From: The Department of Cariology, The Royal Dental School, Stockholm, and the Department of Pharmacology, The Royal Veterinary College, Stockholm.

AUTORADIOGRAPHIC INVESTIGATIONS OF THE DISTRIBUTION OF F18 IN MICE AND RATS

by

YNGVE ERICSSON
SVEN ULLBERG

Considerable work has been done in investigating the distribution, metabolism, and physiological action of fluorine in the animal body (reviews: *Largent* 1954, *Bredemann* 1956, *Sellman & collab.* 1958). Great difficulties are encountered, however, in the chemical analysis of small quantities of fluorine in organs and body fluids; the widely varying analytical figures given by different authors illustrate this (review: *Bredemann* 1956).

The use of radioactive fluorine has so far overcome these difficulties only to a limited extent, owing to the short half-life, about 110 minutes, of F18, the only isotope that can be used. F18-studies on the absorption, metabolism and excretion of fluorine have been published by *Volker & collab.* 1941, *Wills* 1952, *Wallace-Durbin* 1953, 1954, *Hein & collab.* 1954, 1956, *Perkinson & collab.* 1955, *Ericsson* 1958 a. *Patricia Wallace-Durbin*'s studies on rats have been particularly extensive and illuminating. Studies with F18 of the reactions of fluorine with dental enamel have been performed by *Myers & collab.* 1952, *Mühlemann & collab.* 1955, *Myers* 1955, *Brudevold* 1957, *Hardwick & collab.* 1958 and *Ericsson* 1958 b.

Autoradiographic demonstration of the distribution and metabolism of F18 has, to our knowledge, only been done using ground surfaces of hard tissue slabs (*Wallace, Myers, Hardwick*

& collab. loc. cit.). The time ordinarily required for embedding, sectioning and mounting of histological specimens has precluded autoradiographic study of thin sections.

By the combination of rapid methods for the separation and purification of F18 with a rapid method for sectioning we have been able to produce autoradiograms of thin sections through the whole body of small experimental animals. The technique has permitted survival times up to one hour after the injection of solutions containing F18. The methods and findings will be presented below together with a few representative pictures.

PRODUCTION OF F 18

F18 was produced by neutron irradiation of analytically pure lithium hydroxide in the uranium reactor of the Atomenergi Co., Stockholm. The reactions are:

(1) ${}_3Li^6 + {}_0n^1 \rightarrow {}_2He^4 + {}_1H^3$,
(2) ${}_1H^3 + {}_8O^{16} \rightarrow {}_0n^1 + {}_9F^{18}$.

Contaminating activity, almost entirely due to Na24, was removed by glass distillation with $HClO_4$ at about 140° C. using a slow air stream. A distillate of about 10 ml was taken up in 1 ml 1.5-N NaOH, which required about half an hour. After neutralization with HCl drop by drop to pH 5—8 the distillate consisted of a carrier-free solution of F18 with physiologically compatible pH and ionic strength. The radioactive fluorine which distilled over as hydrofluosilicic acid could be assumed to be completely hydrolyzed to fluoride ions in the solution (*Feldman & collab.* 1957). The decay curves on the following day revealed a slight residual activity of Na24. This contamination could be calculated to have been between 0.05 and 0.1 % of the total activity at the beginning of the autoradiographic exposure and thus was negligible.

The distillate was used for intravenous or intraperitoneal injection into mice and rats. The activity of the solution was about 10—15 μc per ml at the time of the injection. The animals were sacrificed, embedded and sectioned according to the technique to be described.

AUTORADIOGRAPHIC TECHNIQUE

The autoradiography was made according to methods described previously by *Ullberg* (1954). Certain modifications had to be made owing to the rapid decay of F18.

At different time intervals after the injection of radiofluorine the experimental animal was anesthesized and killed by immersion in carbon dioxide-acetone at about —45° C.

The frozen animal was then transferred to a freeze-room kept at a temperature of —10°. Here it was mounted in ice on a heavy microtome with a specially made large stage. The sectioning was started immediately after mounting the frozen animal in ice — this was the reason for not using a lower temperature than —45° when freezing the animals. To get whole sections, adhesive tape was pressed, before each section was cut, on to the surface of the block in the plane of sectioning — the tape holding the section together. The sections were made even through hard tissues such as bone and teeth. It proved possible to make 20 μ sagittal sections through the whole animal almost immediately after mounting. Time did not permit dehydration of the sections before exposure.

The exposure was done by apposition against x-ray film Gevaert Dentus Rapid. Direct exposure in the freeze-room at —10°C. proved to result in some chemical fogging of the emulsion. In some of the exposures, therefore, pliofilm, thickness about 10 μ, was used as an intervening layer between the sections and the photographic emulsions. However, the pliofilm layer lowered the resolution and the degree of blackening of the autoradiograms. This was a serious disadvantage since already the comparatively high energy of the F18 positrons (maximal energy about 0.65 mev) limits the resolution, and since the activities of the solutions for injection were rather limited. We therefore tried to avoid chemical fogging by making the exposure at a lower temperature. This proved possible, and the majority of exposures were made in boxes half filled with CO_2-acetone — the autoradiographic iron presses and the photographic films being cooled down beforehand. The presses were generally left overnight for exposure. The sections were removed from the films, which were developed. Sections that were reasonably intact and corresponded

to good autoradiograms were stained and then mounted on slides in Canada balsam.

RESULTS

I. Survey autoradiograms

Representative autoradiograms of sections obtained after different survival times are given as figures 1—4 with individual descriptions.

These autoradiograms demonstrate the rapidity of the elimination of fluorine from the blood and soft tissues, owing to uptake by the mineralized tissues and excretion through the kidneys. Except for the kidneys, none of the parenchymatous organs showed any notable uptake, e.g. not the thyroid or the liver. There was no sign of excretion via the bile or the intestinal wall. The uptake in the subcutaneous tissue and the hair follicles seemed slightly elevated. The concentration in the muscles and the fat depots was low. Especially low content of F18 was found in the central nervous system. The quantity of F18 which passed the placenta was also notably small and was concentrated in the mineralized skeletal parts of the fetuses. Some concentration of F18 in the placenta was observed, sometimes forming a dotted pattern.

II. Special studies of skeleton and teeth

Representative enlarged autoradiograms of skeletal parts are given in figures 5—8, with individual descriptions.

The autoradiograms demonstrate that the F18 is nearly exclusively taken up by the mineralized parts of the skeletal tissues, and especially concentrated in the calcification zones. Uncalcified cartilage shows no uptake. In the developing teeth, F18 is concentrated in the outer layer of the enamel and the inner layer of the dentin, especially in the latter. In the erupted teeth there is no F18 uptake visible in the enamel.

III. Special studies of the kidneys

In figures 3 and 9 the fluorine content in the kidneys can be compared with that of other organs. The concentration of fluorine appears to follow the localization of the collecting tubules.

Table 1

Relative activities of kidneys and heart blood after intravenous injection of F18 into rats.

Weight of animal, grams	Survival time, min.	Kidney preparation	Ratio kidney/blood (activities per gram)
62.3	8	right k., cranial 1/3	1.60
	8	» », central 1/3	1.90
	8	» », caudal 1/3	1.85
61.1	10	right kidney	1.38
	10	left »	1.32
65	10	right »	1.94
	10	left »	1.88
168.4	12	right »	2.91
122	15	» »	1.61
68	17	» »	2.78
165	20	» »	1.51
156.5	30	» »	1.58

The F18 content of the kidney in relation to the blood was also studied quantitatively at different time intervals after intravenous injection into rats weighing 61—165 grams. Under ether anesthesia blood was drawn from the heart with a heparinized syringe. Immediately afterwards the kidneys were taken out. In one case the kidney was divided transversely into three approximately equal parts. The blood samples and the kidneys were weighed in nickle dishes and analyzed with a scintillation detector. The error due to the difference in geometry was less than 5 per cent (*Ericsson* 1958 a). Table 1 gives the results. It appears that the whole kidney contained about 1.5 to 3 times as much F18 as the corresponding weight of blood during the first half hour following an intravenous injection.

IV. Special study of the placenta

The dotted appearance of the placenta which was observed on many sections from pregnant mice seemed to indicate that precipitated calcium salts might be responsible for these concentrations of fluorine. Some of these sections were therefore stained with 0.75 % silver nitrate according to von Kossa's method for

calcium deposits. Small calcified granules in the placentae were found to coincide exactly with the dots on the autoradiograms.

DISCUSSION

The absence of any appreciable concentration of F18 in the thyroid or salivary glands is in striking contrast to the selective localization of I131 in these glands. This selectivity with respect to the different halogens argues against any appreciable replacement of iodine in the thyroid by fluorine, as do also many previous investigations with animals and humans (reviews: *Largent* 1954, *Bredemann* 1956, *Sellman & collab.* 1958; *Baumann & collab.* 1956). The low concentration in the salivary glands also helps to explain why some investigators have not been able to find any clear correlation between the amount of fluorine ingested and its concentration in the saliva (*Cox* 1940, *McClure* 1941).

The low F18 uptake in the liver agrees well with the results of analyses of the total fluorine content of the liver (*Delga & Fournier* 1950, *Wallace* 1953, *Largent* 1954), and with the very low fluorine content found in biliary stones, in contrast to the high fluorine content of urinary tract stones (*Zipkin & collab.* 1958).

It has been clearly demonstrated that the placenta constitutes a partial barrier to the fluorine, and that the fetus is thus protected to a considerable degree against overdosage. This is in agreement with recently published results of quantitative fluorine analysis of newborn rats from mother animals on varying fluoride intake (*Büttner & Muhler* 1958). The small quantity of fluorine which passes into the blood of full-term fetuses is rapidly concentrated in the mineralized parts of the skeleton. The exact coincidence of the argyrophil dots of the placenta with the localization of the F18 activity in this organ makes it probable that macroscopic and microscopic precipitates of calcium salts form the simple explanation of the placental barrier to fluorine. Such precipitates are known to be extremely common in the human placenta as well as in that of the mouse.

It has also been demonstrated that bones take up fluorine especially in the calcifying zones and that no fluorine is taken

up by uncalcified cartilage. It would seem that the previous authors who have reported an uptake of fluorine by cartilage or mucopolysaccharides (*Wallace-Durbin* 1954, *Candeli & Scasselati-Sforzolini* 1953, *Ziegler* 1956) have been analyzing specimens containing calcium salts; *Wallace-Durbin's* expression that "F18 is present in cartilage to an extent apparently involved with its potentialities for calcification" indicates that she has been aware of the probable explanation of her finding.

The uptake of fluorine by the calcifying zone of the dentin was found to be greater than the uptake by the corresponding zone of the enamel. This is in accordance with previous results of quantitative analyses of erupted teeth, which have shown a greater fluorine content in the dentin than in the enamel (review: *Bredemann* 1956). It would thus seem that the calcification disorders of the enamel, which are the first known signs of overdosage of fluorine, are due to some specificity of the ameloblasts rather than the concentration of fluorine *per se*; it may be pointed out in this connection that the mineralization of the ameloblasts is intracellular in contrast to that of other mineralizing tissues.

The autoradiographic findings emphasize that, except in the enamel, pathological effects of incipient overdosage are to be looked for in the first place in the kidneys and mineralizing bones. The kidneys have a comparatively high concentration of fluorine in solution for limited time intervals after each ingestion, while the bones store the main part of the retained fluorine as inorganic crystals in the intercellular spaces. As long as no toxic signs can be found in the kidneys and the calcification zones there should be little risk of damage to other organs or tissues. From animal experiments and human observations there is strong evidence that large doses of fluorine are necessary to cause damage to the kidneys or growing bones (*Likins & collab.* 1953, 1954, *Hodge & Smith* 1954, *McCauley & McClure* 1954, *Auskaps & Shaw* 1955, *Zipkin & Scow* 1955, 1956, *Pindborg* 1957, and others).

By the comparatively low F18-activities at our disposal, our experiments have been limited as regards the survival time of the animals, and also as regards the resolution of the autoradiograms. With greater activities it will be possible to follow the

fluorine distribution for a longer time, and, more important still, possibly also to establish the localization on a cellular level in those tissues where F18 is concentrated.

SUMMARY

A rapid method of isolation and purification of F18 (half life about 110 minutes) has been combined with a rapid method for sectioning of whole frozen animals. Thus autoradiograms have been obtained showing the distribution and excretion patterns of fluorine up to one hour after intravenous injection.

The most striking finding on the survey autoradiograms is the extremely rapid incorporation of fluorine in hard tissues (heavy uptake in the skeleton already 2 minutes after intravenous injection).

No appreciable concentration of fluorine has been found in any soft tissue with the exception of the kidneys during the phase of excretion. The F18 content is especially low in the central nervous system and the fetal soft tissues. The liver, the fat depots and the muscles also show a rather low uptake.

The placenta forms a partial barrier to fluorine, probably through its content of precipitated calcium phosphates. The amount of fluorine which passes the placenta is concentrated in the mineralized parts of the fetal skeleton.

The bones take up F18 especially in the mineralization zones. The cartilage shows no affinity to F18.

The unerupted teeth take up F18 in the outer layer of the mineralized enamel and still more in the inner layer of the mineralized dentin. The erupted teeth of adult rats show no visible uptake in the enamel.

RESUME

ETUDE AUTORADIOGRAPHIQUE DE LA REPARTITION DE F18 CHEZ LA SOURIS ET LE RAT

Une méthode rapide d'isolation et de purification de F18 (période environ 110 minutes) a été combinée avec une méthode rapide de sectionnement de petits animaux expérimentaux entièrement congelés. Des autoradiogrammes ont été faits montrant

la répartition et l'élimination du fluor justqu'à une heure après l'injection.

L'observation la plus frappante est l'incorporation extrêmement rapide du fluor dans les tissus durs: absorption massive dans le squelette déjà 2 minutes après injection intraveineuse. Aucune concentration appréciable de fluor n'a été observée dans les tissus mous à l'exception des reins pendant la phase d'élimination. L'absorption de F18 est minime dans le système nerveux central et dans les tissus mous des foetus. Le foie, les dépôts de graisse et les muscles montrent aussi une absorption très faible.

Le placenta forme une barrière partielle au fluor, probablement par son contenu de phosphate de calcium précipité. La quantité de fluor passant à travers le placenta se trouve concentrée dans les parties minéralisées du squelette fœtal.

Les os absorbent F18 particulièrement dans les zones de minéralisation. Le cartilage n'absorbe pas de quantités perceptibles de fluor.

Les dents n'ayant pas encore fait éruption absorbent F18 dans la couche extérieure de l'émail minéralisé et plus encore dans la couche intérieure de la dentine minéralisée. Les dents des rats adultes ne montrent aucune absorption visible dans l'émail.

ZUSAMMENFASSUNG

AUTORADIOGRAPHISCHE UNTERSUCHUNGEN ÜBER DIE VERTEILUNG VON F18 BEI MÄUSEN UND RATTEN

Eine schnelle Methode zur Isolierung und Reinigung von F18 (Halbierungszeit c:a 110 Min.) wurde mit einer schnellen Methode zur Darstellung von Schnitten ganzer, gefrorener Kleintiere kombiniert. Dies ermöglichte es, Autoradiogramme darzustellen, an denen die Verteilung und Ausscheidung des Fluors bis zu einer Stunde nach intravenöser Injektion verfolgt werden konnten.

Der auffallendste Befund an den Übersichtsautoradiogrammen ist die ausserordentlich schnelle Aufnahme des Fluors in die Hartgewebe (starke Aufnahme im Skelett schon 2 Min. nach intravenöser Injektion).

Keine nennenswerte Konzentration von Fluor wurde in den

Weichteilen gefunden, mit Ausnahme der Nieren während der Ausscheidungsphase. Die F18-Aufnahme ist besonders klein im Zentralnervensystem und in den fötalen Weichteilen. Die Leber, die Fettdepots und die Muskulatur zeigen ebenfalls eine niedrige Aufnahme.

Die Placenta wirkt wie eine partielle Barriere gegen Fluor; wahrscheinlich wegen ihres Gehaltes an ausgefälltem Kalziumphosphat. Die Fluormenge, die die Placenta passiert hat, ist in den mineralisierten Teilen des fötalen Skeletts konzentriert.

Die Knochen nehmen F18 besonders in den Mineralisierungszonen auf. Der Knorpel zeigt keine F18-Aufnahme.

Die nicht durchgebrochenen Zähne nehmen F18 in der Aussenzone des mineralisierten Schmelzes und noch mehr in der Innenzone des mineralisierten Dentins auf. Durchgebrochene Molaren ausgewachsener Ratten weisen keine sichtbare Aufnahme im Schmelz auf.

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Adresses:

Yngve Ericsson
The Royal Dental School
Stockholm 3
Sweden

Sven Ullberg
The Royal Veterinary College
Stockholm 51
Sweden

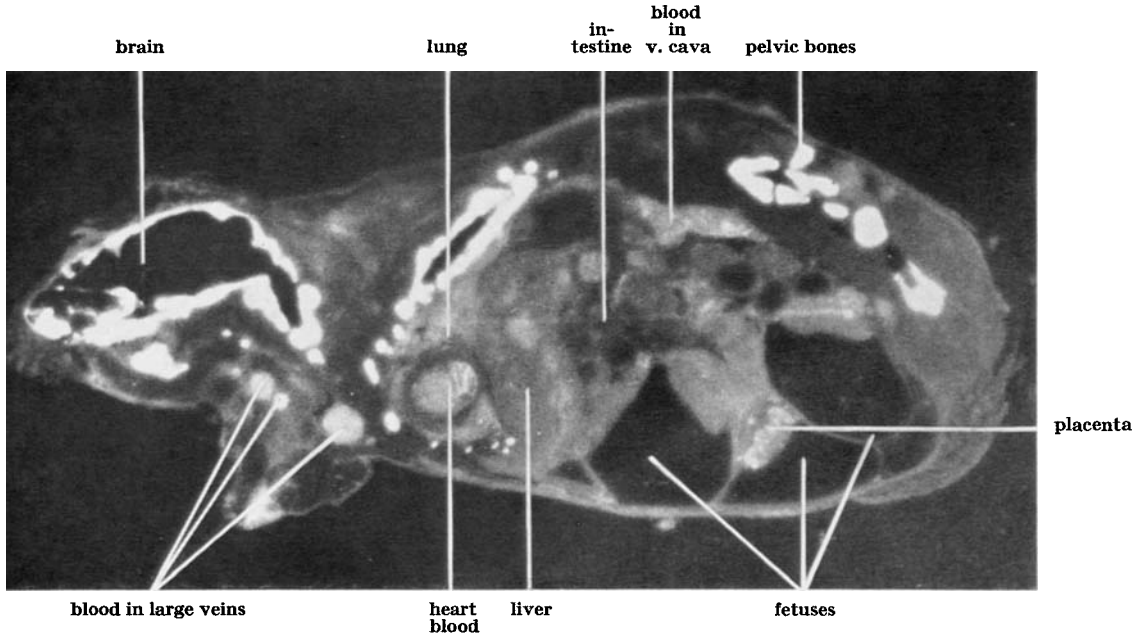


Fig. 1. Autoradiogram showing the distribution of F 18 in a pregnant mouse 2 minutes after intravenous injection. The white areas correspond to high fluorine content. The fluorine very rapidly accumulates in the bones. There is no fluorine detectable in the brain or in the fetuses and fetal fluids. Blood concentration is still high: note e. g. activity in heart blood (1.5 ×).

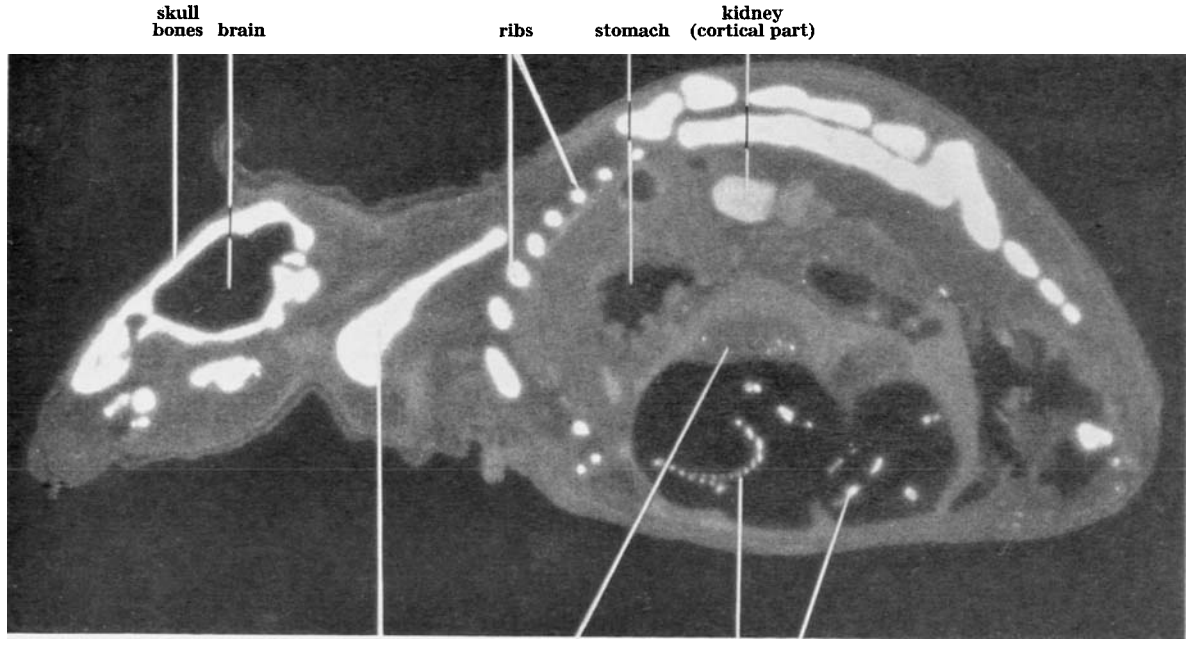


Fig. 2. Autoradiogram showing the distribution of F 18 in a pregnant mouse 30 minutes after intravenous injection. Most of the retained fluorine is taken up in the skeleton. Some radioactivity has now passed the placenta and appears in the fetal bones (full term fetuses with started mineralization). The fetal soft tissues appear totally devoid of F 18 (1.5 ×).

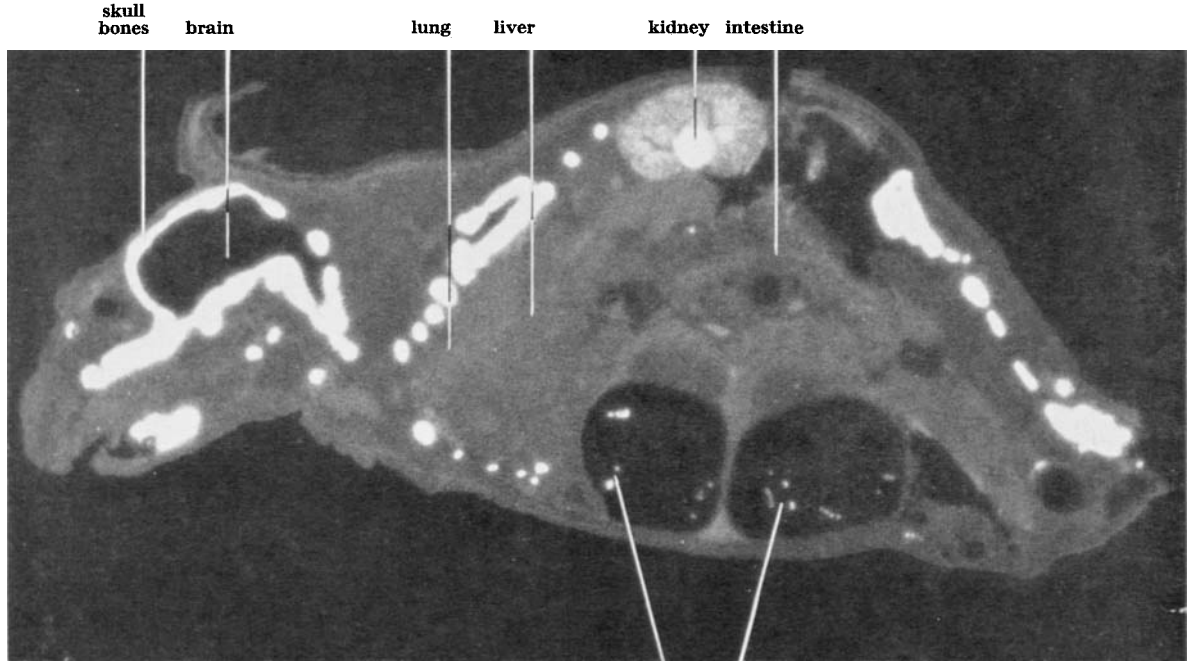


Fig. 3. Autoradiogram showing the distribution in a pregnant mouse 30 minutes after intravenous injection. There is no notable accumulation in any soft tissue except the kidney with the highest conc. in the pelvis. There is no sign of excretion via the bile or the intestinal wall (1.5 ×).

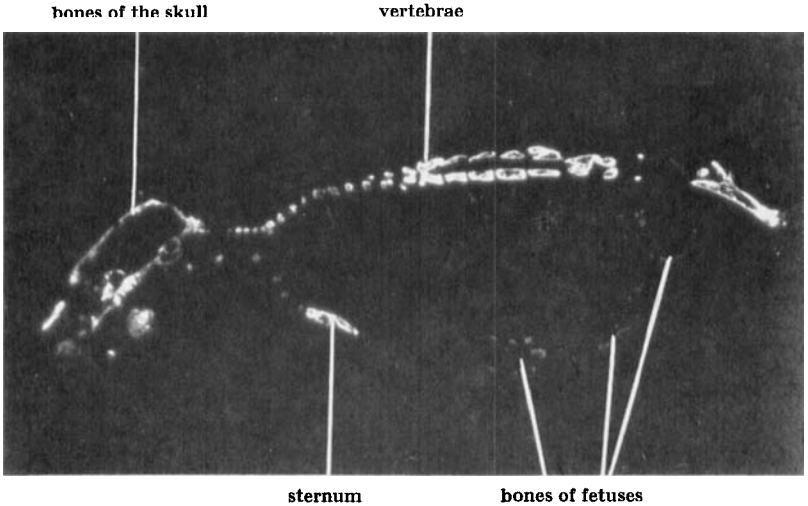


Fig. 4. Autoradiogram showing the distribution of F 18 in a pregnant mouse 60 minutes after intravenous injection. The F 18-activity has decreased, due partly to renal fluorine excretion and partly to radioactive decay. F 18 is now visible almost exclusively in bone (1:1).

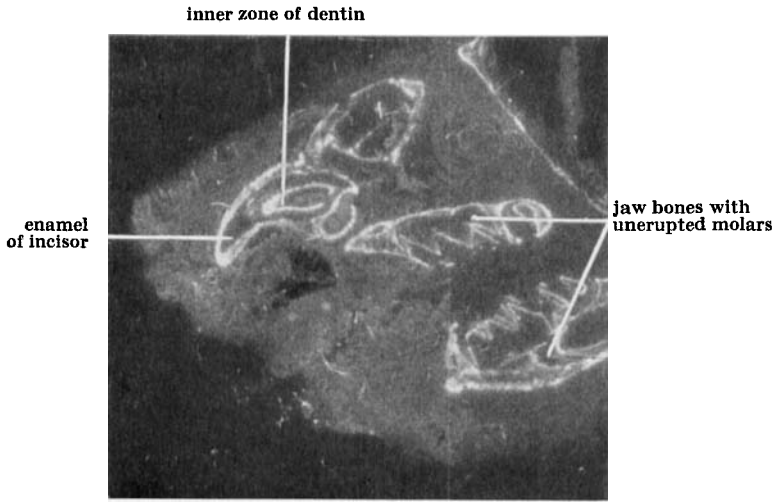


Fig. 5. Autoradiogram showing the incorporation of fluorine in the unerupted teeth of a 14 days old suckling rat one hour after intravenous injection. In the incisor there is a dense inner layer corresponding to the mineralization zone of the dentin. There is a somewhat lower accumulation in the outer layer of the enamel. The molars show the same distribution (4 ×).

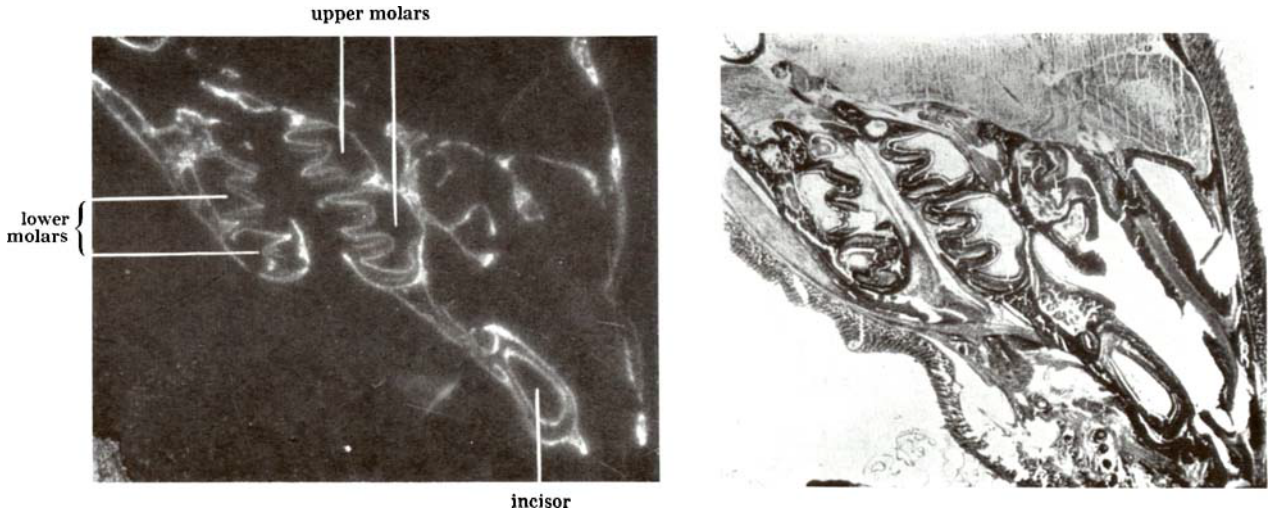


Fig. 6. Autoradiogram (left) and corresponding stained section (right; damaged on transfer after autoradiography) through the jaws and teeth of a 10 days old suckling rat one hour after intraperitoneal injection of F 18. – The unerupted molar teeth show uptake in calcification zones in both enamel and dentin, especially the dentin. The break of the enamel cover on the cusps is clearly visible (5 ×).

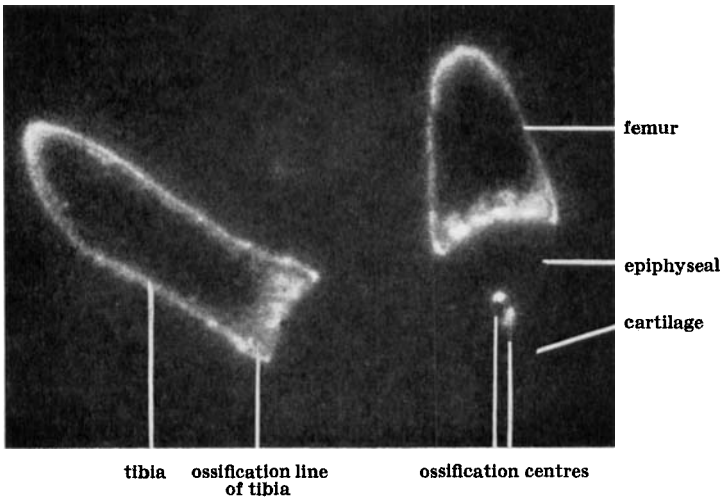
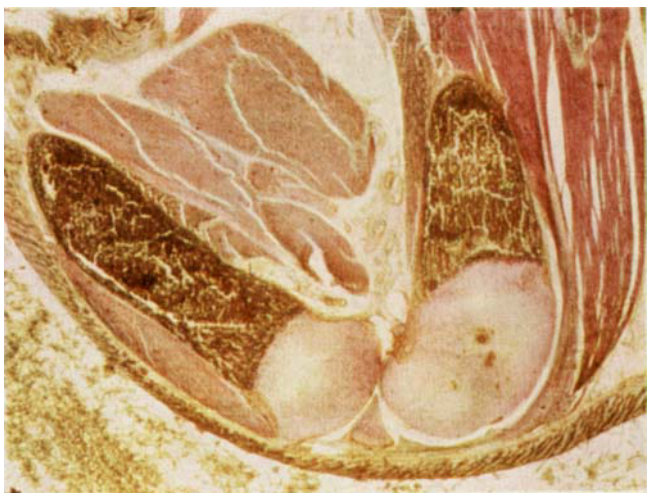


Fig. 7. Autoradiogram (above) and corresponding section (below) through a knee joint from a 10 days old suckling rat, one hour after intraperitoneal injection. No F 18 appears in the cartilage with the exception of two ossification centers. Heavy uptake in metaphyseal ossification zones (8 ×).



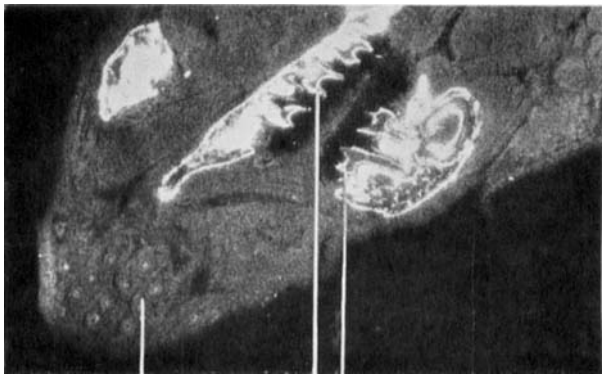


Fig. 8. Autoradiogram showing the distribution of F 18 in the jaws and nose of an adult rat 15 minutes after injection. The uptake which is seen in the molar teeth is in the inner layer of the dentin; no visible uptake in the enamel. – There is a very slight uptake in the salivary gland. Some concentration appears in the hair follicles of the whiskers (3 ×).

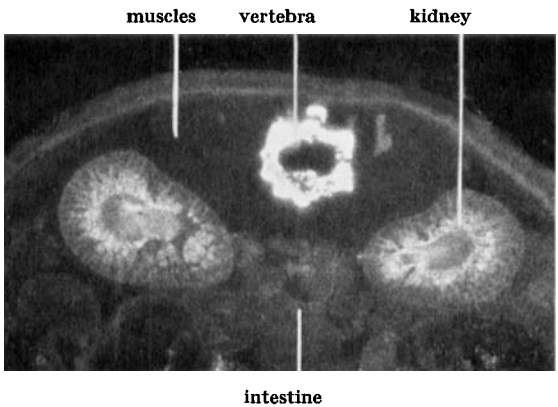


Fig. 9. Autoradiogram of the dorsal part of a transversal section through the kidneys of an adult rat sacrificed 10 minutes after the intravenous injection of F 18. The greatest uptake of F 18 is in the vertebra. In the kidneys there is a concentration especially in the collecting tubules and the hilus. The F 18 content in the muscles and intestine is low. There is a slight concentration to be seen in the subcutaneous tissue (2.5 ×).