SPECIAL ARTICLES

ANDROGENS AND TUMOR GROWTH

THE observation of Murray[1] that male mice bearing ovarian grafts developed spontaneous mammary tumors, although normal males do not, and the observation of Lacassagne[2] that the same effect could be produced in males by means of injected estrogens suggested a possible antagonism between male and female sex hormones as regards their carcinogenic properties.[3] Accordingly, in the fall of 1935 experiments were begun on the effects of urinary androgens on the growth and metastasis of the Brown-Pearce epithelioma of the rabbit. Preliminary observations having proved encouraging the experiments have continued to the present, employing over 300 rabbits. In one paper[4] now in press the results with several chemically pure androgens, one estrogen and androgens extracted from human urine are presented in detail. In another[5] some further evidence is presented of the opposite effects on growth of the most active androgen and the most active estrogen available.

Urinary-extract androgens and chemically pure testosterone propionate, both in small doses, quite definitely inhibited the growth of the primary Brown-Pearce tumor implanted in the testicle. For a study of secondary growths (metastasis) four degrees of malignancy were recognized: (1) no secondary growths; (2) few, *i.e.*, less than four scattered small nodules; (3) several, *i.e.*, 3 to 6 sites with multiple nodules; and (4) extensive, *i.e.*, diffuse involvement of 6 or more sites. A summary of the longer-period experiments, running from 89 to 112 days, is given in Table 1. The androgens were injected daily in olive or sesame oil. Controls with and without oil alone showed no material difference in the spread of secondary growths. The average of these two control groups is taken as the unmolested incidence of such growths when the tumor is of average malignancy. Estradiol monobenzoate did not change the percentage of animals having any degree of metastasis or none. The urinary androgens, however, did very positively shift the incidence from the high side of the scale toward the low side. Still greater was the effect of testosterone propionate (10 to 50 I.U. daily) in the same direction. Instead of twenty-nine per cent. (average of the two control groups) having extensive metastases there were none in the group receiving this most potent androgen.

TABLE 1

LONG PERIOD EXPERIMENTS

	No. of rabbits	Degree of Metastases: Extensive No.	Extensive Per cent.	Several No.	Several Per cent.	Few No.	Few Per cent.	None No.	None Per cent.
Control no oil.	25	8	32	7	28	2	8	8	32
Control oil only	35	9	25.8	8	22.8	7	20	11	31.4
Estradiol Monobenzoate	18	5	27.8	5	27.8	3	16.6	5	27.8
Urinary androgens 4.6 to 216 I.U.	55	4	7.3 (−21)	14	25.4 (−1)	13	23.6 (+10)	24	43.6 (+12)
Testosterone 37 & 39 I.U. .	22	9	40.9 (+12)	7	31.8 (+5)	2	9.1 (−5)	4	18.2 (−14)
Testosterone Propionate 10 & 50 I.U...	20	0	0.0	2	10.0	7	35.0	11	55
Total	175		(2−29)		(−16)		(+21)		(+23)

The figures in parentheses represent the changes in percentage from an average of the two control groups. The shift to the low side of the scale of metastases caused by urinary androgens and by testosterone propionate is impressive. The opposite effect of testosterone is not so great.

Conversely, instead of 32 per cent. having no metastases as in the controls there were 55 per cent. having none. Curiously enough, chemically pure testosterone had a moderate effect in the opposite direction.

In experiments which ran to only 60–62 days pure androsterone and dehydroandrosterone, in doses comparable to those used for most of the urinary androgen injections, had no material effect on either the rate of primary growth or the incidence of secondary growths. It is therefore probable that the urinary extracts contain one or more steroids, extractable by the same method as the known androgens, which are responsible for the inhibiting effects noted. Fractionation of such extracts has already been accomplished, and the chemically different groups will be tried soon for anti-carcinogenic properties.

In the short-period experiments also testosterone propionate in doses of 100 and 250 I.U. daily seemed to exacerbate the metastatic process. Dosage therefore is of great importance.

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EASE OF BODY HEAT LOSS AND RESISTANCE TO INFECTION

WE wish here briefly to report a rather striking dominance exercised over resistance to infection by the ease with which body heat can be lost. White mice

adapted to moist heat (90° F. and 65 per cent. relative humidity) exhibit a resistance to infection only one quarter as great as do litter mates adapted to a cool environment (65° F.), while mice in a control room at 70–75° F. fall midway between those in the hot and cold environment. This occurs when all other factors of life are held as constant as possible for all groups—same diet (Purina dog chow), similar lighting and ventilation, and the use of divided litters for the different groups to minimize the hereditary factor.

We have previously described the rooms and equipment used in this study[1] as well as the dominance exercised by ease of body heat loss over such basic physiologic functions as rate of growth and development, fertility and longevity. This dominance in man and animals seems to work through the internal combustion level allowed the individual. Energy for most physiologic functions can come only from this combustion, but body efficiency is not high, so that a large part of the combustion energy must be dissipated as waste heat. It is the ease or difficulty with which this waste heat can be dissipated that causes internal combustion rate to be dominated by external temperature levels. Men, as well as animals, show direct evidence of this dominance.[2]

Locke[3] has described a "fitness index" which he bases largely on the rate of oxygen consumption, resistance to infection being proportional to the rate of oxygen uptake. And in certain of man's infectious diseases, ability to survive seems definitely related to prevailing mean temperature level.[4] It therefore seemed important that a close analysis be made of all phases of this dependence on ease of body heat loss, the preliminary findings on resistance to infection being set forth in this brief note.

Using a 10-hour broth culture of hemolytic streptococcus kept at standardized virulence by the necessary mouse passages (so that 0.5 cc intraperitoneally kills healthy control mice within 16 hours), the estimates of M.L.D. given in Table 1 were obtained.

Although the M.L.D. was the same for control and cold-room animals, those from the control room died more quickly than did those from the cold. During the period of these tests, the control room temperature was about 70° F., only 5° above that of the cold room. Hot room mice succumbed with only one fourth the culture dosage needed to kill those of the other two groups.

When mice of all three groups were injected with the same amount of broth culture, 0.5 cc of a 1:20 dilution, then within 26 hours 100 per cent. of the hot room mice were dead, 60 per cent. of those from the control room, but only 30 per cent. of those from the cold. In another series injected with 0.5 cc of a 1:55 dilution of broth culture, 60 per cent. from the hot room were dead within 30 hours, but only 12 per cent. from the cold.

TABLE 1

	Survival time in hours
Cold room mice (kept at 65° F) 0.5 cc of culture diluted 1–10	12, 23, 23, 23, 30, 48, 48, 48 (2 did not die)
Control room mice (kept at 70° F) 0.5 cc of culture diluted 1–10	7½, 11, 12, 12, 12, 23, 23, 23, 23, 23, 132 (1 did not die)
Hot room mice (kept at 90° F) 0.5 cc of culture diluted 1–40	24,24, 30, 36, 50, 108 (1 did not die)

There can be left little doubt, therefore, that difficulty in body heat loss and a lowered tissue combustion rate result in a sharply reduced ability to fight infectious invasion. This depressive effect on resistance to infection (also on growth, developmental rate and fertility) is evident within two weeks after the animals have been placed in the warm environment, and is almost complete by the end of three weeks.

The study is being broadened to include other pathogenic organisms and the appearance of various immune bodies in the blood. Undernutrition from dietary inadequacy, either qualitative or quantitative, has been known to make animals less resistant to infection.[5] It is likely that difficulty in body heat loss works in a similar fashion by making impossible the adequate utilization of even the most perfect diet when offered *ad lib.*

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THE MUSCLE HEMOGLOBIN OF SEALS AS AN OXYGEN STORE IN DIVING

IT is well known that the harbor seal, *Phoca vitulina,* can remain submerged for long periods without breathing. Dives of six minutes are common, while a maximum of 15 minutes has been recorded by Millais.[1] The seal's ability to hold its breath when submerged contrasts so strongly with the slight capabilities of terrestrial mammals that one is led to suspect an extra store of oxygen in the seal's case. The

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[1] J. G. Millais, "The Mammals of Great Britain and Ireland," 3 vols. London, 1906.