surveys are presented in Fig. 1. The surveys have indicated large thickness of sediments. Useful information on the sub-surface disposition of sand, clays, clayey sands, sandy shales, sandstones and crystallines has been clearly brought out. Three pockets of thick clay beds have been outltned around Budampadu, Panchallavaram and Penamarru by electrical surveys. E.T.O. well near Panchallavaram (16° 15′ : 80° 59′ 30″) has passed through large thickness of clays and yielded poor quality of water.

The seismic surveys have delineated sandstones (outcropping at Chebrole) with intercalations of clays over the entire area to depths varying from 20 to 100 ms. The thickness of sandstones varies from 100 to 340 m. It is further observed that sandstone peters out further south of Varagani. A crystalline basement ridge has been outlined in the NE–SW direction over a distance of 30 km between Ponnuru and Chivaluru. It is not unlikely that this ridge in the middle of the basin occurring at depths varying from 170 to 385 m controls groundwater flow in the sandstones. The E.T.O. well near Kondamudi (16° 58′ : 80° 36′) reaching depth of 305 m has intersected mostly clay bands with a few sandy layers, and has not touched the crystalline. This location of the well falls within the boundary of the inferred ridge. If the well had gone to a depth of 350 m or so, possibly the crystallines would have been struck. This well had to be abandoned due to the poor quality of water.

Recent drilling carried out by the Agro-Industries Corporation, Andhra Pradesh in the Varagani, has yielded encouraging results and confirmed the presence of sandstone layer at stipulated depths.

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UPTAKE OF RADIOACTIVITY BY BODY FLUIDS AND TISSUES IN RHESUS MONKEYS AFTER INTRAVENOUS INJECTION OR INTRANASAL SPRAY OF TRITIUM-LABELLED OESTRADIOL AND PROGESTERONE

T. C. ANAND KUMAR, G. F. X. DAVID, B. UMBERKOMAN AND K. D. SAINI

Neuroendocrine Research Laboratory, Department of Anatomy, WHO-Research and Training Centre in Human Reproduction, All-India Institute of Medical Sciences, New Delhi 110016, India

THE recurrence of menstrual cycles and ovulation in non-human primates is a direct result of the neurally mediated interaction between the endocrine secretions of the adenohypophysis and the gonads[1,2]. Studies carried out recently have led to the concept that, in addition to the well-documented evidence implicating the involvement of neurons and blood, specialised ependymal derivatives and the cerebrospinal fluid (csf) constitute important cellular and humoral pathways over which the neuro-endocrine regulation of the menstrual cycle is effected[1,3,4]. The finding of sex steroids being transferred into the csf when administered intramuscularly[5] or intravenously[6] and the finding of oestrogen being able to influence gonadotropin secretion when injected into the cerebral ventricles[7] have lent additional support to this concept.

The present studies were carried out to determine whether tritium-labelled oestradiol and progesterone are transferred into the body fluids and taken up by various tissues when they are administered by intranasal spraying. A comparison of the relative uptake of the radioactivity by different tissues is made between monkeys given these steroids by intravenous injection and intranasal spray.

MATERIALS AND METHODS

Eight healthy, intact, adult female monkeys (4·5 to 6·5 kg body weight) in unknown stages of menstrual cycles were used. Four groups of two animals each were either sprayed intranasally (through the right nostril using an atomiser connected to a respiratory pump) or injected intravenously (through the right saphenous vein) with 0·1 mCi of either ^{3}H-oestradiol-17β (0·32 μg; Specific Activity: 85 Ci/mM) or ^{3}H-progesterone (0·37 μg; Specific Activity: 84 Ci/mM) dissolved in 0·2 ml of propanediol after anaesthetising the monkeys with sodium pentabarbitone (30 mg/kg body weight). The duration of injection or the

spray was 1 min. The labelled hormones, procured from the Radiochemical Centre, Amersham, U.K., were tested for purity before use. Samples of blood (1·0 ml per sample) and csf (0·25 ml per sample) were drawn before and at various intervals (Figs. 1, 2) after administering the hormones.

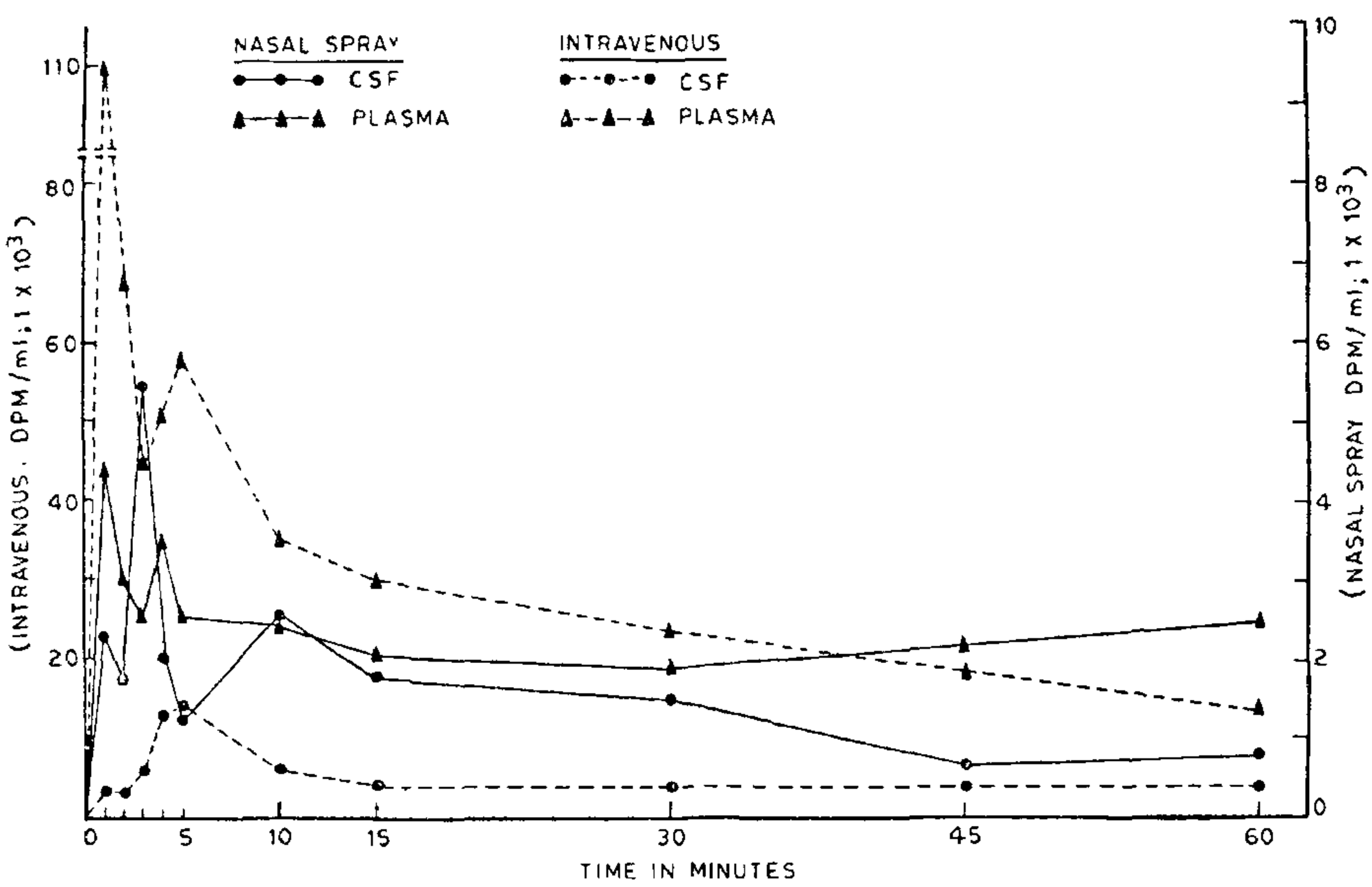

FIG. 1. Temporal distribution of radioactivity in csf and plasma of rhesus monkeys administered ^{3}H-oestradiol either intravenously or by intranasal spraying. The radioactivity shown is the average of that obtained for 2 animals.

The animals were killed 1 hr after administering the hormones and tissues listed in Figs. 3 and 4 were taken. The body fluids were processed for estimating the radioactivity in accordance with previously described technique[5]. The tissues were weighed and dissolved in 1·0 to 2·0 ml of 'Soluene-100' (Packard). Radioactivity was estimated in a Packard Tri-Carb Liquid Scintillation Spectrometer (Model 3320) after adding 10·0 ml of scintillation fluid (PPO and POPOP dissolved in toluene). Radioactivity is expressed as DPM/ml body fluid or DPM/mg tissue by using external standardisation method.

RESULTS

The temporal distribution of the levels of radioactivity in the body fluids after administering the hormones by the two routes is shown in Figs. 1 and 2. The interesting feature of the distribution pattern is that both the steroids are able to enter the csf by 1 min after the administration either by intranasal spray or intravenous injection. While considerable amounts of radioactivity could be detected in the plasma of the ^{3}H-oestradiol-sprayed monkeys, the amount of radioactivity in the plasma of the ^{3}H-progesterone-sprayed monkeys is negligible. The ratios between the plasma : csf and csf : plasma (Table 1) clearly show that the amount of radioactivity is much higher in the csf in the sprayed monkeys as compared with that found in the injected ones. Indeed, the plasma : csf ratio found in the ^{3}H-progesterone injected monkeys is reversed in those sprayed with ^{3}H-progesterone.

Tissues of all the monkeys showed varying amounts of radioactivity (Figs. 3, 4). The salient difference, however, between the two routes of administration is that in the sprayed monkeys the peripheral target tissues such as the liver, ovary, uterus, vagina and the fallopian tube show much lower amounts of radioactivity in comparison with those injected with the labelled hormones. While the olfactory bulb, olfactory mucosa and respiratory

TABLE I

Ratio of radioactivity (DPM/ml) in body fluids of rhesus monkeys I hr after administering 0·1 mCi of ^{3}H-oestradiol-17 B or ^{3}H-progesterone

Hormone	^{3}H-oestradiol-17 B				^{3}H-progesterone			
Route Administered	Intravenous		Nasal Spray		Intravenous		Nasal Spray	
Monkey Nos.	455	468	462	470	453	466	459	469
Plasma : csf ..	6·12	8·17	1·22	1·38	15·64	9·25	0·27	0·15
csf : plasma ..	0·16	0·12	0·81	0·71	0·06	0·11	3·70	6·53

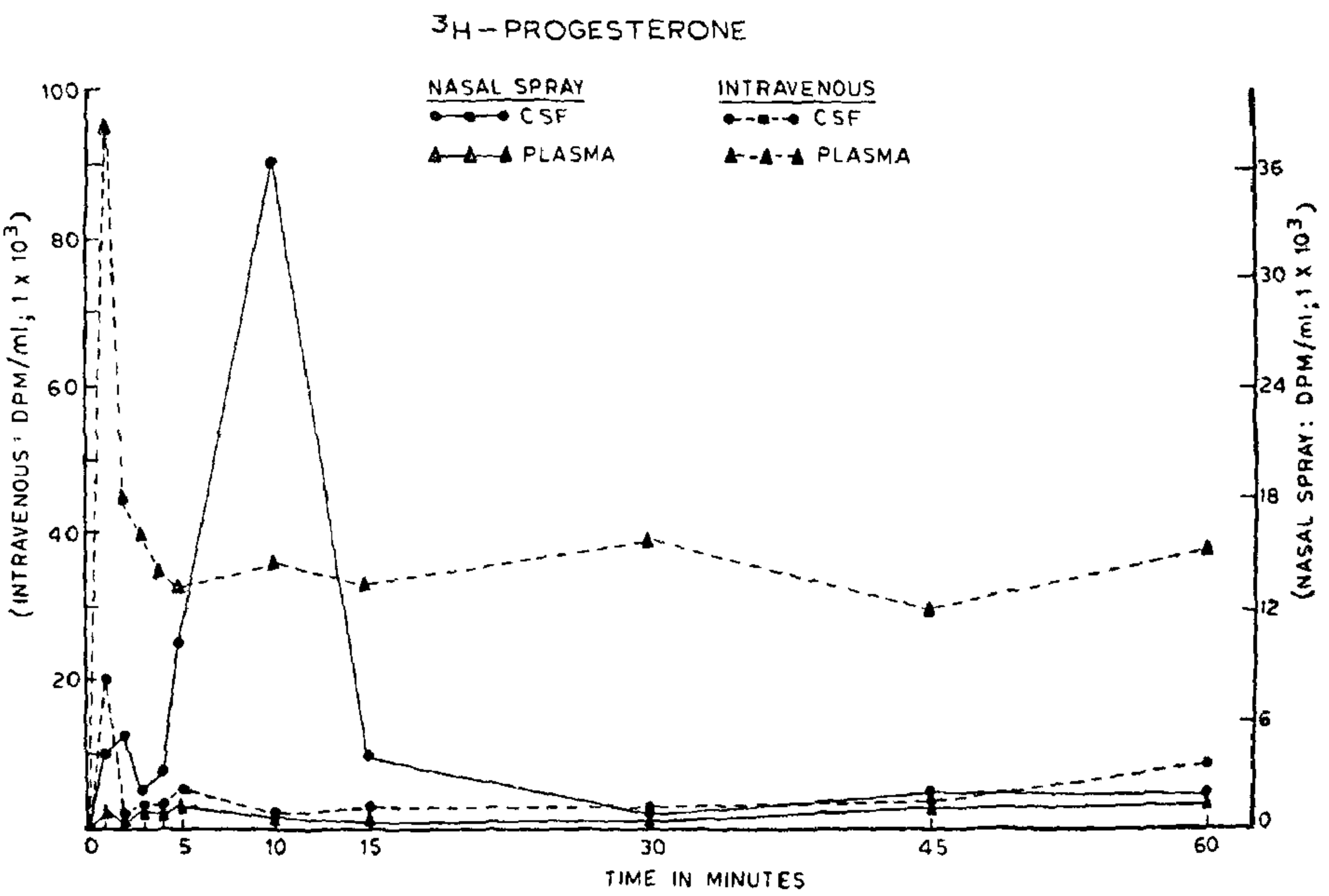

FIG. 2. Temporal distribution of radioactivity in csf and plasma of rhesus monkeys administered ^{3}H-progesterone either intravenously or by intranasal spraying. The radioactivity shown is the average of that obtained for 2 animals.

mucosa showed much higher activity in intranasally sprayed monkeys, the amount of radioactivity in the lungs of these animals was surprisingly low as compared with that found in the lungs of the injected animals.

DISCUSSION

The results of the present studies must be viewed against the low dose of steroids administered to monkeys whose phases of the menstrual cycle were not determined. Since the amounts of exogenous hormones taken up by various tissues depend upon the circulating levels of endogenous hormones and since these levels vary in relation to different phases of the menstrual cycle[4], the amount of radioactivity concentrated by various tissues which reflects hormone-uptake, would vary between different animals. The use of ovariectomised animals and the administration of a standard dose based on the body weight of the animal could

perhaps have considerably reduced this variability between animals. The use of intact animals and low dose of hormones has its own merits in that it has provided the kind of answer to the question set out in designing the present investigation, *i.e.*, can exogenous gonadal steroids reach the csf and also other known target organs if they are sprayed intranasally. The use of intact animals would make the results relevant to naturally occurring conditions rather than to their being relevant to 'hormone-starved' condition obtained in gonadectomised animals.

liver, ovary, uterus, vagina and the fallopian tube in the sprayed animals is much less in comparison with the injected animals.

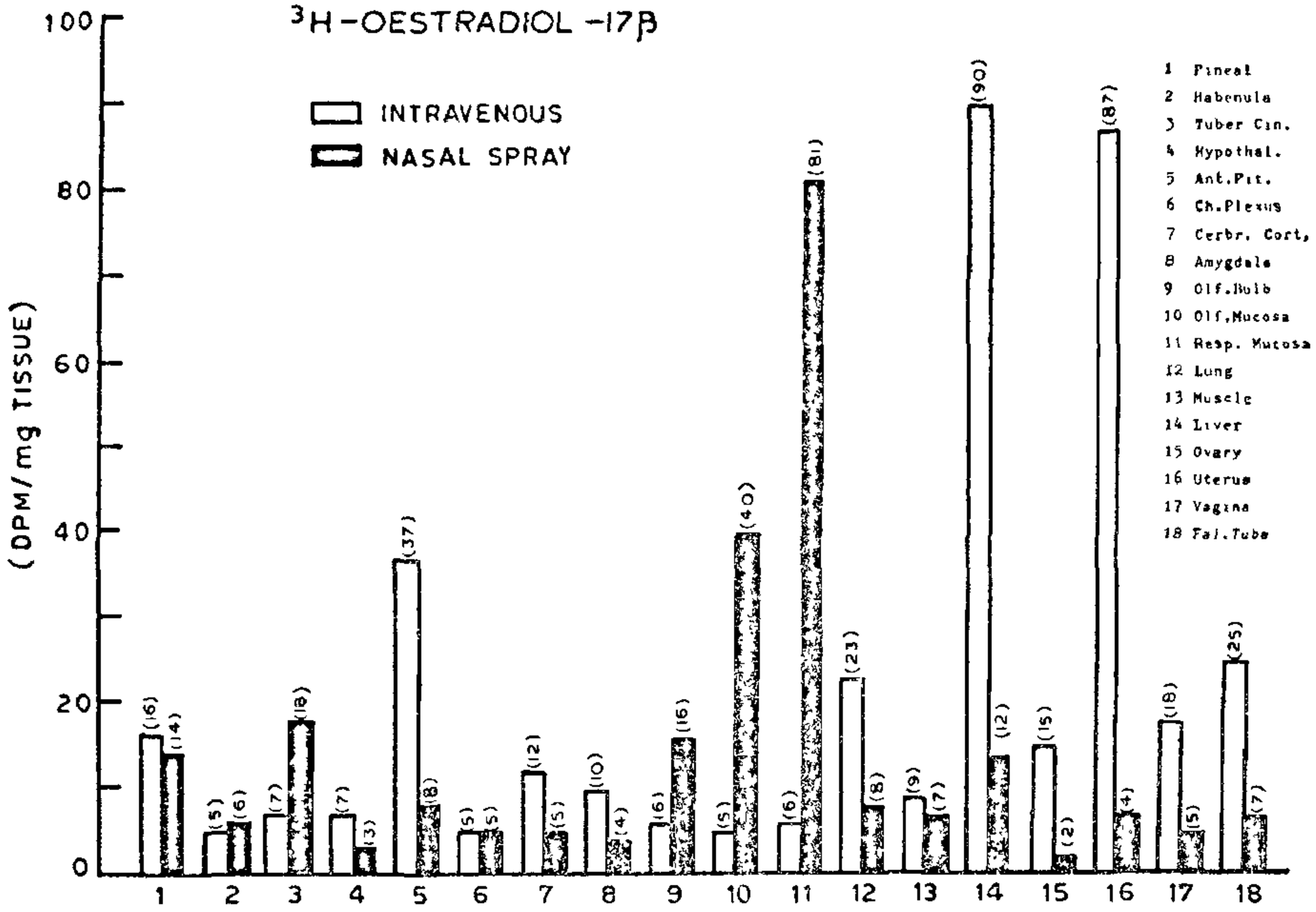

FIG. 3. Radioactivity in various tissues 1 hr after administering ^{3}H-oestradiol to rhesus monkeys either intravenously or by intranasal spraying. Thenumber in parentheses above each bar represents actual DPM/mg tissue. The DPM is the mean of data obtained for 2 monkeys.

The data obtained from the present investigation clearly indicate that gonadal steroids when sprayed intranasally can enter the csf (and plasma) as quickly as they do when injected intravenously. The amount of radioactivity concentrated by the various tissues examined in the brain is comparable between the two routes of administration except for the anterior pituitary in the ^{3}H-oestradiol injected monkeys where the amount of radioactivity was much higher in comparison with ^{3}H-oestradiol sprayed animals. The amount of radioactivity taken up by the peripheral target organs, *viz.*, the

These data support a general inference that the steroids sprayed intranasally preferentially reach tissues known to contain neural mechanisms regulating gonadotropin secretion and they point out a new direction for the future development of fertility regulation technique involving the use of intranasal spray containing naturally occurring steroidal hormones. In this context it would be pertinent to mention that low doses of oestradiol when administered in a manner mimicking the spontaneously occurring increase in endogenous oestrogen prior to the ovulatory LH surge[2] to monkeys as early as day 3 of the menstrual cycle can cause LH surge 12 hrs later[8]. Administration of progesterone to monkeys and women can prevent the spontaneously occurring LH surge and thus inhibit ovulation[9,10].

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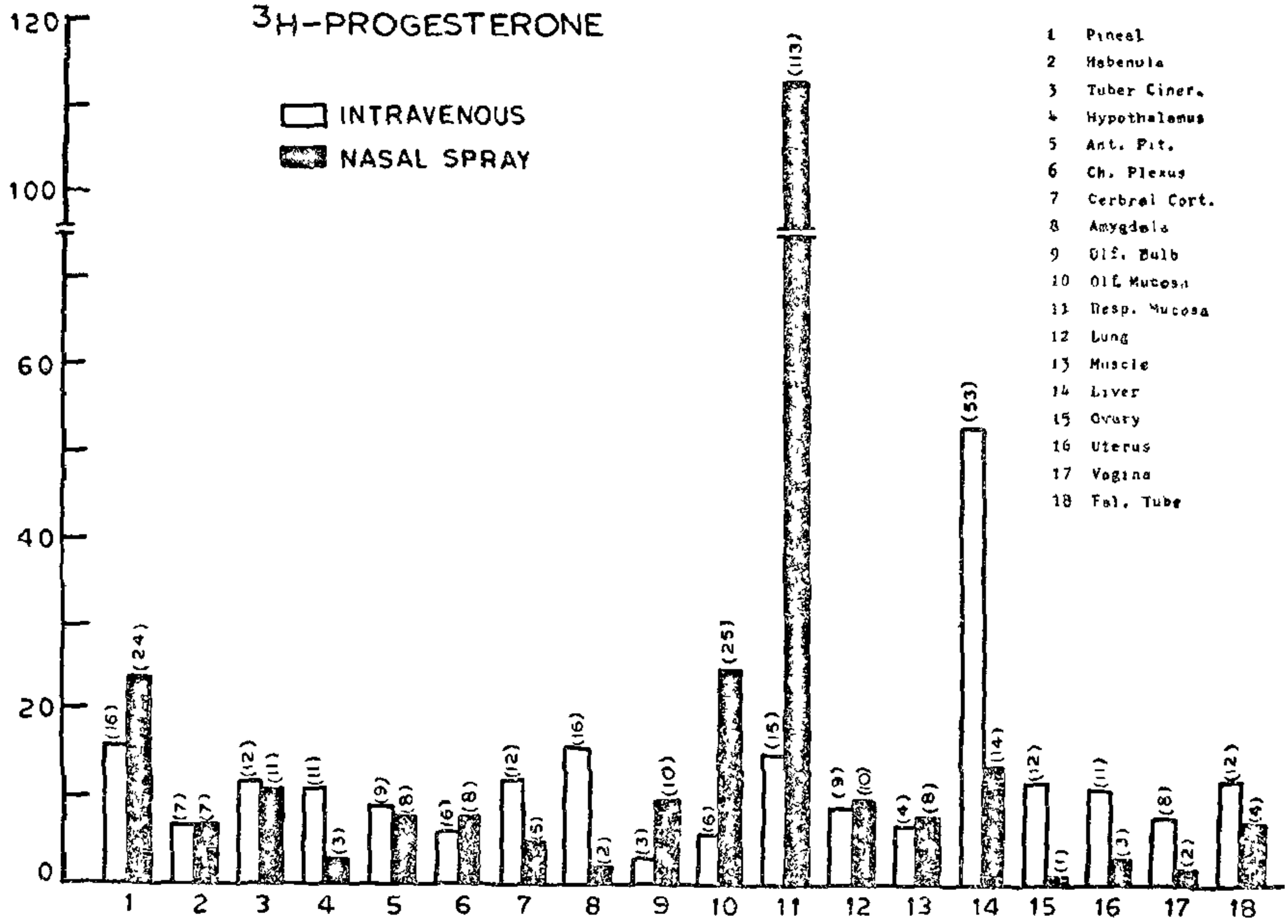

FIG. 4. Radioactivity in various tissues 1 hr after administering ^{3}H-progesterone to rhesus monkeys either intravenously or by intranasal spraying. Thenumber in parenthesis above each bar represents actual DPM/mg tissue. The DPM is the mean of data obtained for 2 monkeys.

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