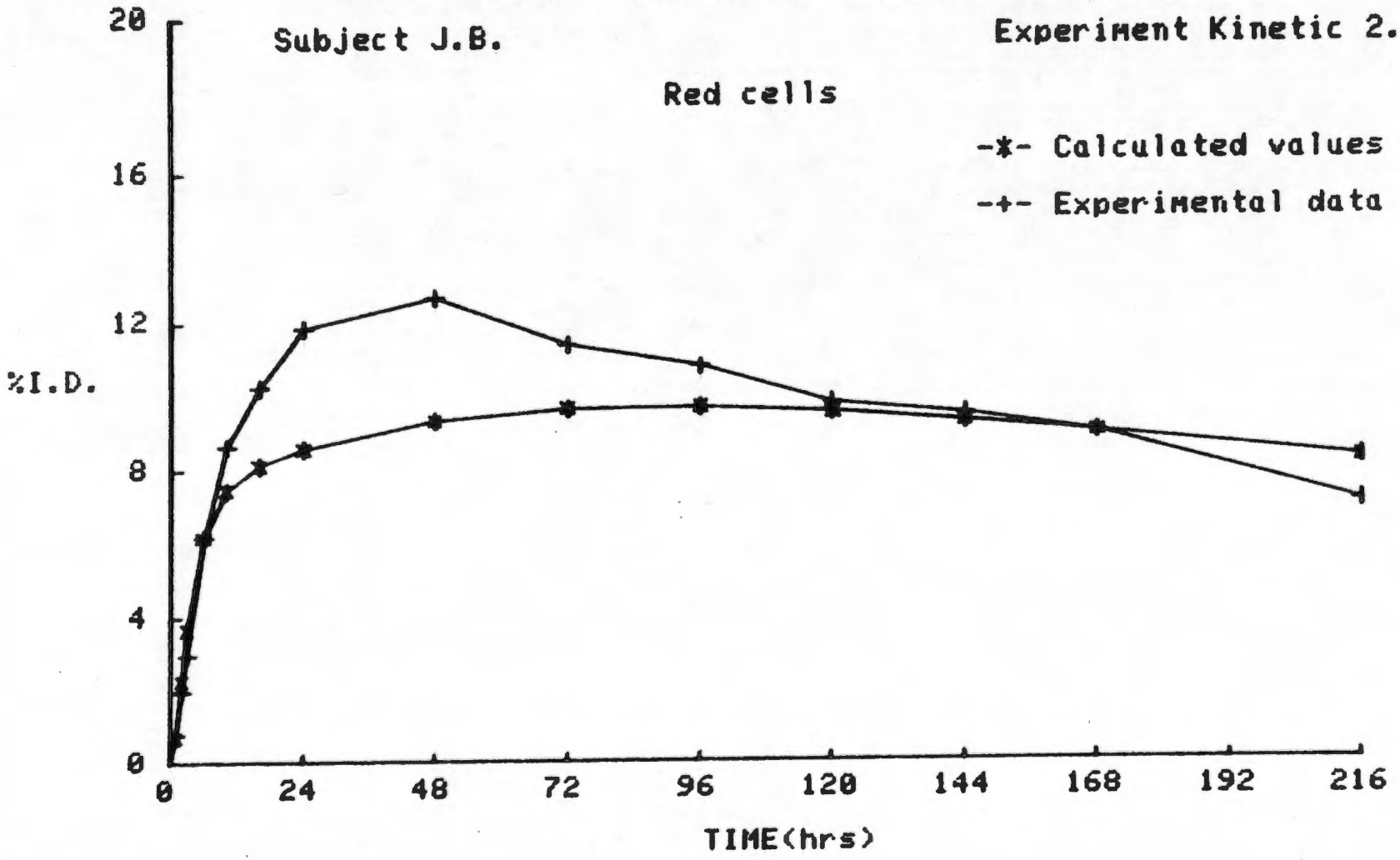


FIGURE. JB-RC-2A

Fit of calculated values to experimental data

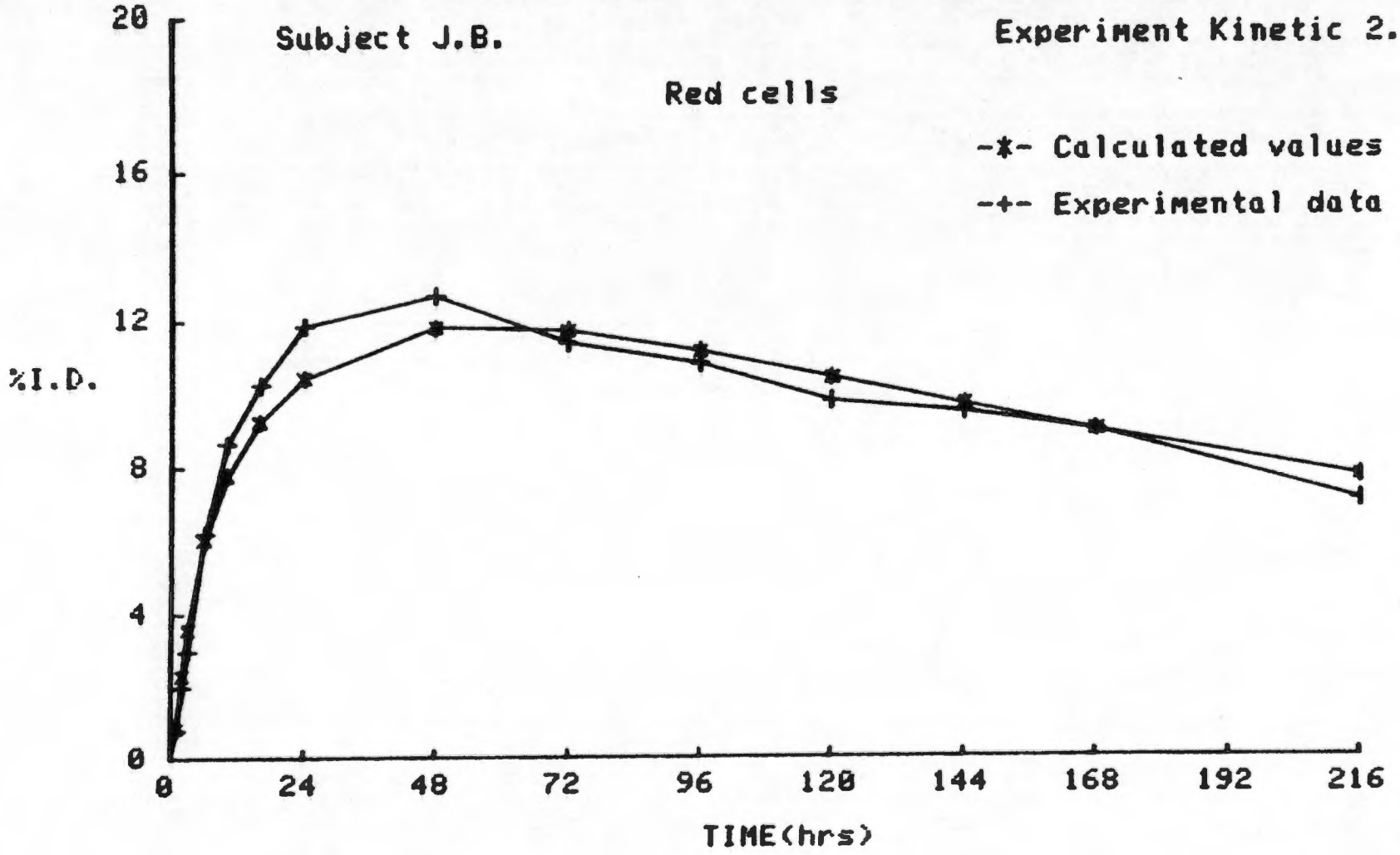


FIGURE. JB-UR-2

Fit of calculated values to experimental data

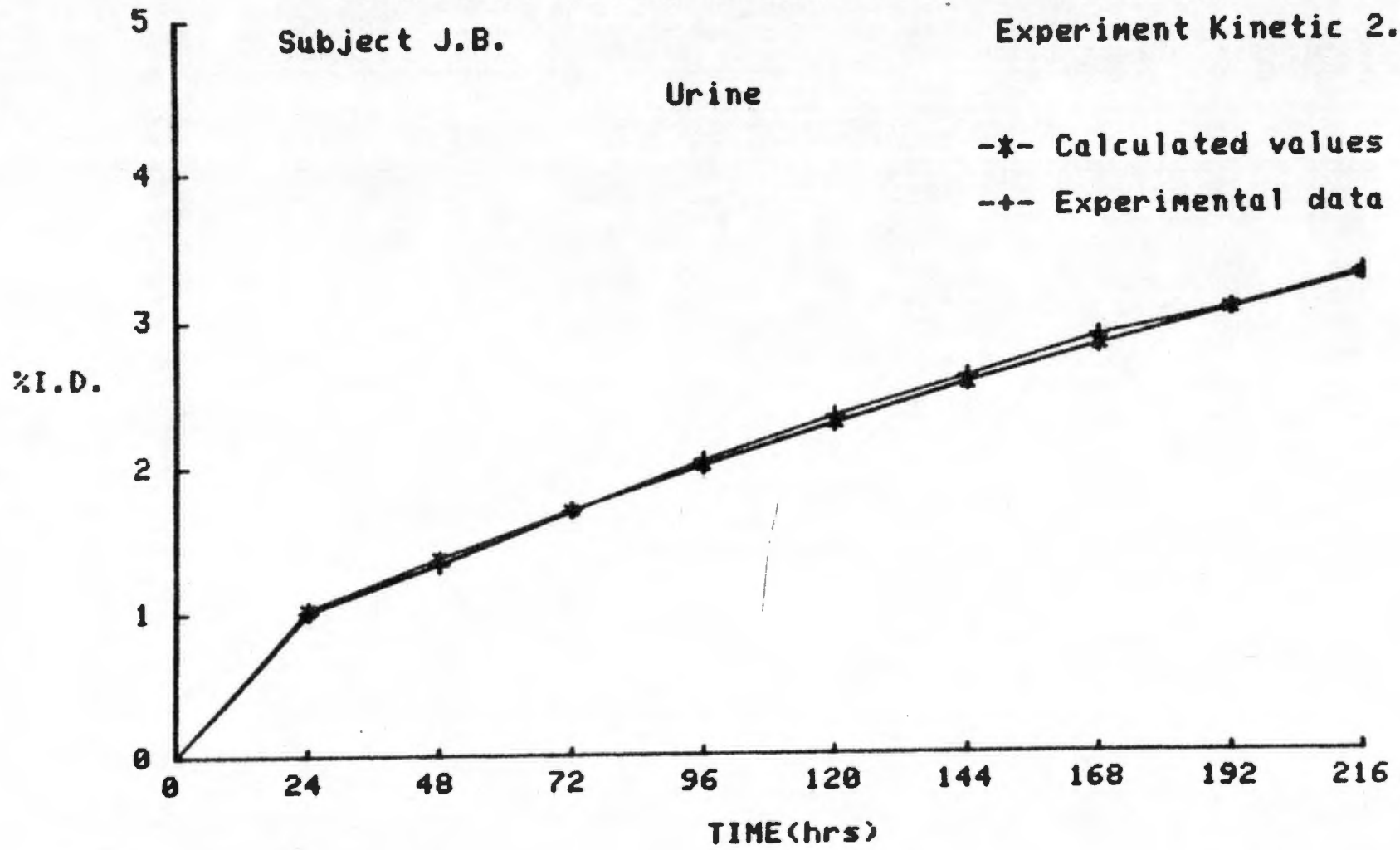


FIGURE. JB-SB-2

Fit of calculated values to experimental data

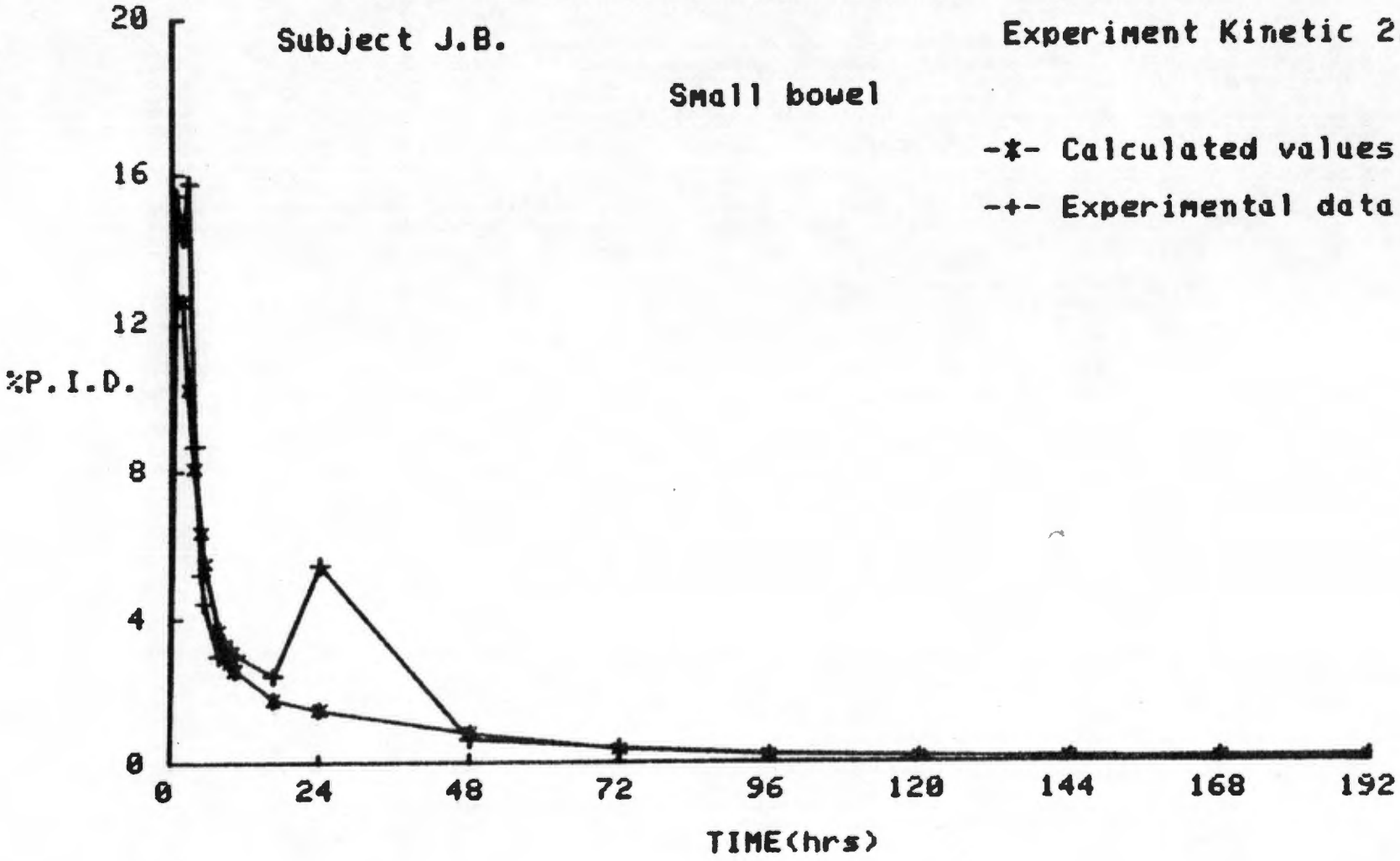


FIGURE. JB-LI-2

Fit of calculated values to experimental data

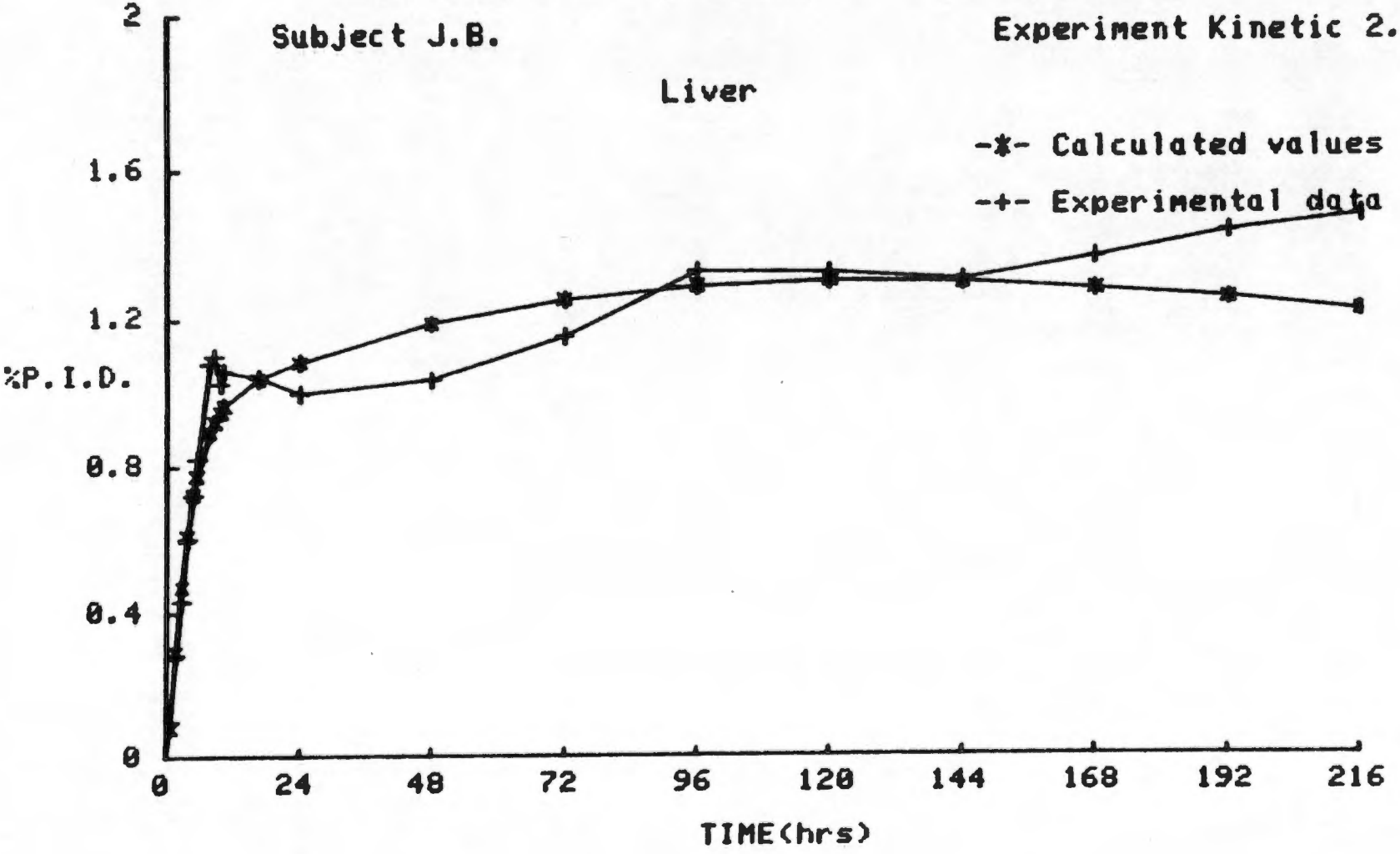


FIGURE. JB-ST-2

Fit of calculated values to experimental data

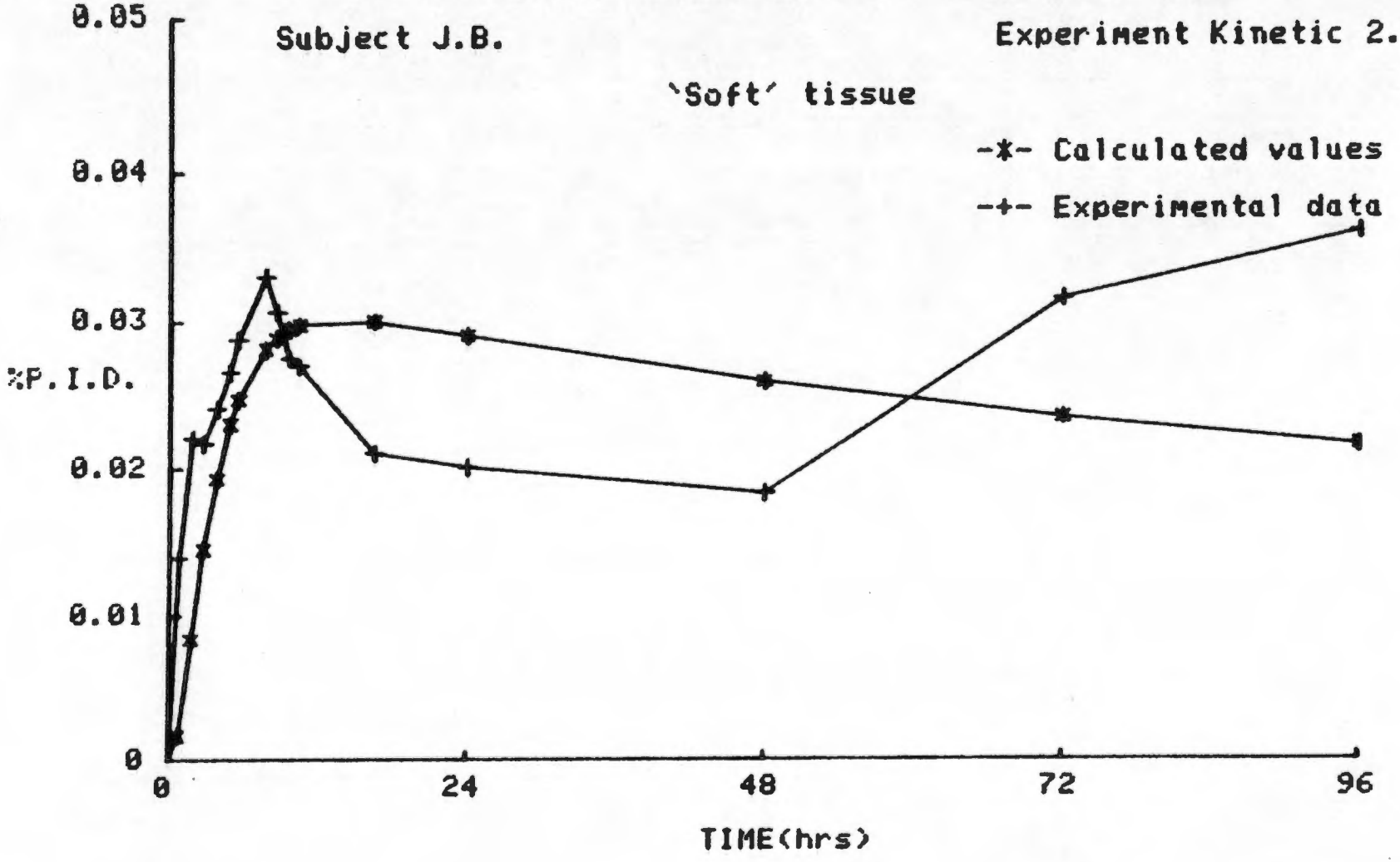


FIGURE. JB-HT-2

Fit of calculated values to experimental data

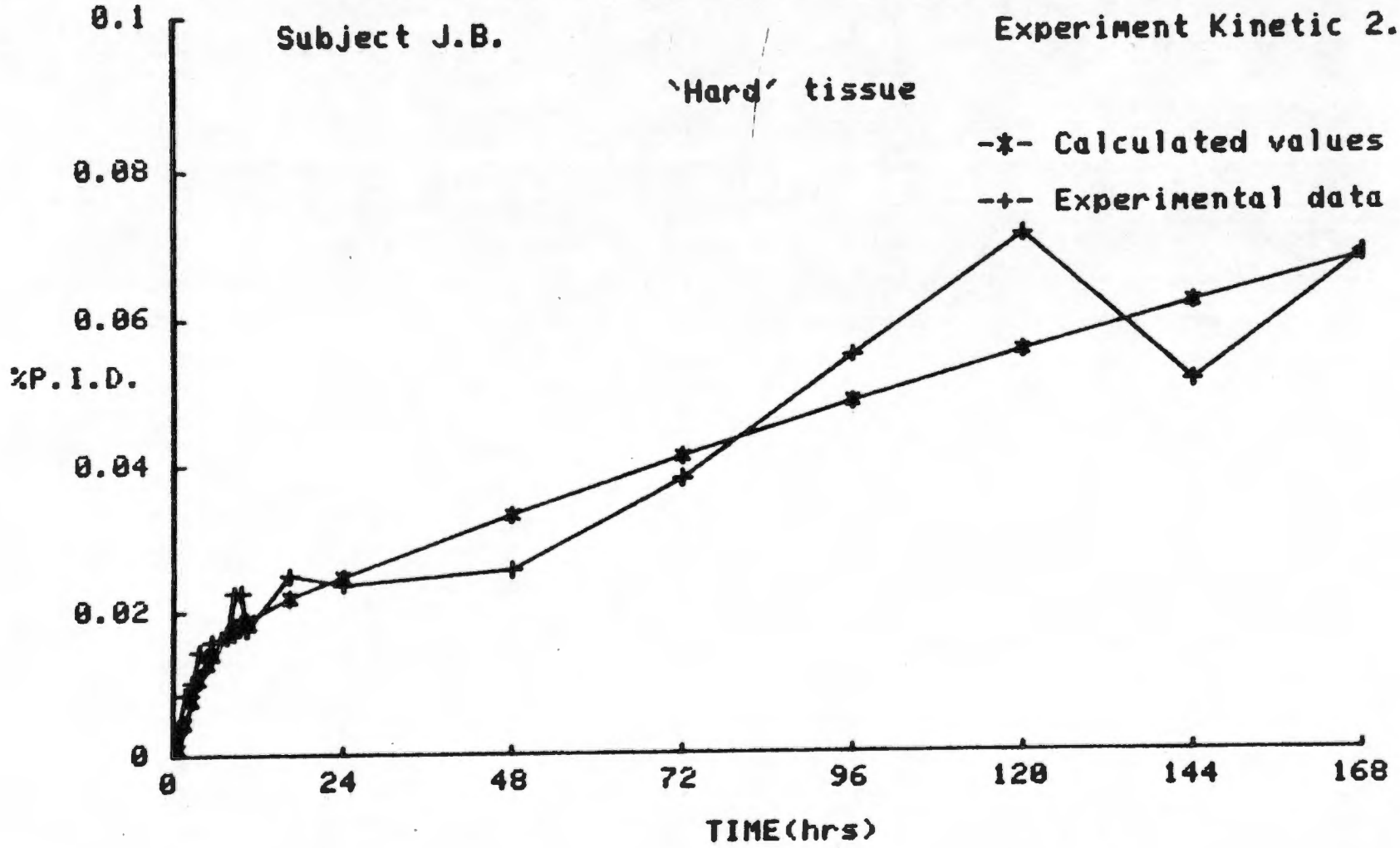


FIGURE. BC-WB-1

Fit of calculated values to experimental data

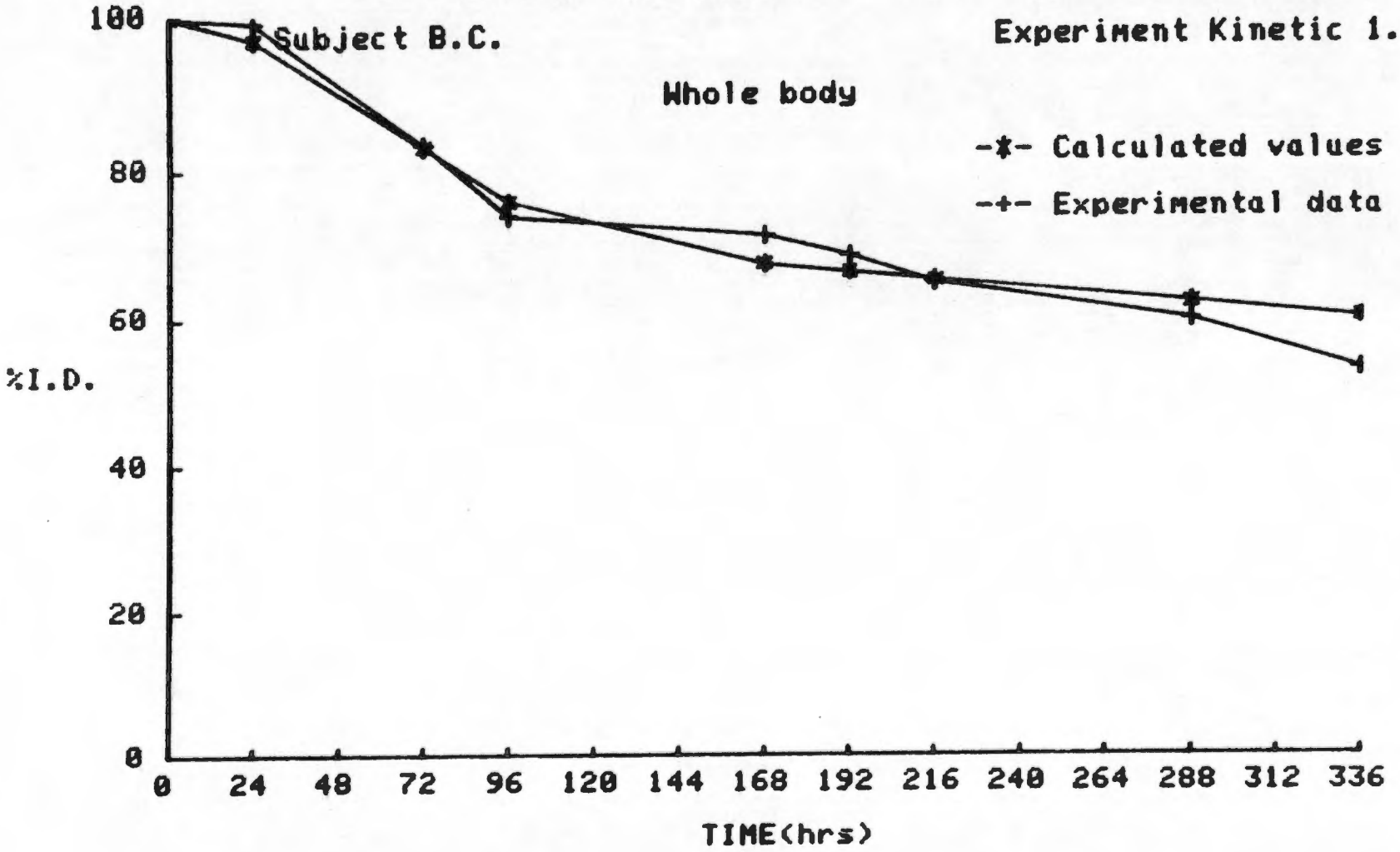


FIGURE. BC-PL-1

Fit of calculated values to experimental data

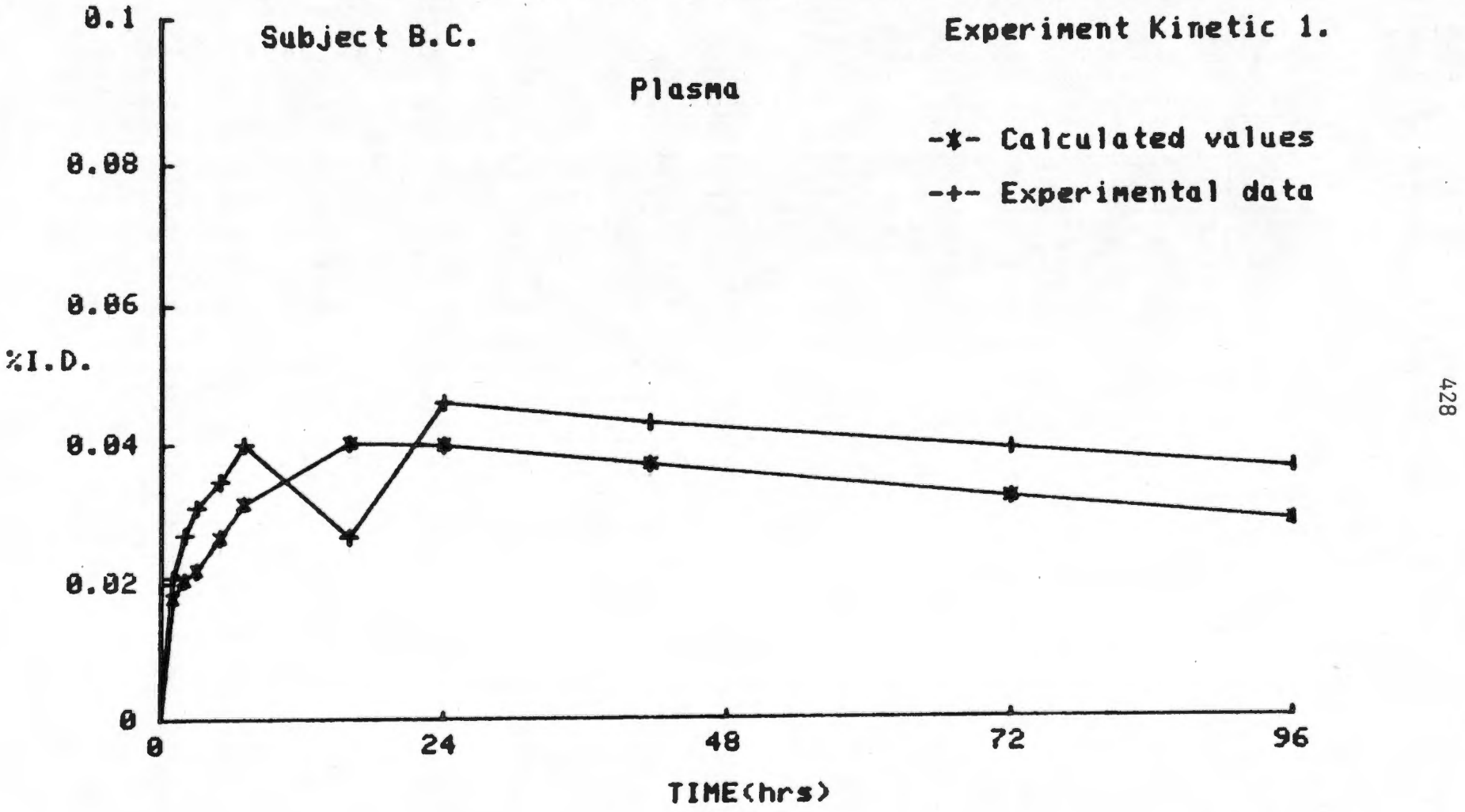


FIGURE. BC-RC-1

Fit of calculated values to experimental data

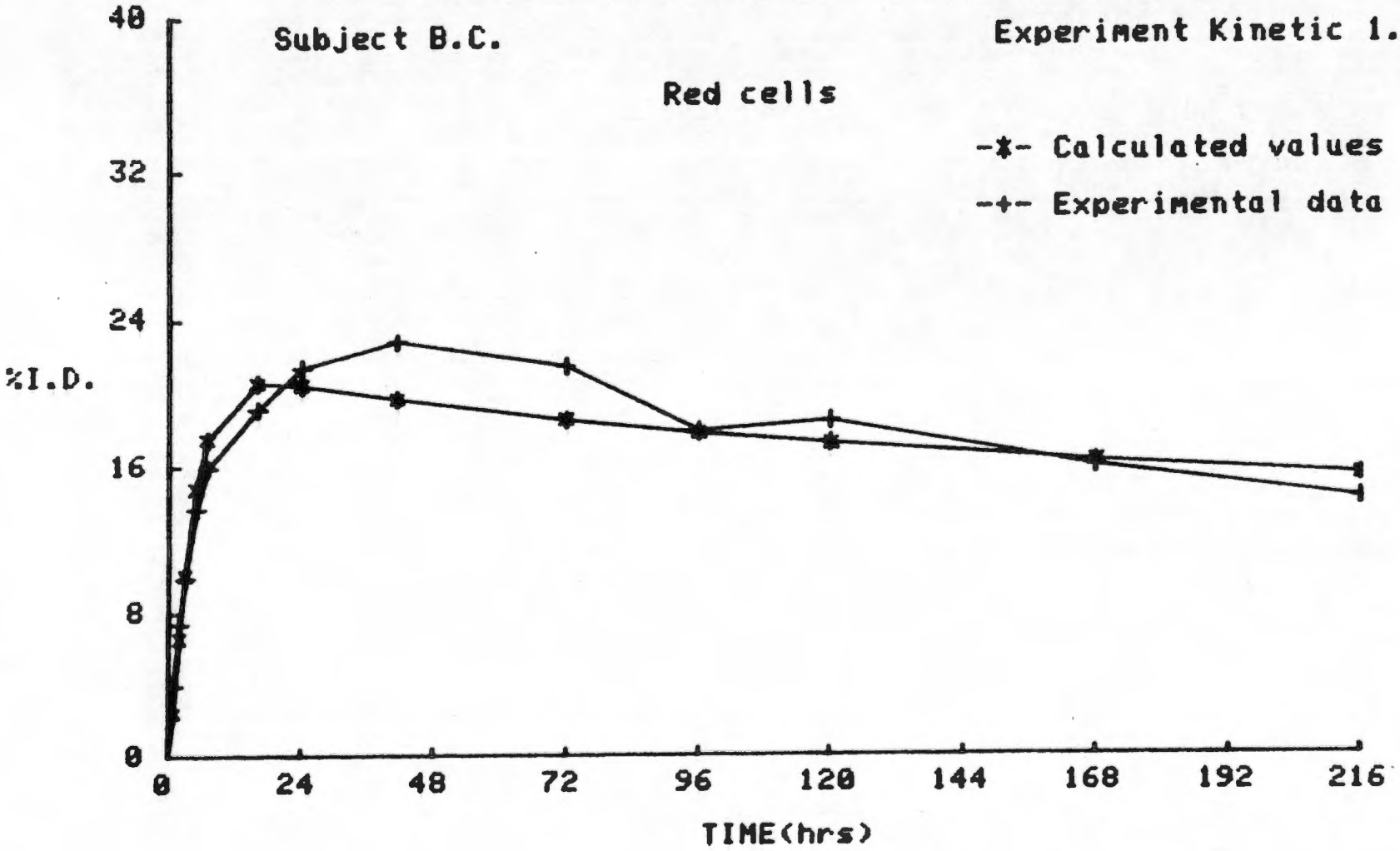


FIGURE. BC-UR-1

Fit of calculated values to experimental data

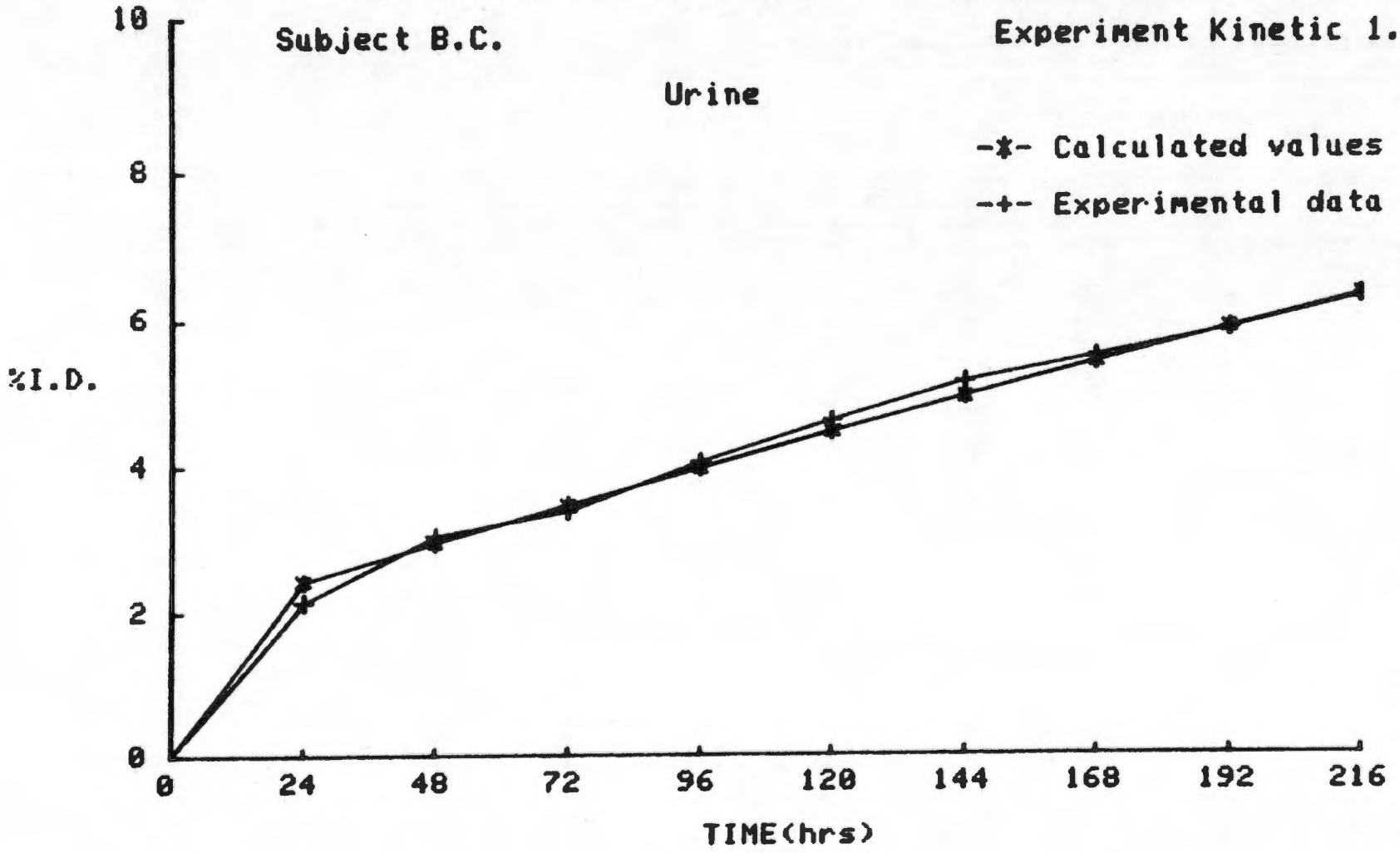


FIGURE. BC-SB-1

Fit of calculated values to experimental data

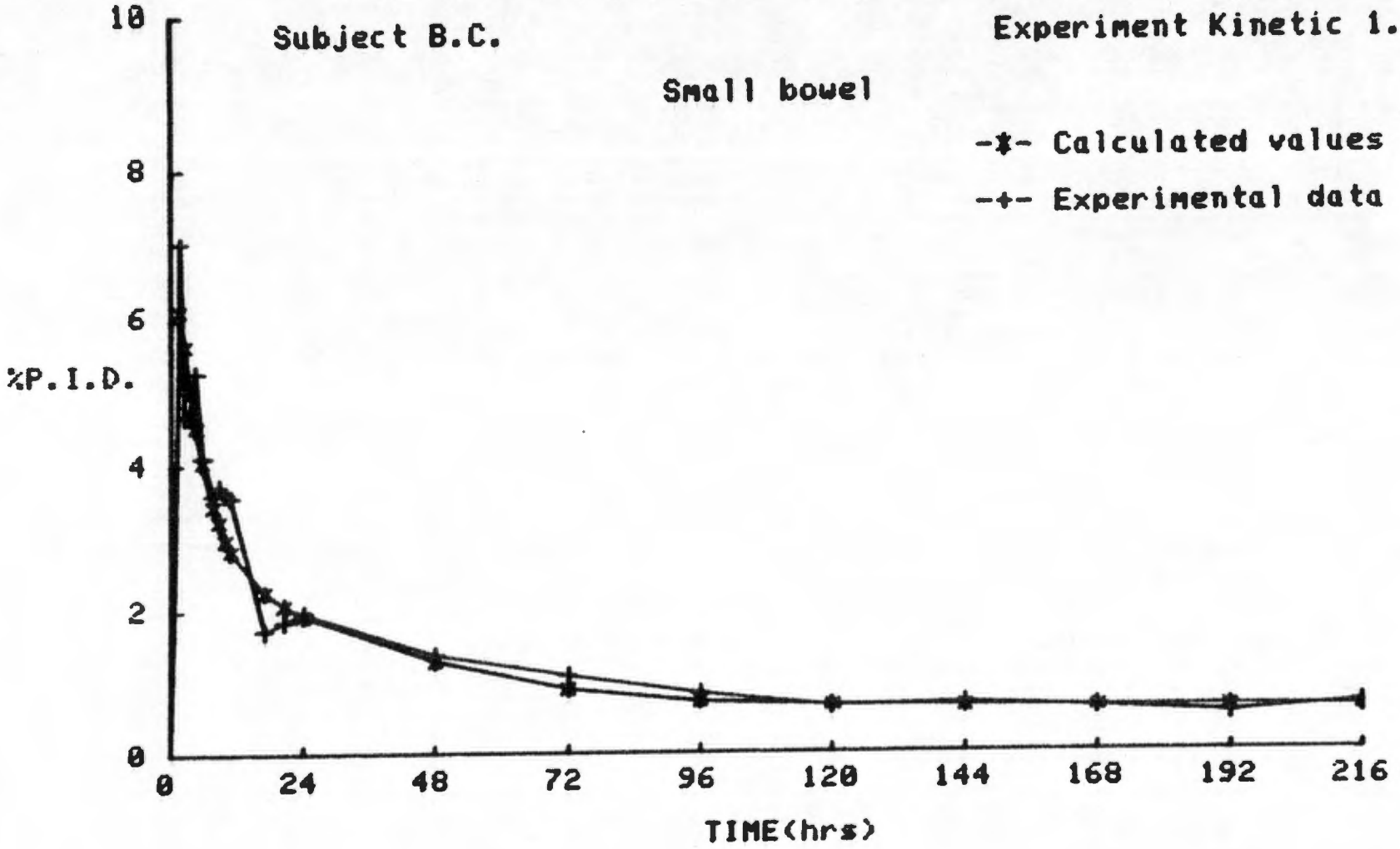


FIGURE. BC-LI-1

Fit of calculated values to experimental data

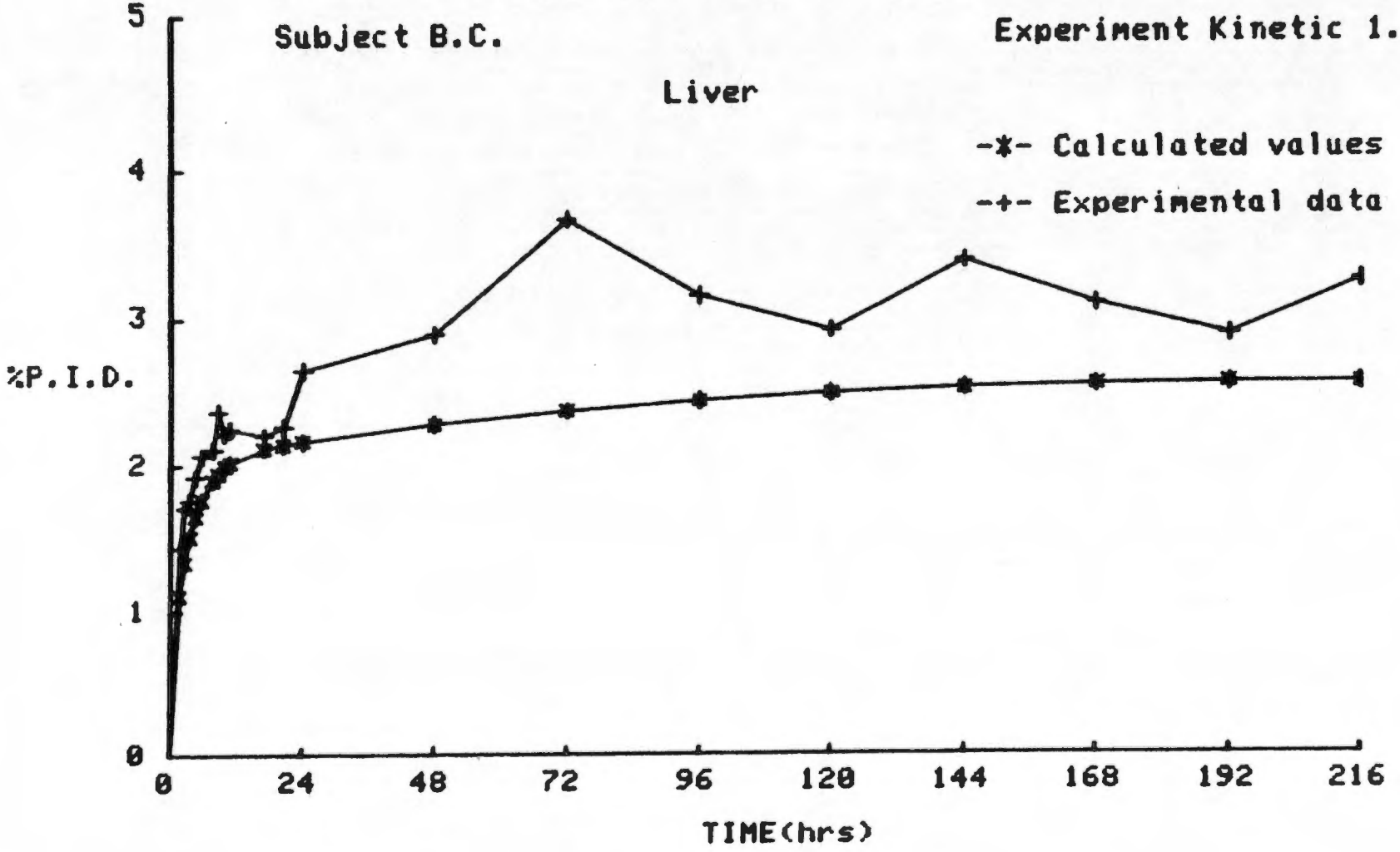


FIGURE. BC-ST-1

Fit of calculated values to experimental data

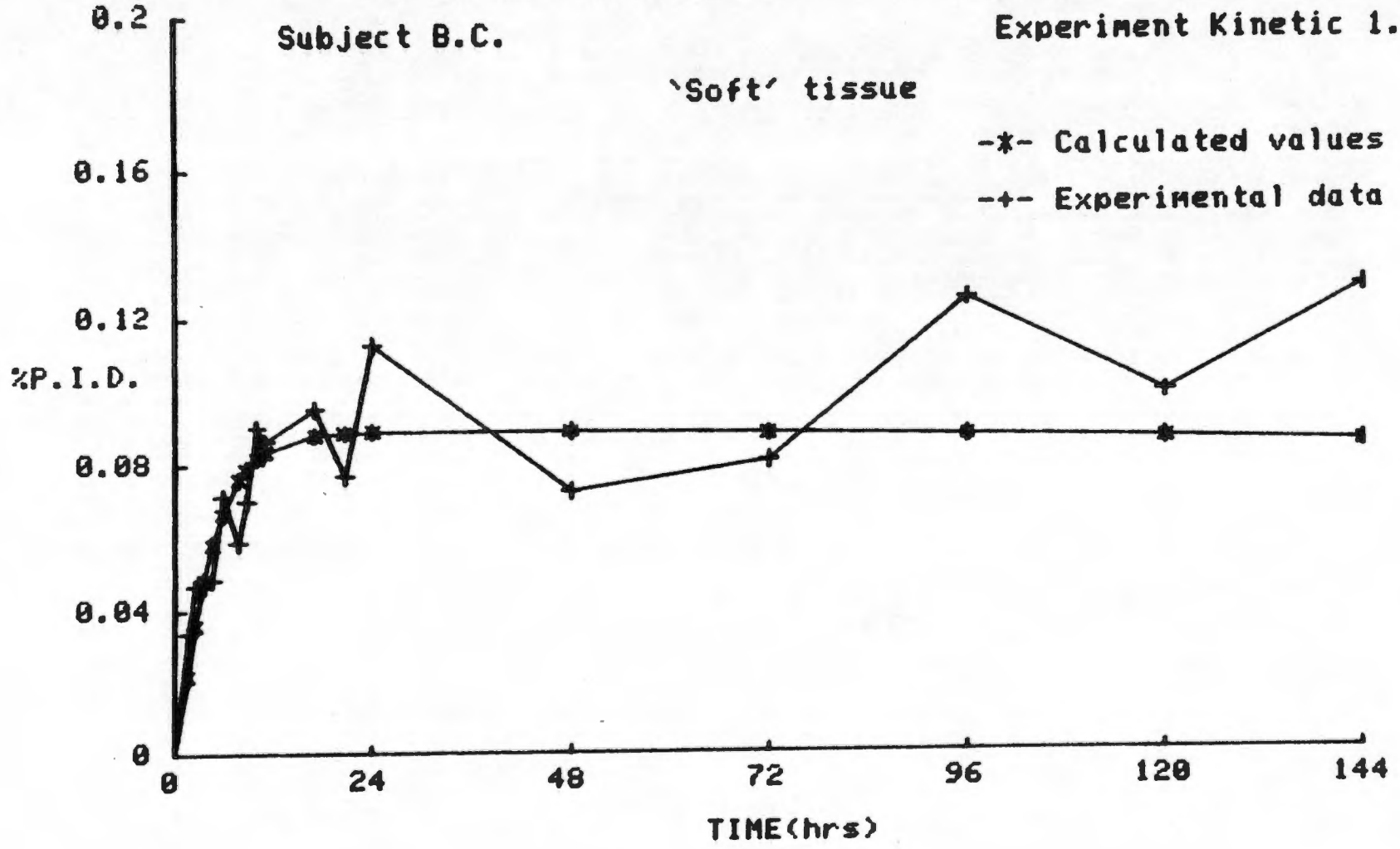


FIGURE. BC-ST-1A

Fit of calculated values to experimental data

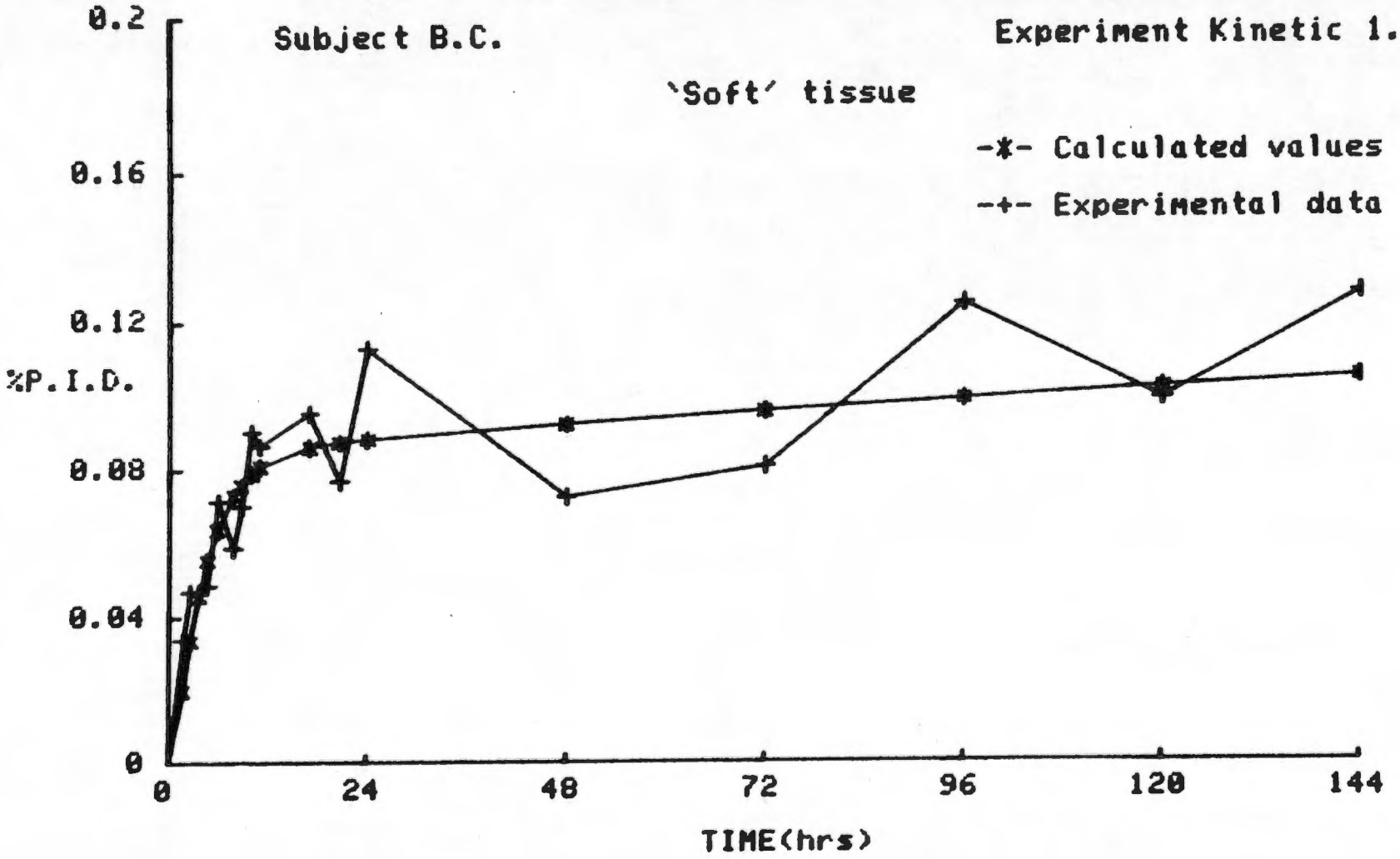


FIGURE. BC-HT-1

Fit of calculated values to experimental data

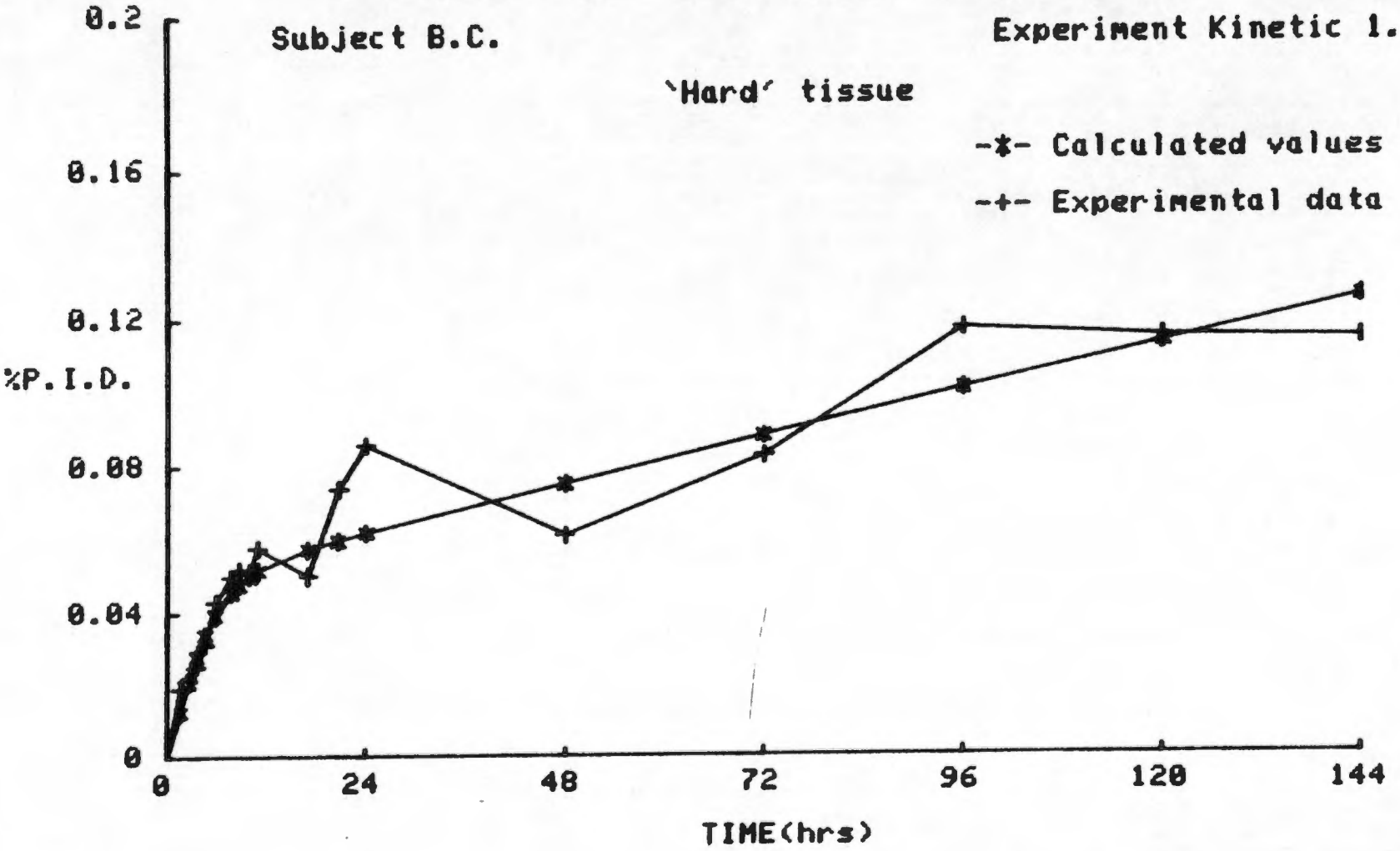


FIGURE. BC-WB-2

Fit of calculated values to experimental data

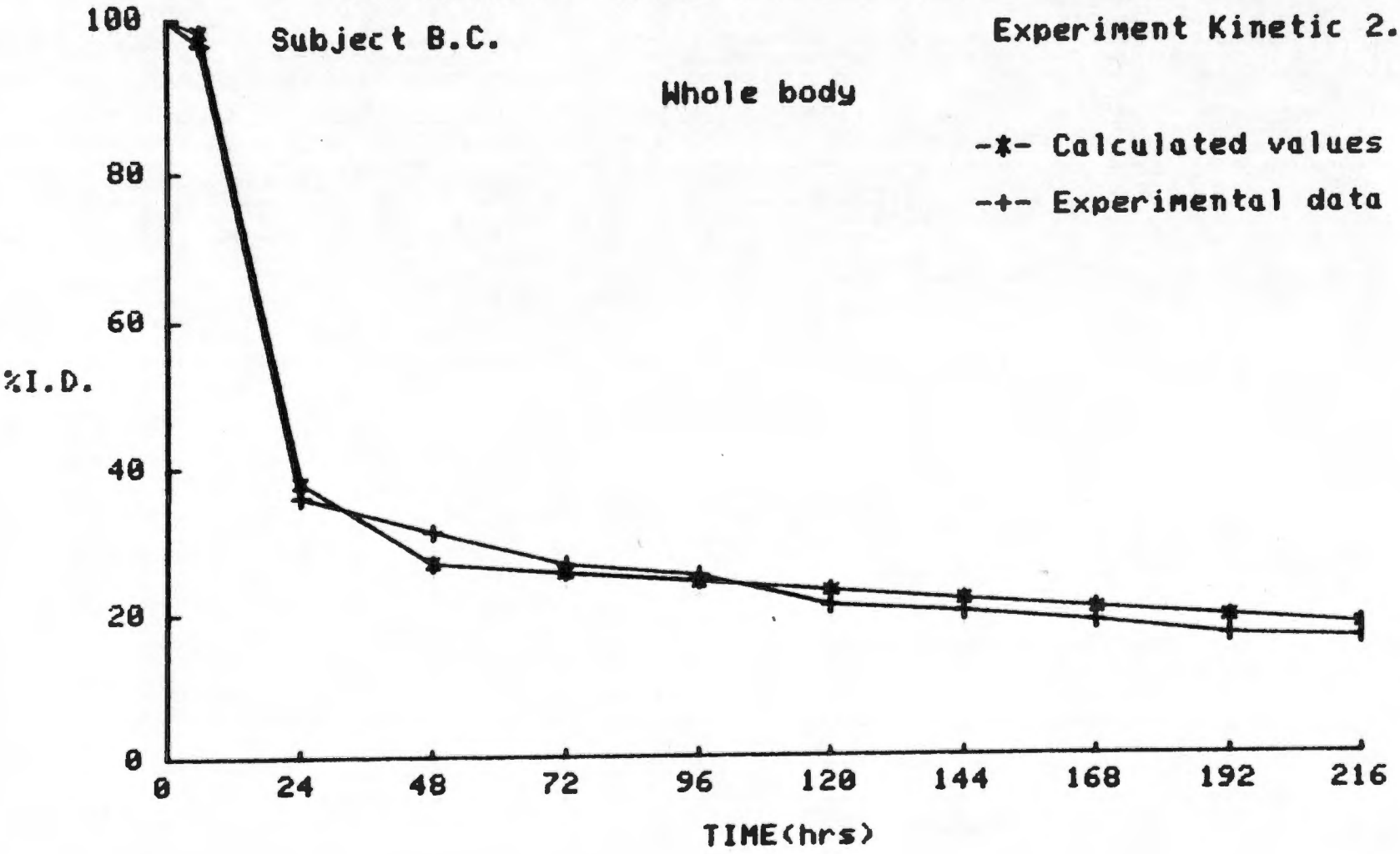


FIGURE. BC-PL-2

Fit of calculated values to experimental data

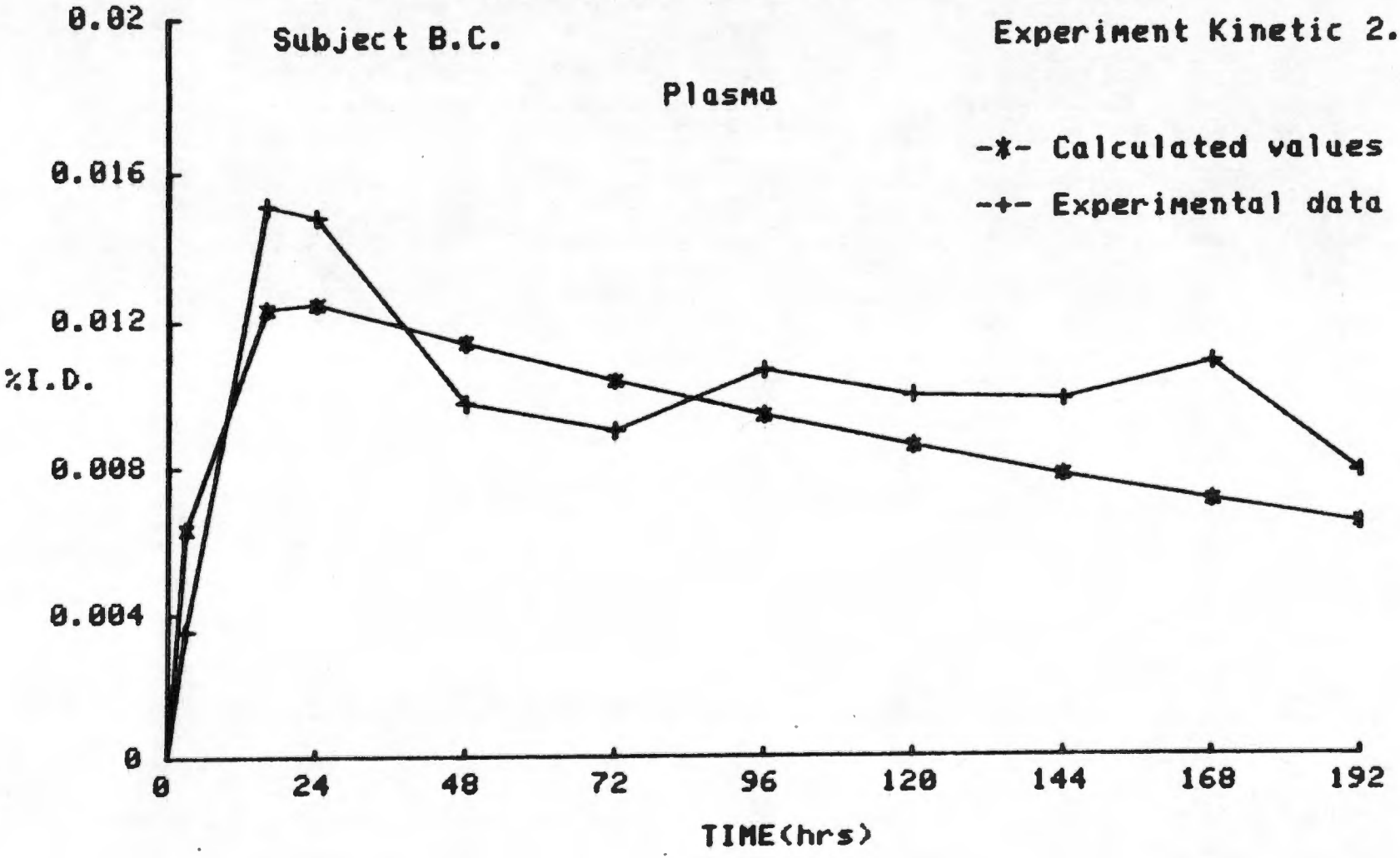


FIGURE. BC-RC-2

Fit of calculated values to experimental data

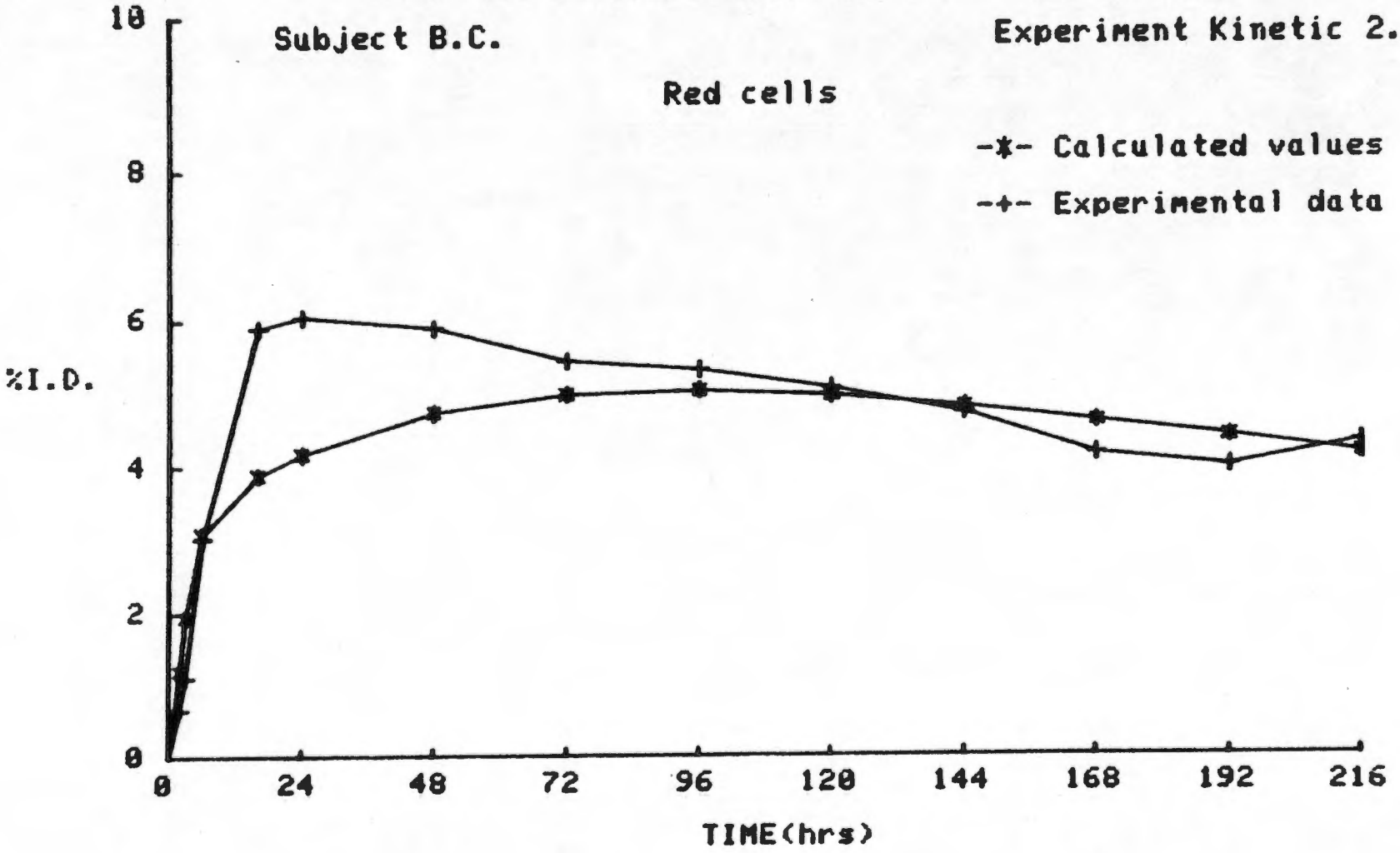


FIGURE. BC-UR-2

Fit of calculated values to experimental data

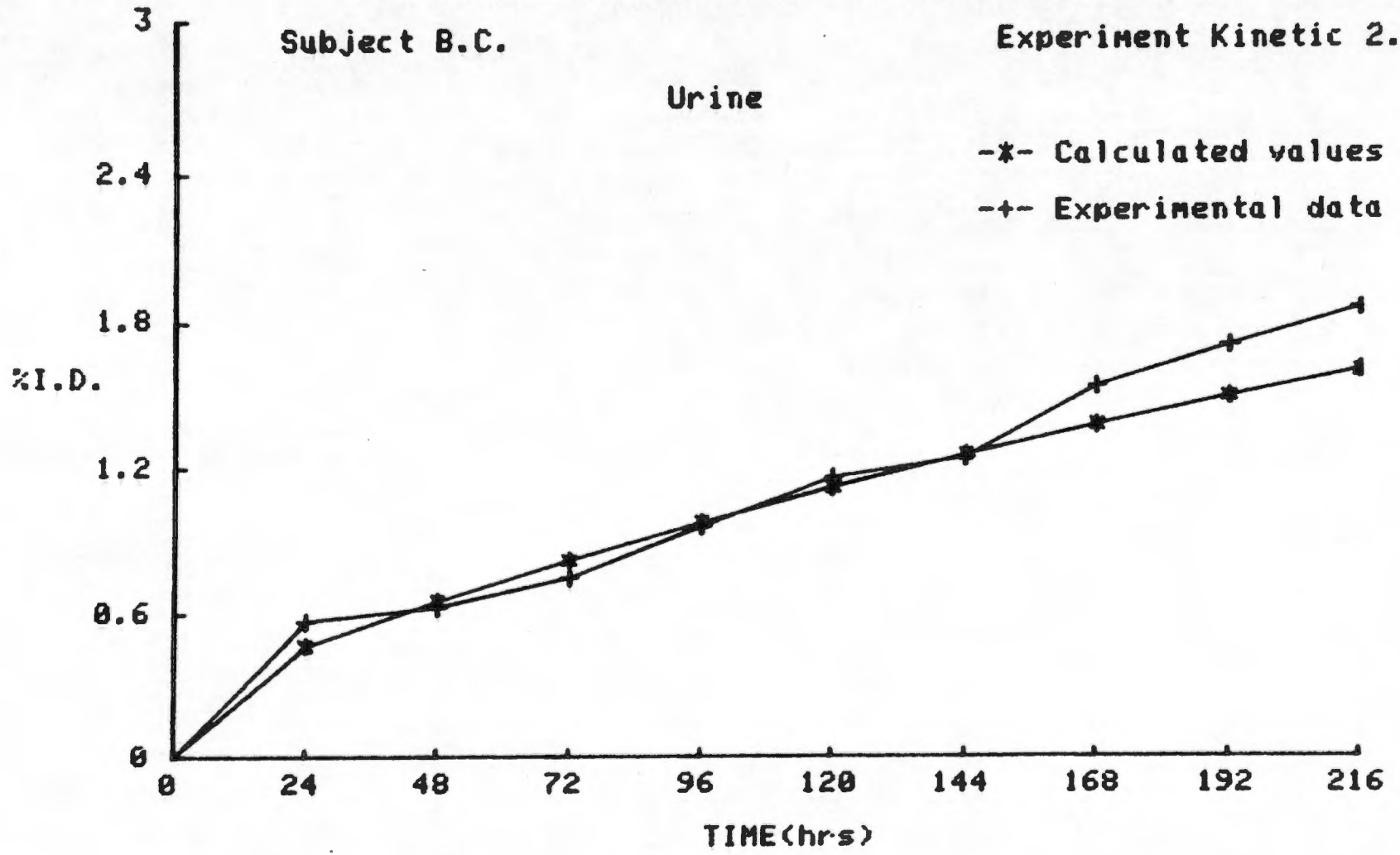


FIGURE. BC-SB-2

Fit of calculated values to experimental data

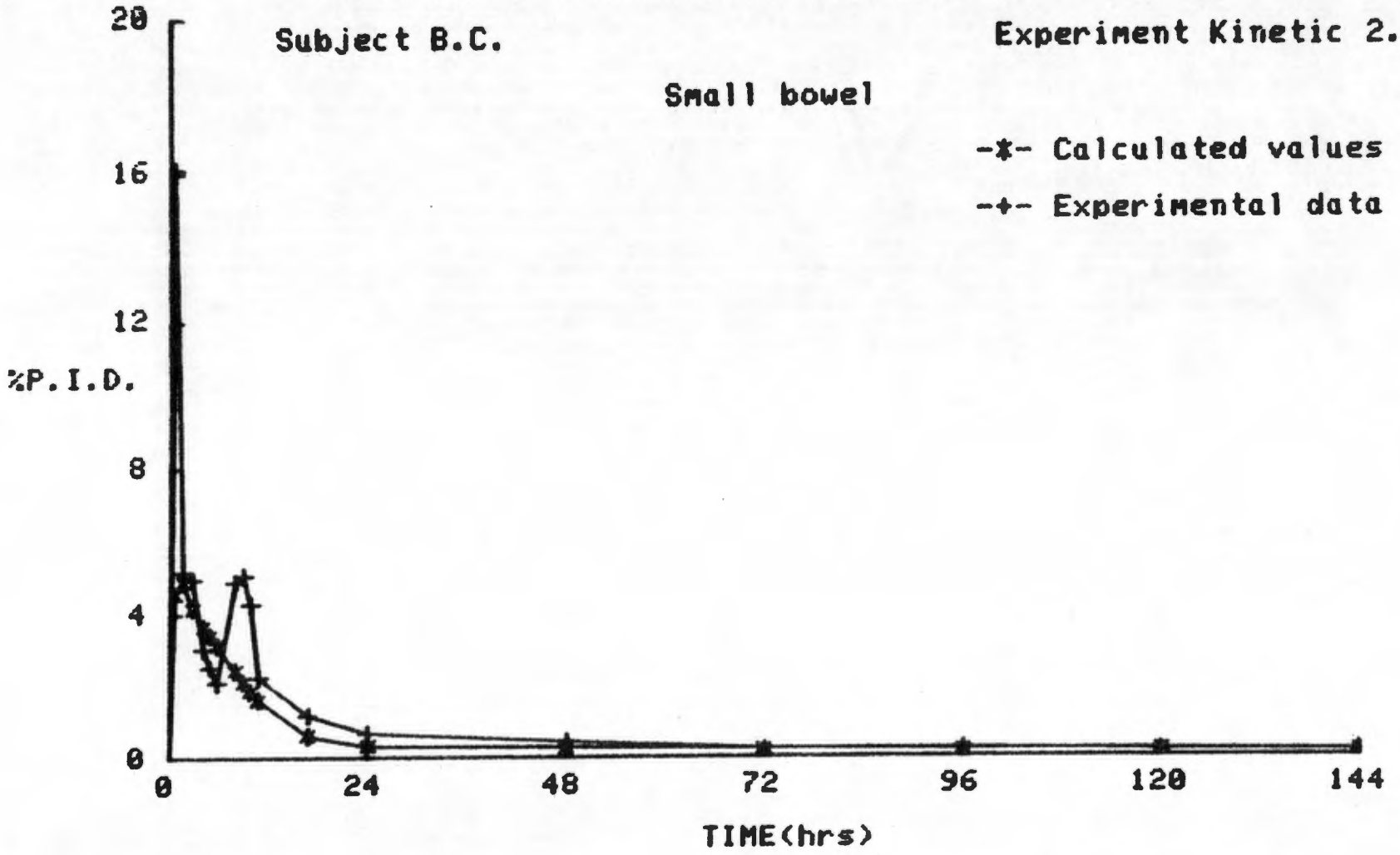


FIGURE. BC-LI-2

Fit of calculated values to experimental data

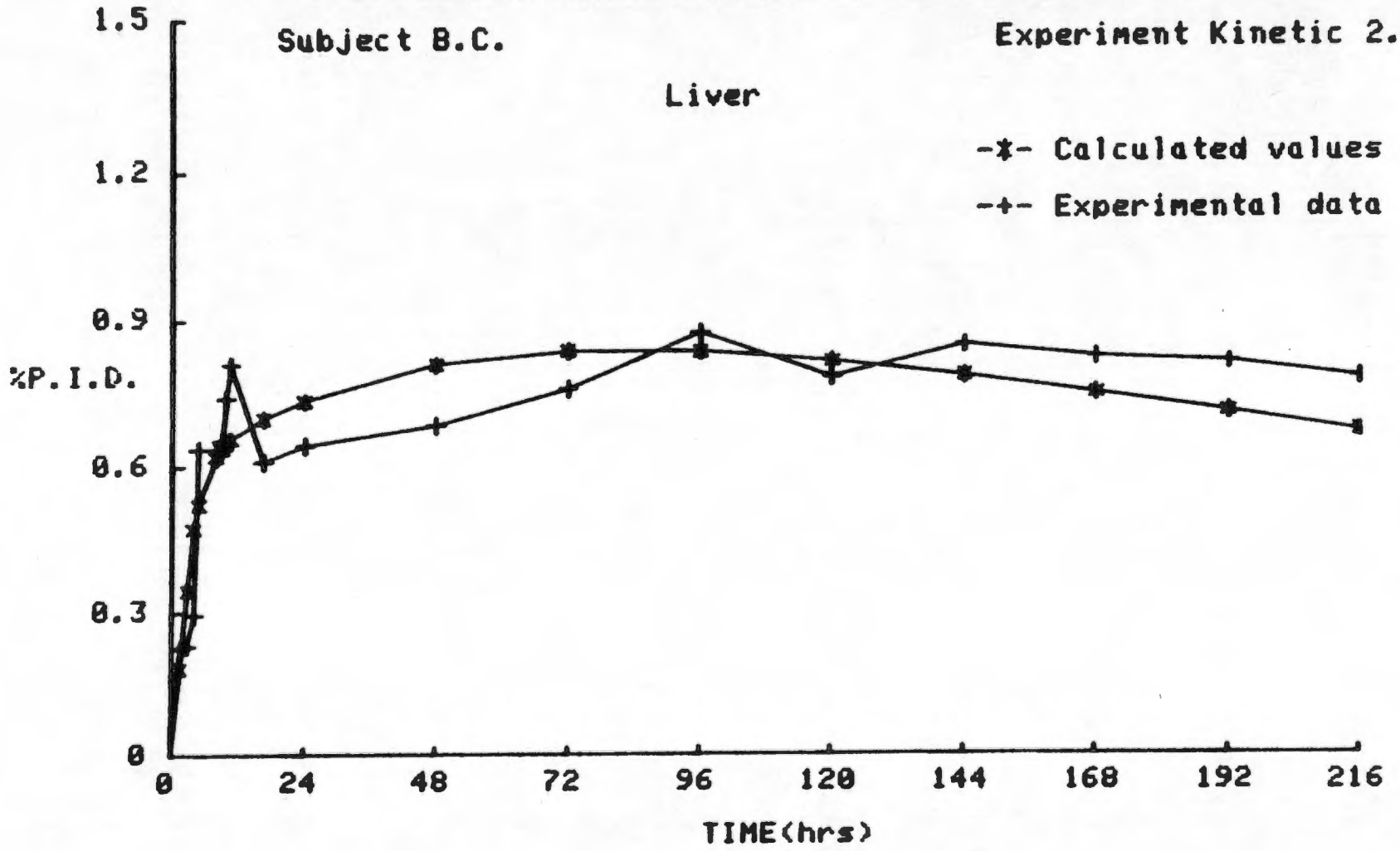


FIGURE. BC-ST-2

Fit of calculated values to experimental data

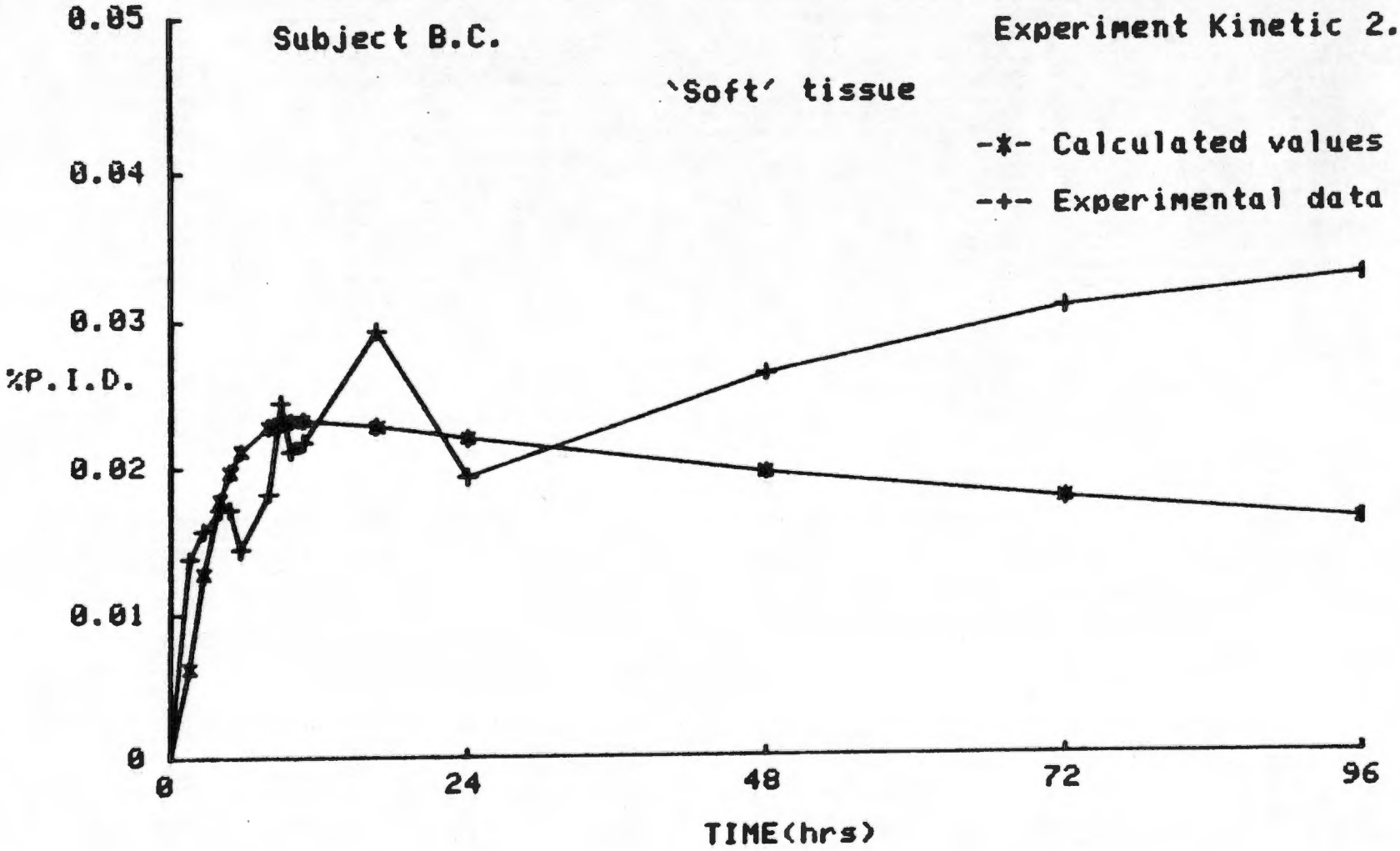


FIGURE. BC-ST-2A

Fit of calculated values to experimental data

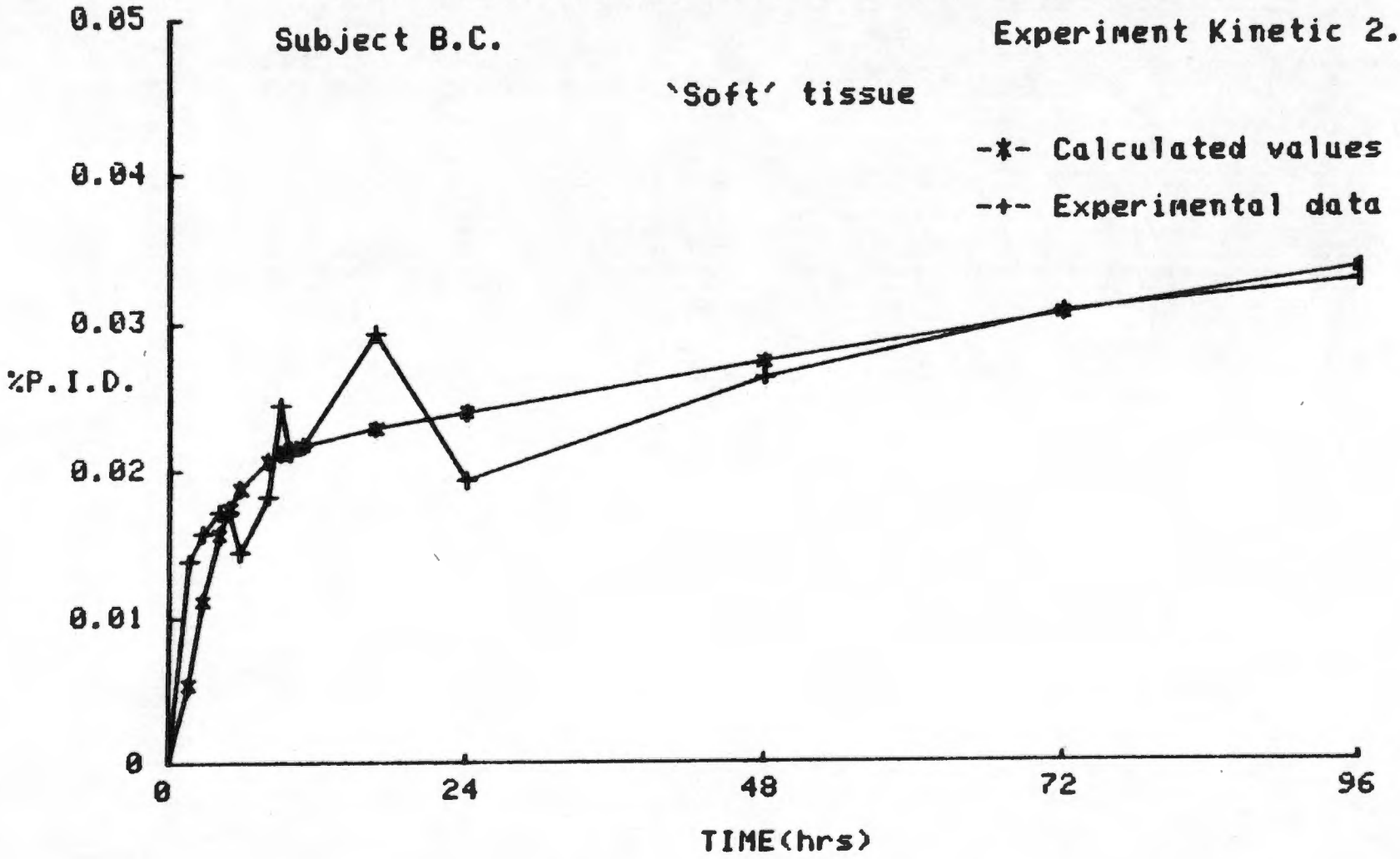
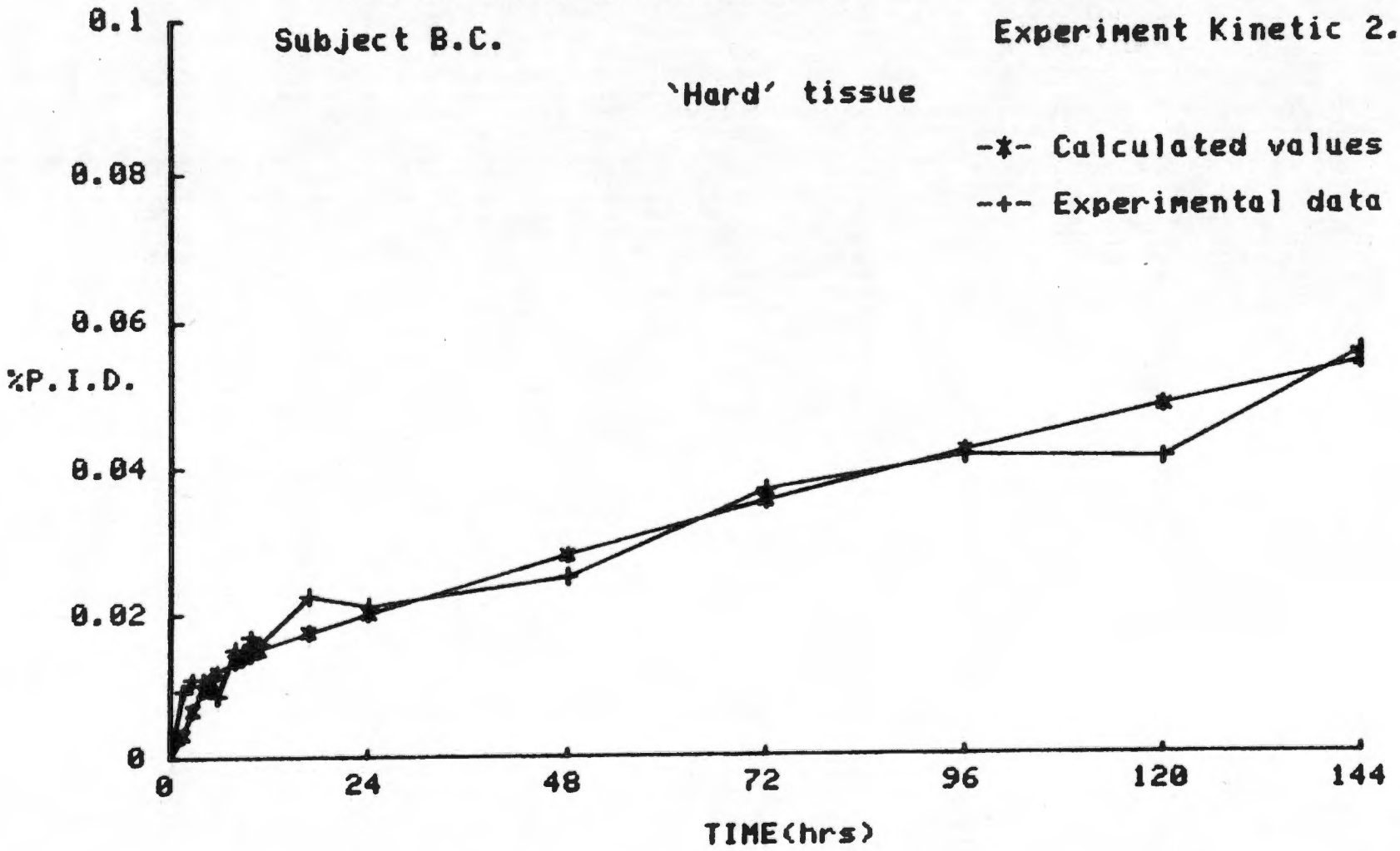


FIGURE. BC-HT-2

Fit of calculated values to experimental data



4444

FIGURE. GE-WB-1

Fit of calculated values to experimental data

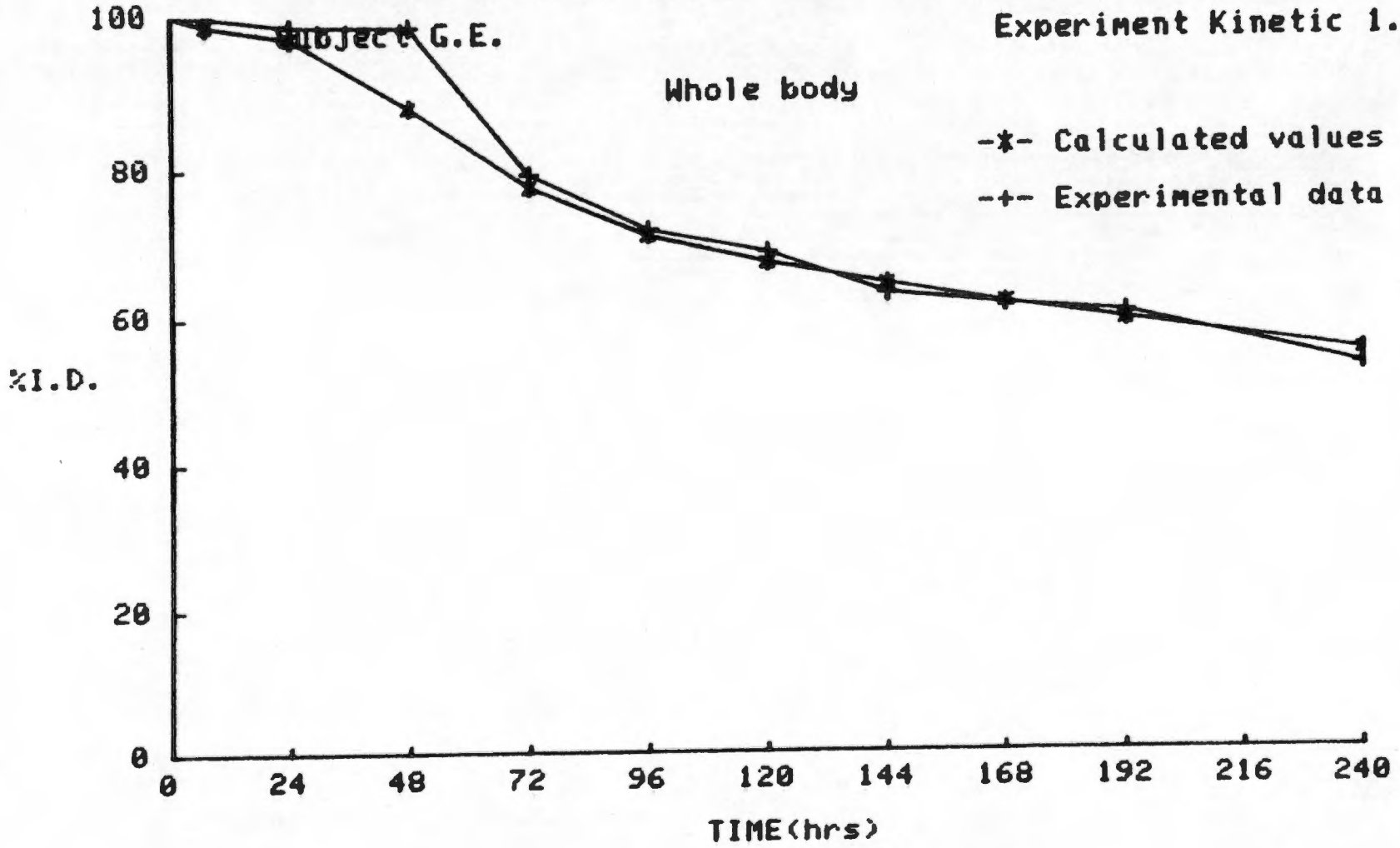


FIGURE. GE-PL-1

Fit of calculated values to experimental data

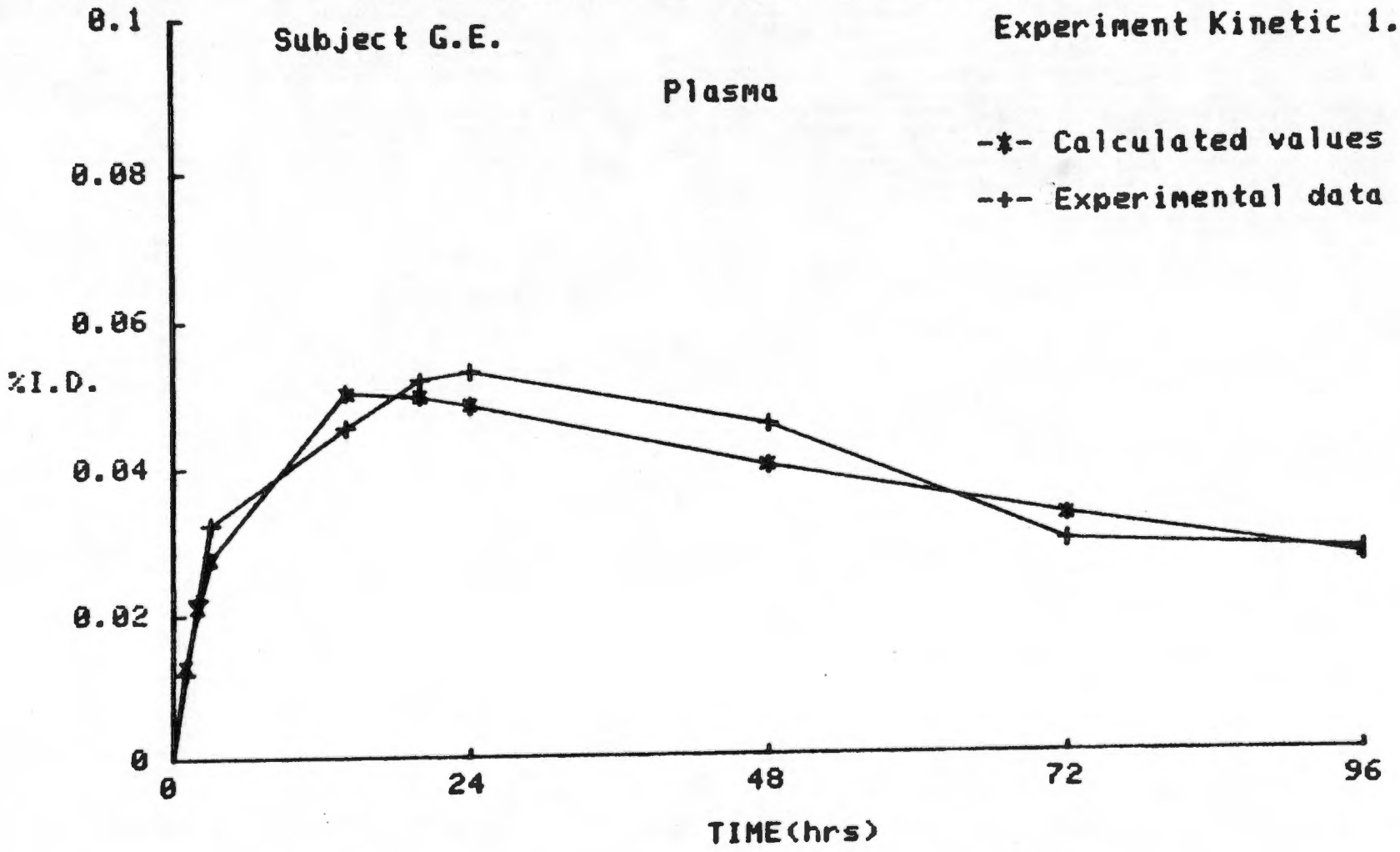


FIGURE. GE-RC-1

Fit of calculated values to experimental data

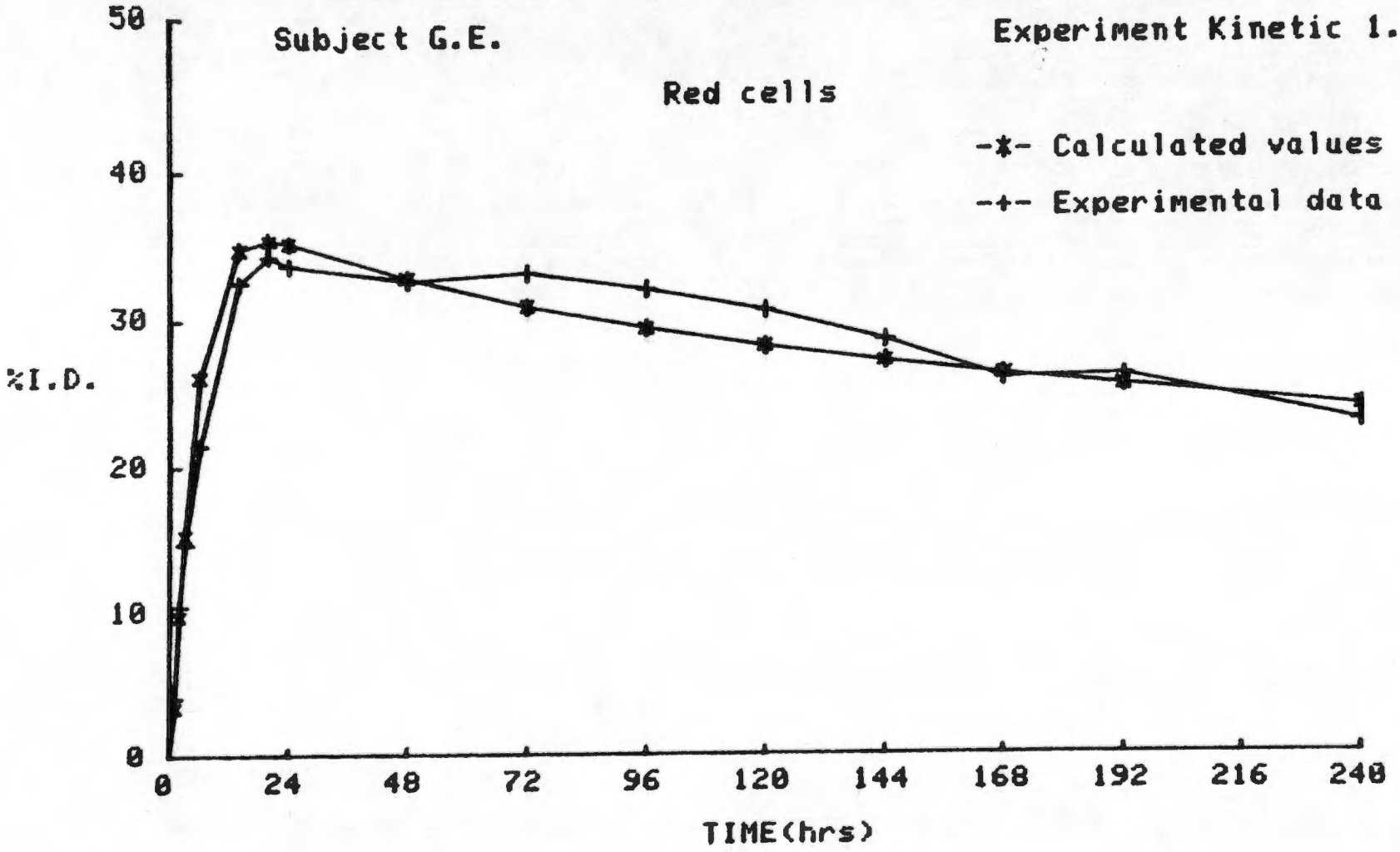


FIGURE. GE-UR-1

Fit of calculated values to experimental data

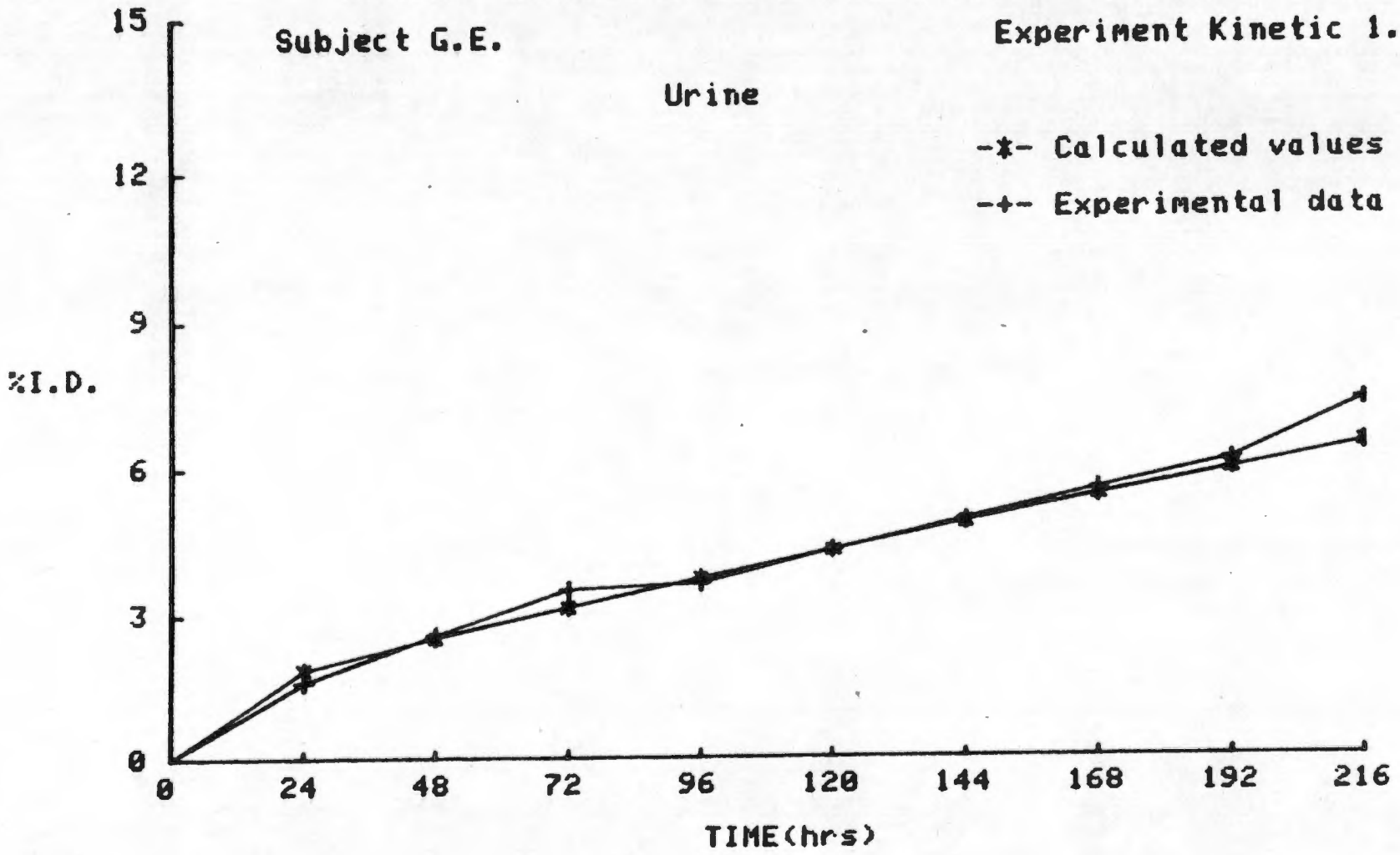


FIGURE. GE-SB-1

Fit of calculated values to experimental data

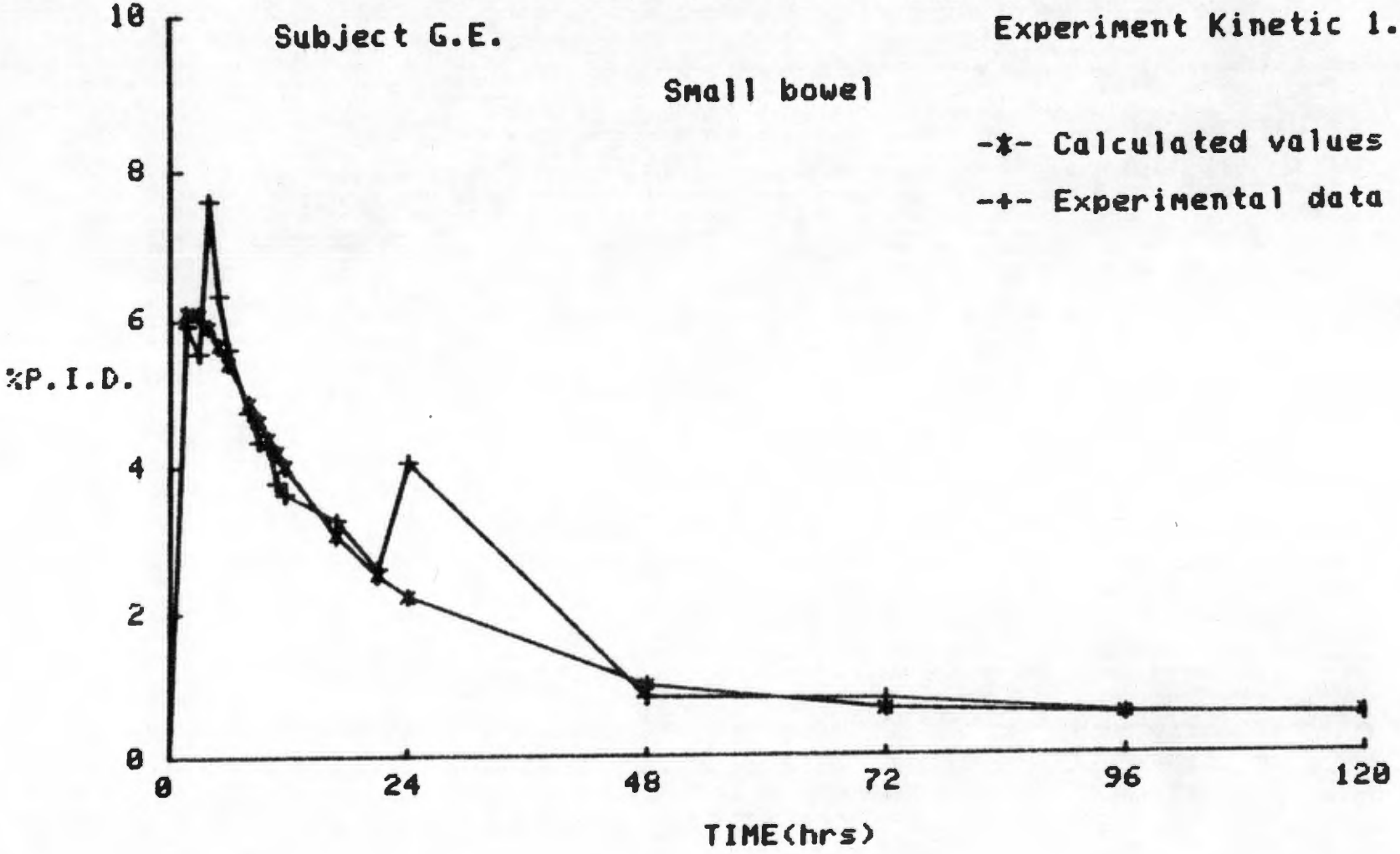


FIGURE. GE-LI-1

Fit of calculated values to experimental data

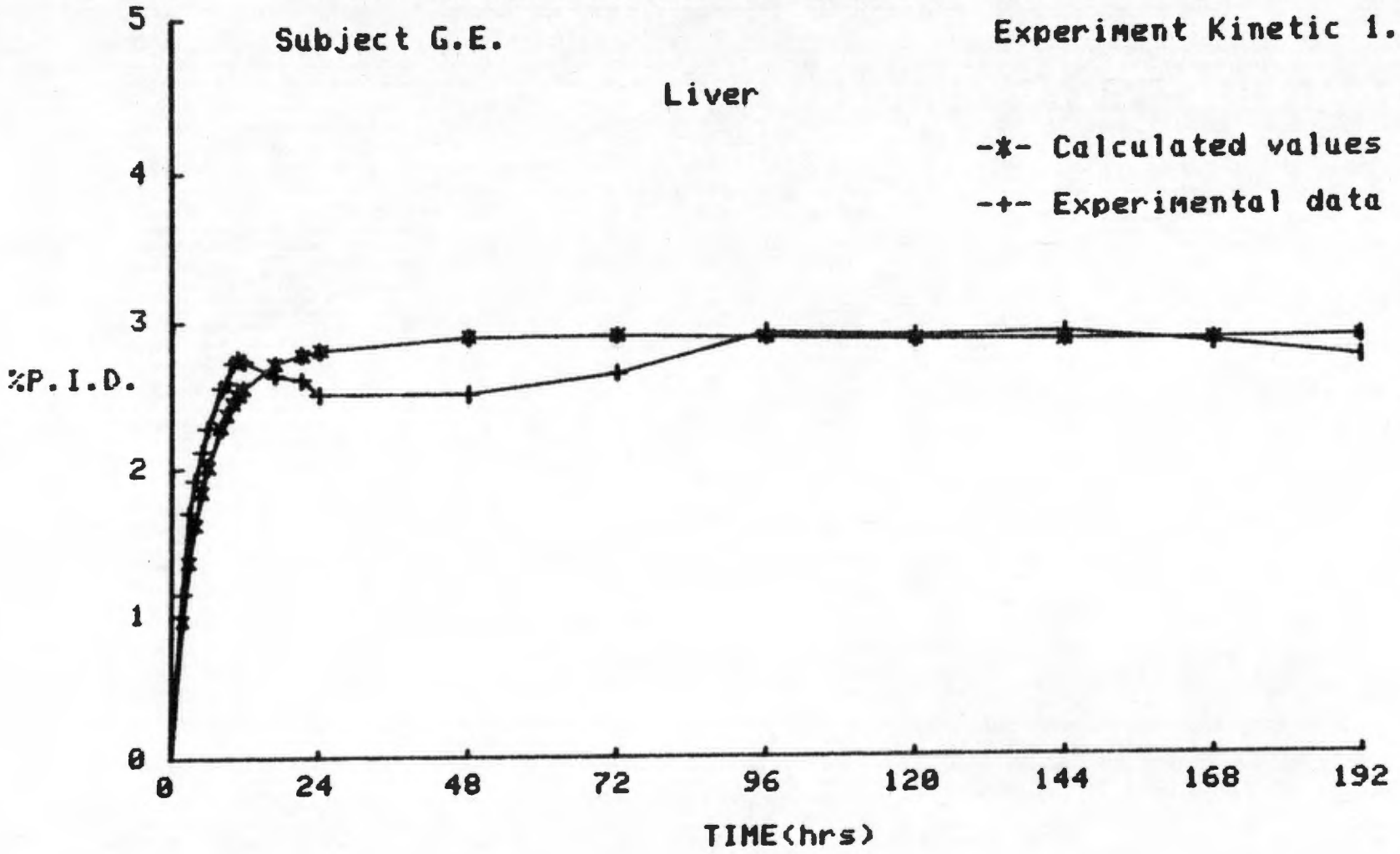


FIGURE. GE-ST-1

Fit of calculated values to experimental data

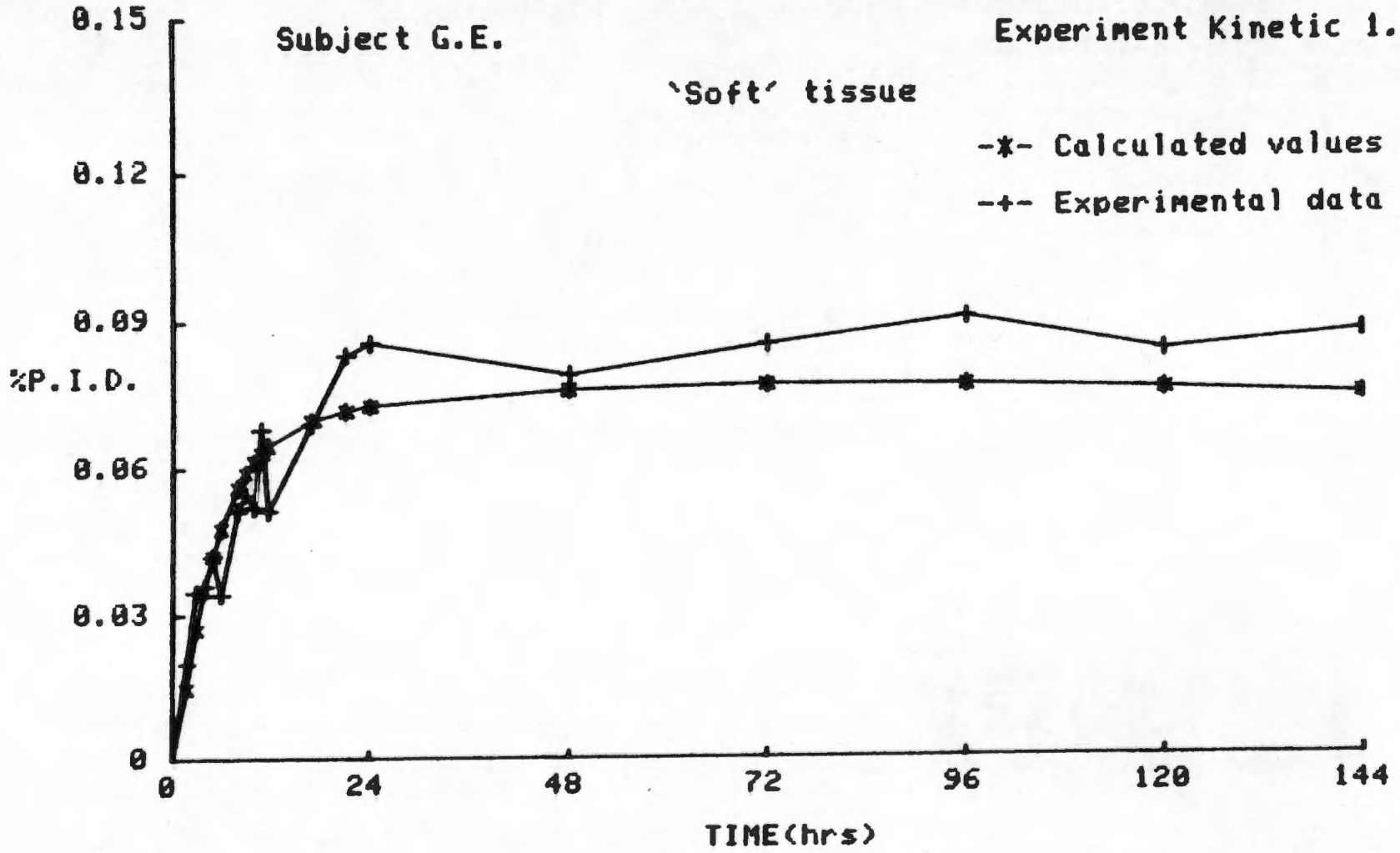


FIGURE. GE-HT-1

Fit of calculated values to experimental data

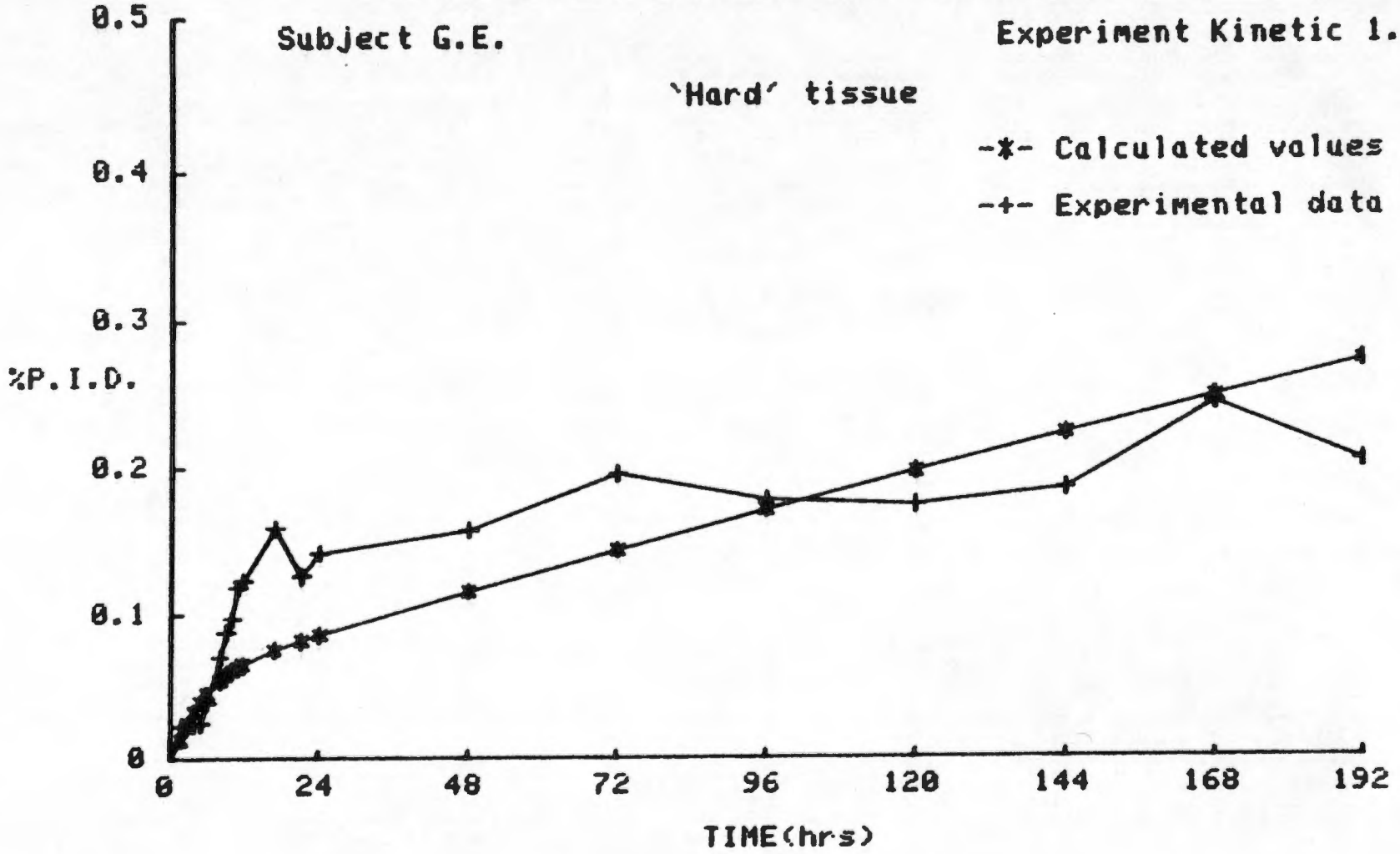


FIGURE. GE-WB-2

Fit of calculated values to experimental data

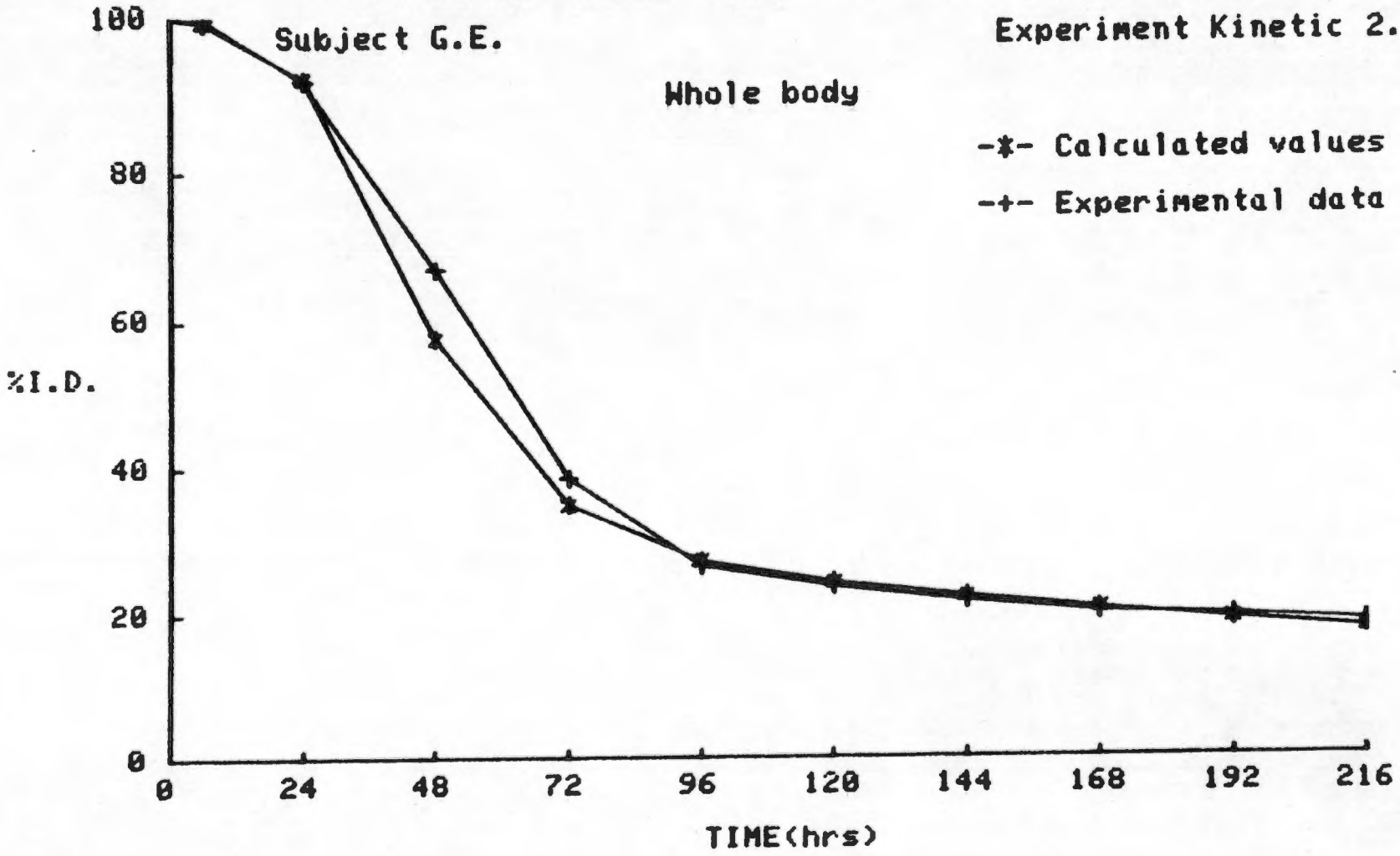


FIGURE. GE-PL-2

Fit of calculated values to experimental data

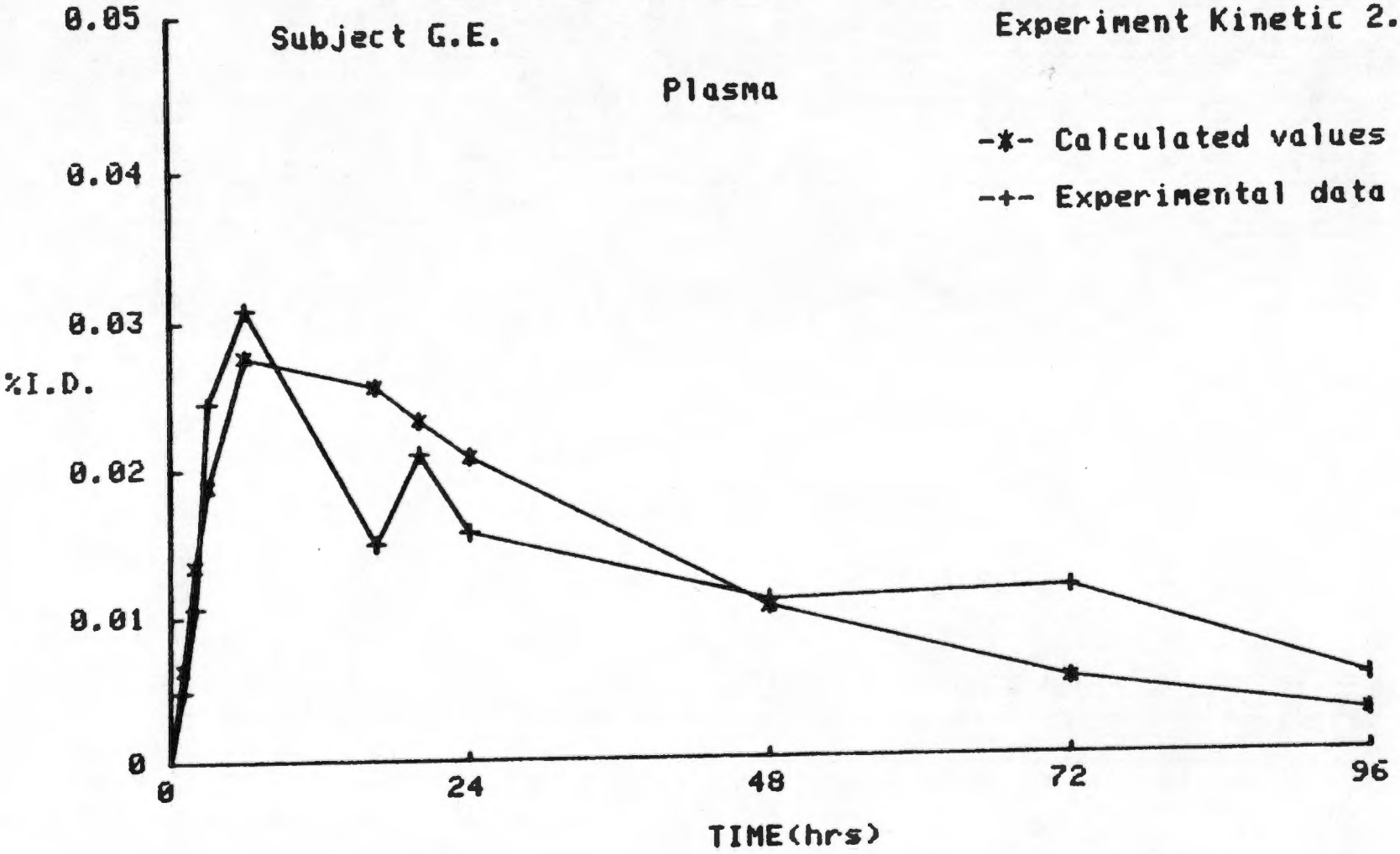


FIGURE. GE-RC-2

Fit of calculated values to experimental data

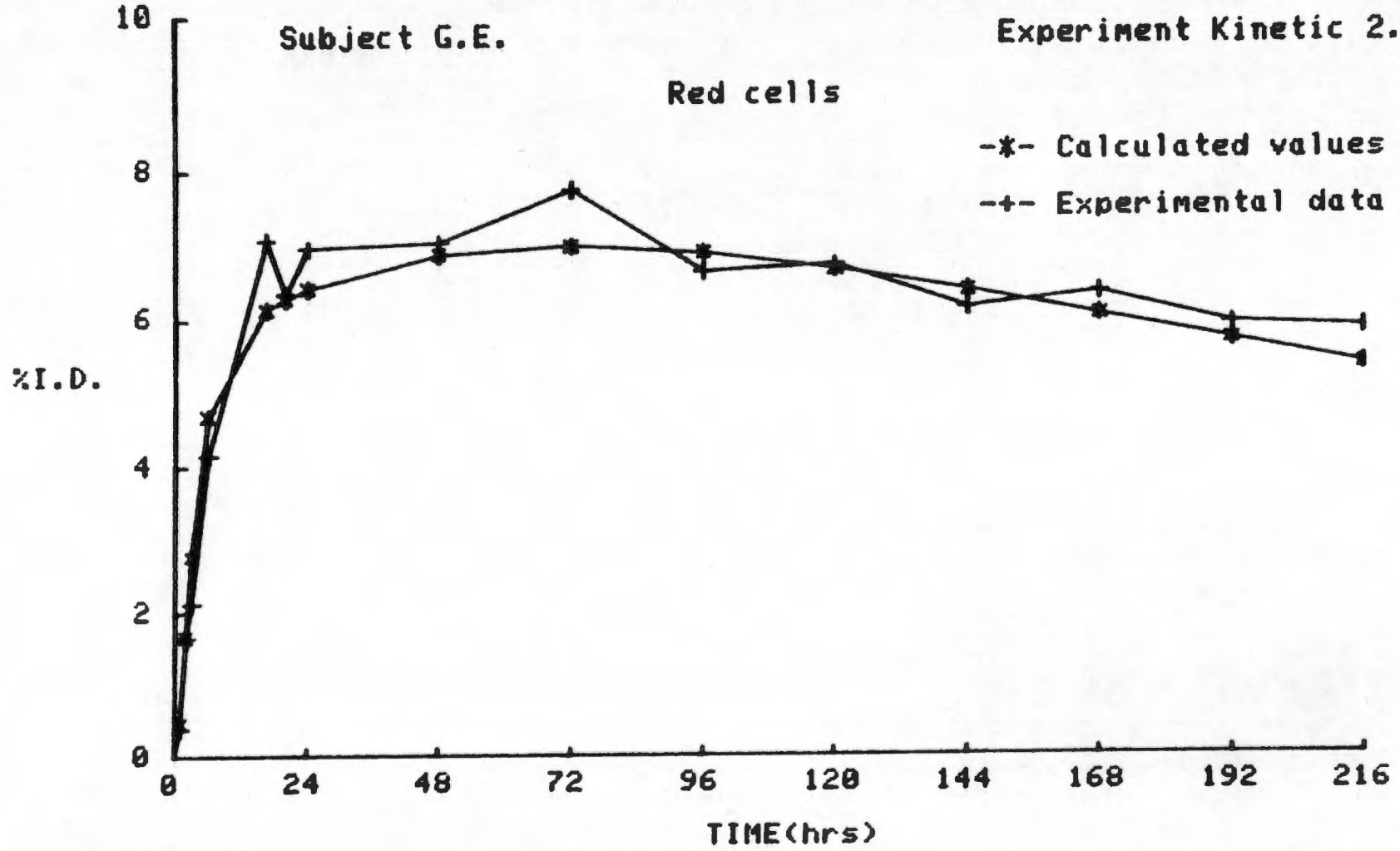


FIGURE. GE-UR-2

Fit of calculated values to experimental data

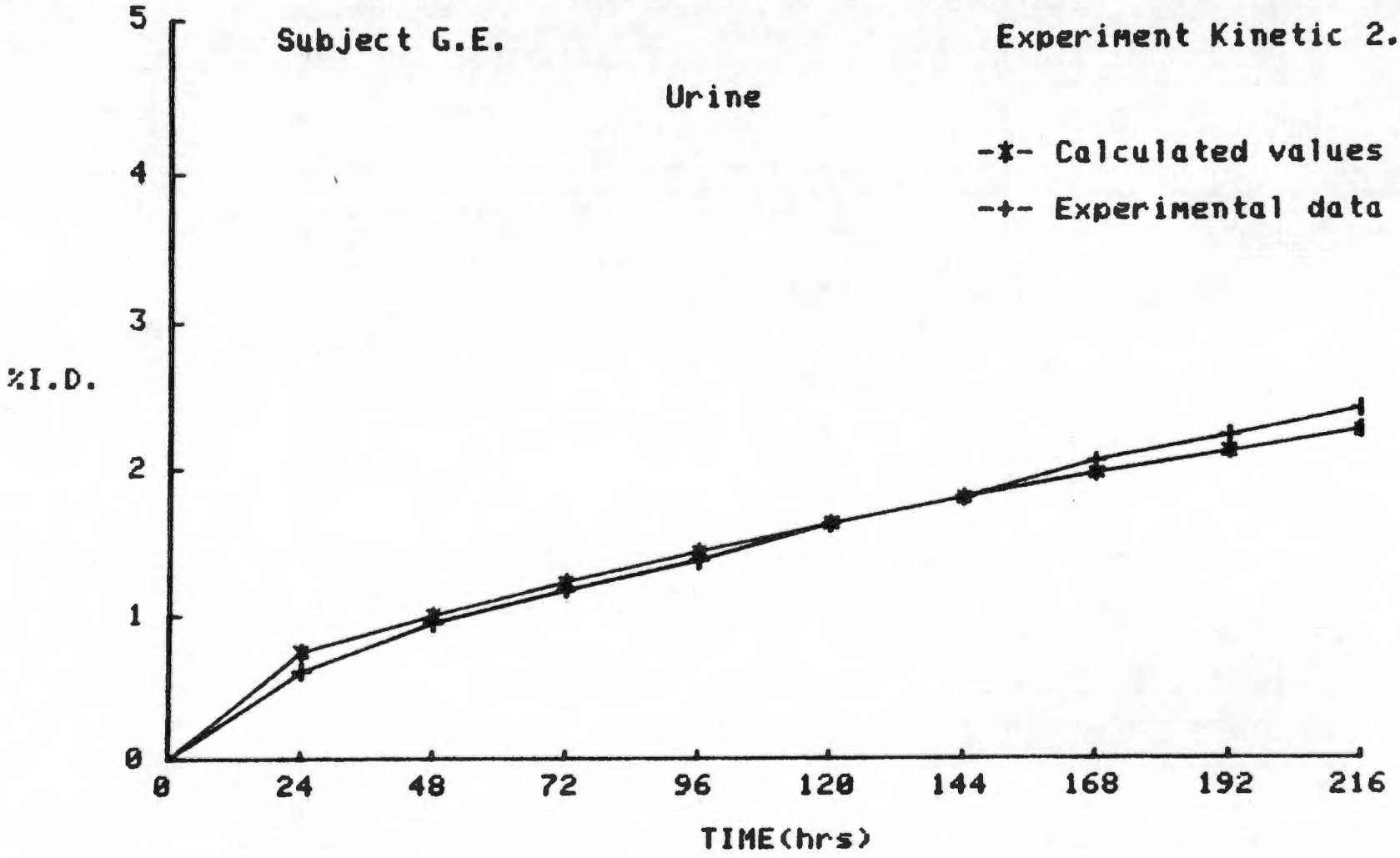


FIGURE. GE-SB-2

Fit of calculated values to experimental data

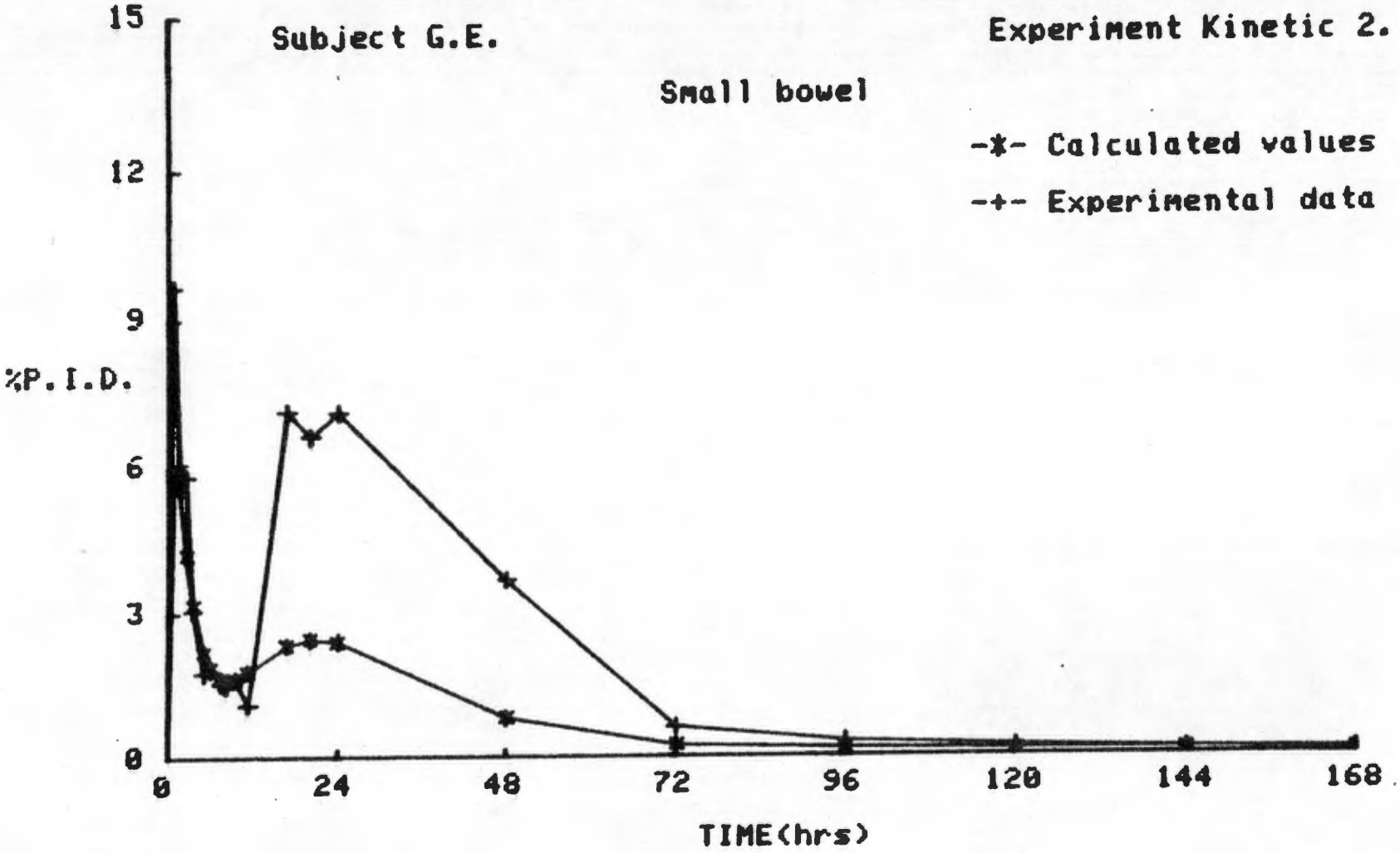


FIGURE. GE-SB-2A

Fit of calculated values to experimental data

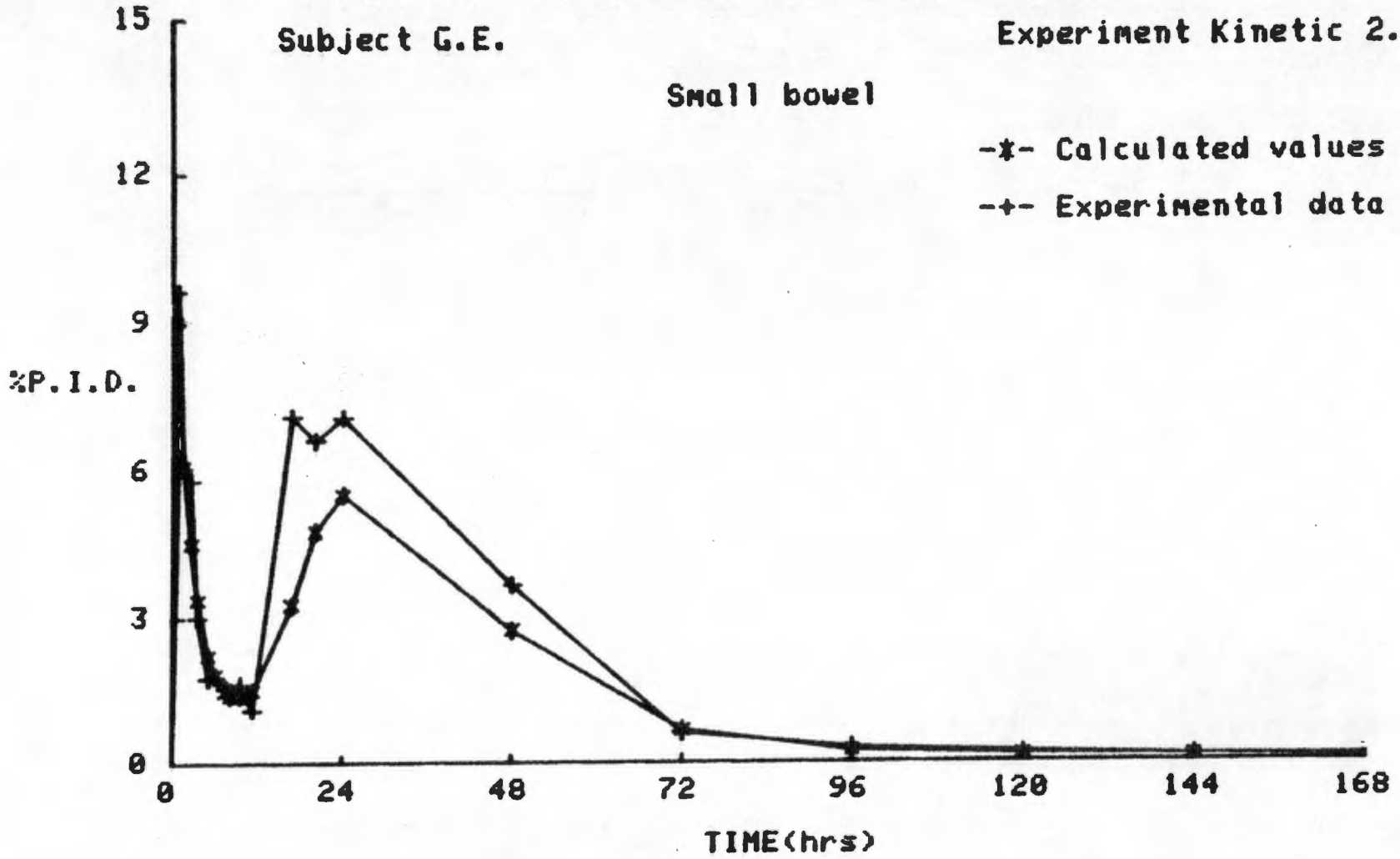


FIGURE. GE-LI-2

Fit of calculated values to experimental data

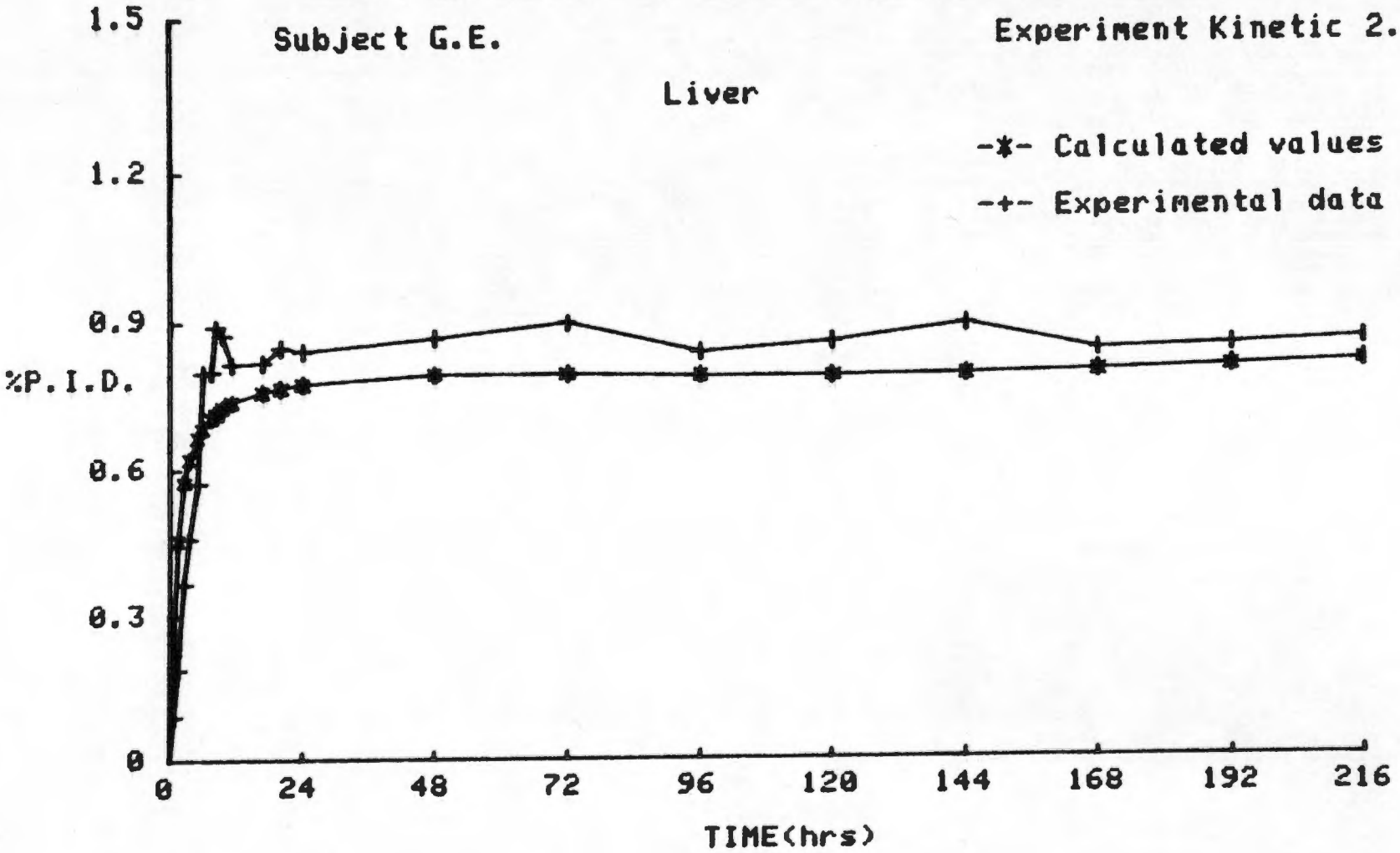


FIGURE. GE-ST-2

Fit of calculated values to experimental data

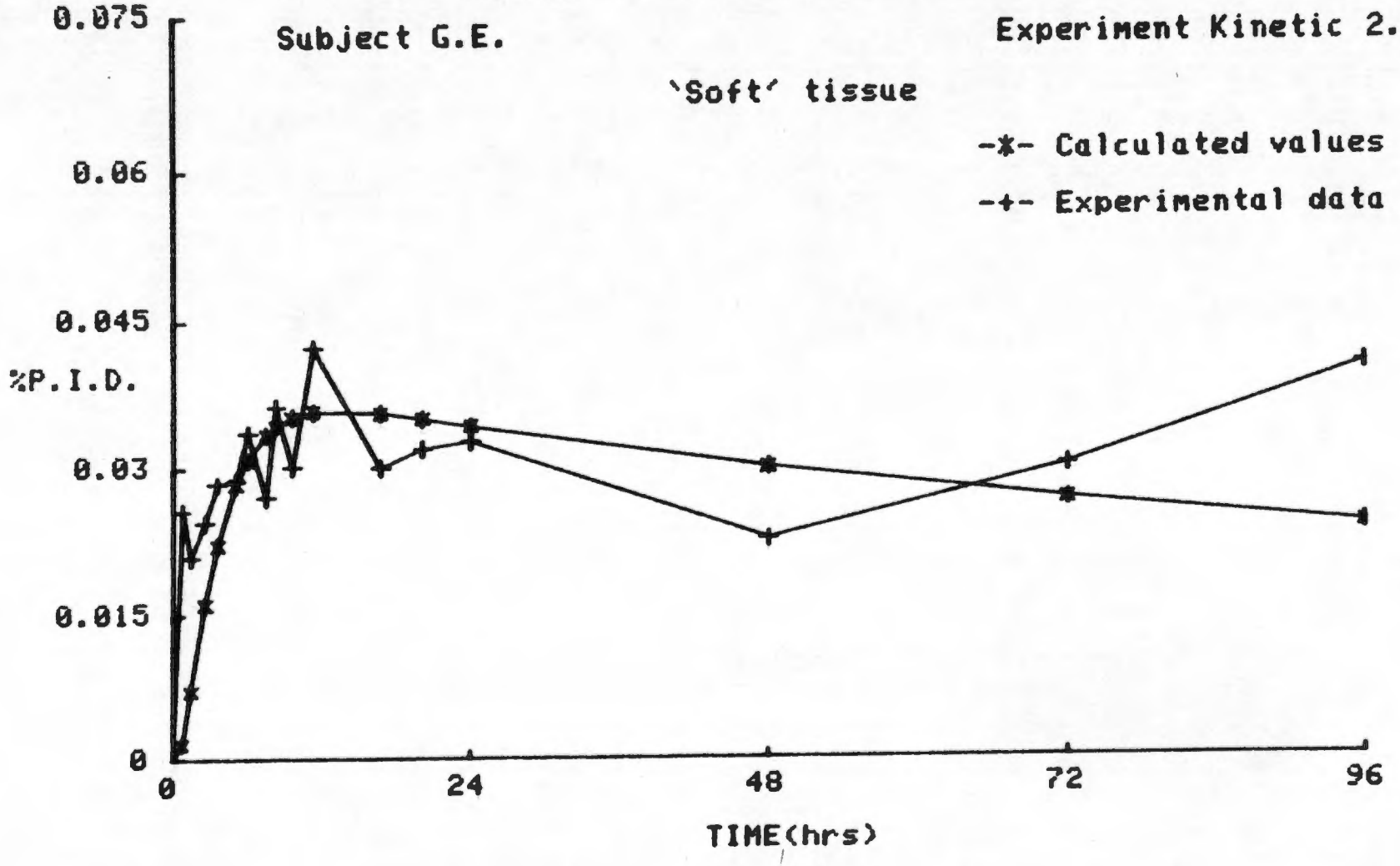


FIGURE. GE-HT-2

Fit of calculated values to experimental data

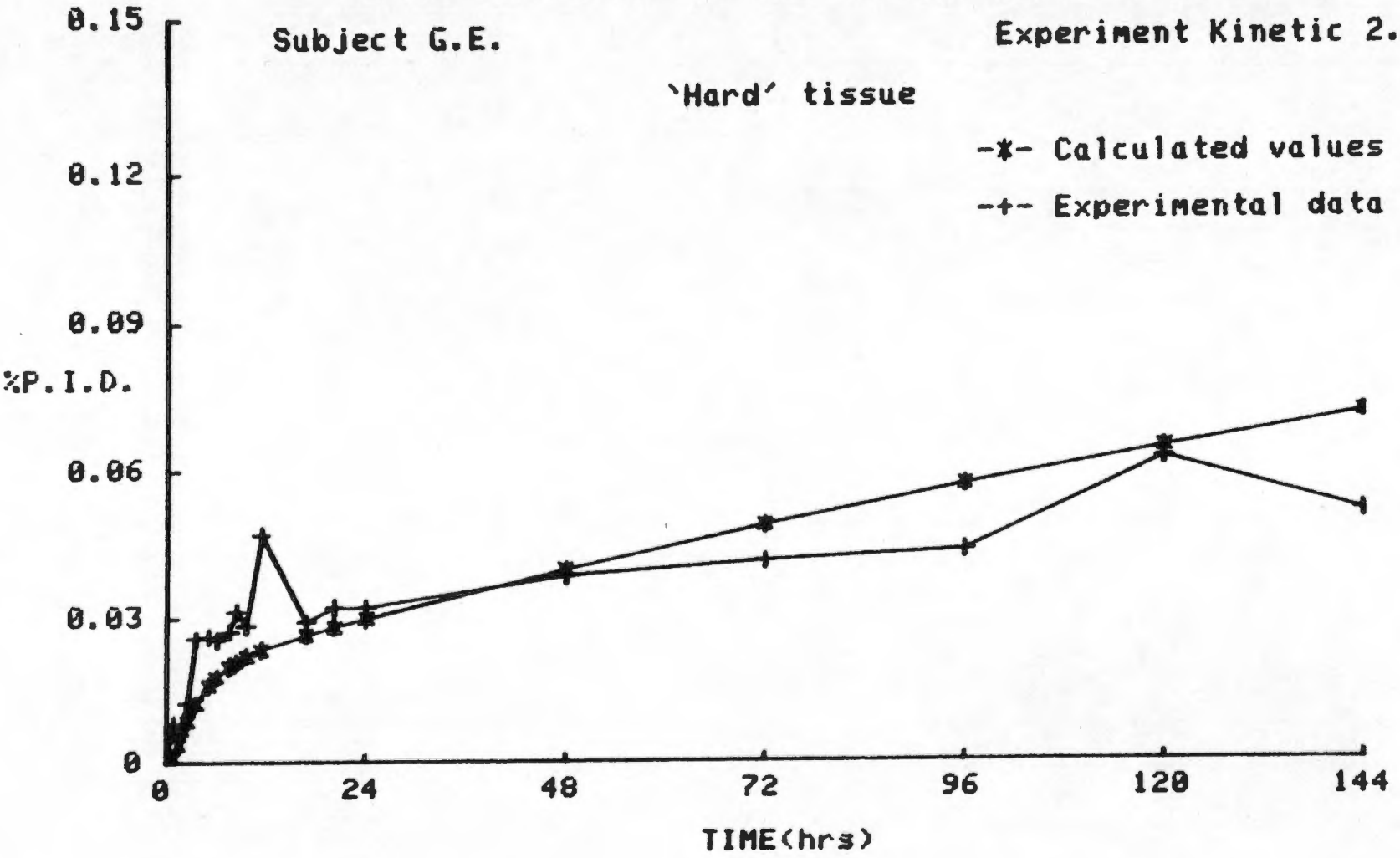


FIGURE. DW-WB-1

Fit of calculated values to experimental data

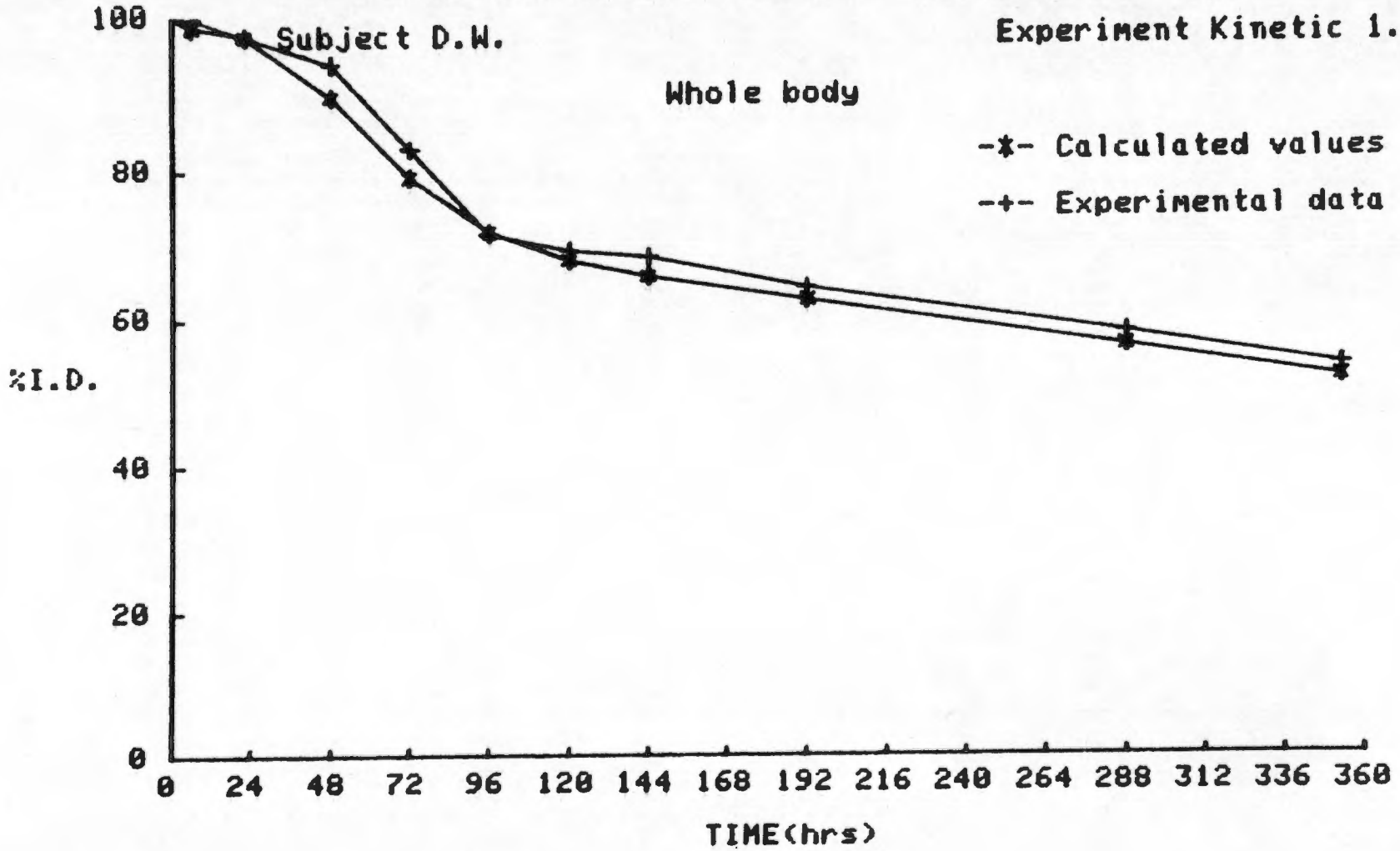


FIGURE. DW-PL-1

Fit of calculated values to experimental data

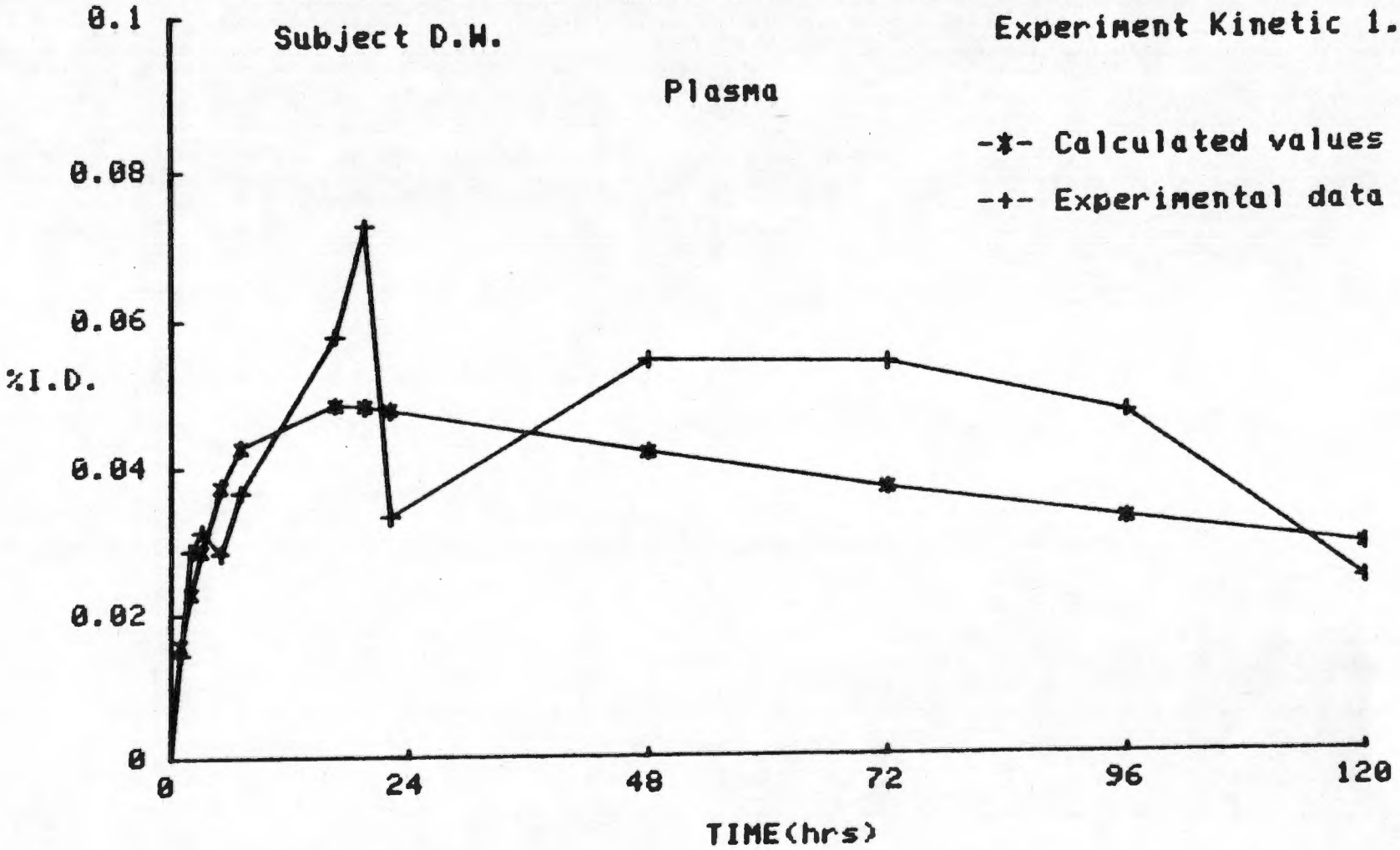


FIGURE. DW-RC-1

Fit of calculated values to experimental data

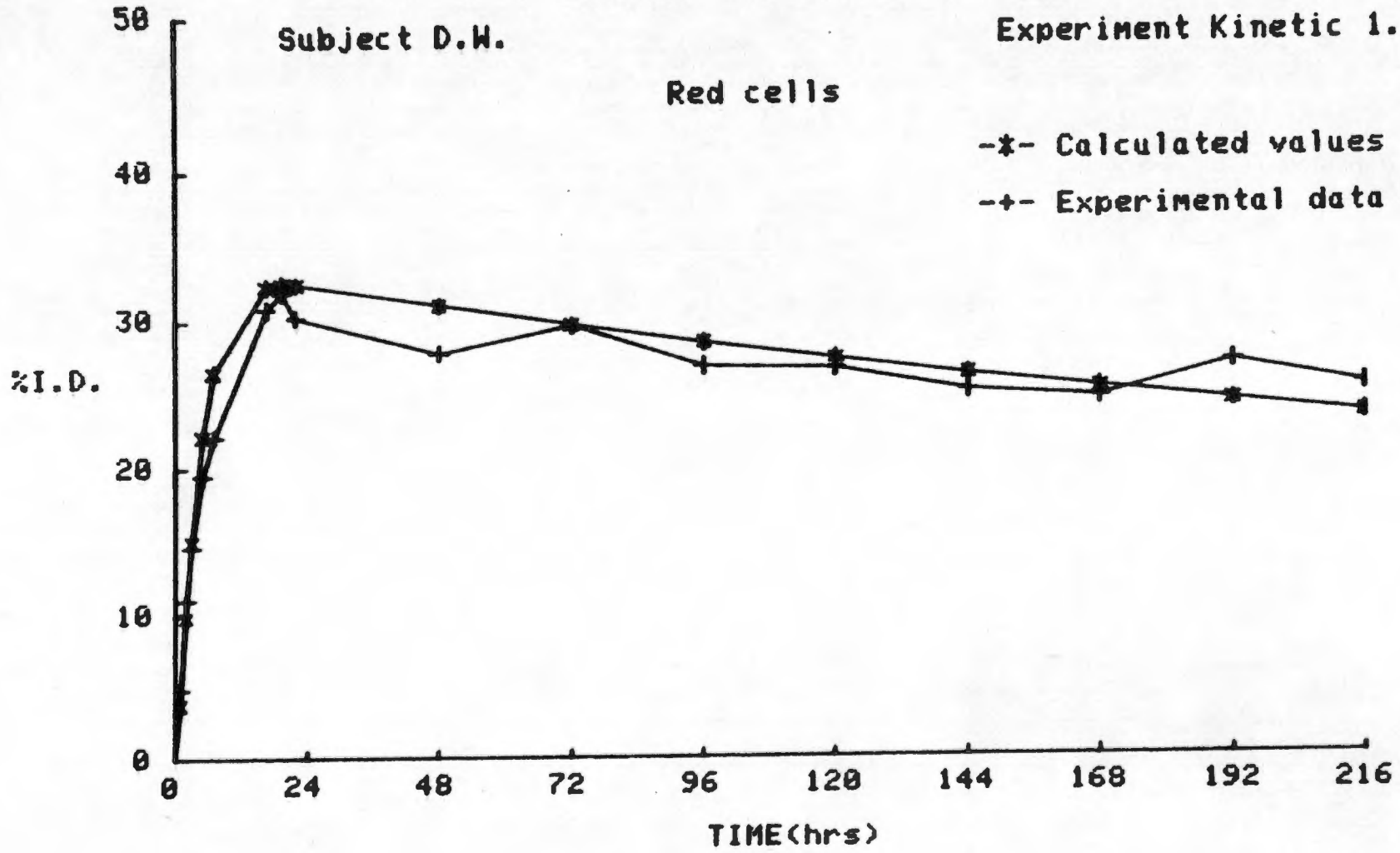


FIGURE. DW-UR-1

Fit of calculated values to experimental data

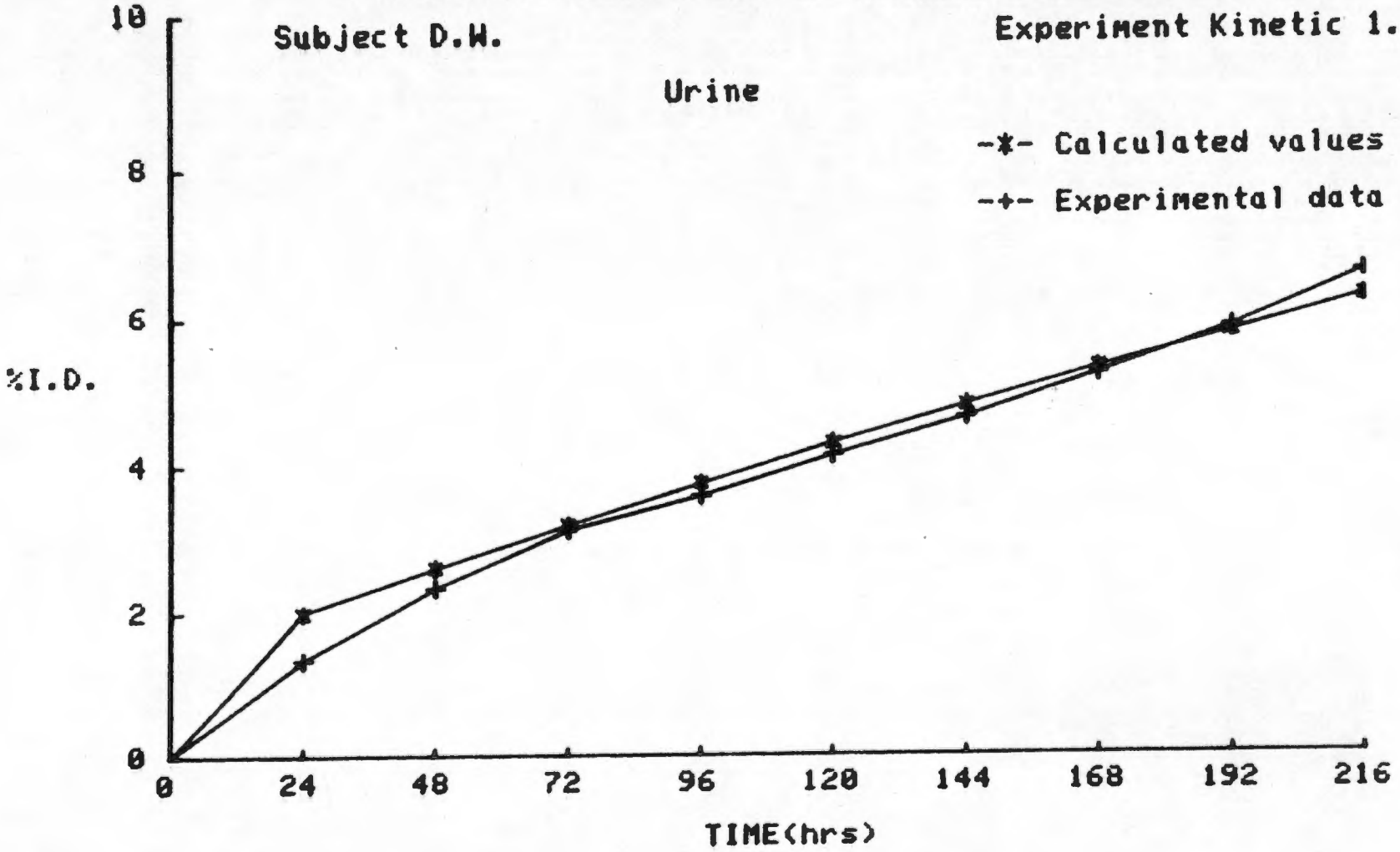


FIGURE. DW-SB-1

Fit of calculated values to experimental data

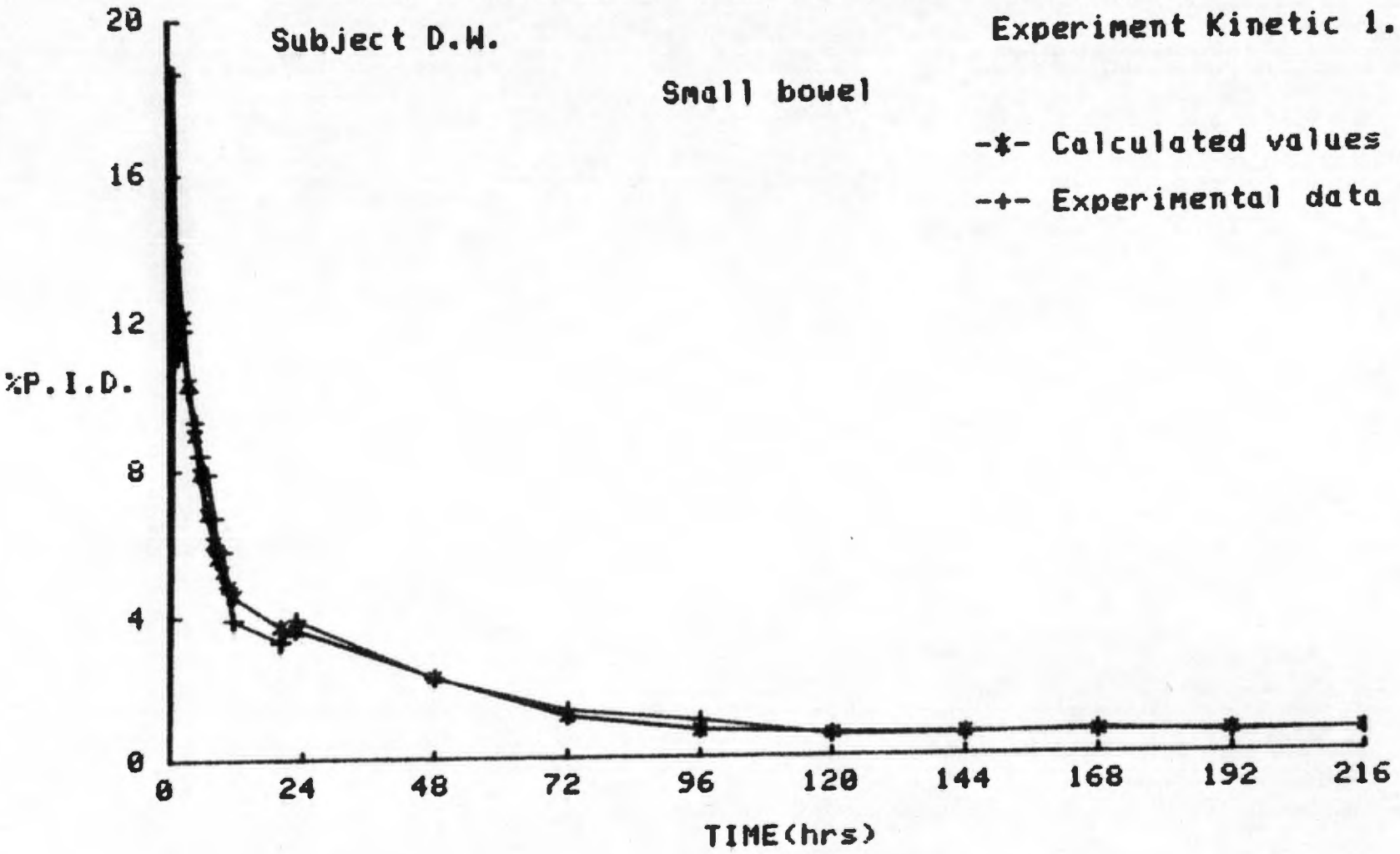


FIGURE. DW-LI-1

Fit of calculated values to experimental data

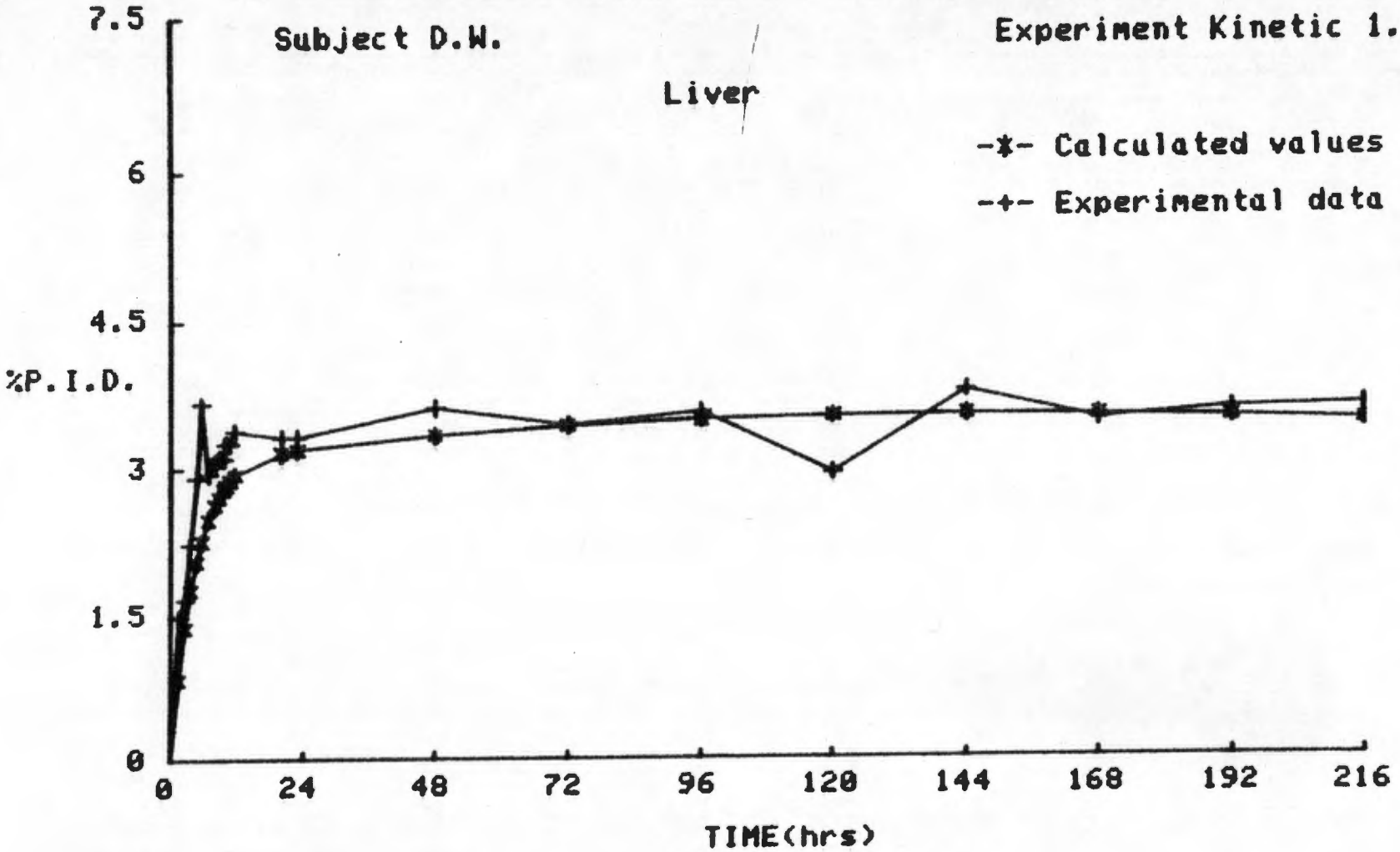


FIGURE. DW-ST-1

Fit of calculated values to experimental data

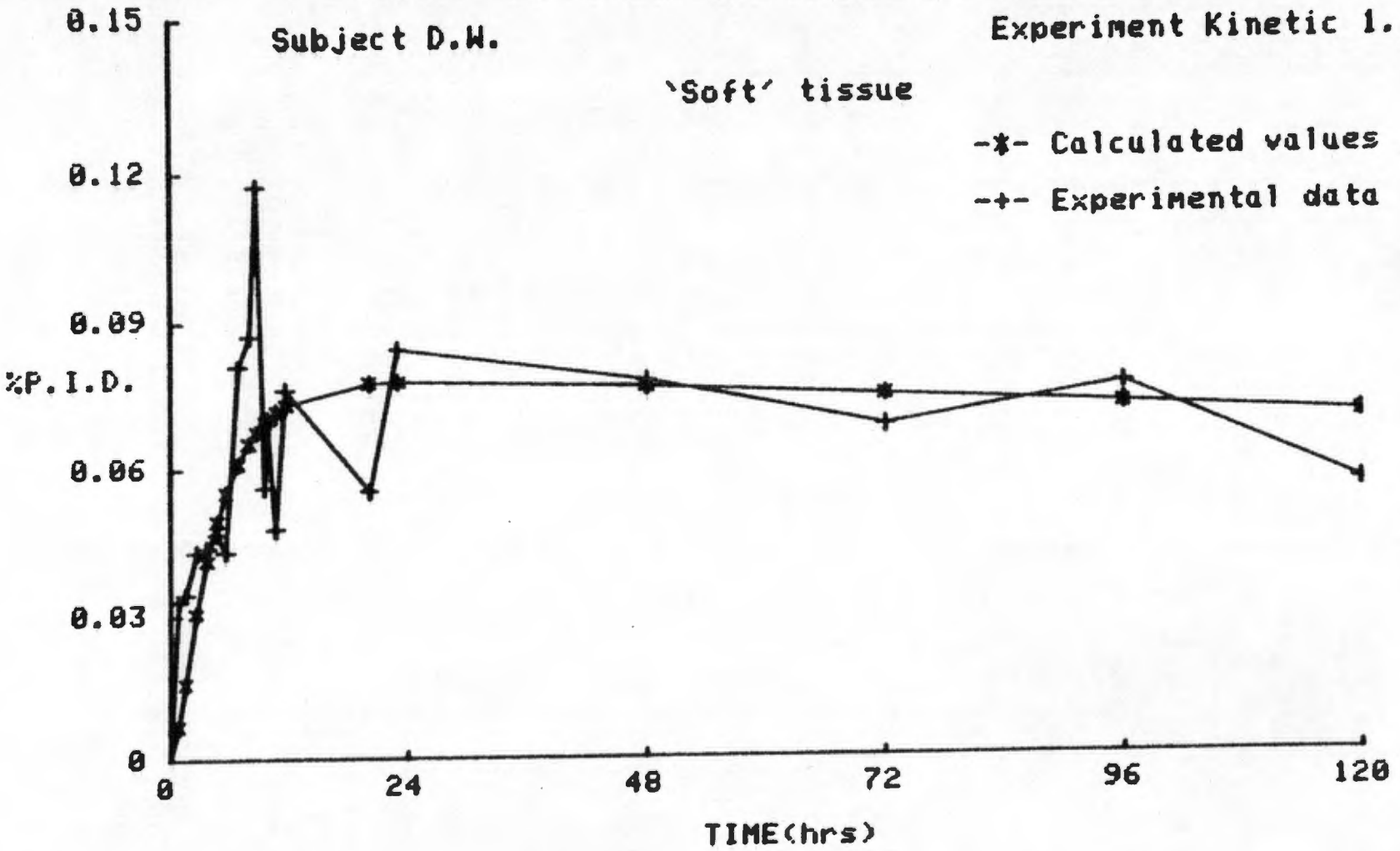
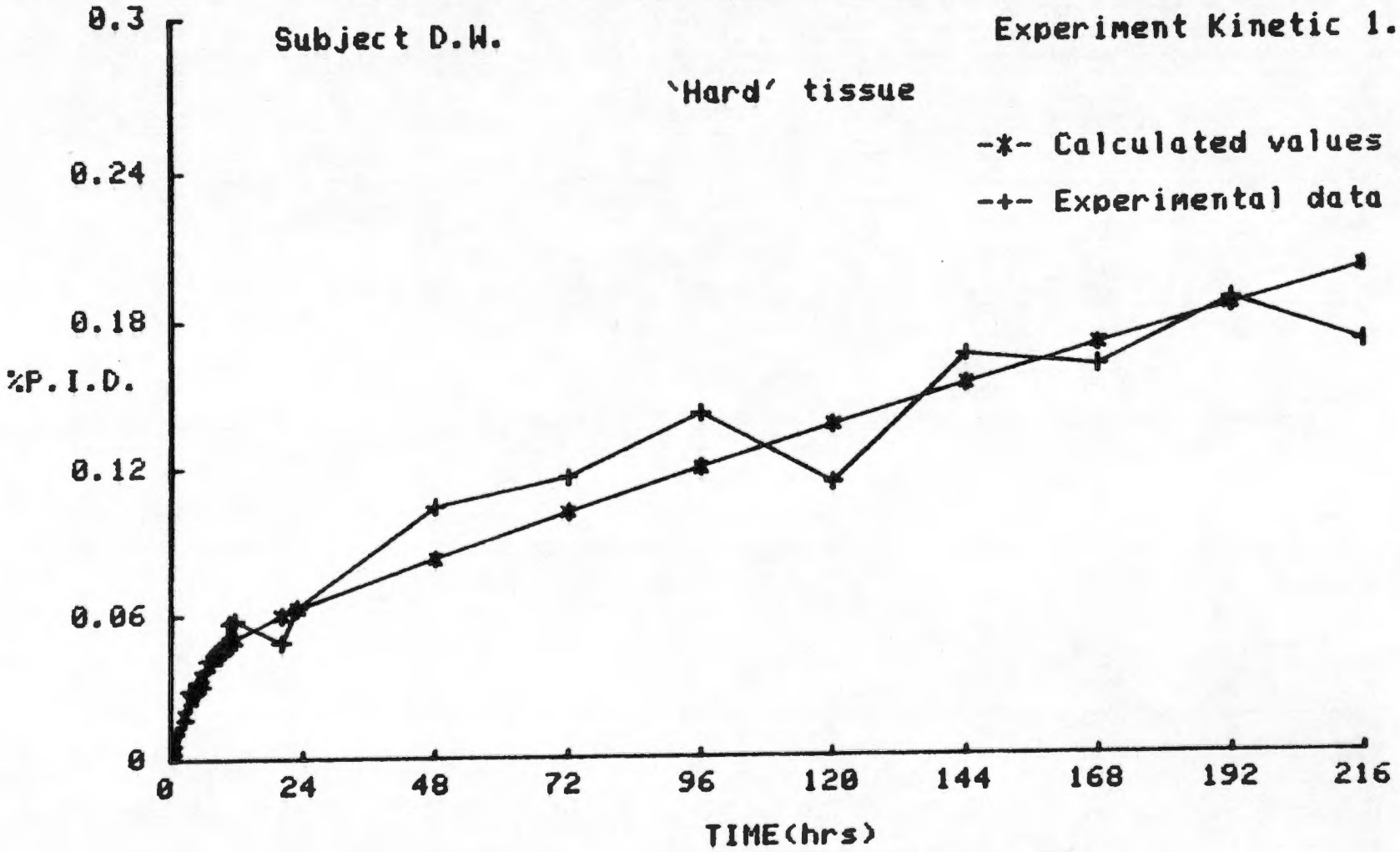


FIGURE. DW-HT-1

Fit of calculated values to experimental data



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APPENDIX A

Quantitative analysis of profile scans

A profile scanner produces a one dimensional image of the distribution of radioactivity in a subject, and it was first described by Pochin (1950). Most of the work done with profile scanning has been qualitative, but it is possible to make a quantitative estimate of the radioactivity in a defined part of the body. Calibration procedures to yield quantitative results have been reported by Tothill and Galt (1971) and Blake and Hering (1973).

The identifing and stripping of profile peaks from the general distribution of radioactivity in blood and tissues are necessary for quantitative results, and although methods have been discussed briefly (Tothill, 1974), no rigorous techniques have been developed. Smoothing, image restoration and other techniques commonly used in gamma ray spectroscopy can be applied to profile scans to improve the accuracy of measurements of organ radioactivity.

A.1 Smoothing and image restoration of profile scans

Image restoration of profile scans has been described by Iinuma and Nagai (1967). They deconvoluted profile scans using iterative approximation procedures. The solution does not converge, however, unless the data are smoothed before deconvolution (Hepburn, 1976). As deconvolution was performed in the spatial domain, the data were

smoothed using a spatial filtering technique, and the method chosen was that of Savitzky and Golay (1964). This has been used in nuclear physics for many years.

A.1.1 Savitzky filter

The Savitzky filter technique of smoothing is basically the least squares fitting of a power function to the observed data. The profile scan data can be defined as an array C. The number of counts in channel i is Ci and i ranges from 1 to n, the number of channels in the scan.

The smoothing value of Ci is defined as Di, and is computed from

$$Di = N_m^{-1} \sum_{j=-m}^{j=m} (am,j\ Ci + j)$$

The constants am,j and the normalizing constant, Nm, are from tables presented by Savitzky and Golay (1964). The index m means that 2m + 1 points (channels) are used in computing Di. As an illustration, a five point smooth (m=2) is computed thus

$$Di = \frac{1}{35} (-3\ Ci_{-2} + 12\ Ci_{-1} + 17\ Ci + 12\ Ci_{+1} - 3\ Ci_{+2})$$

This computation can be repeated for channels i=3 to i=n-2 to give the smoothed profile scan.

The choice of m is very important when statistical variations in count data are smoothed. If m is too large, the smoothed profile scan will tend to have shallow peaks and valleys and will generally be distorted;

if m is too small, the smoothed profile scan will not be smooth, and in the extreme cases will not be as smooth as the raw data.

A.1.2 Iteration approximation method of Iinuma and Nagai

The following expression represents the smoothed profile scan

$$G(x') = \int_{-\infty}^{+\infty} F(x' - x)R(x)dx \qquad (1)$$

where F(x) is the ideal image and R(x) is the point source response of the profile scanner. The deconvolution of equation (1) to find F(x) can be done using iterative approximation methods.

The nth iteration can be expressed as follows:

$$G^n(x') = G^{n-1}(x') + \left\{ G(x') - \int_{-\infty}^{+\infty} G^{n-1}(x' - x)R(x)dx \right\}$$

and

$$H^n(x') \equiv \int_{-\infty}^{+\infty} G^n(x' - x)R(x)dx$$

The following expression is used to define the limit of the approximation.

$$\sum_{x=1}^{N} \frac{\{G(x) - H^n(x)\}^2}{G(x)} \leqslant N$$

N is the total number of increments in the original image, and this expression is based on the criterion that the iteration should be terminated when the difference between iterated images becomes of the order of one statistical standard deviation of G(x).

Convergence will depend on the statistical error of the counts accumulated by the profile scanner. Therefore, in a series of profile scans in which the radioactivity is decreasing because of the physical decay of the radionuclide, the degree of smoothing will have to be increased by increasing the value of m.

The combination of Savitzky filter and the image restoration technique of Iinuma and Nagai was tested by the following experiments. A profile scan obtained with poor resolution conditions was smoothed, image restored and compared with a profile scan obtained with good resolution conditions.

A.1.3 Materials and methods

The experiments were performed on a Nuclear Enterprises NE 8108 'shadow-shield' whole body counter with the profile collimators removed. The adjustable slot collimators were set 2 cm apart and a couch speed of 500 mm/min was used. The pulse height analyser was set to detect the 393 KeV gamma ray of ^{113m}In, and its logic output fed into a 400 channel Inter-technique multichannel-analyser (M.C.A.). The M.C.A. was set to multiscale with a time increment of 690 msec. over 150 channels.

Eight ^{113m}In sources of 100 μCi each were placed with their long axes perpendicular to the direction of motion of the couch. The sources were

25 mm in diameter and 60 mm in length, and they were placed 100 mm apart with two point sources placed at either end to act as marker sources. The digital marker had not been constructed at this stage. Profile scans of sources plus marker sources, marker sources only, and background were recorded in the M.C.A. system. Profile scans were recorded with a collimator slit width of 2 cm (good resolution) and 4 cm (poor resolution). This latter profile scan was performed approximately 2 hours after the former, so that the counts accumulated would be approximately equal. The profile scans, therefore, were statistically comparable.

The data was punched on paper tape, and fed into a Univac 1100 computer via a Tektronix 4051 intelligent terminal. Preparation of the data before smoothing and restoration, was done by aligning the profiles using the marker sources, subtracting the marker sources from total source profiles and subtracting the background from marker source profiles. Smoothing and image restoration were performed on the poor resolution profile using computer programs E.2.1-3. A 17 point Savitzky filter smooth was used and convergence occurred at the 4th iteration (table A.1.1).

A.1.4 Results

The profiles recorded at a slit width of 4 cm are degraded in comparison to those recorded at the smaller slit width, as shown in figure A.1.1. Figure A.1.2 shows the comparison of the restored image of the sources and the image obtained with good resolution. Considering the original degradation of the image, smoothing and image restoration have been successful.

TABLE A.1.1

Convergence of Iinuma and Nagai image restoration technique applied to profile scan obtained with poor resolution conditions

NUMBER OF ITERATIONS	CONVERGENCE
1	2332
2	167
3	158
4	157
5	157

FIGURE A.1.1

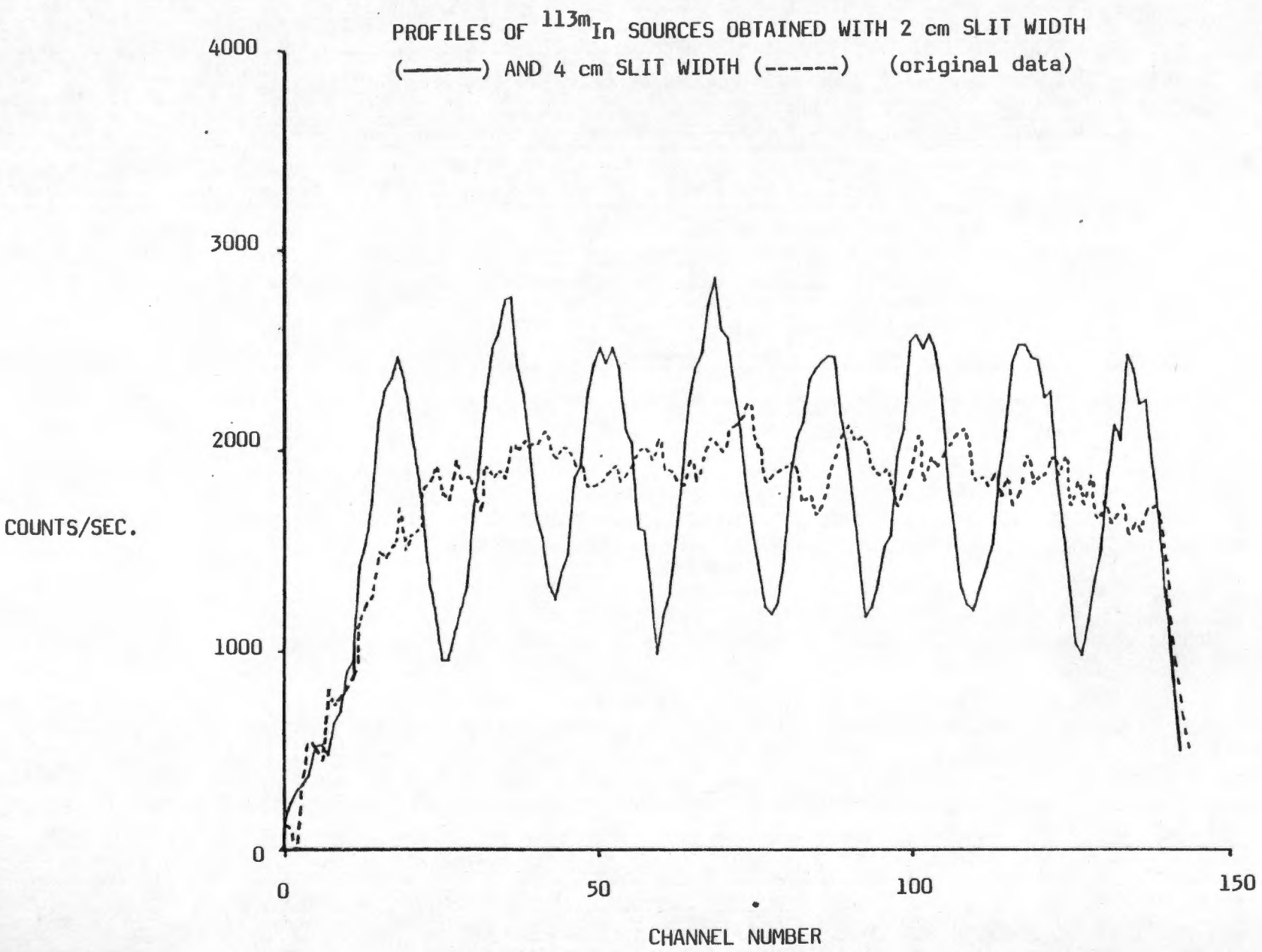
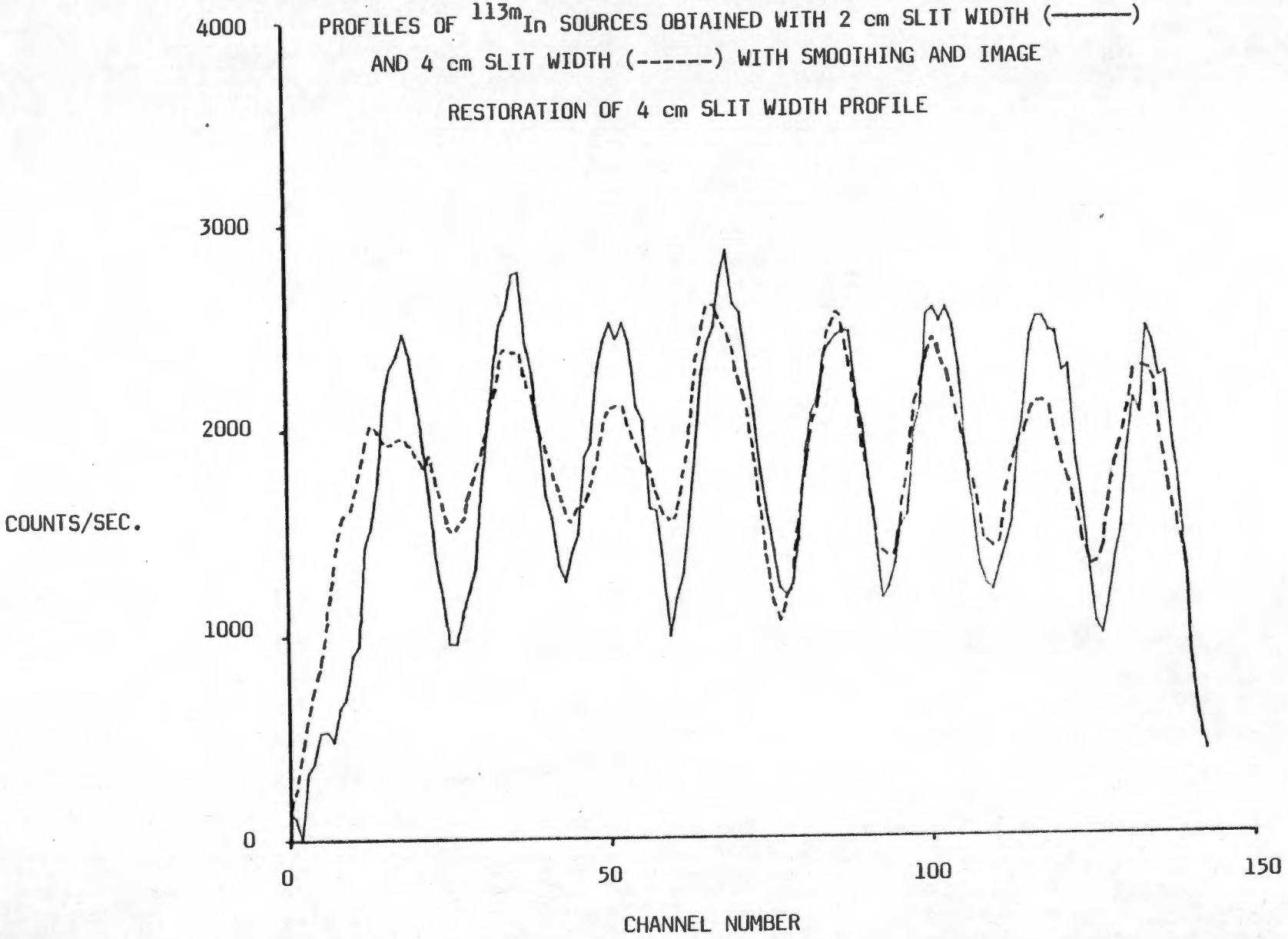

PROFILES OF ^{113m}In SOURCES OBTAINED WITH 2 cm SLIT WIDTH
(———) AND 4 cm SLIT WIDTH (------) (original data)
4000
3000
2000
1000
0
COUNTS/SEC.
0
50
100
150
CHANNEL NUMBER

FIGURE A.1.2


PROFILES OF ^{113m}In SOURCES OBTAINED WITH 2 cm SLIT WIDTH (———)
AND 4 cm SLIT WIDTH (------) WITH SMOOTHING AND IMAGE
RESTORATION OF 4 cm SLIT WIDTH PROFILE
4000
3000
2000
1000
0
COUNTS/SEC.
0
50
100
150
CHANNEL NUMBER

A.2 Determination of the radioactive content of organs in the body

After smoothing and image restoration, the next step is to decide which organs gave rise to the observed profile peaks, to subtract peak backgrounds caused by blood or soft tissue radioactivities, and to separate peaks produced by neighbouring organs.

The correspondence between profile peaks and organs can be found by two dimensional imaging, and by relating the position of the peak to the anatomy of the body. With the wide range of radiopharmaceuticals now available, it is possible to visualise most of the organs of the body and to identify a particular organ with the shape and position of its profile peak.

Blood and E.C.F. backgrounds can be found using non diffusible and diffusible tracers, such as ^{113m}In and ^{82}Br. Profiles obtained with only one of these radionuclides present in the body at one time, can be scaled down by factors related to the radioactivities of the tracers ^{113m}In and ^{82}Br, by the radioactivity of the radionuclide of interest in the blood and E.C.F. and by the different detector responses of the radionuclides.

The tissue background under the peaks of interest can be estimated from data points outside the peak, and a baseline interpolated to distinguish the radioactivity due to background from that in the peak itself. Linear interpolation and interpolation using polynomials for this purpose have been discussed by Covell (1959) and Quittner (1972).

Once the peaks due to organ radioactivities have been isolated, the area under each peak can be found. If the peaks overlap, however, the determination of peak area can be difficult, and the best approach is to perform a weighted least squares fit of the individual peaks, which gives a solution having the smallest statistical error. Data describing the individual profile peaks can be obtained from the specific uptake of radiopharmaceuticals in the organs of interest, or the fit can be performed with an analytical function. Unfortunately, it is difficult to obtain the profiles of an individual organ, unless the radionuclide or radiopharmaceutical is totally specific to that organ, such as ^{131}I in the thyroid. The liver accumulates much more labelled colloid than the spleen, and can be effectively isolated by shielding the spleen with lead. But the opposite, the subtraction or shielding of the liver to give individual profiles of spleen will result in considerable statistical error in the final profiles. Because of these large errors, the least squares fitting of these individual profiles to a composite profile will be invalidated (Salmon, 1974). However, it may be possible to fit an analytical function to the shape of the profile peaks of each organ obtained from subtraction or shielding. The composite profile scan, which may consist of a number of organs, can then be fitted by least squares methods using the appropriate analytical functions for each organ.

A.2.1 Modified Gaussian function

In this study, a single analytical function was developed that could fit each organ profile. The basis of this function is a modified Gaussian

of the form

$$y(x) = A(1 + \alpha_1 (x-p)^m + \alpha_2 (x-p)^n) \exp(-(x-p)^2 /2\sigma^2)$$

which has been proposed by Heath (1964) to fit radionuclide spectra obtained from NaI(Tℓ) detectors. The parameters A, p, σ, α_1, α_2, m and n are determined for each peak. Unfortunately, this modified Gaussian is symmetrical about the value p, and profile peaks of organ radioactivities tend to be unsymmetrical. An additional function is required, which will operate only on one side of the modified Gaussian peak. A sigmoidal type of function (Karam, 1974) was chosen with an analytical form of

$$S = \frac{Smax \times x^k}{x_{50}^k + x^k}$$

that can be made to rise steeply to the value Smax at any value of x by the judicious choice of the constants K and x_{50} (the value of x at Smax/2). This sigmoid type function was incorporated into the modified Gaussian by replacing the parameters α_1 and α_2.

The total expression now becomes

$$y(x) = A(1 + S\left\{ (x-p)^m + (x-p)^n \right\}) \exp(-(x-p)^2 /2\sigma^2)$$

and to check that this expression could fit different organ profiles containing different radioactivities, the phantom experiments in the following section were performed.

A.2.2 Materials and methods

The same experimental set up was used as in A.1.1 except that the resolution of the profile scanner was improved by reducing the slit width between the slot collimators to 5 mm. Organ profile studies were done using a Picker Organ Scanning Phantom. Liver, pancreas and spleen phantoms could be placed individually or together in the abdomen section. Approximately 3 mCi of ^{113m}In was placed in each organ phantom, and the phantom and the perspex shell of the abdomen filled with water. The liver, pancreas and spleen, therefore, were immersed in a scattering medium.

Profiles were recorded of liver and pancreas organ phantoms together and then of each individual organ phantom. The organ phantoms were placed in approximately the correct anatomical positions in the abdomen, and, in each study involving different organ phantoms, care was taken to preserve the original geometrical relationship between phantoms. The spleen phantom was then chosen to provide three profile scans of an organ containing differing amounts of radioactivity. These scans were performed at 0 hour, 1 hour and 2 hours. Finally, the line source response of the profile scanner was obtained using a source of 250 µCi ^{113m}In immersed in water.

The profile scans were corrected for decay, background radiation, smoothed and image restored using the methods described previously. The modified Gaussian function was then fitted to liver, pancreas, spleen and liver/pancreas composite profiles using parametric and non-linear least squares fitting procedures from the Simulation,

Analysis and Modelling (SAAM 25) computer program of Berman and Weiss (1967).

A.2.3 Results

Table A.2.1 shows the effectiveness of the smoothing and restoration techniques, by comparing the object length of the organ phantoms to the smoothed and restored image length. The percentage difference is greatest with the smallest organ (pancreas), because the techniques involved cannot restore completely the sharp leading edges of organ radioactivity. Figures A.2.1-A.2.3 show the fits obtained between calculated and experimental data for pancreas, spleen and liver phantoms and table A.2.2 lists the parameter values. It was found that two modified Gaussian functions were required to fit the restored liver profile. The fits are not perfect, but the total counts under the peaks for the experimental and theoretical profiles agree (table A.2.3).

The spleen profiles obtained with different radioactivities were fitted with the modified Gaussian function, and it can be seen from table A.2.4 that the only parameter which varies appreciably is the peak height. Thus, once the shape of the profile has been fitted with the modified Gaussian, only the height and displacement of the peak will vary with radioactivity and position of the organ.

Figure A.2.4 shows the fit of the modified Gaussian functions to the composite liver and pancreas profile scan. Once the parameters for a particular organ are found, a combination of organ profiles can be fitted using the method of weighted least squares. Using the parameter values found from the composite fit, the number of counts under the

TABLE A.2.1

Comparison of object lengths and image restored lengths of organ phantoms (^{113m}In)

ORGAN PHANTOM	OBJECT LENGTH (cm)	IMAGE RESTORED LENGTH (cm)	% DIFFERENCE
Pancreas	6.5	8.4	+ 29.0
Spleen	10.5	11.5	+ 9.5
Liver	16.0	16.2	+ 1.3

FIGURE A.2.1

COMPARISON OF THEORETICAL PROFILE (------) WITH EXPERIMENTAL PROFILE (———) FOR PANCREAS PHANTOM (^{113m}In)

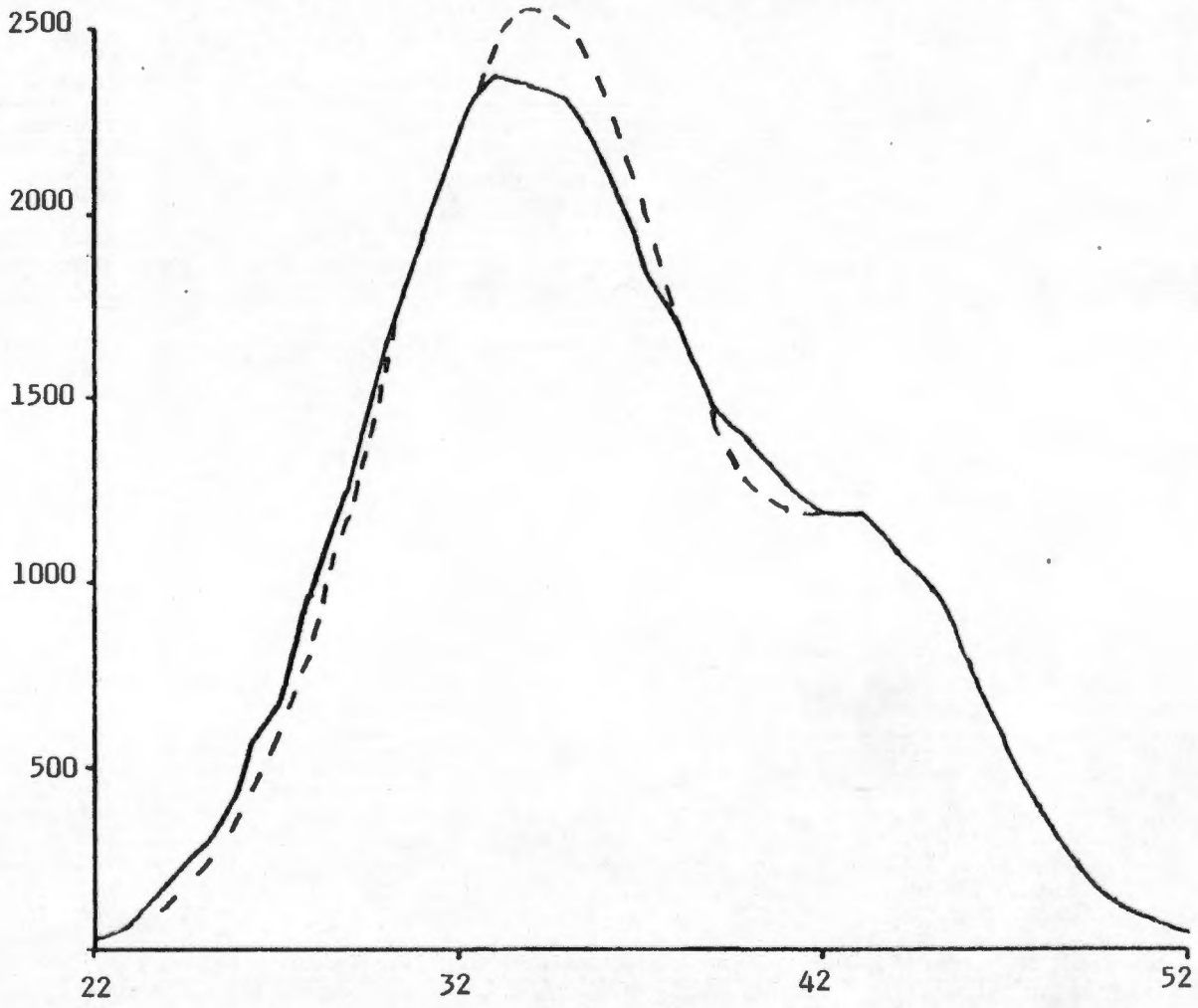


FIGURE A.2.2.

COMPARISON OF THEORETICAL PROFILE (------) WITH EXPERIMENTAL PROFILE (———) FOR SPLEEN PHANTOM (^{113m}In)

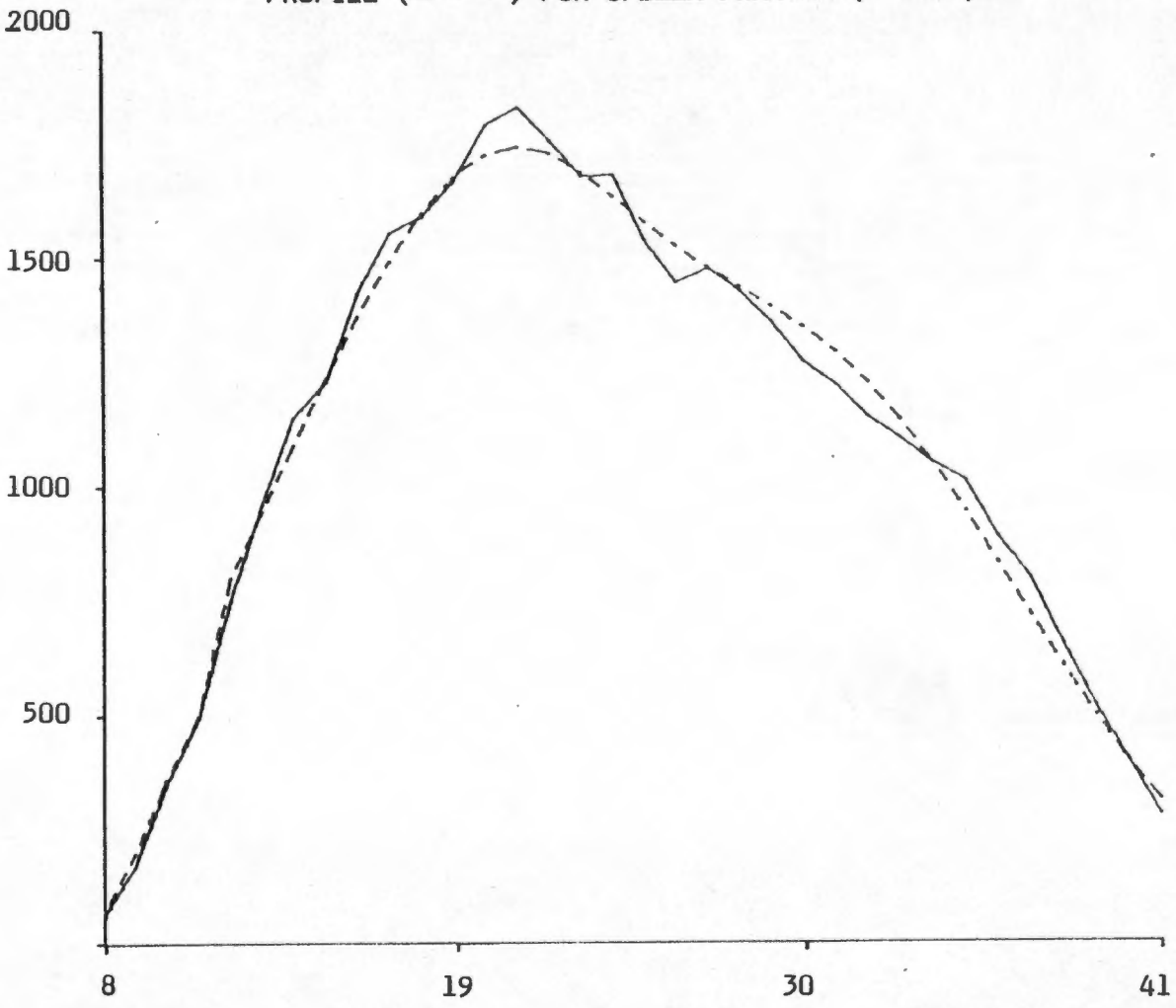


FIGURE A.2.3

COMPARISON OF THEORETICAL PROFILE (------) WITH EXPERIMENTAL PROFILE (———) FOR LIVER PHANTOM (^{113m}In)

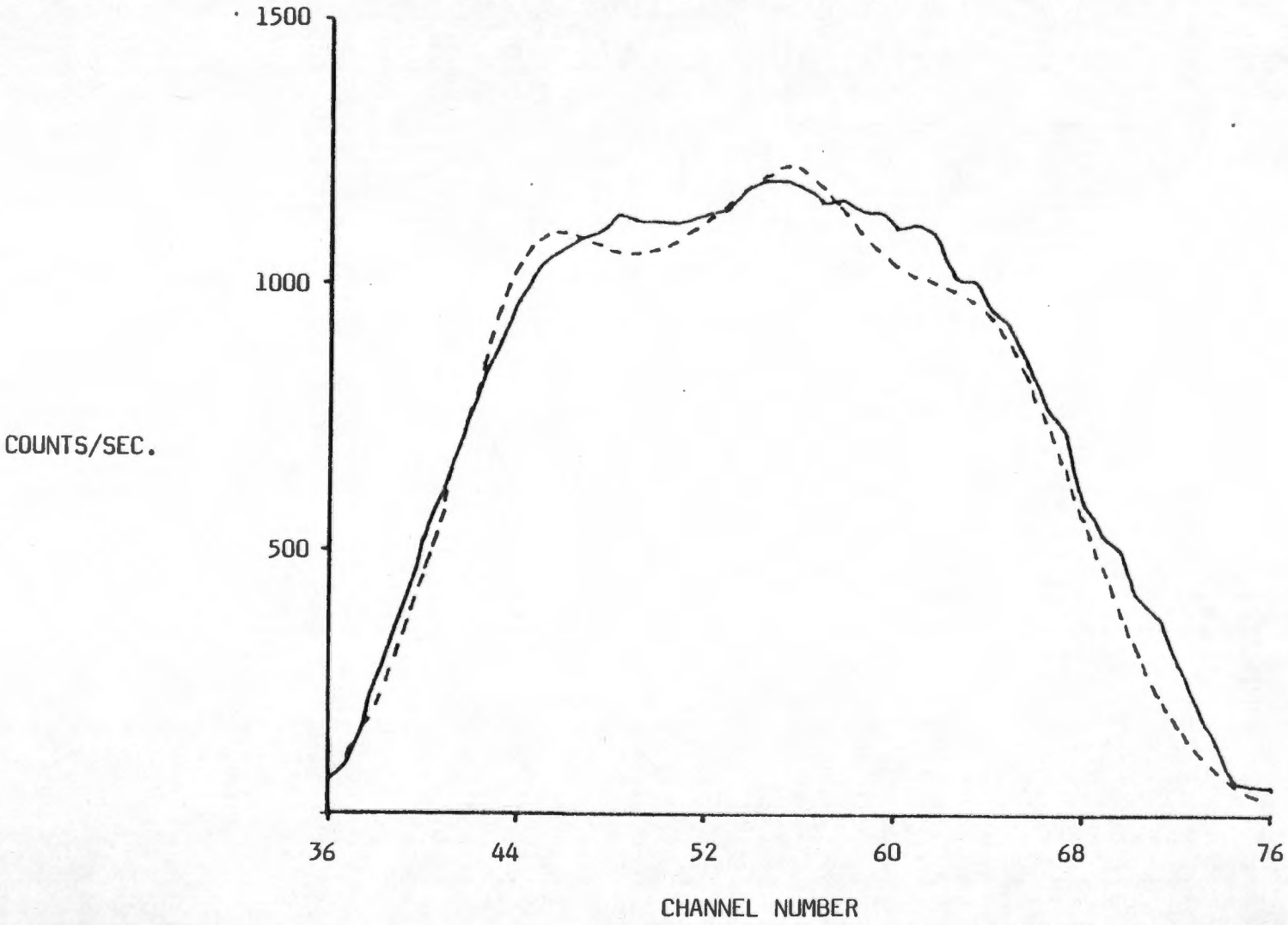


TABLE A.2.2

Parameters of modified Gaussian function

fitted to different organ phantom profiles

(^{113m}In)

PHANTOM	A	p	m	n	σ	Smax	k	x_{50}
Pancreas	2554	34.2	1	5	4.16	7.6×10^{-5}	15.0	38.8
Spleen	1741	20.9	3	3	7.20	4.7×10^{-4}	15.0	21.0
Liver	983	36.9	2	3	4.77	1.3×10^{-3}	20.0	36.3
	1177	51.9	2	3	6.74	1.3×10^{-3}	20.0	36.3

TABLE A.2.3

Comparison between experimental and calculated

total counts in organ phantom profiles

(^{113m}In)

ORGAN	TOTAL COUNTS IN PROFILE (Experimental)	TOTAL COUNTS IN PROFILE (Theoretical)	% DIFFERENCE
Pancreas	33122	34356	+ 3.7
Spleen	37662	36393	- 3.4
Liver	39872	39404	- 1.2

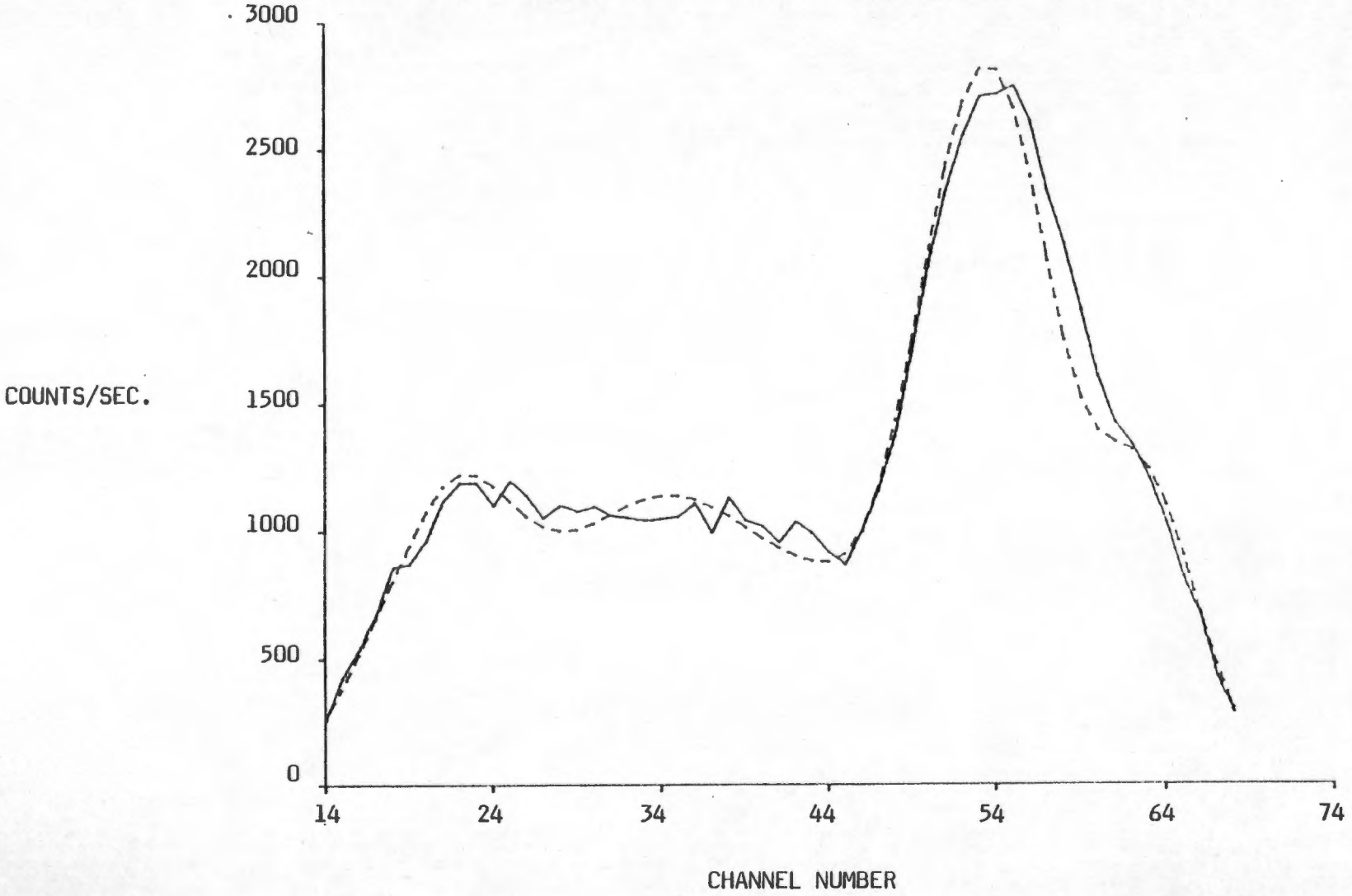
TABLE A.2.4

Parameters of modified Gaussian function fitted to profiles of spleen phantom containing different radioactivities of ^{113m}In

TIME (hours)	A	p	m	n	σ	Smax	k	x_{50}
0	1421	20.9	3	3	6.2	$7x0x10^{-4}$	15	21
1	935	21.5	3	3	6.4	$7.7x10^{-4}$	15	21
2	637	22.4	3	3	6.4	$6.8x10^{-4}$	15	21

FIGURE A.2.4

COMPARISON OF THEORETICAL PROFILE (------) WITH EXPERIMENTAL PROFILE (———) FOR COMBINATION OF LIVER AND PANCREAS (^{113m}In)



modified Gaussian functions can be calculated.

The radioactivity in the organ of interest can then be found from the calibration method of Blake and Hering (1973), the calculated counts under the organ profile peaks and the counts under the profile of a standard containing a known percentage of the administered dose. If whole body counts are being measured concurrently with the profile scans, the percentage ingested dose in the organ of interest can be calculated from the ratio of counts in the organ profile to the counts in the whole body profile, multiplied by the percentage retention in the whole body.

A.3 Determination of modified Gaussian function to fit liver profile peak

A.3.1 Introduction

A profile peak of ^{203}Pb radioactivity, after subtraction of backgrounds, may overlap with other organ peaks. The number of counts under this specific peak can only be accurately found by fitting a number of analytical functions to the series of peaks. A suitable function is the modified Gaussian function described in A.2.1., and once the variable parameters of this function have been found by fitting the function to ^{203}Pb profile peak, the area under the function will give the number of counts in the peak if the fit is good.

There are radiopharmaceuticals which are preferentially taken up in the liver. A modified Gaussian function may be fitted to the profile of liver radioactivity, as there will be minimal interference from radioactivity elsewhere in the body.

A.3.2 Materials and methods

^{113m}In chloride was obtained by elution from a generator (TRC, Code: TFC 3) with 0.05 MHCl and suspended in a colloid form using a labelling kit (TRC, Code: N.82). 1 - 3 mCi of the colloid was injected intravenously and, after 20 minutes, gamma camera studies were done (section 11.4) on each subject to image the hepatic and splenic distribution of the ^{113m}In colloid. The limits of the splenic distribution were marked on the skin of the abdomen. Profile scans were performed (section 11.5), at approximately 30 minutes after injection, with the spleen carefully shielded with lead both anteriorly and posteriorly, so that the resulting profile would be due to liver radioactivity only.

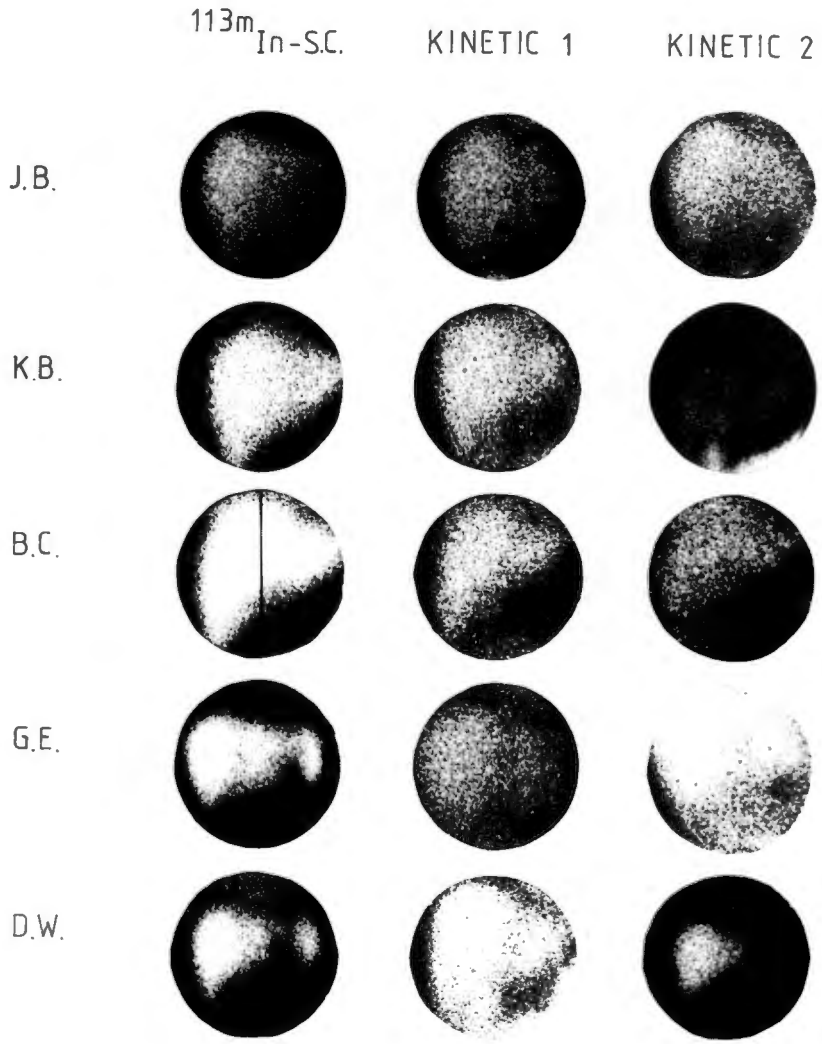
The profiles were corrected for background, smoothed and image restored. Unlike the phantom studies described in Appendix A.2 when two modified Gaussian functions were required to fit the profile peak of the liver phantom, only one function was necessary. This was probably caused by differences in the anatomical shape of the livers of the subjects compared with that of the liver phantom, or by differences in the colloidal distribution compared with uniform distribution of ^{203}Pb in the water contained in the phantom. The modified Gaussian function was fitted to the profiles by parametric and non-linear least squares procedures (SAAM 25, 1967).

A.3.3 Results

Figure A.3.1 shows the similarity of the hepatic distribution of ^{203}Pb and ^{113m}In colloid in each subject, confirming the use of the ^{113m}In

Figure A.3.1

COMPARISON BETWEEN LIVER UPTAKE OF
^{113m}In-S.C. and ^{203}Pb



colloid profile for fitting purposes. The fit of the modified Gaussian function to the profile scan of the liver containing colloidal ^{113m}In is shown in figure A.3.2 for the subject K.B. The values of the parameters resulting from the fit are shown in table A.3.1.

FIGURE A.3.2

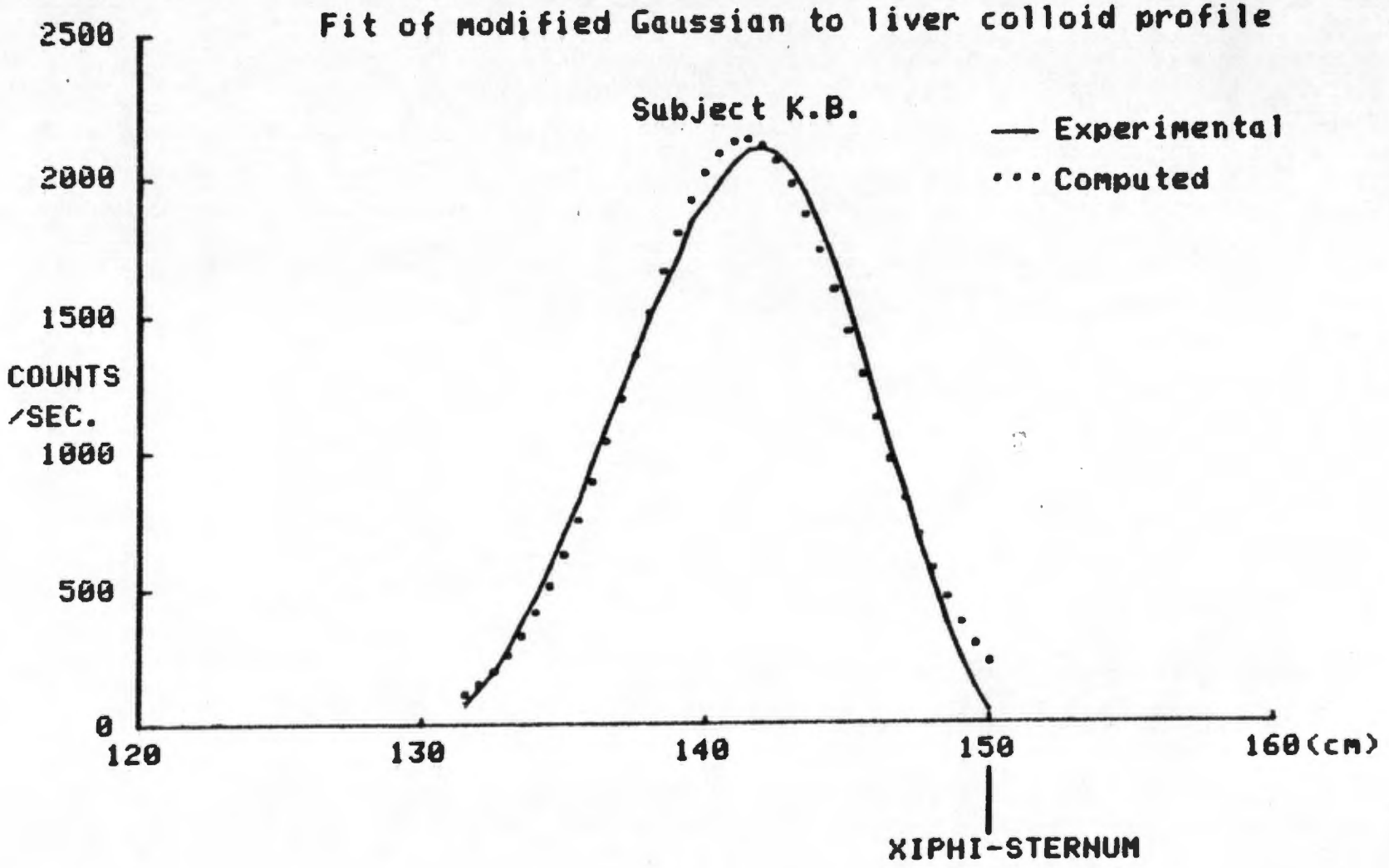

Fit of modified Gaussian to liver colloid profile
Subject K.B.
Experimental
Computed
2500
2000
1500
COUNTS
/SEC.
1000
500
0
120
130
140
150
160(cm)
XIPHI-STERNUM

TABLE A.3.1

Parameters of modified Gaussian function fitted to profile due to ^{113m}In colloid in liver

Subject : K.B.

A	p	m	n	σ	Smax	k	x_{50}
2131	308	2	3	8.14	6.0×10^{-4}	14	309

APPENDIX B

Focussing slot collimators

Two focussing slot collimators were fitted between the movable collimator blocks of the profile scanner to improve its spatial resolution. The collimators were designed to give the best possible resolution taking into account the difficulties of engineering the tapered slabs of lead, the detector diameters, the distance between detectors and collimator blocks and the focal plane of the collimators that had to coincide with the midline between the faces of the detectors.

Figure B.1 shows the dimensions of the collimator designed to give a calculated focal distance at the focal plane of 24 mm. The sensitivity was calculated to be a factor of 4 greater than that obtained with the previous arrangement of collimator blocks set 20 mm apart.

Using a line source of ^{203}Pb, a Full Width at Half Maximum of 21 mm was measured, and sensitivity was improved by a factor of 5. These measurements agree well with the calculated values. Figure B.2 shows the depth response of the two focussing collimators with the 50% isocount lines parallel and continuous between the two collimators.

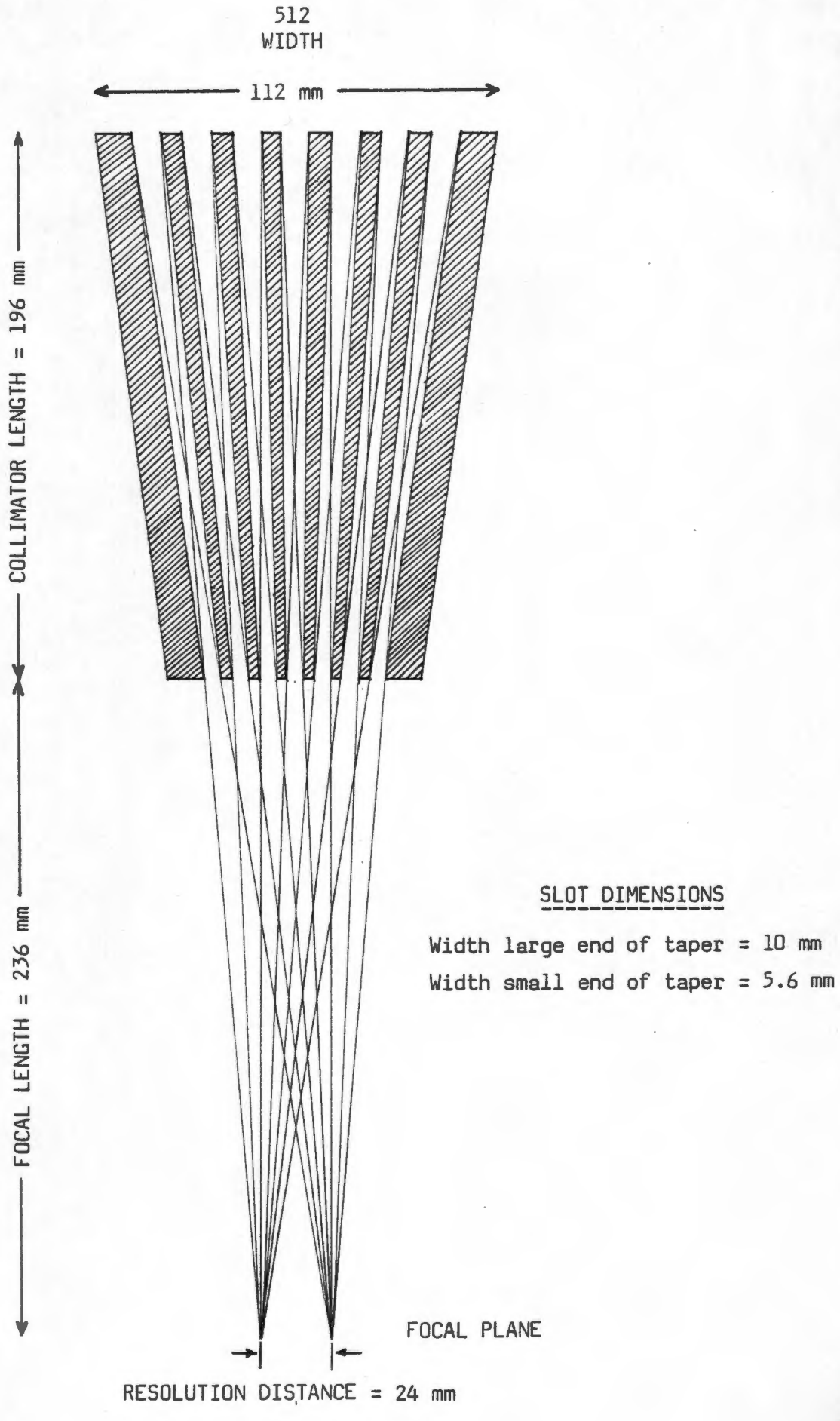


FIGURE B.1 Cross section of profile focussing collimator.

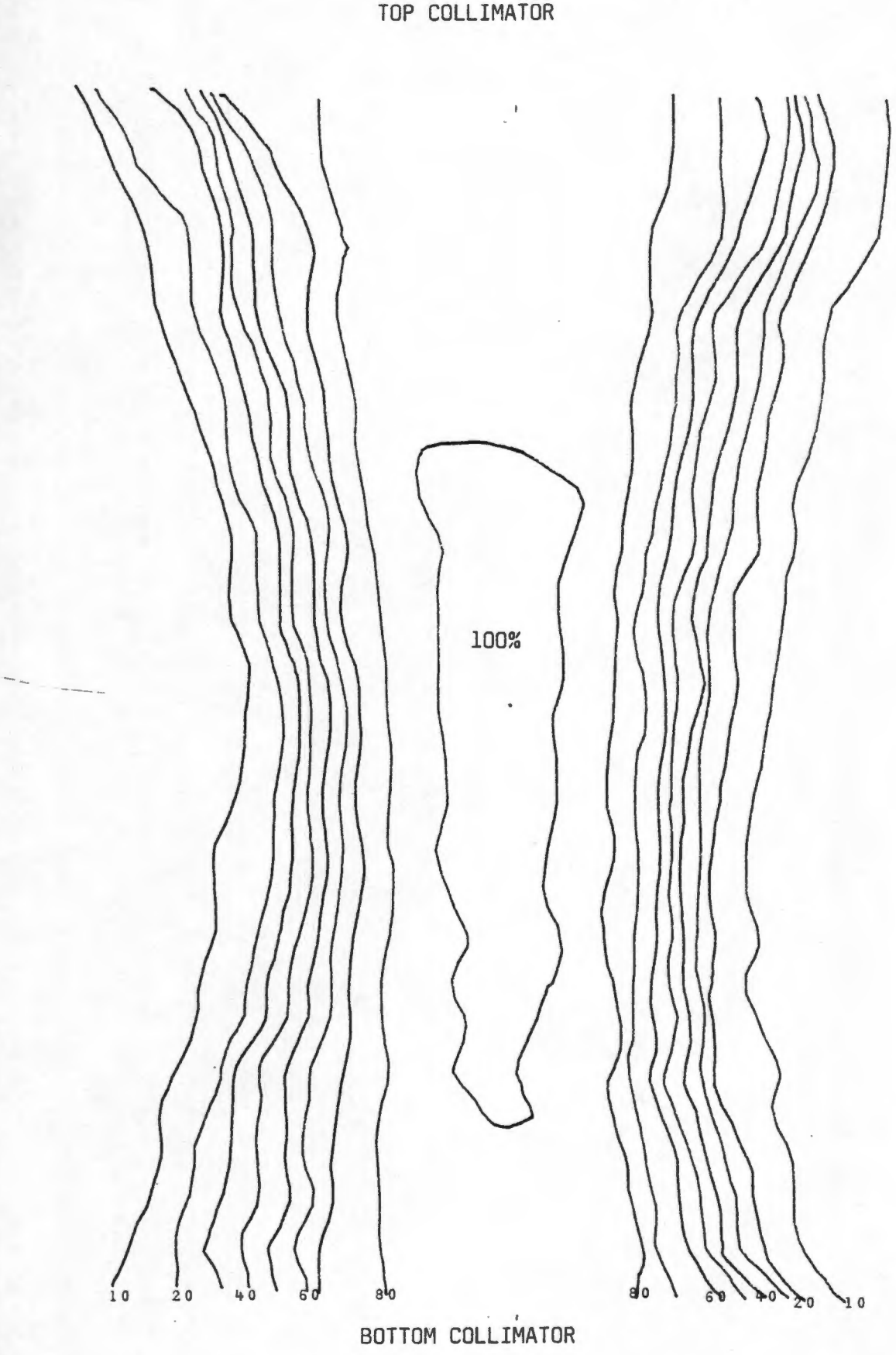


FIGURE B.2 Variation of sensitivity between top and bottom profile focussing collimators shown as isocount contours

APPENDIX C

C.1 Dosimetry of ^{203}Pb

The decay scheme for ^{203}Pb was obtained from published tables (Lederer et al, 1968) and the calculations were based on the formulisation developed by Loevinger and Berman (1968).

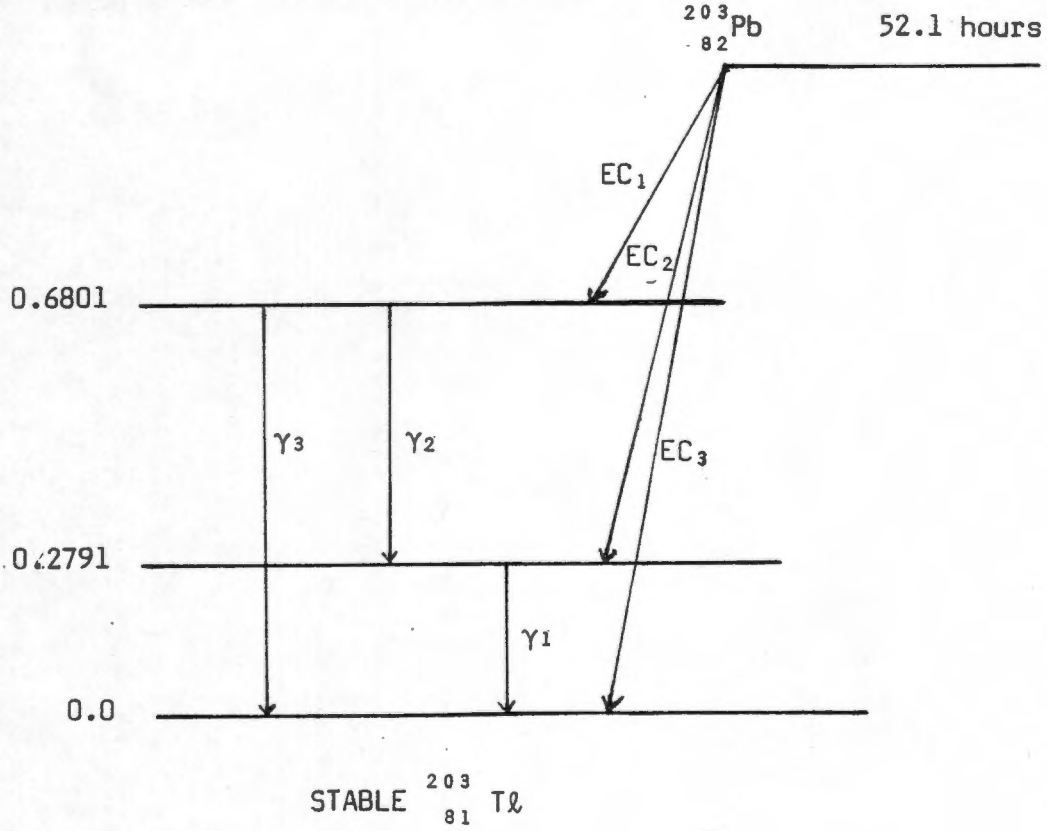


Table C.1.1 shows the 'input' data for the decay of ^{203}Pb and table C.1.2 shows the absorbed dose calculations for the whole body. For the total body absorbed dose, a uniform distribution of 1 mCi ^{203}Pb in the total body of a standard man (70kg) was assumed with no elimination of ^{203}Pb from the body i.e. worst possible case.

$$\overline{D}\ (v \rightarrow v) = \overline{C}v \quad \Sigma i \phi i \Delta i \quad (v \leftrightarrow v)$$

$$\overline{C}v = 1.44\ C\ Teff$$

$$C = \text{concentration of } ^{203}Pb = \frac{1000}{70\ 000}\ \mu Ci/g$$

Teff = effective half life of ^{203}Pb = physical half life = 52.1 hrs.

$$\therefore \overline{D}\ (v \rightarrow v) = \frac{1.44 \times 1000 \times 0.351 \times 52.1}{70\ 000}\ \text{rads}$$

$$= 0.38\ \text{rads}$$

TABLE C.1.1

INPUT DATA

RADIATION	% DISINTEGRATION	TRANSITION ENERGY (MeV)	OTHER NUCLEAR PARAMETERS
Electron capture-1	5	0.1	
Electron capture-2	95	0.5	
Electron capture-3	< 2	0.78	
Gamma-1	100	0.279	E2 + 38% M1 $\alpha K = 0.164$, $\alpha_L = 0.21$
Gamma-2	85	0.401	M1 + 0.09% E2 $\alpha K = 0.14$, $\alpha_L = 0.166$
Gamma-3	15	0.680	E2 $\alpha K = 0.009$, $\alpha_L = 0.01$

TABLE C.1.2

Absorbed dose calculations for whole body

RADIATION	MEAN ENERGY (MeV)	Δi $\left(\frac{\text{g-rad}}{\mu\text{Ci-hr}}\right)$	ϕi	$\Delta i \phi i$
Gamma - 1	0.279	0.465	0.333	0.155
Internal conversion electron	0.191	0.078	1.0	0.078
Auger electrons	-			
X-rays	-			
Gamma - 2	0.410	0.0312	0.334	0.0104
Internal conversion electron	0.322	0.0051	1.0	0.0051
Auger electrons	-			
X-rays	-			
Gamma - 3	0.680	0.0108	0.327	0.0035
Internal conversion electron	0.592	0.0001	1.0	0.0001
Auger electrons	-			
X-rays	-			
K α - 1 X-ray	0.073	0.107	0.5	0.054
K α - 2 X-ray	0.070	0.0535	0.51	0.0273
K β - 1 X-ray	0.084	0.041	0.45	0.018
			$\Sigma \Delta i \phi i$ =	0.3514

C.2 Radiation dosimetry

The subjects who took part in the kinetic studies received the largest radiation doses and these subjects are the only ones considered in this section.

The whole body radiation from ^{203}Pb has been calculated for standard man in Appendix C.1 and the radiation dosimetry for the other radiopharmaceuticals used are listed in table C.2.1. The radiation dose received by each of the subjects is listed in table C.2.2. The radiation dose from ^{203}Pb was determined using the percentage of ^{203}Pb absorbed calculated from model parameters and effective half life equal to the physical half life of ^{203}Pb. Although the half time of retention was measured in the experiments, this was only done over approximately 9 days, and was not used in the calculation. It is probable that there exists a longer half time, which has been found in work with animals (Barton et al, 1978). Using the measured half time of retention would have underestimated the dose.

The radiation doses listed in table C.2.2. were usually received over a calender quarter and are well below the maximum permissible dose for a designated person of 3000 mrem per calender quarter (Ministry of Health, 1964).

TABLE C.2.1

Whole body radiation doses from radiopharmaceuticals used in kinetic studies

RADIOPHARMACEUTICAL	RADIATION DOSE (mrads/mCi)	REFERENCE
^{82}Br	2500	Wang (1969)
^{113m}In Colloid	20	Hine and Johnston (1970)
^{113m}In	17	Van der Merwe et al (1970)

TABLE C.2.2

Whole body radiation received by subjects

SUBJECT	RADIATION DOSE (mrem)
K.B.	440
J.B.	527
B.C.	303
G.E.	436
D.W.	357

APPENDIX D

D.1 SAAM 25 program

The SAAM 25 program was run on a UNIVAC 1100 main frame computer with 524 K words of memory and disk drives, each with a capacity of 200 megabytes. The SAAM 25 package was originally developed for the solution of linear compartmental systems, such as are encountered with radionuclide tracer experiments (Berman et al, 1962 b; Berman, 1965). It is possible to treat simultaneously 25 differential equations that may arise as responses of a system having up to 60 parameters of which a maximum of 25 can be variable.

D.2 SAAM 25 nomenclature

A circle containing a letter or number e.g. (I), (J), (25), is used to represent a compartment schematically and the pathway to compartment (J) from compartment (I) is represented by an arrow with a direction to J from I. The rate constant or primary parameter for the pathway J, I is represented by L(J,I). A summer or secondary parameter, S(H,I), is an operational unit that represents a linear combination of compartments and is expressed mathematically by the relationship.

$$Qc\ (H,T) = \Sigma_I\ S(H,I) \times F(I,T)$$

where Qc (H,T) is the function describing the Summer H,
F(I,T) the functions for compartment (I),
and T is the independent variable.

When only one compartment is involved

$$Qc\ (H,T) = S(H,I) \times F(I,T)$$

and the summer can be eliminated by the use of a proportionality coefficient, K(I)

$$Qc\ (H,T) = K(I) \times F(I,T)$$

The value of F(I,T) at the start of solution or the initial input of tracer into compartment (I) is IC(I).

The symbols representing all these operational entities and the schematic of a two compartmental model is shown in figure D.1. The schematic implies the following set of differential equations.

$$\frac{dF(I,T)}{dT} = -L(J,I) \times F(I,T) - L(\emptyset,I) \times F(I,T) + L(I,J) \times F(J,T)$$

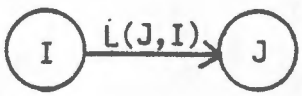
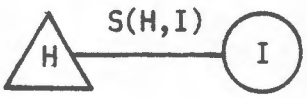
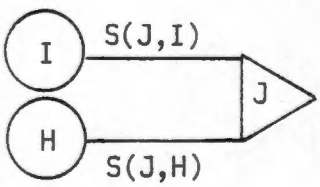
$$\frac{dF(J,T)}{dT} = L(J,I) \times F(I,T) - L(I,J) \times F(J,T) \qquad F(I,\emptyset) = IC(I)$$

These equations are implied in SAAM 25 through entries of the following parameters in parameter input format

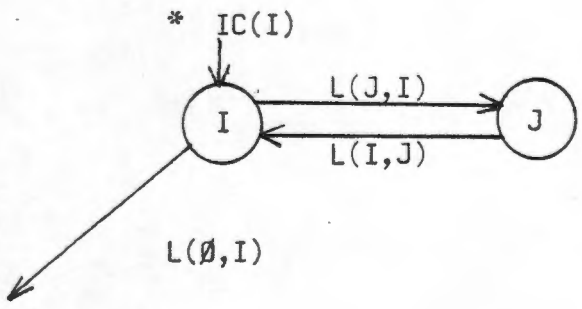
L(Ø,I)
L(J,I)
L(I,J)
IC(I)

FIGURE D.1

SAAM nomenclature and symbols

PROGRAM ELEMENT	DESCRIPTION	SYMBOL
	Compartment	
I	Independent variable	
F(I,T)	F-function I	
IC(I)	Value of F(I,T) at start of solution (Input of tracer)	
L(J,I)	Primary (non-linear) parameter	
S(H,I)	Secondary parameter (linear), summing coefficient	
K(I)	Secondary (linear) parameter, proportionality coefficient	
Qc(J,T)	Function generated from the F(I,T), T and other parameters. For a SUMMER $Qc(J,T) = \sum_{I} S(J,I) \times F(I,T)$	

TWO COMPARTMENT MODEL



D.3 Methods of solution

The implied differential equations are solved by numerical procedures, such as the 4th order Runge-Kutta method (Collatz, 1960), and initial values of parameters L(J,I) and IC(I) are required for solution. The calculated values of F(I,T) are then matched to the observed data Qo(I,T), which can be either absolute or proportional. If the observed data is absolute, obtained by directly 'sampling' a compartment such as red cells, or if the summer and proportional coefficients S(H,I) and K(I) are known, the Qc(I,T) can be calculated directly from the F(I,T). If the S(H,I) and K(I) are not known, their values may be estimated from the observed quantities Qo(I,T) using a least squares linear regression analysis (Anderson, 1958). Qc(I,T) then describes the theoretically calculated values resulting from the matching procedures.

The 'goodness of fit' between Qo(I,T) and Qc(I,T) is then tested using a least squares fitting procedure (Bevington, 1969) and the initial estimates of L(J,I), S(H,I) and K(I) are automatically adjusted until a least squares fit to all the data is obtained.

The final results include values of the adjusted parameters L(J,I), S(H,I) and K(I) with their respective standard deviations. Both calculated values, Qc(I,T), and observed data, Qo(I,T) are listed with the ratio of Qc(I,T) / Qo(I,T), and the residual sums of squares of the fit of Qc(I,T) to Qo (I,T) for each compartment.

D.4 Simulation

The calculation of a specified set of Qc(I,T), given a model and values for L(J,I), S(H,I) and K(I), is referred to as simulation and is equivalent to the same process on an analogue computer.

APPENDIX E

Computer programs

The profile scan analysis was performed using computer programs written in FORTRAN V on a UNIVAC 1100 computer. Curve fitting was performed using SAAM 25 (1967), also on the UNIVAC 1100. All other calculations were performed using programs written in BASIC on a Tektronix 4051 computer.

The most important of these programs are included in this appendix.

E.1 List of BASIC programs

E.1.1 Calculation of retention and S.D. of retention

E.1.2 Weighted linear regression of ℓn (retention) against time

E.1.3 Calculation of surface radioactivity results

E.1.4 Interpolating program for blood and E.C.F. data

E.1.5 ^{113m}In plasma and red cell volume determination

E.1.6 ^{82}Br E.C.F. volume determination

E.1.7 Factor to transform ^{113m}In profile to ^{203}Pb blood profile

E.1.8 Factor to transform ^{82}Br profile to ^{203}Pb E.C.F. profile

E.1.9 Factor to transform ^{113m}In *in vivo* data to ^{203}Pb blood background

E.1.10 Factor to transform ^{82}Br *in vivo* data to ^{203}Pb E.C.F. background

E.1.11 Calculation of % ingested dose in red cells

E.1.12 Calculation of % ingested dose in plasma and E.C.F.

E.1.13 Calculation of accumulative % ingested dose in urine

E.1.14 Area under modified Gaussian function

TABLE:E.1.1

CALCULATION OF RETENTION AND S.D. OF RETENTION

```
100 REM CALCULATION OF RETENTION AND S.D. OF W.B. COUNTS
110 DIM A(15),B(15),C(15),D(15),E(11),F(11),G(4),H(4)
120 PRINT "SUBJECT IDENTIFICATION NO.?"
130 INPUT Z$
140 GO TO 790
150 PRINT "I";
160 PRINT "6HR. COUNTER BACKGROUND=";
170 INPUT B1
180 PRINT "I";
190 PRINT "SUBJECT BACKGROUND=";
200 INPUT P1
210 PRINT "I";
220 PRINT "6HR. STANDARD COUNT=";
230 INPUT S1
240 PRINT "I";
250 PRINT "6HR. SUBJECT COUNT=";
260 INPUT D1
270 A$="TIME"
280 B$="BACKGROUND"
290 C$="STANDARD"
300 D$="SUBJECT"
310 PRINT USING 320:A$,B$,C$,D$
320 IMAGE4A,13X,10A,8X,8A,10X,7A
330 PRINT USING 340:
340 IMAGE4("-"),13X,10("-"),8X,8("-"),10X,7("-")
350 FOR I=1 TO N1
360 INPUT T
370 PRINT "KI";
380 INPUT B2
390 PRINT " KI       /";
400 INPUT T2
410 PRINT "KII";
420 INPUT S2
430 PRINT " KII        /";
440 INPUT T3
450 PRINT "KIII";
460 INPUT D2
470 PRINT " KIII        /";
480 INPUT T4
490 GOSUB 550
500 A(I)=T
510 B(I)=R
520 C(I)=V3
530 NEXT I
540 RETURN
550 R=100*((S1-B1)*(D2-P1*B2/B1))/((D1-P1)*(S2-B2))
560 M1=(S1-B1)*P1*B2/((D1-P1)*(S2-B2)*B1↑2)
570 M2=(D2-P1*B2/B1)/((D1-P1)*(S2-B2))
580 M3=M1*B1/P1
590 M4=M2*(S1-B1)/(D1-P1)
```

```
600 M5=M1*B1/B2
610 M6=M4*(D1-P1)/(S2-B2)
620 M7=M1*B1↑2/(P1*B2)
630 V1=B1*(M1-M2)↑2+P1*(M3+M4)↑2+D1*M4↑2+S1*M2↑2+B2*(M5+M6)↑2
640 V2=D2*M7↑2+S2*M6↑2
650 V3=((V1+V2)*10↑4)↑0.5
660 RETURN
670 INPUT Y$
680 YO=POS("NY",Y$,1)
690 RETURN
700 P$="COMPARTMENT"
710 Q$="TIME"
720 R$="%I.D."
730 S$="S.D."
740 PRINT @3,32: USING 750:P$,Q$,R$,S$
750 IMAGE"J",11A,7X,4A,10X,5A,10X,4A
760 PRINT @3,32: USING 770:
770 IMAGE11("-"),7X,4("-"),10X,5("-"),10X,4("-")
780 RETURN
790 PRINT "WHOLE BODY DATA (YORN)?"
800 GOSUB 670
810 GO TO YO OF 1000,820
820 PRINT "ENTER NO. OF DATA POINTS"
830 INPUT N1
840 PAGE
850 PRINT "I";
860 PRINT "WHOLE BODY DATA"
870 GOSUB 150
880 FIND 18
890 PRINT @3,32: USING 900:Z$
900 IMAGE40X,30A
910 M$="FILE:18"
920 PRINT @3,32: USING 950:M$
930 E$="FINAL WHOLE BODY READINGS"
940 PRINT @3,32: USING 950:E$
950 IMAGE"J",40X,30A
960 GOSUB 700
970 N=25
980 FOR I=1 TO N1
990 PRINT @33: USING 1000:N,A(I),B(I),C(I)
1000 IMAGE3D,9X,6D.6D,X,2(X,7D.6D)
1010 PRINT @3,32: USING 1020:N,A(I),B(I),C(I)
1020 IMAGE"J",3D,9X,6D.6D,2(X,7D.6D)
1030 NEXT I
1040 END
```

TABLE:E.1.2

WEIGHTED LINEAR REGRESSION OF LN(RETENTION) AGAINST TIME

```
100 REM LINEAR REGRESSION OF WHOLE BODY DATA
110 INIT
120 DIM A(9),B(9),C(9),T(9)
130 GO TO 340
140 PRINT "JI";
150 PRINT "TIME"
160 PRINT USING 170:
170 IMAGE18X,4("-")
180 PRINT "KKII";
190 PRINT "% RETENTION"
200 PRINT USING 210:
210 IMAGE36X,11("-")
220 FOR I=1 TO N1
230 PRINT "I";
240 INPUT T1
250 A(I)=T1
260 PRINT "KII";
270 INPUT R1
280 B(I)=LOG(R1)
290 PRINT "KII       +-";
300 INPUT S1
310 C(I)=S1/R1
320 NEXT I
330 RETURN
340 PAGE
350 PRINT "I";
360 PRINT "LINEAR REGRESSION OF WHOLE BODY DATA"
370 PRINT "I";
380 PRINT USING 390:
390 IMAGE36("-")
400 PRINT "J"
410 PRINT "SUBJECT:";
420 INPUT Z$
430 PRINT "J"
440 PRINT "ENTER NO. OF DATA POINTS:";
450 INPUT N1
460 GOSUB 140
470 S3=0
480 S4=0
490 S5=0
500 S6=0
510 S7=0
520 S8=0
530 FOR I=1 TO N1
540 X1=A(I)
550 Y1=B(I)
560 W1=1/C(I)↑2
570 S3=S3+W1
580 S4=S4+W1*X1
590 S5=S5+W1*Y1
```

```
600 S6=S6+W1*X1*X1
610 S7=S7+W1*X1*Y1
620 S8=S8+W1*Y1*Y1
630 NEXT I
640 D1=S3*S6-S4*S4
650 A1=EXP((S6*S5-S4*S7)/D1)
660 B1=(S7*S3-S4*S5)/D1
670 V1=1
680 D2=SQR(1*S6/D1)*A1
690 D3=SQR(1*S3/D1)
700 R1=(S3*S7-S4*S5)/SQR(D1*(S3*S8-S5*S5))
710 PAGE
720 P$="INTERCEPT"
730 Q$="SLOPE"
740 R$="REGRESSION COEFF."
750 S$="LINEAR REGRESSION OF WHOLE BODY DATA"
760 PRINT USING 870:P$,Q$,R$
770 PRINT USING 890:
780 PRINT USING 910:A1,D2,B1,D3,R1
790 PRINT @3,32: USING 800:S$
800 IMAGE40X,60A
810 PRINT @3,32: USING 820:
820 IMAGE40X,48("-")
830 Y$="SUBJECT:"
835 X$="NO. OF DATA POINTS="
840 PRINT @3,32: USING 850:Y$,Z$
850 IMAGE30X, 8A,30A
860 PRINT @3,32: USING 870:P$,Q$,R$
870 IMAGE"J",7X,09A,14X,5A,10X,17A
880 PRINT @3,32: USING 890:
890 IMAGE7X,09("-"),14X,5("-"),10X,17("-")
900 PRINT @3,32: USING 910:A1,D2,B1,D3,R1
910 IMAGE2(5D.4D,"+-",2D.4D,5X),5D.4D
920 PRINT @3,32: USING 930:X$,N1
930 IMAGE"J",19A,2D
940 END
```

TABLE:E.1.3

CALCULATION OF SURFACE RADIOACTIVITY RESULTS

```
100 REM SURFACE RADIOACTIVITY CALCULATIONS
110 INIT
120 DIM E(4),F(4),G(4),H(4)
130 GO TO 1170
140 INPUT Y$
150 YO=POS("NY",Y$,1)
160 RETURN
170 C1=S2/T4-B1/T2
180 C2=S1/T3-B1/T2
190 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
200 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
210 C5=SQR(C3/C1↑2+C4/C2↑2)
220 C6=C1/C2*S
230 RETURN
240 P$="ANKLE"
250 Q$="CALF"
260 R$="LIVER"
270 S$="SMALL BOWEL"
280 RETURN
290 PRINT USING 300:P$,Q$,R$,S$
300 IMAGE5A,12X,4A,14X,5A,13X,11A
310 PRINT USING 320:
320 IMAGE5("-"),12X,4("-"),14X,5("-"),13X,11("-")
330 RETURN
340 PRINT "%I.D. IN STANDARD:";
350 INPUT S
360 PRINT "J"
370 PRINT "BACKGROUND:";
380 INPUT B1
390 PRINT "K                    /";
400 INPUT T2
410 PRINT "J"
420 PRINT "STANDARD:";
430 INPUT S1
440 PRINT "K                  /";
450 INPUT T3
460 PRINT "J"
470 GOSUB 290
480 INPUT S2
490 PRINT "K        /";
500 INPUT T4
510 GOSUB 170
520 G(1)=C6
530 H(1)=C5*C6
540 PRINT "KI";
550 INPUT S2
560 PRINT "KI         /";
570 INPUT T4
580 GOSUB 170
590 G(2)=C6
```

```
600 H(2)=C5*C6
610 PRINT "KII";
620 INPUT S2
630 PRINT "KII        /";
640 INPUT T4
650 GOSUB 170
660 G(3)=C6
670 H(3)=C5*C6
680 PRINT "KIII";
690 INPUT S2
700 PRINT "KIII         /";
710 INPUT T4
720 GOSUB 170
730 G(4)=C6
740 H(4)=C5*C6
750 PRINT "J"
760 PRINT "ENTER CORRECTION FACTOR:";
770 INPUT F9
780 FOR I=1 TO 4
790 G(I)=G(I)/F9
800 H(I)=H(I)/F9
810 NEXT I
820 RETURN
830 PRINT @3,32: USING 300:P$,Q$,R$,S$
840 PRINT @3,32: USING 320:
850 PRINT @3,32: USING 860:G(1),H(1),G(2),H(2),G(3),H(3),G(4),H(4)
860 IMAGE4(1D.3D,"+-",1D.3D,5X)
870 RETURN
880 INPUT X
890 G(1)=X
900 PRINT "K      +-";
910 INPUT Y
920 H(1)=Y
930 PRINT "KI";
940 INPUT X
950 G(2)=X
960 PRINT "KI      +-";
970 INPUT Y
980 H(2)=Y
990 PRINT "KII";
1000 INPUT X
1010 G(3)=X
1020 PRINT "KII      +-";
1030 INPUT Y
1040 H(3)=Y
1050 PRINT "KIII";
1060 INPUT X
1070 G(4)=X
1080 PRINT "KIII      +-";
1090 INPUT Y
```

```
1100 H(4)=Y
1110 RETURN
1120 FOR I=1 TO 4
1130 E(I)=G(I)
1140 F(I)=H(I)
1150 NEXT I
1160 RETURN
1170 PRINT "ENTER BLOOD 100% VALUES - RAW DATA (YORN)?"
1180 GOSUB 140
1190 GO TO YO OF 1310,1200
1200 PAGE
1210 PRINT "I";
1220 PRINT "BLOOD"
1230 PRINT "J"
1240 GOSUB 240
1250 GOSUB 340
1260 L$="100% BLOOD VALUES"
1270 PRINT @3,32: USING 1280:L$
1280 IMAGE"L",40X,30A
1290 GOSUB 830
1300 GOSUB 1120
1310 PRINT "ENTER CALCULATED BLOOD 100% VALUES (YORN)?"
1320 GOSUB 140
1330 GO TO YO OF 1390,1340
1340 PAGE
1350 GOSUB 240
1360 GOSUB 290
1370 GOSUB 880
1380 GOSUB 1120
1390 PRINT "ENTER E.C.F. 100% VALUES-RAW DATA (YORN)?"
1400 GOSUB 140
1410 GO TO YO OF 1510,1420
1420 PAGE
1430 PRINT "I";
1440 PRINT "E.C.F."
1450 PRINT "J"
1460 GOSUB 240
1470 GOSUB 340
1480 M$="100% E.C.F. VALUES"
1490 PRINT @3,32: USING 1280:M$
1500 GOSUB 830
1510 PRINT "ENTER CALCULATED E.C.F. 100% VALUES (YORN)?"
1520 GOSUB 140
1530 GO TO YO OF 1580,1540
1540 PAGE
1550 GOSUB 240
1560 GOSUB 290
1570 GOSUB 880
1580 REM INPUT NEXT FILE
```

```
100 REM SURFACE RADIOACTIVITY CALCULATIONS FOR ORGANS
110 DIM A(5),B(5),C(5)
120 GO TO 1080
130 PRINT "";
140 PRINT "TIME=";
150 INPUT T
160 PRINT "JI";
170 PRINT "BACKGROUND=";
180 INPUT B1
190 PRINT "KI                    /";
200 INPUT T2
210 PRINT "I              ";
220 INPUT B2
230 B1=B2+B1
240 PRINT "J"
250 PRINT "";A$;" BACKGROUND/COUNTER BACKGROUND=";
260 INPUT R1
270 PRINT "K                                                +-";
280 INPUT R3
290 PRINT "J"
300 PRINT "";B$;"BACKGROUND/COUNTER BACKGROUND=";
310 INPUT R2
320 PRINT "K                                                +-";
330 INPUT R4
340 PRINT "JI";
350 PRINT "STANDARD=";
360 INPUT S1
370 PRINT "KI                  /";
380 INPUT T3
390 PRINT "I            ";
400 INPUT S3
410 S1=S3+S1
420 PRINT "J"
430 RETURN
440 PRINT USING 450:A$,B$
450 IMAGE  5A,12X, 7A
460 PRINT USING 470:
470 IMAGE   5("-"),12X, 7("-")
480 RETURN
490 C1=S2/T4-B1/T2
500 C2=S1/T3-B1/T2
510 C3=(SQR(S2)/T4)↑2+(B3/T2)↑2
520 C4=(SQR(S1)/T3)↑2+(B3/T2)↑2
530 C5=SQR(C3/C1↑2+C4/C2↑2)
540 C6=C1/C2*S
550 RETURN
560 INPUT Y$
570 YO=POS("NY",Y$,1)
580 RETURN
590 INPUT S2
```

```
600 PRINT "K        /";
610 INPUT T4
620 INPUT S4
630 S2=S2+S4
640 B3=B1*R1*(1/B1+(R3/R1)↑2)↑0.5
650 B1=B1*R1
660 GOSUB 490
670 RETURN
680 PRINT "KKI";
690 INPUT S2
700 PRINT "KI        /";
710 INPUT T4
720 PRINT "I";
730 INPUT S4
740 S2=S2+S4
750 B3=B1*R2*(1/B1+(R4/R2)↑2)↑0.5
760 B1=B1*R2
770 GOSUB 490
780 RETURN
790 PAGE
800 P$="%I.D."
810 Q$="S.D."
820 PRINT USING 830:P$,Q$
830 IMAGE17X,5A,13X,4A
840 PRINT "BLOOD: ";
850 PRINT " I";
860 INPUT X1
870 PRINT "KII";
880 INPUT Z1
890 PRINT "E.C.F: ";
900 PRINT " I";
910 INPUT X2
920 PRINT "KII";
930 INPUT Z2
940 FOR I=1 TO 4
950 B(I)=B(I)-X1*E(I)/100
960 S6=SQR((Z1/X1)↑2+(F(I)/E(I))↑2)*X1*E(I)/100
970 C(I)=SQR(C(I)↑2+S6↑2)
980 IF I=2 THEN 1040
990 IF I=3 THEN 1040
1000 IF I=4 THEN 1040
1010 B(I)=B(I)-X2*G(I)/100
1020 S6=SQR((Z2/X2)↑2+(H(I)/G(I))↑2)*X2*G(I)/100
1030 C(I)=SQR(C(I)↑2+S6↑2)
1040 PRINT @33: USING 1050:N,A(I),B(I),C(I)
1050 IMAGE3D,9X,6D.6D,2(7D.6D)
1060 NEXT I
1070 RETURN
1080 PRINT "ENTER NO. OF DATA POINTS"
1090 INPUT N1
```

```
1100 PRINT "ENTER %I.D.IN STANDARD"
1110 INPUT S
1120 N=17
1130 FIND 17
1140 FOR J=1 TO N1
1150 PRINT "ENTER ANKLE AND CALF DATA (YORN)?"
1160 GOSUB 560
1170 GO TO YO OF 1340,1180
1180 PAGE
1190 PRINT "I";
1200 PRINT "ANKLE AND CALF DATA"
1210 PRINT "J"
1220 A$="ANKLE"
1230 B$="CALF"
1240 GOSUB 130
1250 GOSUB 440
1260 GOSUB 590
1270 A(1)=T
1280 B(1)=C6
1290 C(1)=C5*C6
1300 GOSUB 680
1310 A(2)=T
1320 B(2)=C6
1330 C(2)=C5*C6
1340 PRINT "ENTER LIVER AND SMALL BOWEL DATA (YORN)?"
1350 GOSUB 560
1360 GO TO YO OF 1560,1370
1370 PAGE
1380 PRINT "I";
1390 PRINT "LIVER AND SMALL BOWEL DATA AT T=";T;"HRS"
1400 PRINT "J"
1410 A$="LIVER"
1420 B$="S.BOWEL"
1430 GOSUB 130
1440 GOSUB 440
1450 GOSUB 590
1460 A(3)=T
1470 B(3)=C6
1480 C(3)=C5*C6
1490 GOSUB 680
1500 A(4)=T
1510 B(4)=C6
1520 C(4)=C5*C6
1530 PRINT "J"
1540 GOSUB 800
1550 NEXT J
1560 END
```

TABLE:E.1.4

INTERPOLATING PROGRAM FOR BLOOD AND E.C.F. DATA

```
100 REM INTERPOLATION OF BLOOD AND E.C.F. PLOTS USING DIGITISER
110 INIT
120 PAGE
130 DIM A(15),B(15)
140 PRINT "SUBJECT IDENTIFICATION NO."
150 INPUT Z$
160 PRINT "ENTER COMPARTMENT"
170 INPUT B$
180 PRINT "ENTER COMPARTMENT NO."
190 INPUT N
200 PRINT "JJENTER FROM DIGITISER:","J"
210 PRINT "ORIGIN"
220 GOSUB 950
230 IF X=-1 THEN 220
240 PRINT "KI",X,Y,"G"
250 LET X1=X
260 LET Y1=Y
270 GOSUB 950
280 IF X=-1 THEN 300
290 GO TO 270
300 PRINT "MAX-XAXIS"
310 GOSUB 950
320 IF X=-1 THEN 310
330 PRINT "KI",X,Y,"G"
340 LET X2=X
350 LET Y2=Y
360 GOSUB 950
370 IF X=-1 THEN 390
380 GO TO 360
390 PRINT "MAX-YAXIS"
400 GOSUB 950
410 IF X=-1 THEN 400
420 PRINT "KI",X,Y,"GJ"
430 LET X3=X
440 LET Y3=Y
450 GOSUB 950
460 IF X=-1 THEN 480
470 GO TO 450
480 PRINT "JENTER FROM KEYBOARD:"
490 PRINT "JMAX-X    ";
500 INPUT X8
510 PRINT "MAX-Y    ";
520 INPUT Y8
530 C1=X8/(X2-X1)
540 C2=Y8/(Y3-Y1)
542 PRINT "ENTER NEW T VALUES (YORN)?"
544 INPUT L$
546 LO=POS("NY",L$,1)
548 GO TO LO OF 620,550
550 PRINT "ENTER NO. OF DATA POINTS"
```

```
560 INPUT N1
570 PRINT "ENTER T VALUES"
580 FOR I=1 TO N1
590 INPUT T
600 A(I)=INT(T/C1+0.5)
610 NEXT I
620 PRINT "JJ==========NOW DIGITISE COORDINATES==========J"
630 I=1
640 INPUT @2,32:X,Y
650 IF X=-1 THEN 640
660 X6=X-X1
670 Y6=Y-Y1
680 X7=INT(X6+0.5)
690 IF X7<>A(I) THEN 640
700 A(I)=X7
710 B(I)=Y6
720 PRINT "GGGG"
730 IF X7=A(N1) THEN 760
740 I=I+1
750 GO TO 640
760 P$="COMPARTMENT"
770 Q$="TIME"
780 R$="%A.D."
790 S$="S.D."
800 PRINT @3,32:"L"
810 PRINT @3,32:Z$
820 PRINT @3,32:"J"
830 PRINT @3,32:"INTERPOLATED ";B$;" VALUES"
840 PRINT @3,32: USING 850:P$,Q$,R$,S$
850 IMAGE"J",11A,7X,4A,10X,5A,10X,4A
860 PRINT @3,32: USING 870:
870 IMAGE11("-"),7X,4("-"),10X,5("-"),10X,4("-")
880 FOR I=1 TO N1
890 A(I)=A(I)*C1
900 B(I)=B(I)*C2
910 PRINT @3,32: USING 920:N,A(I),B(I)
920 IMAGE"J",3D,10X,6D.2D,5X,7D.2D
925 A(I)=INT(A(I)/C1+0.5)
930 NEXT I
940 END
950 FOR I=1 TO 5
960 INPUT @2,32:X,Y
970 NEXT I
980 RETURN
```

TABLE:E.1.5

IN-113M PLASMA AND RED CELL VOLUME DETERMINATION

```
100 REM IN-113M PLASMA AND RED CELL VOLUME DETERMINATION
110 INIT
120 DIM A(3),B(3),C(3),T(3)
130 GO TO 560
140 PRINT "JI";
150 PRINT "%A.D. IN STANDARD=";
160 INPUT S
170 A$="TIME"
180 PRINT "JI";
190 PRINT "BACKGROUND=";
200 INPUT B1
210 PRINT "KI                    /";
220 INPUT T2
230 PRINT "JI";
240 PRINT "STANDARD=";
250 INPUT S1
260 PRINT "KI                  /";
270 INPUT T3
280 D$="SAMPLE"
290 PRINT "J"
300 PRINT USING 310:A$,D$
310 IMAGE4A,13X, 6A
320 PRINT USING 330:
330 IMAGE4("-"),13X, 6("-")
340 FOR I=1 TO N1
350 INPUT T1
360 PRINT "KI";
370 INPUT S2
380 PRINT " KI       /";
390 INPUT T4
400 GOSUB 460
410 A(I)=T1
420 B(I)=LOG(C6/T(I))
430 C(I)=C5/T(I)
440 NEXT I
450 RETURN
460 C1=S2/T4-B1/T2
470 C2=S1/T3-B1/T2
480 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
490 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
500 C5=SQR(C3/C1↑2+C4/C2↑2)
510 C6=C1/C2*S
520 RETURN
530 INPUT Y$
540 YO=POS("NY",Y$,1)
550 RETURN
560 PAGE
570 PRINT "I";
580 PRINT "IN-113M PLASMA AND RED CELL VOLUME DETERMINATION"
590 PRINT "I";
```

```
600 PRINT USING 610:
610 IMAGE48("-")
620 PRINT "J"
630 PRINT "SUBJECT?"
640 INPUT Z$
650 PRINT "ENTER HAEMATOCRIT (%)"
660 INPUT H1
665 H1=H1*0.9*0.97
670 PRINT "ENTER NO. OF PLASMA SAMPLES"
680 INPUT N1
690 PRINT "ENTER SAMPLE VOLUMES"
700 PRINT "J"
710 FOR I=1 TO N1
720 PRINT "SAMPLE#";I;"=";
730 INPUT X
740 T(I)=X
750 NEXT I
760 PRINT "I";
770 PRINT "IN-113M PLASMA READINGS"
780 GOSUB 140
790 S3=0
800 S4=0
810 S5=0
820 S6=0
830 S7=0
840 S8=0
850 FOR I=1 TO N1
860 X1=A(I)
870 Y1=B(I)
880 W1=1/C(I)↑2
890 S3=S3+W1
900 S4=S4+W1*X1
910 S5=S5+W1*Y1
920 S6=S6+W1*X1*X1
930 S7=S7+W1*X1*Y1
940 S8=S8+W1*Y1*Y1
950 NEXT I
960 D1=S3*S6-S4*S4
970 A1=EXP((S6*S5-S4*S7)/D1)
980 B1=(S7*S3-S4*S5)/D1
990 V1=1
1000 D2=SQR(1*S6/D1)*A1
1010 D3=SQR(1*S3/D1)
1020 R1=(S3*S7-S4*S5)/SQR(D1*(S3*S8-S5*S5))
1030 PAGE
1040 P$="INTERCEPT"
1050 Q$="SLOPE"
1060 R$="REGRESSION COEFF."
1070 S$="IN-113M PLASMA AND RED CELL VOLUME DETERMINATION"
1080 PRINT USING 1190:P$,Q$,R$
```

```
1090 PRINT USING 1210:
1100 PRINT USING 1230:A1,D2,B1,D3,R1
1110 PRINT @3,32: USING 1120:S$
1120 IMAGE40X,60A
1130 PRINT @3,32: USING 1140:
1140 IMAGE40X,48("-")
1150 Y$="SUBJECT:"
1160 PRINT @3,32: USING 1170:Y$,Z$
1170 IMAGE30X, 8A,30A
1180 PRINT @3,32: USING 1190:P$,Q$,R$
1190 IMAGE"J",7X,09A,14X,5A,10X,17A
1200 PRINT @3,32: USING 1210:
1210 IMAGE7X,09("-"),14X,5("-"),10X,17("-")
1220 PRINT @3,32: USING 1230:A1,D2,B1,D3,R1
1230 IMAGE2(5D.4D,"+-",2D.4D,5X),5D.4D
1240 V2=100/A1
1250 V3=V2*H1/(100-H1)
1260 V4=V2+V3
1270 V5=(V2+0.49)/1.29
1280 V6=V5*H1/(100-H1)
1290 V7=V6+V5
1300 D4=V2*D2/A1
1310 D5=V3*D2/A1
1320 D6=SQR(D4↑2+D5↑2)
1330 D7=V5*D2/A1
1340 D8=V6*D2/A1
1350 D9=SQR(D7↑2+D8↑2)
1360 H$="EQUIVALENT ALBUMIN PLASMA VOLUME(ML)"
1370 I$="EQUIVALENT ALBUMIN RED CELL VOLUME(ML)"
1380 J$="EQUIVALENT ALBUMIN TOTAL BLOOD VOLUME(ML)"
1390 IMAGE10X,3(5D.4D,"+-",2D.4D,20X)
1400 IMAGE"J",7X,33A,2X,36A,2X,38A
1410 IMAGE7X,33("-"),2X,36("-"),2X,36("-")
1420 PRINT @3,32: USING 1400:H$,I$,J$
1430 PRINT @3,32: USING 1410:
1440 PRINT @3,32: USING 1390:V5,D7,V6,D8,V7,D9
1450 END
```

TABLE:E.1.6

BR-82 E.C.F. VOLUME DETERMINATION

```
100 REM BR-82 E.C.F. VOLUME DETERMINATION
110 DIM B(3),C(3),T(3)
120 GO TO 660
130 PRINT "I";
140 PRINT "BLOOD COUNTS"
150 PRINT "JI";
160 PRINT "%I.D. IN STANDARD=";
170 INPUT S
180 PRINT "JI";
190 PRINT "BACKGROUND=";
200 INPUT B1
210 PRINT "KI                    /";
220 INPUT T2
230 PRINT "JI";
240 PRINT "STANDARD=";
250 INPUT S1
260 PRINT "KI                  /";
270 INPUT T3
280 A$="PLASMA COUNTS"
290 B$="RED CELL COUNTS"
300 C$="URINE COUNTS"
310 PRINT "J"
320 PRINT USING 330:A$,B$,C$
330 IMAGE13A,4X,15A,4X,12A
340 PRINT USING 350:
350 IMAGE13("-"), 4X,15("-"),4X,12("-")
360 FOR I=1 TO 3
370 IF I=1 THEN 520
380 IF I=2 THEN 560
390 IF I=3 THEN 610
400 GOSUB 450
410 B(I)=C6/T(I)
420 C(I)=C5/T(I)
430 NEXT I
440 RETURN
450 C1=S2/T4-B1/T2
460 C2=S1/T3-B1/T2
470 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
480 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
490 C5=SQR(C3/C1↑2+C4/C2↑2)
500 C6=C1/C2*S
510 RETURN
520 INPUT S2
530 PRINT "K        /";
540 INPUT T4
550 GO TO 400
560 PRINT "KI";
570 INPUT S2
580 PRINT "KI        /";
590 INPUT T4
```

```
600 GO TO 400
610 PRINT "KII";
620 INPUT S2
630 PRINT "KII        /";
640 INPUT T4
650 GO TO 400
660 PAGE
670 PRINT "I";
680 PRINT "BR-82 E.C.F. VOLUME DETERMINATION"
690 PRINT "I";
700 PRINT USING 710:
710 IMAGE32("-")
720 PRINT "SUBJECT:";
730 INPUT Z$
740 PRINT "J"
750 PRINT "ENTER VOLUME OF PLASMA SAMPLE(ML):";
760 INPUT X
770 T(1)=X
780 PRINT "J"
790 PRINT "ENTER VOLUME OF RED CELL SAMPLE(ML):";
800 INPUT X
810 T(2)=X
820 PRINT "J"
830 PRINT "ENTER VOLUME OF URINE SAMPLE(ML):";
840 INPUT X
850 T(3)=X
860 PRINT "J"
870 PRINT "ENTER TOTAL PLASMA VOLUME(ML):";
880 INPUT V1
890 PRINT "K                                              +-";
900 INPUT V6
910 PRINT "J"
920 PRINT "ENTER TOTAL RED CELL VOLUME(ML):";
930 INPUT V2
940 PRINT "K                                                  +-";
950 INPUT V5
960 PRINT "J"
970 PRINT "ENTER TOTAL URINE VOLUME(ML):";
980 INPUT V3
990 PAGE
1000 GOSUB 130
1010 V4=(100-B(3)*V3-B(2)*V2)/B(1)*0.93*0.977
1020 C8=0.93*0.977*(V3*C(3)*B(3)+V2*C(2)*B(2)+B(2)*V5)/B(1)+V4*C(1)
1030 PRINT "JJJ"
1040 D$="BR-82 EXTRACELLULAR VOLUME(ML)"
1050 PRINT USING 1060:D$
1060 IMAGE20X,30A
1070 PRINT USING 1080:
1080 IMAGE20X,30("-")
1090 PRINT USING 1100:V4,C8
```

```
1100 IMAGE30X,5D.2D,"+-",2D.2D
1110 PRINT "JJ";
1120 PRINT "%I.D./ML PLASMA"
1130 PRINT "KI";
1140 PRINT "%I.D./ML RED CELLS"
1150 PRINT "KII";
1160 PRINT "%I.D./ML URINE"
1170 PRINT USING 1180:B(1),C(1)
1180 IMAGE"J",3D.3D,"+-",3D.3D
1190 PRINT USING 1200:B(2),C(2)
1200 IMAGE"KI",3D.3D,"+-",3D.3D
1210 PRINT USING 1220:B(3),C(3)
1220 IMAGE"KII",3D.3D,"+-",3D.3D
1230 END
```

TABLE:E.1.7

FACTOR TO TRANSFORM IN-113M PROFILE TO PB-203 BLOOD PROFILE

```
100 REM CALCULATION OF FACTOR TO SUBTRACT BLOOD
110 REM BACKGROUND FROM PROFILE SCANS
120 PAGE
130 PRINT "CALCULATION OF FACTOR FOR PROFILE BLOOD BKGD. SUBTRACTION
140 PRINT USING 150:
150 IMAGE57("-")
160 INIT
170 DIM A(30),B(30),C(30),D(30)
180 PRINT "J"
190 PRINT "ENTER SUBJECT IDENTIFICATION:";
200 INPUT Z$
210 PRINT "J"
220 PRINT "ENTER PB-203/IN-113M RESPONSE FACTOR:";
230 INPUT C9
240 PRINT "J"
250 PRINT "ENTER PB-203 ACTIVITY(MCI):";
260 INPUT R9
270 PRINT "J"
280 PRINT "ENTER IN-113M ACTIVITY(MCI):";
290 INPUT R8
300 PRINT "J"
310 PRINT "ENTER DECAY TIME OF IN-113M PROFILE(FRACTIONAL HRS):";
320 INPUT T8
330 PRINT "J"
340 PRINT "ENTER %I.D. WHOLE BODY AT T=6.0HRS:";
350 INPUT W9
360 PRINT "J"
370 PRINT "ENTER NO. OF DATA POINTS:";
380 INPUT N1
390 A$="TIME"
400 B$="IN-113M BACKGROUND FACTOR="
410 C$="%A.D.BLOOD"
420 D$="STANDARD COUNTS"
430 E$="IN-113M PROFILE * FACTOR"
440 C8=R9*EXP(0.378*T8)/(C9*R8)
450 PAGE
460 PRINT USING 470:A$,C$,D$
470 IMAGE4A,14X,10A,14X,15A
480 PRINT USING 490:
490 IMAGE4("-"),14X,10("-"),14X,15("-")
500 FOR I=1 TO N1
510 INPUT T1
520 A(I)=T1
530 PRINT "IK";
540 INPUT B1
550 B(I)=B1
560 PRINT "IIK       ";
570 INPUT S1
580 C(I)=S1
590 D(I)=B(I)*C(I)*W9*R9*EXP(0.378*T8)/(C9*R8*100^2*C(1))
```

```
600 NEXT I
610 PRINT @3,32: USING 620:
620 IMAGE"L"
630 PRINT @3,32: USING 640:Z$
640 IMAGE30X,40A
650 PRINT @3,32: USING 660:
660 IMAGE"J"
670 PRINT @3,32: USING 680:B$,C8
680 IMAGE18X,26A,3D.3D
690 PRINT @3,32: USING 700:
700 IMAGE"J"
710 PRINT @3,32: USING 720:A$,E$
720 IMAGE18X,4A,10X,24A
730 PRINT @3,32: USING 740:
740 IMAGE18X,4("-"),10X,24("-")
750 FOR I=1 TO N1
760 PRINT @3,32: USING 770:A(I),D(I)
770 IMAGE18X,3D.3D,22X,2D.4D
780 NEXT I
790 END
```

TABLE:E.1.8

FACTOR TO TRANSFORM BR-82 PROFILE TO PB-203 E.C.F PROFILE

```
100 REM CALC. OF CORRECTION FACTORS FOR SUBTRACTION
110 REM OF 'SOFT TISSUE' E.C.F. BACKGROUND PROFILE SCANS
120 PAGE
130 PRINT "CALCULATION OF FACTOR FOR PROFILE E.C.F. BKGD. SUB."
140 PRINT USING 150:
150 IMAGE55("-")
160 INIT
170 DIM A(30),B(30),C(30),D(30)
180 PRINT "SUBJECT IDENTIFICATION:";
190 INPUT Z$
200 PRINT "ENTER PLASMA VOLUME(ML):";
210 INPUT V1
220 PRINT "ENTER RED CELL VOLUME(ML):";
230 INPUT V2
240 PRINT "ENTER E.C.F. VOLUME(ML):";
250 INPUT V3
260 PRINT "ENTER URINE VOLUME(ML):";
270 INPUT V4
280 PRINT "ENTER BR-82 %I.D./ML IN PLASMA:";
290 INPUT P9
300 PRINT "ENTER BR-82 %I.D./ML IN RED CELLS:";
310 INPUT R9
320 PRINT "ENTER BR-82 %I.D./ML IN URINE:";
330 INPUT U9
340 PRINT "ENTER PB-203 ACTIVITY(MCI):";
350 INPUT A9
360 PRINT "ENTER BR-82 ACTIVITY(MCI):";
370 INPUT A8
380 PRINT "ENTER BLOOD BACKGROUND FACTOR FOR IN-113M:";
390 INPUT F9
400 PRINT "ENTER PB-203/BR-82 RESPONSE FACTOR:";
410 INPUT F8
420 PRINT "ENTER %I.D. WHOLE BODY AT T=6.00HRS.:";
430 INPUT W9
440 PRINT "ENTER NO. OF DATA POINTS:";
450 INPUT N9
460 D9=V1*P9
470 D8=V2*R9
480 D7=V4*U9
490 D6=100-D9-D8-D7
500 D5=(D9+D8)/(100-D7)
510 C9=F9*D5*F8*A8/A9
520 PAGE
530 A$="TIME"
540 B$="%I.D. SOFT TISSUE E.C.F."
550 C$="STANDARD COUNTS"
560 D$="BR-82 PROFILE*FACTOR"
570 E$="FACTOR*IN-113M PROFILE FOR BR-82 SUBTR.="
580 PRINT USING 590:A$,B$,C$
590 IMAGE4A,14X,24A,X,15A
```

```
600 PRINT USING 610:
610 IMAGE4("-"),14X,24("-"),5X,15("-")
620 FOR I=1 TO N9
630 INPUT T1
640 A(I)=T1
650 PRINT "IK";
660 INPUT B1
670 B(I)=B1
680 PRINT "IIK           ";
690 INPUT S1
700 C(I)=S1
710 D(I)=100*A9*B(I)*C(I)*W9/(D6*F8*A8*C(1)*100^2)
720 NEXT I
730 PRINT @3,32: USING 740:
740 IMAGE"L"
750 PRINT @3,32: USING 760:Z$
760 IMAGE30X,40A
770 PRINT @3,32: USING 780:
780 IMAGE"J"
790 PRINT @3,32: USING 800:E$,C9
800 IMAGE18X,40A,3D.3D
810 PRINT @3,32: USING 820:
820 IMAGE"J"
830 PRINT @3,32: USING 840:A$,D$
840 IMAGE18X,4A,10X,24A
850 PRINT @3,32: USING 860:
860 IMAGE18X,4("-"),10X,20("-")
870 FOR I=1 TO N9
880 PRINT @3,32: USING 890:A(I),D(I)
890 IMAGE17X,3D.2D,15X,2D.4D
900 NEXT I
910 END
```

TABLE:E.1.9

```
FACTOR TO TRANSFORM IN-113M IN VIVO DATA TO PB-203 BLOOD BKGD
100 REM DETERMINATION OF PB-203 100% VALUES IN BLOOD
110 INIT
120 DIM G(4),H(4),T(4),S(4),Q(4),P(4)
130 GO TO 900
140 GOSUB 2430
150 C1=S2/T4-B1/T2
160 C2=S1/T3-B1/T2
170 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
180 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
190 C5=SQR(C3/C1↑2+C4/C2↑2)
200 C6=C1/C2*S8
210 RETURN
220 P$="ANKLE"
230 Q$="CALF"
240 R$="LIVER"
250 S$="SMALL BOWEL"
260 RETURN
270 PRINT USING 280:P$,Q$,R$,S$
280 IMAGE5A,12X,4A,14X,5A,13X,11A
290 PRINT USING 300:
300 IMAGE5("-"),12X,4("-"),14X,5("-"),13X,11("-")
310 RETURN
320 PRINT "%A.D. IN STANDARD:";
330 INPUT S8
340 PRINT "J"
350 PRINT "BACKGROUND:";
360 INPUT B1
370 PRINT "K                    /";
380 INPUT T2
390 PRINT "J"
400 PRINT "STANDARD:";
410 INPUT S1
420 PRINT "K                  /";
430 INPUT T3
440 PRINT "J"
450 GOSUB 270
460 INPUT S2
470 PRINT "K        /";
480 INPUT T4
490 GOSUB 150
500 G(1)=C6
510 H(1)=C5*C6
520 PRINT "KI";
530 INPUT S2
540 PRINT "KI        /";
550 INPUT T4
560 GOSUB 150
570 G(2)=C6
580 H(2)=C5*C6
590 PRINT "KII";
```

```
600 INPUT S2
610 PRINT "KII        /";
620 INPUT T4
630 GOSUB 150
640 G(3)=C6
650 H(3)=C5*C6
660 PRINT "KIII";
670 INPUT S2
680 PRINT "KIII        /";
690 INPUT T4
700 GOSUB 150
710 G(4)=C6
720 H(4)=C5*C6
730 PRINT "J"
740 PRINT "ENTER CORRECTION FACTOR:";
750 INPUT F9
760 PRINT "K                                    +-";
770 INPUT F8
780 FOR I=1 TO 4
790 Q(I)=EXP(S9*S(I))*EXP(1.05E-4*T(I))/F9
800 P(I)=S(I)*Q(I)*S7-Q(I)*F8/F9
810 G(I)=G(I)*Q(I)
820 H(I)=G(I)*Q(I)*((H(I)/G(I))↑2+(P(I)/Q(I))↑2)↑0.5
830 NEXT I
840 RETURN
850 PRINT @3,32: USING 280:P$,Q$,R$,S$
860 PRINT @3,32: USING 300:
870 PRINT @3,32: USING 880:G(1),H(1),G(2),H(2),G(3),H(3),G(4),H(4)
880 IMAGE4(1D.3D,"+-",1D.3D,5X)
890 RETURN
900 PAGE
910 PRINT "            DETERMINATION OF IN-113M POINT COUNT %A.D."
920 PRINT USING 930:
930 IMAGE11X,42("-")
940 PRINT "J"
950 PRINT "ENTER SLOPE OF IN-113M CLEARANCE:";
960 INPUT S9
970 PRINT "K                                                +-";
980 INPUT S7
990 PRINT "J"
1000 PRINT "ENTER IN-113M INJECTION TIME(FRACTIONAL HRS.):";
1010 INPUT T9
1020 PRINT "J"
1030 PRINT "                        TIME OF MEASUREMENT(FRACTIONAL HRS.)
1040 PRINT USING 1050:
1050 IMAGE20X,36("-")
1060 PRINT "J"
1070 PRINT "STANDARD:";
1080 INPUT T8
1090 PRINT "J"
```

```
1100 GOSUB 220
1110 GOSUB 270
1120 INPUT T7
1130 PRINT "KI";
1140 INPUT T6
1150 PRINT "KII";
1160 INPUT T5
1170 PRINT "KIII";
1180 INPUT T4
1190 T(1)=T7-T8
1200 T(2)=T6-T8
1210 T(3)=T5-T8
1220 T(4)=T4-T8
1230 S(1)=T7-T9
1240 S(2)=T6-T9
1250 S(3)=T5-T9
1260 S(4)=T4-T9
1270 PAGE
1280 PRINT "I";
1290 PRINT "POINT COUNTS"
1300 PRINT "J"
1310 GOSUB 220
1320 GOSUB 320
1330 L$="100% BLOOD VALUES(IN-113M)"
1340 PRINT @3,32: USING 1350:L$
1350 IMAGE"L",40X,45A
1360 GOSUB 850
1370 END
```

TABLE:E.1.10

FACTOR TO TRANSFORM BR-82 IN VIVO DATA TO PB-203 E.C.F. BKGD

```
100 REM DETERMINATION OF PB-203 100% VALUES IN E.C.F.
110 DIM E(4),F(4),G(4),H(4),B(3),C(3),A(4),K(4),D(4),L(4)
120 GO TO 520
130 P$="ANKLE"
140 Q$="CALF"
150 R$="LIVER"
160 S$="SMALL BOWEL"
170 RETURN
180 PRINT USING 190:P$,Q$,R$,S$
190 IMAGE5A,12X,4A,14X,5A,13X,11A
200 PRINT USING 210:
210 IMAGE5("-"),12X,4("-"),14X,5("-"),13X,11("-")
220 RETURN
230 INPUT X
240 G(1)=X
250 PRINT "K      +-";
260 INPUT Y
270 H(1)=Y
280 PRINT "KI";
290 INPUT X
300 G(2)=X
310 PRINT "KI      +-";
320 INPUT Y
330 H(2)=Y
340 PRINT "KII";
350 INPUT X
360 G(3)=X
370 PRINT "KII      +-";
380 INPUT Y
390 H(3)=Y
400 PRINT "KIII";
410 INPUT X
420 G(4)=X
430 PRINT "KIII      +-";
440 INPUT Y
450 H(4)=Y
460 RETURN
470 FOR I=1 TO 4
480 E(I)=G(I)
490 F(I)=H(I)
500 NEXT I
510 RETURN
520 PAGE
530 PRINT "I";
540 PRINT "PB-203 100% BLOOD VALUES"
550 PRINT USING 560:
560 IMAGE18X,20("-")
570 PRINT "J"
580 GOSUB 130
590 GOSUB 180
```

```
600 GOSUB 230
610 GOSUB 470
620 PAGE
630 PRINT "I";
640 PRINT "BR-82 FACTORS"
650 PRINT USING 660:
660 IMAGE18X,13("-")
670 PRINT "J"
680 PRINT "ENTER BR-82 CORRECTION FACTOR FOR ANKLE:";
690 INPUT F9
700 D(1)=F9
710 PRINT "K                                                    +-";
720 INPUT F5
730 L(1)=F5
740 PRINT "J"
750 PRINT "ENTER BR-82 CORRECTION FACTOR FOR CALF :";
760 INPUT F8
770 D(2)=F8
780 PRINT "K                                                    +-";
790 INPUT F4
800 L(2)=F4
810 PRINT "J"
820 PRINT "ENTER BR-82 CORRECTION FACTOR FOR LIVER:";
830 INPUT F7
840 D(3)=F7
850 PRINT "K                                                    +-";
860 INPUT F3
870 L(3)=F3
880 PRINT "J"
890 PRINT "ENTER BR-82 CORRECTION FACTOR FOR S.BOWEL:";
900 INPUT F6
910 D(4)=F6
920 PRINT "K                                                    +-";
930 INPUT F2
940 L(4)=F2
950 PAGE
960 PRINT "I";
970 PRINT "BLOOD VOLUMES"
980 PRINT USING 990:
990 IMAGE18X,13("-")
1000 PRINT "J"
1010 PRINT "ENTER TOTAL PLASMA VOLUME(ML):";
1020 INPUT V1
1030 PRINT "K                                              +-";
1040 INPUT V6
1050 PRINT "J"
1060 PRINT "ENTER TOTAL RED CELL VOLUME(ML):";
1070 INPUT V2
1080 PRINT "K                                                +-";
1090 INPUT V5
```

```
1100 PRINT "J"
1110 PRINT "ENTER TOTAL URINE VOLUME(ML):";
1120 INPUT V7

100 PAGE
110 GO TO 760
120 C1=S2/T4-B1/T2
130 C2=S1/T3-B1/T2
140 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
150 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
160 C5=SQR(C3/C1↑2+C4/C2↑2)
170 C6=C1/C2*S
180 RETURN
190 P$="ANKLE"
200 Q$="CALF"
210 R$="LIVER"
220 S$="SMALL BOWEL"
230 RETURN
240 PRINT USING 250:P$,Q$,R$,S$
250 IMAGE5A,12X,4A,14X,5A,13X,11A
260 PRINT USING 270:
270 IMAGE5("-"),12X,4("-"),14X,5("-"),13X,11("-")
280 RETURN
290 PRINT "%I.D. IN STANDARD:";
300 INPUT S
310 PRINT "J"
320 PRINT "BACKGROUND:";
330 INPUT B1
340 PRINT "K                    /";
350 INPUT T2
360 PRINT "J"
370 PRINT "STANDARD:";
380 INPUT S1
390 PRINT "K                  /";
400 INPUT T3
410 PRINT "J"
420 GOSUB 240
430 INPUT S2
440 PRINT "K        /";
450 INPUT T4
460 GOSUB 120
470 G(1)=C6
480 H(1)=C6*C5
490 PRINT "KI";
500 INPUT S2
510 PRINT "KI        /";
520 INPUT T4
530 GOSUB 120
540 G(2)=C6
550 H(2)=C6*C5
560 PRINT "KII";
570 INPUT S2
580 PRINT "KII       /";
590 INPUT T4
```

```
600 GOSUB 120
610 G(3)=C6
620 H(3)=C6*C5
630 PRINT "KIII";
640 INPUT S2
650 PRINT "KIII        /";
660 INPUT T4
670 GOSUB 120
680 G(4)=C6
690 H(4)=C6*C5
700 RETURN
710 PRINT @3,32: USING 250:P$,Q$,R$,S$
720 PRINT @3,32: USING 270:
730 PRINT @3,32: USING 740:G(1),H(1),G(2),H(2),G(3),H(3),G(4),H(4)
740 IMAGE4(1D.3D,"+-",1D.3D,5X)
750 RETURN
760 PRINT "I";
770 PRINT "BR-82 SURFACE RADIOACTIVITY"
780 PRINT USING 790:
790 IMAGE18X,18("-")
800 PRINT "J"
810 PRINT "ENTER BR-82 %I.D./ML PLASMA:";
820 INPUT X1
830 PRINT "K                                        +-";
840 INPUT X2
850 B(1)=X1
860 C(1)=X2
870 PRINT "J"
880 PRINT "ENTER BR-82 %I.D./ML RED CELLS:";
890 INPUT Y1
900 PRINT "K                                              +-";
910 INPUT Y2
920 B(2)=Y1
930 C(2)=Y2
940 PRINT "J"
950 PRINT "ENTER BR-82 %I.D./ML URINE:";
960 INPUT Z1
970 PRINT "K                                    +-";
980 INPUT Z2
990 B(3)=Z1*V7
1000 C(3)=Z2*V7
1010 PRINT "I";
1020 PRINT "J"
1030 GOSUB 190
1040 GOSUB 290
1050 B1=B(1)*V1+B(2)*V2
1060 B2=B(1)*V1*C(1)+B(2)*V2*C(2)+B(1)*V6+B(2)*V5
1070 FOR I=1 TO 4
1080 F(I)=E(I)*D(I)*((F(I)/E(I))↑2+(L(I)/D(I))↑2)↑0.5
1090 E(I)=E(I)*D(I)
```

```
1100 K(I)=(100-B(3)-B(1)*V1-B(2)*V2)*D(I)/100
1110 H(I)=(H(I)-B1*F(I)/(100-B(3))-E(I)*B2/(100-B(3)))/K(I)
1120 H(I)=H(I)+(G(I)-E(I)*B1/(100-B(3)))*D(I)*C(3)/(100*K(I)^2)
1130 H(I)=H(I)-K(I)*E(I)*B1*C(3)/((100-B(3))*K(I))^2
1140 H(I)=H(I)+(G(I)-E(I)*B1/(100-B(3)))*V1*D(I)*C(1)/(100*K(I)^2)
1150 H(I)=H(I)+(G(I)-E(I)*B1/(100-B(3)))*B(1)*D(I)*V6/(100*K(I)^2)
1160 H(I)=H(I)+(G(I)-E(I)*B1/(100-B(3)))*C(2)*D(I)*V2/(100*K(I)^2)
1170 H(I)=H(I)+(G(I)-E(I)*B1/(100-B(3)))*B(2)*D(I)*V5/(100*K(I)^2)
1180 H(I)=H(I)-(G(I)-E(I)*B1/(100-B(3)))*K(I)*L(I)/K(I)^2
1190 G(I)=(G(I)-E(I)*B1/(100-B(3)))/K(I)
1200 NEXT I
1210 M$="100% E.C.F. VALUES"
1220 PRINT @3,32: USING 1230:M$
1230 IMAGE18X,18A
1240 PRINT "J"
1250 GOSUB 710
1260 END
```

TABLE:E.1.11

CALCULATION OF %INGESTED DOSE IN RED CELLS

```
100 REM CALCULATION OF %I.D. IN RED CELLS
110 DIM A(15),B(15),C(15),D(15),E(11),F(11),G(4),H(4)
120 PRINT "SUBJECT IDENTIFICATION NO. ?"
130 INPUT Z$
140 GO TO 630
150 PRINT "I";
160 PRINT "%I.D. IN STANDARD=";
170 INPUT S
180 A$="TIME"
190 B$="BACKGROUND"
200 C$="STANDARD"
210 D$="SAMPLE"
220 PRINT USING 230:A$,B$,C$,D$
230 IMAGE4A,13X,10A,8X,8A,10X,6A
240 PRINT USING 250:
250 IMAGE4("-"),13X,10("-"),8X,8("-"),10X,6("-")
260 FOR I=1 TO N1
270 INPUT T1
280 PRINT "KI";
290 INPUT B1
300 PRINT " KI       /";
310 INPUT T2
320 PRINT "KII";
330 INPUT S1
340 PRINT " KII        /";
350 INPUT T3
360 PRINT "KIII";
370 INPUT S2
380 PRINT " KIII        /";
390 INPUT T4
400 GOSUB 460
410 A(I)=T1
420 B(I)=C6
430 C(I)=C5
440 NEXT I
450 RETURN
460 C1=S2/T4-B1/T2
470 C2=S1/T3-B1/T2
480 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
490 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
500 C5=SQR(C3/C1↑2+C4/C2↑2)
510 C6=C1/C2*S
520 RETURN
530 P$="COMPARTMENT"
540 Q$="TIME"
550 R$="%I.D."
560 S$="S.D."
570 PRINT @3,32: USING 580:P$,Q$,R$,S$
580 IMAGE"J",11A,7X,4A,10X,5A,10X,4A
590 PRINT @3,32: USING 600:
```

```
600 IMAGE11("-"),7X,4("-"),10X,5("-"),10X,4("-")
610 RETURN
620 NEXT I
630 PAGE
640 PRINT "ENTER NO. OF DATA POINTS"
650 INPUT N1
660 PRINT "ENTER RED CELL SAMPLE VOLUME(ML)"
670 INPUT V5
680 PRINT "ENTER TOTAL RED CELL VOLUME(ML):";
690 INPUT V6
700 PRINT "K                                                    +-";
710 INPUT V7
720 PAGE
730 PRINT "I";
740 PRINT "RED CELL DATA"
750 GOSUB 150
760 FIND 15
770 PRINT @3,32:"L"
780 PRINT @3,32: USING 790:Z$
790 IMAGE40X,30A
800 M$="FILE:15"
810 PRINT @3,32: USING 840:M$
820 J$="FINAL RED CELL READINGS"
830 PRINT @3,32: USING 840:J$
840 IMAGE"J",40X,30A
850 GOSUB 530
860 N=13
870 FOR I=1 TO N1
880 B(I)=B(I)*V6/V5
890 C(I)=B(I)*(C(I)↑2+(V7/V6)↑2)↑0.5
900 PRINT @33: USING 910:N,A(I),B(I),C(I)
910 IMAGE3D,9X,6D.6D,2(X,7D.6D)
920 PRINT @3,32: USING 930:N,A(I),B(I),C(I)
930 IMAGE"J",3D,9X,6D.6D,2(X,7D.6D)
940 NEXT I
950 END
```

TABLE:E.1.12

CALCULATION OF %INGESTED DOSE IN PLASMA AND E.C.F.

```
100 REM CALCULATION OF %I.D.IN PLASMA AND E.C.F.
110 DIM A(15),B(15),C(15),D(15),E(11),F(11),G(4),H(4)
120 PRINT "SUBJECT IDENTIFICATION NO. ?"
130 INPUT Z$
140 GO TO 630
150 PRINT "I";
160 PRINT "%I.D. IN STANDARD=";
170 INPUT S
180 A$="TIME"
190 B$="BACKGROUND"
200 C$="STANDARD"
210 D$="SAMPLE"
220 PRINT USING 230:A$,B$,C$,D$
230 IMAGE4A,13X,10A,8X,8A,10X,6A
240 PRINT USING 250:
250 IMAGE4("-"),13X,10("-"),8X,8("-"),10X,6("-")
260 FOR I=1 TO N1
270 INPUT T1
280 PRINT "KI";
290 INPUT B1
300 PRINT " KI       /";
310 INPUT T2
320 PRINT "KII";
330 INPUT S1
340 PRINT " KII        /";
350 INPUT T3
360 PRINT "KIII";
370 INPUT S2
380 PRINT " KIII        /";
390 INPUT T4
400 GOSUB 460
410 A(I)=T1
420 B(I)=C6
430 C(I)=C5
440 NEXT I
450 RETURN
460 C1=S2/T4-B1/T2
470 C2=S1/T3-B1/T2
480 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
490 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
500 C5=SQR(C3/C1↑2+C4/C2↑2)
510 C6=C1/C2*S
520 RETURN
530 P$="COMPARTMENT"
540 Q$="TIME"
550 R$="%I.D."
560 S$="S.D."
570 PRINT @3,32: USING 580:P$,Q$,R$,S$
580 IMAGE"J",11A,7X,4A,10X,5A,10X,4A
590 PRINT @3,32: USING 600:
```

```
600 IMAGE11("-"),7X,4("-"),10X,5("-"),10X,4("-")
610 RETURN
620 NEXT I
630 PAGE
640 PRINT "ENTER NO. OF DATA POINTS"
650 INPUT N1
660 PRINT "ENTER PLASMA SAMPLE VOLUME(ML)"
670 INPUT V3
680 PRINT "ENTER TOTAL PLASMA VOLUME(ML):";
690 INPUT V1
700 PRINT "K                                                    +-";
710 INPUT V5
720 PAGE
730 PRINT "I";
740 PRINT "PLASMA DATA"
750 GOSUB 150
760 FIND 13
770 PRINT @3,32:"L"
780 PRINT @3,32: USING 790:Z$
790 IMAGE40X,30A
800 G$="FINAL PLASMA READINGS"
810 PRINT @3,32: USING 840:G$
820 M$="FILE:13"
830 PRINT @3,32: USING 840:M$
840 IMAGE"J",40X,30A
850 GOSUB 530
860 N=11
870 FOR I=1 TO N1
880 B(I)=B(I)*V1/V3
890 C(I)=B(I)*(C(I)↑2+(V5/V1)↑2)↑0.5
900 PRINT @33: USING 910:N,A(I),B(I),C(I)
910 IMAGE3D,9X,6D.6D,2(X,7D.6D)
920 PRINT @3,32: USING 930:N,A(I),B(I),C(I)
930 IMAGE"J",3D,9X,6D.6D,2(X,7D.6D)
940 NEXT I
950 PRINT "ENTER E.C.F. VOLUME(ML):";
960 INPUT V2
970 PRINT "K                                                +-";
980 INPUT V4
990 FIND 14
1000 PRINT @3,32:"L"
1010 PRINT @3,32: USING 1020:Z$
1020 IMAGE40X,30A
1030 M$="FILE:14"
1040 PRINT @3,32: USING 1070:M$
1050 H$="FINAL E.C.F. READINGS"
1060 PRINT @3,32: USING 1070:H$
1070 IMAGE"J",40X,30A
1080 GOSUB 530
1090 N=11
```

```
1100 V5=(V4↑2+V5↑2)↑0.5
1110 V4=(V2-V1)*((V5/(V2-V1))↑2+(V4/V2)↑2)↑0.5/V1
1120 V2=(V2-V1)/V1
1130 FOR I=1 TO N1
1140 C(I)=C(I)/B(I)
1150 B(I)=B(I)*V2
1160 C(I)=B(I)*(C(I)↑2+(V4/V2)↑2)↑0.5
1170 PRINT @33: USING 910:N,A(I),B(I),C(I)
1180 PRINT @3,32: USING 930:N,A(I),B(I),C(I)
1190 NEXT I
1200 END
```

TABLE:E.1.13

CALCULATION OF ACCUMULATIVE %INGESTED DOSE IN URINE

```
100 REM CALCULATION OF %I.D. IN ACCUMULATIVE URINE
110 DIM A(15),B(15),C(15),D(15),E(11),F(11),G(4),H(4)
120 PRINT "SUBJECT IDENTIFICATION NO. ?"
130 INPUT Z$
140 GO TO 630
150 PRINT "I";
160 PRINT "%I.D. IN STANDARD=";
170 INPUT S
180 A$="TIME"
190 B$="BACKGROUND"
200 C$="STANDARD"
210 D$="SAMPLE"
220 PRINT USING 230:A$,B$,C$,D$
230 IMAGE4A,13X,10A,8X,8A,10X,6A
240 PRINT USING 250:
250 IMAGE4("-"),13X,10("-"),8X,8("-"),10X,6("-")
260 FOR I=1 TO N1
270 INPUT T1
280 PRINT "KI";
290 INPUT B1
300 PRINT " KI       /";
310 INPUT T2
320 PRINT "KII";
330 INPUT S1
340 PRINT " KII        /";
350 INPUT T3
360 PRINT "KIII";
370 INPUT S2
380 PRINT " KIII        /";
390 INPUT T4
400 GOSUB 460
410 A(I)=T1
420 B(I)=C6
430 C(I)=C5
440 NEXT I
450 RETURN
460 C1=S2/T4-B1/T2
470 C2=S1/T3-B1/T2
480 C3=(SQR(S2)/T4)↑2+(SQR(B1)/T2)↑2
490 C4=(SQR(S1)/T3)↑2+(SQR(B1)/T2)↑2
500 C5=SQR(C3/C1↑2+C4/C2↑2)
510 C6=C1/C2*S
520 RETURN
530 P$="COMPARTMENT"
540 Q$="TIME"
550 R$="%I.D."
560 S$="S.D."
570 PRINT @3,32: USING 580:P$,Q$,R$,S$
580 IMAGE"J",11A,7X,4A,10X,5A,10X,4A
590 PRINT @3,32: USING 600:
```

```
600 IMAGE11("-"),7X,4("-"),10X,5("-"),10X,4("-")
610 RETURN
620 NEXT I
630 PAGE
640 PRINT "ENTER NO. OF DATA POINTS"
650 INPUT N1
660 PRINT "ENTER 24HR. URINE VOLUMES"
670 U1=0
680 FOR I=1 TO N1
690 U2=24+U1
700 PRINT USING 710:U1,U2;
710 IMAGE3D,"-",3D,":"
720 INPUT U3
730 D(I)=U3
740 U1=U1+24
750 NEXT I
760 PAGE
770 PRINT "I";
780 PRINT "URINE DATA"
790 GOSUB 150
800 FIND 16
810 PRINT @3,32:"L"
820 PRINT @3,32: USING 830:Z$
830 IMAGE40X,30A
840 M$="FILE:16"
850 PRINT @3,32: USING 880:M$
860 K$="FINAL URINE READINGS"
870 PRINT @3,32: USING 880:K$
880 IMAGE"J",40X,30A
890 GOSUB 530
900 N=12
910 E(1)=0
920 F(1)=0
930 FOR I=1 TO N1
940 B(I)=B(I)*D(I)/150
950 C(I)=C(I)*B(I)
960 E(I+1)=B(I)+E(I)
970 F(I+1)=SQR(C(I)↑2+F(I)↑2)
980 PRINT @33: USING 990:N,A(I),E(I+1),F(I+1)
990 IMAGE3D,9X,6D.6D,2(X,7D.6D)
1000 PRINT @3,32: USING 1010:N,A(I),E(I+1),F(I+1)
1010 IMAGE"J",3D,9X,6D.6D,2(X,7D.6D)
1020 NEXT I
1030 END
```

TABLE:E.1.14

AREA UNDER MODIFIED GAUSSIAN FUNCTION

```
100 REM CALCULATION OF AREA UNDER MOD. GAUSSIAN FUNCTION
110 DIM A(100),P(10)
120 PAGE
130 PRINT "CALCULATION OF AREA UNDER MOD. GAUSSIAN FUNCTION"
140 PRINT USING 150:
150 IMAGE6X,45("-")
160 PRINT "J"
170 PRINT "ENTER START CHANNEL:";
180 INPUT S9
190 PRINT "J"
200 PRINT "ENTER FINISH CHANNEL:";
210 INPUT F9
220 PRINT "J"
230 PRINT "ENTER NO. OF PARAMETERS:";
240 INPUT N9
250 PRINT "J"
260 FOR I=1 TO N9
270 PRINT "     P(";I;")=";
280 INPUT X9
290 P(I)=X9
300 NEXT I
310 I=1
320 A(1)=0
330 IF S9=F9 THEN 440
340 X1=S9
350 GOSUB 490
360 Y2=Y1
370 X1=S9+1
380 GOSUB 490
390 Y3=Y1
400 A(I+1)=A(I)+(Y3+Y2)/2
410 I=I+1
420 S9=S9+1
430 GO TO 330
440 PRINT "J"
450 PRINT "AREA=";
460 PRINT USING 470:A(I),A(I)↑0.5
470 IMAGE6D," +-",6D
480 END
490 Z1=P(2)-X1
500 Z2=P(6)*X1↑P(7)/(P(8)↑P(7)+X1↑P(7))
510 Y1=P(1)*(1+Z2*(Z1↑P(3)+Z1↑P(4)))*EXP(-(Z1↑2)/(2*P(5)↑2))
520 RETURN
```

E.2 List of FORTRAN V programs

E.2.1 Conversion of profile scan data (ASC II) to binary data.

E.2.2 Savitzky filter and Iinuma and Nagai image restoration (Binary data)

E.2.3 Subtraction of profile scans (Binary data)

TABLE:E.2.1

CONVERSION OF PROFILE SCAN DATA(ASCII) TO BINARY DATA

```
      COMMON/TAPIN/IDAT(4096)
      COMMON ICR,ILP,ITAP,IDIS
      DIMENSION REF(12),TAG(12)
      DATA ICR,ILP,ITAP,IDIS/5,6,11,12/
      REAL IDAT
      INTEGER TAG,REF,NULL
      J=0
      K=0
      NULL='      '
      WRITE(ILP,31)
   31 FORMAT(/' LAST TAG (A6)-("RETURN" IF NEW FILE) :'/)
      READ(ICR,9) TAG(1)
    9 FORMAT (A6)
      WRITE(ILP,32)
   32 FORMAT(//' INPUT TAG,NCHAN (A6,I4)-("RETURN" TO END) :
     '/)
      IF (TAG(1).EQ.NULL) GO TO 1
   10 CALL NTRAN (IDIS,2,12,REF,J)
      IF (J.EQ.-1) CALL NTRAN (IDIS,22)
      IF (J.LE.-2) GO TO 20
      CALL NTRAN (IDIS,2,4096,IDAT,K)
      IF (K.EQ.-1) CALL NTRAN (IDIS,22)
      IF (K.LE.-2) GO TO 20
      IF(TAG(1).NE.REF(1)) GO TO 10
    1 READ (ICR,6) REF(1),NCHAN
    6 FORMAT(A6,I4)
      IF (NCHAN.EQ.0) GO TO 7
       IF (NCHAN.LT.0) CALL DIGIT (NCHAN)
      IF( NCHAN.GT.0)CALL INTAP (REF(1),NCHAN)
       NCHAN=IABS(NCHAN)
      II=NCHAN+1
      DO 2 I=II,4096
    2 IDAT(I)=0
      CALL DISOUT (REF)
      WRITE (ILP,8) REF(1)
    8 FORMAT (15X,A6,' TRANSFERRED TO DISC')
      GO TO 1
   20 WRITE (ILP,11) J,K
   11 FORMAT (///8X,'MAIN'/,8X,'J=',I6/8X,'K=',I6)
    7 CALL NTRAN (IDIS,10)
      WRITE(ILP,5)
    5 FORMAT(/,14X,'****** FINISH & KLAAR ******'/)
      CALL DISLIS
      END
```

```
 1              SUBROUTINE DISOUT(REF)
 2              DIMENSION REF(12)
 3              COMMON/TAPIN/IDAT(4096)
 4              COMMON ICR,ILP,ITAP,IDIS
 5              REAL IDAT
 6              LL=0
 7              MM=0
 8              CALL NTRAN(IDIS,1,12,REF,LL)
 9              IF(LL.EQ.-1) CALL NTRAN(IDIS,22)
10              IF(LL.LE.-2) GO TO 2
11              CALL NTRAN(IDIS,1,4096,IDAT,MM)
12              IF(MM.EQ.-1) CALL NTRAN(IDIS,22)
13              IF(MM.LE.-2) GO TO 2
14              RETURN
15            2 WRITE (ILP,2001) LL,MM
16         2001 FORMAT(//8X,'DISOUT',/8X,'LL=',I6,/8X,'MM=',I6/)
17              RETURN
18              END
```

TABLE:E.2.2

SAVITZKY FILTER AND IINUMA AND NAGAI IMAGE RESTORATION

```
 7            DIMENSION TDATA(6),TSHAPE(6),TITLE(12),DIT(4096), A(20
              0),STD(200)
 8            DIMENSION JDAT(4096)
 9            COMMON /TAPIN/ IDAT(4096)
10            COMMON ICR,ILP
11            INTEGER TIT,TSHAPE,TDATA,TAG
12             DATA TIT,ICR,ILP/6H      ,5,6/
13          111 DO 11 I=1,4096
14            JDAT(I)=0
15            IDAT(I)=0
16           11 DIT(I)=0.0
17            DO 12 I=1,200
18           12 A(I)=0.0
19            CALL NTRAN(11,22,10)
20            READ (ICR,1)TAG,IDUM,IBGLSR,ISTART,ISTOP,NSPT,NSM00,TS
              HAPE
21            1 FORMAT(A6,I4,5I5,6A6)
22            IF (TSHAPE.EQ.TIT) GO TO 33
23            NS=ISTOP-ISTART+1
24            NINT=NS/2
25            DO 13 I=1,200
26           13 STD(I)=0.0
27            IF (TAG.NE.TIT) CALL INTAP(TAG,12,2)
28            CALL INTAP(TSHAPE(1),11,2)
29             DO 813 I=1,4096
30             IDAT(I)=IDAT(I)-IBGLSR
31          813 IF(IDAT(I).LT.0) IDAT(I)=0
32            IF(NSM00.GT.0) CALL SM00TH(NSPT,NSM00,4096,ISTART,IST0
              P)
33            TOT=0
34            DO 31 I=ISTART,ISTOP
35            DIT(I)=FLOAT(IDAT(I))
36           31 TOT=TOT+DIT(I)
37            WRITE(ILP,2)TSHAPE,TAG,IBGLSR,ISTART,ISTOP,NSPT,NSM00,
               TOT
38            2 FORMAT(1H1,':',3X,6A6,//,1X,'TAG= ',A6,1X,'IBGLSR=',I5
              ,
39             1    3X,'ISTART=',I4,3X,'ISTOP=',I4,
40             *  3X,'NSPT=',I2,3X,'NSM00=',I2,//,
41             2    6X,'TOTAL COUNTS IN STANDARD PEAK=',F11.1,///,6X,'
               CHAN',
42             3  6X,'IDAT', 9X,'X',10X,'STD',/)
43             DO 32 I=ISTART,ISTOP
44             J=I-ISTART+1
45             STD(J)= DIT(I)/TOT
46           32 WRITE(ILP,3) I,DIT(I),J,STD(J)
47            3 FORMAT(I10,F10.1,I10,F13.4)
48           33 READ (ICR,22) IBGDAT,ISHIFT,ITR,NBLK,IBEG,IFIN,NDPT,ND
              SM0,TDATA
49           22 FORMAT(8I5,6A6)
```

```
      IF(NBLK.EQ.0) GO TO 99
      READ (ICR,4)TITLE
    4 FORMAT(12A6)
      CALL NTRAN(11,22,10)
      CALL INTAP(TDATA(1),11,2)
      III=4096-ISHIFT
       DO 814 I=1,III
  814 JDAT(I+ISHIFT)=IDAT(I)-IBGDAT
      DO 815 I=1,4096
      IDAT(I)=JDAT(I)
  815 IF(IDAT(I).LT.0) IDAT(I)=0
      WRITE(ILP,91)TDATA,IBGDAT,ISHIFT,ITR,NBLK,IBEG,IFIN, N
     DPT,NDSMO
       WRITE(ILP,95) TITLE(1)
   91 FORMAT(1H1,':',3X,6A6,///,1X,'IBGDAT=',I5,3X,'ISHIFT='
     ,I3,3X,
     *  'ITR=',I3,3X,'NBLK=',I3,3X,
     1 'IBEG=',I4,3X,'IFIN=',I4,3X,'NDPT=',I2,3X,'NDSMO=',I2
     ,3X)
   95 FORMAT(///,'-----------------',A6,'------------------
     -',/)
      WRITE(ILP,92)(JK,JK=1,ITR)
   92 FORMAT(11X,'0',15I7)
      WRITE (ILP,2111)
 2111 FORMAT(/)
      DO 719 J=IBEG,IFIN
      IDAT(J-IBEG+1)=IDAT(J)
  719  DIT(J-IBEG+1)=IDAT(J)
      IFIN1=IFIN+1
      DO 717 I=IFIN1,4096
      IDAT(I)=0
  717 DIT(I)=0.0
      IF(NDSMO.GT.0) CALL SMOOTH(NDPT,NDSMO,4096,IBEG,IFIN)
      CHISQ=0.0
      SRAW=0.0
      SSMOO=0.0
      DO 718 I=IBEG,IFIN
      SRAW=SRAW+DIT(I)
      SSMOO=SSMOO+IDAT(I)
       CHISQ=CHISQ+(DIT(I)-IDAT(I))**2
  718 DIT(I)=0.0
      DIFF=SSMOO-SRAW
      NS1=NINT+1
      NCHAN=(4096+1)/NBLK
      ITR1=ITR+1
      DO 392 I=1,NCHAN
  392 DIT(I)=FLOAT(IDAT(I))
      DO 43 IT=1,ITR1
      LTR=(IT-1)*NCHAN
      LTOP=LTR+IFIN
```

```
 96              LBOT=LTR+IBEG
 97              H=0.0
 98              DO 35 J=IBEG,IFIN
 99              D=0.0
100              DO 37 K=1,NS
101              L=J+NS1-K+(IT-1)*NCHAN
102              IF(L.GT.LTOP) GO TO 37
103              IF(L.LT.LBOT) GO TO 37
104              D=D+STD(K)*DIT(L)
105           37 CONTINUE
106              JJ=NCHAN*IT+J
107              H=H+(DIT(J)-D)**2.0
108              DIT(JJ)=DIT(JJ-NCHAN)+ DIT(J)-D
109           35 CONTINUE
110              IF(IT.GT.1)  A(IT-1)=H
111           43 CONTINUE
112              DO 61 I=1,4096
113              DIT(I)=DIT(I)+0.5
114              IDAT(I)=IFIX(DIT(I))
115              IF(IDAT(I).LT.0) IDAT(I)=0
116           61 CONTINUE
117              DO 67 I=IBEG,IFIN
118           67 WRITE(ILP,18)I,(IDAT((J-1)*NCHAN+I),J=1,ITR1)
119           18 FORMAT(1H ,I4,16I7)
120              WRITE (ILP,171)
121          171 FORMAT(1H1,':',1X,'IT',5X,'SSM00',7X,'SRAW',3X,'SSM00-
                 SRAW',3X,
122             1   'CHISQ', 7X,'H', 5X,'H-SSM00',//)
123              DO 17 I=1,ITR
124              C=A(I)-SSM00
125           17 WRITE(ILP,19)I,SSM00,SRAW,DIFF,CHISQ,A(I),C
126           19 FORMAT(1H ,I3,2E11.4,2E10.1,E10.4,E10.1)
127              CALL INTAP(TITLE(1),12,1)
128              WRITE (ILP,283)TITLE(1)
129          283 FORMAT(////,5X,A6,' WRITTEN ON DISC',////)
130              GO TO 111
131           99 WRITE(ILP,284)
132          284 FORMAT(//////5X,'END OF OPERATION'///)
133               CALL DISLIS(12)
134              CALL EXIT
135              END
```

```
      SUBROUTINE SMOOTH(IPT,ISMOO,JCHAN ,INITL,IFINAL)
      DIMENSION DATA(4096),M(26,25)
      COMMON/TAPIN/IDAT(4096)
      DATA M/26*0,26*0,4,1,2,1,22*0,26*0,35,-3,12,17,12,-3,2
     0*0,26*0,
     1    21,-2,3,6,7,6,3,-2,18*0,26*0,
     2    231,-21,14,39,54,59,54,39,14,-21,16*0,26*0,
     3     429,-36,9,44,69,84,89,84,69,44,9,-36,14*0,26*0,
     4   143,-11,0,9,16,21,24,25,24,21,16,9,0,-11,12*0,26*0,
     5    1105,-78,-13,42,87,122,147,162,167,162,147,122,87,4
     2,-13,-78,
     6    10*0,26*0,
     7   323,-21,-6,7,18,27,34,39,42,43,42,39,34,27,18,7,-6,-
     21,8*0,26*0,
     8   2261,-136,-51,24,89,144,189,224,249,264,269,264,249,
     224,189,
     *   144,89,24,-51,-136,6*0,26*0,
     A    3059,-171,-76,9,84,149,204,249,284,309,324,329,324,
     309,284,249,
     B   204,149,84,9,-76,-171,4*0,26*0,
     C     805,-42,-21,-2,15,30,43,54,63,70,75,78,79,78,75,70
     ,63,54,
     D   43,30,15,-2,-21,-42,2*0,26*0,
     E   5135,-253,-138,-33,62,147,222,287,322,387,422,447,46
     2,467,462,
     F   447,422,387,322,287,222,147,62,-33,-138,-253/
      DO 4 I=1,4096
    4 DATA(I)=FLOAT(IDAT(I))
      ISMOV=0
    6 IF(ISMOV.EQ.ISMOO) GO TO 7
      JPT=IPT/2
      JPT1=JPT+INITL
      JCHOP=IFINAL-JPT
      DO 1 I=JPT1,JCHOP
      J1=I-JPT
      J2=I+JPT
      N=1
      SDAT=0.0
      DO 2 J=J1,J2
      N=N+1
    2 SDAT=SDAT+M(N,IPT)*IDAT(J)
      DATA(I)=SDAT/M(1,IPT)
    1 CONTINUE
      DO 5 I=1,4096
      DATA(I)=DATA(I)+0.5
    5 IDAT(I)=IFIX(DATA(I))
      ISMOV=ISMOV+1
      GO TO 6
    7 RETURN
      END
```

TABLE:E.2.3

SUBTRACTION OF PROFILE SCANS

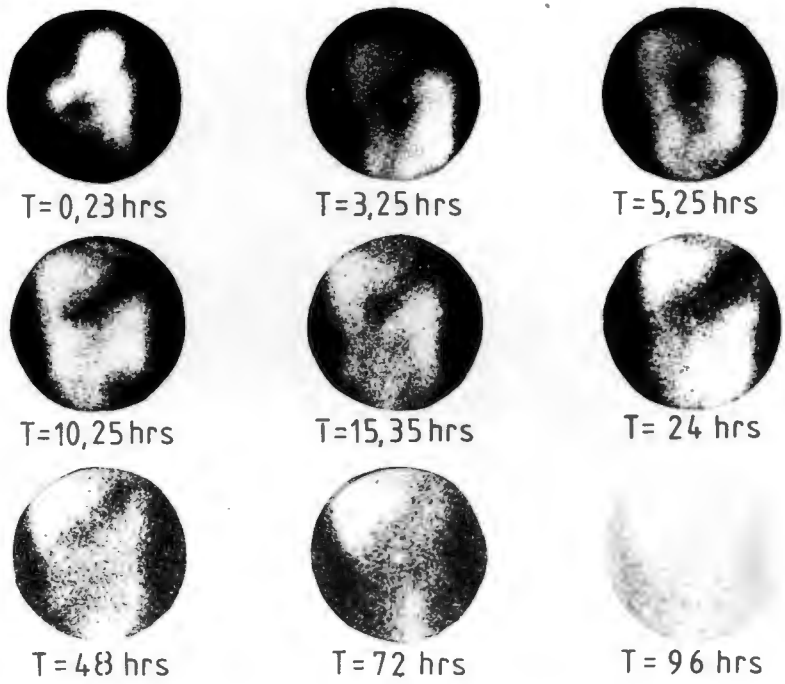
```
 1              COMMON/TAPIN/IDAT(4096)
 2              COMMON ICR,ILP
 3              DIMENSION JDAT(4096),KDAT(4096)
 4              DATA ICR,ILP/5,6/
 5              INTEGER REFDAT,REFLST,REFNEW
 6              JJ=1
 7           10 WRITE(ILP,4)
 8            4 FORMAT(/1X,' REFDAT REFLST ')
 9              READ (ICR,2) REFDAT,REFLST
10            2 FORMAT (1X,2(A6,1X))
11              IF(JJ.EQ.1) GO TO 16
12           20 REFLST=REFNEW
13              REFDAT=REFNEW
14           16 WRITE(ILP,17)
15           17 FORMAT(1X,' REFNEW -REFBG J N ---FACT---')
16              READ(ICR,18)REFNEW,REFBG,J,N,FACT
17           18 FORMAT(1X,2(A6,1X),2(I1,1X),F10.3)
18              CALL NTRAN(11,10,22)
19              CALL INTAP(REFBG,11,2)
20              N=N+1
21              NCHAN=(4096+1)/J
22              IF (J.EQ.1) NCHAN=4096
23              NSTART=(N-1)*NCHAN
24              DO 7 K=1,J
25              KCH=(K-1)*NCHAN
26              DO 7 I=1,NCHAN
27            7 JDAT(KCH+I)=IDAT(NSTART+I)
28              CALL NTRAN(11,10,22)
29              CALL INTAP(REFDAT,11,2)
30              DO 8 I=1,4096
31              KDAT(I)=IDAT(I)-JDAT(I)*FACT+0.5
32              IF(KDAT(I).LT.0) KDAT(I)=0
33            8 CONTINUE
34              CALL NTRAN(11,10,22)
35              CALL INTAP(REFLST,11,2)
36              DO 21 I=1,4096
37           21 IDAT(I)=KDAT(I)
38              CALL INTAP(REFNEW,11,1)
39              WRITE (ILP,1)REFNEW
40            1 FORMAT(1X,A6,'  TRANSFERRED TO DISC')
41              IF(JJ.EQ.2) GO TO 9
42              JJ=2
43              GO TO 20
44            9 WRITE(ILP,3)
45            3 FORMAT(///,2X,'----FINITO----'///)
46              CALL DISLIS(11)
47              CALL EXIT
48              END
```

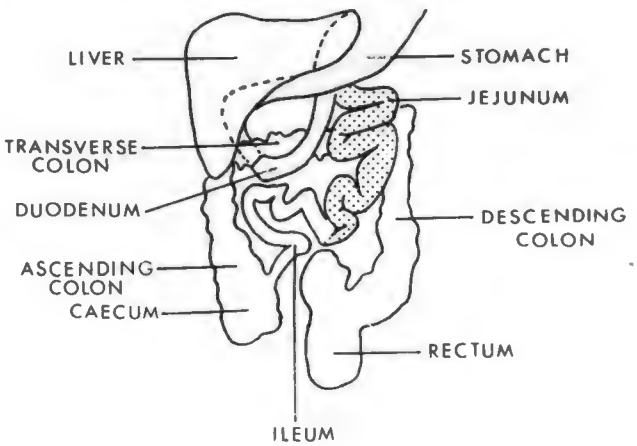
23 APR 1981


```
1               SUBROUTINE DISLIS
2               COMMON /TAPIN/IDAT(4096)
3               COMMON ICR,ILP
4               DIMENSION NAME(12)
5               REAL IDAT
6               M=0
7               N=0
8               L=0
9                IDIS=12
10              WRITE (ILP,2)
11            2 FORMAT(1H1,/' SPECTRA FOUND'/)
12              CALL NTRAN (IDIS,10,22)
13            1 CALL NTRAN(IDIS,2,12,NAME,M)
14              IF(M.EQ.-1) CALL NTRAN(IDIS,22)
15              IF(M.LE.-2) GO TO 4
16              N=N+1
17              CALL NTRAN(IDIS,2,4096,IDAT,L)
18              IF (L.EQ.-1) CALL NTRAN (IDIS,22)
19              IF (L.LE.-2) GO TO 4
20              WRITE (ILP,3) N,NAME(1)
21            3 FORMAT(1X,I3,4X,A6)
22              IF(N.GT.1000) RETURN
23              GO TO 1
24            4 WRITE(ILP,5)M,L
25            5 FORMAT(//8X,'DISLIS'/,8X,'M=',I6,/,8X,'L=',I6/)
26              RETURN
27              END
```

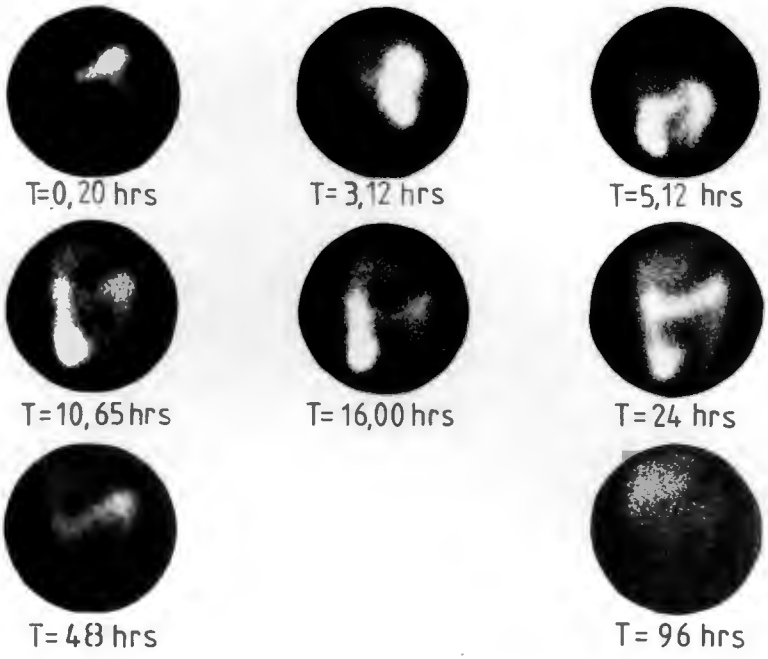
22 JAN 1981

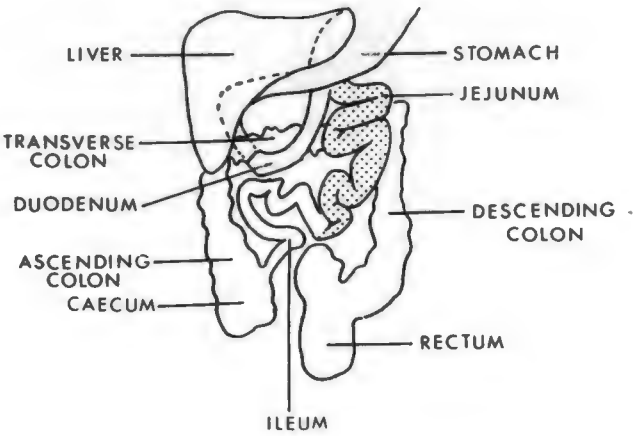
SUBJECT: D.W. EXPERIMENT: KINETIC 1



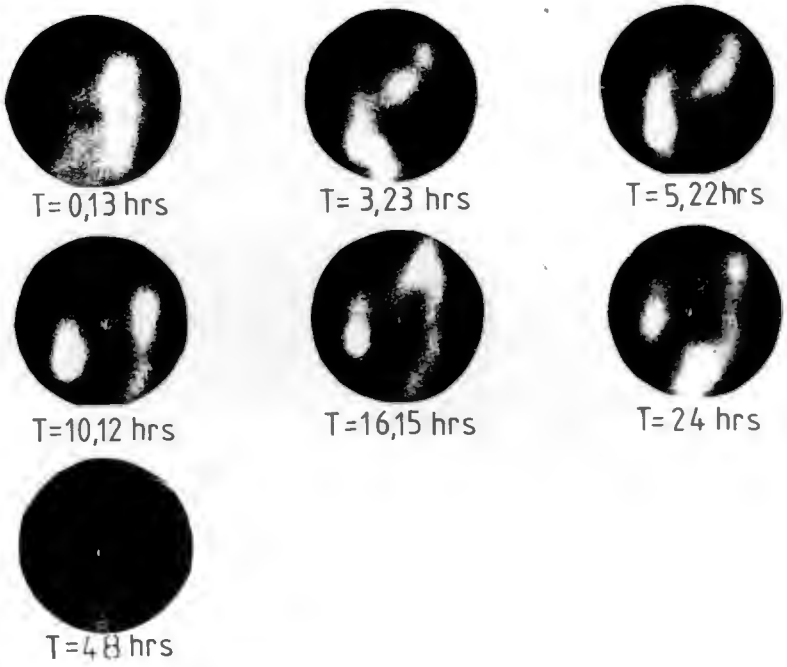


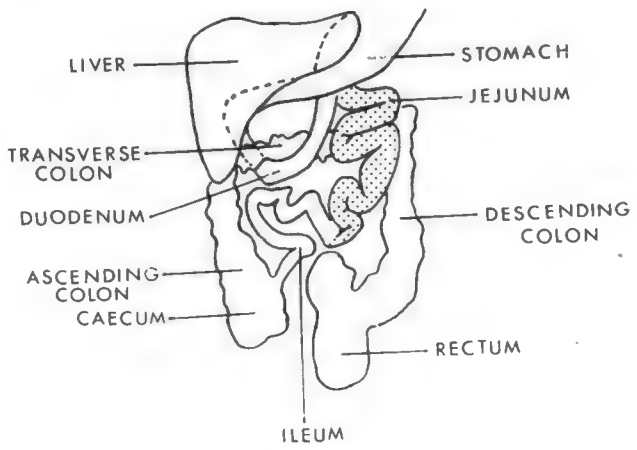
SUBJECT: K.B. EXPERIMENT: KINETIC 2



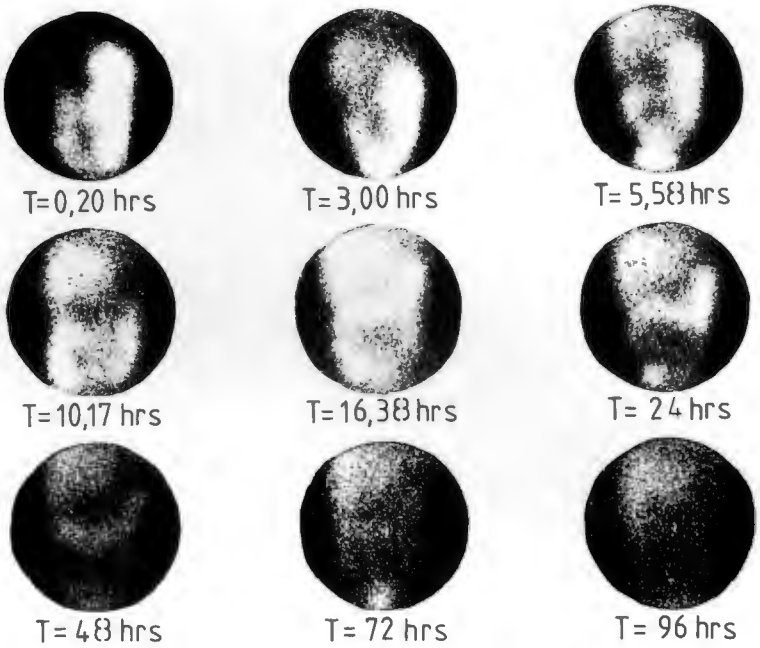


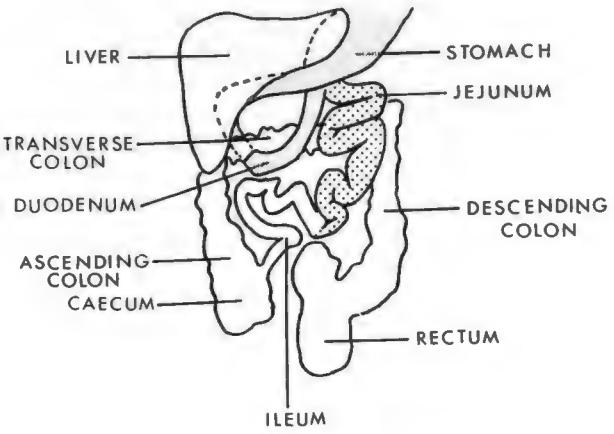
SUBJECT: D.W. EXPERIMENT: KINETIC 2



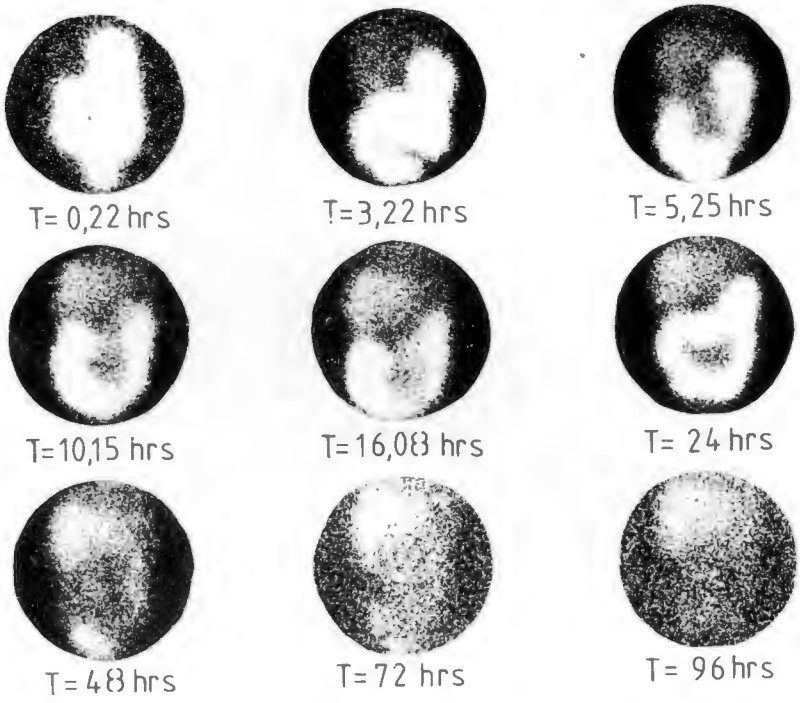


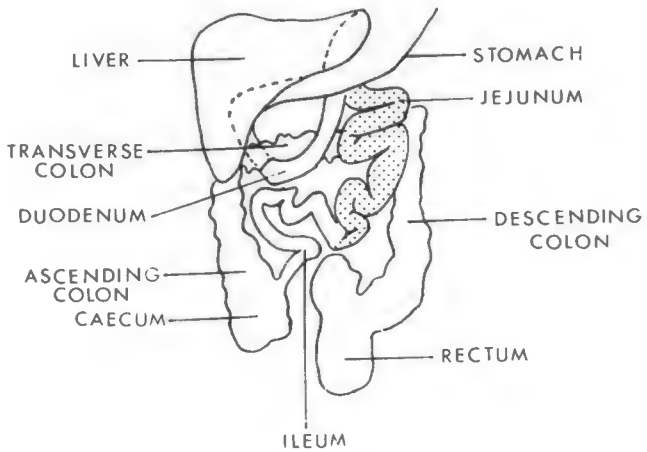
SUBJECT: J.B. EXPERIMENT: KINETIC 1



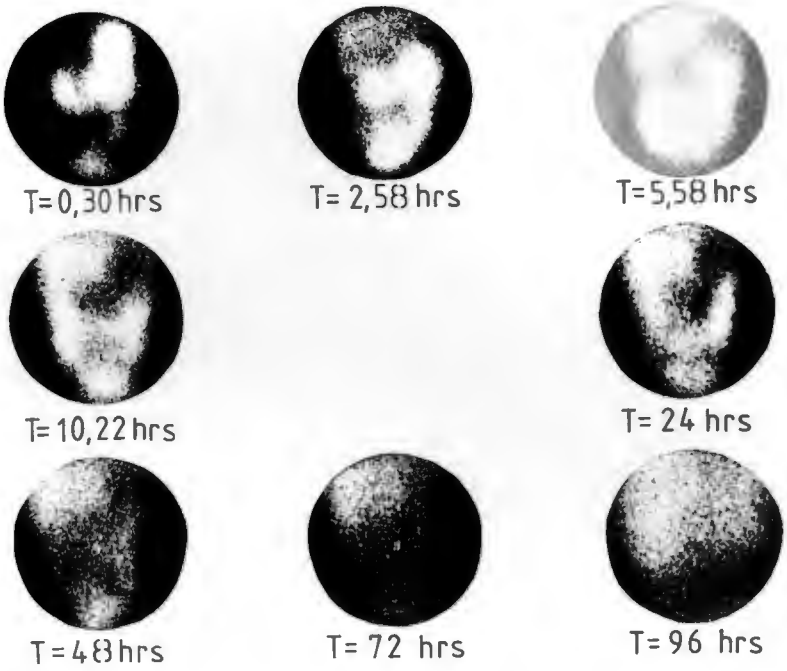


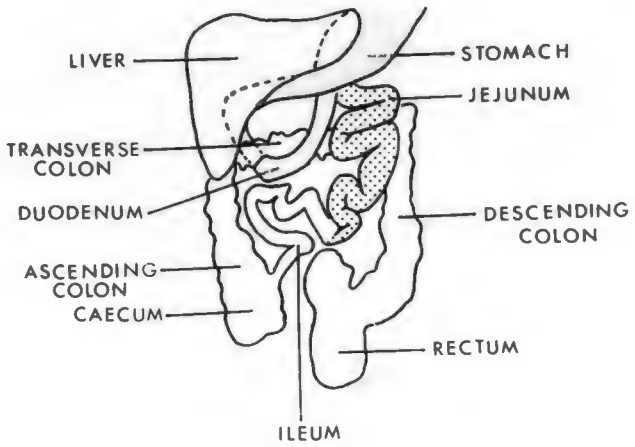
SUBJECT: J.B. EXPERIMENT: KINETIC 2



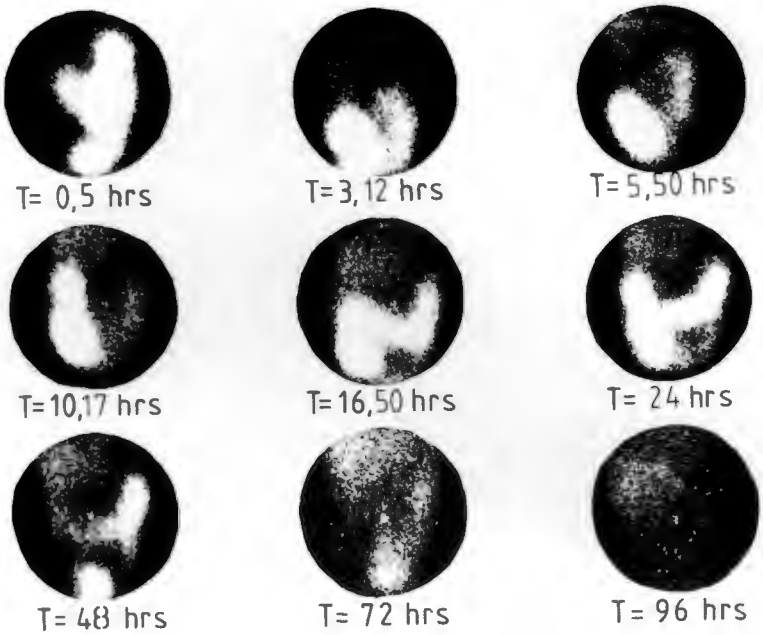


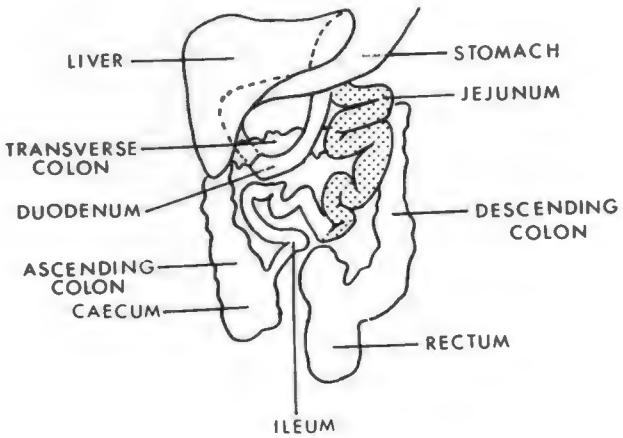
SUBJECT : G.E. EXPERIMENT : KINETIC 1



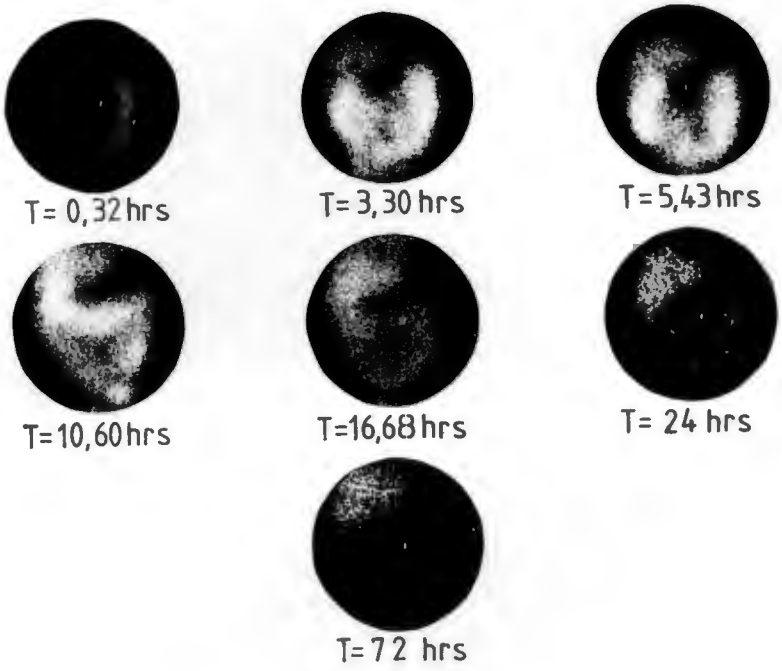


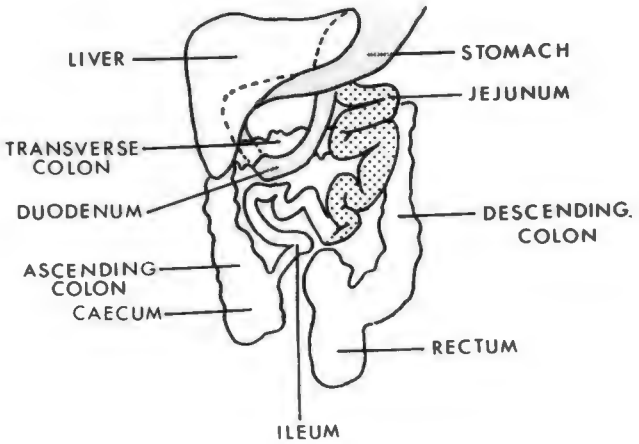
SUBJECT: G.E. EXPERIMENT: KINETIC 2





SUBJECT: B.C. EXPERIMENT: KINETIC 1





SUBJECT: B.C. EXPERIMENT: KINETIC 2