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Effort has involved the plasma concentrations of 14 hormones in 10 rigorously selected younger men who have recovered well from a myocardial infarction, and in 34 suitable controls. Concentrations of 11 hormones were normal. Concentrations of 3 were abnormal: estrone was elevated from the normal average of 47 pg/ml to 80 pg/ml, dehydroisoandrosterone was elevated from normal 338 ng/dl to 474 ng/dl, triiodothyronine was decreased from normal 117 ng/dl to 97 ng/dl. All three of these adbnormalities are in the direction of femaleness, i.e. women normally have higher levels of estrone and dehydroisoandrosterone and lower levels of Ttii-odothyronine than men. Two of the abnormalities, those of estrone and dehydroisoandrosterone are also found in obese men. A "discriminant" composed of all 3 of the individually abnormal hormones yields nearly total separation of the post-infarct group from normal controls; there is only 1 overlap. 24 hour urine analyses were accomplished on 6 men with abnormal and 21 men with normal coronary arteriograms. Total androgen metobolite excretion was lower in the abnormals than in the normals, and the excretion of androsterone glucuronide was markedly lower.

Keywords: Hormones; Cardiac patients; (KT)

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Final Report: Contract F 49620-78-C-0076
1 May 1978 to 30 April 1979

24-HOUR MEAN PLASMA HORMONE LEVELS IN MEN WITH CORONARY HEART DISEASE

Principal Investigator: Barnett Zumoff, M.D.

1. The series of normal control men studied has been extended to a present total of 34 men between the ages of 21 and 85. This broad range is essential to determine the shape of the age vs. concentration curve, so that a decision can be made about whether the patient vs control comparison must use strictly age-matched controls (if the normal population's values vary with age) or can be made with the total normal population (if the latter's values do not vary with age). The following are the findings:

(a) Cortisol, dehydroisoandrosterone (DHA), dehydroisoandrosterone sulfate (DHAS), androsterone (A), androsterone sulfate, estrone, estradiol, triiodothyronine, thyroxine, luteinizing hormone, follicle-stimulating hormone, and prolactin do not vary with age in normal men.

(b) Testosterone and dihydrotestosterone fall slightly from the 3rd decade of life to the 4th, but are essentially constant between age 30 and age 85.

Accordingly, the post-infarction patients, whose ages range from 44 to 53, have been compared with controls aged 30-85 with respect to testosterone and dihydrotestosterone and with the total normal population with respect to the other 11 hormones.

2. The number of post-infarction patients has been extended to 10, all from the Montefiore Center population. Canvassing of the 26 post-infarction patients still being followed by the Travis group yielded no suitable study patients: 6 letters were undeliverable because of non-current addresses, 12 were not answered, 3 elicited the information that the addressee had died, and 5 elicited agreement to participate in the studies; unfortunately, none of these 5 met the rigorous selection standards outlined in the original grant application, because of complicating disease (congestive failure, diabetes, hypertension, cirrhosis, etc.) and/or medications (diuretics, digitalis, antiarrhythmics, etc.).

3. No differences between post-infarct patients and controls have been seen for 11 hormones (Table I); abnormalities have been observed for three: estrone, dehydroisoandrosterone, and triiodothyronine.

(a) Estrone* has been found to be elevated to a mean values of 80 pg/ml, compared with 47 in normals ($P < 0.0001$) (Fig. 1). Since the original grant application was submitted, we have become aware of another old report and two new reports of elevated plasma estrogens in post-infarction patients, in addition to the previous one. These results differ in detail: Wagner et al. and Korenman et al. found increased estradiol but not estrone in men with previous infarctions; Entrican et al. found increases in both estrone and estradiol, as Phillips had. We find increased estrone but not estradiol.

(b) Dehydroisoandrosterone has been found to be elevated to a mean value of 474 ng/dl, compared with 338 ng/dl in normals ($P < 0.01$) (Fig. 2). There have been no previous published reports of plasma DHA levels in coronary heart disease.

(c) Triiodothyronine (T_3) has been found to be decreased to a mean value of 97 ng/dl compared with 117 ng/dl in normal controls ($P < 0.05$) (Fig. 3). Three of the patients had values below the lower 95% confidence limit of normal, and were thus in the myxedema range. These 3 patients were not conventional examples of the "low-T_3 syndrome"; they were not bedridden, febrile, cachectic, malnourished, in pain, etc -- indeed they were in apparent good health, ambulatory, and working. Thyroxine (T_4) levels were not significantly decreased in the post-infarction patients. There have been no previous published reports about plasma levels of T_3 or T_4 in coronary heart disease, though Gertler and White reported a tendency to lower basal metabolic rates in young post-infarction patients.

These three abnormalities in post-infarct patients have two extremely interesting correlations:

(a) All three are in the direction of femaleness, since women have higher estrone levels than men, higher DHA levels than men (Fig. 4), and lower T_3 levels than men (Fig. 5). Indeed, the quantitative values for all 3 hormones in the post-infarct men are indistinguishable from those of normal women. This apparent paradox (i.e. increased femaleness of hormone pattern in a disease in which females have a lower incidence than males) is curious and thought-provoking, but not readily explainable.

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* Our original application referred to our findings of elevated estradiol - this was a typographical error -- estrone was meant.

(b) Two of the abnormalities, elevated estrone and elevated DHA, are also seen in the grossly obese young men we have been studying (Figs. 6 and 7). This raises the possibility that the increased CHD risk of obese men may be mediated by hormonal abnormalities.

4. A "discriminant" composed of all 3 of the individually abnormal hormones (DHA x estrone ÷ triiodothyronine) yields nearly total separation of the post-infarct group from normal controls; there is only 1 overlap ($P < 0.0001$) (Fig. 8).

5. We have succeeded in establishing a functioning procedure whereby men who have had coronary arteriography for evaluation at USAFSAM are contacted regarding volunteering for 24-hour plasma hormone studies at Montefiore. To date, 8 men with abnormal arteriograms and 6 with normal arteriograms have been studied; results are pending.

6. A new "arm" of the study has been activated. One 24-hour urine collection is obtained early in his visit from every USAFSAM examinee who is expected to have coronary arteriography, and is sent (frozen) to Montefiore for measurements of 4 cortisol metabolites, 6 androgen metabolites, and 6 estrogen metabolites. The studies are carried out "blind" at the Montefiore end. So far we have completed analyses of urine from 6 men with abnormal arteriograms and 21 men with normal arteriograms.

The estrogen metabolites, individually and as a total group, showed no difference between groups.

Total androgen metabolite excretion was lower in the abnormals than in the normals (6.4 mg/g creatinine vs 8.2 mg/g creatinine; $P = 0.05$), and the excretion of androsterone glucuronide was markedly lower (2.4 mg/g creatinine vs 3.4 mg/g creatinine; $P < 0.025$) (Fig. 9). If an excretion of 3.0 mg/g creatinine were used as a "diagnostic cut-off" in this group, (i.e. $\geq$ 3.0 would be normal and <3.0 would be abnormal), this parameter would have a sensitivity of 100%, a specificity of 76%, and a diagnostic efficiency of 81%, values which compare more than favorably with treadmill testing or thallium scanning.

Total cortisol metabolite and free cortisol excretion showed no difference, but the ratio of allotetrahydrocortisol to tetrahydrocortical (i.e. 5α/5β) was decreased in the abnormals (0.6 vs 0.94; $P < 0.025$) (Fig. 10). The sensitivity, specificity, and diagnostic efficiency of this parameter were also high, but not so high as those of androsterone glucuronide excretion. Since the 5α/5β ratios for androgen metabolites and cortisol metabolites were highly correlated (Fig. 11), using the two "discriminant" parameters together gave no better discrimination than using androsterone glucuronide alone.

7. The findings of excessive plasma estrone and DHA and deficient plasma T_3 in post-infarction patients and deficient urinary 5α metabolites of androgens and cortisol in patients with abnormal arteriograms who have not had a myocardial infarction support the working hypothesis of this study that patients with coronary heart disease have an abnormal endogenous hormonal environment.

8. We are developing plans to test the effects of DHA, estrone, T_3, androsterone, and allotetrahydrocortisol in the in vivo animal model of arteriosclerosis produced by balloon de-endothelialization of the aorta, and in in vitro systems of arterial smooth-muscle cell culture. Specific plans for these studies will be incorporated in our next contract renewal application.

TABLE I

Comparison of 24-hr Mean Hormone Levels of 11 Hormones that did not Differ Significantly from Normal in Post-MI Men.

Hormone	Average for Normal Men	Average for Post-M.I. Men
Cortisol (µg/dl)	7.0	7.0
Testosterone (ng/dl)	445	471
Dihydrotestosterone (ng/dl)	101	107
Dehydroisoandrosterone Sulfate (µg/dl)	71	84
Androsterone (ng/dl)	59	55
Androsterone Sulfate (µg/dl)	44	47
Estradiol (pg/ml)	31	30
Thyroxine (µg/dl)	5.8	4.9
LH (mIU/ml)	12	14
FSH (mIU/ml)	8.4	8.1
Prolactin (ng/ml)	13	12

24- HOUR MEAN PLASMA ESTRONE CONCENTRATION IN NORMAL MEN AND MEN WHO HAVE HAD A MYOCARDIAL INFARCTION

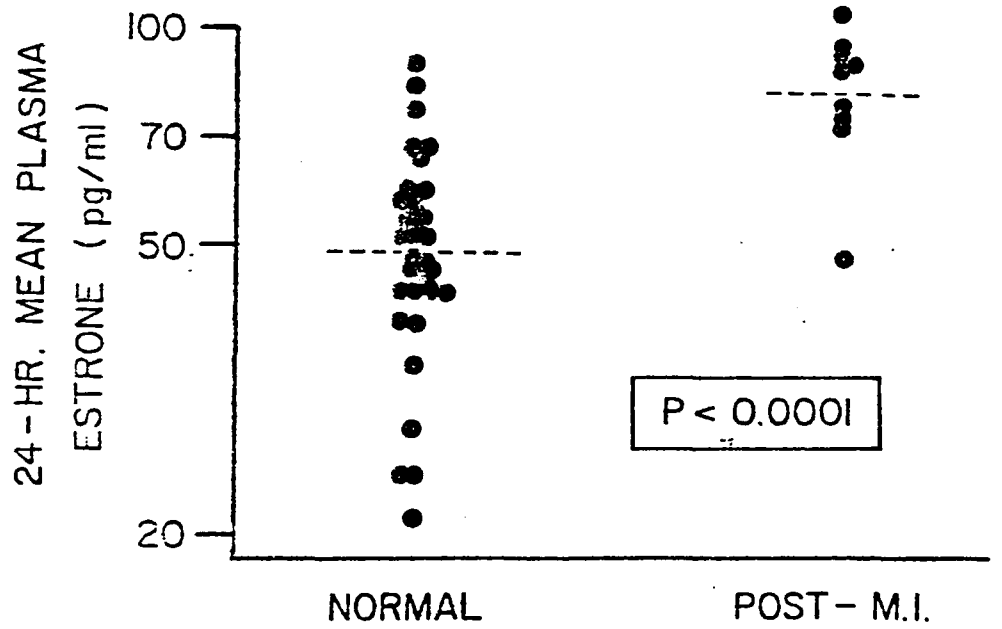

FIGURE 1

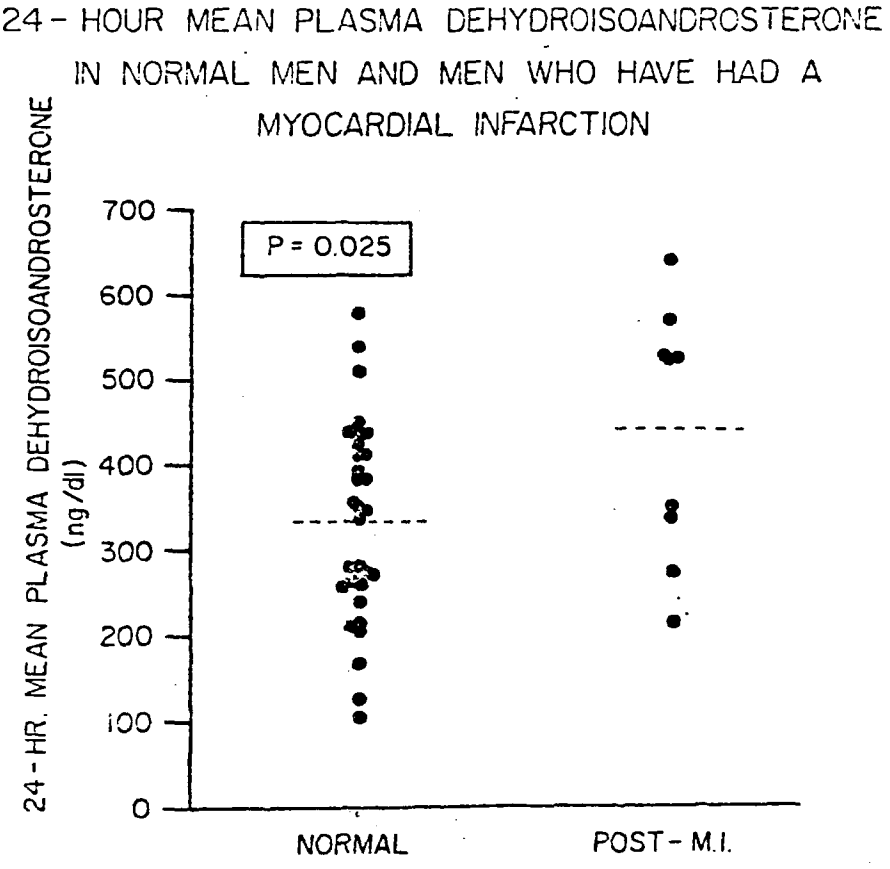
24 - HOUR MEAN PLASMA DEHYDROISOANDROSTERONE
IN NORMAL MEN AND MEN WHO HAVE HAD A
MYOCARDIAL INFARCTION
24 - HR. MEAN PLASMA DEHYDROISOANDROSTERONE (ng/dl)
700
600
500
400
300
200
100
0
P = 0.025
NORMAL
POST - M.I.

FIGURE 2

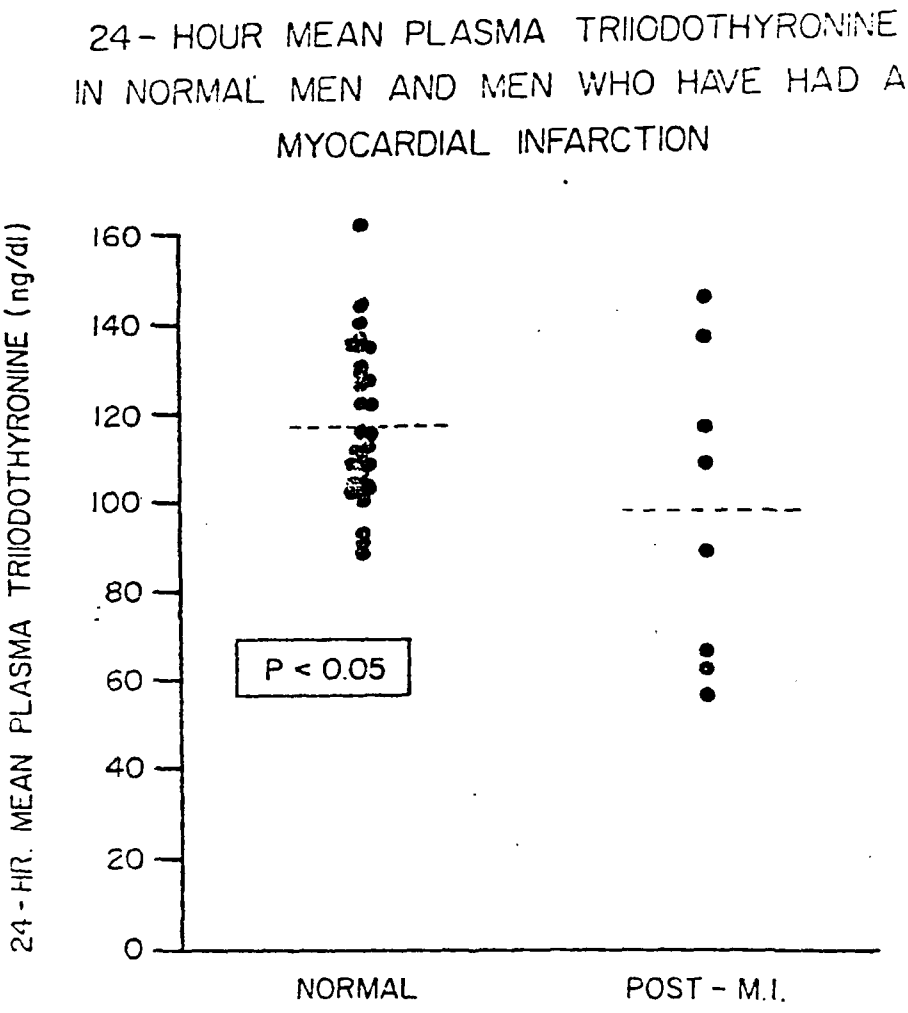
24 - HOUR MEAN PLASMA TRIIODOTHYRONINE IN NORMAL MEN AND MEN WHO HAVE HAD A MYOCARDIAL INFARCTION
24 - HR. MEAN PLASMA TRIIODOTHYRONINE (ng/dl)
160
140
120
100
80
60
40
20
0
P < 0.05
NORMAL
POST - M.I.

FIGURE 3

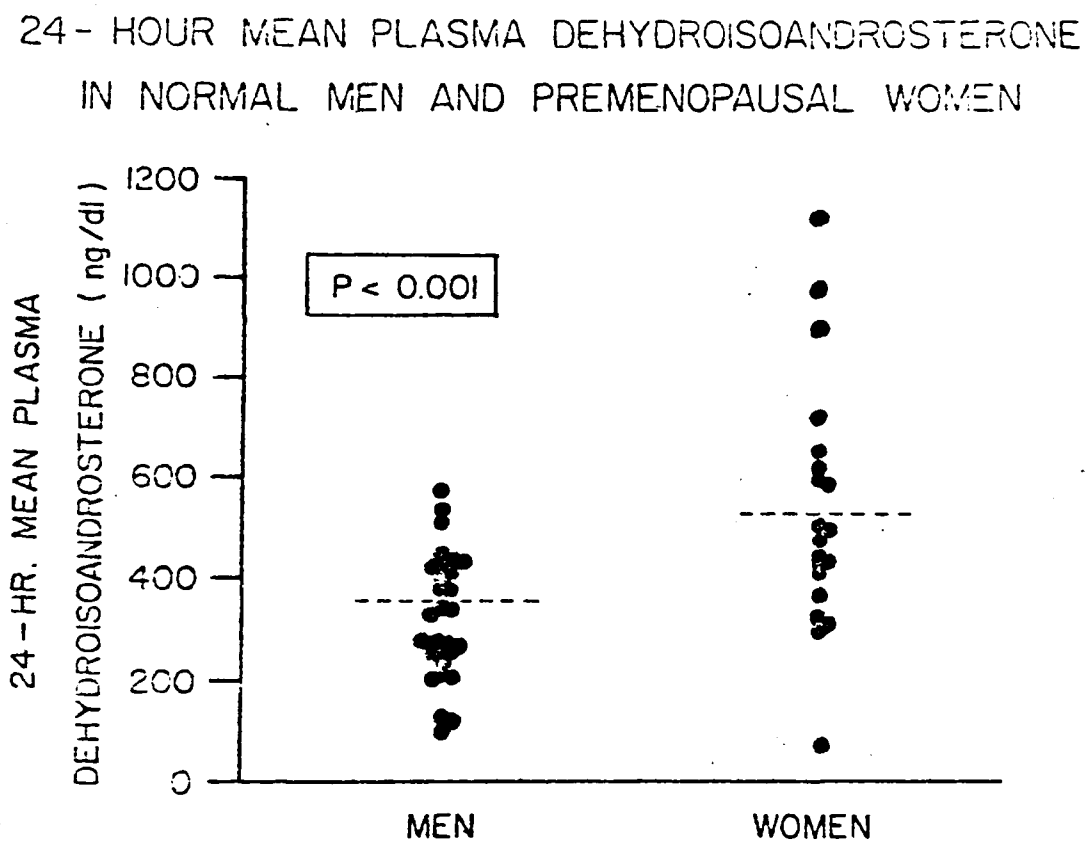
24- HOUR MEAN PLASMA DEHYDROISOANDROSTERONE
IN NORMAL MEN AND PREMENOPAUSAL WOMEN
24-HR. MEAN PLASMA
DEHYDROISOANDROSTERONE (ng/dl)
1200
1000
800
600
400
200
0
P < 0.001
MEN
WOMEN

FIGURE 4

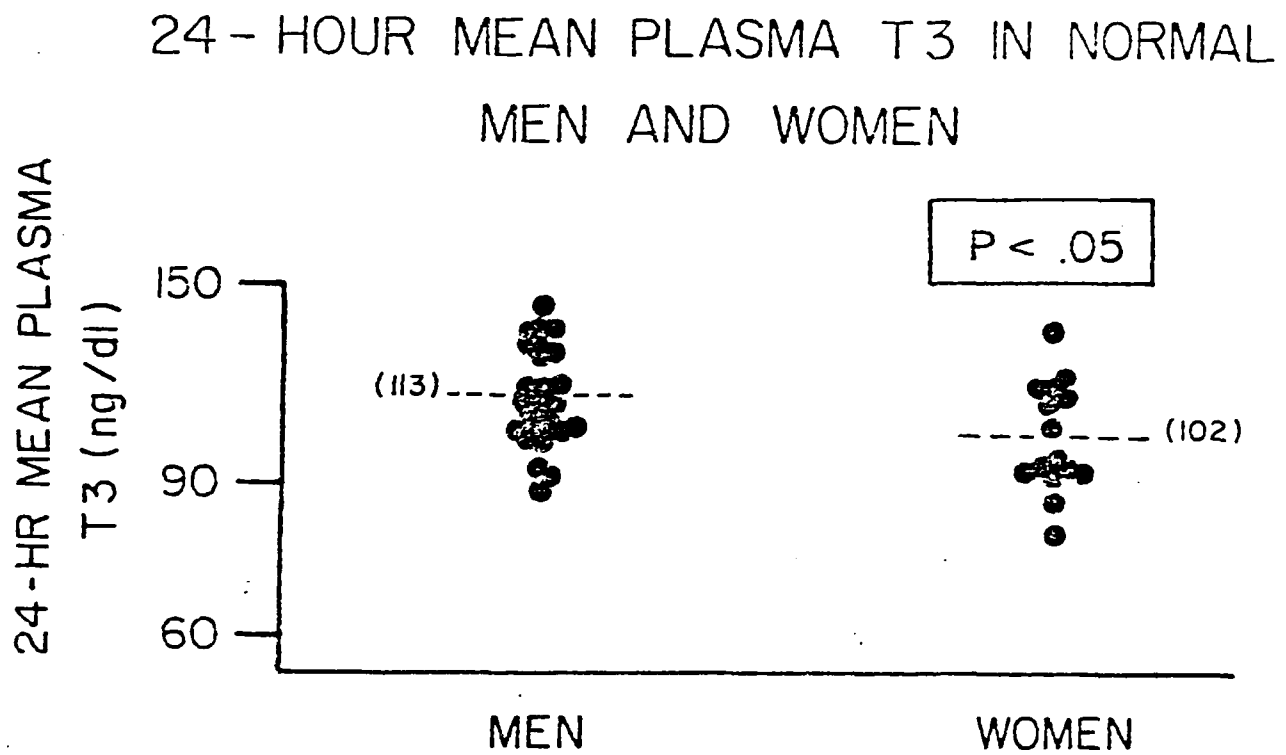
24 - HOUR MEAN PLASMA T3 IN NORMAL MEN AND WOMEN
24-HR MEAN PLASMA T3 (ng/dl)
150
90
60
(113)
(102)
P < .05
MEN
WOMEN

FIGURE 5

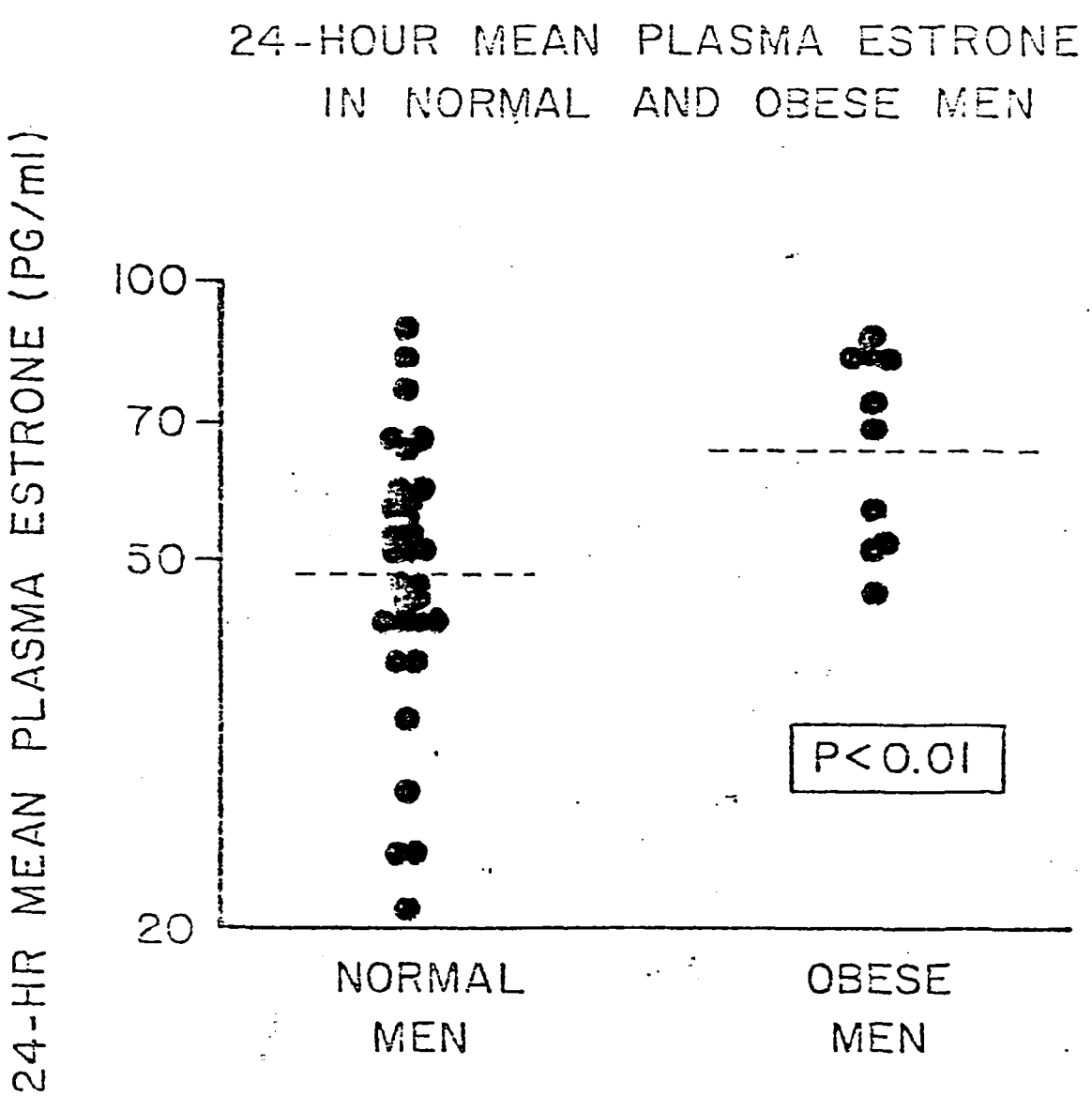
24-HOUR MEAN PLASMA ESTRONE
IN NORMAL AND OBESE MEN
24-HR MEAN PLASMA ESTRONE (PG/ml)
100
70
50
20
P<0.01
NORMAL MEN
OBESE MEN

FIGURE 6

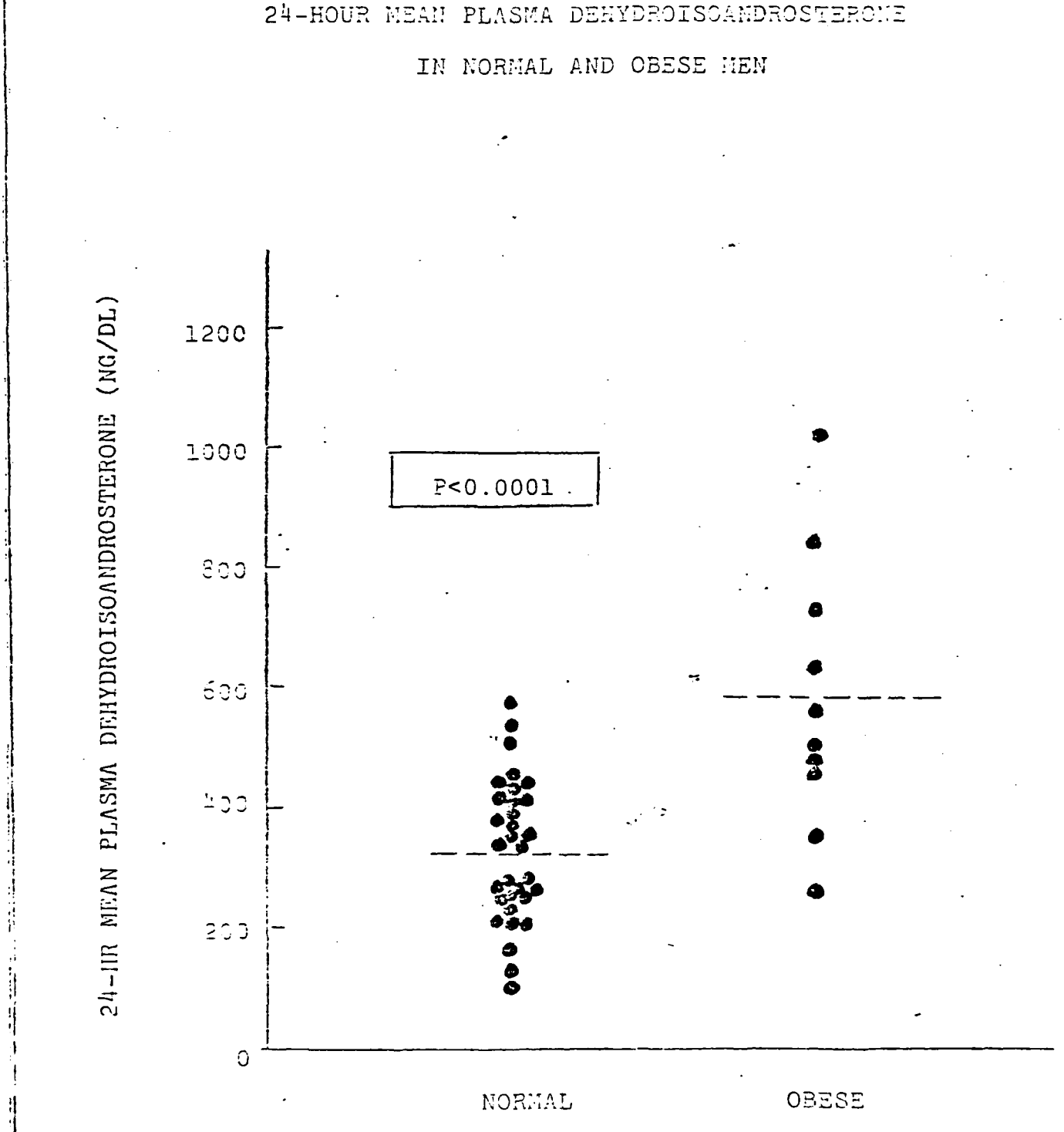
24-HOUR MEAN PLASMA DEHYDROISOANDROSTERONE
IN NORMAL AND OBESE MEN
24-HR MEAN PLASMA DEHYDROISOANDROSTERONE (NG/DL)
1200
1000
800
600
400
200
0
P<0.0001
NORMAL
OBESE

FIGURE 7

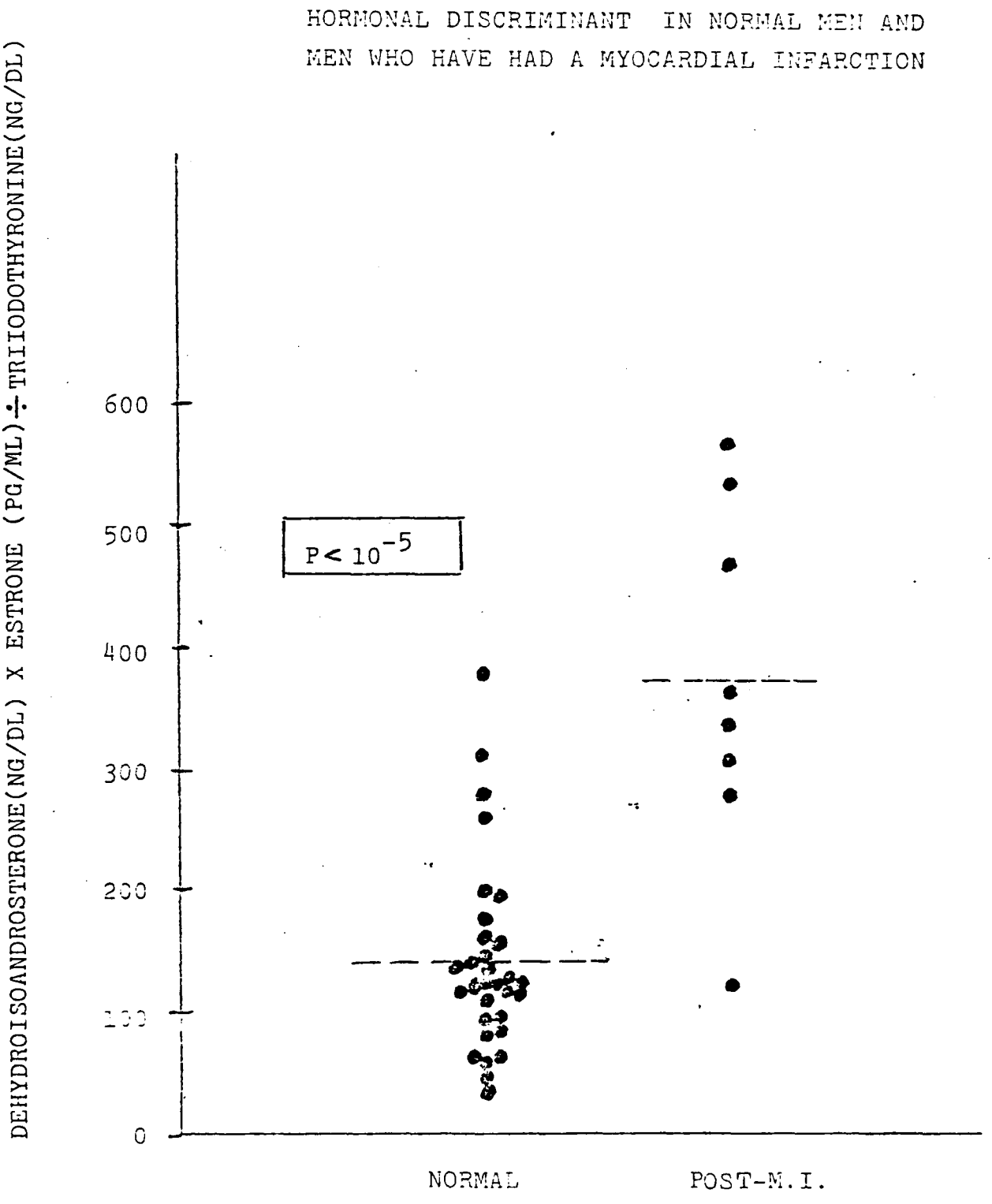
HORMONAL DISCRIMINANT IN NORMAL MEN AND MEN WHO HAVE HAD A MYOCARDIAL INFARCTION
DEHYDROISOANDROSTERONE(NG/DL) X ESTRONE (PG/ML) ÷ TRIIODOTHYRONINE(NG/DL)
600
500
400
300
200
100
0
P< 10^-5
NORMAL
POST-M.I.

FIGURE 8

URINARY ANDROSTERONE GLUCURONIDE EXCRETION IN MEN
WITH NORMAL AND ABNORMAL CORONARY ARTERIOGRAMS

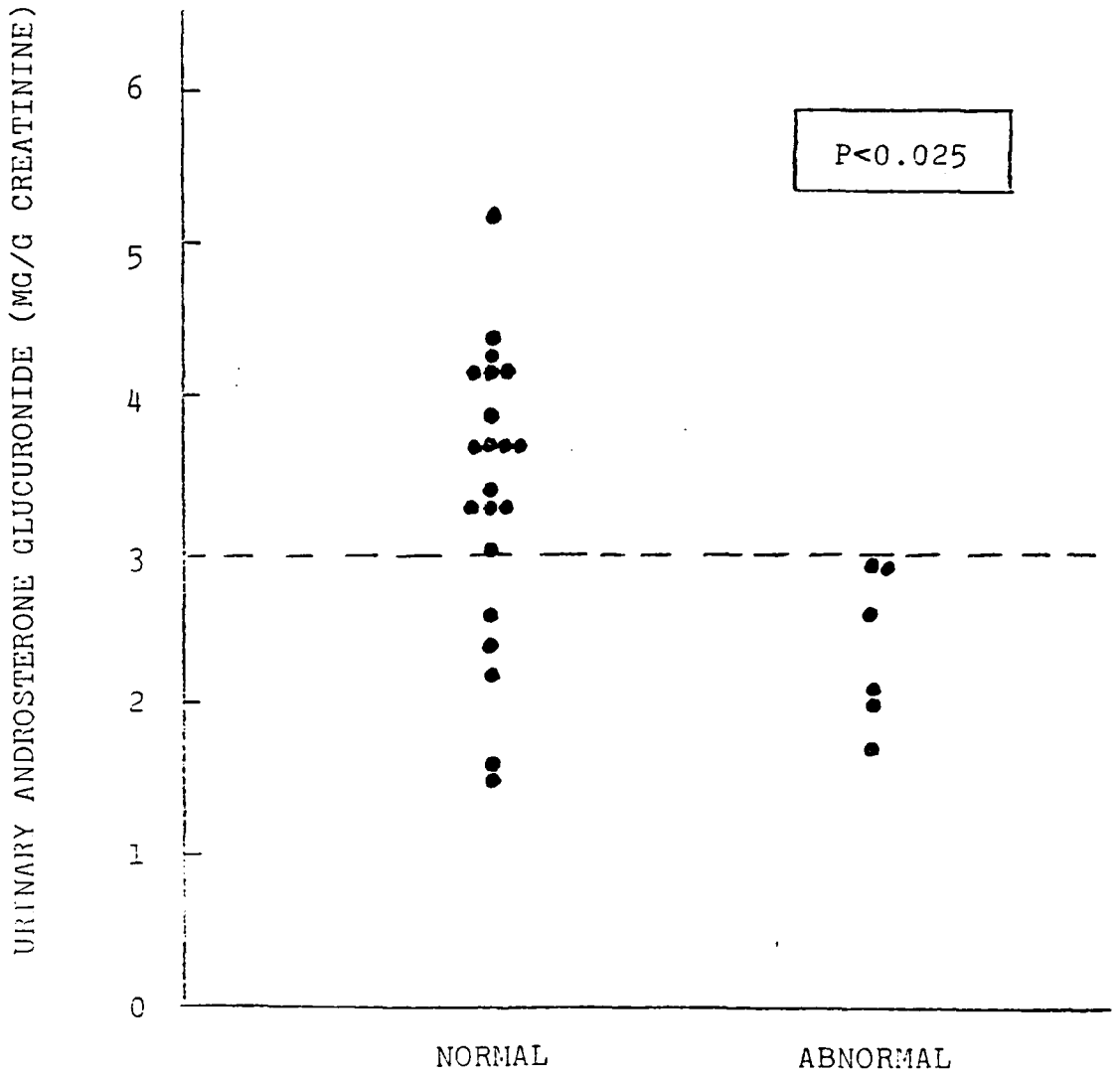

FIGURE 9

URINARY ATHF/URINARY THF IN MEN WITH
NORMAL AND ABNORMAL CORONARY ARTERIOGRAMS

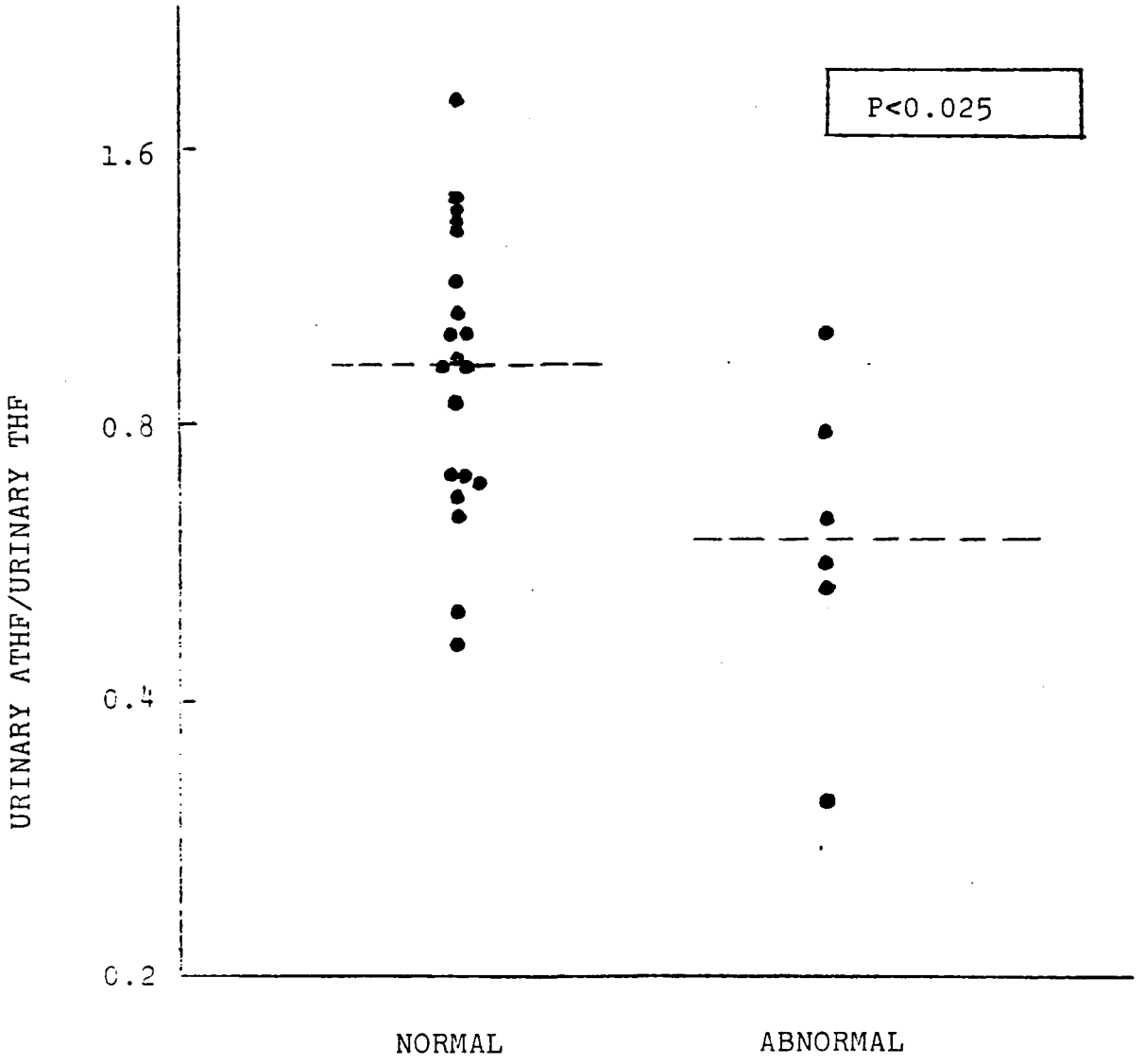

FIGURE 10

RELATIONSHIP OF 5α/5β RATIO OF URINARY ANDROGENS
TO 5α/5β RATIO OF URINARY CORTICOIDS

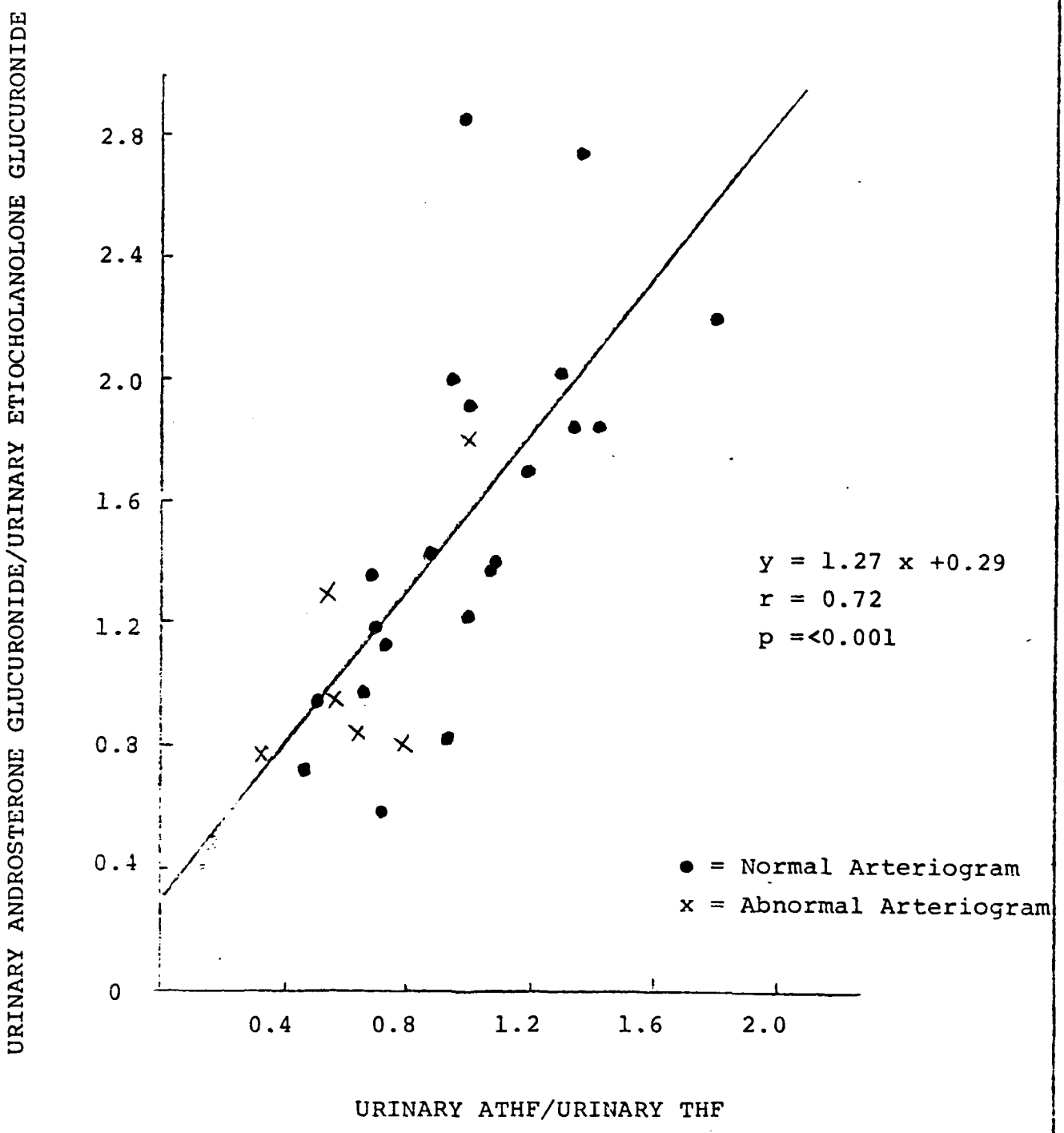

FIGURE 11