METABOLIC STUDIES IN MAN USING STABLE ISOTOPES

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Summary

In this project, stable isotope compounds and stable isotope pharmaceuticals were used (with emphasis on the application of ^{15}N) to study several aspects of nitrogen metabolism in man [1-5]. Of the many methods available, the ^{15}N stable isotope tracer technique holds a special position because the methodology for application and nitrogen isotope analysis is proven and reliable. Valid routine methods using ^{15}N analysis by emission spectrometry have been demonstrated. Several methods for the preparation of biological material were developed during our participation in the Coordinated Research Programme. In these studies, direct procedures (i.e. use of diluted urine as a sample without chemical preparation) or rapid isolation methods were favoured [6,7]. Within the scope of the Analytical Quality Control Service (AQCS) enriched stable isotope reference materials for medical and biological studies were prepared and are now available through the International Atomic Energy Agency. The materials are of special importance as the increasing application of stable isotopes as tracers in medical, biological and agricultural studies has focused interest on reliable measurements of biological material of different origin [8].

To investigate how the liver or other organs are influenced by malabsorption, malnutrition, and contaminants from the environment, several urine tests were developed:

The [^{15}N]glycine test to characterize liver function and exogenous or endogenous influences on protein turnover [9].

Examples of investigation: quantitative determination of parameters of protein metabolism in healthy man, measurement of the rate of protein synthesis and breakdown in patients with liver diseases, protein metabolism of expeditioners during wintering in Antarctica, studies on metabolic effects of recombinant human growth hormone in girls with Turner syndrome.

The [^{15}N]ammonium test to assess hepatic ammonia detoxification [10-15].

Examples of investigation: liver damage in children with metabolic liver diseases, hepatitis and cirrhosis, influence of hormonal contraceptive drugs on liver metabolism, studies on the postnatal development of urea synthesis in preterm infants, characterization of the functional state of the liver in athletes, studies on chronic kidney insufficiency, hepatic detoxification capacity of children in highly polluted industrial regions (waste gas of coke factories).

The [^{15}N]methacetin test to assess hepatic microsomal biotransformation capacity [2,16,17].

Examples of investigation: age-dependence of the cytochrome-P_{450}-dependent monooxygenase activity of healthy persons, detection, discrimination and follow up studies of liver disease in adults, pregnant women and children, assessment of developmental aspects of monooxygenase capacity in the neonatal period, hepatic detoxification capacity as a result of intrauterine growth retardation, assessment of the hepatic glucuronidation, monitoring of side effects of therapeutic drugs (antibiotics), influence of certain toxins at the workplace or from the environment, differential diagnosis of cholestasis.

[$^{15}N_2$]urea test to detect gastric Helicobacter pylori infection [18,19].

[^{15}N]taurocholate test to detect failures in the enterohepatic bile acid circulation [20].

[^{15}N]hippurate test to measure the glycine synthesis capacity of the liver [6].

Validation of methodologies to measure protein and energy metabolism in humans.

A multiple tracer study (^{15}N, ^{13}C, ^{2}H, ^{18}O) to validate the methodology of protein and energy metabolism studies in man was completed. For the mathematical description of metabolic parameters, both compartmental and non-compartmental models, such as the modified model of Sprinson-Rittenberg, the San Pietro-Rittenberg model, two models of the albumin metabolism, and a 10-pool model of nitrogen and protein metabolism were used. By means of a single or multiple pulse infusion and priming techniques, whole body nitrogen and protein metabolism in various metabolic states were studied:

Metabolism in healthy man to establish standard or reference values

Metabolism during selected pathophysiological conditions (liver diseases)

Metabolism under stress conditions (wintering in Antarctica)

Metabolism during and/or after therapeutic treatments with amino acid solutions, hormones, or pharmaceuticals

Metabolism at different levels of nitrogen intake [9].

In pilot experiments, the ^{15}N NMR technique was applied to study hepatic glycine turnover under stress conditions *in vivo*, using a ^{15}N-glycine load and implanted NMR coils

in rats. Previously, corresponding experiments with isolated rat livers had already been done to investigate the time course of enzyme activity under various conditions [21].

Development of mathematical programmes

For handling and evaluating ^{15}N tracer data, the programs PATMETH and PROPROT were developed [22]. In a paper on theoretical problems of tracer kinetics and the modelling of inhomogeneous compartments with age-dependent elimination rates, the basic equations for one generalized compartment and for systems of such compartments are given together with their general solution and illustrated by examples [23,24]. Mathematically, it turns out that models consisting of partial differential equations include ordinary, delayed and integro-differential equations, a general fact which is treated in context of linear tracer kinetics. The examples include standard compartments as a degenerate case, systems of standard compartments (compartment blocks), models resulting in special residence time distribution, models with pipes, and systems with heterogeneous particles.

REFERENCES AND ANNOTATIONS

[1] FAUST, H., JUNG, K., KRUMBIEGEL, P., The development of licensed stable isotope drugs, Zfl-Mitt. **150** (1989) 151-159.

For quite a long time the authors have been engaged in preparing the scientific basis for the use of stable isotopes in medicine. Within the scope of governmental regulations for stable isotope application in human medicine and food production industry (1970), the governmental registration of the first stable isotope drugs was obtained in 1983 and 1987. The licensed drugs [^{15}N]glycine, [^{15}N]methacetin and [^{15}N]ammonium chloride are used now in clinical practice for specialized liver function tests and general investigations on nitrogen metabolism.

[2] KRUMBIEGEL, P., TEICHMANN, B., BOEHM, H., Nitrogen-15 methacetin urine test: A method to study the development of hepatic detoxification capacity, Eur. J. Pediatr. **149** (1990) 393-395.

The [^{15}N]methacetin urine test was used to study human O-demethylase activities to characterize the maturation of hepatic detoxification capacity. The study involved 43 healthy subjects aged 1 day - 47 years. The urinary ^{15}N elimination rates were measured following oral administrations of an aqueous [^{15}N]methacetin solution. Age-dependent normal values of hepatic drug elimination capacity were established. Parameters were the ^{15}N elimination half-life and cumulative elimination of the ^{15}N dose as a percentage over a 9 h period. The maximum elimination rate (% dose/h) and peak time can give additional information. The ^{15}N method is a simple, non-invasive and non-radioactive liver function test avoiding disadvantages of ^{14}C and ^{13}C breath tests. The [^{15}N]methacetin test is suitable and useful in studying the hepatic development at birth and pathological changes of the microsomal detoxification capacity in early childhood.

[3] KRUMBIEGEL, P., BERTHOLD, H., Evaluating environmental exposure on children: How can stable isotope techniques contribute? Isotopenpraxis. Isotopes in environmental and health studies **28** (1992) , in press.

The authors review the recent literature, including their own approaches of stable isotope techniques applied to determining environmental effects on the health of children. The techniques involve the measurement of variations in natural isotope abundances of some elements with environmental significance, the use of enriched stable isotopes for in vivo and *in situ* tracer studies, in vitro isotope dilution techniques, and organ function tests using stable isotope labelled compounds. These techniques are non-invasive and can be expected to contribute new insights into the behaviour of different pollutants and their effect on children's health. Some of the techniques have been used in clinical research and diagnosis but their adaption for investigations of clinically healthy children exposed to environmental pollution is desirable. Currently, as one of the specific aims of the Leipzig group of Human Exposure Research, the experience in biochemical and clinical isotope applications is being adapted to the environmental challenges in the heavily polluted industrial regions of Saxony.

[4] KRUMBIEGEL, P., Stable Isotope Pharmaceuticals, G. Fischer Verlag Jena, Stuttgart, New York 1991.

This introductory survey on the use of stable isotopes in medicine, complemented by discussion of ethical issues relevant to topic, will serve as a textbook as well as a reference for the pharmaceutical researcher.

[5] KRUMBIEGEL, P., ^{13}C- and ^{15}N-labeled non-biogenic compounds used as stable isotope drugs for human liver function tests, Isotopenpraxis **25** (1989) 58-60.

As a result of liver diseases, the elimination of certain drugs from the body is delayed. Labelling a suitable drug with ^{13}C, the $^{13}CO_2$ elimination rate serves as a liver function parameter. Current contributions to the $^{13}CO_2$ breath test method are reviewed and related to the $^{14}CO_2$ breath test proposals. In spite of several advantages of ^{13}C-labeled agents, some dissatisfaction has remained with the tests, especially at using them with infants. It is the necessity of face masks and the uncertainty to consider endogenous CO_2 contributions diluting the exhaled $^{13}CO_2$. The problems are avoided if the other molecule site of the drug is labeled which is known to be eliminated via urine. With ^{15}N as a tracer, a suitable urine test using [^{15}N]methacetin as a licensed stable isotope drug has been proposed and put into practice.

[6] FAUST, H., JUNG, K., KRUMBIEGEL, P., JUNGHANS, P., REINHARD, R., Progress in the biomedical use of ^{15}N, Zfl-Mitt. **150** (1989) 161-180.

Biochemical and ^{15}N sample chemical methods are briefly summarized for the application of the ^{15}N tracer technique for biomedical and clinical investigations in connection with the use of the automated emission spectrometric ^{15}N analyzer NOI-6e. On the basis of this technique, new ^{15}N liver function tests ([^{15}N]ammonium test, [^{15}N]methacetin test, [^{15}N]glycine test) have been developed and their application in the clinical practice is demonstrated. Further applications of

the ^{15}N tracer methods in paediatrics and for the study of the nitrogen metabolism under arctic stress conditions are shown. Proved methods for the experimental work with the ^{15}N tracer technique (priming) and the mathematical evaluation of ^{15}N tracer experiments are presented.

[7] FISCHER, H., MEIER, G., NITSCHKE, W., SCHMIDT, G., Emissionsspectroscopic ^{15}N analysis, Zfl-Mitt. **150** (1989) 267-279.

The emissionspectroscopic ^{15}N analysis is a powerful tool for ^{15}N tracer experiments in agriculture, biology, and medicine. Advantages of the NOI-6e and NOI-6PC ^{15}N analyzer systems are the low sample amount, the short measuring time, and the high handling comfort. In the future methods for the simultaneous determination of total nitrogen and of nitrogen-15 will become increasingly important.

[8] FAUST, H., JUNG, K., REINHARDT, R., Traditional cooperation between the IAEA and the CIIRR, Zfl-Mitt. **150** (1989) 331-338.

Review on the activities of the Central Institute for Isotope and Radiation Research (CIIRR), Leipzig, within the scope of the cooperation with the International Atomic Energy Agency.

[9] JUNGHANS, P., WAGNER, B., NICKEL, A., FAUST, H., Tracer kinetics and metabolic models in medicine, Zfl-Mitt. **150** (1989) 181-204.

In the present paper a survey of methods applied to the interpretation and evaluation of tracer kinetic data is given. For their mathematical description both compartmental and non-compartmental models, like the modified model of SPRINSON and RITTENBERG, the SAN PIETRO-RITTENBERG model, two models of the albumin metabolism and a 10-pool model of the N and protein metabolism were used. By means of single or multiple pulse, infusion and priming techniques the N and protein metabolism in various metabolic states (e.g. healthy man, pathological and stress conditions, therapeutic treatments) were studied.

[10] MENSCHIKOWSKI, M., JUNG, K., JUNGHANS, A., PETZKE, K.J., ALBRECHT, V., The influence of a steroid hormone and of physical exercise on protein metabolism of rats, Exp. Clin. Endocrinol. **92** (1988) 341-348.

Influences of an anabolic steroid hormone preparation and of a physical exercise training program on the nitrogen and protein metabolism were studied in rats with the help of the ^{15}N tracer technique and the emission spectrometric ^{15}N isotope analysis. For the determination of the dynamic parameters of the protein metabolism graphic (stochastic) and computer aided compartmental methods were compared. Using as a stochastic approach the area-method the animals showed significant differences in the protein turnover parameters under the influence of hormone treatment and (or) physical stress by swimming exercise in comparison to the controls.

[11] JUNG, K., FAUST, H., MATKOWITZ, R., [^{15}N]Ammonium test for liver function diagnosis, Z. Med. Lab. Diagn. **30** (1989) 169-174.

The functional state of the liver can be assessed by oral administration of ^{15}N-labelled ammonium chloride (tracer) and subsequent isotope analysis of [15N]urea and [^{15}N]ammonia in urine. Clinical tests based on the ratio of the excess abundances of [^{15}N]ammonia to [^{15}N]urea excreted in urine 3 hours after oral administration of the tracer gave values for patients with liver diseases which differed significantly from those of healthy subjects.

[12] JUNG, K., METZNER, Chr., TEICHMANN, B., Der [^{15}N]Ammoniumtest in der klinischen Forschung, Gastroenterol, J. **49** (1989) 118-121.

By use of the [^{15}N]ammonium test the liver function is investigated under influence of hormonal contraceptives in women and in children with liver diseases. With the described noninvasive nonradioactive isotope test the ammonia detoxification capability and the urea synthesis capacity of the liver is determined by measuring of the ^{15}N-excretion in ammonia and urea in the urine after oral administration of [^{15}N]ammonium chloride. The [^{15}N]ammonium test shows a significant influence of the hormonal contraceptives on the liver function and gives diagnostic evidence for liver diseases in children.

[13] WAGENKNECHT, C., JUNG, K., KINZEL, A., BARLEBEN, H., GERIKE, U., JUNKER, L., HEINE, H., Untersuchungen zum Stickstoff- und Eiweißtoffwechsel sowie der Zelllproliferation bei Patienten mit Hypertonie und Ateriosklerose mit Hilfe eines ^{15}N-Markierungstestes, Z. Klin. Med. **45** (1990) 1435-1437.

A ^{15}N-labelling test was used to characterize nitrogen and protein metabolism as well as cellular proliferation in patients with hypertension and arteriosclerosis. [^{15}N]ammonia and [^{15}N]urea excretions were measured by means of a [^{15}N]ammonium test in twelve patients with arterial hypertension of II and III severity grades, following oral application to them of [^{15}N]ammonium chloride. The results thus obtained were compared to values recorded from a control group. Incorporation of ^{15}N into fibrinogen, lymphocytes, thrombocytes, and granulocytes was investigated in four patients. The possibility was established to determine alterations to nitrogen and protein metabolism in the context of various cardiovascular diseases.

[14] BARLEBEN, H., WAGENKNECHT, C., JUNG, K., JUNKER, L., REIMANN, H., HAMANN, K. HEINE, H., ^{15}N-Tracertechnische Untersuchungen zum Eiweißstoffwechsel bei Arteriosklerosepatienten, Klin. Wochenschr. **68** (1990) 518-522.

The incorporation of the stable isotope ^{15}N in plasma proteins and blood cells after oral application of 3 g $^{15}NH_4Cl$ (95 atom percent ^{15}N) per 70 kg body weight was followed up in 11 patients with ischemic heart disease or peripheral arteriosclerosis and in 7 healthy control subjects. Preliminary results indicate that the turnover of plasma protein, especially fibrin, is elevated in patients with arteriosclerosis. Investigations of platelet suggest a decreased turnover of platelet protein in patients with arteriosclerosis as compared to control subjects. Possible reasons for these alterations are discussed.

[15] BOEHM, G., TEICHMANN, B., JUNG, K., Development of urea-synthesizing capacity in preterm infants during the first weeks of life, Biol. Neonate **59** (1991) 1-4.

The urea-synthesizing capacity of the liver was studied in 20 healthy preterm infants during the first month of life. The urea-synthesizing capacity was estimated by the ratio of ^{15}N abundances of ammonia and urea in the 6-hour urine after administration of 3 mg ^{15}N-labelled ammonium chloride/kg body weight. The ratio increases with increasing protein intakes from the 3rd week of life. On protein intakes of more than 3 g/kg/day from the 3rd week to the end of the 2nd month of life, the ratio decreases suggesting a maturation of the urea cycle during the first weeks of life.

[16] BOEHM, G., MÜLLER, D.M., TEICHMANN, B., KRUMBIEGEL, P., Influence of intrauterine growth retardation on parameters of liver function in low birth weight infants, Eur. J. Pediatr. **149** (1990) 396-398.

To establish nutritional management of low birthweight infants according to their individual metabolic situation, hepatocellular partial function was studied in 13 appropriate (AGA) and 11 small-for-gestational-age (SGA) low birthweight (LBW) infants during the first weeks of postnatal life. The concentrations of total bile acids and of alpha-amino-nitrogen in serum, the renal excretion of urea and ammonia and the renal excretion of ^{15}N after enteral administration of 3 mg ^{15}N-labelled methacetin g/kg were measured. In comparison to AGA infants, SGA infants had elevated serum concentrations of total bile acids and of alpha-amino-nitrogen, decreased excretion of urea, increased excretion of ammonia in urine, and lower urinary ^{15}N-excretion after enteral administration of ^{15}N-labeled methacetin. The data suggest that hepatocellular functions are influenced by intrauterine growth retardation resulting in a reduced metabolic capacity in SGA infants. The metabolic differences between SGA and AGA infants should be considered in the nutritional management of LBW infants.

[17] BOEHM, G., SENGER, H., SPENCKER, F.B.,HANDRICK, W., TEICHMANN, B., KRUMBIEGEL, P., Effects of two antibiotics on hepatic function on low birth weight infants: ampicillin vs. cefotaxime, Pediatr. Infect. Dis. J. **10** (1991) 739-742.

In 21 low birth weight infants with two regiments of antibiotic therapy during the first 3 days of life possible hepatotoxic side effects were studied 8 days after the last administration of the tested drugs. Fourteen of the infants were treated with ampicillin/gentamycin and 7 received cefotaxime/gentamycin. The serum concentrations of total bile acids, the activities of transaminases in serum and the cumulative ^{15}N excretion in urine after administration of 3 mg of ^{15}N-labeled methacetin/kg of body weight were used as markers of hepatotoxic side effects. Neither the concentrations of total bile acids (22.6 + 12.1 and 19.4 + 10.8 mM, respectively) nor the activities of transaminases (alanine aminotransferase, 0.27 + 0.06 vs. 0.30 + 0.09 μmol/second/L; aspartate aminotransferase, 0,46 + 0,11 vs. 0.49 + 0,10 ≒ mol/second/L) were different between the two groups. In contrast the cumulative ^{15}N excretion in urine was significantly lower in the group treated with cefotaxime/gentamycin than in the group treated with ampicillin/gentamycin (17.2 + 6.4 vs. 33.0 + 5.1 % of intake; $P < 0.01$) and also

lower than the reported age-related reference values. On the 28th day of life no differences could be found between the cumulative ^{15}N excretion in the urine of the infants treated with cefotaxime/gentamycin and the reported age-related reference values of this test. The results indicate a limited capacity of the monooxygenase system of the liver of low birth weight infants during the first weeks of life and a specific reversible influence of cefotaxime on this hepatocellular system. Further investigations are required to evaluate the clinical relevance of this drug-specific inhibition of the hepatic monooxygenase pathway.

[18] KRUMBIEGEL, P., FAUST, H., TEICHMANN, B., SPENCKER, F.-B., ROGOS, R., Rapid non-invasive diagnosis of gastric Campylobacter pylori infection by a simple [$^{15}N_2$]urea urine test, Eur. J. Nucl. Med. **16** (1990) 423.

When stable isotope labelled [$^{15}N_2$]urea was administered orally with a test meal, the high urease activity of Campylobacter pylori-infected individuals yielded ^{15}N-labelled ammonia. The ^{15}N abundance of the urinary ammonia and urea could be detected easily 3 hours later using a simple microdiffusion technique and emission spectrometric ^{15}N analysis. Individuals without gastric urease activity eliminated practically no [^{15}N]ammonia over this period. This corresponds to an ^{15}N (ammonia)/ ^{15}N (urea) ratio less than 0.05. Infected individuals showed ratios above 0.08 and reached ratios more than 0.20. Ten healthy subjects and fifteen patients with gastroscopic diagnosed C. pylori infection were involved in the study, which was approved by the departmental Ethical Committee. The new test has reliably identified all patients with positive cultures. We conclude that the test is well suited for repeated application using the advantages of the non-distressing, non-radioactive, and simple method.

[19] KRUMBIEGEL, P., FAUST, H., TEICHMANN, B., SPENCKER, F.-B. [$^{15}N_2$]Harnstoff-Urin-Test - Eine neue, nichtinvasive Methode zur Diagnostik der Helicobacter pylori-Gastritis, Z. Klin. Med. **46** (1991) 691-692.

For the detection of mucosal Helicobacter pylori infection we present a new test method the protocol of which is quite different to the usual, invasive detection methods. It is based on the oral administration of the harmless, stable isotope labeled diagnostic agent [$^{15}N_2$]urea and emission spectrometric measurements of the ^{15}N abundances of urea and ammonia in urine 3 hours later. For the ^{15}N measurements the urinary ammonia was separated using a simple microdiffusion technique. Then was the urea N liberated in the remaining urine sample with sodium hypobromite for ^{15}N analysis. Individuals without gastric urease activity eliminated practically no [$^{15}N_2$]ammonia over this period corresponding to an urinary ^{15}N(ammonia)/^{15}N(urea) ratio R = 0.022 + 0.007 (mean + SD; n = 8). Patients with gastroscopically confirmed infection showed highly-significantly increased ratios; R = 0.121 + 0.056 (n = 8). An extended clinical study is under preparation.

[20] KRUMBIEGEL. P., SENGER, H., SPRINZ, H., Sodium [^{15}N]taurocholate - a new stable isotope pharmaceutical to investigate the enterohepatic bile acid circulation non-invasively, Eur. J. Nucl. Med. **18** (1991) 671.

Sodium [^{15}N]taurocholate (1) was synthesized by reacting [^{15}N]taurine - which was obtained from sodium 2-bromoethanesulphonate and [^{15}N]ammonia, cholic acid, and the coupling reagent EEDQ. The identity and purity were confirmed by ^{1}H and ^{15}N NMR spectroscopy, mass spectroscopy, and thin layer chromatography using unlabelled taurocholate and supposed impurities as reference substances. (1) was administered orally (7 mg/kg body mass) to a healthy proband first, in order to thoroughly study its reliability as a true marker of bile acid turnover. Urine and faeces were collected over 7 days. Urinary ^{15}N amounts (representative of deconjugated [^{15}N]taurine and faecal ^{15}N amounts [representative of eliminated (1)] were estimated to find convenient sampling intervals for further studies. Balance investigations have shown that (1) should be well suited for a non-invasive, non-radio-active, simple urine test in paediatrics. The Local Ethical Committee has approved the study which is being continued including children with defects in enterohepatic bile acid circulation.

[21] KRUMBIEGEL, P., GRÜNDER, W., BUCHALI, K., KELLER, T., Synchronized ^{13}C-^{15}N-NMR spectroscopy to follow kinetics of glycine metabolization in the rat liver nondestructively, Isotopenpraxis **26** (1990) 518-519.

A method is proposed for reiterated measurements by turns of ^{13}C and ^{15}N NMR signals at intact rat liver tissue. Eight minutes after Wistar rats had been injected [1,2-13C; ^{15}N]glycine, the liver was excised and stored in the triple resonance probe-head of a 2.1 Tesla NMR spectrometer. Alternatively ^{13}C and ^{15}N spectra were taken over some hours. Continued enzymatic activities of the liver tissue were seen in terms of metabolic changes of each of the carbon and nitrogen groups of glycine. Different half lives were found for the disappearance of the groups. The measurements gave insights into the kinetics and metabolism of an amino acid as an example to follow the vitality of an isolated organ non-destructively.

[22] WAGNER, B., NICKEL, A., KRUMBIEGEL, P., TEICHMANN, B., PATMETH - ein Programmsystem zur Bearbeitung von Patientendateien und zur Auswertung von [15N]Methacetin-Lebertests, Z. Klin. Med. **46** (1991) 467-470.

A general introduction to the principle underlying the [^{15}N]methacetin liver function test is followed, in this paper, by an account of the PATMETH programme system. PATMETH can be used for two different purposes, handling of gastroenterology patient files and evaluation of the [^{15}N]methacetin test. The latter may be done, using ^{15}N data in a file on the basis of a three-compartment model. The following liver performance indices were found to be obtainable from calculations of that kind: elimination half-time, amount of dosage eliminated up to nine hours as well as maximum elimination rate and its juncture. These indices may then be entered to the meters, may be used for differential diagnosis. The first two indices, elimination half-time and amount of dosage eliminated within nine hours, are printed out in what is called a medical letter and are compared to normal values. Clinical routine diagnosis and medical isotope research are major applications for PATMETH.

[23] WINKLER, E., Tracer kinetics: Modelling by partial differential equations of inhomogeneous compartments with age-dependent elimination rates. Part 1: General theory, Isotopenpraxis **27** (1991) 225-228.

Mathematical models in tracer kinetics are usually based on ordinary differential equations which correspond to a system of kinetically homogeneous compartments (standard compartments). A generalization is possible by the admission of inhomogeneities in the behaviour of the elements belonging to a compartment. The important special case of the age-dependence of elimination rates is treated in its deterministic version. It leads to partial differential equations (i. e., systems with distributed coefficients) with the "age" or the "residence time"of an element of the compartments as a variable additional to "time". The basic equations for one generalized compartment and for systems of such compartment are given together with their general solutions.

[24] WINKLER, E., Tracer kinetics: Modelling by partial differential equations of inhomogeneous compartments with age-dependent elimination rates. Part 2: Examples of application, Isotopenpraxis **27** (1991) 228-233.

The general theory of inhomogeneous compartments with age-dependent elimination rates given in part I in a deterministic frame by sets of partial differential equations is illustrated by examples. Mathematically, it turns out that models consisting of partial differential equations include ordinary, delayed and integro-differential equations, a general fact which is treated here in the context of linear tracer kinetics. The examples include standard compartments as a degenerate case, systems of standard compartments (compartment blocks), models resulting in special residence time distributions, models with pipes, and systems with heterogeneous particles.