ing epithelial cells. The bronchi showed areas of necrosis and ulceration with partial collapse of the finer bronchioles and widespread atelectasis. The characteristic cytoplasmic inclusion bodies were found in the epithelial cells of the bronchial tree in all 9 of the fatal cases. In 5 the inclusions were found in the cells within the alveolar spaces. With the hematoxylin and eosin stain the ground substance of the inclusions appeared homogeneous, staining bright red or acidophilic. The diameter of the bodies varied from 3 to 6 microns. A clear halo was noted about the body in many places, and small vacuoles were seen within the ground substance of several inclusions.

The serum of ferrets, which were inoculated with fresh frozen lung specimens, failed to show any antibodies capable of neutralizing influenza virus.†

Repeated examinations of the bronchial exudate showed type specific pneumococci in but one of the fatal cases (type XXVII) and in but 6 of the cases surviving (4 of type XXIII and 2 of type XXVII).

Summary. A new form of primary, acute pneumonitis of infants is described. The disease is characterized by its predilection for young infants, its epidemic nature or high degree of contagiousness, the constancy of its symptomatology from case to case and its pathology, including the occurrence of typical cytoplasmic inclusion bodies in the epithelial cells of the bronchial tree.

11907

Anesthetic Effect of Steroid Hormones.*

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In the course of our experiments on the physiology of steroid hormones, we were surprised to note how difficult it is to produce acute overdosage phenomena even if enormous doses are given. Thus even a single subcutaneous injection of 100 mg of testo-

† The author is indebted to Dr. Thomas Francis, Jr., for carrying out this test.

* The expenses of this investigation were defrayed through a grant in aid received from the Schering Corporation of Bloomfield, New Jersey. The author is also indebted to Dr. A. D. Odell of Charles E. Frosst and Company for the androsterone, to Dr. Stanley Cook of Ayerst, McKenna and Harrison, Ltd., for the pregnanediol, and to Drs. G. Stragnell and E. Schwenk of the Schering Corporation for all the other steroids used in this investigation.

sterone, progesterone or desoxycorticosterone acetate (D.C.A.) given in 0.4 ml of peanut oil to rats weighing 100 g caused no detectable ill effects. It was felt that this might be due to the slow rate of absorption of oily solutions from the subcutaneous tissue. As most of these compounds are practically insoluble in water and hence cannot be given intravenously, we recently administered a series of steroid hormones in oily solution by the intraperitoneal route in the hope that from this location, absorption may be especially rapid and that we may thus learn more about the pharmacological effects of acute overdosage with steroids.

For our first experiment, we divided 30 male and 30 female albino rats weighing 90-135 g (average: 107 g) into 5 groups of 6 males and 6 females each. The first of these groups was treated with D.C.A., the second with progesterone, the third with testosterone, the fourth with α-estradiol and the fifth with cholesterol. Each animal received a single intraperitoneal injection of 35 mg of the compound in 1.5 ml of peanut oil. Fifteen minutes after the injection, all the females in the D.C.A. and progesterone groups were deeply anesthetized but only one male of the former and 2 of the latter group showed a comparable degree of anesthesia while the remaining males were either quite normal or only very slightly anesthetized. The females of the testosterone group were also deeply anesthetized but more than one hour was required for this effect to take place. However, here again, the males—though not larger in size than the females—were not nearly as much affected as the latter. The animals receiving estradiol or cholesterol showed no signs of anesthesia and survived the injection indefinitely. On the other hand, all females in the progesterone and D.C.A. groups died within 6 hours after the injection as well as one of the males in each of these 2 groups. Among the testosterone-injected rats, only one female died. The surviving animals of all groups awakened within a few hours and showed no ill effects after the anesthesia. This experiment indicated that progesterone and D.C.A. may both lead to acute overdosage symptoms if administered by the intraperitoneal route and that their anesthetic effect as well as their toxic action is greater in females than in males. These observations were confirmed by many subsequent experiments on male and female rats and mice of different sizes. Although space does not permit the full description of all our observations, we should like to emphasize that the individual sensitivity of the animals shows wide variations but if these active steroids are administered in suitable doses they cause a quiet deep anesthesia which is not preceded by any

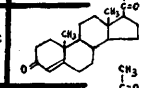
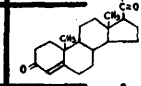
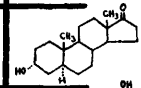
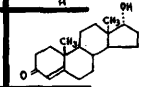
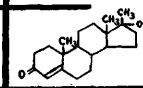
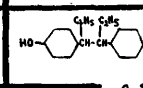
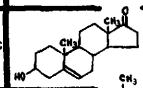
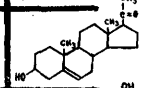
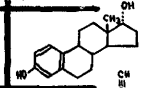
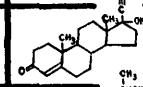
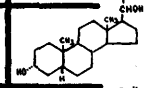
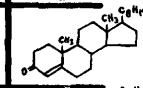
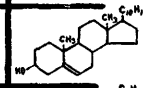
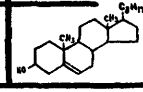
obvious sign of excitation and from which the animals recover without ill effects. This anesthesia is so deep that we often performed prolonged abdominal operations in rats anesthetized with D.C.A. or progesterone. At the height of the anesthesia, there is some peripheral vasodilatation which leads to hyperemia of the paws and ears and a slight decrease in body temperature. If lethal doses are administered, death is apparently due to anesthesia of the respiratory centers since outside of occasional small extravasations in the lungs, no obvious pathological changes could be detected and the heart continued to beat long after respiration stopped. The fact that it is really the increased rate of absorption which is responsible for this anesthetic action received support from the observation that general anesthesia may also be produced by the intravenous administration of D.C.A. in propylene glycol solution.

In order to obtain some information concerning the correlation between chemical structure and anesthetic effect, a series of compounds have been tested. In some cases part of the compound had to be given in a fine crystalline suspension rather than in solution. Most of them, however, could be kept dissolved in the concentration used by heating the solutions and then cooling them down to body temperature just before the injection. Each compound was tested on a group of 8 female albino rats weighing 79-130 g (average: 105 g). Five mg of each compound were injected in 0.25 ml of peanut oil every 30 minutes until 50% of the animals in a group were completely anesthetized. Table I compares the chemical structure of the compounds used with their anesthetic action. Some of these compounds could not be obtained in absolutely pure form and therefore we determined the melting points of all our samples to indicate the degree of their purity. No effort has been made as yet to determine the safety margin between the full anesthetic and the lethal dose but the fact that many of our animals died should not lead to the conclusion that this safety margin is small since for the sake of uniformity, we reinjected all animals of the groups in which more than 50% were still awake, including those which were already deeply anesthetized. It should also be emphasized that testosterone, though distinctly anesthetic, appears to have a very delayed action so that the full effect of the preceding dose was not yet in evidence after 30 minutes when the next dose was to be injected. Unless a lower dose caused deep anesthesia in 50% of the animals, injections were continued at the rate of 5 mg every half hour until a total dose of 50 mg was reached.

This table in which the compounds are arranged as far as possible

TABLE I.

ANESTHETIC EFFECT OF STEROIDS

COMPOUND	FORMULA	M.P. OF SAMPLE USED	DOSE REQUIRED TO PRODUCE DEEP ANESTHESIA IN 50% OF ANIMALS	DEATHS OUT OF 8 RATS	REMARKS
DESOXYCORTICOSTERONE ACETATE		149-150°	5 MG.		ANESTHESIA NOT PRECEDED BY EXCITATION OR CONVULSIONS.
PROGESTERONE		128°	15 MG.	1	ANESTHESIA NOT PRECEDED BY EXCITATION OR CONVULSION.
ANDROSTERONE		177-178°	50 MG.	2	SLOWLY DEVELOPPING BUT VERY PROLONGED ANESTHESIA RARELY PRECEDED BY CONVULSIONS.
TESTOSTERONE		153°	50 MG.	4	SLOWLY DEVELOPPING BUT VERY PROLONGED ANESTHESIA IN SOME CASES PRECEDED BY CONVULSIONS.
METHYLTESTOSTERONE		160°	50 MG.		SOMEWHAT LESS POTENT THAN TESTOSTERONE BUT HAS ACTIVITY OF SIMILAR TYPE.
DIETHYLSTILBESTROL		166°	——	1	50 MG. CAUSE SLIGHT ANESTHESIA IN SOME ANIMALS. LARGER DOSES ELICIT DEEP ANESTHESIA WITHOUT CONVULSIONS.
Δ^5-DEHYDRO-ISO-ANDROSTERONE		137°	——	3	50 MG. CAUSE ONLY SLIGHT ANESTHESIA PRECEDED BY INTENSE CONVULSIONS.
Δ^5-PREGNENE-3(β)-OL-20-ONE		183°	——	—	IN 50 MG. DOSE ACTIVITY VERY SLIGHT.
α-ESTRADIOL		176°	——	—	IN 50 MG. DOSE ACTIVITY QUESTIONABLE.
ETHINYLTESTOSTERONE		265-268°	——	—	INACTIVE UP TO 50 MG. BUT THIS MAY BE DUE TO ITS VERY LOW SOLUBILITY IN OIL.
PREGNANE-3(α),20(α)-DIOL		237-238°	——	—	INACTIVE UP TO 50 MG. BUT THIS MAY BE DUE TO ITS VERY LOW SOLUBILITY IN OIL.
Δ^4-CHOLESTENONE		80.5°	——	—	INACTIVE UP TO 50 MG.
STIGMASTEROL		168-169°	——	—	INACTIVE UP TO 50 MG.
CHOLESTEROL		148°	——	—	INACTIVE UP TO 50 MG.

in decreasing order of activity shows no evident correlation between chemical structure and activity. However, only hormonally active

steroids proved to have an anesthetic effect even though the activity was not limited to compounds with any one specific type of hormonal action.

Another experiment was planned to determine the site at which detoxification of acutely administered steroids takes place. Three groups of rats were used. Each of these consisted of 12 females weighing 138-220 g (average: 190 g). The first group was partially hepatectomized according to the method of Waelsch and Selye[1] while the second group was bilaterally nephrectomized. On the day after the operation, all these rats as well as the third group of intact controls received 2 intraperitoneal injections of 5 mg of D.C.A. in 0.25 ml of peanut oil, the second injection being given 30 minutes after the first. Just before the second injection, 4 of the hepatectomized rats were in deep anesthesia, 2 were still unaffected while the rest were but slightly anesthetized. At this time, none of the nephrectomized or intact rats showed any signs of anesthesia. Two hours after the second injection 2 of the hepatectomized animals died, the rest were in deep anesthesia. Among the nephrectomized animals, 4 were in deep anesthesia but the rest were entirely unaffected. Subsequently, the hepatectomized animals remained in anesthesia until they died while the nephrectomized animals recovered completely from the anesthesia before they eventually died from uremia. The intact rats never showed any signs of anesthesia from this dose of D.C.A. which is below the anesthetic level for normal animals of this size. It is evident that hepatectomy increases sensitivity to the anesthetic effect of D.C.A. This probably indicates that the liver plays an important rôle in the detoxification of this compound since Waelsch and Selye[1] showed that anesthetics—such as tribromethanol (avertin)—which are detoxified in the liver keep partially hepatectomized animals asleep for an unusually long period while the anesthesia caused by magnesium salts—which are not detoxified by the liver—remains uninfluenced by this intervention. Whether the slight increase in D.C.A. sensitivity due to nephrectomy should be interpreted as showing that this organ also plays a rôle in the detoxification of steroids is open to question since nephrectomy damages the animals and may thus sensitize them in a non-specific manner.

The fact that absorption of these water-insoluble, oil-soluble compounds may greatly be accelerated by administering them to surface membranes is perhaps of more than purely academic interest especially since a similar improvement in absorption rate may per-

[1] Waelsch, H., und Selye, H., *Naunyn-Schmidebergs Arch.*, 1931, **161**, 115.

haps be achieved in man by applying such compounds to mucous membranes.

Summary and Conclusions. Various steroid hormones, especially D.C.A. and progesterone produce deep anesthesia in rats and mice if injected into the peritoneum whence they can be rapidly absorbed. After recovery from the anesthesia such animals show no ill effects. Partially hepatectomized rats are much more sensitive to the anesthetic effect of the steroids than intact controls. This probably indicates that the liver plays an important rôle in the detoxification of these compounds. Males are less sensitive than females of the same size.

11908

Availability of Sodium Pyruvate for Human Brain Oxidations.*

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We have previously described a method for the study of the availability of various substrates for human brain metabolism *in vivo*.[1] In the absence of glucose during therapeutic insulin shock it has been shown that the metabolism of the brain is diminished. This is indicated by an extremely low oxygen uptake of the brain[2, 3] in association with characteristic changes of the cortical brain potentials[4] and the onset of clinical coma. Intravenous administration of glucose rouses the patient and restores the normal arterio-venous oxygen difference.[5] In previous publications we have reported that as little as 4 g of glucose administered intravenously invariably roused the patients from coma and approximately doubled the oxygen uptake of the brain.[6] Ethyl alcohol had no effect on the clinical

* Aided by a grant from the Havelock Ellis Fund for Psychiatric Research.

1 Wortis, J., and Goldfarb, W., *Science*, 1940, **91**, 270.

2 Damashek, W., Myerson, A., and Stephenson, C., *Arch. Neur. and Psychiat.*, 1935, **33**, 1.

3 Himwich, H. E., Bowman, K. M., Wortis, J., and Fazekas, J. F., *J. Nerv. and Ment. Dis.*, 1939, **89**, 273.

4 Hoagland, H., Cameron, D. E., and Rubin, M. A., *Am. J. Psychiat.*, 1937, **94**, 183.

5 Himwich, H. E., Frostig, J. P., Fazekas, J. F., and Hadidian, Z., *Am. J. Psychiat.*, 1939, **96**, 371.